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Genetic Privacy and the Use of Archival Patient Materials in Research

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Dramatic advancements in basic science and technology, significantly stimulated by the Human Genome Project, have led to remarkable progress in our understanding of normal and abnormal genomic structures. They have already transformed biomedical research and promise equally profoundly in coming decades to transform the practice of medicine, as well as strategies of disease prevention and health promotion. At the same time, however, these accomplishments generate powerful societal concerns about the acquisition, protection and use of information that is considered to be uniquely personal and private; may sometimes be predictive; and, if misused, can result in insurance and employment discrimination, or painful disruption of personal and familial equanimity.

If the issues surrounding genetic privacy are not challenging enough, the explosive growth of genetic knowledge is taking place concurrently with extraordinary advancements in electronic information technology, and at a time when the American health care delivery system is itself undergoing a dramatic "industrial revolution" that many fear is undermining medical professionalism. These changes, too, are having profound effects on individual and societal equanimity and have generated wide-spread concerns about a general erosion of individual privacy and the security of sensitive personal information of all kinds. These pervasive concerns become heightened with respect to *medical* information, where the privacy issues raised by all three areas of rapid change converge, and approach alarm when that information is labeled "*genetic*."

The issues of individual privacy with which society is now wrestling are difficult, and they are infused with emotion, which tends to confound dispassionate public discourse. They lie at the intersection of disease diagnosis and management, biomedical research, and public health, and they require the adjudication of important, but competing, private and public goods. Given that we are still in the dawn of both the new genetics and information ages, the parameters that we establish to guide this public policy debate may prove in the long run to be nearly as important as the initial round of legislative and regulatory solutions that come forth. For all of the questions cannot be answered now, nor even asked; and society will surely continue to revisit these matters as the power and reach of science and technology continue to expand at an ever accelerating pace.

In recent years, under the impetus of the Human Genome Project, the privacy issues have come to sharp focus on the nature of the informed consent process that should guide genetic testing and access to human tissues for research, and have received considerable attention in two different venues, one professional, the other legislative. The former is reflected in a number of studies and position papers, many sponsored by the ELSI Program, others by patient advocacy groups like the National Action Plan for



Breast Cancer. These contributions have offered a heavy dose of bioethical, legal and patient advocacy perspectives, but a remarkable deficiency of input from the broad scientific and medical communities. Throughout this period, the absence of firm scientific direction from either the NIHGR or the NIH has been noteworthy. At present, the genetic privacy issues rest largely with the National Bioethics Advisory Commission, which was charged by the President when first convened about 16 months ago with examining the problem of stored tissue samples as one of its initial tasks.

The legislative venue is represented by sundry bills that have been introduced into the Congress and state legislatures, and by laws recently enacted in many states. While some of the Congressional bills attempt to deal broadly with the privacy of *medical* information, others focus more narrowly on genetic privacy and the discriminatory misuse of *genetic* information in the health insurance markets and employment. Unfortunately, many of the genetic privacy initiatives, especially in the states, have appeared to be hasty responses to public pressure, and most bear the scars of heavy lobbying by the insurance industry. As a result, these efforts have produced a discordant legislative patchwork that has been described as a "morass of erratic law, both statutory and judicial. . . ."

In this presentation, I shall first attempt to provide some context for these discussions, next make an observation about the deliberative processes to date, and finally, offer several several specific recommendations that are intended to stimulate the dialogue and help bring a biomedical perspective, which has been sorely lacking, to the difficult task of finding the proper balance between the important competing claims of private interest and public benefit.

The history of medical progress is deeply rooted in the careful study of archival patient materials, that is, medical records and tissue samples. Our nations' hospitals, and especially the academic medical centers, collectively contain an enormous archive of human tissue samples that, together with their correlated clinical records, comprise a unique resource that records the prevalence and protean expressions of human disease over time. The samples were removed for medical reasons, under sparing consent language that usually included a proviso for research and educational uses, and were submitted to the pathology laboratory for routine diagnostic evaluation, after which portions of the specimens were permanently stored as part of the patient's medical record, in accordance with sound medical practice and legal and accreditation requirements. Although not collected for research purposes, these specimens have served as a rich source of materials for clinico-pathological investigations that have provided over the past more than 100 years, most of the vocabulary and much of the foundation of modern medicine. The tissue collections have been considered and managed (*de facto*, if not *de jure*) as a unique *public* research resource, the accessibility and use of which has immeasurably advanced medical knowledge, profoundly changed public health practices and enormously benefited all humankind. Yet, the results of the studies have historically been of little immediate consequence to individual patients (or "sources") from whom the tissues had been obtained. Accordingly, the practice and standard of informed consent for this vast body of research has been quite minimal.

What has now changed dramatically has been the introduction into practice of powerful new techniques that pathologists and other investigators can apply in the research laboratory to fixed, paraffin-embedded and even sectioned tissue specimens not only to demonstrate specific abnormalities of gene structure and expression, but often to infer whether the changes are of somatic origin or present in the source's



germline DNA and, therefore, heritable. The power of these approaches provides unique insights into the mechanisms of human disease that cannot be obtained by other means; and they offer the promise of major advancements in diagnosis, prognosis, therapy, and even prevention. At the same time, however, by their nature these results may on occasion be construed to have major predictive consequences for individual patient sources and their families. This fact has wrested the entire topic of research on human tissue samples from its historic state of repose in obscurity and thrust it sharply into the consciousness of a public already uneasy about the possible disclosure and misuse of private information, and susceptible of being roiled by anything containing the iconic words "gene" or "genetic."

The public discourse to date, as well as the products it has generated, have been disappointing in at least four major respects. **First**, I find it extraordinary, and sad, that in attempting to deal with issues that largely center on protecting the security and preventing the misuse of genetic information developed in research, so little creativity or effort has been directed at strengthening the protection of that information, while so much has been aimed at burdening its acquisition by erecting complicated new barriers to the conduct of "genetic" inquiry and encumbering the ongoing creation of the knowledge base. **Second**, the discourse has been confounded by semantic ambiguity and confusion of thought by its failure to distinguish between two quite different issues, *genetic testing*, which raises legitimate considerations of definition and appropriate informed consent, and *genetic information*, which can be obtained or inferred from a myriad of clinical and research sources, and raises concerns of security, prevention of inappropriate disclosure, and penalties for hurtful misuse.

Third, it has been too readily taken as given that *genetic information* is unique and different in kind from all other forms of private, sensitive and often predictive information that may exist in a medical record. To the contrary, I would argue, as have many others, that the distinction is fallacious and that efforts to operationalize it will inevitably fail. This becomes particularly clear when attempts are made to segregate "genetic information" from all other medical information present in a clinical record for purposes of special restriction, protection or regulation. The concept of uniqueness is problematic for another reason: it provides much of the conceptual underpinning for the proposition that patients/sources have enduring property rights in their excised tissue samples and thereby undergirds the more vexing provisions of the stringent consent protocols that have been proposed for research on those samples. And **fourth**, there has in general been far too little engagement to date with the broad community of scientists, not only molecular scientists who work with human tissue samples, but the many other health researchers, for whom archival patient records are primary research materials. Accordingly, the proposals offered come down too heavily on the side of private interest at the expense of public benefit and thereby distort the delicate equipoise that must always be sought in research involving human subjects. To help redress that perceived imbalance, I offer the following observations and recommendations:

1. Much more careful attention must be paid to the definition of terms to enhance public understanding, sharpen the focus and precision of public discourse, and avoid both confusion and unintended consequences. In the context of contemporary molecular biology, the terms "genetic research," "genetic sample," and "genetic test," as they have often been used, are far too inclusive and imprecise to be used without very careful circumscription as the basis for new research guidelines or regulations. Genetic testing, *appropriately defined*, should unarguably meet a high standard of informed consent. However, the definition of a genetic test should be markedly narrowed to focus on the purpose of the study rather than



on the particular kinds of research methodologies to be used. For example, such a test might be one that is carried out on asymptomatic individuals, or populations, to determine the presence or distribution of particular heritable risk factors of *established predictive significance* for purposes of genetic counseling, public health or disease prevention. For purposes of this discussion, I would expressly exclude genetic studies carried out for the purposes of diagnosis and treatment of *expressed disease*.

Research studies on human tissues removed for medical reasons ordinarily should not be defined as genetic tests even if they involve examination of gene structure and function. Research results are nascent data, typically obtained under experimental conditions that would not meet the accreditation standards for diagnostic clinical laboratories. Research results cannot be fully interpreted until they have been adequately replicated, and only after they have been validated analytically and clinically can the medical community determine whether they provide the basis for a useful genetic test that should be introduced into practice. Accordingly, research results as a rule should *not* be considered diagnostic and should *not* be entered into a medical record or communicated directly to a tissue source.

In contrast to genetic test, *genetic information* should be broadly defined, both to reflect the reality and to enhance the efficacy of legislative efforts to prevent discrimination based on genetic information in employment and the insurance markets. Such legislation at the federal level should be vigorously pursued -- and enacted. It would have a very beneficial effect on this entire debate.

2. In the public deliberations to date about genetic privacy and the use of human tissue samples in research, a tremendous amount of effort has centered on the thorny issues of informed consent. I believe that this effort has been largely misdirected and that continuing to wage battles over the bioethical and legal niceties of informed consent is not a practicable way to resolve the central issue of how to give due respect to the protection of patient privacy while at the same time continuing to facilitate research access to archival patient materials. It should be clearly understood that *whether those patient materials are tissue samples or medical records* the consent issues are really indistinguishable. This fact has become crystal clear in the current rounds of intense discussion that are taking place around the several medical information privacy bills that have recently been, or will shortly be, introduced in the Congress.

Current regulations and practices involving informed consent have been elaborated with great care to deal with circumstances involving the direct interaction of investigators with prospective human research subjects, a context in which the stringent requirements of the informed consent protocol are both reasonable and feasible. That is, it is possible to describe to the prospective subject in detail the objectives, duration, procedures, risks and benefits of the study, whether the investigators have conflicting personal, financial or other interests, and any other matters deemed appropriate by the investigators or the cognizant IRB. *None* of these circumstances obtains with respect to tissue specimens excised for medical reasons, or, for that matter, to any retrospective (or secondary) non-interventional research requiring access to archival patient materials. With respect to tissue samples, which can be preserved indefinitely and have been accumulating in the archives of some academic medical centers for over 100 years, it is impossible to predict or even imagine, let alone describe, the kinds of research questions or experimental technologies with which those samples may be involved in future months or years. Entirely similar considerations apply to medical records. Accordingly, for secondary research on human tissue specimens (or patient records), prospective, specific informed consent is quite literally an



impossibility.

To deal with this problem, three alternative generic approaches to the issue of consent have been proposed. The first is embodied in the generally, but not universally, accepted proposition that different stringencies of informed consent should apply to the use of human tissue samples or medical records in research, depending on whether or not the samples are linkable to specific individuals. Many, although not all, agree that a minimum burden of informed consent -- indeed, none -- should apply to samples that are "anonymous," that is, totally and irrevocably unlinked to patient sources. Although sample anonymity is compatible with some research protocols (and with *all* uses of tissues in professional education), in most retrospective studies, it is necessary to be able to obtain additional or follow-up clinical information in order to establish the diagnostic, prognostic, or epidemiological significance of the findings. Thus, although the specific identities of the subjects almost never need be known to the investigators, the archival research materials (*once again, whether tissue samples or medical records*) must remain linked to their patient sources. Thus, the anonymity route does not offer a general solution.

The second generic approach calls for specific re-consent from the patient source, or next of kin, for each research use of a tissue sample (or medical record). Given the age distribution of the materials typically involved in these studies, and considering the large, distributed populations that must often be accessed either to amass sufficient experimental material or to ensure that the sample is appropriately structured and unbiased, those experienced in such studies believe that any requirement for serial re-consent would be not only chillingly burdensome and costly, but would introduce a susceptibility to uncontrolled selection and confounding biases that would be vitiating. The third generic approach would turn the concept of stringent informed consent on its head by substituting for an informed discussion of a specific research protocol, speculation about hypothetical future uses of tissue specimens, that invites prospective subjects to direct, limit and prohibit the future uses of their specimens. Such an approach, if widely implemented, could very well cripple the future research utility of the human tissue archive, as it would a medical record archive (witness the current Minnesota experience). Moreover, to introduce such speculative discourse into clinical settings typically freighted with anxiety is to risk transforming a process designed to accomplish informed consent into one that too often would lead to "uninformed denial."

3. There is general agreement that the current practice of burying in routine hospital admission and operative consent forms language that permits the use of medically removed tissue specimens for research and education is inadequate. The very same concerns are being expressed about access to medical records for secondary research, where obtaining authorization is even more erratic, and typically ignored. However, the current debates over medical information privacy legislation have vividly illustrated the limitations, the difficulties and the potentially severe adverse consequences that can attend any of the different solutions to the problem of patient consent for retrospective research that have been proposed.

Although the outcome of these debates remains to be determined, what seems certain is that institutions that conduct such studies will be required to implement and enforce policies dealing with the protection of patient confidentiality and security of patient data, and provide their patients with adequate *notice* of both the policies and the full range of uses of medical records that are projected to meet the diverse needs of the health care delivery system. The debate about consent itself is strongly leaning toward the position of requiring *none* when the records to be used are not directly identifiable of individual patients, and of



deferring decisions when the records are to be directly identifiable, pending further study to resolve the extremely divergent views on this matter that have been expressed by the various stakeholders.

4. The necessary trade-off for access to medical information that is proposed in the medical information privacy bills couples severe administrative, civil and criminal sanctions for inappropriate disclosure with the requirement of significant strengthening of the protection of all medical information collected, created and used in the course of delivering medical care, in supporting the operations of the health care delivery system, and in research. The language typically proposed mandates that institutions *shall establish and maintain appropriate administrative, technical and physical safeguards to protect the confidentiality, security, accuracy and integrity of medical information*. Notwithstanding these protective provisions, the fact that all of these bills, without exception, find it necessary to delineate in statute extensive access to patient-identified medical information greatly troubles privacy and patient advocacy groups. Efforts, in turn, to curtail such access elicit vehement objections from the health care and pharmaceutical industries, and thus far have invariably failed. This controversy has been largely responsible for the difficulty that has been encountered in trying to move any of these bills forward in the legislative process. It is important to understand that the menu of statutorily authorized access does not restrict, exempt or make special provisions for any special subcategories of medical information, such as genetics, mental health, or sexually transmitted diseases.

5. The seeming impossibility of maximally securing the confidentiality of medical information used in the *setting of clinical care delivery, payment and oversight* has led the AAMC to propose an alternative approach to securing the protection from unauthorized disclosure and hurtful misuse of all medical information collected, created and used in the conduct of medical research. We have argued that all institutions that engage in research on human subjects, or in retrospective, non-interventional research on archival patient materials, must have in place confidentiality policies and procedures, with sanctions for violators, that meet federal standards. Included in the proposed policies could be the "administrative, technical and physical safeguard" language that appears in all of the medical information privacy bills pending in the Congress. For academic medical centers, all of which currently operate under the provisions of the federal Common Rule, those standards could most effectively be vetted and monitored by an assurance process, similar to those now required of all institutions that perform federally sponsored biomedical research.

Further substantial strengthening of the security of research records and databases would be accomplished by having the federal government issue to each institution that filed a satisfactory assurance a protective mechanism modeled on the existing Certificate of Confidentiality, which would embrace the institution's entire human subjects research database and protect it and the research staff from the forced disclosure of any confidential, identifiable medical information -- including genetic information -- created or used in research. The existence of such a mechanism would essentially guarantee research subjects that individually-identifiable medical information developed in research could not be forcibly disclosed without their express authorization to anyone, including insurers, employers, family members, health care organizations, government agencies or law enforcement authorities. The AAMC believes that this *combination* of protective mechanisms would contribute substantially to allaying public anxiety and would ensure that retrospective, non-interventional research on archival patient materials -- that is, on medical records and human tissue samples -- could continue to be carried out under circumstances that



would in fact be of no more than minimal risk.

6. It is important to emphasize that the embrace of the Certificate of Confidentiality is explicitly restricted by statute to research records; it does not protect clinical records used in patient care delivery. For these reasons, the security provisions just described would not be completely effective unless there were a further provision that created a fire-wall around the research database and ensured that those data could not freely commingle with the medical records or databases used in the day-to-day activities of the clinical care delivery system. Although it can easily be conceived that such a fire-wall might on occasion raise thorny ethical issues of investigator responsibility, we believe that the alternative, that is, to permit any regular channels between clinical and research records, would fatally breach the protective net that is the heart of the proposed assurance mechanism and imperil one's ability to assure potential research subjects that their research data will be maximally secure from unauthorized disclosure. Under this provision, an investigator conducting retrospective research who discovers information that he/she believes would be important to the care of particular research subjects would bring the matter to the attention of the cognizant IRB for disposition. In no instance would the investigator attempt to contact the subjects directly, or enter the research data in the subjects' clinical records.

7. Finally, because research on archival patient materials may require the culling of samples from large databases in different institutions, often, in many states, any new federal legislation that is crafted to deal with the privacy of medical information, or genetic information, should be preemptive of state legislation and set a uniform national standard. As the AAMC stated in a recently published policy statement: "Vital public purposes are served by the availability of medical information that covers the full spectrum of human experiences with health and disease over time. These purposes include the better understanding of disease causes and processes, health care delivery practices, health care outcomes, health care organization, financing, regulation and accreditation, and the quality and efficiency of health care delivery. These public purposes are sufficiently compelling that any new legislation or proposed regulations must assure the continued availability of and access to medical information for these purposes. "

The rapid pace of scientific and technological advancements, especially in the biomedical and information sciences, and the ongoing transformation of the health care delivery system, make it inevitable that challenging issues of medical and genetic privacy, informed consent and the ownership and custodianship of patient data will continue to arise. Society will continue to be vexed by troubling questions that lie at the boundary between its commitment to and respect for individual autonomy and privacy and its compelling interest in promoting the benefits that flow from the generous public investment in research. It is important that the policies that emerge from the current debate be attentive to patient privacy and respectful of informed consent. But at the same time, these policies must be very carefully crafted so that they do not unduly encumber access to the invaluable research treasure that is represented by the human tissue and medical records archives, nor impede the continuing accession of these materials for the support of future research. Policies to be developed must thoughtfully and sensitively balance the competing values of private interest and public benefit and not be unduly or precipitously shaped by emotionally charged and often exaggerated public fears.