

## Is Genetics Research "Minimal Risk"?

by Jon F. Merz

A body of commentary has evolved in the last several years suggesting that germ-line genetics research—that is, genetic alterations capable of being passed from parents to progeny—poses more than minimal risk to identifiable human subjects. The Office for Protection from Research Risks, for example, stated in 1993 that uncertain, probabilistic genetic information "can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. . . . The fact that genetic studies are often limited to the collection of family history information and blood drawing should not, therefore, automatically classify them as 'minimal risk' studies qualifying for expedited review."<sup>1</sup> Likewise, if such studies are not "minimal risk," they do not qualify for alteration or waiver of requirements for fully informed consent (45 CFR 46.116(d)).

Several commentators have reached similar conclusions, calling for more stringent regulation of the storage of human tissues and detailed informed consent of persons whose tissues are used in research.<sup>2-5</sup> Various genetics and pathology societies have likewise weighed in, specifying that detailed informed consent should be secured prior to the use of identifiable tissues in genetics research.<sup>6-8</sup> The potential for generating information of diagnostic significance that could threaten stigmatization or discrimination warrants what has been termed an "extended informed consent."<sup>9</sup>

This body of commentary suggests that the risks of genetics research may be more than "minimal." This view was reinforced in a recent survey of subscribers to the "mcw-bioethics" and "mcw-

IRB" discussion lists maintained at the Medical College of Wisconsin.<sup>10</sup> This study of a convenience sample found that a majority of self-selected respondents (51 of 65 [74%]) believed the risk of storage of blood for use in future studies of the role of germ-line genetic mutation in causing disease is greater than "minimal." Higher risk judgments were strongly associated with respondents' concerns about subject identifiability and perceived harms that could result from use or misuse of the information generated by such studies, including stigmatization, insurer or employer discrimination, breach of confidentiality, and discovery of unwanted and uncertain information about future disease risks.

What is it about germ-line genetics research that leads many to believe it poses more than minimal risk to people? "Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45 CFR 46.102(i)). Clearly, information of a genetic nature may be generated in routine medical exams, communicated to patients, and documented in the medical record. A family history can provide quite diagnostic information from which risks having genetic causes can be inferred, and insurers historically have used such information for risk stratification. Further, the number of tests for germ-line genetic mutation being used in clinical medicine is growing rapidly as new disease-associated genes are identified. Why, then, is there special concern about genetics research?

Clinical genetic information may be distinguished from that resulting from research. Research results are much more uncertain than information produced by medical technologies that have made it into clinical care. Results

may be ambiguous or may fail to be validated, and hasty clinical use can lead to unnecessary psychological distress, possible socioeconomic harms, and unproved use of medication or surgery in an attempt to mitigate perceived risks.<sup>11</sup> This led the National Advisory Council for Human Genome Research to suggest that all genetics tests should be used solely in research protocols, because much remains unknown about the prevalence or penetrance of different mutations or about multifactorial (multigenic or environmental) causes of disease.<sup>12</sup>

Further, clinical care is predicated upon a patient-physician relationship. Patients expect that information and medical technologies will be utilized in their best interest by the physician into whose care they entrust themselves. Research, on the other hand, is performed primarily to contribute to generalizable knowledge. Of course, certain types of research have clinical characteristics, involving an intervention or procedure that holds out the possibility of direct therapeutic benefit to an individual subject. Arguably, research using human tissues also takes on a clinical aspect when individuals are identifiable,<sup>13</sup> because there will be pressure to use or communicate information of perceived clinical relevance to subjects or their physicians<sup>14</sup> (even when such use is proscribed because the lab is not CLIA approved) (42 USC 263a).

The emerging standard of care in clinical molecular genetics is to counsel patients before testing about the nature, clinical meaning, uncertainties, and likely ramifications of possible test results.<sup>11,15</sup> This permits patients to protect themselves by asserting a "right not to know" and forgoing testing, by undergoing tests anonymously to ensure the secrecy of the test results, or by only undergoing tests within a clinical study that can offer greater assurance of confidentiality. Genetic testing is thus seen as justifying an "enhanced autonomy" approach to clinical decision-making and informed consent, perhaps because the relative

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role of the physician is diminished. While genetic information may be generated in a medical examination, it is not clear that molecular testing is yet "routine," and, to the extent molecular testing is being used in clinical care, it appears that special safeguards are being adopted to enable patients to protect themselves.<sup>11,16</sup>

Thus, it is reasonable to conclude that germ-line genetics research does present more than "minimal risk" to identifiable subjects, absent special safeguards to reduce the risks. Special concerns have been raised because identifiable tissues and DNA can be retrieved and used by researchers with little or no interaction with or knowledge of individuals (or family members similarly affected by information developed in research). These individuals may not even be ill, and it is clear that no clinical relationship need exist before research is performed. Thus, tissue research threatens to undermine the enhanced protections—prior informed consent, the right not to know, and the right to absolutely refuse testing—developed in the clinic.

This analysis suggests that use of tissues in germ-line genetics research should only be performed with tissues that have been de-linked from all identifying codes or information, or that detailed informed consent should be secured from individuals about whom genetic information developed in research would apply. Potential subjects should be given detailed information about the purpose of the

research, possible risks and benefits, and the likely results and uncertainties, and they should be provided with meaningful choices about the maintenance of links with their identity and about the communication of results. Waiver or modification of informed consent, or proceeding with germ-line genetics studies with identifiable tissues under a general consent for research,<sup>8</sup> should not be permitted, and protocols involving such study should not be given expedited review.

#### ACKNOWLEDGMENTS

Support was provided by a grant from the Annenberg Public Policy Center to the Center for Bioethics at the University of Pennsylvania. Thanks are extended to Robert J. Levine and an anonymous reviewer for comments on earlier drafts of this paper.

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search projects conducted or funded by the federal government.

As the administrator of RCRC and a participant in a Phase I research project, I discovered that study subjects had no idea what an IRB was, or what role it plays in a clinical study. As a result of my experience, I developed an information sheet entitled, "The Informed Consent and the Institutional Review Board:

Their Role in Protecting Subject Rights." The IRB members were interested in hearing about my experience and reviewed the information sheet. It has since become our policy to incorporate this document along with the Subjects' Bill of Rights as part of the approved informed consent.

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#### Identifying Subjects about the IRB's Role

Although Research Consultant's Review Committee (RCRC), a central IRB, reviews only studies regulated by the FDA, the documents on the following page could be used in re-