

Informed Consent for Genetic Research

Aaron Hamvas, MD; Katherine K. Madden, RN; Lawrence M. Nogee, MD; Michelle A. Trusgnich, BS; Daniel J. Wegner, BS; Hillary B. Heins, BS; F. Sessions Cole, MD

Background: Rapid technological advances in genetic research and public concern about genetic discrimination have led to anticipatory safeguards in the informed consent process in the absence of legal examples of proven discrimination. Despite federal and state regulations to restrict access to personal health information, including genetic information, institutional review boards have required the addition of language to informed consent documents that warns about the risks of discrimination with participation in genetic research.

Objective: To determine the reasons that families refused consent for their infant's participation in a study evaluating a genetic cause of respiratory distress syndrome.

Design: Survey conducted between February 1, 2002, and March 31, 2003.

Setting: Academic, tertiary free-standing children's hospital.

Participants: A convenience sample of 465 families were approached for consent. The 135 families who refused consent were surveyed.

Main Outcome Measures: Reasons for refusal.

Results: Of the nonconsenting families, 79% spontaneously and specifically identified institutionally required language in our consent form concerning the risk of denial of access to health insurance and employment as the primary reason for refusal; 97% indicated that their fears resulted directly from language in our consent form. Only 20% of families who refused consent cited inadequate time to consider the study.

Conclusions: The institutionally required description of risk of genetic discrimination due solely to participation in genetic research was the primary reason for refusal to consent in this cohort. Information about federally and institutionally mandated protections for confidentiality of participants in genetic research should be included in the informed consent document to balance the description of hypothetical risks and more accurately inform subjects.

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From the Edward Mallinckrodt Department of Pediatrics, Division of Newborn Medicine, Washington University School of Medicine and St Louis Children's Hospital, St Louis, Mo (Drs Hamvas and Cole, Mss Madden, Trusgnich, and Heins, and Mr Wegner); and the Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Md (Dr Nogee).

INFORMED CONSENT PROTECTS individual autonomy by legally requiring competent subjects or, if incompetent, surrogates to authorize involvement in research or clinical care without coercion and with full disclosure.^{1,2} The history of medicine provides no examples of requirements for informed consent for research or clinical care prior to the mid 20th century.³ In the United States, beginning in 1914, a series of landmark legal decisions established the right for a competent individual to be the sole decision maker about "what shall be done with his own body"^{2(pS154)} (*Schloendorff v Society of New York Hospitals*, 105 NE 92 [NY 1914]). Internationally, prompted by unethical human experimentation by German physicians during World War II, personal autonomy, freedom from coercion, freedom to withdraw, and full

disclosure of information were formalized as necessary components in research consent in 1947 in the Nuremberg Code and subsequently reaffirmed in the Declaration of Helsinki. In 1979 in the United States, reacting to specific examples of subject abuse in the interest of research, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued the Belmont Report, the current conceptual basis for informed consent for research subjects.⁴ The requirements for protection of research subjects through the informed consent process described in that report were codified into federal policy in the Code of Federal Regulations (45 CFR, Part 46 [1983, 1991]) and apply to all federally funded research.

In response to increasing public concern about the privacy of medical infor-

Table 1. Characteristics of Infants of Families Approached for Consent*

	Consented (n = 330)	Declined (n = 135)	P Value
Birth weight, mean \pm SD, kg	2.0 \pm 1.1	2.7 \pm 1.0	<.001
Gestational age, mean \pm SD, wk	32 \pm 5	36 \pm 5	<.001
Sex			.60
M	171 (52)	74 (55)	
F	159 (48)	61 (45)	
Race			
African American	113 (34)	38 (28)	.20
White	202 (61)	95 (70)	
Hispanic	6 (2)	1 (1)	
Other	9 (3)	1 (1)	
Age at recruitment, mean \pm SD, d	13 \pm 30	45 \pm 52	<.001
Recruiting location			
NICU	250 (76)	67 (50)	<.001
Outpatient surgery suite	80 (24)	68 (50)	

Abbreviation: NICU, neonatal intensive care unit.

*Data are presented as number (percentage) unless otherwise indicated.

mation but without specific examples of genetic discrimination or research abuse, which historically initiated similar legislation, the Clinton Health Security Act was passed in 1993 and included a separate section entitled "Privacy of Information."⁵ This section outlines the basis for the national standards for medical record privacy that were recently implemented in the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The HIPAA regulations apply to all medical research, are enforced by the Office for Civil Rights and the Secretary of Health and Human Services, and may result in either civil or criminal penalties. In contrast to federal and state legislation concerning informed consent, which responded to specific legal cases or egregious abuses of research subjects from the 1940s through the 1970s, concerns about unregulated access to an individual's genetic information that might lead to discrimination in access to employment or insurance, which prompted HIPAA, were largely hypothetical. Respected physician-scientists who sought to minimize insurance and employment stigmatization associated with genetic testing were among those who voiced these concerns.^{6,7} In parallel attempts to safeguard individual autonomy, 41 states have enacted legal protections for genetic discrimination.⁸

Few legal examples of discrimination based on new genetic technology have subsequently been reported. In 2001, using the protections outlined in the Americans for Disabilities Act, the US Equal Employment Opportunity Commission (EEOC) forbid Burlington Northern Sante Fe Railway from testing employees for a deletion of chromosome 17 after they had submitted disability claims for carpal tunnel syndrome (*EEOC v Burlington Northern Sante Fe Railway*).⁹ In *Chevron USA Inc v Echazabal* (122 SCt 2045 [2002]), the US Supreme Court, also citing regulations in the Americans for Disabilities Act, upheld an employer's right to make disability-related employment decisions based on risks to an employee's own health, although the control of access to personal health information remained with the employee.¹⁰ Despite the scarcity of documented threats,

enactment of HIPAA, and state-specific legal protection, the public has continued to voice what Wertz has called "genetic dread."^{11(p 496),12} A recent report by the Institute of Medicine (Washington, DC) concerning protection of human subjects did not discuss genetic discrimination as a risk to subjects and cited the death of a participant in a gene replacement therapy study as its principal example of the risk of genetic research.¹³ The Washington University (St Louis, Mo) Human Studies Committee has attempted to react to the public's concern about genetic discrimination by developing a separate informed consent document for participation in genetic research that requires acknowledgment of risks of genetic discrimination in access to employment and insurance similar to those described in HIPAA. Other institutional review boards have taken a similar approach.¹⁴⁻¹⁸ The availability of data concerning the effect of recently required institutional language on informed consent for genetic research is limited.¹⁹⁻²¹

Genetic research in children is further complicated by surrogate parental decision making based not only on evaluation of risks and benefits for the child but also on the implications of participation for the entire family. We are studying the contribution of genetic variation in the surfactant protein B gene to the risk of respiratory distress syndrome in infants. This study has permitted us to evaluate parents' reasons for refusal to consent. We report that potential loss of employment or insurance due to participation in genetic research, as described in required language in the informed consent document, is the primary reason for refusal to consent for genetic research.

METHODS

SUBJECT POPULATION

Between February 1, 2002, and March 31, 2003, 465 consecutively eligible families were approached for consent for their infants to participate in a study of genetic risk of respiratory distress syndrome in a neonatal intensive care unit (NICU) and outpatient surgery suite (**Table 1**).

CONSENT PROCESS

Before approaching families, we obtained assent from the attending neonatologist, surgeon, and/or anesthesiologist and consulted the nursing staff. Families in the NICU were approached twice during a 24-hour period before a decision to participate was determined. Families in the outpatient surgery suite were approached shortly after arrival and just after their infant went to the operating room. Typically, 1 of us (K.K.M.) first explained the study, which included a single blood sample and airway aspirate obtained at the same time as clinically indicated blood sampling and airway suctioning. Furthermore, we described our legal and ethical obligations and procedures to ensure confidentiality as well as the risks of participation, which included implications for insurability or employment if their involvement in genetic research became known outside the investigative team. The family was also informed that involvement or refusal would not affect the care of their infant, would not offer any direct benefit to their infant, and was completely optional and anonymous. The family was then left with the consent form to review and given an opportunity for private discussion. At a second meeting within 24 hours of initial contact, the same member of the study team answered ques-

tions and sought consent. If the families consented to the study (330 [71%] of 465), sample procurement was coordinated with relevant health care professionals. Of the families who refused consent (135 [29%] of 465), more than half spontaneously explained their reasons for refusal without prompting. Those who did not spontaneously share this information, including those who passively declined participation by delaying a decision until the required samples could not be obtained, were asked, "Do you mind telling me the reason(s) you declined participation?" All but 2 families shared their concerns either verbally or by pointing to specific statements in the consent form. No one was prompted for a response. These responses were then placed into 4 categories (**Table 2**).

To determine if our experience could be generalized, we sought information about other institutions' consent form language by searching academic institutions whose Web sites allowed outside access to this information (n=9), through informal discussions with colleagues at other institutions (n=4), and through a query posted through IRB Forum, a Web site designed for members of research review committees (n=2) (<http://www.irbforum.org>, administered through the Children's Hospital of Philadelphia, the Joseph Stokes Jr Research Institute, and the Leonard and Madlyn Abramson Pediatric Research Center, Philadelphia, Pa). The Washington University Human Studies Committee approved the study.

DATA ANALYSIS

To compare groups of participants, χ^2 or Fisher exact tests were used for categorical variables, and *t* tests were used for continuous variables.

RESULTS

Clinical and demographic characteristics of families who were approached are described in Table 1. There were no differences in the racial or sex distributions among the families who agreed and those who declined to participate (Table 1), reflecting the ethnic composition of the patients in the St Louis Children's Hospital NICU population as a whole (data not shown). Families of infants with respiratory distress syndrome were significantly more likely to consent than families of control infants (79% vs 54%, respectively; $P < .001$) (**Table 3**). Some families actively refused consent (n=80), and some passively declined by delaying a decision until the required samples could not be obtained during routine clinical care (n=55). Among the 133 families who declined consent and shared their reasons, 25 (19%) felt that they did not have enough time to consider their involvement in the study. In explaining their reasons for declining to participate, 79% of families (105/133) specifically identified institutionally required language in the consent form regarding the risks of loss of access to health benefits or employment as their primary reason for declining (Table 2). This concern was cited equally by parents whose infants were in the NICU (62/66) and those with infants in the outpatient surgery suite (43/67). In response to the question, "What is the source of your concern?" 97% of nonconsenting families (129/133) directly indicated that the language in the consent form raised their concerns. Institutionally required statements included the following: (1) "An insurance company might consider participation in genetic research in a family study an in-

Table 2. Reasons for Declining Consent*

	NICU	Outpatient Surgery Suite	Total
Access to health insurance or employment	62	43	105 (79)
Unanticipated use of DNA	4	14	18 (13)
General invasion of privacy	0	10	10 (7)
Concern for infant's physical harm	0	0	0 (0)
Concern that infant would not be well cared for if refused by the study	0	0	0 (0)

Abbreviation: NICU, neonatal intensive care unit.

*Data are presented as number (percentage).

Table 3. Nonconsent Based on Infant Diagnosis and Location*

	Consent (n = 330)	Nonconsent (Passive/Active) (n = 135)
Total	250	67
Respiratory distress syndrome		
NICU	250	67 (39/28)
Outpatient surgery suite	0	0
Controls (total)	80	68
NICU	32	0
Outpatient surgery suite	48	68 (16/52)

Abbreviation: NICU, neonatal intensive care unit.

*Data are presented as number of participants.

dication that there is a family history of a genetic condition"; (2) "If your baby's participation in a genetic study becomes known outside of the research (for example, if your baby's participation were noted in her/his medical record), your baby (and family members) may be unable to obtain health, life, or disability insurance"; and (3) "You and/or your baby might also be refused employment or be terminated from your current employment."

The location (NICU vs outpatient surgery suite) where infants were recruited had a significant effect on the rate of consent: 81% of families recruited in the NICU (including all families of controls) consented, whereas only 48 families (41%) recruited from the outpatient surgery suite did ($P < .001$) (Table 3). Of the 25 families who felt that they did not have adequate time to consider the study, 22 were approached in the outpatient surgery suite. In an attempt to improve participation among the control subjects scheduled for outpatient surgery by increasing the time available for study consideration, 17 families were mailed packets containing the consent form as well as a cover letter that explained the study 7 days before the procedure. The cover letter included the signatures of the attending surgeon and the research team. These families were then approached, as described previously, on the morning of their infant's procedure. None of these families chose to participate.

The language in the consent forms for genetic testing obtained from our informal survey of other academic institutions was variable. All forms included the risks to insurability and employment; however,

most had a qualifying statement (eg, "There is a small chance. . . ." or "The effect on insurability or employment is unknown. . . .") immediately following the mention of these risks.

COMMENT

The social context through which an individual or family views informed consent for genetic research may be determined by many factors, including religion, family preferences, previous experience with research, insurance industry policies, interaction with the research team, and perception of risk of psychological or medical discrimination.^{13,15,22} Historically, the informed consent process has relied on formal, institutionally governed, and legally defined language requirements in the consent document to preserve individual autonomy and protect the rights of research subjects.²² Recently, institutions have struggled to develop proactive informed consent language that adequately describes the risks and benefits of participation in genetic research. This language has been developed in the context of long-term availability of individual DNA samples, rapid acquisition of new knowledge concerning genotype-phenotype correlation, and technology that increases the capacity for interrogation of an individual's genetic composition. However, it has also been constructed in the absence of specific legal precedent.^{23,24} The development of language that anticipates new knowledge has been influenced by institutional protectionism against hypothetical liability rather than preservation of individual autonomy, research subject protection, and full disclosure. The ability of this language to facilitate informed consent has recently been questioned.²⁵ Our study suggests that the threats of loss of employment and loss of insurability described in our informed consent document significantly define the social context through which families view consent for genetic research. To our knowledge, these theoretical risks are not supported by any data suggesting that genetic discrimination has ever or is likely to occur merely from participating in a genetic study.^{11,22,26,27} Because so many non-genetic influences contribute to the risk of disease and most genetic information currently available does not permit the direct assessment of risk, institutionally required alarmist statements tend to perpetuate misconceptions about the current state of genetic technology rather than promote deliberate discussion with families or patients.^{22,28} We suggest that information about federally and institutionally mandated protections for confidentiality of participants in genetic research should be included in the informed consent document to balance the description of hypothetical risks and more accurately inform subjects.

Our study has several methodological limitations. First, we did not seek to elicit opinions from families concerning all potential contributing factors to their consent decisions; we relied solely on the spontaneous identification of problems by parents. Our data may thus underestimate or exaggerate the significance of required consent form language concerning employment or insurance. Second, the performance of our study in 2 different clinical environments may have blurred impor-

tant characteristics of the informed consent process (eg, less time was available for discussion and consent document review in the outpatient surgery setting). However, families in both the NICU and outpatient surgery suite pointed to the same language as the cause of their refusal to participate. Third, although we have anecdotal reactions to the consent form language from families who did participate, we did not obtain that information systematically. We can surmise only that they had similar reactions to those who did not participate but felt that the benefits of participation outweighed the risks delineated by the language. Fourth, the considerations that parents take into account in balancing the risks and benefits of participation may be different for their children than for themselves. Finally, as our informal inquiry highlighted, the recommended language for participation in genetic studies varies among institutions. Thus, even if comparable data about rates of consent and reasons for refusal were available, it would be difficult to determine if our experience is nationally representative with respect to other institutions that may or may not have similar language. Despite these limitations, the spontaneous and specific uniformity in responses of nonconsenting families suggests that the currently required language in our informed consent document for genetic research scares rather than informs families. Among families of critically ill infants in this study, the opportunity to benefit other children appeared to outweigh the risk of genetic discrimination described in the consent form.

Although data concerning the effectiveness of HIPAA or other federal and state laws to protect against genetic discrimination are not yet available,^{15,27,29,30} our experience suggests that the institutionally required language in some informed consent documents for genetic research fails to balance the description of undocumented risk of genetic discrimination with a description of the extraordinary legislative and infrastructural safeguards in place to maintain confidentiality. These unbalanced priorities in current consent form language prompt unfounded fears and could lead to unintended consequences in the validity of genetic studies, which require sufficiently large groups of affected and unaffected subjects to avoid exaggeration or underestimation of allele frequencies due to ethnic stratification, environmental selection, or genotype-phenotype heterogeneity.³¹⁻³³

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As of March 15, 2004, the language in the Washington University consent form for participation in genetic research was modified as follows: "You and family members may be unable to get health, life, or disability insurance if the information in this study becomes known. Rarely, you may have problems getting or keeping a job. This could hap-

What This Study Adds

The ability to interrogate the human genome has raised appropriate concerns about the risks to insurability and employment resulting from a breach in confidentiality. The extent to which this risk deters people from participating in genetic research has not been evaluated. To our knowledge, this study is the first to determine that families who choose not to participate in genetic research do so in response to these unquantifiable risks. Understanding the factors that potential subjects consider in determining their participation in genetic research warrants further study and is essential to developing a balanced approach to informed consent.

pen if you talk to your doctor about your participation without asking that the information be kept out of your medical record. Having genetic information in your medical record may allow insurance providers to get this information."

Corresponding author and reprints: Aaron Hamvas, MD, Division of Newborn Medicine, St Louis Children's Hospital, One Children's Place, St Louis, MO 63110 (e-mail: Hamvas@kids.wustl.edu).

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