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RESEARCH ON GENETIC HYPERSENSITIVITIES TO ENVIRONMENTAL EXPOSURES: MORAL AND SOCIAL ISSUES

By

Richard R. Sharp

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ABSTRACT

RESEARCH ON GENETIC HYPERSENSITIVITIES TO ENVIRONMENTAL EXPOSURES: MORAL AND SOCIAL ISSUES

By

Richard R. Sharp

Current projections suggest that the Human Genome Project (HGP) will complete the first human genetic reference sequence (a map of all the genes in the human body) by the year 2003. The completion of the HGP reference sequence represents a crowning achievement in molecular genetics and marks the beginning of a new era in the study of human disease. The complete HGP reference sequence will allow researchers to explore the effects of genetic variation on the development of complex diseases, such as asthma, cancer, diabetes, and coronary heart disease.

The expected availability of the HGP reference sequence is prompting researchers to plan more comprehensive studies of genetic influences on disease. One example of this trend is the Environmental Genome Project (EGP), sponsored by the National Institute of Environmental Health Sciences, one of the National Institutes of Health. The EGP plans to study how genetic differences between individuals may influence how they respond to adverse environmental exposures. By identifying potential genetic hypersensitivities to environmental exposures, the EGP promises to advance our understanding of disease susceptibility and thereby assist in the development of disease-prevention and intervention strategies. Nonetheless, despite these potential health benefits,

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projects like the EGP also present a number of ethical, legal, and social concerns.

This dissertation examines the moral and social issues presented by the study of genetic hypersensitivities to adverse environmental exposures. These issues include concerns about: (1) the increasing geneticization of complex disease, (2) the protection of human subjects in molecular epidemiologic research, and (3) the potential implications of genetic-susceptibility research for socially identifiable groups. The recent explosion of interest in genetic susceptibility to complex disease makes these issues of great practical importance. Moreover, in addition to their practical relevance, examining these issues also helps to shed light on traditional questions in research ethics.

A central theme of the dissertation is that the study of genetic hypersensitivities to environmental exposures presents new moral and social issues. Bioethicists often focus their discussions of genetic research on rare, highly predictive "disease genes". Such genetic influences on disease, however, are the exception rather than the rule. As researchers begin to examine more subtle genetic influences on disease, it is important that we consider the extent to which these discussions of rare, highly predictive disease genes are appropriate guides in other context. This topic has not been fully explored by ethicists and other commentators on genetic research. A central aim of the dissertation is to illustrate how the moral and social issues presented by the study of more subtle genetic influences on disease differ from those considered in connection with highly predictive disease genes.

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I would not have been able to complete my graduate work without the help of many people. I would like to thank Dr. J. Carl Barrett and Dr. Thomas Eling for allowing me to work with them at the National Institute of Environmental Health Sciences and encouraging me to continue thinking about the social implications of genetic research. I also would like to acknowledge the financial support I received from the National Institute of Environmental Health Sciences. The views expressed in the dissertation, however, should not be understood to represent the positions of either the National Institute of Environmental Health Sciences or the National Institutes of Health.

I also would like to thank the members of my dissertation committee: Dr. Frederick Gifford (chairperson), Dr. Leonard Fleck, Dr. Joseph Hanna, Dr. Richard Hall, and Dr. Rebecca Grumet. All have been very supportive and generous with their time. I especially would like to thank Dr. Gifford for helping me to better understand how philosophy of science can inform discussions in medical and research ethics.

Throughout my graduate work, my family and friends have been very supportive. I especially want to thank my parents, Roy and Nancy Sharp, for their unconditional support, and my wife Linda for her on-going encouragement and patience.

TABLE OF CONTENTS

LIST OF TABLES

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LIST OF ABBREVIATIONS

AMA	American Medical Association
ApoE4	apolipoprotein E4
BRCA1	breast cancer gene one
BRCA2	breast cancer gene two
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CGAP	Cancer Genome Anatomy Project
EGP	Environmental Genome Project
ELSI	Ethical, Legal, and Social Implications (Program)
HGDP	Human Genome Diversity Project
HGP	Human Genome Project
HLA	human leukocyte antigen
IRB	Institutional Review Board
NAGPRA	Native American Grave Protection and Repatriation Act
NAT	N-acetyltransferase
NCI	National Cancer Institute
NHGRI	National Human Genome Research Institute
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
OMIM	Online Mendelian Inheritance in Man
OPRR	NIH Office of Protection from Research Risks
PKU	phenylketonuria
TGF-α	transforming growth factor alpha

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Introduction

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CHAPTER ONE

MORAL AND SOCIAL ISSUES PRESENTED BY RESEARCH ON GENETIC HYPERSENSITIVITIES TO ENVIRONMENTAL EXPOSURES

Introduction

Looking at the history of molecular genetics, one cannot help but be struck by two conflicting, yet equally pervasive, themes. On the one hand, there is a series of revolutionary developments that have resulted in a much better understanding of the process of genetic inheritance and have suggested far-reaching clinical applications of this new knowledge. In 1953, Watson and Crick discovered the structure of the DNA molecule and suggested a mechanism by which discrete genes are passed from generation to generation. A series of subsequent experiments revealed the genetic code and demonstrated that the incredible complexity of biological proteins can be explained in terms of finite sequences of just four nucleotides. Later, there is Southern's use of radio-labeled probes to identify and separate individual DNA fragments; Sanger's development of DNA-sequencing techniques; Mullis's PCR amplification methods; and a whole host of other techniques for identifying, characterizing and manipulating DNA samples.

Alongside these developments is the corresponding application of these techniques in clinical settings and the development of genetic tests for inherited abnormalities. Armed with the tools of molecular genetics, clinicians can now determine which children will suffer from terrible diseases like Lesh-

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Nyhan syndrome and Tay-Sachs disease. Looking to the future, improvements in gene-manipulation technologies hold the promise of "gene therapies" that dramatically reduce the suffering caused by many of these diseases. Thus, the history of molecular genetics is in many ways a story of scientific triumph—a story suggesting even more wonderful possibilities to come.

Unfortunately, however, there is another less optimistic theme running throughout the history of molecular genetics. Tests for many genetic conditions have been grossly abused. The US Airforce was accused of using genetic tests for the sickle-cell allele to discriminate against black pilots (Duster 1989). Health insurers have used such tests to avoid the burdens of caring for those who suffer from various genetic maladies. Mandatory state-sponsored screening programs have eroded the privacy of many, and pre-employment tests for genetic susceptibilities to occupational exposures threaten to limit individual choices further. Genetic tests also have been used to selectively abort various "undesirables", reminding us of past eugenics programs and sterilization campaigns. Finally, perhaps more than any other single event, it was reaction to the announcement in February of 1997 that scientists had successfully cloned an adult mammalian sheep that epitomizes the fears surrounding molecular genetics (Wilmut et al. 1997). With that announcement, many began to ask if the wonders of molecular genetics come at too high a price—whether potential misuses of genetic knowledge and technologies outweigh the benefits of being able to foresee, manipulate, and possibly control our fates.

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This concurrent optimism and concern about molecular genetics makes this one of the most controversial areas of contemporary social discussion. Many believe that molecular genetics will radically transform our lives. The problem is that no one is entirely clear exactly *how* our lives will be changed as a result of these developments. Philip Kitcher describes the situation very well when he writes (Kitcher 1996, p. 18),

> Alternatively inspiring and appalling, kaleidoscopic images of possible futures whirl by. We sense that the molecular revolution will make large differences—how large, we do not know—in the lives our children will lead, we sense that we have the power now to channel the impact the new biology will have on society, but the kaleidoscope shifts too quickly. We do not know how to stop it, how to bring these images into focus, how to decide which of them represents something for which we should genuinely hope or of which we have reason to be afraid.

Geneticists, biomedical researchers, philosophers, ethicists, and others continue to struggle to bring these kaleidoscopic images into perspective and sort through the tangle of interwoven issues presented by contemporary molecular genetics. When offered, "solutions" to these problems are understood as tentative and open to revision. In many areas, just clarifying the issues constitutes substantial progress.

This dissertation examines the moral and social issues presented by one aspect of contemporary molecular genetic research, namely, the study of genetic hypersensitivities to environmental exposures. The project is motivated

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by a belief that progress can only be made by focusing on narrow aspects of the inter-related controversies surrounding genetic research. Collectively, the issues presented by molecular genetics are overwhelming, and general conclusions few. By focusing on these issues individually, however, they may be manageable.

Conceptual overview

This dissertation examines the moral and social implications of research on genetic hypersensitivities to adverse environmental exposures. Several recent proposals to examine how genetic variation may affect disease susceptibility have made this topic especially timely (Albers 1997; Brown and Hartwell 1998; Collins, Brooks, and Chakravarti 1998; Collins, Guyer, and Chakravarti 1997; Kaiser 1997; Kuska 1996; McBride 1996; Schafer 1998). Moreover, a careful examination of these issues helps to shed light on several traditional topics in research ethics, including questions relating to informed consent, the protection of research participants, the release of research data, and implications of research for socially identifiable groups. The principal goal of the dissertation is to identify emerging issues and clarify differing perspectives on the moral and social issues presented by research on genetic hypersensitivities to environmental exposures.

This introductory chapter surveys several of the moral and social issues surrounding genetic-hypersensitivity research. The issues that are introduced and described are subsequently examined in more detail in the following

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chapters. Moreover, in both this introductory chapter and the dissertation as a whole, these issues are discussed in relation to one of the more prominent examples of contemporary research of genetic hypersensitivities, namely, the Environmental Genome Project (EGP). This project, sponsored by the National Institute of Environmental Health Sciences, one of the National Institutes of Health, exemplifies the type of genetic-hypersensitivity research that is likely to be of great interest to researchers over the next few years. Hence, a careful examination of the moral and social issues presented by the EGP is useful for thinking about the general direction of contemporary molecular genetic research and its broader social implications.

The Environmental Genome Project

Individuals differ greatly in their responses to chemicals, drugs, radiation, smoking, alcohol, and other environmental exposures. These differential responses are the result of complex interactions between many different factors, including an individual's genetic make-up, age, sex, nutritional status, and overall health. Moreover, the vast majority of diseases—many forms of cancer for example (Perera 1997)—are the consequence of these complex interactions between environmental and genetic influences. Hence, a better understanding of how individuals respond to adverse environmental exposures is crucial to understanding the development of disease.

To better understand how genetic differences between individuals influence how they respond to environmental exposures, the National Institute

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of Environmental Health Sciences (NIEHS) recently proposed the Environmental Genome Project (EGP) (Albers 1997; Cannon 1997; Kaiser 1997). Launched in 1997, the principal goal of the EGP is to better understand genetic influences on environmental response and the development of environmentally associated diseases (Albers 1997; Brown and Hartwell 1998; Cannon 1997; Kaiser 1997). The EGP is premised on the idea that identifying genetic hypersensitivities to adverse environmental exposures will allow clinicians to target preventive efforts, and early intervention programs, to those individuals who are most at risk of developing disease. Hence, the information learned through the EGP may be instrumental in accurately estimating disease risks, developing more effective disease-prevention strategies, and designing new disease interventions.

Unlike many other types of genetic research, however, the EGP is not searching for "disease genes". Rather, the genes to be studied in connection with the EGP are believed to play some role in the development of disease, but only in conjunction with other genetic and environmental factors. For example, one category of genes to be studied in connection with the EGP are genes involved in the detoxification of carcinogens. Variation within this class of genes can affect the functioning of associated gene products, and thus may limit an individual's ability to metabolize these carcinogens properly. As a result, individuals who possess certain alleles—and who also are exposed to particular carcinogens—may be at increased risk of developing cancer. These alleles, and others to be studied in connection with the EGP, are not "disease

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genes", however, since they are limited predictors of future disease. Nonetheless, in connection with other environmental factors these genetic influences may make significant contributions to the development of disease and are important factors to consider in assessing disease risks.

Geneticists use the term "penetrance" to describe the extent to which alleles are predictive of future disease. An allele is said to be highly penetrant if a large percentage of individuals who possess that allele develop an associated disease. For example, the alleles associated with Huntington's disease and cystic fibrosis are highly penetrant. By contrast, the EGP will focus on less penetrant alleles. These alleles are more loosely associated with disease, but in combination with certain environmental exposures they may play an important role in explaining why some individuals develop disease while others do not.

Moral and social issues presented by the Environmental Genome Project

As with many other developments in molecular genetics, the EGP has been viewed with both optimism and concern. In fact, in many ways current thinking about the EGP closely parallels early discussions of the Human Genome Project (HGP). At the outset of both projects advocates stressed the potential health benefits that might be gained, while skeptics remained concerned about the moral and social implications of the work. Similarly, broader social implications of the two projects were quickly recognized as important points to be addressed concurrently with the research. Like the

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Human Genome Project, NIEHS also plans to support research on the ethical, legal, and social implications of the EGP (Cannon 1997). Nonetheless, when each of the two projects were begun, there was considerable uncertainty about the significance of these larger social implications and what should be done to minimize any potential harms that might result from the research.

In this context, a noteworthy essay was published in 1991 by Eric Juengst (Juengst 1991). That essay introduced and described the Ethical, Legal and Social Implications (ELSI) Program at the National Center for Human Genome Research.[1] Juengst's goal in his essay was to highlight some of the moral and social issues that were emerging as focal points for the new ELSI program. Since that time, the ELSI program has grown to become one of the largest and most well regarded bioethics programs in the country, sponsoring the work of hundreds of researchers and coordinating bioethics activities both nationally and internationally (Marshall 1996; Meslin, Thomson, and Boyer 1997). In 1991, however, Juengst and others involved with the HGP had no way of anticipating these developments. Looking back, the issues identified in his essay may seem vague and poorly defined. At the time, however, the essay served an important purpose. The essay identified areas requiring additional study and thereby served as a guide to others interested in joining in these discussions.

In many ways, Juengst's essay serves as an inspiration to many of us who are interested in the moral and social issues presented by projects like the EGP. At this point, the moral and social implications of research on genetic

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hypersensitivities to environmental exposures are still unclear and no one is certain how serious these implications may be. Thus, like Juengst's 1991 essay, this dissertation attempts to define and clarify emerging issues.

In addressing the ethical and social implications of projects like the EGP, ethicists today are fortunate to be able to draw upon the work that has already been done. Ethicists have been thinking about these issues since the early 1970s. Moreover, the ELSI program, and related research on the Human Genome Project, has added to this scholarship on the moral and social issues presented by genetic research. Much of this work is directly relevant in thinking about projects like the EGP. Concerns about genetic privacy and the possibility of discriminatory uses of genetic information, for example, should continue to be addressed in this new context.

Nonetheless, discussions of genetic research often focus on rare genes that are highly predictive of future disease. It is unclear whether the perspectives that have emerged from these discussions are appropriate in the context of research on common genes that are more loosely associated with disease (Hunter and Caporaso 1997; Schulte, Hunter, and Rothman 1997; Soskolne 1997; Wilcox et al. 1999). Interpreting the results of genetic tests for these less penetrant alleles, for example, is much more difficult than interpreting tests for highly predictive alleles (Collins 1996). Hence, projects like the EGP should prompt us to examine the extent to which traditional bioethical perspectives apply to research on common genes that appear to play some role in the development of disease, but are limited predictors of an

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individual's disease risks. Moreover, projects like the EGP may present issues that are entirely unique, and that may present themselves as this area of research develops.

To date, several ethical, legal, and social implications are emerging as important areas to address in connection with projects like the EGP (Baird 1995; Geller et al. 1997; Grandjean and Sorsa 1996; Hunter and Caporaso 1997; Juengst 1995; Kodish et al. 1998; Parker 1995; Soskolne 1997). These include issues associated with: (1) the consent of research participants, (2) genetic privacy and confidentiality, (3) medical responsibility and the perception of individuals at risk of developing disease, (4) disclosure of research results, (5) implications for non-participants, and (6) clinical applications of research findings. These issues, while they are not new, take on new shape in connection with research on genetic hypersensitivities to environmental exposures. Each of these issues is discussed in more detail in the following sections.

Informed consent of research participants

Projects like the EGP often involve the collection of large numbers of biological samples. As part of the EGP, for instance, researchers plan to assemble a set of DNA samples that reflect the genetic diversity of the US population and make a set of immortalized cell lines available for the identification and study of genetic hypersensitivities to environmental exposures. This collection of cell lines will provide researchers with a

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replenishable source of genetic material. The samples for the EGP could be compiled from existing sample collections or could involve collecting new samples. Unfortunately, however, there are a number of difficult moral considerations relating to the collection of samples for large-scale biological repositories, particularly repositories that contain immortalized cell lines and DNA samples (American College of Medical Genetics Storage of Genetic Materials Committee 1995; American Medical Association Council on Ethical and Judicial Affairs 1998; Annas 1993; Annas 1994; American Society of Human Genetics 1996; Clayton et al. 1995; Elias and Annas 1994; Knoppers and Laberge 1989; Knoppers and Laberge 1995; Kopelman 1994; Reilly 1992; Reilly, Boshar, and Holtzman 1997; Weir and Horton 1995a; Weir and Horton 1995b).

One of the most difficult issues surrounding large-scale sample collections relates to the nature of the informed consent obtained from sample providers. If sample providers have only a general idea of how their sample may be used by researchers who have access to the sample repository, it is not clear that participants are capable of offering truly *informed* consent (Knoppers and Laberge 1989; Lyttle 1997). Moreover, while some sort of consent may have been obtained at the time of the initial contribution, it often is difficult, if not impossible, to accurately predict the ways in which future scientific developments may suggest novel uses of the collected samples. If these future applications cannot be foreseen, then clearly sample contributors cannot offer their informed consent for these uses.

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In the context of the EGP, concerns about the adequacy of informed consent are made more difficult by the fact that at the time DNA samples are collected, researchers will not be able to provide a detailed list of the specific genes to be examined or the particular diseases that may be associated with those genes. Participants will be told about the general risks and benefits of studying genetic hypersensitivities to environmental exposures, but will not be told the specific types of information that may be discovered in connection with research done with their sample. This is because it is expected that as the project develops, the EGP will consider many different genes—perhaps as many as 200 different genes (Albers 1997; Cannon 1997; Kaiser 1997)—focusing at any given time on those particular genes whose function is better understood. This flexibility, while it allows for the most efficient use of limited resources, makes it difficult to convey to potential sample contributors the information needed for making an informed decision about their participation. In short, it is unclear whether the individuals being asked to participate in the EGP will have sufficient information about the studies to be performed using their samples to warrant saying that these participants are offering truly *informed* consent.

These concerns about the adequacy of informed consent, however, are not limited to the EGP. Research on genetic hypersensitivities to environmental exposures requires epidemiologic studies that follow individuals over long periods of time. Hence, at the beginning of such studies there will be many uncertainties about future scientific developments and the

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types of information that may be available as the research progresses. In other words, studies of genetic hypersensitivities to environmental exposures, in general, present concerns about the adequacy of informed consent. In this context, the central issue presented is whether individuals being asked to participate in such research can make a fully informed decision about their participation if they are told about the *general* risks and benefits of such research, but not told about the particular types of information that may be collected in connection with their sample.

Moreover, projects like the EGP present many other related issues involving the collection of DNA samples and the protection of human subjects. These issues include concerns about the social implications of using race or ethnicity to classify samples, controlling access to samples, determining the conditions under which samples are released to other researchers, and interpreting a participant's right to withdraw from research involving widely distributed cell lines. Concerns about the scope of informed consent, while the most immediate of these issues, are part of a larger set of concerns about protecting research participants.

Genetic privacy and confidentiality

Much has already been written about the special nature of genetic information and its potential to be used in discriminatory ways (Andrews et al. 1994; Annas, Glantz, and Roche 1995; McCarrick 1993; Rothstein 1997). Much of this discussion, however, has focused on rare genetic conditions associated

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with genes that are highly predictive of future disease. By beginning with these types of genetic influences on disease, commentators have tended to focus on issues related to information gathering and information disclosure—issues concerning who ought to have access to information about an individual's genetic make-up.

While these issues are clearly important, they take on special significance in the context of rare genes of high penetrance. If an individual has a particular genetic condition that is uncommon and that manifests itself in ways that cannot be effectively dealt with, then obviously that individual will want to have as much control as possible over that information. Because of the rarity of the condition, individuals may be singled out as different, and perhaps as deserving of different treatment in some way or another. Moreover, the highly penetrant nature of the genetic influence often makes it difficult for individuals to do anything in response to their situation. Allowing affected individuals to control access to this type of genetic information also is supported by long-recognized bioethical principles, including the principle of nonmaleficence, respect for autonomy, and traditional views on the confidentiality of medical information (Beauchamp and Childress 1994). Hence, the moral perspective that emerges from an examination of rare genes that are highly predictive of disease stresses the importance of allowing individuals to determine who has access to their genetic information.

Things may change significantly, however, when we shift our attention to other types of genetic variation (Gold 1996; Wilcox et al. 1999). For example,

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with respect to common genes that are more loosely associated with disease, it is not clear whether individuals ought to have *as much control* over third-party access to genetic information. This suggestion may seem odd in light of a growing commitment to the idea that individuals should be able to control access to personal genetic information, but if a large percentage of the population has the same allele, or a closely related allele, then discrimination is not as likely. In addition, persons who are met with discrimination based on their having a common allele may respond by joining forces with the large number of similarly situated individuals, thereby empowering themselves politically. Finally, with respect to alleles of low penetrance, it may be possible to respond to a genetic disadvantage by changing the environment in which one lives. Hence, there may be compelling reasons for collecting and disclosing genetic information to public-health officials and researchers studying ways to improve public health.

In short, it is not clear that the moral paradigm that has emerged from the analysis of rare, highly penetrant genetic conditions is always an appropriate guide in contexts involving other types of genetic influences on disease (Hunter and Caporaso 1997; Juengst 1995; Parker 1995; Wilcox et al. 1999). Though commentators on genetic research involving highly penetrant alleles are correct in highlighting the potential for discriminatory uses of such genetic information, it is not obvious that these considerations apply with the same force to more common alleles of low penetrance, or that concerns about

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the protection of genetic privacy necessarily outweigh the potential benefits of disclosing other types of genetic information to third parties.

Individual responsibility for health

Recall that one of the primary goals of the EGP is to identify associations between particular alleles and increased vulnerability to adverse environmental exposures. Suppose EGP researchers are successful and identify a number of alleles that markedly increase an individual's risk of developing a specific disease, but only in contexts where they are subjected to certain environmental exposures. While such information is important for understanding and preventing disease, the availability of this information may have a number of implications with regard to how we view an individual's responsibility for his or her overall health.

Suppose, for instance, that the environmental exposures that are associated with certain alleles are very common and difficult to avoid, exposure to low levels of direct sunlight, for example. An individual may be able to avoid such exposures, but only by taking extraordinary measures. Knowing that these precautions are available, it is unclear how we should view individuals who fail to take such extraordinary measures to lower their risk of disease. Insurers, for example, may claim that individuals who do not minimize their exposure to these agents are responsible for any subsequent illness because they are knowingly placing themselves at risk. Employers asked to pay for health costs through workers's compensation may refuse, appealing to the

idea that it was the individual who knowingly took a job that placed him or her at high risk given their genetic disadvantages. Currently, it is unclear how to resolve such disputes or the extent to which this information might be inappropriately used to avoid responsibility for illness. These disputes relate to problems about possible discriminatory uses of genetic information, but the more basic issue is how information on genetic hypersensitivities to environmental exposures may alter our views on individual responsibility for one's health.

To further illustrate this point, suppose that several alleles are identified that markedly increase the risks associated with second-hand smoke. Moreover, suppose that these alleles are found in a significant percent of the population. Given such circumstances, there might be large-scale efforts to mandate that smoking parents have their children screened for the presence of these alleles. Parents who refuse might even be accused of child abuse. With knowledge comes responsibility. In the context of projects like the EGP, the question is how information gathered through this type of research will alter our current conceptions of medical responsibility. Moreover, as the examples above illustrate, these are not just abstract, philosophical concerns. Determining who is responsible for an individual's health has very clear implications for workers's compensation benefits, medical and life insurance claims, child-custody disputes, employment choices, and a whole host of other decision-making areas (Rothstein 1994-95).

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Closely related to this point about medical responsibility are concerns about the impact genetic-hypersensitivity research may have on how we view at-risk, but currently non-symptomatic individuals. Much has already been written about the possibility of individuals with genetic disadvantages coming to see themselves as ill, even though they are not exhibiting any symptoms of the disease and may never develop the illness (Weir, Lawrence, and Fales 1994). Projects like the EGP may indirectly foster such a tendency, especially if the associations between particular alleles and specific diseases are difficult to quantify.

Disclosure of research results to participants

The EGP and projects like it also raise a number of issues relating to the disclosure of study information to research participants. Clinicians and genetic researchers continually wrestle with the problem of how to communicate genetic information to individuals effectively and in a manner that does not suggest a sort of genetic determinism (Juengst 1995; Thomson 1994). In the context of the EGP, these issues are complicated by the type of genetic information involved. Specifically, given the probabilistic nature of the associations between allelic variants and increased vulnerability to environmental exposures, and the corresponding difficulties involved in validating gene-environment associations (Schulte and Perera 1993), it is unclear whether investigators should disclose any results to study participants (Schulte and Singal 1996). If results are disclosed, they may be viewed in an

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The EGP and related projects will have to find ways of educating prospective participants about the inappropriateness of genetic determinism in connection with alleles of low penetrance. The difficulty of this task is increased by the fact that many people currently appear to accept some form of genetic determinism and believe that an individual's genetic make-up determines, to a large extent, his or her overall health (Hubbard and Wald 1993; Lewontin 1991; Nelkin and Lindee 1995). The widespread acceptance of this view will make it difficult for researchers studying genetic hypersensitivities to environmental exposures to convey their findings to participants in a way that avoids placing too much weight on the identification of genetic influences on disease.

Implications for non-participants

In addition to these concerns about disclosing results to individual participants, the release of research findings can have broader implications for socially identifiable groups. It is often the case that allelic variants are more prevalent in some populations than in others. As specific alleles are associated with increased vulnerability to particular environmental exposures, it is likely that some genetic hypersensitivities will be associated with socially identifiable groups. The adverse association of genetic susceptibilities with race or ethnicity could threaten the employment and insurance opportunities

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available to entire groups of individuals (Caplan 1994; King 1998) . Broader forms of discrimination and stigmatization, for example in adoption efforts or child-custody disputes, also are possible (Wolf 1995). In this respect, the association of Ashkenazi Jews with BRCA1 mutations, and increased risk of breast cancer, is suggestive of the types of risks presented by projects like the EGP (American Jewish Congress 1998; Stolberg 1998; Struewing et al. 1997).

In response to these potential risks, some have proposed that existing human subjects protections be supplemented with community-based reviews of genetic research (Foster, Bernsten, and Carter 1998; Foster, Eisenbraun, and Carter 1997; Freeman 1998; Greely 1997; North American Regional Committee of the Human Genome Diversity Project 1997). This suggestion has been controversial and the effectiveness of these supplemental protections has been called into question (Juengst 1998a; Juengst 1998b; Reilly and Page 1998; Reilly 1998). Additional debate and empirical research is needed to determine how best to incorporate the perspectives of non-participants in the review of genetic research. The community-review model, and its limits, remain relatively unexplored.

Clinical applications of research findings

While research on genetic hypersensitivities to environmental exposures may help to better understand the etiologies of complex diseases, this information may prove difficult to incorporate into clinical practice. One reason for this is the difficulty of validating associations between genetic variants and

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particular diseases (Schulte and Perera 1993). Moreover, even where clear associations can be made between a genetic variant and increased vulnerability to a particular environmental exposure, non-therapeutic pressures may influence applications of this information. Employers, for instance, may wish to screen workers for heightened genetic sensitivity to chemicals used in the workplace (Vineis and Schulte 1995). Moreover, where genetic tests for differential sensitivity to environmental exposures are available, some individuals may choose to forego testing for fear that they may be denied employment or insurance opportunities. Hence, responsibly incorporating the findings of projects like the EGP into clinical practice may be difficult.

Moreover, a better understanding of genetic hypersensitivities to environmental exposures may force us to reexamine a central distinction in discussions of the ethics of genetic manipulation, namely, the distinction between genetic interventions that aim at "enhancing" an individual's genetic make-up and interventions that are "therapeutic" in nature. This distinction is widely believed to be morally significant (Anderson 1989). Genetic manipulations that are therapeutic are seen as morally permissible applications of gene-manipulation techniques, while altering an individual's genetic make-up for "enhancement" purposes is viewed as morally problematic. Projects like the EGP, by providing information on genetic hypersensitivities, may blur this widely recognized moral distinction. For instance, if an individual discovers that he or she possesses a particular allele of low penetrance and that this allele may be related to an environmentally

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associated disease, the individual may want to respond not by altering his or her environment, but by altering his or her genetic make-up. In such a case, it is not clear that this is a genuinely "therapeutic" intervention, because the individual is neither ill, nor symptomatic, and may never develop the illness in question.

Overview of the dissertation project

In many ways, the EGP and other projects examining genetic influences on environmental response represent a new type of genetic research, with their emphasis on the incorporation of detailed genomic information into our understanding of disease susceptibility. In light of the novelty of the research, it is not surprising that the moral and social implications of genetic-hypersensitivity research have not been adequately discussed in the existing bioethics literature. These new concerns ultimately may require us to develop more precise moral classifications and new bioethical paradigms. Minimally, it is certainly the case that in order to maximize the benefits to be derived from studying genetic hypersensitivities, and to minimize any associated harms, the ethical, legal and social implications of projects like the EGP must receive further attention.

The following chapters examine several of the moral and social issues presented by research on genetic hypersensitivities to adverse environmental exposures. Chapter two provides a brief overview of the scientific advances that have made it possible for contemporary researchers to study subtle

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genetic influences on complex disease. That chapter highlights three stages in the development of genomic research: (1) the identification of human genes through projects like the Human Genome Project, (2) the identification of common allelic variants within these genes, and (3) the elucidation of gene functioning and the effects of allelic variation. In addition, chapter two describes several contemporary research projects examining genetic susceptibility to disease, including the Cancer Genome Anatomy Project, the Environmental Genome Project, and proposed extensions of the Human Genome Project. Finally, drawing upon the work of several authors (Caporaso and Goldstein 1995; Holtzman 1994; Juengst 1995), chapter two presents a conceptual framework for classifying different types of genetic influences on disease. While the dissertation does not provide a comprehensive review of current research on genetic hypersensitivities to environmental exposures, it provides important background information for subsequent discussions of the moral and social issues presented by such research.

Advocates of research on genetic hypersensitivities to environmental exposures often stress the potential health benefits of such research. While these potential benefits provide a sound rationale for examining genetic influences on environmental response, the study of genetic hypersensitivities may reinforce a troublesome tendency to "geneticize" disease, that is, to view genetic factors as the primary or fundamental causes of human health and illness. Chapter three examines the moral and social implications of the increasing geneticization of complex disease. There it is argued that several

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scientific and ethical perspectives suggest that we should resist the increasing geneticization of disease. These considerations include: (1) threats to alternative approaches to the study of multifactorial disease and disease prevention, and (2) potential misuses of genetic information resulting from an inappropriate emphasis on genetic influences on disease.

Chapter four examines issues relating to informed consent. Current thinking about informed consent for genetic research suggests that in seeking consent from prospective research participants, researchers should specify the particular genes and diseases under consideration (American College of Medical Genetics Storage of Genetic Materials Committee 1995; American Society of Human Genetics Ad Hoc Committee on DNA Technology 1988; American Society of Human Genetics 1996; Clayton et al. 1995; Knoppers and Laberge 1989; NIH Office of Protections from Research Risks 1993; Reilly, Boshar, and Holtzman 1997). This requirement, what we might call the specificity requirement, is believed to be especially important in the context of genetic research, because many genetic studies have the potential to reveal highly predictive information about individuals and to radically affect the lives of study participants and their families. Hence, many believe that consent processes that fail to satisfy the specificity requirement do not allow participants to assess the potential risks and benefits of their participation, thus making genuinely *informed* consent impossible. Chapter four examines the reasons offered in support of the specificity requirement. Focusing on molecular epidemiology and research on genetic hypersensitivities to

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environmental exposures, chapter four defends the idea that open-ended forms of consent are acceptable for a limited class of genetic research protocols and that a strong commitment to the specificity requirement is misguided. In addition, a model consent form is presented and used to explore the general requirements of informed consent in connection with molecular epidemiologic research.

Chapters five, six, and seven each examine the issue of genetic discrimination and how the study of genetic hypersensitivities to environmental exposures could adversely affect socially identifiable groups. The issue of genetic discrimination is far too broad, however, to discuss without providing a specific context. Hence, these chapters focus on concerns that have been voiced by Native American communities in connection with research on genetic variation that is unique to, or more prevalent among, their members. These include: (1) concerns about possible discrimination and stigmatization, (2) skepticism about whether the benefits of disease-susceptibility research outweigh its potential risks, and (3) concerns about possible threats to existing social arrangements (Dukepoo 1998; Grounds 1996; McPherson 1995; National Research Council 1997; Wallace 1998).

Alarmed by the possible consequences of genetic research, some Native American organizations have called for a general moratorium on all genetic research involving Native Americans (North American Indigenous Peoples Summit on Biological Diversity and Biological Ethics 1997; Rural Advancement Foundation International 1993). In contrast to this perspective,

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researchers have tended to discount many of the worries expressed by indigenous communities, arguing that the risks presented by genetic research are minimal. Chapter five suggests that this conceptual gap between indigenous peoples and researchers results from the conflation of several types of genetic research and a corresponding failure to distinguish different types of research-related risks. It is argued that by more carefully distinguishing these types of genetic research, and identifying different levels of participant risk, indigenous communities and researchers are more likely to engage in meaningful dialogue about the actual risks and benefits of genetic research involving Native Americans.

Chapter six further considers how Native American communities may be affected by various proposals to examine genetic differences between populations. Drawing upon the conceptual categories introduced in chapter five, chapter six assesses the respective risks and benefits of two proposed research projects. The first is the EGP. The second is the Human Genome Diversity Project (HGDP), an international proposal to study genetic variation in indigenous communities worldwide (Cavalli-Sforza et al. 1991). Though some indigenous communities have viewed the collective risks of these two projects as roughly equivalent, chapter six argues that there are important differences between the EGP and the HGDP. The conceptual categories introduced in chapter five help to define and clarify these differences.

Finally, chapter seven discusses how supplemental community-based reviews of genetic research can play a role in identifying and minimizing

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potential risks to socially identifiable groups. While community-based reviews may help to identify population-specific risks, they have been criticized as both impractical and morally problematic. Chapter seven clarifies the goals of community review and the various forms that it can take. Several problems with involving communities in the review of genetic research also are discussed. The chapter concludes by offering suggestions on how these problems might be addressed, thus providing a limited defense of supplemental community-based reviews.

Why it is important to consider these issues

There are several reasons why it is important for philosophers and ethicists to consider the moral and social implications of research on genetic hypersensitivities to environmental exposures. Perhaps the most obvious reason for discussing these issues is that how they are resolved has significant practical implications—for researchers, research participants, and others who may be affected by the research. Moreover, philosophers can contribute much to these discussions by clarifying concepts and central points of disagreement. For example, distinguishing various types of research-related risks may help identify risks that otherwise could go unnoticed (see chapter five).

Another benefit of examining the moral and social issues presented by genetic-hypersensitivity research is that such work may help us to better understand how genetic information is both similar to, and yet different from,

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other types of medical information. For example, by carefully distinguishing several types of genetic influences on disease, we may find that different types of genetic information require different standards of protection. Perhaps information on highly penetrant alleles should be given very rigorous protection, while information on less penetrant alleles should be treated in the same way as other types of medical information.

Finally, examining the issues presented by genetic-hypersensitivity research helps to shed light on several traditional issues in research ethics. Obtaining genuinely informed consent, for example, is especially difficult in this new context because of public misperceptions about genetic influences on disease. Studying genetic hypersensitivities to disease thus may suggest new approaches to conveying the limited predictive value of some types of genetic information and new ways of approaching the consent process for genetic research.

For each of these reasons, it is important for philosophers and ethicists to examine research on genetic hypersensitivities to adverse environmental exposures and genetic susceptibilities to complex disease. It is hoped that this dissertation plays a role in fostering these discussions.

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Acknowledgements

This work was supported in part by the National Institute of Environmental Health Sciences. Portions of this chapter were presented at the 32nd Annual Meeting of the International Association of Cancer Registries (Atlanta, August 18, 1998) and at a conference on Genomic Research on Populations Exposed to Environmental Toxins (Boston, November 14, 1998). The author wishes to thank Carl Barrett and Gwen Collman for their thoughtful comments on earlier drafts.

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CHAPTER TWO

GENETIC INFLUENCES ON DISEASE: HISTORICAL BACKGROUND AND FUTURE RESEARCH

Abstract

It is expected that the Human Genome Project (HGP) will complete the first human genetic reference sequence by the year 2003. Biomedical researchers hope to use this reference sequence to identify functionally important variation within genes. Allelic variation can affect the functioning of associated gene products and thus may play a role in the development of complex diseases such as asthma, cancer, diabetes, and coronary heart disease. Already, a new wave of research is examining how subtle genetic differences between individuals can alter their disease risks. For example, the Environmental Genome Project sponsored by the National Institute of Environmental Health Sciences is currently studying how allelic variation in environmental response genes can affect how individuals respond to adverse environmental exposures. This, and related research, is premised on the idea that a better understanding of gene-environment interactions will lead to more accurate estimates of disease risks and assist in the development of disease-prevention strategies directed at those individuals who are most vulnerable. This chapter reviews several key scientific developments that have contributed to recent interest in examining genetic variation and its effect on environmental response. The aim

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Introduction

Recent advances in molecular genetics have generated much excitement about the study of genetic susceptibilities to complex diseases such as arthritis, asthma, Alzheimer's disease, cancer, coronary heart disease, and diabetes (Brown and Hartwell 1998; Collins, Brooks, and Chakravarti 1998; Collins, Guyer, and Chakravarti 1997; Gottesman and Collins 1994). Researchers believe that subtle genetic differences between individuals often play an important role in determining who develops disease (Chakravarti 1998; Haines and Pericak-Vance 1998; King, Rotter, and Motulsky 1992; Schafer and Hawkins 1998; Scriver et al. 1995). Genetic differences alone, however, are rarely sufficient to explain why one individual develops disease while another is spared. Rather, genetic variation can affect how individuals respond to adverse environmental exposures, thus making individuals who possess certain alleles more vulnerable to their harmful effects.

Interest in genetic susceptibility to complex disease is producing a new field of biomedical research, combining the respective expertise of epidemiologists, clinical geneticists, population geneticists, and molecular biologists. This emerging field has been dubbed "molecular epidemiology" (Ambrosone and Kadlubar 1997; Hulka, Wilcosky, and Griffith 1990; McMichael 1994; Schulte and Perera 1993; Shields 1996; Shpilberg et al. 1997; Wilcox

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1995). The goals of molecular epidemiology include, (1) understanding how genetic variation affects disease risks, (2) elucidating disease mechanisms by studying genetic influences on disease, and (3) incorporating genetic information into disease-prevention efforts (Schulte 1993). Molecular epidemiologists are interested in studying genetic influences on environmental response, because they hope that a better understanding of environmental response will help in understanding disease processes and ultimately assist in developing more effective ways of preventing disease.

This chapter reviews several important scientific developments that have made it possible for researchers to study genetic influences on environmental response and the development of complex disease. This overview describes three overlapping stages of genomic research. The first stage is the identification of genes that appear to play an important role in the development of disease. The second stage is the identification of common genetic variations within these genes. Finally, the third stage is the analysis of the functional implications of genetic variation within genes. In addition to this historical background, the chapter also describes current and planned research in molecular epidemiology. The chapter does not provide a comprehensive survey of the scientific literature, however, since the scope of these investigations makes a comprehensive review impossible. Rather, the goal is to provide background information that will inform later discussions of the moral and social issues presented by research on genetic hypersensitivities to environmental exposures.

Genetic influences on disease

For centuries, physicians have noted familial patterns of disease. It is only recently, however, that a better understanding of genetic inheritance has allowed biomedical researchers to identify specific genetic causes of disease (Caskey 1993; Caskey 1992). Researchers first associated a disease (Down's syndrome) with a chromosomal abnormality in 1959 (Lejeune, Gautier, and Turpin 1959). This discovery quickly found its way into clinical practice with the development of amniocentesis and pre-natal diagnosis in the late 1960's (Jacobson and Barter 1967; Kan, Golbus, and Dozy 1976). A decade later, researchers interested in sickle-cell anemia produced the first genetic map of a "disease gene" (Kan and Dozy 1978). Additional research on related hemoglobinopathies led to the first association of a particular disease (β-thalassemia) and a specific genetic mutation described in terms of the nucleotide sequence (Orkin et al. 1982). This work enabled researchers to develop disease detection methods specific to individual alleles (Conner and al. 1983).

Many early advances in our understanding of genetic influences on human disease are associated with hemoglobinopathies like sickle-cell anemia. Researchers have since taken the tools and methodologies developed in that context and applied them to the study of other diseases. DNA-based diagnostic tests are now available for Huntington's disease, Lesch-Nyhan syndrome, cystic fibrosis, duchenne muscular dystrophy, fragile-X syndrome, Tay-Sachs disease, and many others (McKusick 1998). Today,

new "disease genes" are announced weekly. In fact, to keep pace with the speed with which these genes are identified, an on-line database has been created (OMIM 1999). As of 7 March 1999, this database described 586 genes associated with disease phenotypes (OMIM 1999).

Many biomedical researchers believe that these successes are just the tip of the iceberg (Gottesman and Collins 1994; Haines and Pericak-Vance 1998; Khoury 1997). Researchers are particularly interested in examining genetic influences on common multifactorial diseases (Brown and Hartwell 1998; Collins, Brooks, and Chakravarti 1998; Collins, Guyer, and Chakravarti 1997; Zhang, Zhao, and Merikangas 1997). Already, specific alleles have been associated with increased risk of breast cancer, colon cancer, Alzheimer's disease, obesity, and other complex diseases. In addition, DNA-based diagnostic tests for many of these genes are available. However, unlike tests for Huntington's disease and Tay-Sachs disease, the results of these genetic tests are more difficult to interpret (Collins 1996). A woman who knows that she carries an allele associated with certain forms of hereditary breast cancer, for instance, may be told that she is roughly 50% more likely than other women to develop breast cancer (Kahn 1996). Carrying that allele, however, does not mean that she will necessarily develop the disease. Rather, the genes associated with common multifactorial diseases like breast cancer, while they provide some information about the likelihood of future disease, are limited predictors of an individual's risks.

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Penetrance and prediction

Geneticists use the term "penetrance" to distinguish genes that are highly predictive of phenotype from those that are more loosely associated with phenotype. Penetrance can be defined as "the percentage of individuals with a given genotype who exhibit the phenotype associated with that genotype" (Suzuki et al. 1989, p. 83). Thus, alleles of high penetrance are closely associated with particular phenotypes, in many different individuals and in a wide range of environments. Examples of highly penetrant alleles include those associated with Huntington's disease, cystic fibrosis, and Tay-Sachs disease. Individuals who carry one of these alleles are very likely to exhibit the associated disease phenotype, irrespective of other environmental and genetic influences.

Notice, however, that the concept of penetrance is population relative. The percentage of individuals with a given genotype who also exhibit the associated phenotype is dependent upon the population considered. Consider, for example, phenylketonuria (PKU). Individuals with PKU are unable to metabolize phenylalanine properly because of a sequence irregularity in the gene that codes for phenylalanine hydroxylase. As a result, phenylalanine rapidly accumulates in the bodies of individuals with PKU and they develop disease symptoms, including severe mental retardation. The altered gene associated with PKU is highly predictive of disease phenotype in many populations and in many different environments, since phenylalanine is a common amino acid. Hence, the allele associated with PKU is considered a

highly penetrant allele. Nonetheless, one can imagine a population in which phenylalanine is uncommon. In such a population, significantly fewer individuals with the PKU allele would exhibit the associated disease phenotype. As a result, in that population the PKU allele would not be highly penetrant, since the percentage of individuals who possess the allele and subsequently develop the associated disease would be low. Thus, the concept of allelic penetrance is population specific.[1]

Moreover, the phenotypic implications of highly penetrant alleles can vary considerably from individual to individual. For example, individuals who are homozygous for cystic fibrosis alleles exhibit the disease to varying degrees of severity (Centers for Disease Control 1997). Some individuals appear to be unaffected and do not present any clinical symptoms (Centers for Disease Control 1997). Hence, there are limitations to the predictive value of even the most highly penetrant alleles.

Fortunately, highly penetrant disease alleles generally are rare in populations (Cavalli-Sforza, Menozzi, and Plazza 1994). By contrast, less penetrant alleles are much more common. These less penetrant alleles are believed to play some role in disease, or susceptibility to disease, but only in conjunction with other genetic components or environmental exposures. For example, genes coding for human leukocyte antigen (HLA) have been associated with increased vulnerability to xenobiotics (Khoury and Dorman 1993). HLA-B27, for instance, has been associated with hypersensitivity to beryllium and thus increased risk of chronic beryllium disease. Another

example of an allele of low penetrance is the gene that codes for transforming growth factor alpha (TGF-α). Pregnant women who smoke, and who also possess specific variants of the TGF-α gene, are at increased risk of giving birth to children with facial clefts (Cannon 1997). Similarly, cytochrome p450 mutations have been associated with decreased ability to detoxify carcinogens and increased risk of bladder cancer (Cannon 1997). These less penetrant alleles, though they are associated with particular diseases, have limited predictive value. Other risk factors often are much better predictors of an individual's disease risks—smoking or diet, for example.

Frequently, it is not clear why some genes are better predictors of disease risks than others. Where allelic variation is a limited predictor of disease risk, presumably there are other intervening events that influence the development of disease (Strohman 1997). These intervening factors may include particular exposures encountered by individuals (e.g. ionizing radiation or chemical toxins) and/or other genes (e.g. tumor suppressor genes and DNA repair genes). Moreover, like highly penetrant alleles, the severity of the disease associated with these less penetrant alleles may vary considerably from individual to individual. These complexities, however, are what researchers hope to make sense of by examining genetic hypersensitivities to environmental exposures.

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The distinction between highly penetrant and less penetrant alleles is one of degree. Genes can be classified along a continuum, ranging from alleles that are highly predictive of disease, to alleles with limited predictive value. This general continuum is often described in terms of a broad distinction between "disease genes" and "susceptibility genes" (Caporaso and Goldstein 1995; Holtzman 1994). Highly penetrant alleles are characterized as disease genes since they are highly predictive of whether an individual will develop the associated disease. Similarly, less penetrant alleles, while they are associated with disease phenotypes, are described as (increased) susceptibility genes because they are more limited predictors of future disease. The distinction between disease genes and susceptibility genes is helpful in drawing attention to the fact that not all genes are highly predictive of future events (Wilcox et al. 1999). Nonetheless, a more fine-grained classification is more useful for thinking about the wide range of genetic influences on disease.

Two considerations are especially helpful in distinguishing various types of genetic influences on disease (Juengst 1995). First is the distinction between, (1) highly penetrant alleles that are strongly associated with disease phenotypes, and (2) less penetrant alleles that are more limited predictors of future disease. Second is the distinction between, (1) unavoidable genetic influences on disease, and (2) genetic influences that can be countered through preventive or therapeutic means. Moreover, the first distinction

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(between highly penetrant alleles and less penetrant alleles) is separable from the second distinction (between unavoidable genetic influences and avoidable influences). An allele may be highly penetrant, yet treatable through therapeutic means (e.g. PKU). Furthermore, combining these two conceptual distinctions offers a useful way of distinguishing various types of genetic information and genetic influences on disease (see Table 1).

For example, Eric Juengst has used these two considerations to distinguish several categories of genetic testing (Juengst 1995). Juengst distinguishes between, (1) prognostic tests, (2) predictive tests, (3) prophylactic tests, (4) probabilistic tests, and (5) genetic profiles (Juengst 1995). The first of Juengst's categories, prognostic and predictive tests, involve testing for highly penetrant alleles. Prognostic tests identify highly penetrant alleles that are associated with unavoidable health problems. Thus, such tests are highly predictive of future disease. For example, testing for the allele associated with Huntington's disease would qualify as a prognostic test. By contrast, while predictive tests also identify highly penetrant alleles, the genetic dysfunctions identified through predictive tests can be addressed therapeutically. Newborn screening for PKU, for instance, is a predictive genetic test since the symptoms of PKU can be ameliorated by limiting dietary intact of phenylalanine.

The remaining three categories of genetic tests distinguished by Juengst involve the detection of less penetrant alleles (Juengst 1995). Probabilistic and prophylactic tests both involve testing for increased risk of disease. They are distinguished from prognostic and predictive tests based

upon the penetrance of the alleles being identified. Probabilistic and prophylactic tests are distinguished from each other using the avoidable-unavoidable criterion. Moreover, probabilistic tests identify a genetic susceptibility to disease that cannot be addressed through preventive or therapeutic means. Tests for apolipoprotein (Apo) E4, for instance, would constitute a probabilistic genetic test since Apo E4 is associated with increased risk of Alzheimer's disease, but no effective therapy is available (Tsai et al. 1994). Similarly, perhaps testing for BRCA1 and BRCA2 mutations should be considered probabilistic tests, since the only preventive intervention currently available for breast cancer is a radical mastectomy. By contrast, prophylactic genetic tests also involve testing for statistically increased risk of disease, but involve conditions where therapeutic or preventive intervention is available. Tests for genetic hypersensitivity to an avoidable environmental exposure, for example, are prophylactic tests. Testing for mutations in the gene coding for α_1-antitripsin, for instance, would qualify as prophylactic tests since mutations in this gene have been associated with increased vulnerability to carcinogens found in cigarette smoke (World Health Organization 1995). Hence, individuals who possess these mutations may respond to their genetic hypersensitivity by avoiding cigarette smoke.

The last category of genetic tests discussed by Juengst is what he calls "genetic profiling" (Juengst 1995). Genetic profiling involves the identification of alleles that are very loosely associated with disease. Unlike probabilistic and prophylactic testing, genetic profiling identifies alleles that have not been

associated with statistically increased risk of disease, though some connection with phenotype is believed to exist. Though Juengst is not explicit on this point, presumably the difference between genetic profiling and these other two categories is one of degree. Genetic profiling involves testing for alleles of very low penetrance (and thus low predictive value). Tests for more penetrant alleles, though not highly penetrant alleles, constitute probabilistic or prophylactic tests.

Contrary to Juengst, however, I believe it is more useful to stress the idea that tests for less penetrant alleles range from those that have very little predictive value to those that suggest substantially increased risk of disease. This continuum of tests thus ranges from tests for N-acetyltransferase mutations and a slightly increased—though still statistically significant—risk of bladder cancer (described later in this chapter), to tests for BRCA1 and BRCA2 mutations and substantially increased risk of breast cancer. Juengst's distinction between genetic profiling and probabilistic/prophylactic testing suggests a sharp line between associations that are statistically significant and those that are not significant. This way of distinguishing the two categories is misleading, however, because it obscures the wide range of predictive values that fall between these two extremes. An association between an allele and a disease phenotype may be slight, but still statistically significant. Hence, it is better to focus on the extent of the association between the identified allele and the corresponding disease phenotype.

Continuing with this idea suggests a third set of terms. Let us distinguish between "risk profiling" and "preventive profiling". Risk profiling and preventive profiling both involve the identification of alleles of low penetrance (and thus limited predictive value). But while, risk profiling involves the identification of unavoidable increased risk, preventive profiling involves the identification of increased risk that can be addressed through preventive interventions. Tests for HLA-B27, for instance, would qualify as preventive profiling since increased risk of chronic beryllium disease can be addressed by minimizing exposure to beryllium. Similarly, loose associations between alleles and increased risk of disease, such as between cyclooxeganase-1 and breast cancer (Cannon 1997), qualify as risk profiling. (These distinctions are summarized in Table 1.)

The Human Genome Project

The Human Genome Project (HGP) is the most ambitious product of the search for genetic influences on disease. The HGP was begun in 1988, when the National Institutes of Health and the Department of Defense jointly agreed to fund a project to identify, and sequence, all of the approximately 50,000 to 100,000 genes found in human cells (Cook-Deegan 1994; Kevles 1992). Moreover a central aim of the HGP is to create a public database containing a complete nucleotide reference sequence for all of these individual genes (Collins et al. 1998; Marshall 1998; Waterston and Sulston 1998).

The principal benefit of the HGP is that it will provide researchers with a guide that they can use to further study genetic influences on biological processes. The HGP reference sequence often is described as a "map" of the human genome. This metaphor is instructive since the reference sequence suggests what researchers are likely to encounter at specific locations on human chromosomes. However, if one were to take a DNA sample from a given individual and examine the actual nucleotide sequence that he or she has at a specific location on a given chromosome, it may be a different sequence than that suggested by the reference sequence "map". This is because the reference sequence will describe the general structure of the human genome, but will not tell researchers what particular variations on that structure may exist in various individuals. To put this point another way, the reference sequence will not describe "the" human genome. Rather, the reference sequence will tell researchers where individual genes are in relation to each other, and the *general* nucleotide sequence of the gene. However, the HGP reference will not describe the immense genetic variation that exists between the genomes of any two individuals (Cavalli-Sforza et al. 1991; Kidd, Kidd, and Weiss 1993).

Nonetheless, despite these limitations, the HGP reference sequence will provide a useful tool that researchers can use to identify genetic differences between individuals and between populations. The reference sequence will provide a baseline that can be used to compare particular genomes. While

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much more work will be needed to identify these differences, the HGP will provide a starting point for this subsequent research.

Polymorphic variation within genes

Common sequence variants within genes are called genetic polymorphisms (Suzuki et al. 1989). A genetic polymorphism is a sequence variation that exists at a frequency of greater than 1% in a population. Since some polymorphisms affect the associated gene products, identifying polymorphisms and understanding their biological effects can be instrumental in better understanding disease pathways. Nonetheless, genetic polymorphisms are not necessarily associated with an increase in an individual's disease risks (as compared to a standard reference sequence). In fact, most polymorphisms do not appear to have any implications for an individual's overall health. Other polymorphisms may actually be beneficial (as judged in comparison to a standard reference sequence). For example, a polymorphism might protect an individual from an environmental cause of disease or increase an individual's response to a therapeutic drug. There are, however, a number of polymorphisms that do appear to be associated with increased risk of disease. Polymorphisms in genes that metabolize or detoxify chemicals, for instance, may alter an individual's ability to effectively process a specific chemical, to respond to a given environmental exposure, or to repair DNA damage.

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Identifying genetic polymorphisms often can provide clues about particular gene products. For instance, polymorphisms can suggest functionally important locations on associated proteins, locations that may play a significant role in enzymatic activity. As Walter Gilbert has described it, our understanding of the structure of the human genome is suggesting a new paradigm for biological thinking, one in which genomic structure no longer merely reflects function, but can *suggest* function (Gilbert 1992).

Recognizing the importance of polymorphic variation for understanding the functioning of gene products, researchers are already trying to identify genetic polymorphisms on a large scale. The Cancer Genome Anatomy Project (CGAP) sponsored by the National Cancer Institute, for example, is currently trying to identify polymorphisms within genes that are thought to play a role in the development of cancer (Kuska 1996; McBride 1996; NCI). Similarly, the National Human Genome Research Institute is supporting the development of a public database of nucleotide polymorphisms in a broader class of genes (Collins, Brooks, and Chakravarti 1998; Collins, Guyer, and Chakravarti 1997; NHGRI 1998). Several major pharmaceutical companies also are involved in the search for polymorphisms, particularly those involved with the metabolism of pharmaceutical drugs. These efforts are natural extensions of the HGP. Each of these projects, however, like the HGP, are *sequencing projects*. Their primary purpose is to catalogue sequence information, not to understand the function of gene products or the implications of genetic variation for the functioning of gene products.

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The Environmental Genome Project

It is expected that the Human Genome Project will complete a "working draft" of the human genome reference sequence by the year 2003 (Collins et al. 1998; Marshall 1998; Waterston and Sulston 1998). With the completion of that effort, researchers will have identified all (or nearly all) human genes. The next stage of genomic research, one that has already begun, is to better understand the various functions of these genes (Collins et al. 1998). This includes identifying sequence variation within genes (Collins, Guyer, and Chakravarti 1997) and determining the effect that such variation has on the functioning of gene products (Brown and Hartwell 1998; Guengerich 1998). Many of these variations within genes appear to play a role in the development of complex diseases, for example, by affecting how an individual responds to adverse environmental exposures (Zhang, Zhao, and Merikangas 1997).

One example of this new area of research is the Environmental Genome Project (EGP), sponsored by the National Institute of Environmental Health Sciences, one of the National Institutes of Health (Albers 1997; Cannon 1997; Kaiser 1997). Beginning with a standard reference sequence like those compiled in connection with the Human Genome Project, the EGP will examine sequence variation within genes that appear to play an important role in the development of environmentally associated diseases. Since the EGP will draw extensively on the information collected through the Human Genome Project, as well as the sequencing technologies developed therein, the EGP can be thought of as an extension of the work begun in connection with the Human

Genome Project (Human Genome News 1998). However, while the EGP will collect sequence information, that is not the principal goal of the project, as it is in the Human Genome Project. Rather, the goal of the EGP is to understand the biological significance of such genetic information. Thus, in many ways, the EGP and projects like it represent a new stage of genomic research.

The EGP will focus on variation within genes that may be associated with differential response to environmental exposures (Albers 1997; Cannon 1997; Kaiser 1997). Specifically, the EGP has three main objectives (Albers 1997; Brown and Hartwell 1998; Cannon 1997; Kaiser 1997): (1) to identify functionally important polymorphisms in genes that may be associated with differential response to adverse environmental exposures, (2) to incorporate genomic information into epidemiologic and functional studies of gene functioning, and (3) to promote applications of genomic information in efforts to improve public health (including work that addresses the ethical, legal and social implications of research on common genetic polymorphisms). Stated more generally, the goal of the EGP is to collect information on the genetic basis of environmentally associated diseases.

The EGP will consist of several phases. The first phase of the project involves the selection of candidate genes to be studied. The National Institute of Environmental Health Sciences has established an oversight group to prioritize a set of genes that appear to play an important role in environmentally associated diseases. The plan is to identify approximately 200 genes to be studied more carefully (Cannon 1997). The second phase of the project

involves the identification of common genetic polymorphisms in these genes. Finally, the third stage of the EGP involves the analysis of these polymorphisms. In this stage, researchers will use functional assays and population-based studies to look at how genetic differences affect response to environmental exposures.

N-acetyltransferase polymorphisms

An example of the type of genetic variation to be studied in connection with the EGP are polymorphisms in N-acetyltransferase genes (Ishibe and Kelsey 1997; Vineis and Schulte 1995). N-acetyltransferases (NAT) are a class of enzymes involved in the metabolism of arylomatic amines (common carcinogens found in cigarette smoke, well cooked meat, and many occupational settings). Two NAT genes are known to be polymorphic, NAT1 and NAT2. Of the two genes, NAT2 polymorphisms have been studied more extensively. Fourteen different polymorphisms have been identified in the NAT2 gene (Blum et al. 1991). In addition, many epidemiologic and *in vivo* studies have examined the biological effects of these polymorphisms (Blum et al. 1991; Caporaso, Landi, and Vineis 1991; Cartwright et al. 1982; Deguchi, Mashimo, and Suzuki 1990; Evans, Eze, and Whibley 1983).

Laboratory studies suggest that NAT2 polymorphisms can affect the rate of arylomatic amine detoxification (Deguchi, Mashimo, and Suzuki 1990). Some polymorphisms are associated with slower detoxification, while others are associated with more rapid detoxification. Moreover, the rate of

detoxification appears to have implications for the development of disease. Epidemiologic studies suggest that individuals who detoxify carcinogenic arylomatic amines slowly (slow detoxifiers) are at increased risk for developing colorectal and bladder cancers (Caporaso, Landi, and Vineis 1991; Evans, Eze, and Whibley 1983). The increased risks for slow detoxifiers have been estimated as 1.5 times greater for bladder cancer and 1.8-2.5 times greater for colorectal cancer (Vineis and Schulte 1995).

The benefits of molecular epidemiology

The example of N-acetyltransferase polymorphisms suggests a very basic question, namely, since such polymorphisms are associated with very slight increases in disease risk, why are researchers interested in pursuing this type of research? In other words, apart from academic interests in better understanding basic biological processes, what benefits might accompany the study of NAT polymorphisms and other alleles of low penetrance?

Advocates of projects like the EGP hope that the information collected will produce a better understanding of the relationships between specific genetic polymorphisms and individual response to environmental exposures. The possible benefits of studying how genetic variation may affect response to environmental exposures include: (1) more accurate estimates of disease risks, (2) more effective disease-prevention strategies and earlier disease diagnosis, (3) pharmaceutical drugs with fewer adverse side effects, and (4) a

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better understanding of basic disease mechanisms. Each of these anticipated benefits is described in more detail below.

Estimating disease risks. Individuals respond to environmental exposures differently. Nonetheless, estimates of disease risk often treat individuals as though they are all the same. Understanding how genetic risk factors affect individual response to environmental exposures could allow preventive strategies to be tailored to each individual. Such individual-specific risk estimates could lead to more effective disease prevention strategies and earlier diagnosis of disease—by prioritizing efforts intended for those who are most at risk of developing disease. Moreover, projects like the Environmental Genome Project ultimately may play a role in the production of DNA-based diagnostic tools for determining individual sensitivities to environmental assaults. These same tools also could assist in assessing the effects of adverse exposures, for example, by providing biological markers of exposure (Groopman, Kensler, and Links 1995; Harris 1996; Perera 1996).

Disease prevention and intervention strategies. If we know who is most at risk, then perhaps we can monitor those individuals more carefully and if there are modifiable risk factors involved (e.g. smoking or occupational exposures), then perhaps we can point out the implications of failing to reduce these risks. These benefits may come for individuals who have been screened for the presence or absence of a particular polymorphism, or they could be generalized to entire populations. If a particular polymorphism is more common in some populations than in others, recognizing the role it plays in the

development of environmental disease could be useful in describing the disease risks for that particular population (e.g. descendents of individuals from a particular geographical region). Thus, prevention and early intervention programs could be tailored to particular individuals as well as entire groups of individuals (Christiani 1996; Groopman, Kensler, and Links 1995; Mohrenweiser and Jones 1998; Perera 1995; Perera and Dickey 1997; Perera et al. 1996).

Pharmacogenomic tools. Drugs themselves constitute a type of environmental exposure. As such, understanding how genetic variation affects how individuals respond to these exposures may help to minimize the adverse effects of some pharmaceuticals. If a known polymorphism makes some individuals especially susceptible to the adverse effects of given drug, then perhaps individuals can be screened for the presence of this polymorphism before being given that drug. Moreover, individuals respond to therapeutic agents in different ways. Some of these differential responses may be attributable to genetic differences between individuals, particularly differences in genes involved in the metabolism and detoxification of xenobiotics. Furthermore, some of these polymorphic variants may increase the effectiveness of certain pharmaceuticals. Knowing which individuals carry such polymorphisms could increase their effectiveness (Bailey, Bondar, and Furness 1998; Collins 1999; Housman and Ledley 1998).

Elucidating disease mechanisms. The most immediate benefits of studying sensitivity genes are improvements in our understanding of disease

chanisms. This information may be viewed as intrinsically valuable, but could be useful in designing treatments. Better understanding the ogical pathways that are implicated in a disease may help design drugs inhibit related parts of that pathway. Similarly, understanding why a icular polymorphism either increases or decreases risk may suggest a way ountering the disease, for example, by inhibiting a particular enzyme or easing its activity (Ambrosone and Kadlubar 1997; Hecht 1994; Ishibe and sey 1997; Schork, Cardon, and Xu 1998).

nclusion

Interest in studying genetic hypersensitivities to environmental osures stems naturally from other trends in medical and genetic research. example, the utility of DNA-based diagnostic tests for various disease and ceptibility genes has increased clinical interest in developing a broader ge of predictive tests for genetic influences on the development of disease. ilarly, concerns about the adverse effects of pharmaceuticals, and a desire make therapeutic drugs safer, has heightened interest in projects that mine how genetic variation affects individual response to environmental osures. In addition, the anticipated completion of the Human Genome ject, and the recognition of the need to examine variation *within* genes, has tributed to interest in studying how genetic differences between individuals y affect how they respond to environmental exposures.

Nonetheless, while studies of genetic hypersensitivities to environmental exposures follow naturally from other areas of genetic research, these studies are different in at least two important ways. First, studies of genetic hypersensitivities focus on sensitivity genes—not disease or susceptibility genes. Second, genetic-hypersensitivity research examines relatively common genetic differences between individuals (and between populations). Hence, these studies affect all of us, not just those individuals who have a particular disease, or who because of their family history, suspect that they may be at risk.

Finally, though genetic-hypersensitivity research aims to identify genetic differences between individuals, these differences may be many, and each may have a subtle effect on the functioning of associated gene products. Hence, understanding these genetic influences on disease will take considerably longer than the mere identification of the genes themselves. Consequently, while many studies of polymorphic variation are already being done, we should expect that many more studies of this sort will come in the years ahead. For this reason, it is important that we carefully examine the broader moral and social implications of this new direction in genetic research.

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Notes to chapter two

1. In fact, the very concept of a genetic trait is population relative. Chapter three will discuss this idea in more detail, examining its implications for how we think about genetic causation and the concept of a genetic disease.

Table 1

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Table 1. Distinguishing various types of genetic information by their clinical significance

	Disease Genes	Susceptibility Genes	Sensitivity Genes
No therapeutic response available	Prognostic information	Probabilistic information	Risk profiling
Therapeutic or preventive interventions available	Predictive information	Prophylactic information	Preventive profiling
	High Penetrance	Moderate Penetrance	Low Penetrance

Table 1. The clinical significance of genetic information can be used to distinguish different types of genetic data collected in connection with the study of genetic influences on disease. Two considerations are especially important, namely, (1) whether therapeutic or preventive interventions can ameliorate symptoms of the associated disease, and (2) whether the identified allele is highly penetrant (and thus highly predictive of disease phenotype).

Abstract

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CHAPTER THREE

THE GENETICIZATION OF COMPLEX DISEASE

Abstract

The previous chapter discussed how a better understanding of genetic influences on environmental response may help to explain why some individuals are more likely than others to develop diseases like asthma, cancer, coronary heart disease, and diabetes. Ultimately, that knowledge could lead to more accurate estimates of disease risks, more effective disease-prevention strategies, earlier diagnosis of disease, and earlier treatment interventions. While these potential benefits provide a sound rationale for examining genetic hypersensitivities to environmental response, continued research in this area is likely to reinforce the perception that genes are the primary causes of health and illness. This chapter argues that this tendency—what is sometimes called the "geneticization" of disease—presents a number of troubling moral and social issues. Stressing genetic contributions to complex disease, (1) threatens non-genetic approaches to the study of disease and disease prevention, (2) shifts our social priorities from modifiable causes of disease to unalterable genetic influences, (3) increases the likelihood that genetic information will be used in discriminatory ways, (4) presents concerns about stigmatizing symptomless carriers of sensitivity alleles, and (5) may alter our views of medical responsibility, placing excessive

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Introduction

There is considerable variation in how individuals respond to unhealthy environmental exposures. A classic example is how individuals respond to cigarette smoke. Many life-long smokers eventually develop lung cancer. Nonetheless, there are individuals who, despite being exposed to very high levels of cigarette smoke over an extended period of time, never develop cancers of any sort. So it is with other adverse environmental exposures, including exposure to asbestos, ionizing radiation, allergens, and high-fat diets. Some individuals exposed to these environmental conditions develop an associated disease, while others appear unaffected.

Moreover, a number of different factors influence how individuals respond to environmental exposures, including an individual's age, sex, health status, and genetic make-up. In addition, several of these factors *in combination* often play an important role in estimating an individual's disease risks. For instance, older men who eat a lot of well cooked beef, and who also possess certain cytochrome p450 mutations, are at increased risk of developing colon cancer (Lang et al. 1994, cited in Guengerich 1998). Consequently, biomedical researchers are interested in studying the synergistic interactions between these various risk factors.

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Researchers are especially interested in examining how genetic differences between individuals may affect how they respond to adverse environmental exposures (Brown and Hartwell 1998; Collins, Guyer, and Chakravarti 1997; Kaiser 1997; Kuska 1996). This interest in genetic influences on environmental response stems in part from recent developments in DNA-sequencing technologies (Schafer and Hawkins 1998). Automated DNA sequencers, DNA microarrays, and other technologies, now make it possible for researchers to study subtle genetic differences between individuals and between populations (Marshall and Hodgson 1998; Ramsay 1998). Add to these technological advances recent excitement about gene therapies, and it is easy to understand why researchers are interested in studying genetic influences on the development of complex diseases.

Interest in genetic susceptibility to disease has generated several recent proposals to examine genetic influences on environmental response (Campbell 1996; Ishibe and Kelsey 1997; Rothman and Hayes 1995; Shields and Harris 1991; Yang and Khoury 1997). For example, as described in the previous chapter, the Environmental Genome Project (EGP) plans to examine hundreds of alleles that appear to play an important role in the development of environmentally associated diseases (Albers 1997; Brown and Hartwell 1998; Cannon 1997; Kaiser 1997). Similarly, the National Cancer Institute's Cancer Genome Anatomy Project (CGAP) will examine variation in genes that are believed to be associated with increased risk of cancer (Kuska 1996; McBride 1996; National Cancer Institute 1999; O'Brien 1997).

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Projects like the EGP and the CGAP are viewed by many as first steps toward realizing the clinical benefits of understanding how genes may affect our responses to adverse environmental exposures (Gottesman and Collins 1994; Khoury 1996). These benefits are of two kinds—benefits to individuals and improvements in public health. At both levels, the benefits of studying genetic influences on environmental response include more accurate estimates of disease risks, disease-prevention programs targeted to those who are most at-risk, earlier diagnosis of disease, and earlier treatment interventions (Khoury 1997).

In addition to these potential benefits, however, research on genetic influences on environmental response also present a number of worries. Recall from chapter one, for example, that in addition to common concerns about the potential for genetic discrimination and stigmatization, such research presents broader worries about shifts in our views of medical responsibility and perceptions of individuals who are particularly susceptible to the harmful effects of adverse environmental exposures. Many of these worries stem from the fact that research on genetic hypersensitivities to environmental exposures is likely to contribute to the perception that genes are the primary causes of health and illness.

This increasingly common, though misguided, view of the relationship between genes and disease has been described as the "geneticization"[1] of disease (Edlin 1987; Lippman 1991). Many diseases traditionally associated with environmental, occupational, or behavioral factors are being redescribed

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(and reconceived) as genetic diseases (Baird 1990; Haines and Pericak-Vance 1998; Hubbard 1990; Hubbard and Wald 1993; Keller 1991; King, Rotter, and Motulsky 1992). This trend is evident in the number of review articles stressing the importance of genetic contributions to complex diseases like Alzheimer's disease (Blacker and Tanzi 1998; Goate 1997; Lendon, Ashall, and Goate 1997; Rubinsztein 1997; Slooter and Duijn 1997), coronary heart disease (Cambien 1996; Cambien et al. 1997; Gelb 1997; Peyser 1997), alcoholism (Agarwal 1997; Agarwal and Goedde 1992), schizophrenia (DeLisi 1997; Gershon et al. 1998; O'Donovan and Owen 1996; Tsuang 1998), obesity (Bouchard 1995; Bray and Bouchard 1997; Comuzzie and Allison 1998), and many forms of cancer (Caporaso and Goldstein 1995; Claus 1995; Easton and Peto 1990; Goddard and Solomon 1993). Similarly, the increasing geneticization of disease is reflected in the deterministic language used by the media in reporting discoveries in contemporary genetic research (Nelkin and Lindee 1995). Moreover, additional support for the existence of a conceptual shift toward genetic influences on disease comes from the growing number of professional commentaries on the importance of "genetic medicine" (Caskey 1993; Caskey 1997; Caskey and McKusick 1990; Hughes and Caskey 1991; Korenberg and Rimoin 1995; McCabe 1996; McKusick 1993; Worton 1993).

Frequently, the evidence in support of viewing diseases like those mentioned above as genetic diseases is speculative and open to considerable interpretation (Hubbard and Wald 1993). Nonetheless, lack of convincing evidence for significant genetic contributions to these complex diseases has

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not slowed the increasing perception—common among both laypersons and researchers—that genes are the primary determinants of human health and illness. Consider, for example, the following language used to describe genetic contributions to disease (Baird 1990, p. 208),

> We cannot continue to think about disease as an outside enemy and talk about it in images of war. We hear of battling killer diseases, breakthroughs in chemotherapy, a campaign against TB—all World War I images. There is an inherent danger in thinking that way about ill health: if we continue to wage war against disease, we may end up waging war on ourselves. We need to see our own genetic individuality as a potential origin of disease.

While the author goes on to acknowledge environmental influences on the development of disease, she clearly wants her readers to reconceptualize disease causation, and place more emphasis on genetic contributions to health and disease.

This growing emphasis on genetic contributions to complex disease has a number of important practical implications (Edlin 1987). For example, this shift in emphasis affects the types of research projects that receive funding priority. Moreover, the increasing geneticization of disease also influences public perceptions of disease, and ideas about how individuals ought to respond to their disease risks. Whether a disease is thought of as "genetic", "environmental", "occupational", or "multifactorial" affects how we view individual responsibility for maintaining one's health. These disease

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classifications also affect how we view individuals who choose not to avoid particular environmental exposures, employers who dismiss susceptible workers, and physicians who recommend genetic therapies. Thus, the geneticization of disease has broader implications for how we think about the respective roles of physicians, researchers, regulatory agencies, activists, and patients. How we perceive the causes of these diseases determines, at least in part, who we identify as responsible for improving public health.

These considerations suggest that there are a number of important practical reasons for examining how research on genetic hypersensitivities to environmental exposures may reinforce the increasing geneticization of complex disease. Moreover, examining this topic may help shed light on more general conceptual issues concerning the nature of genetic causation, an on-going point of contention for philosophers of science (Gifford 1990; Wendler 1996).

This chapter examines two aspects of the increasing geneticization of disease. The first issue is whether there is a principled way to distinguish genetic diseases from environmental, occupational, and multifactorial diseases. The second issue is whether the increasing geneticization of disease will exacerbate problems relating to the misuse of genetic information—for example, by increasing genetic discrimination or stigmatization. It is argued that, despite our growing understanding of how genes influence our responses to environmental exposures (and hence, how

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genes affect our susceptibilities to complex diseases), we should resist the increasing geneticization of disease.

Disease classifications and genetic causation

It may strike some as strange to suggest that we should "resist" the geneticization of disease. Some may argue that questions about genetic contributions to disease are, to a large extent, empirical questions. If scientists are discovering that genes play an important role in susceptibility to many so-called "environmental" diseases, then those diseases are more "genetic" than previously thought. From this perspective, there is an objective answer as to whether diseases like cancer and asthma should be considered genetic or environmental diseases. Hence, suggesting that we should "resist" the geneticization of disease, may sound to some like an objection to the fact that the world does not reflect our expectations.

This perspective reflects what is perhaps the most obvious way to distinguish genetic diseases from environmental (or occupational[2]) diseases, namely, that environmental diseases are caused by environmental exposures, while genetic diseases result from genetic abnormalities (Wachbroit 1994). Despite the clear intuitive appeal of this perspective, however, there are serious conceptual difficulties with the idea that genetic diseases are caused by genes while environmental diseases are caused by environmental exposures. A closer look at this criterion will suggest that there is no objective way to distinguish genetic diseases from environmental diseases, and that subjective

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judgments always influence our disease classifications. Moreover, this conclusion suggests that we should distinguish disease categories using a practical standard, where the potential risks and benefits of various disease classifications serve as guides in determining how we should conceptualize disease. Thus, despite problems with the intuitive way of distinguishing genetic and environmental diseases categories described above, a closer look at this approach helps shed light on the broader concepts of genetic disease and disease causation.

Philosophers of science often comment on the ways in which causal attributions are dependent upon subjective features of our experiences (Mackie 1965). Consider, for example, the simple event of lighting a match. Many different causal conditions are required for a match to light: the simultaneous presence of both oxygen and combustible materials, the absence of water, frictional forces between the match and another surface, perhaps a desire to smoke a cigarette, and so on. Each of these causal conditions is required for the match to light, the whole set being jointly sufficient for the lighting of the match. Moreover, no one factor is inherently more important than the others because all are required for the event to occur.

Nonetheless, one member of the set of jointly sufficient causal conditions often is singled out as *the cause* of the event. In the example above, for instance, we might say that it was the smoker's desire to smoke a cigarette that ultimately caused the lighting of the match. In a purely objective sense, however, this causal element is no more important than any of the other

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contributing factors, since all are required for the match to light. When we single out one causal factor as different from the others it is because we have an interest in highlighting that contributing factor. In this example, we might be interested in why the match was lit at the time it was as opposed to some earlier time. This interest may lead us to stress the absence of the individual's desire to have a cigarette earlier, but the presence of this condition later. It is our interest in this difference between the two time periods, however, that prompts us to single out one of the causal factors as different from the others. Thus, causal attributions are dependent upon the subjective interests of the person asserting a causal connection.[3]

A more complicated and highly unusual example offered by Richard Hull nicely illustrates this point. Hull writes (Hull 1979, p. 61),

> A college co-ed has a premarital affair with a male student of whom her parents strongly disapprove and who has promised to marry her, and she conceives as a result. When he learns of it, her boyfriend jilts her. She comes from a conservative home and does not feel that she can turn to her parents for help and advice. Her roommate is studying hard for exams and rebuffs her attempts at soliciting a sympathetic ear. She becomes even further depressed over the reaction of the infirmary physician who confirms the pregnancy and lectures her on loose ways but offers nothing but scorn at her tentative broaching of the subject of an abortion. She wanders out onto the San Francisco Bay Bridge and stands looking over the rail. A passing motorist yells, "Jump!" She

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climbs onto the rail; other motorists stop and watch her. She leaps off and drops into the waters of the bay.

In this example, how should we describe *the cause* of this woman's death? The parents may blame the boyfriend for their daughter's death. The police may say it was a suicide. The roommate may blame herself. A medical malpractice attorney may try to implicate the doctor. The coroner may describe the cause of her death as asphyxia. A sociologist might highlight the effective isolation of the automobile as an important causal factor. Residents of the San Francisco Bay area may blame the roads commission for failing to erect guardrails on the bridge, and so on. Depending upon one's interest in the event, and the type of question one wants to answer, any of these causal attributions may be appropriate. However, there is no objective sense in which a single one of these contributing factors is *the cause* of the event.

Extending this point to causal attributions relating to disease, consider the case of phenylketonuria (PKU), a disease often cited as a paradigmatic example of genetic disease (Gifford 1990; Hull 1979; Lappe 1979). Individuals with PKU possess a mutated form of the gene that codes for an enzyme responsible for converting phenylalanine to tyrosine. Without a functional form of this enzyme, phenylalanine accumulates in the body, causing a number of physiological problems. Perhaps the most significant of these problems is the accumulation of phenylalanine in the developing brains of children. High levels of phenylalanine inhibit the development of the myelin sheath which protects the neurons, and if untreated, ultimately will result in severe mental retardation.

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Because this consequence results from a mutation in the gene that codes for the enzyme responsible for converting phenylalanine to tyrosine, PKU is commonly considered a genetic disease.

Nonetheless, despite this seemingly clear and direct connection between a genetic mutation and poor health, PKU is not the result of genetic factors alone. Children who are placed on diets that limit their intake of phenylalanine do not subsequently develop problematically high levels of phenylalanine in their brains, and consequently do not develop the sort of mental retardation associated with PKU. Thus, even a paradigmatically "genetic" disease like PKU is the consequence of both genetic and environmental factors (Gifford 1990; Hull 1979; Lappe 1979).[4] The decision to highlight genetic contributions to the disease reflects our subjective interests in highlighting those factors. If, by contrast, our interests were to lie in other areas—in preventive strategies, for example—we might highlight other contributing causes of PKU (such as diet). However, since both environmental and genetic factors must be present for the dysfunctions associated with PKU to manifest themselves, there is no objective sense in which genetic contributions are more important.

To further illustrate how subjective influences affect our decision to label a disease as "genetic" or "environmental", consider a second example involving arsenic poisoning, a classic example of an environmentally associated disease (Hesslow 1984). Individuals who suffer from arsenic poisoning have been exposed to high levels of arsenic. Nonetheless, it is not

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the presence of high levels of arsenic alone that causes the problems associated with arsenic poisoning. Another relevant causal factor is our inability to effectively process arsenic. If human beings had a gene that coded for an arsenic-metabolizing enzyme, we would not suffer from arsenic poisoning. Hence, one member of the set of jointly sufficient causal conditions for arsenic poisoning is our lack of a genetic sequence coding for a specific enzyme (as in the PKU example above). Arsenic poisoning is not caused by environmental exposures alone but is in part the result of our genetic make-up. Since both environmental and genetic factors are involved in arsenic poisoning, the decision to highlight environmental factors as more significant again reflects a subjective interest in drawing attention to those contributions to disease.[5]

The lesson from these examples is clear—all disease is the consequence of both genetic and environmental factors.[6] Hence, we cannot accept the intuitive criterion for distinguishing genetic and environmental diseases (that genetic diseases are caused by genes, while environmental diseases are caused by environmental exposures). Disease classifications inevitably reflect our interests in highlighting certain members of the set of jointly sufficient causal conditions instead of others.[7]

Nor is it possible to quantify the respective contributions of genetic and environmental influences on disease. An analogy offered by Richard Lewontin helps to see this point (Lewontin 1974):

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> [I]f two men lay bricks to build a wall, we may quite fairly measure their contributions by counting the number laid by each; but if one mixes the mortar and the other lays the bricks, it would be absurd to measure their relative quantitative contributions by measuring the volumes of bricks and of mortar. It is obviously even more absurd to say what proportion of a plant's height is owed to the fertilizer it received and what proportion to the water, or to ascribe so many inches of a man's height to his genes and so many to his environment.

With respect to disease, this analogy suggests that since genetic and environmental contributions combine in synergistic, and not merely additive ways to determine disease phenotype, it is meaningless to try to quantify the respective influences of genetic and environmental factors.[8]

These conclusions suggest that there is nothing unscientific about opposing the increasing geneticization of disease. If all disease is the result of both genetic and environmental factors, and if subjective interests determine which members of the set of contributing factors we choose to stress, then science alone cannot tell us whether we should (or should not) reconceive complex diseases, such as asthma, cancer, and diabetes, as genetic diseases. Instead, we should distinguish genetic and environmental disease based on pragmatic considerations.

Thus, to assess whether it is appropriate to reconceive certain complex diseases as genetic diseases, we need to consider the practical implications of this shift in perspective. Toward this end, the following sections discuss

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several moral and social problems associated with the increasing geneticization of disease. It will be argued that emphasizing genetic contributions to complex disease, (1) threatens non-genetic approaches to the study of disease and disease prevention, (2) shifts our social priorities from modifiable causes of disease to unalterable genetic influences, (3) increases the likelihood that genetic information will be used in discriminatory ways, (4) presents concerns about stigmatizing symptomless carriers of sensitivity alleles, and (5) may alter our views of medical responsibility, placing excessive burdens on those who are at increased risk, and inappropriately excusing others from their moral obligations. Collectively, these concerns suggest that we should resist the increasing geneticization of complex disease.

The geneticization of research funding

When clinicians and biomedical researchers describe a disease as "genetic", "environmental", or "occupational", they do more than simply place a disease in a given conceptual category. These categories also have normative significance. Disease classifications suggest specific views about how a disease ought to be understood and studied. For example, classifying a disease as "genetic" suggests that researchers should focus on studying the genes and biochemical pathways associated with the disease, and that environmental factors make less important etiologic contributions to the disease. Thus, relabeling an "environmental" disease as "genetic" undermines the legitimacy of non-genetic approaches to understanding the

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disease. Moreover, since there is a limited amount of research funding available, such redescriptions threaten financial support for non-genetic approaches to studying disease, and may place serious practical constraints on the development of new (non-genetic) disease-prevention and intervention strategies.

Contrary to this line of reasoning, it might be argued that there is always a certain amount of dogmatism in science and that some approaches to the study of disease inevitably will be more widely supported than others. Preference for some approaches over others is not problematic, however, because there will always be researchers who do not share the orientation of the majority, and who will continue to study disease from alternative perspectives. Given the diversity of research interests, it may seem unlikely that researchers will be forced to abandon non-genetic approaches to the study of disease. Instead, the increasing geneticization of complex disease simply reflects a shift in research priorities.

This objection misses the point, however. The issue is not whether researchers will continue to study disease from non-genetic, or non-mechanistic, perspectives. The concern is that the increasing geneticization of complex disease *delegitimates* other perspectives that are worth pursuing. Moreover, the delegitimization of non-genetic approaches to disease is, in one sense, *a priori*. Researchers expect that both genetic and environmental contributions play a role in the development of most diseases. However, by redescribing complex diseases as "genetic", researchers bestow a special

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In addition, the delegitimization of non-genetic approaches to the study of disease is especially troublesome in light of the past successes of these approaches. The history of medical research contains dozens of examples of successful interventions involving the modification of behavior or the avoidance of adverse environmental exposures. This history suggests that there is good reason to continue to give high priority to non-genetic approaches to the study of disease. While there has been much excitement about the promises of "genetic medicine" (Caskey 1993; Caskey 1997; Caskey and McKusick 1990; Hughes and Caskey 1991; Korenberg and Rimoin 1995; McCabe 1996; Worton 1993), these new approaches to disease should compliment existing methodologies, not replace them. The increasing geneticization of disease, however, makes it difficult to maintain an appropriate balance of research funding for genetic and non-genetic approaches to disease.[9]

The geneticization of social priorities

As genes are increasingly viewed as the primary determinants of health and disease, less emphasis will be placed on social causes of disease. In

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addition to affecting research priorities, this shift in emphasis also has implications for our social priorities.

To illustrate how the geneticization of disease may affect social priorities, it is useful to compare the current emphasis on genetic contributions to disease with past eugenic thinking. Like eugenic programs of the past, the geneticization of disease places too much emphasis on genetic contributions to complex phenomena (Kevles 1985; Paul 1995; Reilly 1991). Similarly, elements of genetic reductionism and determinism (*supra* n. 1) can be found both in past eugenic thinking and the current geneticization of disease (Kevles 1985). For example, eugenic programs sought to reduce complex social problems, such as poverty and crime, to issues of improving our genetic constitutions. Likewise, the geneticization of complex disease reduces complex biological problems to issues of gene expression and regulation. In both cases, however, reductionist thinking oversimplifies complex problems. Moreover, in the same way that eugenicists sought a "quick fix" for complex social problems, redescribing complex diseases as genetic problems also suggests that a "quick fix" is possible. In other words, in the same way that past eugenic thinking discouraged efforts to address social aspects of complex problems, the current geneticization of disease may discourage efforts to examine social contributions to disease.

Moreover, in thinking about the social implications of the geneticization of disease, we should not underestimate the appeal of reductionist explanations (Duster 1989). A revival of the ideological underpinnings of past eugenics

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movements could create new pressures for individuals to make "genetically responsible" choices. However, unlike past efforts, presumably political forces would prevent mandatory sterilization campaigns, and other eugenic horrors, from returning (Kevles 1994; Paul 1994). Nonetheless, it is not unreasonable to suppose that the increasing geneticization of disease will result in more individuals being pressured to take genetic tests that they would avoid otherwise. For example, physicians may inadvertently place subtle pressures on patients, encouraging them to investigate their particular genetic vulnerabilities.

Discrimination against symptomless carriers of "bad genes"

Another consequence of the geneticization of disease is an increase in the likelihood that information about genetic susceptibilities to disease will be used in discriminatory ways. Alleles associated with increased vulnerability to particular environmental exposures may only modestly increase an individual's risk of disease. The geneticization of disease, however, may prompt some to overstate the risks associated with particular alleles. Health and life insurers, for example, may view sensitivity alleles as significant factors to take into consideration in assessing insurance premiums (Rothstein 1993). While other (non-genetic) factors may be much better predictors of an individual's disease risks, the increasing geneticization of disease may lead insurers to overemphasize genetic information in their actuarial assessments of individual (and group) insurance premiums.

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A related problem is that the geneticization of disease may result in some individuals being arbitrarily singled out as at higher risk than others. We each possess a number of alleles that make us particularly vulnerable to certain environmental assaults. The particular vulnerabilities we possess, however, vary from person to person. Moreover, as noted previously, these allelic differences explain, in part, why we suffer the individual diseases we do. Nonetheless, since each of us has a number of susceptibilities to disease, "we are all at risk for something".[10] Despite these shared risks, however, insurers may have access to limited pieces of information about an individual's (or a population's) genetic susceptibilities to disease. Hence, in using this information to raise set insurance rates, insurers may arbitrarily burden those individuals about whom some information is known. Yet from a larger perspective, such individuals are really no more at risk—in terms of expected costs of care and years of life—than anyone else. It just happens that these individuals (or groups) know more about their *particular* disease susceptibilities. As such, individuals who know their genetic hypersensitivities to environmental exposures may be burdened by inappropriately high insurance costs.[11]

In addition, the geneticization of complex disease may lead to more invidious examples of discrimination. For example, genetic susceptibilities may be associated with certain racial or ethnic groups (Caplan 1994; King 1998). The increasing geneticization of disease may exaggerate the discriminatory potential of such associations by suggesting that genes are the

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primary determinants of human health and disease. Consequently, alleles associated with increased susceptibility to disease may be perceived (mistakenly) as "disease genes", even though those who possess them are at only slightly increased risk of disease.

Finally, the geneticization of disease could lead to more subtle types of discrimination.[12] History suggests that genetic information may play a role in discriminating against already socially disadvantaged groups (Billings et al. 1992; Kevles 1985; Nelkin 1989; Rothstein 1994-95). We should recognize the possibility that information about genetic hypersensitivities to environmental exposures may play a role in creating, and perpetuating, social constraints limiting the opportunities available to historically disadvantaged groups (Caplan 1994; Wolf 1995).

Stigmatizing susceptibility

Though there is a sense in which "we're all at risk for something," the identification of genetic risk factors for complex diseases could stigmatize individuals with known genetic hypersensitivities "Carriers" of genetic hypersensitivity alleles may be associated with genetic weakness. Moreover, associating genetic susceptibility with weakness may reinforce the pathology of genetic susceptibility. This could add to the social burdens faced by those with known genetic hypersensitivities to adverse environmental exposures (Juengst 1999).

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Moreover, the geneticization of disease could exacerbate the problems of genetic stigmatization by extending the list of alleles that are thought of as "bad genes". As more and more alleles are associated with particular diseases, more individuals face risks associated with stigmatization. Moreover, emphasis on genetic contributions to disease may encourage genetic fatalism, the idea that the adverse effects of "bad genes" will eventually present themselves, thus adding to the burdens that may accompany a genetic stigma. If genetic susceptibilities are equated with future disease, individuals may be defined by, and reduced to, their eventual fates. Compare, for example, the labels we attach to "cancer families" and "Down's babies" (Juengst 1999).

Implications for views of medical responsibility

Finally, the geneticization of complex disease has implications for how we view medical responsibility. If the primary determinants of human disease are believed to be genetic factors, and if these genetic determinants are difficult (if not impossible) to alter, then individuals with these "disease genes" might be excused from doing things to improve their health. As more genes associated with hypersensitivity to adverse environmental exposures and increased risk of disease are discovered, the geneticization of disease threatens to expand the list of so-called "disease genes". If this happens, individuals with known genetic susceptibilities to disease might be excused from improving their health—even in those cases where there are significant environmental and behavioral contributions that can be effectively controlled.

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Similarly, as gene therapies are developed and become available, the geneticization of disease may place serious pressures on individuals to modify certain susceptibility genes.[13] These pressures may be inappropriate when weighed against the risks of gene therapy and the extent to which these genes influence an individual's disease risks. While such difficulties are to a large extent the result of fundamental misunderstandings about the significance of genetic contributions to disease, these misperceptions may be exaggerated by the increasing geneticization of disease.

Moreover, the geneticization of complex disease has implications for how we view other types of medical responsibility. For example, employers have already used biological differences between individuals to divert responsibility for limiting environmental and occupational exposures in the workplace (Billings and Beckwith 1992; Draper 1991; Gostin 1991). The geneticization of disease may make it easier for employers to avoid responsibility for the health of their employees. If genetic influences come to be seen as the primary causes of disease, then adverse occupational exposures may be viewed as less important in the development of work-related illnesses. Thus, inappropriately viewing genetic hypersensitivities to occupational exposures as "disease genes" may make employers less accountable for minimizing occupational hazards.

Nonetheless, the geneticization of disease also may create new moral obligations for employers (Vineis and Schulte 1995). Employers may wish to screen employees for genetic hypersensitivities to occupational exposures.

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Doing so may be viewed as a moral obligation relating to the improvement of worker health. This new obligation, however, may not be beneficial for workers, since it shifts the locus of disease causation from the occupational exposures encountered in the workplace to the genetic constitution of the workers's themselves. Instead of viewing occupational exposures as the causes of poor health, susceptible workers may be seen as problems in need of correction.

Disease classifications and the language of disease

It is tempting to say that the problems described above result from laypersons inappropriately responding to a shift in research priorities. To some extent, this perspective is correct, and educating the public about the limited nature of genetic influences on complex disease would help reduce the problems highlighted above. Nonetheless, blaming laypersons fails to appreciate the power of genetic language (Nelkin and Lindee 1995). Moreover, researchers have an obligation to do what they can to counter negative social applications of their work. This includes clarifying the language they use to present their findings and countering the increasingly genetic orientation of discussions of disease in the press.

In light of the foregoing remarks, one might draw the conclusion that complex diseases, such as cancer and diabetes, should be described as "environmental" diseases. While this approach would do much to counter the tendency to over-state genetic influences on disease, we should hesitate to adopt this type of classification as well. Many of the difficulties noted above with

regard to the geneticization of disease also argue against classifying complex diseases as "environmental" diseases. For example, in the same way that describing a disease as "genetic" delegitimates non-genetic approaches to the study of the disease, labeling a disease as "environmental" also delegitimates alternative approaches. In the second case, however, the classificatory label discourages genetic approaches to studying the disease. In addition, classifying complex diseases as "environmental" diseases may present analogous moral and social concerns, particularly in relation to medical responsibility. For instance, emphasizing environmental contributions to disease may place unrealistic burdens upon individuals, requiring that they avoid certain environmental exposures, and inappropriately assigning blame to those who subsequently develop disease.

In light of these considerations, the best alternative is to avoid all classifications of disease in terms of their respective genetic or environmental contributions. Although such classifications are currently common, one may ask what would be lost if we were to drop this terminology. If there are no significant practical advantages to maintaining these classifications, then the problems outlined above suggest that we ought to avoid these disease categories altogether.

In addition to this terminological point, there is another important lesson to draw from the discussion above. Clinicians and biomedical researchers have an obligation to do what they can to minimize the troublesome implications of the geneticization of complex disease. When patients ask

whether cancer is a genetic disease, their doctors should explain why it is not altogether appropriate to think of cancer as a genetic disease, even though there are clearly genetic factors that influence who develops cancer and who does not. Similarly, when researchers read about the recent announcement of a "gene for" ___ (the reader can fill in his or her favorite example of a complex disease), they should try to counter the spread of this misinformation by explaining that ___ is the result of complex interactions between a number of different contributing factors, both genetic and non-genetic.

Conclusion

The problems described above suggest that we should resist the increasing geneticization of disease. Nonetheless, concerns about the shifting of research priorities, and inappropriate uses of genetic information, are not new (Andrews et al. 1994). What is new is that the study of genetic hypersensitivities to environmental exposures threatens to exacerbate these problems by contributing to the increasing geneticization of complex disease. Where genes are limited, or poor, predictors of disease risks, genetic influences should not be stressed at the expense of other known risk factors. Thus, the geneticization of disease heightens several broader moral and social concerns surrounding the collection of genetic information.

In addition, there is a larger conclusion to be drawn from the discussion above, namely, that we should not be surprised to learn that researchers have discovered genes "for" many complex diseases. All diseases involve both

environmental and genetic contributions. Moreover, while technological advances have led to a much better understanding of genetic contributions to many complex diseases, this does not imply that these diseases should now be considered "genetic" diseases. Such discoveries merely reflect the fact that researchers are devoting a lot of energy and resources toward finding disease-susceptibility genes, and do not change the fact that both environmental and genetic contributions are involved in the development of complex diseases.

Admittedly, however, resisting the geneticization of disease will not be easy. Medical researchers, in particular, are likely to reject the notion that non-empirical, pragmatic considerations should be used to determine whether a disease is, or is not, a "genetic" disease. How, then, should we respond to researchers who maintain that there is ample evidence that many complex diseases are in fact "genetic" diseases? For example, what should we say to the geneticist who says that breast cancer is genetic because there are well-documented patterns of familial inheritance, linkage-disequilibrium studies in support of genetic influences, and even particular alleles that have been associated with increased risk of breast cancer?

In response to such questions, we should begin by acknowledging that recent work done on complex diseases like breast cancer has given us a much better understanding of the genetics and biochemistry of these diseases. This is important work that may someday radically change the way that medicine is practiced. We should also point out that genes are only part of the story behind diseases like breast cancer. Cancer, like many diseases, is a multi-step

process (Beckmann et al. 1997; Fearon 1997; Vogelstein and Kinzler 1993). However, emphasizing genetic contributions, while failing to acknowledge other contributing factors, has a number of social consequences. Stressing genetic influences on complex diseases like breast cancer may result in problematic shifts in research priorities. Moreover, emphasizing genetic influences on disease may lead to morally problematic uses of genetic information. Finally, we should point out that the breast-cancer genes this geneticist likely has in mind, namely BRCA1 and BRCA2, are an important part of the story behind some types of breast cancer, but by no means do these genes explain why breast cancer (in general) occurs (Easton et al. 1995; Miki et al. 1994). Talking about the gene(s) *for* a complex disease like breast cancer obscures this important point.

Studying genetic influences on response to environmental exposure may significantly improve our understanding of many complex diseases. This knowledge could lead to major improvements in our lives and in our health. Nonetheless, genetics is not going to replace medicine. The geneticization of complex disease threatens to do exactly that. Hopefully we will resist this troublesome trend and recognize the importance of countering the increasing geneticization of complex disease.

Notes to chapter three

1. It is not clear who first coined the term "geneticization". Susan Wolf credits Abby Lippman for introducing the term (Wolf 1995, n. 73; Lippman 1991). However, in an earlier paper, Joseph Edlin introduced the term "geneticism" to describe growing emphasis on genetic contributions to disease (Edlin 1987).

For the purposes of this chapter, the "geneticization of disease" describes a tendency to view genes as the primary determinants of health and disease. The term "geneticization" also has been used to suggest a gene-first attitude toward the causes of other phenotypic properties, for example, that genes are the primary determinants of an individual's personality traits (Hubbard and Wald 1993). Hence, it is important to distinguish the geneticization of disease from the related concept of genetic determinism. Though the two perspectives both reflect a type of reductionist thinking, genetic determinism maintains that genes determine specific phenotypes (Keller 1991; Lewontin 1991). In other words, genetic determinism holds that certain genes are sufficient causes of particular phenotypes. By contrast, the concept of geneticization allows for significant non-genetic causal contributions to disease, but maintains that genetic factors are the most important members of the set of jointly sufficient causal conditions for disease. In this sense, the concept of geneticization might be thought of as a more limited, and perhaps more tenable, form of genetic determinism.

2. The following discussion focuses on the distinction between environmental and genetic diseases. This discussion could easily be extended to the distinction between occupational diseases and genetic diseases.

3. In this context, a "causal attribution" is understood to mean a unique causal attribution singling out one or more members of the set of jointly sufficient causal conditions as *the cause(s)* of the event.

4. Richard Lewontin makes the related point a measure of a trait's heritability—understood as the proportion of phenotypic variation in a population explainable by the genotypic variation in that population (Gifford 1990)—is sometimes mistakenly seen as an indirect measure of that trait's "phenotypic plasticity" (Lewontin 1974). The fallacy is that heritability, in this technical sense, tells us nothing about whether the trait can be modified by environmental changes. Even a trait with a heritability of 1.0 in a population need not be unalterable by environmental changes, because measures of heritability are population relative. The example of PKU nicely illustrates this general point.

5. This general point about the importance of genetic contributions to environmental (and occupational) diseases also can be extended to infectious diseases. For example, if human beings possessed a gene that allowed us to avoid infection by the HIV virus we would not suffer from AIDS. Current research on the CCR5 negative allele suggests that some individuals do in fact possess such a genetic mutation and thus nicely illustrates the importance of

genetic contributions to infectious disease (Abel and Dessein 1997; Littman 1998; Roger 1998).

6. A possible exception to this general claim may be physical trauma, or dysfunctions caused by forces that are external to an individual's body (*Churchill's Medical Dictionary* 1989). Even here though, one might ask if physical trauma could be avoided were human beings to possess a set of genes that allowed us to respond to certain physical assaults without the dysfunctions associated with trauma. If it is possible to construct a reasonable account of how these genes could make it possible for human beings to avoid trauma, then there would be a sense in which physical trauma was, in part, a genetic disease. The absence of this set of genes would be one member of the set of jointly sufficient causal conditions responsible for trauma (as in the arsenic-poisoning example above).

7. Similar defenses of this perspective can be found in (Gifford 1990; Hesslow 1984; Hull 1979; Lappe 1979).

8. Lewontin goes on to thoughtfully discuss the implications of this point (Lewontin 1974). He suggests that the meaninglessness of trying to quantify the respective causal contributions to an individual phenotype has led geneticists to shift their attention to a different set of questions. These questions pertain to the analysis of variance, namely, explaining the amount of phenotypic variance explainable by environmental and genotypic variance. Nonetheless, for Lewontin, these analyses of variance should not mislead us into thinking that geneticists are identifying some important causal fact of the

matter. Rather, he suggests that the appropriate object of study is the norm of reaction, a representation of causal relationships between phenotype and genotype-environment combinations.

9. Carl Cranor makes a similar point about the dangers of overemphasizing *either* genetic or environmental contributions to disease (Cranor 1991).

10. Francis Collins, the current director of the National Human Genome Research Institute, often uses this phrase to highlight the idea that we all possess a number genetic hypersensitivities to adverse environmental exposures (Cannon 1997).

11. Some commentators have suggested that concerns about how genetic information may be incorporated into current health and life insurance practices in arbitrary and discriminatory ways provide a compelling rationale for radical reforms (Hudson and al. 1995), including the socialization of the American healthcare system (Daniels 1994).

12. Susan Wolf has referred to these larger forms of genetic discrimination as "geneticism" (Wolf 1995). This term is meant to highlight parallels with traditional forms of institutionalized racism and sexism.

13. Some women who test positive for BRCA1 mutations choose to respond to their increased risks of breast cancer by having a radical mastectomy (Biesecker et al. 1993; Decker 1993; Geller et al. 1997). Such responses to genetic susceptibilities to disease demonstrate that individuals may take radical steps in response to genetic risks. This further suggests that

individuals who perceive themselves at risk of future disease may seek genetic therapies for their condition—despite the risks that might accompany such interventions.

CHAPTER FOUR

MOLECULAR EPIDEMIOLOGY AND THE SCOPE OF INFORMED CONSENT

Introduction

Identifying genetic hypersensitivities to adverse environmental exposures, and quantifying the increased disease risks attributable to genetic differences between individuals, will require large population-based studies that associate individual polymorphisms with expressed phenotypes (Khoury 1996; Khoury 1997). Moreover, even with large sample sizes, associations between individual sensitivity alleles and differential responses to specific environmental exposures are likely to be difficult to identify because of the number of confounding variables and the relatively weak associations between these alleles and particular phenotypes (Guengerich 1998; Haines and Pericak-Vance 1998; Pennisi 1998). As a result, researchers are interested in designing studies that examine possible associations between many different alleles and environmental exposures concurrently. The above-described Environmental Genome Project (EGP) illustrates this approach (Albers 1997; Brown and Hartwell 1998; Cannon 1997; Kaiser 1997). The EGP will examine allelic variation in approximately two hundred different genes and study how these differences affect how individuals respond to various environmental assaults (Cannon 1997).

By examining many alleles and exposures concurrently, the EGP and projects like it increase the likelihood of identifying polymorphisms that are

associated with increased vulnerability to environmental exposure. However, by considering many different genes and exposures, such projects also complicate the process of informed consent (Hunter and Caporaso 1997; Soskolne 1997). While it is certainly possible for researchers to provide an overview of the respective roles that several alleles are believed to play in the development of disease, it is less clear whether researchers can effectively convey information about a study's potential risks and benefits when many alleles and multiple biological pathways are implicated (AMA and The Council on Ethical and Judicial Affairs 1998; Lyttle 1997). Moreover, presenting prospective participants with information about several hundred different alleles and their respective biological roles—in lay terms and in a reasonable amount of time—would seem nearly impossible (Knoppers and Laberge 1989; Kopelman 1994). Hence, as more and more genes and exposures are considered concurrently, it becomes increasingly difficult to insure that individual participants are fully informed about the possible risks and benefits of their participation in the research.

At the extreme, the danger is that consent becomes a blanket permission for genetic research in general. It is doubtful that consent of such wide scope can be fully (or even marginally) informed (Lyttle 1997; Reilly 1992). Consequently, asking for broad permissions to use research materials to study many different genes and biological pathways would appear to be morally problematic (Knoppers and Laberge 1989; Kopelman 1994; Reilly 1992). Yet this is exactly what researchers studying genetic hypersensitivities

to environmental exposures would like to be able to do. Hence, the challenge facing these molecular epidemiologists is to come up with a way to insure that individual participants are genuinely informed about the risks and benefits of their participation in a study, even when the study involves examining many different alleles and multiple exposures concurrently. Ideally, this consent will be both broad enough to permit researchers to pursue diverse research interests, yet specific enough to allow individual participants to meaningfully assess the possible risks and benefits of their participation.

Difficult as this may be, the task is made still harder because researchers interested in studying genetic hypersensitivities to environmental exposures often will not have a clear idea of the particular alleles that may be associated with a given exposures at the time the study is proposed. At the time the study is begun, researchers may believe that there are genes that affect environmental response, yet they may not know which particular genes are important. Moreover, even if particular alleles are suspected, researchers may not know how penetrant these alleles are. Thus, they may not be able to say how predictive these alleles may be of future disease.

These uncertainties are the norm in much of molecular epidemiology, and they often remain even after a study is completed (Schulte 1993; Schulte and Perera 1993b). This uncertainty adds to the difficulties involved in presenting research-related risks to prospective participants. Moreover, if researchers discover that a particular allele under study is in fact highly predictive of disease, this may introduce a whole host of psychosocial risks

that may not have been discussed carefully with participants at the time they agreed to participate. These considerations have led some to suggest that many types of molecular epidemiologic research may fail to provide participants with enough information to assess potential research-related risks carefully, thus compromising the consent that is provided.

Even if one does not accept this conclusion, certainly it is the case that studies in molecular epidemiology present unusual challenges for the Institutional Review Boards (IRBs) that are asked to review these research proposals. On the one hand, these studies seem to resemble traditional epidemiologic studies where, apart from risks presented by a loss of confidentiality or the drawing of blood, there are very few potential harms to research participants. On the other hand, studies of genetic hypersensitivities to environmental exposures resemble other types of genetic research and may be seen as presenting significant psychosocial risks for participants. A particular genotype, perhaps in conjunction with certain environmental exposures, for instance, could be highly predictive of an individual's risk of developing a given disease. Hence, information collected by molecular epidemiologists could have implications for the insurability and employability of participants (Andrews et al. 1994; Billings et al. 1992; Brandt-Rauf and Brandt-Rauf 1997; Kass 1997; NIH-DOE Working Group 1993; Rothstein 1993; Schulte, Hunter, and Rothman 1997; Vineis and Schulte 1995). In addition, these studies could affect how subjects view themselves (Brock 1992; Juengst 1999)—as especially vulnerable, for instance—and their relationships with

family members (Andrews 1997; NIH Office of Protection from Research Risks 1993).

Moreover, whether studies in molecular epidemiology are viewed as similar to other types of epidemiologic research, or whether the risks they present are viewed as analogous to those presented by other types of genetic research, has consequences for the process of informed consent. For example, if the risks presented by molecular epidemiologic research are viewed as similar to those presented in other types of genetic research—namely, as potentially significant threats to the welfare of participants—then these risks would warrant treating studies in molecular epidemiology with the same care that is given to other types of genetic research. Providing genetic counselors, for instance, may be necessary to convey the significance of research results to participants. Alternatively, if the risks presented by molecular epidemiologic research are seen as comparable to those associated with traditional epidemiologic studies, then a case could be made for treating these studies as "minimal risk" (45 CFR 46.110; 46 CFR 8392). From this perspective, genetic counseling would not be necessary, nor perhaps would full IRB review be required.

To date, IRBs have had to struggle with the issues raised by molecular epidemiology without much guidance. Very little attention has been given to the moral and social implications of research on genetic hypersensitivities to environmental exposures (Grandjean and Sorsa 1996; Hunter and Caporaso 1997; Samet and Bailey 1997; Schulte, Hunter, and Rothman 1997; Soskolne

1997). Consider, for example, the IRB guidelines issued by the NIH Office of Protection from Research Risks (NIH-OPRR) (NIH Office of Protection from Research Risks 1993). The NIH-OPRR guidelines distinguish four categories of genetic research and discuss several issues that IRBs ought to consider in each of these research settings. The four categories of genetic research that are distinguished are: (1) pedigree studies, (2) positional cloning studies, (3) DNA diagnostic studies, and (4) gene therapy research (NIH Office of Protection from Research Risks 1993). Unfortunately, however, the moral and social issues presented by molecular epidemiology are not discussed separately, and to make matters worse, studies in molecular epidemiology do not easily fit into any of the categories that are discussed in the NIH-OPRR guidelines. Thus, IRBs are left with very little guidance.

Though these issues cannot be resolved in the abstract, and must be contextualized to specific research proposals, there are several broader points that help to clarify informed consent in molecular epidemiology. This chapter examines the consent process for studies of genetic hypersensitivities to environmental exposures, focusing on the scope of informed consent. Current thinking on this issue suggests that when studying genetic differences between individuals, researchers should limit the permissions they seek to highly specific purposes. This chapter will try to get clearer on what this requirement, what we might call the specificity requirement, entails. Moreover, the philosophical arguments in support of this requirement also will be examined.

The thesis that will be defended is that since the risks presented by many types of molecular epidemiologic research often are quite limited, the scope of informed consent may be broader than is generally permitted in other types of genetic research. More generally, this suggests that the scope of informed consent should be commensurate with the degree of risk presented by the research. As risks increase, so too should the focus of the permissions being granted by participants.

This position permits multiple uses of research materials, even when these materials can be connected with an identifiable individual. Consequently, the position being advanced here is contrary to the views expressed by several professional societies that have discussed informed consent in connection with genetic research (American College of Medical Genetics 1995; American Society of Human Genetics 1996). None of these professional societies, however, have explicitly considered what informed consent entails in the context of molecular epidemiologic research. Hence, in examining these issues, the chapter fills an important void in current discussions of informed consent in genetic research.

The specificity requirement of consent for genetic research

Commentators have often noted that genetic research presents special challenges to traditional informed consent practices (Clayton 1997; NIH Office of Protection from Research Risks 1993). In response to the difficulties presented by the collection of genetic information, several professional

societies and task forces have issued statements on informed consent for genetic research (American College of Medical Genetics 1995; American Society of Human Genetics 1996; Clayton et al. 1995; NIH Office of Protection from Research Risks 1993). A common theme in these recommendations is the need for researchers to be as specific as possible in describing the research study and its potential risks for participants. This requirement, what we might call the specificity requirement, is supported by the idea that consent procedures in which research objectives and study methods are described in an imprecise or vague manner do not enable participants to make a genuinely informed decision about their participation. It would be inappropriate, for instance, for researchers to ask individuals to participate in "medical research" or "future studies of cancer".

Moreover, the specificity requirement is believed to be especially important in the context of genetic research (Annas 1993; Annas 1994). Some types of genetic information are highly predictive of one's future health, thus the discovery of such information can radically affect the lives of study participants and their families. Because of this, many believe that researchers have a special obligation to limit the permissions they seek from research participants if the collection of genetic information is involved (American College of Medical Genetics 1995; American Society of Human Genetics 1996; Clayton et al. 1995; NIH Office of Protection from Research Risks 1993).

Though a commitment to the specificity requirement is not universal among commentators on genetic research (Elias and Annas 1994), there is

clearly growing support for this perspective. Consider, for example, a recent statement issued by the American Society of Human Genetics (American Society of Human Genetics 1996). The ASHG condemns consent practices that permit the use of research materials for multiple, unspecified types of genetic research, claiming that,

> [S]ubjects should be given options regarding the scope of the subsequent investigations, such as whether the sample can be used only for a specific disease under investigation, or for other unrelated conditions. It is inappropriate to ask a subject to grant blanket consent for all future unspecified genetic research projects on any disease or in any area if the samples are identifiable in those subsequent studies (p. 473).

Though the ASHG position permits broader forms of consent for non-identifiable samples, there is a clear prohibition against generic or blanket consent for identifiable[1] samples (samples that can be linked with an individual donor).

A similar position appears in a consensus statement prepared by a joint National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC) working group on informed consent for genetic research on stored tissue samples (Clayton et al. 1995).[2] The NIH-CDC consensus statement claims that,

> [I]t is not desirable to ask sources to sign statements in which they agree to the use of their identifiable samples for research without being

informed about the scope and potential consequences of the projects (p. 1791).

This policy recommendation, like the ASHG statement, maintains that where samples can be connected with an identifiable individual, the permissions sought by researchers should be narrowly defined.

Finally, consider similar statements that appear in the NIH-OPRR guidelines for IRBs mentioned above (NIH Office of Protection from Research Risks 1993). The NIH-OPRR guidelines state that with regard to genetic research,

> The information presented to subjects in the informed consent process should be as specific as possible. ... Where a new study proposes to use samples collected for a previously conducted study, IRBs should consider whether the consent given for the earlier study also applies to the new study. Where the purposes of the new study diverge significantly from the purposes of the original protocol, and where the new study depends on the familial identifiability of the samples, new consent should be obtained.

This policy also reflects a clear commitment to the specificity requirement. In addition, the NIH-OPRR position appears to go a little further than the other two policy statements in that the NIH-OPRR position suggests that special attention be given not only to identifiable samples, but also to samples where the identity *of the contributor's family* is available.

While there appears to be an emerging consensus in support of the idea that in seeking informed consent from potential participants in genetic research, including molecular epidemiology, researchers should limit the permissions they seek to specific research objectives, it is not entirely clear how we should define this requirement of specificity. As a working definition, let us define the specificity requirement as the view that in seeking informed consent from prospective participants in genetic research, researchers have an obligation to specify, (1) the individual disease or diseases being studied, or (2) the specific gene or genes being considered (see Clayton et al. 1995, pp. 1791-1792). Moreover, the specificity requirement maintains that where future uses of the samples or collected information can be anticipated at the time that the initial informed consent is sought, these subsequent uses also must be described to potential participants (National Bioethics Advisory Commission 1999; NIH Office of Protection from Research Risks 1993). The specificity requirement suggests that failure to inform participants about any of these points constitutes an inappropriate failure to disclose, and as such, violates the general requirements of informed consent.[3]

Though this way of defining the specificity requirement may fail to fully capture this emerging perspective on genetic research, it provides a starting point for further discussion. Moreover, several arguments support some version of the specificity requirement for genetic research. The first argument is that researchers seeking broad permissions for the use of research materials—consent to "medical research" or "genetic research", for

instance—fail to provide participants with enough information to allow them to make a reasonably well informed assessment of the risks and benefits of their participation (American Medical Association Council on Ethical and Judicial Affairs 1998; Elias and Annas 1994; Lyttle 1997). Without this information, participants cannot provide genuinely *informed* consent. Second, advocates of the specificity requirement argue that it helps protect participants from potential misuses of genetic information collected by researchers (Clayton et al. 1995; Knoppers and Laberge 1989; Kopelman 1994). Finally, it can be argued that consent practices that violate the specificity requirement treat research participants as a means to achieve scientific ends and fail to show appropriate respect for participants as persons (Knoppers and Laberge 1989; Knoppers and Laberge 1995; Kopelman 1994).

In the following sections, each of these arguments is examined more carefully. By identifying several difficulties with the case in support of the specificity requirement, these sections open the door for additional discussion of the scope of informed consent in molecular epidemiologic research.

Informational standards and the specificity requirement

Genuinely informed consent for research requires that prospective participants be in a position to assess the potential risks and benefits of their participation (Appelbaum, Lidz, and Meisel 1987; Faden and Beauchamp 1986; 45 CFR 46). This requirement of informed consent, what has been called the information requirement (Beauchamp and Childress 1994), would appear to

be violated by consent processes that seek broad permissions to use research materials for non-specific, or poorly defined, purposes. By failing to specify either the disease(s) to be studied or the gene(s) being examined, consent processes that violate the specificity requirement fail to give prospective participants enough information to meaningfully assess the risks and benefits of their participation (Clayton et al. 1995). Without this information, participants cannot provide genuinely *informed* consent (American Medical Association Council on Ethical and Judicial Affairs 1998; Lyttle 1997).

This idea that researchers seeking informed consent must provide prospective participants with all the information they need to assess the risks and benefits of their participation is unassailable and fundamental to the very notion of informed consent. Nonetheless, a problem with the above-mentioned criticism of open-ended forms of consent is that there are many occasions where biomedical researchers and clinicians already seek broad permissions from research participants and patients. These requests, however, are rarely viewed as threats to the integrity of the informed consent process.

To illustrate this idea, consider the consent typically sought in connection with a physical examination (Elias and Annas 1994). Patients are rarely told about the various medical problems that may be detected by a routine exam or the individual tests done using blood samples collected in connection with these examinations. Many of the tests performed, however, have the potential to be highly stigmatizing—testing for the human

immunodeficiency virus for example—and may present significant risks to patients.

Other examples of non-specific permissions can be found in biomedical research. Current regulatory requirements, for instance, permit researchers to use non-identifiable samples for a wide-range of research purposes. In fact, research that involves only non-identifiable samples is not governed by current federal regulations at all (45 CFR 46.101(b)). As such, researchers have broad discretion with respect to the use of these biological materials.

In addition to these examples where very broad permissions are routinely sought, there are other aspects of standard consent processes that are non-specific to varying degrees. In many cases, this is a function of the educational disparities that often exist between researchers and participants. Researchers often know substantially more about the research being conducted than they can communicate effectively to participants who do not share their educational background and professional interests. In other cases, while it may be possible to inform participants about the many details and assumptions involved a study—in language that participants can understand—it would take far too much time to provide participants with the background information necessary for them to understand this information. In other situations, presenting such detail could result in "information overload", where the net result of providing additional facts is less retention of information by participants (Elias and Annas 1994). Researchers often are selective in

what they disclose to participants, and as a result, consent processes are always non-specific to some degree or another.

Perhaps more relevant to informed consent in molecular epidemiologic research, there also are examples where biomedical researchers seek broad permissions for the use of research materials, not because of a knowledge gap between researchers and participants, but because the researchers know very little about what they will encounter as the study progresses. For example, researchers might collect information and biological samples to be used in studying a family of related cancers. As the research proceeds, investigators may come to view one of these cancers as central to their research objectives. At the beginning of the study, however, researchers may not be in a position to say which one of these cancers will emerge as more interesting than the others. Hence, researchers may seek broad permissions from study participants to allow flexibility in their study design. These examples, and the others described above, suggest that broad forms of consent do not necessarily violate the information requirement of informed consent.

The specificity requirement and the protection of research subjects

A second argument in support of the specificity requirement is that broad forms of consent fail to provide adequate protections for research participants and make potential misuses of research materials more likely. Current policies and regulations governing informed consent were established in part as a way to protect participants from potential research abuses (Faden and

Beauchamp 1986). As part of the protection of human subjects, informed consent allows each individual to determine the level of risk that he or she is comfortable incurring in relation to the potential benefits that may result from the research. Broad, open-ended permissions do not provide participants with sufficient information about those risks and benefits. Without this information, participants could unknowingly place themselves at unacceptably high levels of risk, as judged by themselves against the potential benefits of the study.

This argument derives much of its force from the implicit assumption that genetic information presents special risks to participants (Allen 1997; Andrews et al. 1994; NIH Office of Protection from Research Risks 1993). It is these risks that require researchers to be more specific with respect to their research objectives, and more limited in the permissions they seek from research subjects (Clayton 1997; Clayton et al. 1995; Knoppers and Laberge 1989). Moreover, several reasons can be offered in support of the idea that genetic information should be treated as different from other types of medical information (Annas 1993; Murray 1997). Unlike other types of medical information, genetic information about an individual does not change over time. Moreover, genetic information may provide information about an individual's parents siblings, and children. In addition, genetic technologies are developing so quickly that it is difficult to foresee what information may be available about individuals in the future. Finally, genetic information is uniquely personal and may be likened to a "probabilistic future diary" (Annas 1993) in that it says much about what an individual's future life is likely to be like.

Interestingly, however, the arguments in support of treating genetic information as different from other types of clinical information do not carry as much force in the context of molecular epidemiologic research (Wilcox et al. 1999). The allelic variants studied by molecular epidemiologists often are relatively common in a population and limited predictors of disease risks (Hulka, Wilcosky, and Griffith 1990; Schulte and Perera 1993a). Such alleles may affect an individual's disease risks, but only in connection with other genes and environmental exposures. In fact, often times there are much better predictors of an individual's overall disease risks—for instance, whether he or she wears a seatbelt or smokes. Since the genetic information collected by molecular epidemiologists often is a limited predictor of future health, the arguments for treating such genetic information differently from other types of clinical information are not as compelling. Thus, if broader forms of consent are permissible for non-genetic research, then they ought to be permitted in genetic research as well.

Against this line of reasoning, however, it might be objected that researchers investigating or probing for various genetic determinants of disease may accidentally identify an allele that is highly predictive of disease, perhaps in conjunction with a particular environmental exposure. Such unexpected discoveries suggest that it may be prudent to limit informed consent for genetic research to specific alleles, in order to protect against unforeseeable research-related harms.

While certainly the odds of such unexpected findings increase as a function of the number of alleles considered, a problem with this objection is that the associations that molecular epidemiologists are hoping to establish between individual alleles and complex diseases will be very difficult to confirm and quantify (Schulte and Perera 1993b). Moreover, it is often the case that alleles that are initially believed to be highly predictive of disease subsequently turn out to be much more limited predictors (Wilcox et al. 1999). Initial studies of BRCA1 and BRCA2 mutations and breast cancer, for instance, suggested a strong genetic influence that was subsequently refuted by additional research (Kodish et al. 1998).

Nonetheless, in seeking informed consent from research participants, unanticipated risks should be discussed. As in all research, unforeseen results can arise. If unforeseen results arise, participants should be given options about their participation. Just as in other types of research, participants should have the right to withdraw from a genetic study if these new results increase the level of risk presented by the study or are viewed by participants as significant in some other way (45 CFR 46.116).

Concerns about the scope of informed consent, however, can make it difficult to extend this option to research participants. Consider, for example, a biological repository established by the NIH and the CDC (Collins, Brooks, and Chakravarti 1998). The NIH-CDC resource was created to promote the discovery of genetic polymorphisms that may be associated with increased disease risks. Concerns about the wide range of research that might be

conducted using this resource, however, led the NIH and the CDC to remove all potentially identifying information from the samples, including all phenotypic information, the names of sample donors, place of recruitment, etc. (Collins, Brooks, and Chakravarti 1998). After these biological samples were collected, all connections with their contributors were destroyed. Concerns about the scope of informed consent thus led researchers to preclude the possibility of donors subsequently withdrawing their samples at a later time—something explicitly prohibited by current federal regulations (45 CFR 46.116). This response to concerns about the scope of informed consent is arguably much worse than retaining identifiers. Moreover, other options—multiple layers of coding, for instance—could have allowed individuals to determine for themselves the level of risk that they are comfortable with incurring without precluding their right to withdraw from the research.

Respecting research participants as persons

A third argument in support of the specificity requirement claims that broad forms of consent fail to respect research participants as persons (Knoppers and Laberge 1989; Knoppers and Laberge 1995; Kopelman 1994). Allowing multiple, unspecified uses of research materials suggests that once an individual's biological sample or personal information has been collected, researchers can do whatever they wish with the collected sample or information. The symbolic consequence of this loss of an individual's ability to determine what can and cannot be done with research materials is that it

suggests that individuals may be used as a means for the advancement of science and medicine. In seeking broad permissions from research participants, researchers are implicitly saying that there are situations where participants do not need to be told about the details of the research. Such consent practices injure research participants by failing to treat them as persons and are inconsistent with a general commitment to respect subjects as persons (Knoppers and Laberge 1995).

Treating participants with respect, however, is about the relationship between researchers and individual participants, not necessarily about the particular items discussed through a consent process. Clearly, all relevant information should be given to prospective participants so that they can determine whether the balance of risks and benefits is acceptable. Treating people with respect, however, also means allowing them to exercise their decision-making independence, even when they may want to participate in a research study where not all the risks can be foreseen. In such cases, where researchers candidly discuss the research with participants, and where there is no deception, researchers can treat participants as active collaborators in research (as opposed to research "subjects"), thereby showing a special respect for participants as persons.

Reassessing non-specific consent in molecular epidemiology

The discussions above show that the case in support of the specificity requirement is not as strong as one might suspect from the general support it

is currently receiving from professional societies. Nonetheless, demonstrating that there are difficulties with these arguments does little to establish that we should endorse more open-ended forms of consent for research in molecular epidemiology. Three additional considerations, however, argue that the specificity requirement is overly restrictive in connection with molecular epidemiologic research, namely, (1) the limited risks presented by many studies in molecular epidemiology, (2) the public health benefits of allowing broader uses of collected samples, and (3) potential restrictions on individual autonomy resulting from the acceptance of the specificity requirement.

The risks of molecular epidemiologic research. Concern about broad forms of consent in molecular epidemiologic research reflect more general concerns about the collection of genetic information. These discussions would benefit from drawing a distinction between rare, highly penetrant alleles and common alleles of low penetrance (Wilcox et al. 1999). Studies of the first type of alleles, what we earlier described as "disease alleles" (Caporaso and Goldstein 1995), often present significant risks for research participants. Research on "sensitivity alleles" (common alleles of low penetrance), by contrast, is similar to other types of epidemiologic research and as such presents many of the same types of risks encountered in other areas of biomedical research.

Compare again, for instance, how we view consent for a battery of blood tests. There are risks associated with routine blood tests, but these risks are relatively minor and unlikely. Hence, less specific forms of consent are

acceptable in this context. Contrast this, for example, with the highly detailed consent that is appropriate for invasive surgical procedures where the risks often are substantial and much more likely. These examples suggest the principle that the scope of the consent sought by researchers should be commensurate with the risks presented by the procedure—where the risks are unlikely and few, the permissions sought may be broader and more open-ended.

Applying this principle to molecular epidemiologic research suggests that concerns about the scope of informed consent are overstated. Narrowly defined permissions are appropriate in connection with the study of highly penetrant alleles because the risks presented by the research are significant. This paradigm of genetic causation, however, does not apply to the genes of interest to molecular epidemiologists. In that context, individual genetic variants are limited predictors of disease risks, hence the collection of such genetic information presents much more limited risks for research participants.

Public health considerations. It is important to note how concerns about the scope of informed consent *per se*, as separate from concerns about the risks to research participants, could place serious constraints on proposals to study the relationships between genetic variation and human health. Molecular epidemiologic research promises to significantly improve our understanding of disease and disease susceptibility (Gottesman and Collins 1994; Khoury 1996; Khoury 1997). Prohibitions against generic consent for molecular

epidemiologic research must be weighed against those possible losses of important public-health information.

Many biomedical researchers are currently searching for genetic contributions to a broad range of diseases and health conditions. Research on how genetic variation may affect phenotypic variation and differences in environmental response may depend upon researchers having access to collections of biological samples that allow them to pursue many gene-environment associations simultaneously (Collins, Brooks, and Chakravarti 1998; Khoury 1997). "Hunting" for such associations will not be possible unless certain broad forms of consent are permitted.

At the same time, noting these losses should not be construed as "the ends justifying the means." Rather, the point is that overly rigorous standards of consent in this area—protections that are disproportional to the risks presented to participants—may themselves cause harm (Wilcox et al. 1999). Different types of genetic research present different risks (and benefits). Hence, the process of, and standards for, informed consent may be different in various research contexts.

Constraints on individual autonomy. A blanket prohibition against non-specific consent for genetic research also could place serious constraints on the autonomy of potential research participants. One can easily imagine a context in which an individual would like to contribute to the advancement of cancer research and is willing to provide biological samples "for genetic research relating to cancer". The specificity requirement, however, would

prohibit such an individual from participating in biomedical research in this manner, despite his or her interest.

This consequence seems decidedly paternalistic and would appear to be at odds with a growing commitment to individual autonomy with regard to healthcare decision-making. If an individual wishes to grant broad discretion to cancer researchers, and is both familiar with and willing to accept the general risks that may accompany this broad permission—insurance and employment risks, for example—then a commitment to patient autonomy would suggest that he or she ought to be able to participate. Since we grant individuals considerable latitude with regard to other biomedical decisions, it seems inconsistent to restrict individual decision-making in this area of biomedical research.

Conclusion

A strong commitment to the specificity requirement is misguided in the context of molecular epidemiology. Instead of focusing on the scope of the consent *per se*, the central issue that IRBs should consider is the degree of risk presented by the research. Where the risks are limited and few, broader forms of consent may be appropriate. Where the risks are significant, consent should be narrowly tailored and limited to specific research objectives. This position allows for circumstances where researchers may legitimately seek broad, open-ended permissions for the use of research materials in molecular epidemiologic research.

While ultimately these standards of consent will be determined by the individual IRBs that must wrestle with and resolve these issues in the context of specific research protocols, these questions clearly have broader implications for the protection of human subjects. As such, it is important for professional societies and commentators on genetic research to revisit these issues as new types of genetic research are explored. Currently, however, these discussions are lagging behind the pace of genetic research and need to consider how research on genetic susceptibilities to disease may affect our views on the specificity of informed consent.

Moreover, current discussions of the specificity of informed consent often fail to distinguish between several important types of genetic information. By considering rare "disease alleles" and less penetrant "sensitivity alleles" together in examining the scope of informed consent in genetic research, an emerging consensus places inappropriate restrictions on the scope of informed consent for molecular epidemiologic research. These restrictions do not provide additional protections for human subjects and may themselves cause harm. The scope of the consent sought by researchers should be commensurate with the level of risk presented by the research. Hence, where the risks are few, broad permissions may be morally acceptable. This point has significant practical implications, since many types of molecular epidemiologic research require that researchers have the flexibility to explore many different courses of research.

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Notes to chapter four

1. There is some lack of clarity about what constitutes an identifiable sample, for instance, whether coded samples should be considered identifiable or non-identifiable. The forthcoming National Bioethics Advisory Commission (NBAC) report on The Use of Biological Materials in Research should be helpful in establishing standard terminology with respect to biological samples (National Bioethics Advisory Commission 1999). Early drafts of the NBAC report treat coded samples as identifiable, hence this use of the term is adopted here.

2. The NIH-CDC policy statement prepared by the joint NIH-CDC working group is not an officially approved policy for either organization, though their findings have been very influential. The influence of the NIH-CDC policy statement is evident, for example, in the forthcoming NBAC report mentioned in note 1 (National Bioethics Advisory Commission 1999). Many of the recommendations made in the NBAC report reiterate findings of the NIH-CDC working group.

3. In this context, the requirements of informed consent are treated as professional standards, not just regulatory or legal standards.

CHAPTER FIVE

RISKS TO SOCIALLY IDENTIFIABLE GROUPS: NATIVE AMERICAN CONCERNS ABOUT GENETIC RESEARCH

Abstract:

Indigenous communities have expressed concern about the study of genetic polymorphisms that are unique to, or more prevalent among, their members. These concerns range from worries about discrimination and stigmatization, to concerns about possible threats to tribal sovereignty. At the same time, there is considerable skepticism about the value of genetic research for local communities, prompting some indigenous peoples to conclude that the benefits of genetic research are outweighed by its potential risks. This conclusion has led some Native American advocacy organizations to call for a general moratorium on all genetic research involving Native participants. In contrast to these perspectives, researchers have tended to discount many of the worries expressed by indigenous communities, maintaining that the risks presented by genetic research are minimal. To a large extent, this conceptual gap between Native communities and researchers results from both sides conflating several types of genetic research and failing to distinguish various research-related risks. By more carefully distinguishing categories of genetic research, and identifying different levels of participant risk, indigenous communities and researchers are more likely to engage in meaningful dialogue about the actual risks and benefits of genetic research involving indigenous peoples.

Introduction

Genetic research presents special challenges for the protection of human subjects (Andrews et al. 1994; NIH Office of Protection from Research Risks 1993). Revealing genetic information about an individual can have consequences for family members (Andrews 1997) and others who share a common social identity (Caplan 1994; King 1992). For example, published findings may associate socially identifiable populations with predisposition to disease (King 1998; Wolf 1995). These associations could lead to group discrimination or stigmatization. Thus, the choices of individual research participants can have broader implications for other individuals with a shared familial, ethnic, racial, or social identity.

The possibility that individual decisions about research participation may place entire categories of persons at risk has led some to propose supplemental protections against research-related risks. These protections include maintaining the anonymity of participating populations (Foster and Freeman 1998) and conducting community-based reviews of proposed research (Foster, Bersten, and Carter 1998; Greely 1998; North American Regional Committee of the Human Genome Diversity Project 1997). However, many have criticized these precautions as impractical and morally problematic (Juengst 1998a; Juengst 1998b; Reilly and Page 1998; Reilly 1998).

One of the central points of contention in this recent debate about supplemental protections is the extent to which socially identifiable groups are placed at risk by research on genetic differences between populations. Some

commentators deny that genetic research places collectives at risk, arguing that such concerns are "intangible (and largely undocumented) fears" (Reilly and Page 1998). Similarly, many scientists who have taken note of these worries about genetic research suggest that these concerns are exaggerated and that the potential benefits of genetic research far outweigh any risks that might be presented (Baer 1993; Cavalli-Sforza et al. 1991; Collins, Guyer, and Chakravarti 1997; Gottesman and Collins 1994; Kidd, Kidd, and Weiss 1993; Wallace 1998; Weiss, Kidd, and Kidd 1992).

This tendency to minimize the potential research-related risks to socially identifiable populations stands in stark contrast to the recent mobilization of several communities that perceive themselves to be at risk from genetic research. Groups of Jewish Americans, for instance, have expressed concern about their association with BRCA1 mutations and predisposition to breast cancer (American Jewish Congress 1998; Stolberg 1998). Similarly, the past association of African Americans with sickle-cell disease (Phoenix et al. 1995) has revived concerns about racist policies supported by the identification of genetic polymorphisms that are more common among blacks (King 1992; King 1998).

The current conceptual gap between these communities that perceive themselves to be at risk and those who advocate genetic research raises a number of broad social questions. For example, it may be the case that these differing perspectives on genetic research indicate a need for additional public education regarding the significance of genetic information (National Research

Council 1997). If so, this suggests that researchers should work to educate participating communities about their research prior to seeking consent from individual participants. Alternatively, different perceptions of the risks presented by genetic research may reflect fundamental sociocultural differences between the individuals studying genetic variation and the populations being studied. This later possibility would argue for the involvement of members of the study population in the design and review of the research (Foster et al. 1999).

To better understand the potential risks of research on genetic differences between populations, it will be useful to examine the concerns voiced by Native American communities. Research on human genetic variation has become a controversial issue among indigenous peoples. The Human Genome Diversity Project (HGDP), a proposal to collect DNA samples from indigenous populations worldwide (Cavalli-Sforza et al. 1991; Kidd, Kidd, and Weiss 1993), has generated widespread concern about potential exploitation and harm (Harding and Sajantila 1998; Lock 1994; Macilwain 1996; McPherson 1995; Rothman 1998). This concern about the HGDP has given rise to a more general climate of suspicion regarding all genetic research. Some Native American advocacy organizations, for example, have called for a general moratorium on all genetic studies involving Native participants (Harry 1996; Indigenous Peoples Coalition 1997; National Congress of American Indians 1998; Rural Advancement Foundation International 1993).

In these and other discussions of research involving indigenous populations, the potential risks of genetic research tend to be treated as

relatively uniform from one study to another. This tendency is common among scientists (Harding and Sajantila 1998; Wallace 1998), bioethicists (Knoppers, Hirtle, and Lormeau 1996; Wolf 1995), and other commentators on the protection of human subjects (Reilly 1998). In contrast to this tendency, it will be argued that maintaining distinctions between several types of genetic research, and their associated research-related risks, is an essential step in facilitating meaningful dialogue between researchers and the communities from which participants are recruited. To a large extent, it is the lack of such clear conceptual categories that has produced the current discrepancy between the perspectives of researchers and indigenous populations, leading the former to discount population-specific concerns and the latter to reject all types of genetic research. Moreover, these conceptual distinctions help to elucidate the basis of these moral disagreements and can be used to more thoroughly evaluate individual proposals to study genetic differences between populations (see chapter six).

Research involving Native American communities

It will be useful to begin with an example that illustrates many of the concerns of Native American communities. The example is hypothetical, but reflects a number of current research practices.

> Suppose that as part of their ongoing research on alcoholism in Native American communities a group of researchers is interested in determining whether some Native Americans possess certain allelic

variants related to the metabolism of alcohol. The specific genetic variants researchers are interested in are located in a gene that codes for an alcohol-metabolizing enzyme and could potentially be associated with a predisposition to alcoholism. These researchers contact several Native American communities in an effort to recruit participants. Each of these communities declines to participate, however, and expresses concern about the potential implications of the proposed research. Of special concern is the possibility of discrimination or stigmatization resulting from the research.

Undissuaded, the researchers decide to contact a commercial DNA repository for samples. For approximately fifty dollars per sample, the researchers receive roughly half of the samples they need from these commercial sources. When the originally contacted Native American communities discover this new approach to acquiring samples they contact the researchers and ask them to stop. The researchers do not stop, however, and instead proceed to take out newspaper advertisements in a number of cities with large numbers of Native American residents. The researchers plan to supplement their existing collection of samples with these additional samples. Further, knowing that the disapproval of Native American leaders and spokespersons has attracted a lot of pubic attention, and may discourage participants from volunteering, researchers decide to pay contributors up to two hundred dollars for each blood sample.

With these financial incentives, the researchers have little difficulty collecting the additional samples they need. They perform their analyses and eventually publish their findings in a prominent scientific journal. The following week a newspaper article declares that, "Researchers have discovered the genetic origins of Indian alcoholism." Though only a hypothetical example, there is much to be learned from this story.[1]

First, it is important to note that the researchers described above have not done anything illegal or prohibited by current regulations governing research involving human subjects. It is true that in many cases federal regulations require researchers to have their work reviewed by an Institutional Review Board (IRB) when it involves information or biological samples collected from human subjects (45 CFR 46). However, there are several circumstances where this requirement does not apply or can be waived. If, for example, the research is supported entirely by private funds, it typically is not subject to federal oversight (45 CFR 46.101). Other types of research that are exempt from federal regulation include research involving biological materials previously collected from now-deceased individuals, and research using publicly available samples, so long as "subjects cannot be identified, directly or through identifiers linked to the subjects" (45 CFR 46(b)(4)). In each of these cases, IRB approval is not required because the research is exempt from all (federal) regulatory oversight.

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Moreover, in other cases where the research involves collecting new biological samples, it still is possible that the work may be conducted without being reviewed by a "full" IRB. If the research involves only "minimal risk" to individual participants, and researchers obtain informed consent from sample donors, then the research may be eligible for "expedited" review (45 CFR 46.110). In such cases, the IRB chair, or a representative of the chair, often reviews the research independently and reports their findings to the IRB. The approval of the full IRB is not required, however. In practice, what this means is that the research, while it receives "IRB approval", is likely to be reviewed by a single individual.

Finally, in the example above, even if an IRB were to review the research described, their charge would be to insure that *individual participants* are protected from research-related risks, not to insure that *communities*, or other socially identifiable groups, are protected. In fact, current regulatory policies explicitly instruct IRBs not to consider the broader social implications of research under review (45 CFR 46.111; NIH Office of Protection from Research Risks 1993).

A second point to take away from the example above is that researchers interested in studying Native American communities are not required to obtain permission from the community itself. It is true that, because of their legal status within the US, federally recognized tribal governments have the authority to require supplemental regulatory requirements governing research conducted on tribal lands. In fact, some tribes do require that research

conducted on their lands be reviewed by a special tribal IRB (for example, see Akwesasne Research Advisory Committee, Akwesasne Task Force on the Environment 1996). In addition, research supported by the Indian Health Service (IHS), or research conducted through an IHS clinic, also is subject to review by a supplemental IRB (Freeman 1998). In both cases, these supplemental IRBs are concerned not only with protecting the rights and welfare of individual research participants, but with broader implications for tribal communities. Their aim is to identify possible research-related risks to those communities, and where possible, to minimize potential harms to participating tribes (Freeman 1998). However, while these review mechanisms partially address the problems described above and provide important protections for communities, they have limited application. In the hypothetical example above, for instance, the researchers would not have been required to consult a tribal IRB before conducting their research, unless the study was conducted on tribal lands or involved the IHS.

Nonetheless, even if the research described in the example above does not involve any legal or regulatory improprieties, we can still criticize the research on moral grounds. The researchers above seem to be trying to avoid certain regulatory mechanisms by seeking volunteers from among individuals who do not reside on tribal lands. Their intention would appear to be to carry out the research, irrespective of what Native American communities may think of the work. In a sense, the researchers are obtaining their samples through a sort of "black market". The idea is that if they cannot conduct their work with the

help of tribal authorities, they can always recruit volunteers who live in other areas. The only drawback is that this may mean that the researchers will have to pay more to conduct their studies. Their reliance on these "bootlegged" samples, and the related failure to acknowledge the perspectives of Native American communities, is part of what is morally objectionable about the research described above.

To expand upon this point, there are two distinct types of moral problems suggested by this hypothetical example. First, there are concerns about possible harms to the community. These concerns often relate to direct harms such as discrimination and stigmatization, but also may include harms involving the loss of benefits. In the example above, for instance, the community may be directly harmed by discrimination and stigmatization resulting from the publication of research findings and the release of a press report on the research. In addition, the community may be harmed by its loss of certain benefits. For example, had the researchers been forced to renegotiate with the Native American communities that they initially contacted, perhaps the two groups could have reached an agreement involving the provision of services to the community in return for their participation in the research project. These benefits may be viewed by the community as an acceptable exchange for the possible risks that are incurred as a result of their participation.

Moreover, in addition to concerns about harms to the community, the example above also suggests a second set of concerns, namely, concerns

about wronging the community (Capron 1991). Many of the moral problems surrounding this example relate to the fact that the researchers knew that the communities were upset about their work, but they continued anyway. This approach wrongs the community, apart from any particular harms that might occur.

To illustrate this, consider how we might respond to having our house burglarized. Suppose someone were to enter our home and take a number of valuable personal possessions. Clearly this would be a harm to us. But imagine that someone were to break into our home and go through a number of personal possessions without taking any of them. We would not be *harmed* by such an intruder, though we would be *wronged* by such an action. The intruder has invaded the privacy of our homes and done so without our permission. The problem is not that we have suffered directly as a result, but that the ability to control who enters our homes and who has access to our personal possessions has been taken out of our hands.

Similarly, to return to the example above, these Native American communities have not only been harmed by the researchers, they also have been wronged. In this context, the wrong involves these communities being unwillingly involved in a research study and their decision-making control being overridden by indirect means. Furthermore, by failing to acknowledge the concerns expressed by these communities, the researchers also have wronged them by demonstrating a lack of respect for the collective decision-making authority of the community. Even if a newspaper article is never

released, and no individuals suffer discrimination as a result of information collected by researchers, the communities still have been wronged by being treated in a disrespectful manner and unwillingly involved in this research.

Thus, there are several lessons to take away from the hypothetical example above. First, current federal regulations governing research involving human subjects allow Native American communities to be involved in genetic research studies without their permission, namely through the actions of individuals who share a common genetic heritage with the community. Some of these individuals may be subtly pressured into participation by financial incentives. Moreover, after such samples have been collected, researchers have very broad license to perform various types of research using the collected samples, so long as they cannot be linked to an identifiable individual. Second, current regulations do not require IRB review for all research involving Native participants. Though supplemental tribal IRBs review some research involving Native Americans, much research involving indigenous peoples falls outside the jurisdiction of these IRBs. Third, Native American communities can be both harmed and wronged by genetic research, even research that is consistent with existing regulatory policies governing the protection of human subjects.

Native American concerns about genetic research

The points above suggest that Native American communities have good reason to be concerned about genetic research. In addition, several recent

conferences have explored how Native American communities may be placed at risk by genetic research.[2] Hence, it is possible to be more specific about the individual concerns that have been voiced by Native American communities to date.[3]

First, many Native Americans are concerned that genetic research could reveal information about particular tribes that could alter their political and legal statuses (Foster et al. 1999). For example, suppose that researchers discover that members of a given tribe are, from a genetic perspective, no more similar to each other than they are to individuals outside the tribe. That finding could be used to oppose continued tribal status for that group. The general idea is that opponents of continued tribal status for a given Native American community could appeal to the idea that the population is not sufficiently different, or biologically discrete, to warrant identifying the group as a separate tribe. While we might argue about whether biological differences should be used to distinguish social groups, this potential threat to political sovereignty is viewed by many Native Americans as a serious risk presented by genetic research.

Second, many Native American communities are skeptical about scientific research in general and are concerned about the number of research studies that have focused on Native Americans. Indigenous communities often voice concerns about being overstudied without receiving significant benefit from much of this research (Deloria 1995). Native critics describe a history of "helicopter researchers"—researchers who rush in, collect information or

samples, then rush off never to be heard from again. Such interactions treat Native peoples as objects—research "subjects"—not as active "participants" in the research. Couple these concerns with a more general skepticism about governmental authorities and federally-sponsored research, and it is easy to understand the caution of indigenous peoples when it comes to genetic research.[4]

Third, there also are concerns that are specific to the religious and spiritual beliefs of some Native American communities (Deloria 1995). Many Native American cultures maintain that the body is sacred and is not the property of any single individual. Though this belief is not embraced in all tribal communities, or by all Native Americans, this perspective suggests that even the use of hair samples for genetic research is problematic if the samples are not returned at a later date (Foster et al. 1999). Thus, the collection of blood for the creation of immortalized cell lines, something common in many types of genetic research, is especially problematic for persons who hold these religious beliefs. Similarly, there are concerns about how genetic research may contribute to the commodification of life and the patenting of biological materials (Rural Advancement Foundation International 1993; Rural Advancement Foundation International 1997).

Fourth, some Native Americans are concerned about the development of commercial products stemming from genetic research. Some of these concerns are spiritual, but other concerns relate to the possible exploitation of Native resources. If the participation of indigenous peoples is crucial to the

development of commercial products, then many communities want to insure that they receive a portion of the commercial gains (Rural Advancement Foundation International 1993; Rural Advancement Foundation International 1997).

Finally, there are concerns about discrimination and stigmatization (Foster, Bersten, and Carter 1998; Foster and Freeman 1998). Native American communities continue to struggle with a number of historical prejudices. If genetic research reveals additional differences between Native Americans and others, this information might be used by some to continue to stigmatize and discriminate against Native Americans. This is especially important in light of the apparent immutability of genetic information.

It is also interesting to note what is *not* on this list of Native American concerns about genetic research. Researchers often believe that it is important to include Native Americans in their research because of the possible benefits that might be derived from the work. From their perspective, researchers may feel a moral obligation to *include* Native American participants in genetic research, particularly research that aims at better understanding disease or improving health. It is interesting that these concerns about inclusion are rarely voiced by Native Americans themselves (Dukepoo 1998). Perhaps the long history of governmental dishonesty in the treatment of indigenous peoples, and a perceived lack of benefit from scientific research more generally, combine to produce this general skepticism about the value of participating in genetic research.

Native American concerns about genetic research reflect a wide range of community interests, including economic, political, cultural, and religious concerns. While some of these concerns are broad complaints about genetic research in general, others apply narrowly to specific types of genetic research. Thus, to better understand these perspectives on genetic research, the following sections distinguish several types of genetic research and identify the most salient risks presented by each category of research.

Categories of genetic research

Not all studies of human genetic variation present the same kinds of risks and benefits. One consequence of this is that, not all research on genetic variation permits the same kinds of human subjects protections. Studies of disease susceptibility (Brown and Hartwell 1998; Khoury 1997), for instance, are markedly different from studies of population histories (Cavalli-Sforza et al. 1991; Kidd, Kidd, and Weiss 1993; Stoneking 1997; von Haeseler, Sajantila, and Paabo 1995; Weiss, Kidd, and Kidd 1992). Similarly, the collection and storage of biological materials for multiple research purposes presents different risks than studies limited to specific research objectives (Collins, Brooks, and Chakravarti 1998; Weir 1998).

Research on disease susceptibility. Research on genetic susceptibility to disease offers the promise of improved prevention and treatment (Brown and Hartwell 1998; Collins, Guyer, and Chakravarti 1997; Gottesman and Collins 1994; Khoury 1996). From the perspective of an entire population, the

health benefits of disease-susceptibility research may be perceived as much greater than the benefits to individual study participants. Often, a population afflicted with a high incidence of a specific disease—a circumstance that also makes it especially well-suited for studies of gene-environment interactions—may be strongly motivated to participate in genetic research so that future generations may lead healthier lives (Foster, Eisenbraun, and Carter 1997/98).

The primary risks presented by studies of genetic susceptibility are those involving the adverse association of a population with a genetic predisposition for a specific disease (Caplan 1994; Kegley 1996; King 1992). For example, employment and insurance discrimination (Andrews et al. 1994; Gostin 1991; Rothstein 1993), as well as broader forms of stigmatization (Wolf 1995), could result from such associations.

Research on population histories. In contrast to disease-susceptibility research, studies of population histories offer few if any benefits for participants. Instead, such research primarily benefits academic disciplines such as anthropology, archaeology, linguistics, and population biology. The findings of these studies often are irrelevant, or even objectionable, to members of study populations (Deloria 1995). For example, a population's version of its own history, and its narratives about its origin and identity, may be contradicted by genetic findings. As a result of this contradiction, members of study populations may suffer psychosocial stress and the community as a whole could find its social arrangements disrupted. In the case of Native

American communities, retelling a population's history also could affect the community's legal and political interests, such as its claims for land, indigenous status, and items of cultural patrimony currently held in museums (Grounds 1996). While genetic findings could, in principal, support indigenous histories and claims, the possibility of negative applications of such information has caused many populations to oppose genetic research on population histories altogether (Harry 1996; Indigenous Peoples Coalition 1997; Macilwain 1996; National Congress of American Indians 1998).

Biological repositories. Genetic studies that are limited to specific research questions often focus on single populations, making them amenable to fairly precise risk-benefit assessments. In contrast, research proposals involving the collection of biological materials from more than one population, and allowing multiple uses of the samples collected, present greater difficulties for the review of human subjects protections (Annas 1993; Annas 1994; Clayton et al. 1995; Knoppers and Laberge 1989; Reilly 1992). In addition, individual sample contributors, and the communities from which samples are obtained, may not be able to anticipate the possible risks entailed by sample collections that are open to a wide variety of scientific uses (Lyttle 1997).

Collective risks for socially identifiable groups

In discussions of genetic research involving Native American communities, both researchers and Native American advocacy organizations

have confused the above-described categories of genetic research. As a result, these discussions fail to distinguish various research-related risks presented by genetic research. This has led to a tendency among researchers to discount the concerns of indigenous peoples, and a corresponding tendency in Native communities to over-state the risks of genetic research. To correct these confusions, and better understand the sources of disagreement between Native American communities and researchers, a more precise conceptual framework is needed. Thus, the following sections attempt to distinguish between different types of research-related risks presented by genetic research.

Though genetic research can present risks both to individuals and to socially identifiable groups, not all collective risks are similar. Some risks, what we might call "external risks", stem from the adverse use of genetic information by outsiders—insurers or employers for example. These risks are different in kind from what we might call "intra-community risks", which involve the use of genetic information by members of the same population—to stigmatize fellow community members, for example. Within each of these two general categories, several subcategories also can be distinguished. Each of these categories of collective risks should be considered in the review of human subjects protections. Frequently, however, only external risks are considered (if collective risks are discussed at all).

External Risks

Harms inflicted by outsiders are the most commonly considered collective risks to persons with a shared social identity. Perhaps the best known example is the genetic discrimination suffered by African Americans with sickle-cell trait (Phoenix et al. 1995). Nonetheless, other ethnic, familial, and social identities can be harmed by association with genetic information. These external collective risks include economic, social, legal, and political threats.

Economic risks. Employment and insurance discrimination often are considered in the evaluation of genetic research studies. These threats exist both for individual participants and to the socially identifiable groups of which they are members. Although few actual cases of genetic discrimination have been documented (Billings et al. 1992; Gostin 1991; Rothstein 1993), this continues to be a risk presented by genetic research, at least until a federal genetic anti-discrimination law is enacted (Annas, Glantz, and Roche 1995).

Social risks. The adverse association of genetic information with social identity also may lead to broader forms of stigmatization (Wolf 1995). While this may not have direct economic consequences, members of the population may be limited in their opportunities for social interaction, including marriage, adoption efforts (Simon and Altstein 1997), and child-custody claims (Rothstein 1994-95). Askenazi Jews, for instance, have expressed (non-economic) concerns about their association with BRCA1 mutations and susceptibility to breast cancer (American Jewish Congress 1998).

Legal and political risks. Finally, populations with unique legal and political statuses, such as sovereign American Indian communities, may find those statuses challenged by genetic findings (Grounds 1996). Genetic information could be used to retell a population's history, thereby undermining its ability to assert legal claims based on oral tradition. Compare, for example, recent controversy surrounding the discovery of human remains in Washington (Morell 1998a; Morell 1998b). Those remains, dubbed "Kennewick Man", have been interpreted as "Caucasoid" in appearance. This has led some to conclude that Europeans, rather than Native Americans, were the first peoples to inhabit North America (Morell 1998b). Hence, many Native American legal claims based on primacy of residence may be undermined by this discovery. For example, establishing primacy of residence is relevant for the enforcement of the Native American Grave Protection and Repatriation Act (NAGPRA), which gives Native American tribes the ability to petition for the return of human remains and artifacts currently held in museums that receive federal funding. Genetic research, particularly research on population histories, may present similar risks if "scientific" histories of populations contradict traditional Native histories.

Intra-Community Risks

Genetic information also can be interpreted by members of a study population in ways that disrupt existing social arrangements and beliefs. Such disruptions can take several forms. Rarely, however, are intra-community risks

considered in the review of research involving human subjects. In contrast to this position, many indigenous communities maintain that concerns about the disruption of social arrangements are just as valid as those currently recognized by bioethicists and others involved in the review of genetic research (Deloria 1995; Grounds 1996). If the disruption of families, for instance, is regarded as a legitimate research-related risk (Andrews et al. 1994; NIH Office of Protection from Research Risks 1993), then the disruption of community stability also should be considered.

Risks to shared identities. Social identities often are based on specific historical narratives. Moreover, a shared social identity frequently gives individuals a sense of belonging to a particular community. Hence, if genetic findings contract a community's understanding of its own history, this may constitute a threat to the shared social identity of community members (Deloria 1995). This in turn creates stress for those individuals who depend on that community for guidance in their personal decision-making.

For example, many archeologists maintain that a land bridge existed between Alaska and Siberia approximately 15,000 years ago. Moreover, it is believed that this land bridge provided a migration route for the peopling of North America. Genetic studies of population histories may help to confirm the existence of such a land bridge (Starikovskya et al. 1998). However, many Native Americans believe that this account of the peopling of the Americas is inconsistent with traditional Native origin narratives. Hence, the land-bridge explanation is seen as a threat to traditional Native religious beliefs that are

founded, in part, on these origin narratives (Deloria 1995). The acceptance of the land-bridge explanation thus presents risks to the collective social identities of many Native American communities.

Risks to established social equilibria. The relationships between social groups within a population—such as families and religious organizations—also may be disrupted by genetic research. For example, in a study of genetic testing in one Native American community, a testing program was seen as a threat to the community's religious organizations (Foster et al. 1999). One of the primary roles of these religious organizations was to prevent the development of disease through ceremonial activities. Hence, tests for disease susceptibility were seen as undermining the traditional status of religious ceremonies. Of special concern was that genetic tests could delegitimate the relevance of traditional ceremonies for younger members of the community. Thus, this example illustrates how even the most well-intentioned project can change the social dynamics of a community.

The publication of genetic research findings also has the potential to disrupt existing social arrangements. For example, genetic findings may suggest that a socially homogeneous population is biologically more heterogeneous than was thought previously. In one study of disease susceptibility, for instance, it was found that participating Native American families had many more European ancestors than was thought by study participants.[5] This finding was not released, however, because of concern that those families whose members participated in the study might be viewed by

other community members as less "Native" than others. In that community, a minimum "blood quantum" was required of political officials (Strong and Van Winkle 1996). Thus, the perception of participating families as of lessor Native ancestry would restrict their opportunities for political and social advancement within the community.

Risks to cultural and moral authority. A study that bypasses a population's collective decision-making procedures and relies exclusively on individual informed consent can place the moral authority of these decision-making procedures at risk. In many indigenous communities, members are keenly aware of matters about which they can speak as individuals and those about which they must defer to collective tribal authorities (Foster, Bersten, and Carter 1998). If members voice their individual opinions on some matters before a collective decision has been made, it can be seen as undermining the authority of established tribal leaders.

Moreover, relying exclusively on individual informed consent reflects a Euro-American moral standard. By contrast, many indigenous moral traditions require a process of collective decision-making prior to individual choice. Thus, seeking only individual informed consent can be viewed as a form of cultural domination since it fails to respect existing indigenous moral standards (Young 1990).

Conclusion

Genetic research can present collective risks to socially identifiable groups. Nonetheless, the risks presented by genetic research can differ considerably depending on the type of study being conducted. Moreover, recognizing these differences has important implications for the protection of research participants.

The primary risks of research on disease susceptibility are external risks. Maintaining population anonymity (Foster and Freeman 1998), and collecting biological materials for specific research purposes (Collins, Brooks, and Chakravarti 1998; Freeman 1998), can help to minimize many of these risks. Nonetheless, while population anonymity may protect participating communities from many external risks, failing to identify a population also may limit the medical benefits of the research. Moreover, even with population anonymity and narrow research objectives, disease-susceptibility research may present some intra-community risks in the recruitment of participants.

Unlike studies of disease susceptibility, research on population histories must name study populations for the results to be meaningful (Greely 1998). This increases the likelihood of external harm. Studies of population histories also present a much broader range of intra-community risks since they have the potential to call into question many different community beliefs. Studies of population histories can minimize possible risks by limiting the use of research materials to specific questions, and restricting subsequent uses of collected samples (Freeman 1998). Collecting biological samples for multiple

purposes, or allowing the use of samples for broadly defined studies of population histories, make it difficult to identify and minimize both external and intra-community risks.

Native American concerns about projects like the HGDP are not unfounded. Scientists promoting the HGDP have consistently understated its risks (Lock 1994; Rothman 1998), been unclear about the project's objectives (National Research Council 1997), and confused its benefits with those of disease-susceptibility research (Knoppers, Hirtle, and Lormeau 1996; Wallace 1998). Each of these factors has contributed to the problems surrounding the evaluation of the project (National Research Council 1997). However, the tendency of some indigenous peoples to extend their concerns about the HGDP to all genetic research reflects the same confusion that has led many scientists to dismiss indigenous concerns out of hand—namely, the conflation of different types of genetic research and the failure to distinguish their associated research-related risks.

Researchers and members of indigenous communities often fail to appreciate the other's perspective on the risks of genetic research. For example, intra-community risks often are more salient to members of indigenous populations and thus have become focal points in indigenous critiques of genetic research (Grounds 1996). In contrast, researchers tend to minimize such intra-community risks, in part because these types of harms are not easily identified or understood by outsiders. Thus, distinguishing external and intra-community risks helps to shed light on the respective positions of

researchers and indigenous communities. Furthermore, a better understanding of these differing perspectives on genetic research is essential for narrowing the current conceptual gap between researchers and Native American advocacy organizations.

Moreover, taking both types of collective risks into consideration in the review of genetic research, offers a balanced way of weighing the risks and benefits of individual research proposals. This is illustrated in the following chapter, where these conceptual distinctions are used to distinguish, and evaluate, two proposals to examine genetic differences between populations.

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Notes to chapter five

1. Research similar to that described in this hypothetical case has been done by Jeff Long and his colleagues (Long 1998). Long's research, however, is similar only in subject matter, not in approach, since he sought input from the communities involved and his research was supported by tribal authorities.

2. Recent conferences on Native American concerns about genetic research include, the Tenth Annual Indian Health Service Research Conference: The Promises and Perils of Genetic Research (Albuquerque, NM, April 27-29, 1998), the North American Conference on Genetic Research and Native Peoples: Colonialism through Biopiracy (Polson, MT, October 11-12, 1998), and Anthropology, Genetic Diversity, and Ethics (Milwaukee, WI, February 12-13, 1999).

3. The following discussion of Native American concerns is not meant to be exhaustive. This list of concerns is derived from a review of the existing literature and from a limited set of personal experiences and conversations. There is a clear need for accurate empirical information on how genetic research is perceived within Native American communities. Moreover, the concerns described here should not be associated with any specific Native American community, organization, or tribe. This author believes that many Native Americans communities share these concerns to some degree or another. However, there is very little empirical evidence to support this claim.

4. Richard Grounds, a cultural anthropologist who studies how indigenous communities perceive scientific research, suggests that specific concerns

about genetic research must be viewed within their historical context (Grounds 1996). He maintains that past incidents of intentional deception and deliberate governmental harm of Native Americans continue to influence how indigenous communities view current efforts to enlist their cooperation in scientific research. This general skepticism about the federal government and scientific research also may help to explain why detractors of genetic research involving indigenous peoples sometimes associate this research with genocidal efforts to exterminate Native Americans, suggesting that genetic research may be a ploy to develop biological weaponry against Native Americans (Rural Advancement Foundation International 1993).

5. This example was suggested to me by Morris Foster. Ancestral claims often are linked to leadership opportunities in Native American communities (Strong and Van Winkle 1996). However, because of concern about the potential for identifying the communities described, no additional references are provided.

CHAPTER SIX

STUDYING GENETIC DIFFERENCES BETWEEN POPULATIONS: DISTINGUISHING BIOMEDICAL AND ANTHROPOLOGIC INTERESTS

Abstract

Distinguishing different types of research interests, and their associated research-related risks, is helpful in evaluating proposals to study human genetic variation. For example, studies of disease susceptibility present different risks than studies of population histories. The previous chapter distinguished several types of collective risks presented by genetic research. This chapter draws upon that conceptual framework to assess the respective risks and benefits of two proposed research projects, thus illustrating the usefulness of those categories. The first project is the Environmental Genome Project discussed above. The other is the Human Genome Diversity Project, an international proposal to study genetic variation in indigenous communities worldwide, which is described further in this chapter. Though some indigenous communities have viewed the collective risks of these two projects as roughly equivalent, this chapter argues that there are important differences between these proposals. The conceptual categories presented in chapter five help to define and clarify these differences.

Introduction

Researchers from many different disciplines are interested in studying human genetic variation. Population biologists hope to use genetic information

to understand phenotypic similarities and differences between groups (Baer 1993; Cavalli-Sforza et al. 1991). Anthropologists believe that studying genetic variation will help to clarify population histories and patterns of migration (Kidd, Kidd, and Weiss 1993; Stoneking 1997; Weiss, Kidd, and Kidd 1992). Biomedical researchers are interested in how genetic variation may affect individual and group risks for various diseases (Brown and Hartwell 1998; Collins, Guyer, and Chakravarti 1997; Khoury 1997).

A number of groups that have suffered as a result of past research on population differences are concerned about this growing interest in the study of human genetic variation (Gutin 1994; Stolberg 1998). Native American communities, in particular, are concerned about interest in their genetic heritage (Grounds 1996; Macilwain 1996). These concerns have lead some to call for a general moratorium on all genetic research involving indigenous peoples (Harry 1996; Indigenous Peoples Coalition 1997; National Congress of American Indians 1998; Rural Advancement Foundation International 1993).

Many of the concerns that have prompted these calls for a general moratorium on genetic research involving indigenous peoples are clearly legitimate. Some of the concerns expressed, however, only apply to certain types of research. This chapter distinguishes two fundamentally different interests in the study of genetic variation—biomedical interests and anthropologic interests. While research proposals reflecting each type of scientific interest may present moral difficulties, there are important general differences with respect to the risks and benefits of the two types of research.

There also are important differences regarding the possible protections that might accompany individual research proposals. These differences can be illustrated by comparing the Environmental Genome Project (Brown and Hartwell 1998; Cannon 1997; Kaiser 1997) with the Human Genome Diversity Project (Cavalli-Sforza et al. 1991; Human Genome Organisation 1994; Kidd, Kidd, and Weiss 1993). Proposals for a general moratorium on all genetic research involving indigenous peoples disregard these important differences between biomedical and anthropologic research. Consequently, these proposals, if taken seriously, could result in Native American communities losing out on the benefits of biomedical research, despite the fact that many of the concerns of indigenous peoples principally apply to athropologic research.

Biomedical interests: the Environmental Genome Project

Advocates of genetic research often stress the potential medical benefits of their work (Collins, Guyer, and Chakravarti 1997; Gottesman and Collins 1994). For example, researchers tell us that genetic differences between individuals can affect their disease risks (Brown and Hartwell 1998; King, Rotter, and Motulsky 1992). Geneticists also claim that each of us is particularly susceptible to many different diseases (Khoury 1996; Khoury 1997). Thus, a better understanding of human genetic variation could lead to earlier diagnosis of disease, earlier clinical interventions, and more effective disease-prevention strategies.

In the summer of 1997, the National Institute of Environmental Health Sciences, one of the National Institutes of Health, launched a multi-year project to study how genetic differences and environmental exposures combine to determine an individual's disease risks (Albers 1997; Kaiser 1997). That project, called the Environmental Genome Project (EGP), is interested in studying genetic susceptibility to environmentally associated diseases such as asthma, cancer, diabetes, and birth defects. Researchers hope that the information collected through the EGP will improve our understanding of how genetic determinants and environmental factors interact to affect disease risks.

The main benefits of the EGP relate to disease prevention. A better understanding of who is at risk will facilitate the design of more effective preventive programs. Since individuals are not equally at risk, nor are they at risk for the same diseases, knowing that someone is especially susceptible to a particular disease could enable them to take steps to reduce their risks. Moreover, the potential benefits of the EGP fall into two categories, (1) benefits to individuals who, by knowing that they are at increased risk, can take steps to reduce their exposures to adverse conditions, and (2) improvements in public health resulting from increased awareness of population-specific hypersensitivities to disease. At both levels, it is the case that effective disease prevention depends upon accurate estimates of risk.

Nonetheless, though advocates of genetic research often stress the importance of genetic contributions to disease, it is important that we do not overemphasize this point (Hubbard and Wald 1993; Lewontin 1991). Human

health is the result of complex interactions between many different contributing factors, including an individual's age, sex, diet, lifestyle, exercise, socioeconomic status, genetic make-up, and environmental exposures. Genetic contributions are just one part of the story behind our overall health.

Anthropologic interests: the Human Genome Diversity Project

The Human Genome Diversity Project (HGDP) is a proposed international effort to collect and store biological samples from indigenous peoples around the world (Baer 1993; Harding and Sajantila 1998; Kidd, Kidd, and Weiss 1993; Wallace 1998; Weiss, Kidd, and Kidd 1992). Proposed by Luca Cavalli-Sforza in 1991 (Cavalli-Sforza et al. 1991), and currently sponsored by the Human Genome Organisation (HUGO), the HGDP plans to identify and characterize some of the genetic differences that exist between populations.

The goals of the HGDP are described in a summary document issued by HUGO (Human Genome Organisation 1994). The stated goals of the project are,

> To arrive at a much more precise definition of the origins of different world populations by integrating genetic knowledge ... with knowledge of history, anthropology and language. ... Ultimately, [the organizers hope] to create a resource for the benefit of all humanity and for the scientific community worldwide.

The focus of the HGDP is on anthropology, linguistics, and population biology. The organizers believe that genetic information can better inform our understanding of population histories, migration patterns, and interconnections between groups.

Nonetheless, the principal goal of the HGDP is not to conduct these studies of population histories, but to support such work by creating a comprehensive collection of DNA samples from human populations around the world. This proposed collection of immortalized cell lines could then be used by researchers to explore a broad range of scientific questions relating to genetic differences between populations. Hence, the HGDP is not just one project, but a first step toward many different anthropologic studies.

Evaluating proposals to study genetic variation

While the EGP and the HGDP have very different objectives, as will be explained in what follows, both projects are interested in examining genetic differences between populations. Consequently, several Native American advocacy organizations oppose each of the projects (Harry 1996; Indigenous Peoples Coalition 1997; National Congress of American Indians 1998; Rural Advancement Foundation International 1993). Nonetheless, these blanket rejections of all genetic research involving indigenous peoples gloss over several important differences between the EGP and the HGDP.

The discussion of research-related risks in the previous chapter can be used to identify, and highlight, several important differences between the EGP

and the HGDP. Moreover, other discussions of genetic research suggest additional points to consider in evaluating proposals to study genetic differences between populations (Andrews et al. 1994; National Research Council 1997; NIH Office of Protection from Research Risks 1993; Reilly, Boshar, and Holtzman 1997). These considerations include:

1. the clarity and scope of the research objectives,
2. the possible benefits of the research, including *who* benefits from the work,
3. the possible risks of the research and who is placed at risk, and
4. the possible protections available to minimize research-related risks.

To better understand the differences between the EGP and the HGDP, it is important to examine what each of these considerations suggests about the two projects.

1. Clarity and scope of research objectives. Beginning with the clarity and scope of the research, we see a stark contrast when we compare the primary objectives of the HGDP and the EGP (for an overview, see Table 2). The HGDP is interested in better understanding the historic relationships between groups and using genetic information to construct accounts of population histories and world migrations. The EGP, by contrast, is interested in learning more about genetic susceptibility to disease and why some individuals, and populations, are more likely to develop certain diseases instead of others. Moreover, these differences between the EGP and the HGDP are important because the reconstruction of population histories may not be

valued by study populations, and may even be seen as objectionable (Deloria 1995; Grounds 1996). Improving public health, by contrast, is widely recognized as an important goal.

Another difference between the two projects can be seen when we consider the scope of each proposal. The HGDP describes its goals in a very vague way—so vague that questions about what researchers will be doing with the samples they collect, and what types of genetic diversity they may be interested in studying, remain unanswered (National Research Council 1997). To a large extent, this consequence follows from the fact that the HGDP intends to create a general biological repository to be used for studying a broad range of anthropologic issues. By contrast, the EGP is interested in genetic variation only to the extent that it affects disease susceptibility and response to environmental exposures.

Similarly, when we ask about the possibility that research materials could be used for other purposes, we see another important difference between the two projects. Secondary uses of research materials are possible in connection with the HGDP, but are unlikely to result from the EGP. Moreover, the possibility of secondary use of HGDP samples results from a lack of clarity in its description of the conditions under which samples will be released (National Research Council 1997) and the fact that the sponsors of the HGDP want the repository to be available for a wide range of research interests (Human Genome Organisation 1994). By contrast, the specificity of the research objectives in the EGP minimizes this possibility.

2. *Benefits and beneficiaries*. A second point to consider in evaluating research on genetic variation is the possible benefits of the research (see Table 3). In this context, we see another contrast between the HGDP and the EGP. In the HGDP, the clear beneficiaries of the research are anthropologists, population biologists, and linguists. While it is possible that indigenous communities also could be interested in these studies, negative reaction to the HGDP suggests that shared interests in studying population histories are unlikely. In the EGP, however, the primary beneficiaries include the researchers themselves, but also may include members of study populations. As a result of the EGP, individuals from participating communities may be more aware of their particular disease susceptibilities, and consequently, may be able to avoid harmful exposures to which they are especially vulnerable (Cannon 1997; Khoury 1997). Thus, when we ask whether the communities participating in these two studies could benefit as a result of their involvement, we see that the EGP may provide benefits to participating groups, while such benefits are unlikely to result from the HGDP.

It is noteworthy, however, that neither project is likely to provide benefits to those individuals who volunteer to participate (apart from small monetary incentives for participation). Thus, it is important to avoid overstating the benefits of either project for individual participants.

3. *Risks and who is placed at risk*. The third set of considerations relate to possible risks and who is placed at risk (see Table 4). With respect to research-related risks, it is important to consider both external and intra-

community risks. External risks include possible discrimination, stigmatization, and other harms resulting from the actions of individuals outside the communities from which participants have been recruited. Intra-community risks, by contrast, arise within the community itself as a result of the participation of individual members.

Both the EGP and the HGDP present external risks to participating communities. Both projects seek to identify genetic differences between populations. These differences could be misused by outsiders to limit the opportunities available to members of certain communities. For example, the EGP, by associating disease susceptibility with a particular population, could cause individuals and communities to be stigmatized as vulnerable (Caplan 1994; Wolf 1995), denied medical or life insurance (King 1992; King 1998; Rothstein 1993), or subjected to broader forms of social discrimination (Rothstein 1994-95; Wolf 1995). Similarly, the HGDP also presents external risks, including possible threats to the unique legal and political statuses of federally recognized Native American tribes (Grounds 1996). An indigenous community's status as a federally recognized tribe is in part based upon its ability to establish the existence of sociocultural traditions before the time of European colonization. Population histories resulting from the HGDP—historic accounts based in part on genetic findings—could undermine the legitimacy of oral histories. Moreover, community efforts to reclaim cultural patrimony, including items currently held in federal and state museums, could be

undermined by the HGDP, since these claims also are based upon oral histories.

In addition to these concerns about external risks, the HGDP may present several intra-community risks to indigenous communities. By using genetic information to redescribe a community's history, the HGDP could cause individual community members significant psychosocial stress. Shared group identities help us to define ourselves and our relationships with others. Hence, claims about group histories and interconnections between populations may have important practical implications (Deloria 1995). For example, individuals in one community may view themselves as historically related to individuals in another community. This perceived connection may have produced a number of cooperative relationships and shared community activities. Were the HGDP to demonstrate that there is no genetic, and hence no ancestral relationship, between the two communities, this could undermine community relations.

4. Protections available to minimize research-related risks. Finally, in evaluating proposals to study genetic differences between populations, attention should be given to the possible protections that could minimize research-related risks (see Table 5). One such protection is preserving the anonymity of participating individuals, something possible in both the HGDP and the EGP. Another safeguard is maintaining the anonymity of participating communities (Foster and Freeman 1998). While maintaining the anonymity of

populations is possible in the EGP, it would be very difficult, if not impossible, to do within the framework of the HGDP (Greely 1998).

Conclusion

Calls for a moratorium on all genetic research involving indigenous participants obscure important differences between research proposals. Similarly, at the other extreme, blanket endorsements of all genetic research, and unqualified statements about the benefits of studying genetic variation, also serve to hide important differences between individual projects. It is important that current discussions move beyond such sweeping generalizations. An unqualified rejection of all genetic research ultimately could prevent Native American communities from receiving many of the health benefits of genetic research. Similarly, a blanket endorsement of all genetic research could fail to protect indigenous communities from the genuine risks presented by some types of genetic research.

As we shift from gross generalizations about all genetic research, and begin to evaluate research proposals individually, review should focus on the balance of possible harms and benefits, as well as the protections that might be put in place to minimize research-related risks. Carefully distinguishing different types of collective risks is an important part of these risk-benefit assessments. The HGDP and the EGP, for instance, each present different types of collective risks. Moreover, while there may be protections available to minimize many of these risks, both projects will continue to present some

collective risks for participating communities. In the context of the EGP, these risks must be balanced against the possible benefits that communities also could receive. With respect to the HGDP, such risks—in the absence of any benefits to participating communities—suggest that the project is morally objectionable and should not be done (Lock 1994; McPherson 1995; National Research Council 1997; Rothman 1998).

Finally, one way to better identify, and minimize, the collective risks of research on genetic differences between populations is to involve community members in the design and review of these studies. Intra-community risks, in particular, often are difficult for individuals outside the community to identify and understand (Foster et al. 1999). Unfortunately, however, involving participating communities in the review process can be difficult. The following chapter discusses some of the problems with this approach. There, it is argued that, despite several conceptual and practical difficulties, community-based reviews of genetic research can help minimize research-related risks and better protect socially identifiable groups.

Table 2. Objectives of human genetic variation research

	Human Genome Diversity Project	Environmental Genome Project
What are the primary objectives of the research?	To better understand the historic relationships between groups and to use genetic information in constructing accounts of population migrations	To learn more about genetic predisposition to disease and why some individuals or groups are more likely to develop environmentally associated diseases
Is the scope of the research clearly defined and properly limited?	No	Yes

Table 3. Possible benefits of human genetic variation research

	Human Genome Diversity Project	Environmental Genome Project
Who are the primary beneficiaries of the research?	Anthropologists, population biologists, linguists, and others interested in studying population relationships	Biomedical researchers and members of specific groups who might avoid harmful exposures or seek treatments earlier
Will participants receive benefits as a result of their participation (apart from small monetary incentives)?	No	Not likely
Could participating communities receive benefits as a result of the participation of community members?	Not likely	Yes

Table 4. Possible risks of human genetic variation research

	Human Genome Diversity Project	Environmental Genome Project
Could individuals (or communities) suffer external discrimination or stigmatization as a result of their participation?	Yes	Yes
Could the research undermine repatriation efforts or the political sovereignty of participating communities?	Yes	No
Could the research disrupt existing community relationships, or affect how community members interact with each other?	Yes	Not likely

Table 5. Possible protections available to minimize the risks presented by human genetic variation research

	Human Genome Diversity Project	Environmental Genome Project
Is it possible to maintain the anonymity of participating individuals?	Yes	Yes
Is it possible to maintain the anonymity of participating groups?	No	Yes

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CHAPTER SEVEN

STUDYING GENETIC DIFFERENCES BETWEEN POPULATIONS: THE ROLE OF COMMUNITY REVIEW

Abstract

As we have seen, research on human genetic variation can present collective risks to socially identifiable groups. Research that associates race with a genetic disposition to a disease, for example, presents risks of group discrimination and stigmatization. To protect against such research-related risks, some have proposed supplemental community-based reviews of research on genetic differences between populations. Involving diverse communities in the review of genetic research may help to identify, and minimize, collective risks that otherwise could go unnoticed. This chapter clarifies the goals of community review and the various forms that it may take. While, these supplemental community-based reviews of genetic research have been criticized as both impractical and morally problematic, many of these criticisms have been directed against *group consent*—the more specific idea that communities should have the authority to approve or veto research involving their members. As discussions of community-based reviews move beyond their initial focus on group consent, and begin to consider other approaches to involving communities in the review process, it is important to examine the extent to which criticisms of group consent also apply to these other approaches. It will be argued that while several criticisms initially introduced in connection with group consent also weigh against other methods

of involving communities in the review process, these challenges to community review can be answered. Thus, the chapter provides a limited defense of community review.

Introduction

Genetic variation appears to affect individual susceptibility to multifactorial diseases such as asthma, cancer, coronary heart disease, and diabetes (King, Rotter, and Motulsky 1992; Scriver et al. 1995). Advances in DNA-sequencing technologies now make it possible to study subtle genetic influences on disease and how slight genetic differences between individuals affect their disease risks (Haines and Pericak-Vance 1998; Marshall and Hodgson 1998; Schafer and Hawkins 1998). In addition, since certain genetic variants are more common in some populations and less common in others, researchers can use these new tools to estimate the disease risks of entire populations (Brown and Hartwell 1998; Collins, Guyer, and Chakravarti 1997). A better understanding of how genetic variation affects both individual and group susceptibilities to disease could lead to improved strategies for disease prevention, more accurate assessments of disease risks, earlier disease detection, and earlier clinical interventions (Collins, Brooks, and Chakravarti 1998; Gottesman and Collins 1994; Khoury 1996; Khoury 1997).

We have seen that despite these potential health benefits, however, there are a number of difficult ethical, legal, and social issues presented by the study of genetic differences between populations (Bailey 1997; Baird 1995;

Hunter and Caporaso 1997; Juengst 1995; McPherson 1995; National Research Council 1997; Parker 1995; Samet and Bailey 1997; Schulte, Hunter, and Rothman 1997; Soskolne 1997; Wallace 1998). One such issue is how to protect communities from potential harms resulting from an individual community member's choice to participate in genetic research. For example, research associating disease susceptibility with race or ethnicity could lead to discrimination or stigmatization (Caplan 1994; King 1992; King 1998). The association of African-Americans with sickle-cell disease (Phoenix et al. 1995), and Ashkenazi Jews with BRCA1 mutations (American Jewish Congress 1998; Stolberg 1998; Struewing et al. 1997), both suggest that genetic research can present risks for socially identifiable groups.

These concerns have led some to suggest that research on genetic differences between populations should not be done (Indigenous Peoples Coalition 1997; National Congress of American Indians 1998; Rural Advancement Foundation International 1993). Others maintain that more precautions are needed, and have proposed supplemental human subjects protections for genetic-variation research (Foster, Bersten, and Carter 1998; Foster, Eisenbraun, and Carter 1997/98; Foster et al. 1999; Greely 1997; North American Regional Committee of the Human Genome Diversity Project 1997; Human Genome Organisation 1994). This latter approach stresses the need for community involvement in the review process, particularly when research aims to identify genetic differences between populations. Proponents of community review argue that by involving communities in the review process,

researchers can better identify, and minimize, research-related risks (Foster, Bersten, and Carter 1998; Foster et al. 1999; Freeman 1998; North American Regional Committee of the Human Genome Diversity Project 1997).

In its strongest form, community review is suggested as a mandatory supplement to existing human subjects protections. Weaker forms recommend that researchers consult with communities, but do not require community involvement. Between these two extremes, community review can take many forms, ranging from informal dialogue between scientists and the community, to the negotiation of a formal agreement between researchers and the population placed at-risk by the research (Foster et al. 1999). Whatever method is employed, however, the goal of community review is to incorporate population-specific perspectives in the review of genetic research.

The suggestion that existing human subjects protections be supplemented with community review has been met with much criticism. In particular, critics have strongly objected to the notion of "community approval" (Reilly 1998) or "group consent" (Juengst 1998b). Giving communities the authority to veto a research proposal has been described as "morally hazardous" and "practically useless" (Juengst 1998b), as "paternalistic" and "inherently demeaning" (Reilly 1998), and as "too extreme" (National Research Council 1997). Moreover, critics of community review have not limited their attacks to group consent alone. Some have denied that research on genetic differences between populations presents significant risks to socially

identifiable groups, arguing that such concerns are "intangible (and largely undocumented) fears" (Reilly and Page 1998).

While the focus of this recent debate has been on the practicality and value of group consent, it is unclear whether other methods of incorporating community perspectives in the review of genetic research present the same difficulties. For example, if group consent is morally problematic in part because it contributes to reductionist attitudes toward socially defined groups (Juengst 1998a; Juengst 1998b), then perhaps other efforts to consult with members of socially defined groups, or involve community members in the review of research proposals, are problematic as well.

This chapter examines the extent to which several common criticisms of group consent also argue against other approaches to involving communities in the review of genetic research. The first sections present the central elements of the community-review process and distinguish several types of community review. Following this, a number of criticisms of group consent are discussed. These criticisms include claims that: (1) group consent is not necessary because the risks presented by genetic-variation research are minimal; (2) group consent often is impossible because it is unclear who to consult; (3) group consent will not protect populations placed at risk by genetic variation research; and (4) group consent could harm the very groups that it purports to protect. Though each of these criticisms have been advanced in connection with group consent, they have implicitly been generalized to constitute objections to other approaches to involving communities in the

review of genetic research. It is argued that two of these objections to group consent also present difficulties for other approaches to involving communities in the review process. These concerns include questions about whether community review will adequately protect at-risk populations, and worries about indirect harms resulting from community review. While these two considerations suggest problems for many forms of community review, the chapter concludes by offering suggestions on how these problems might best be addressed, thus providing a limited defense of community review.

Community review offers a promising way to address the unique sociocultural implications of research on human genetic variation. Though initial discussions of community involvement in the review of genetic research have focused on considerations relating to group consent, it is important to begin considering other methods of involving communities in the review process. Toward that end, identifying those objections that apply to broader forms of community review is essential for advancing current discussions beyond considerations of group consent alone. While there are significant practical and conceptual problems surrounding community review—problems that are identified, but not fully resolved in the following discussions—these difficulties should not lead us to categorically reject all forms of community participation in the review of genetic research.

Community review

Recent debate about how to incorporate the perspectives of socially identifiable groups in the review of genetic research has been wrought with confusion. Much of this unclarity stems from a lack of common terminology. Commentators have used a wide range of terms to present their respective positions on involving communities in the review process, including "community approval" (Reilly 1998), "group consent" (North American Regional Committee of the Human Genome Diversity Project 1997; Juengst 1998b), "community participation" (Freeman 1998), "community review" (Foster et al. 1999), and "communal discourse" (Foster, Eisenbraun, and Carter 1997/98). Unfortunately, without common terminology these individual discussions fail to fully engage each other.

In response to this difficulty, the term *community review*[1] will be used as a general category describing various approaches to involving socially identifiable groups in the review of genetic research.[2] Hence, community review includes community approval, group consent, communal discourse, and other methods of consulting with communities about the potential implications of genetic research. Moreover, community review involves the active participation of community members in the evaluation of a research proposal. Asking non-members to serve as surrogates for the community—members of Institutional Review Boards, for instance—does not constitute community review.

Community review is meant to supplement other human subjects protections and can be incorporated into existing review mechanisms. Institutional Review Boards (IRBs), for example, could require community review for research that examines genetic differences between populations. IRBs could then consider the findings of these reviews in their evaluation of research proposals. Similarly, institutions awarding research grants could require that investigators actively involve community members in the design of research protocols and make the receipt of research monies contingent upon the verification of such collaborations.

Different forms of community review all share in common the goal of incorporating population-specific perspectives in the review of research that could potentially harm socially identifiable groups. A primary objective of community review is to identify, and minimize, research-related risks to participants, communities, and others who share a common social identity. Genetic research can present unique, population-specific, risks to participating communities (Foster et al. 1999). The involvement of community members often is essential for identifying such sociocultural risks, and for developing strategies that reduce the likelihood of harms to collectives (Foster, Bersten, and Carter 1998; Foster, Eisenbraun, and Carter 1997/98; Freeman 1998; North American Regional Committee of the Human Genome Diversity Project 1997).

In addition to identifying and minimizing research-related risks, community review serves several other goals (Foster et al. 1999; Greely 1997;

North American Regional Committee of the Human Genome Diversity Project 1997). Community review helps to inform researchers and participating communities about shared areas of interest and concern. Involving communities in the review process also shows respect for the social and cultural structures in place within those communities. Moreover, direct person-to-person exchanges can help to establish trust between researchers and study populations, thereby promoting genuine partnerships between the two groups.

In addition to these benefits, community review can help protect individual research participants by assisting them in assessing the risks and benefits of their participation in a research study. In deciding whether to participate in research, individuals often find it desirable to know how others may be affected by the research. Without community review, individual participants must struggle to make these assessments on their own. Thus, community review can help individuals to make more informed decisions about their participation in research.

Community review can take many forms (Foster et al. 1999). What distinguishes the various types of community review is the methodology each employs to achieve the goals described above. As a general framework, consider the following possibilities, each of which constitutes a type of community review. These possibilities are listed in order of increasing community involvement in the review process.

Community Dialogue. This form of review includes both formal and informal discussion of genetic research and its implications for a socially identifiable group. These discussions may be initiated by researchers or arise independently within a community. In either case, the goal of community dialogue is to identify the collective risks and benefits of a research proposal or a type of genetic research. Community dialogue is meant to identify collective concerns, and where possible, to consider ways of minimizing research-related risks, but does not provide a comprehensive review of the research in question.

Community Consultation. This type of review is more structured. Community consultation documents and records the concerns of a socially identifiable group so that others may incorporate these perspectives in their assessments of the research. How these perspectives are documented may vary, ranging from structured community forums to the creation of an independent community review panel. Unlike community dialogue, community consultation is meant to provide a comprehensive review of the research.

Formal Community Approval (Disapproval). An even more structured type of community review is the negotiation of a formal or contractual agreement between researchers and a community. This arrangement can be thought of as roughly analogous to

obtaining informed consent from individual research participants. Entire communities could be asked to give their permission for a research study. Alternatively, a community could be told about a research proposal and be given the option of "opting out" of the study.

Community Partnership. This type of review emphasizes finding mutual areas of interest and developing partnerships between researchers and communities. These discussions take place early in the design of a research project and the community is thought of as an active collaborator in the research.

This conceptual framework is admittedly sketchy and should be thought of as an evolving classification. Moreover, the categories are not meant to be exhaustive, as other useful approaches may be possible. These general categories, however, reflect several current strategies for involving communities in the review process (American Indian Law Center 1994; Macaulay et al. 1998; Maddocks 1992; Canada Tri-Council Working Group on Ethics 1997; Weijer, Goldsand, and Emanuel 1999).

Furthermore, these types of community review should not be considered exclusive. Over the course of a research study, an individual community could be involved in several forms of review, and the type of community review employed could vary depending on the stage of the research. For example, the design and review of an initial research proposal could employ community dialogue as a way of identifying community concerns. Subsequent

consideration of these concerns could prompt researchers to seek community approval at a later stage in the research, perhaps in connection with the publication of research findings. Moreover, the various forms of community review described above are highly dependent upon each other. Community partnership, for instance, can be achieved only after extensive community dialogue.

Tailoring review to the community

The form of community review that is most appropriate for a given community, or a particular study, depends upon several factors. Formal community approval, for example, requires that there be authorities empowered to speak for the community at large (North American Regional Committee of the Human Genome Diversity Project 1997). Similarly, community consultation assumes the existence of shared communal interests and values. Culturally heterogeneous populations may not possess such shared interests, and thus may not be able to reach consensus about the most salient research-related risks. Other factors affecting the form that community review should take include: the size of the community, the extent of shared social structures, the frequency with which individual members interact with each other, the collective risks presented by the study, and the nature and scope of the proposed research.

Discussions of community review typically have focused on just one of these factors involved in determining the appropriate form of community review,

namely, the existence of cultural or political authorities who can speak on behalf of the community as a whole (North American Regional Committee of the Human Genome Diversity Project 1997; National Research Council 1997). This focus is useful in considering the possibilities for formal community approval, but is less helpful for thinking about other types of community review. In fact, relying upon cultural and political authorities to speak for the community as a whole may be dangerous, since the views of these representatives may fail reflect the diversity of perspectives that exist in the larger community. Keeping the goals of identifying, and minimizing, research-related risks in mind, two of the above-mentioned factors suggest themselves as useful ways to determine the most appropriate form of community review: (1) the frequency of social interaction between community members, and (2) the extent of shared sociocultural beliefs and values that are distinctive to the community.

The frequency of social interaction between community members and the existence of distinctive beliefs and interests within a community are useful in this capacity because both affect the types of collective risks presented by genetic research. For example, if interactions between community members are infrequent, and their distinctive beliefs few, then genetic research is unlikely to present risks that are unique to the community's particular sociocultural structures. In such communities, the primary risks presented by genetic research are potential misuses of genetic information by others outside the community. These risks, what we might call "external" risks, include discrimination and stigmatization of community members. These external

risks, however, are not unique to any particular community. As a result, they often can be identified by individuals who are not themselves members of the community placed at risk (though these external threats may be more readily identifiable by community members themselves). Hence, where the primary risks are caused by the actions of outsiders and are not linked to distinctive interactions between community members, supplemental community review may not be necessary. However, community dialogue or consultation could assist in identifying collective research-related risks and may be useful in determining how the community views the significance of these risks.

In contrast, in communities where the frequency of social interaction is high, and where there are a number of distinctive sociocultural beliefs that help to distinguish members of the community from outsiders, genetic research can present additional collective risks. For example, these two factors can heighten the external risks of a research study because the community's cultural discreteness makes it easier for outsiders to single out members as different from others. Moreover, frequent social interactions can create a social equilibrium among community members. This equilibrium could be disrupted by genetic research. For example, a Native American community that makes use of traditional means of disease prevention (e.g. collective preventive rituals) may find those social structures called into question by research on disease susceptibility (Foster, Eisenbraun, and Carter 1997/98; Foster et al. 1999). In those circumstances, genetic research could undermine the legitimacy of traditional means of disease prevention by suggesting that non-

traditional influences play a more important role in the development of disease. Similarly, relationships between communities could be affected by research on population differences. Genetic findings could reveal that a community that views itself as historically or ancestrally related to another community is mistaken and that there are no historic relationships between the two groups (Grounds 1996).

In each of these scenarios, genetic information could be highly disruptive to existing social arrangements, quite apart from any external risks involving discrimination or stigmatization. These unique population-specific risks, what I earlier called "intra-community" risks, are unlikely to be identified, fully understood, by outsiders because they result from the disruption of interactions among community members. Thus, where the frequency of social interaction is high, and where there are a number of distinctive sociocultural beliefs and practices that help define community membership, community review is essential for identifying research-related risks (Foster, Eisenbraun, and Carter 1997/98; Foster et al. 1999).

Against this line of reasoning, it might be argued that IRBs and other review panels could be instructed to pay special attention to possible intra-community risks, including the disruption of existing community arrangements and relationships with other communities. IRBs could then take these risks into consideration in standard risk-benefit assessments of the proposed research, and supplemental community review would not be necessary.

One difficulty with this approach, however, is that outsiders may fail to identify intra-community risks. Consider, for example, the experiences of the Indian Health Service (IHS) Headquarters IRB. The IHS IRB is charged with evaluating research proposals supported by the IHS or conducted using IHS facilities (Freeman 1998). The IHS IRB currently includes twenty members who are Native American, including biomedical researchers, health professionals, and laypersons (personal communication, William L. Freeman, chairperson of the IHS IRB). Despite the inclusion of many Native American members on the IHS IRB, and a heightened sensitivity to issues that may be unique to Native populations, there have been several instances where the IHS IRB has failed to identify intra-community risks that were of concern to Native communities (Foster et al. 1999). If the IHS IRB, with its unique composition, and wide range of experiences with Native communities, can fail to identify such intra-community risks, it is likely that IRBs with more traditional memberships will fare much worse in identifying the population-specific concerns of the communities with which they work. Community members themselves, however, often are well positioned to identify these potential risks. Thus, the active involvement of community members in the review of genetic research is essential for identifying intra-community risks in communities with sociocultural traditions and structures that differ from those of IRB members.

Considering both the frequency of social interaction within a community, and the extent of distinctive sociocultural beliefs, is useful in assessing the types of collective risks presented by research on human genetic variation.

These risks can then be used to determine the form of review that is most appropriate in a given community. This point has not been fully recognized, however, since discussions of community review frequently focus on group consent and do not consider other types of community involvement in the review of genetic research. (Table 6 summarizes how frequency of social interaction and degree of sociocultural distinctiveness combine to affect collective risks and thus determine the most appropriate form of community review.)

As discussions of community involvement in the review of genetic research move beyond their initial focus on considerations relating to group consent, and begin to consider other methods of involving communities in the review process, it is important to distinguish various types of review. Criticisms introduced in connection with group consent may not apply to other forms of community review. In the following sections, criticisms of group consent are examined more carefully to see to what extent they also apply to other forms of community review.

Why community review is necessary

Critics of group consent argue that supplemental protections are not necessary because there have been few, if any, incidents of discrimination or stigmatization resulting from research on human genetic variation (Reilly and Page 1998; Reilly 1998). Generalizing this concern to other types of community review, this perspective suggests that calls for increased community

participation in the review of genetic research are premature and based on "intangible (and largely undocumented) fears" (Reilly and Page 1998).

As a general criticism of community review, a problem with this position is that it fails to appreciate the various goals of community review. Community review is not concerned exclusively with protecting individuals (and socially identifable groups) from research-related harms. In addition to identifying and minimizing research-related risks, community review demonstrates respect for diverse cultural traditions, helps individuals to make more informed decisions about their participation in research, and promotes partnerships between researchers and communities. Hence, even if community review fails to provide additional protections for research participants, there may be other reasons to employ community review. In any case, however, the discussion above suggests that community review does help to protect against research-related risks, particularly intra-community risks.

The examples described in previous chapters illustrate how research on human genetic variation can present unique, population-specific, risks. Genetic research can disrupt a community's social dynamics or alter a community's understanding of its history. Some critics of community review, however, dismiss such potential harms as an inherent part of scientific research (Reilly 1998). Advocates of community review, by contrast, suggest that it is a mistake to view the risks associated with the disruption of existing social arrangements as trivial (Foster, Eisenbraun, and Carter 1997/98; Foster et al. 1999). Support for viewing the disruption of community relationships as a

significant research-related risk can be found by comparing the bioethical literature on genetic testing. That literature repeatedly stresses the idea that research participants should be told about the unique psychosocial implications of genetic information (Andrews et al. 1994; NIH Office of Protection from Research Risks 1993) and its potential to affect family relationships (Andrews 1997). Consistency suggests that the risks presented to existing *social* relationships be handled in the same manner. In fact, doing otherwise may amount to an imposition of Euro-centric values on communities who place great value on such social relationships.

It might be objected, however, that by treating potential risks to sociocultural traditions as significant enough to warrant supplemental protections, advocates of community review are implicitly saying that those traditions, and the individuals who maintain them, are in need of special assistance (Reilly 1998). Moreover, by giving special attention to the protection of local social arrangements, it may be the case that community review overstates the influence of science. Throughout its history, science has called many cultural beliefs and worldviews into question, yet many of the sociocultural traditions founded upon these beliefs continue and are able to survive these scientific assaults. Darwinian evolution, for instance, calls traditional Christian origin narratives into question, yet Christianity has endured. Hence, claiming that supplemental community review is necessary to protect non-traditional belief systems against the threats of science can be viewed as paternalistic, because the implicit claim is that these belief systems

are not resilient enough to endure scientific discoveries that oppose them (Reilly 1998).

In response to this criticism, it is important to stress that the goal of community review is not to protect non-traditional belief systems. Rather, community review is meant to identify risks that research participants and other community members view as important. If a community is concerned about how a research proposal could potentially disrupt existing social arrangements, then this is something that ought to be taken into consideration in the review of the research. However, this does not imply that these concerns should be overriding, or that they should be accepted at face value. A community may voice concerns about a research proposal that, upon closer inspection, turn out to be misguided. Similarly, a community may over-state the risks of the research. In arguing that community concerns should be taken into consideration in the review of genetic research, advocates of community review are suggesting that collective implications should be factored into risk-benefit evaluations of genetic research. In other words, community review promotes deliberation about collective risks by explicitly taking them into consideration in the review of genetic research. While these collective implications should weigh in these deliberations, they should not *outweigh* all other considerations.

Finally, in thinking about the need for community review, it should be noted that current bioethical thinking stresses the importance of preventive ethics (Parker 1994). The Ethical, Legal, and Social Implications (ELSI) Program developed in connection with the Human Genome Project, for

instance, illustrates that we are no longer willing to wait for a moral disaster to happen before we consider the social consequences of genetic research (Juengst 1991; Marshall 1996; Meslin, Thomson, and Boyer 1997). There is nothing uncommon about taking steps to reduce the likelihood of morally problematic consequences, even though few, if any, problems have actually occurred. Thus, the lack of widespread discrimination or stigmatization stemming from the study of genetic differences between populations should not persuade us that community review is unnecessary.

Delimiting communities and other practical considerations

A second set of objections to group consent appeals to practical difficulties surrounding the identification of community members (Juengst 1998a; Juengst 1998b; National Research Council 1997; Reilly and Page 1998; Reilly 1998). Critics maintain that group consent requires a clear understanding of what constitutes a community, and a way of determining who is empowered to speak for the group as a whole (Juengst 1998b; Reilly 1998). Even with unlimited time and resources, these critics argue that in most circumstances it will be difficult to determine the relevant group to consult and who has the authority to speak for that group. Extending this criticism to community review more generally, this perspective suggests that other types of community participation are problematic because they also depend upon defining the relevant community to consult and the relevant spokespersons

within that community. Hence, other forms of community review also may be impossible to carry out.

Delimiting communities. Suppose, for instance, that someone has identified an allele associated with a rare form of cancer and that researchers are interested in determining whether African-Americans are more likely than the general population to possess this genetic variant. If one wanted to consult "the African-American community" about how it views this research proposal, one would have to say who is and who is not a member of that community. Some individuals may be socially identified as African American, but not consider themselves to be members of "the African-American community". Others may argue that since genetic differences transcend national lines, researchers ought to consult individuals of African descent in other parts of the world as well. Moreover, even if we could agree on who is and who is not a member of the relevant community, it is unclear how we should handle differences of opinion within this population, particularly between widely recognized leaders and spokespersons. These conceptual difficulties suggest to critics of community review that by imposing unrealistic burdens upon researchers, supplemental regulatory requirements would inevitably stop many deserving research projects from being carried out (Reilly and Page 1998; Reilly 1998).

While this criticism is correct in noting that there may be times when it is unclear how the community-review process should be adapted to a particular community or research project, these difficulties do not reduce the need for

community involvement. Compare, for example, current thinking on the assent of minors (Ondrusek et al. 1998; VanDe Veer 1981; Zinner 1995). Legally, children are not empowered to offer their consent for a medical procedure. Nonetheless, there are many circumstances where children are capable of assessing how a procedure may affect their lives. In such situations, appeals to autonomy suggest a moral requirement for some type of approval, or assent, from the child (Zinner 1995). The exact form this approval takes is highly dependent upon the procedures involved, the potential risks to the child, the child's level of development, and many other factors (Ondrusek et al. 1998). There may be circumstances where it is unclear whether the child's assent is necessary at all. Despite these conceptual difficulties, however, the moral arguments in support of seeking assent from children have led many to advocate the process, even though there are many problematic areas of application.

The conceptual difficulties surrounding the assent of minors closely parallel the conceptual problems noted in connection with community review. In each case, there are problematic areas of application and uncertainty about the limits of the process. Nonetheless, in the same way that the moral imperatives supporting the assent of children are not undermined by problematic areas of application, so too with community review. Appeals to beneficence, for instance, can be used to support the goals of identifying and minimizing research-related risks to communities. Similarly, respect for diverse sociocultural traditions supports the need for community review.

Though there may be problematic areas of application, these difficulties alone do not invalidate or undermine these moral arguments in support of community review. Instead, what these concerns show is that additional effort should be spent trying to overcome problems with implementing community review.

Furthermore, the comparison with the assent of minors is instructive, because over time many of the conceptual difficulties in this area have become manageable. Institutional Review Boards asked to consider whether a child's assent is necessary in particular studies, for example, have been able to reach consensus and general professional standards have emerged (45 CFR 46). In the same way that the conceptual issues presented by the assent of minors appeared intractable before they were contextualized to particular circumstances, perhaps the challenges facing community review also will be more manageable when they are not addressed in the abstract.

Other practical considerations. Another common complaint against community review is that it is too costly and too difficult to implement as a matter of regulatory policy. Such criticisms are misguided, however, and often are the result of equating community review with formal community approval (Reilly and Page 1998). That form of review is demanding, but is not applicable in all situations. Advocates of community review stress that the form of review must be tailored to the unique circumstances of the communities involved (Foster et al. 1999). In large heterogeneous communities, for example, community discourse at local recruiting sites may be an appropriate way to incorporate community perspectives in the review process without imposing

excessive obligations upon researchers. Once community review is no longer thought of exclusively as formal approval, a number of interesting, practically manageable options are possible.

Furthermore, concerns about the costs of community review consider only the short-term costs of involving communities in the review of genetic research. The long-term success of genetic research, however, depends on the continued confidence and support of the public. Community review can play an important role in maintaining public confidence in genetic research by reassuring laypersons that scientific practices and priorities are determined, at least in part, by local communities. Hence, the short-term costs of implementing community review are likely to be outweighed by the long-term benefits of such a policy.

Will community review protect at-risk populations?

Critics of group consent also question whether supplemental protections will benefit socially identifiable populations placed at risk by research on genetic differences (Juengst 1998a; Juengst 1998b; Reilly 1998). These critics cite two factors that combine to undermine the protections provided by group consent. First, there are difficulties resulting from the fact that individuals are members of multiple communities, many of which are nested within each other (Juengst 1998a; Juengst 1998b). Second, there are problems caused because community membership often is defined externally, resulting in communities that are widely dispersed (Juengst 1998b; Reilly

1998). In widely dispersed populations, individuals may be viewed as members of the same community, though they rarely interact with each other socially. How these two factors combine to undermine the effectiveness of community review is discussed below.

The nesting of communities. A community of individuals may view themselves, and may be viewed by others, as part of one or more larger communities. For example, individuals who consider themselves Mohawk may do so because they reside in a discrete community that, because of shared sociocultural traditions and historical beliefs, considers itself a Mohawk community. In the United States and Canada, many Mohawk communities have distinct local identities. Moreover, where several of these individual Mohawk communities are located on a single reservation, they can be viewed together as constituting a larger, politically-defined community as well. Collectively, several of these reservation-based communities can themselves be thought of as defining a common Mohawk national community. Furthermore, the Mohawk nation is itself a part of the League of Iroquois, a political and religious organization comprised of six culturally related Native America communities. In addition, at a broader level of inclusiveness, Mohawk communities are themselves part of the Native American population in general as represented, for instance, by the National Congress of American Indians, a political advocacy organization.

Critics allege that the nesting of communities compromises the protections provided by group consent (Juengst 1998a; Juengst 1998b).

Seeking group consent at the level of discrete local communities may provide little or no protection for communities at broader levels of inclusiveness. Similarly, consulting larger communities may fail to identify the unique cultural concerns of local communities. Generalizing these concerns, the nesting of communities suggests similar problems for other forms of community review, since the risks perceived by local communities may differ substantially from those expressed by communities at broader levels of inclusiveness.

In response to these concerns, it is important to stress that discussing research proposals with participating communities at the level of local recruitment sites can help to identify population-specific concerns and thus provides a level of protection to those specific local communities that choose to participate. Hence, the value of community review at local recruitment sites should not be overlooked. In addition, these local reviews may help identify concerns that exist at broader levels of inclusiveness—risks that might not be identified otherwise.

The objection raised above thus can be reduced to the question of how we should handle situations where the collective implications of the research differ considerably depending on the level of inclusiveness one is interested in. In such situations, community review should take place in more than one context. For example, a particular Mohawk community may be involved in reviewing a research proposal, but there may be additional issues about how the research may affect Native Americans more generally. If these issues are sufficiently different from those facing the individual tribe, then a supplemental

review at the more general level is warranted. If the goal of identifying and minimizing research-related risks is kept in mind, however, the problems presented by the nesting of communities can be addressed through multiple community reviews. This would only be called for in situations where the collective risks of the research are sufficiently different between communities (or between different degrees of inclusiveness within nested communities). This may be the case, for instance, when there are possible conflicts of interest between communities (or between nested communities).

Nonetheless, multiple levels of community review present additional difficulties. For example, it is unclear how to handle situations where a community located at one level of review "vetoes" a research proposal (Juengst 1998b; National Research Council 1997). Does a veto by a community at a higher level of inclusiveness preclude researchers from seeking permission in the constituent communities comprising that larger community (e.g. should a veto issued by the National Congress of American Indians preclude an individual Mohawk tribe from participating)? Are there circumstances where local communities should be allowed to veto research on populations defined at broader levels of inclusiveness (e.g. should one Mohawk tribe be able to veto research on speakers of Iroquois languages)? Are researchers obligated to share the fact that one community has vetoed the research with other communities who may be asked to participate? These questions, and others, though unlikely to present themselves regularly, should receive further attention. They can only be resolved, however, with additional empirical

information on how individuals perceive their respective memberships in, and obligations to, communities that are nested within each other.

Externally defined communities. A related objection to group consent, one that also can be extended to other forms of community review, notes how features of community organization can undermine the effectiveness of community involvement in the review process. Community membership often is defined externally. Individuals of the same skin color, for instance, though very heterogeneous in their individual beliefs, may be considered members of a single community. Similarly, individuals who are speakers of Iroquois languages may be viewed as members of a single community, though they may share very few distinctive sociocultural beliefs in common. Moreover, members of externally defined communities may have limited social interactions with each other. Thus, individual members of such communities may rarely discuss issues of common concern.

It has been argued that these two features of externally defined communities—the dispersion of individual members and the lack of frequent social interactions between members—combine to limit the effectiveness of community review (Juengst 1998b). These features allow researchers to seek out particularly compliant individuals and subgroups within larger communities. For example, researchers interested in studying Iroquois speakers could recruit participants exclusively from among individuals who no longer reside on tribal lands. Similarly, researchers could approach only those

communities that have a reputation for being especially compliant with scientists.

Such morally problematic recruitment strategies, or "forum shopping" (Reilly 1998), could be reinforced by policies requiring investigators to seek supplemental community review for population-specific genetic research (Juengst 1998b; National Research Council 1997), particularly if these requirements are perceived by researchers as unnecessarily burdensome. As a result, some individuals and communities placed at risk by research on genetic differences between populations will not be consulted and their concerns may not be heard. These recruitment practices also could reinforce public skepticism about genetic research and its benefits for socially identifiable groups, thereby decreasing the participation of some communities. This in turn could translate into fewer benefits for socially identifiable populations and under-served communities.

In assessing this criticism of community review, it is important to note that "forum shopping" and other problematic recruitment practices already take place. There is anecdotal evidence, as discussed in chapter five for instance, that to avoid scrutiny by tribal IRBs researchers often recruit Native American participants from biomedical facilities that are not located on tribal lands (and do not receive support from the Indian Health Service). Similarly, some Native American tribes are asked to participate in biomedical research quite regularly, while others are rarely asked. A plausible explanation of these recurring

requests is that these tribes are viewed as particularly compliant with researchers.

For the objection above to be persuasive, critics of community review must show that supplemental community-based reviews will *increase* these problematic recruitment practices. However, this is not obviously the case, and thus critics of community review need to provide evidence for this claim. This requires better information on current recruitment practices. While we should be mindful of the possibility that community review could expand the current problem, the lack of empirical data on this issue suggests that it is too early to reject community review on these grounds alone. For example, one place where additional empirical information is needed is with regard to why researchers may be returning to some communities more frequently than others. The explanation suggested above is that these communities are easier to work with than others. Another explanation is that over time communities that have participated in research have become more aware of the issues and concerns that present themselves. In other words, these communities are better informed and capable of making more reflective decisions about how the research may and may not affect them.

Lastly, it is important to note that these two challenges to the effectiveness of community review—concerns about the nesting of communities and concerns about inappropriate recruitment strategies resulting from the dispersion of communities—both address only one function of community review. As noted above, community review is not just about

providing additional protections against research-related risks. Community review may be useful in achieving other goals quite apart from its role in providing supplemental protections.

Could community review harm at-risk populations?

A final concern voiced in connection with group consent relates to the extent to which supplemental community-based reviews may indirectly cause harm to the very communities they purport to protect. Critics contend that implementing community review will harm socially identifiable groups by reifying race, ethnicity, and other socially constructed categories (Juengst 1998a; Juengst 1998b; Reilly and Page 1998). The claim is that community review will reinforce the idea that biological differences underlie social differences between communities. This reductionist stance toward community membership could detract from the sociocultural uniqueness of the community. Worse still, the focus on genetic differences as defining of community membership may give discriminatory policies the backing of science, thereby contributing to a new "scientific racism" (Juengst 1998b). Critics conclude that the harms indirectly resulting from community review are far more troublesome than those that the review process is meant to address.

In response to this objection, one might argue that the harms associated with genetic reductionism are not the consequence of community review, but the consequence of researchers choosing to study genetic features of socially defined groups. From this perspective, it is not community review

per se that produces this reductionist attitude, but the design of the research and the use of social categories that is the problem. While critics of community review could counter that supplemental community-based review adds to the problem by failing to take a more proactive stance against the idea that social categories correspond to biological categories, it is clearly the research itself that is the principal cause of these moral concerns.

Moreover, if concerns about the reification of social categories are sufficiently troublesome, then perhaps community review can be used to prevent some such research from being conducted (or suggest ways of modifying research designs to avoid problems associated with the reification of social categories). As long as social categories are used to identify and recruit research participants, however, genetic research presents collective risks to these socially defined groups. Community review offers a response to this problem.

Furthermore, even accepting the claim that community review may contribute to the reification of social categories, these indirect harms may not be sufficient to warrant a rejection of community review. If, for instance, the benefits of community review are substantial, then these benefits may outweigh potential harms. In this regard, it is useful to compare arguments that have been offered against preferential treatment programs and their use of racial classifications. One criticism of preferential treatment programs is that they may contribute to the perception that individuals of certain races are in need of special assistance, perhaps owing to inherent deficiencies (Steele

1990; Thomas and Court 1995). In other words, the use of race-based classificatory schemes in preferential treatment programs may contribute to increased racism and thus may be criticized as self-defeating. However, the existing threats presented by institutionalized racism are viewed by many as sufficiently troublesome to justify preferential treatment programs, despite of their potential to foster more subtle, indirect types of racism in the future (West 1993).

Similarly, assuming community review may indirectly contribute to problematic attitudes toward race, perhaps the decision to employ community review should (in some cases) be viewed as necessary. The benefits of community review—including the identification of external and intra-community risks to existing sociocultural traditions, as well as its expression of respect for socially identifiable communities—may be viewed as significant enough to justify community review, despite its problems. In short, the analogy with preferential treatment programs suggests that simply identifying indirect harms is insufficient to justify an outright dismissal of community review. These possible harms must be balanced against the benefits that might result.

In addition to these considerations, a larger issue raised by this objection to community review is whether social categories should be used in connection with research at all. The use of race as a biomedical variable has been subject to much criticism because frequently race is implicitly assumed to be a biological, not a social, category (Gamble and Blustein 1994; LaVeist 1996; Osborne and Feit 1992). A recent article in the *Journal of the American*

Medical Association presents this concern very nicely. In that article, the authors claim that (Osborne and Feit 1992, p. 275),

> When race is used as a variable in research, there is a tendency to assume that the results obtained are a manifestation of the biology of racial differences; race as a variable implies that a genetic reason may explain differences in incidence, severity, or outcome of medical conditions. Researchers, without saying so, lead readers to assume that certain racial groups have a special predisposition, risk, or susceptibility to the illnesses studied. Since this presupposition is seldom warranted, this kind of comparison may be taken to represent a subtle form of racism.

If racial classifications rarely correspond to biological categories, then perhaps we would do better to avoid racial categories in biomedical research altogether (Juengst 1998a; Juengst 1998b), or at least be clear when race is being used as a surrogate for socioeconomic status (Keil et al. 1992).

A problem with this approach, however, is that the manner in which research results are presented often affects the impact of the research. Compare, for example, the following two announcements of research findings:

> A1. Biomedical researchers have identified a mutation in the X gene. This mutation appears to markedly increase an individual's sensitivity to Y exposures, thereby increasing their risk of disease Z. Researchers are recommending that carriers of this mutation take special care to avoid Y exposures.

A2. Biomedical researchers have identified a mutation in the X gene. This mutation appears to markedly increase an individual's sensitivity to Y exposures, thereby increasing their risk of disease Z. *Since these X mutations are found in approximately 75% of all individuals of African descent, researchers are recommending that African Americans take special care to avoid Y exposures.*

Clearly, presenting these research findings in the second way will have a much broader effect on public health. Conveying the information in this manner, while it opens the door for difficulties associated with discrimination, stigmatization, and even forms of racism, allows biomedical findings to reach many more individuals.

People often think of themselves in terms of their membership in various social groups. If biomedical researchers want to convey their findings in ways that have broad implications for public health, then biomedical results have to be presented in a format that is easy to understand. Thus, using social categories like race in biomedical research may be essential for furthering the goal of improved public health.

The general point, however, is not to provide a comprehensive defense of the use of racial classifications in biomedical research. Rather, it is to show that concerns about racism, and other problems associated with the reification of social categories, must be balanced against the possible benefits of using social categories in biomedical research. This is an issue for scientific research in general, however, and is not unique to community review *per se*.

Moreover, the role of educational efforts designed to counter reductionist attitudes toward race and ethnicity have not been fully explored. Research is needed to better understand how best to convey to laypersons the limited biological significance of race and ethnicity. Until more discussion has taken place, however, it is premature to reject community review based solely upon its potential to reify social categories.

Conclusion

Proposals for community review have been met with much criticism. Many of these objections focus on group consent and have only limited applicability for other types of community review. Other criticisms, however, though initially presented in connection with group consent, present fundamental difficulties for other forms of community review. These challenges include: (1) determining the extent to which community review will adequately protect communities placed at risk by research on genetic differences between populations, and (2) assessing whether community review itself may present risks for socially identifiable groups by altering views of race and ethnicity. These difficulties, however, are not unmanageable.

Initial discussions of community review have focused on group consent and the problems surrounding this approach to involving communities in the review of genetic research. If community review is not thought of exclusively as a formal approval process, however, it becomes much more practicable to carry out. Moreover, the specific form that community review should take

depends upon a number of factors, including the nature of the collective risks presented by the research, the relative sociocultural homogeneity of the population, the frequency of social interaction between members, the presence or absence of recognized decision-making authorities, and the scope of the research. Keeping these points in mind opens up a wide range of possibilities with respect to the form that community review may take.

Research on genetic differences between populations can present a number of risks for identifiable social groups. Community-based reviews of such research can provide some protection against collective research-related risks. Though this approach is not without its problems, it is far too early in the discussion to accept broad rejections of community review. By distinguishing general criticisms of community review from criticisms that are specific to group consent alone, current discussions of community review can begin to consider the difficult issues that remain unresolved. Thus, my attempts to respond to several of these criticisms should not be viewed as definitive solutions to these problems, but as contributions to an on-going discussion. I believe these issues should be focal points in future discussions of community review.

Table 6. The appropriate form of community review is dependent upon several factors, including: (1) the frequency of social interaction among community members, and (2) the extent to which community members share distinctive interests and sociocultural values. Relating these two features of communities provides a general schema for understanding collective research-related risks and determining the form of community review that is most appropriate for a given community.

Table 6. The collective risks presented by genetic research help determine the most appropriate form of community review

	Limited, Unstructured Social Interactions Between Community Members	Frequent, More Structured Social Interactions Between Community Members
Fewer Distinctive Beliefs, Interests and Practices Defining Community Membership (i.e. Individual Members are Less Readily Identifiable as Different)	General ethnic, racial, or national populations, e.g. Ashkenazi Jews, Native Americans, Puerto Ricans The primary risks of population-specific research are external risks, including discrimination and stigmatization; limited social interactions make intra-community risks unlikely Community discourse can help to identify external risks and shared areas of concern; where experienced reviewers are sensitive to external risks, community review may not be required (although supplemental community review may be helpful in assessing how the community views the magnitude of these potential research-related risks)	Culturally heterogeneous, but localized, communities, e.g. several discrete Native American tribes residing on a single reservation, residents of a local neighborhood or town The primary risks involve the disruption of existing social arrangements within the community; the lack of shared sociocultural beliefs and interests may make it difficult to achieve consensus regarding research-related risks The localization of these communities makes community discourse, consultation, and partnership possible; community participation can help to identify risks involving the disruption of existing social arrangements
More Distinctive Beliefs, Interests and Practices Defining Community Membership (i.e. Individual Members are More Readily Identifiable as Different)	Communities possessing a high degree of cultural homogeneity, but whose members are geographically, socially, politically, or linguistically distanced from each other, e.g. the Amish, the Iroquois, the Hmong Limited social interactions make intra-community risks unlikely; the primary risks are external risks Both community discourse and community consultation are possible; shared sociocultural beliefs may make it easier to reach consensus about community concerns; without social units empowered to give approval for the community as a whole, formal community approval is impossible	Highly localized communities with frequent social interactions between members and a shared set of defining communal beliefs, interests and practices, e.g. a single highly localized Mohawk tribe, a single Amish community, External research-related risks are heightened by the localization of these communities; local social arrangements may make it difficult for outsiders to identify intra-community risks Formal community approval and community partnership are both possible; community review can help to identify external risks and is essential for identifying potential intra-community harms

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Notes to chapter seven

1. The term "review" is used here because it has both evaluative and non-evaluative connotations. Hence, *community review* can be understood to include formal evaluations (e.g. group consent), as well as other methods of identifying collective research-related risks that stop short of comprehensive evaluations (e.g. community consultation).

2. The dissertation considers the role of community review in connection with research that aims to identify genetic differences between populations. This includes many types of disease-susceptibility research, as well as anthropologic research that uses genetic differences as a way of tracking the migration of populations. Nonetheless, much of what is said about community review and its role in identifying collective research-related risks also applies to other types of research. Many types of population-specific behavioral research, sociological research, and research on stigmatizing conditions implicate many of the same considerations discussed here in connection with genetic research. Arguably, whenever researchers attempt to make scientific claims about socially identifiable groups, the research presents collective risks to those groups.

CONCLUSION

This dissertation has examined how the study of sensitivity genes complicates concerns about the moral and social implications of genetic research. While commentators on genetic research have concentrated on the ethical issues presented by the study of rare, highly predictive disease genes, little attention has been given to the study of sensitivity genes. Thus, the dissertation fills an important gap in contemporary discussions of the moral and social implications of genetic research by identifying, and clarifying, how the study of sensitivity genes requires us to reexamine familiar concerns about the broader social implications of genetic research.

For example, it was argued that studies of sensitivity genes exacerbate concerns about deterministic views of genetic contributions to disease. Discoveries of particular sensitivity alleles increase the likelihood of over-stating genetic influences on disease. In response, it was argued that we can resist this tendency to "geneticize" disease by clarifying the concept of genetic causation and demonstrating how disease classifications inevitably reflect subjective interests. Moreover, once it is recognized that practical considerations can and should be used to determine whether diseases ought be categorized as "genetic" or "environmental", a strong case can be made that the increasing geneticization of disease presents a number of moral problems and is something that we should try to counter.

Another area where the study of genetic hypersensitivities to environmental exposures complicates familiar questions in research ethics is in the process of obtaining informed consent from research participants. The moral perspective that has emerged from the study of disease genes stresses the need to obtain highly specific permissions from participants in genetic research. Nonetheless, while this paradigm is currently gaining support from a number of professional research societies, it should not be extended to the study of sensitivity alleles, since these alleles are much less predictive of future disease. As a result, collecting information on sensitivity alleles presents fewer risks for participants.

Still another place where philosophical analysis better informs contemporary moral debate is in clarifying the risks presented by research on sensitivity genes. Research on genetic hypersensitivities to environmental exposures is revealing that some populations are particularly susceptible to certain adverse exposures. Consequently, this research heightens concerns about potential research-related risks to socially identifiable groups. By examining the debate between Native American advocacy organizations and genetic researchers, the discussions above illustrate how more nuanced conceptual distinctions are needed. For example, it was argued that in assessing the collective risks presented by studies of genetic differences between populations, it is important to distinguish between external and intra-community risks to socially identifiable groups. These conceptual distinctions not only help to better understand the sources of moral disagreement in discussions

of research involving Native American populations, they also help in identifying potential research-related risks for socially identifiable groups.

Finally, the potential research-related risks presented by the study of genetic differences between populations should prompt us to reconsider the adequacy of existing human subjects protections. It was argued above that many types of research on genetic differences between populations could benefit from supplemental community-based reviews of research proposals. These community reviews help to identify, and minimize, research-related risks—particularly intra-community risks—that otherwise could go unnoticed by standard review practices. Moreover, while current debate on the need for supplemental community review has focused on obtaining the permission of participating communities—that is, on obtaining "group consent"—it was argued that we should concentrate on more practicably workable methods of incorporating community-specific concerns in the review process. As shown above, clarifying these other approaches and their limits is essential for balancing diverse perspectives on research, particularly when the research involves culturally pluralistic populations.

Over the past three decades, philosophers and ethicists have carefully followed advances in molecular genetics and thoughtfully examined the broader social implications of genetic research. As biomedical researchers increasingly focus on the study of genetic hypersensitivities to environmental exposures, commentators on genetic research should keep pace, and shift their attention to this new area of research as well. In this regard, I hope this dissertation has

shown why it is important to distinguish the moral and social issues presented by research on rare, highly predictive disease genes from the issues presented by studies of common sensitivity genes.

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