Specimens and Syncretism: Reconciling Science, Public Health, Politics and Personhood in Research with Human Biological Materials

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Table of Contents

Chapter 1: Introduction

This paper addresses the ethical rationale and framework for oversight of research with human biological specimens.[1] The scope of this analysis entails research use of specimens that have already been collected (secondary use); the paper will not address issues regarding the appropriate ethical oversight and procedures for *de novo* collection of specimens, whether in a clinical setting or research setting. The first part of the paper addresses privacy concerns as one of the main drivers of regulation. The current regulations governing government-funded human subjects research in the US, the Common Rule,[2] regulate research with data or specimens only when they are linked to individual identifiers, enabling researchers to potentially identify the individual from whom the data or specimens were obtained. Anonymized or de-identified data or specimens fall outside the scope of the Rule. The first part of this project, then, considers the ethical rationale for regulation vis-à-vis privacy concerns specifically. The second part will address non-privacy concerns arising in specimen research, focusing on mostly on concerns that are distinct from those arising in research with data. For example, views about individuals' desire to control the overall disposition of their specimens, opinions about how tissue samples may embody a representation of the whole person, and the concept of respect and dignity associated with human remains are all issues that uniquely arise in the context of specimen research. Furthermore, group harms or group identity can take on special significance with regard to biological materials; and international collaborative research involving specimens gives rise to a set of distributive justice concerns

[1] While there is scientific research with specimens of all types, human, animal and otherwise, for simplicity, throughout this work the term *specimens* will refer only to *human biological specimens*, because oversight of this research entails some unique ethical considerations.

[2] DHHS regulations at 45 CFR 46 and analogous regulations at 17 other federal departments and agencies. The Common Rule was recently revised after an extensive period of consultation and debate through the rulemaking and public comment process. See the Notice of Proposed Rulemaking, published in September 2015: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/nprm-home/; and the Final Rule https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html.

Studies of stakeholder views about specimen research reveal multiple layers of cultural and scientific significance that are not, by and large, associated with research with data. Individuals and groups may hold beliefs about quasi-spiritual significance materials derived from the human body, while sometimes simultaneously appreciating the importance of the advancement of science in the service of better health. The layers of ritual associated with uses of materials derived from the human body, and imposition of multiple layers of meaning, recall the syncretism of religious traditions. Rituals change and intermingle as they are overlaid, over time, in a set of evolving practices. Deciphering the moral significance of the rituals associated with use of biospecimens (in clinical testing and in research) is my project in part two of this paper. This deeper look at the multiple meanings associated with use of human biological materials is necessary to appropriately calibrate the oversight systems and policies that apply to research, as the current Common Rule, even after significant revisions, does not adequately address the fundamental ethical issues and tensions at stake. This paper argues for a new ethical framework for oversight of research with specimens, one that departs dramatically from the Common Rule (45 CFR 46)

Chapter 2: Privacy Concerns and the Work of the National Commission

It is helpful to begin with a look back at the work of the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission), whose scholarship informed and shaped our current human subjects regulatory structure. A large part of the Commission's activities was centered on the question of the appropriate scope of the regulations for the protection of human subjects, and specifically, the distinction between clinical care and biomedical research. Among the commissioned papers prepared for the work of the Commission and collected as appendices to the Belmont Report, several addressed the topic of the distinction between research and clinical care. While an earlier human subjects protection policy, implemented at NIH in 1966, made no mention of this distinction and solely addressed the concept of "subjects at-risk," the National Commission carefully laid out a definition of research that would distinguish research activities from those entailed in clinical practice, even recognizing that sometimes a physician would offer an experimental treatment to an individual patient in an effort to find effective treatment for that individual. Therefore, the Commission's definition of research, "systematic investigation designed to produce generalizable knowledge," reflects the idea that a physician conducting research may depart from acting in the best interest of the patient, at least in part, in the pursuit of knowledge.[3]

The distinction between research and clinical care is important for the regulation of biomedical research involving direct interventions on human subjects, because this departure from standard

[3] It is also true that a physician might depart from best standard of care if, for example, a patient refuses treatment or is adamant that they prefer a non-validated approach; however, these exceptions to standard medical practice are based on the patient's preferences, not on research goals of the physician or researcher. The scenario in which a patient chooses a non-standard treatment does not create tension between best interest of patient and interest of science; rather, it raises the question of how the physician should respond to a patient making a choice that may be in some ways not in her best interest. So the relevant questions would be, how much should the physician attempt to intervene on the patient's choice, and should the physician acquiesce to the demand for non-standard treatment, or not? These problems are important, yet distinct from the problem of managing the tension in research between scientific pursuits and best interests of patients.

clinical practice may a pose a threat to the best interests of the subjects. In a clinical context, they would expect to receive medical care chosen solely to promote and protect their own health—but not so, or not merely so, in research. In contrast to the practice/research distinction in the clinical setting, in research involving only *secondary use* of human subjects data or specimens, without direct intervention on subjects, this definition of research fails to demarcate how or why *research* might be more concerning than *non-research* activities with the same sources. In particular, research with data is not inherently more morally problematic than other activities with data, and in many ways is less so. For example, activities like quality improvement using hospital data and program evaluation in a health care setting also involve access to private identifiable data, but do not undergo the type of oversight used for research. Usually no IRB review is conducted and no informed consent is sought for use of data in these scenarios. Similarly, if specimens were used to evaluate a lab's clinical testing algorithms in a quality improvement/quality control (QI/QC) program, no informed consent would be sought; or if infection control policies in a hospital mandated that source of a nosocomial infection be investigated—all these are activities involving data and specimens that have identifiable information associated with them, yet would not be considered research activities designed to produce generalizable knowledge. The basic point is that *the defining characteristics of research, namely systematic investigation designed to produce generalizable knowledge, do not necessarily implicate greater privacy risks than non-systematic, non-generalizable uses of those same data.*

Privacy Concerns as the Basis for Regulation of Research with Human Subjects Data and Specimens

We recall that the scope of the Common Rule includes only data and specimens that are both

private and individually identifiable.[4] Any data or specimens that are considered public, or through which human subjects cannot be identified through reasonable efforts, fall outside the rule's scope. Given that privacy is the main concern, how might privacy issues arise in the research use of private identifiable data or specimens? There are two relatively obvious ways: breaches (inappropriate or inadvertent release or disclosure of data or information from specimens); or through some other kind of misconduct. Absent either of these occurrences, remaining privacy concerns may relate to the general idea of privacy rather than evidence of specific threats to privacy. Concerns can revolve around such issues as worries about lack of individual control over personal data; or concerns about government interference in the private lives of citizens; or a sense of embarrassment or discomfort knowing that certain others are privy to intimate details of one's life. These worries are equally relevant to research and non-research activities. For example, inadvertent breach of confidentiality (leaving laptops on trains, etc.) can happen in non-research settings. Hacking of electronic databases is now commonplace and affects large and small organizations, government agencies and others—quite independently of engagement in research activities. Specific risks that would pertain only to research would be risks due to misconduct in which researchers are uniquely involved. There is no empirical evidence that researchers are more likely than say, public health officials (Diana 2014), hospital administrators (Cox, Turner and Zapotosky 2016), or officials in the US Office of Personnel Management (Office of Personnel Management 2015), to experience problems with data breaches involving sensitive data. In other words, the distinction between research uses of individually

[4] Research with data and specimens and data are included in the scope of the rule through the definition of human subject at 45 CFR 46.102(f): "*Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information." Because specimens are used to generate health related information, which is by default considered private, use of these materials (when individual identifiers are linked to the specimens) constitutes human subjects research.

identifiable private data, and non-research uses, fails to provide a justification for separate and distinct privacy regulation in the research context. Privacy should be protected in all transactions with private identifiable data, whether or not the transactions involve research. Other, non-research activities with private identifiable data, such as the transmission of health records used for payment of insurance claims; or quality control testing for individual clinical lab tests; or records of prescription drug purchases—any of these activities involve private identifiable health information and any of them could be misused or leaked inappropriately. In sum, concerns about privacy of identifiable data do exist, independently of whether the data are used for research.

The National Commission tied research consent for use of identifiable private information to the same standard used for biomedical research, in part, most likely, because during that same time period privacy concerns had come to the forefront of political discourse. Civil rights movements of the 1960s and 1970s motivated a number of unsavory government actions in tracking and surveillance of citizens' groups; misconduct in the Nixon White House raised the specter of government corruption and dishonesty; and the need for protection of the rights of citizens to self-expression and freedom from government intrusion were common themes. Against this political backdrop, a rigorous approach to the protection of individual privacy interests is understandable. The new regulatory regime was to be applied to government funded research—in the wake of the scandal regarding the Public Health Service Syphilis Study at Tuskegee which exposed the flaws of a government-run research system in which scientists had free reign without ethical oversight or regulation. At the same time, the advent of computer technology in the 1970s and onwards put the creation and reproduction of larger datasets within reach, again raising concerns about possible misuse of data or privacy risks, particularly with regard to data about individual citizens held by the federal government (Ware 1973; Miller 1969; Westin 1966). The Privacy Act of 1974, a development concurrent with the inception of the National Commission and its critical work on human subjects protection, embodied some of the concerns of the day. The Act

regulated federal government collection and use of private identifiable information. It mandated that data could only be collected for legitimate agency purposes, and required agencies to provide to individuals the government-held information about them. The National Commission viewed the movement to protect privacy of individual private data as consistent with, and part of, its overall mission to protect rights of subjects in research. However, in extending the provisions of informed consent and IRB review to research with data, the Commission did not tackle privacy concerns directly. As I will discuss below, informed consent does little to secure subjects' privacy and may provide only an illusion of protection. Informed consent is sought as a measure of respect for autonomous decision-making of individuals included in the research; this allows individuals to decide about the acceptability of research projects that would use their own biological material. However, the nature of the claim that subjects have a right to decide about research with specimens that have already been collected (secondary uses) is less than obvious, as will be explored in the next section.

Is some research with specimens morally problematic?

If privacy threats associated with use of data or specimens are not inherently more severe in research than in non-research activities,[5] then are there other reasons to worry about research? The temptation may be to immediately respond in the affirmative: research is a problematic activity; people's interests may be affected or risks may arise. Yet the answer is not as obvious in the world of data and specimen research as in research involving direct interventions with human subjects (i.e., clinical research). There are no burdens or risks for individuals whose previously

[5] There may be diverse types of data used in research and non-research activities, including, for example, health care data, sociodemographic data, employment data, etc. The point is that for any set of data, there are both research and non-research activities going on. For the non-research activities, most people are unaware of the extent to which private records are being used; or are only aware in a general sense. For example, health insurers are receiving claims from medical providers, processing payments, etc., using identifiable health information from individual patients. Program evaluators use identifiable data in assessing social services programs, and so on.

collected data or specimens are used, apart from the minimal privacy risks already discussed. Regarding specimens, some ethicists and regulators believe that human subjects who have provided specimens have a right to express objections on moral grounds to types of research activities they find objectionable—irrespective of privacy interests (Javitt 2013). In other words, the purpose of the research activity itself, or the procedures entailed, may be objectionable to some parties. The analogous argument could be made for research with data; some research activities with human subjects data could be offensive or morally objectionable, although usually these issues are raised in the context of specimen research. Yet the current Common Rule is not oriented around this concern, because there is no method for expressing disapproval of research with de-identified data, which might be just as objectionable but which falls outside the rule. (If de-identified research were regulated, researchers would need to at least obtain IRB approval of any research projects proposed, even though individual consent would be precluded if the original individuals could not be identified.) Therefore, by its scope and definitions, the Common Rule only allows subjects the right to decline research that involves identifiable data or specimens—the kind of research might potentially affect their privacy interests—at which point they may also express a view about the nature of the research itself. In short, with its focus on identifiable private data, the National Commission prioritized privacy over all other issues with regard to human subjects concerns in data research.

In spite of the Common's Rule's singular focus on the privacy concerns raised by specimen and data research, there may be other reasons to regulate research more stringently even if there is no significant difference in risks when comparing research and non-research activities. For example, there may be justification based on a history of scandal and abuse in research, or a lack of trust in the research enterprise, and a desire for transparency. Despite the idea of commitment to responsible research and transparency, however, the net result of the current regulatory system for

data and specimens is that very significant amounts of research are conducted using de-identified materials (data or specimens) to avoid regulatory delays and complications. So, if the desired result is more transparency, this approach has failed. And if this unregulated research were to be brought into the scope of the regulations, a massive overload of the regulatory system would ensue, as will be discussed in the next section. It is also the case that there are other, less burdensome mechanisms of promoting transparency than requiring individual informed consent and IRB review for every single project involving data and specimens.

A second rebuttal to the claim that research deserves regulation even when there are no significant differences between research and non-research activities is that the nature of scandals regarding data and specimens are different from those involving interventions on the human body . The initial worries about research with specimens and data were related to privacy, especially the specter of government intrusion on private lives of citizens, and concerns about privacy related to government activities led to the passage of the Privacy Act of 1974 (Public Law 93-579, 1974). Subsequently other privacy concerns arose, related to access by insurers and other that might gain access to private health information, leading to regulations for privacy of health-related information like the Health Insurance Portability and Accountability Act (HIPAA, 1996; Chesney 2001). The genesis of these concerns was not specifically that *researchers* would have access to private information, but about others gaining access and using the information in inappropriate, harmful or discriminatory ways. In contrast, scandals that are specific to the research enterprise have arisen with regard to biomedical research that involves risks to subjects and/or failure to deliver adequate medical care are notable (Reverby 2012).

Finally, one of the few substantive concerns about research with data or specimens that could cause harm to subjects relates to group effects such as stigma related to research findings. These kinds of problems are not handled well with the individual one-off informed consent model and

in fact are part of the larger argument of this paper: different oversight mechanisms are needed.

The problem of sweeping data and specimen research into the Common Rule: big net, too many fish.

Even at the time of the National Commission's work, commentators and scholars recognized that an unreasonably large number of activities with identifiable data would be swept up in the scope of the Rule. A commissioned paper (Campbell and Cecil 1974) addressing the work of the Commission addresses use of identifiable information in a range of research activities, noting that the existing regulation at PL 93-348, the Public Health Service Act, included in its scope research with identifiable private information. The authors commented, "There is general agreement that these areas of research are and should be covered by PL93-348 and other rights-of-subjects legislation. Probably 99% of such research already is confirming to such standards in the sense of not violating the rights-of-subjects specified. There are essentially no publicized cases of violations in these areas. The problem raised by PL93-348 is the monstrous bureaucratic burden of requiring this vast area of low-risk research to go through formal institutional review processes."

In the earliest framing of the new human subjects regulations, a list of activities involving private identifiable data was exempted from the rule. Campbell and Cecil (1974) describe how operational monitoring within an institution would not constitute research, and go on to state, "These proposed regulations have obvious ambiguities, but rather than suggest specific refinements, it seems better to wait, allowing operating agencies to define their activities as they choose until specific problems emerge. We must remember that there are Rights-of-Participants issues in every social institution and profession, public and private, whether doing research or not, and this Commission must avoid taking on this whole responsibility." These non-research

activities were recognized as legitimate and necessary for the functioning of federal institutions and agencies as well as private organizations, posed low risk to human subjects, and were well established and accepted. Therefore, imposing a new regulatory burden, requiring IRB review, informed consent (or waiver) and associated documentation was viewed as an unreasonable and unjustified burden. The list of exemptions was designed to remove several classes of activities from the purview of the Rule. The difficulty is that there is no clear conceptual boundary between those activities that were exempted and many other activities that were not. These difficulties became apparent in a controversy arising in 2005 (Kuehn 2008) in relation to a quality improvement study from Johns Hopkins University that involved a checklist for improving the quality of critical care. The Office of Human Research Protections (OHRP) shut down the study because the agency believed the study should have undergone IRB review and approval and should have met other criteria in the Common Rule; the study investigators and the Johns Hopkins IRB had classified the study as exempt from the Rule. The ensuing controversy about the boundaries of research and quality improvement spawned an array of commentaries and analyses, most of which concluded that QI activities did not require the same oversight as other kinds of research activities, but a clear rationale or boundary-setting criterion was lacking (Baily 2008, Kim, Ubel and DeVries 2009; Grady 2007; Savel, Goldstein and Gropper 2009).

In a quixotic effort to make some sense of this regulatory tangle, commentators and regulators focused on the language in the regulatory definition of research: systematic investigation designed to produce generalizable knowledge. While the need to regulate research with data under the Common Rule was never fully fleshed out at a normative level, commentators dutifully tried to apply the definition of research as the litmus test for regulation. Therefore, guidance documents were issued stating that some QI activities constitute research and some do not (OHRP 2012), and some program evaluation studies likewise fall into the research category and others do not. This axiomatic approach did little to clarify the already muddy waters.

The preamble to the newly released revision of the Common Rule alludes to the debates regarding the boundary between research activities and other activities such a QI or program evaluation, but avoids defining a category of exempt activities in these areas, in part because of the difficulty in establishing a bright line between exempt and non-exempt activities for regulatory purposes. The new Rule also carves out a longer list of activities involving secondary use of data for which Common Rule oversight is not required (45 CFR 46. § __.104). For activities in some domains such as national security or criminal justice, there is a clear rationale to avoid sweeping these up into the Rule because other regulatory standards apply. However, for other activities like quality improvement or program evaluation, the rationale for inclusion or exclusion is less clear. For example, the discussion of clinical data registries exemplifies the tangled web of regulation that applies in various cases. The preamble states that "the creation of a clinical data registry design to provide information about the performance quality of institutional care providers, and whose design is not influenced or altered to facilitate research, is not covered by this rule even if it is known that the registry will be used for research studies" while "in contrast, if investigators receive funding from a Common Rule department or agency to design a clinical data registry for research purposes and the registry includes identifiable private information, or involves interacting with individuals (e.g. a research survey) then such an activity involves human subjects research, but may be exempt of it meets one or more of the exemption categories under 104(d)7." What is lacking is an explanation of why regulators believe that some activities need regulating others do not when identical methodologies are used and similar privacy concerns are raised—there is no evidence of a robust conceptual framework underpinning these categories. In fact, commentators have argued that the Common Rule's approach is outdated for precisely this reason (Lantos 2015).

Concurrently with debates about scope of the Rule with regard to the boundary of research versus

non-research, the research community continued to conduct very large volumes of research using de-identified data and specimens, activities that fall outside the Rule's scope completely. Even this seemingly simple solution has its problems, however. De-identification can sometimes mean that important variables are lost and cannot be used in the analysis, and certainly means that linking individuals from different datasets is impossible unless a third party holds a key to identifiers. All of these issues can detract from quality and depth of research investigations.

Along with these problems, new regulatory challenges emerged. The Office of Human Research Protections (OHRP) attempted to provide a path for more opportunities for research with de-identified data by stating that the holder of a dataset containing identifiers could release de-identified data to a research team and the resulting project would not be considered to fall under the rule (would be non-human subjects research) as long as the holders of the identifiers agree not to release them to the researchers. Again, on its surface this seems reasonable. But then questions emerged about whether the holders of the identifiers are considered part of the research team, in some cases, if they collaborate on design or analytic plans. Where does the boundary between "engaged in research" and "not engaged" lie? And again, the lack of clear rationale for needing to regulate these research activities made it impossible to come up with a coherent boundary to distinguish regulated versus unregulated activity (OHRP 2008).

The combination of a sweeping approach to inclusion of data and specimen research in the rule, along with the focus on identifiability and definition of research as the justification for regulation, implicates privacy rights of individuals as the sole, overriding concern of the National Commission regarding data and specimen research. But the process of constructing the Common Rule neglected two key conceptual elements needed for determining proper oversight: a) what distinguishes different types of activities (research versus non-research) with private identifiable data or specimens—do some, but not all, require oversight? On what basis should the distinction

be made? For example, is there a moral distinction between program evaluation with identifiable data and research with such data? And b) for those activities that require oversight, what kind of oversight is needed?

Informed consent, confidentiality, and control in research

Our norms have been determined for the last 40 years by the Common Rule and other regulations associated with these standards. The claim is often made reflexively that informed consent is needed for research using previously collected data, when data are identifiable and previous consent was not given, a view which accords with the regulations. But what is the ethical underpinning of this standard? Is informed consent needed to protect the rights of human subjects whose data or specimens are used in research? Is it specifically protective with regard to privacy?

Informed consent does not protect subjects if they agree to the use of their data in research and investigators subsequently use inadequate data protections measures, allowing breaches to occur. Informed consent offers the chance for control—a person may decline to give consent. Arguably, informed consent requirements are not the best way to protect privacy interests. First, if one forgoes the opportunity to decline the use of one's private data, anyone who does consent should have the confidentiality and security of the information well protected by the best current standards. Consent does not guarantee this—but regulatory and ethical standards for appropriate handling of data would do so. In fact, a 2009 Institute of Medicine (IOM) report on the HIPAA Privacy Rule and health research makes a strong case for the obsolescence of consent as a reasonable protective standard (Gostin, Levitt and Nass 2009). The authors make the point that individuals do not have expertise and access to information to evaluate every potential use of their private information; nor would it be in their interest to impede valuable health research,

providing the data security measures were in place.

The second point, therefore, is that subjects' interests do not only lie in the protection of their private information, but also, like others who are not subjects, individuals have a general interest in receiving the benefits of research: improved protection of public health, advancement of prevention, care and treatment of disease, and other socially valuable downstream effects of the research enterprise. In short, research projects that aim to produce socially valuable findings benefit subjects and non-subjects alike. These benefits may not be obviously evident at the outset of every research project, but the overall trajectory of research aims to produce knowledge that advances important societal goals. Offering every individual the opportunity to agree or decline to use of their data would be reasonable if use of the data posed an unreasonable burden or risk of harm on some individuals, despite the value of the research. But research with data that are well protected poses no burden at all and risks that are widely considered to be minimal. The case has not clearly been made that individuals have a right to decline such research in virtue of a privacy right. There are clear examples in public health law where identifiable data are used in public health programs without express notification or consent of individuals. And as noted, a wide range of non-research activities are conducted with identifiable data without consent, such as quality improvement/quality control (QI/QC) programs in hospitals, program evaluations in many settings, and many types of health services research. Those who do not consent and yet benefit from these programs might also be viewed as free-riders on the consent of others.

A third reason for rejecting consent as a default procedure for research with data and specimens is the cost to the research itself—not only in terms of monetary costs and time, but also in scientific quality. A number of articles document severe detrimental effects on registry data when consent is required, for example (Tu et al 2004; Peto, Fletcher and Gilham 2004). Of course, objections can be raised that individual rights should not be sacrificed in the name of efficiency. But the

problem is precisely this: it is not clear that any rights are being sacrificed. Rather, there are some worries and concerns that are raised about research that do not rise to level of rights violations. Therefore, the question of how to respond to the concerns about research should include an analysis of how morally weighty these concerns are, and how troublesome it would be to give everyone an individual choice about the matter on a case-by-case basis (as in the current standards for informed consent).

Chapter 3: Non-privacy Issues Arising in Research with Specimens

In the Common Rule human subjects regulations, criteria for oversight of human specimens are the same as those for data: in general, any research with specimens or data with individual identifiers linking to the original donor is considered human subjects research, while research with de-identified or anonymized data or specimens is not.[6] Even for those materials that are subject to regulation, confusion and controversy exists about whether consent is required for specific types of research, about what the criteria are for making this determination or for waiving the requirement for consent (Kapp 2006; Hakimian and Korn 2004; Chen, Rosenstein and Muthappan 2005). Also, there are issues that individuals or groups might consider important that are not addressed by individual informed consent.

Specimens that are anonymized or lack individual identifiers currently fall outside the scope of the regulations, although an earlier proposed revision of the Common Rule, a Notice of Proposed Rulemaking (NPRM) issued in September 2015 would have changed this and defined all specimens as inherently identifiable—thus subject to regulation under the rule.

This proposal generated significant controversy due to the fact that a very large percentage of research with specimens currently takes place with de-identified material and hence is not regulated; the changes in the Common Rule, if they had been adopted, would have vastly increased the amount of regulated research. There was a fairly widespread view, expressed in public comments and commentary articles, that this increase in regulatory burden would not have been well justified, and there was concern about how various provisions like consent and IRB review would be handled. Proponents of the changes in the rule claimed that subjects have the

[6] There are certain exceptions (called exemptions) for special cases in which identifiable data or specimens can be used without IRB review or informed consent, such as those in which the data or specimens are publicly available.

right to decide about any future research with their specimens, whether or not the specimens contain identifiers, claiming that subjects have interests in, and rights to control, research with their specimens independently of privacy interests. On the other hand, a number of commentators have argued that there was no rational basis for this claim, given that privacy concerns are largely moot when the specimens are de-identified, and that no specific harms are associated with research of this nature (Lynch, Bierer, and Cohen 2016; Joffe and Magnus 2016; Guerrini, McGuire and Majumder 2016; Grizzle 2015).

As a complicating factor in the debates about whether all specimen research should be regulated regardless of direct identifying personal information, there is concern that genetic information makes many specimens inherently identifiable, whether or not personally identifiable information is associated with specimens. While this issue will not be addressed in detail in this paper, it is important to note that concerns and debates about consent and control in research with specimens emerged before, and largely independently of, the potential for identification of an individual from a completely anonymized biological specimen through sophisticated genetic analysis. Recent developments using genetic analysis and triangulation of different data sources demonstrates that in fact, individuals can be identified using materials and data that are supposedly anonymous (Gymrek et al 2013). But in fact, this is kind of a post-hoc justification for the greater level of concern about specimen research beyond the traditional and fairly limited privacy risks one would face when identifying information is stored and analyzed by researchers. For the purpose of discussing concerns other than privacy, the risk of identification through genetic analysis will not be discussed in detail, but will be assumed to raise ethical issues that are part of the broader landscape of privacy issues being brought to the fore in a rapidly changing technological environment.

With regard to concerns apart from privacy, there are potentially five categories of concerns

raised by specimen research, four of which do not arise in research with data: (1) Symbolism: views of specimens as representations of a person, an embodiment of human dignity; (2) Religious views: special religious or spiritual significance attached to the human body and its remains or parts; (3) Exploitation: concerns about fair distribution of benefits of research and exploitation, power and control in the use, storage, and sharing of specimens in projects involving disadvantaged communities, groups, or countries; (4) Legal issues: issues related to property rights, intellectual property, legal ownership and profit-making with regard to specimens; and (5) Group harms: questions around group welfare and group identity, including stigma and social harm, questions of whether research addresses priorities for health and health care of specific identified groups. While questions of group harm or stigma can also arise in research with data (separate from any specimen involvement), the first four issues, namely personhood, religious views, exploitation, and property rights, tend to intertwine with and complicate discussions about group interests, leading at times into controversy. Furthermore, the conflation and intermingling of these different concepts has made it difficult to tease apart the relevant moral concerns and reach a clear consensus on policies for use of specimens. Arguably, none of the first four issues involve direct harm to donors of specimens, and none of the first four issues are directly addressed in the current research oversight system. The last issue, social harm or stigma due to research findings related to identifiable groups, is the kind of issue that should be considered by IRBs and is more of a classic research ethics concern. Each of these issues will be discussed in turn.

Specimens as representations of the human body, personhood, and dignity.

Specimen research that may raise controversy is the diffuse set of views about the significance of specimens as a representation of the body, of the human soul, or of a deceased person. Evidence about these concerns is indirect. For example, discussion of "right to withdraw from research"

involving specimens seems to implicate a biological specimen as a representation of the whole person. Other biological materials, for example, discarded hair, fingernails, or excreted body fluids, are not seen as a representation of personhood, raising the question of why a biopsy specimen or tube of blood used in research is often viewed differently. There are at least three potential reasons for a "personhood" association with clinical specimens like blood or tissue samples that are not associated with discarded materials like hair clippings, fingernails, or excrement. The first is that in a clinical setting, the materials are used for medical purposes that are specifically associated with health care—raising issues of medical privacy and fiduciary duties in the doctor-patient relationship. The use of biological specimens has a certain meaning in a clinical encounter, in that testing and diagnostic procedures may inform medical treatment or prognosis—and hence have personal meaning for the individual. The second is that the research regulations themselves may have created a set of norms around use of specimens that treats the specimens as representations of a person—specifically because informed consent is often required for their use. So, for example, there are other situations in which informed consent is not required for use of biospecimens, such as quality control testing in clinical laboratories, and these procedures seem to be uncontroversial. So perhaps one reason that use of specimens appears to be morally significant is that the regulations have mandated that special procedures apply (IRB review and informed consent, in many cases)—whether or not any independent moral issues are raised. While it is often the case that regulations are designed to reflect, and protect, social norms, it may also be true the regulations establish social norms where none existed previously. It is possible that the Common Rule requirements for consent have done just that.

The third potential source of concerns may come from deeply rooted traditions, existing in many cultures, regarding the handling of human remains. Unlike discarded materials such as hair, fingernails, or other materials that are considered waste products, the remains of the deceased have special moral and spiritual significance. In certain cultural settings, blood itself takes on

special significance and can invoke notions of witchcraft or foul play. While many western, Eurocentric societies appear to view issues surrounding clinical specimens with scientific detachment, the history of special cultural significance for blood or human tissues lurks in recent cultural history.

Concerns about specimens as representative of the person from whom they were obtained lead to worries about affronts to human dignity. Signs of these diverse meanings crop up in controversies about use of specimens for research in situations when individual identifiers are not associated with the specimens, rendering privacy concerns moot. In these cases, other kinds of cultural or moral objections are raised. Not only do these concerns regarding specimens arise independently of privacy issues, but they also are markedly different than views expressed about research with data. The kinds of concerns that have been expressed in surveys and qualitative studies about research with health data, for example, are usually related to privacy or to a general interest in the purpose of the research (Willison et al 2003; Nair et al 2004). In some studies members of the public are less willing to allow their electronic health records to be used for commercial research than for research at a university or in the public health setting (Grande et al 2013). There are varying expressions of desire for control and preferences for consent or waiver of consent. However, in contrast to attitudes towards specimens, there is no evidence in the empirical literature that the public views health data as requiring special protection because the data represent the whole person or the person's spiritual values. For data research, privacy protections and the general purpose of the research (public health oriented research versus commercial research appear to affect willingness to allow data to be used. In contrast, there are extensive debates about meaning, consent, and control in research with specimens.

Part of the concern about human specimens, one suspects, is not so much about the individual donor but about views of the specimens as representations of the human body. For researchers,

however, the distinction between digitized health data and biological specimens increasingly becomes less and less relevant, as biological assay data and genetic sequences are stored in digital files, and these data are transferred, collated, analyzed and shared without further reference to the biological material from which they were generated.

A number of high profile incidents in the UK illustrate views of at least some members of the public about treatment of the human body and its remains. In the Alder Hey scandal, in a large number of UK hospitals, pathologists had removed entire organs from the deceased during autopsies and had stored the organs for years without consent and without notifying family members (Burton and Wells 2001). There was public outcry, as this practice was seen as abusive and disrespectful, and a series of legislative actions to regulate the handling of human biological materials. In some ways, the regulations governing use of tissue from deceased persons in the UK is more restrictive than that of living persons, reflecting strong public sentiments about the moral importance of treating human remains with decorum and respect. This issue and other concerns about specimens and human remains implicate notions of dignity, respect for the dead, and adherence to cultural norms regarding burial and disposition of the remains of the human body (Robben 2009).

In fact, there is a long and fascinating history of tensions regarding two concepts of the importance of the human body, namely the cultural and spiritual significance of burial of the dead, on the one hand, and the scientific and medical value of study of anatomy through autopsy and dissection, on the other. In the earliest days of scientific study of the structure and function of the human body and its parts, the bodies of paupers and executed criminals were used for dissection and study (Sawday 2013). The ambition and drive of scientists of the day ran headlong into traditional views that dissection of the corpse was inherently disrespectful. Anatomists found access to the materials they needed from the most disadvantaged or scorned members of society.

In the US during the 19th century, a series of scandals concerning robbing of graves highlighted the ongoing conflict between medical schools seeking to train students in anatomy through dissection and study of the human body and members of communities trying to protect the burial sites from pillagers who would exhume and sell the corpses (Sappol 2002).

This tension is echoed to some extent in the current debates about oversight of specimen research which seem to suggest that individuals desiring control over their specimens are facing off against scientists and institutions seeking wider access—although the symbolic nature of specimens as representations of the body are certainly less vivid than human corpses exhumed from the grave.

At the same time, a large body of empirical evidence supports the fact that the vast majority of people are willing to contribute specimens to research projects, including biobanks in which future use is planned (Kettis-Lindblad et al 2006; Meslin and Quaid 2004; Mezuk, Eaton and Zandi, 2008; Johnsson et al 2010; Beskow and Dean 2008). Survey research from a large number of studies shows that many people are content with open-ended consent to future research, and some percentage prefer specific consent to future research projects but are still willing to accept open-ended consent as a viable option.

Social scientists have also investigated factors affecting willingness to donate specimens for research (Pulley et al 2008); altruism, relationships with researchers or clinicians, and generally high levels of trust in research institutions all play a role. In fact, it may be the case that ethicists commenting on specimen issues take a more extreme view regarding the moral significance of specimen research than members of the public at large (Lipworth, Forsyth and Kerridge 2011). Still, there are persistent concerns expressed by some in the bioethics community that even the views of a small minority of patients or members of the public must be given appropriate expression in oversight procedures because, the ethicists allege, fundamental rights are involved.

Given the ambiguous legal and cultural status of human tissue, it is not clear what rights are at stake, if any. If there are threats to basic rights, these should be identified and addressed; if not, oversight procedures must be revised to reflect a more rational approach.

Human dignity

Some scholars are concerned about threats to human dignity from the use of biospecimens in research projects. What does the concept of dignity mean in this context, and if it is under threat, how would it be protected? Dignity with regard to deceased persons, for example, is an idea that takes shape in every culture in the form of traditions and rituals for disposing of physical remains of the deceased, as mentioned above.

The notion of respect is an interest of a different kind than an interest in privacy or protection from social harm. Lack of respect does not necessarily entail harm in the sense of a discernible negative effect on one's prospects (e.g. employment difficulties or social stigma, or one's interests more generally). It is the idea of dehumanizing a person, dishonoring them, or dehumanizing people in general.

However, it is important to consider that the link from specimens to respect for the human body depends on viewing specimens as a representation of the intact, living human body, or of the individual donor herself. Scientists tend not to think of specimens that way, and opinions and views among members of the public seem diverse. As pathologists (Center and Van Diest 2002) have noted, "If material is left over [from a diagnostic or clinical procedures] we have the choice of discarding it using it for the advancement of medicine. Self-determination over the use of one's tissue is in practice limited. Every day we lose millions of cells from our skin, we excrete stools and urine, and we cut our hair and nails—and rarely do we show any signs of wanting to

keep these body element under our control. Even after we have died we are allowed to undertake only a limited number of actions with our own bodies."[7] Many surveys of patient attitudes toward research with specimens indicate that a majority of people do not have strong preferences about deciding about individual research projects (Wendler and Emanuel 2002; Rosenbloom, Madison and Brothers 2013). Some surveys indicate that a minority of patients does want to be aware of and consent to specific projects, but the reasons for these preferences are not always clear. So in spite of notable high profile cases and controversies, it is not clear what percentage of members of the public associate uses of human tissue in the laboratory with concerns about dignity and respect for the body; or how deeply such views are held.

If specimens were viewed as simply biological material that is the object of experimentation, and not as representations of our humanity, ethical objections to their use (apart from privacy issues) would be minimal. It is the notion that the specimen, even when anonymized, represents the person, that brings with it the claims that individuals have autonomy rights with regard to research on such material, or that human dignity is at stake. In a rebuttal to the "no consent should be required" viewpoint cited above, Savulescu (2002) states, "Consent is necessary to respect the autonomy of mature people. Each mature person should be the author of his or her own life….When we involve people in our projects without their consent we use them as a means to our own ends." Note that Savulescu uses the language of involving *people* in our projects. This perhaps unconscious framing of *specimens as people* is part of what underlies some of the divergent and strongly held views about specimen research.

One researcher (Høyer 2002) has described how individuals whose blood samples and health data were used in a biobank characterized their views of the blood as very different from their attitudes

[7] The comment about choices made after death refers to the limitations on what types of disposal of one's own human remains are allowed to be chosen by an individual before death; state laws, religious traditions and customs dictate that only certain procedures are allowed.

towards data from a health questionnaire. When comparing use of data to use of the blood sample, one respondent commented, "Well…I gather that it's just as important to give your answers [to the health questionnaire]…but I guess it feels as if it is more important to contribute [to research] with blood…It feels as if I have given something of myself." Another person stated, "It is part of me…my blood, it really *is* me, straight up. With the questionnaire, I can decide how honest I wish to be…" (Høyer 2002).

Some commentators assert that individual donors' consent for future uses of anonymized specimens is ethically essential. In the book "The Immortal Life of Henrietta Lacks," author Rebecca Skloot (2010) chronicles the story of the descendants of a cancer patient, Henrietta Lacks, whose cells were used to produce an immortalized cell line in the laboratory. The cell line, named HeLa, after the original patient's name, has been used in hundreds of laboratories and tens of thousands of experiments around the world, for decades. Henrietta Lacks was never asked for consent for use of her cells in research, and her family members were unaware of these developments until they were contacted by the author, Ms. Skloot. Gail Javitt (2010) writes that

> …many people do harbor strong possessive, or at least protective, feelings towards their tissue. Such feelings may find their source in religious views on the body—as is the case with Henrietta's daughter, who believed that her mother's soul, in some sense, resides in her cells. Alternatively, they may reside in notions of bodily integrity, i.e., the conviction that, as a matter of autonomy, individuals should retain the power to control the use of their body parts by virtue of the fact that those parts originated in, and once were a part of, their body. Even individuals who do not care about the fate of their excised tissues may well care about whether the information derived from that tissue could help, or harm, them in the future. Thus, there are numerous non-property based reasons rooted in religion, autonomy, or privacy—including individual, family, and group

> privacy—why tissue contributors may care, and therefore should be consulted about, the use of their tissues in research.
>
> Respect for these interests requires that would-be contributors be asked if they are willing to have their tissue used for research, and a meaningful opportunity to decline to have it used. This choice should be provided whether or not the tissue is "deidentified." Deidentification does not change the fact that the tissue was derived from an individual who therefore has an interest in being consulted as to its disposition, although it may alleviate privacy concerns. While some individuals may elect not to contribute their tissues, thereby reducing the number of samples available for research, providing such choice is a requirement of respectful engagement with the contributors.

The story of Henrietta Lacks and the remarkable cell line derived from her tissue is exceptional, and the social and ethical implications of the case will be considered in further detail in the discussion below concerning exploitation. But the everyday uses of specimens are much less dramatic, and much less likely to raise issues about deception, exploitation or profit. For example, tens of thousands of leftover clinical specimens are stored in hospitals and research centers and are used for experiments that are neither dramatic nor controversial. It is not clear what interest the average person would have in whether their leftover clinical specimens, or leftover research specimens, were used for projects examining, for example, basic biochemical functions of cells, or immune responses to pathogens, or mechanisms of genetic regulation of cell growth, or any number of the myriad scientific projects which have no discernable impact on specific values or beliefs of individual donors.

Wendler (2002) posits that consent is required for use of anonymized materials because donors

have an interest in deciding what projects they will contribute to. Wendler acknowledges that simply caring about what projects one contributes to in general does not suffice to create a claim that individual decision-making must be protected. He gives the example, described by Parfit, that one may meet a stranger on the train and learn that the stranger is suffering from an incurable disease. One may have an interest in seeing that that the stranger is cured. But this interest does not rise to the level of a goal one has incorporated into one's life plans. The observer on the train must take some action with regard to the stranger's welfare for this to constitute a meaningful interest for the observer.

Wendler argues that individuals who donate specimens do have a moderately strong interest in the future uses of the specimens. This view implies some ongoing symbolic connection between the person and the specimen—the specimen, in a sense, continues to represent the individual in the "participation" in the research. However donors of specimens often lack any kind of connection to the future research uses of the material. When the specimens are anonymized, there is in fact no way for researchers to maintain contact with donors, and the donor's interest in the research likely to remain at a very general level. Therefore, except in unusual cases, it is unclear whether a general interest or curiosity about research is a morally significant claim on the part of donors.

That said, there are situations in which patients and families have strong positive connection to research through their experience in clinical care or clinical research. A study of parents of childhood cancer patients (Dixon-Woods 2008) found the parents had a strong commitment to supporting research to help future patients, and significant expressions of altruism in willingness to donate their child's specimen for research purposes.

An alternative scenario is one in which donors find the research plan to be inherently unethical—

for example, research to support an agenda that is inherently racist or oppressive. Claims that individuals should be given a choice about not supporting such research should be taken seriously. But the question arises as to the best method to object on a fundamental level to the aims of a specific research project or program. Since research is by nature a collective enterprise that draws upon resources and cooperation of individuals and groups, and often depends on public trust and even public funding, there should be more extensive oversight of research projects than a one-by-one consent process by individual donors. In other words, there are good policy reasons for research projects to be vetted, and some level of control must be maintained over what kind of large cooperative enterprises are supported by the public. But informed consent on an individual level is not a good method to accomplish this aim. Review by funding organizations, transparency in research processes and outcomes, including communication with the public, and review by scientific committees are all preferable mechanisms to ensure the appropriateness of research aims.

Religious views regarding specimen research

In addition to often vague or implicit worries about personhood or dignity, some religious or cultural traditions regarding human tissues come into conflict with medical or research procedures (Campbell 1998). For example, in some cultures, burial rites must include every part of the deceased human remains, such that removal of organs or tissues for autopsy would be problematic (Mfutso-Bengo and Taylor 2002).

An analogous conflict between the demands of medicine and religious views of the integrity of the human body is found in the arena of organ donation. While it is widely recognized that organ donation and transplant are lifesaving procedures, alleviating suffering for millions of people, religious strictures regarding the need to preserve the integrity of the human body can make organ

donation an agonizing or impossible project for the devout. A recent study of various religious traditions elucidated these issues, but interestingly, also noted that families and individuals could be persuaded about the value of donation and could sometimes see a path towards harmonizing their religious principles with these clinical procedures (Oliver et al 2010). This is another example of the syncretic process of recasting the principles and practices in one tradition (devout religious practice) to accord with new rituals (organ transplant). Not all reluctance to authorize research use of specimens in research involves religious objections; however, there may be unstated views about the moral significance of the specimens that conflict with needs or desires to support scientific inquiry and evidence-based medical care. By analogy with the organ donation case, people often hold somewhat contradictory or at least competing views of the meaning of a given set of traditions, and that these competing views can evolve over time and space.

Part of the conflict stems from the recognition of the potential benefit of uses of human tissues—in the example above, in organ donation—contrasted with the religious priority on the integrity and sanctity of the body. In the case of organ donation for the benefit of a needy patient, the potential benefit is clear. What may be less clear to the average observer is that benefit of scientific research with specimens—and the myriad ways that scientific investigations have advanced health care and public health. Not only are many scientific investigations carried out with anonymized specimens, but even when identifiable materials are used, and informed consent obtained, specimen donors often have little idea of the significance of the research, and there is no organized mechanism for providing feedback about specific research projects.

In international research, specific cultural or religious views are often cited as cause for concern with regard to the use of specimens (Grietens et al 2014). It is important to recognize that Western (or Northern) cultural and religious traditions, from high income as well as lower income countries, also come to bear on these questions (Charbonneau and Tran 2013), and that there is a

risk of "exoticization" of non-Western cultures that could result in a trite or hackneyed version of the historical and cultural issues. And like all cultures, traditional views of the body and blood in ritual, medicine and science are complex, dynamic and multi-layered. These cultural views of the human body are affected not only by direct contact with doctors and scientists, but by social, economic and political change (Gershman 2016).

Some ethnographic studies have revealed that although some cultures have specific beliefs about spiritual implications of taking blood, at the same time, members of these communities recognize and value the contributions of modern medical science and biomedical research to their communities' well-being. These cases demonstrate that religious or cultural practices do not necessary entail strict vetoes of research, even if there are conflicting traditions at play; there may be lingering discomfort about the idea of using human tissues in research studies (Barchi et al 2015; Moodley and Singh 2016), but this may not be sufficient to rise to the level of frank objections.

Distributive justice and exploitation in research with specimens

The Henrietta Lacks story raised important issues not only about individual choice, consent, and respect, but also about disenfranchisement, racism, and systematic disadvantage. The Lacks family was not only the family of a woman who had died a tragically early death from cancer, but also a family largely excluded from benefits of regular health care and other social benefits due to structural and institutional racism and poverty. There is a striking disconnect between the great leaps forward in science and the acclaim of for researchers using the HeLA cell line and the grim realities of the lives of African Americans living in poverty in the second half of the twentieth century. While the question of lack of individual compensation to Henrietta Lacks for the source of the HeLA cell line has certainly been raised, a larger and more generalizable question is

whether the benefits of scientific discoveries and advances in health are truly shared equitably. And if not, why should members of the public, particularly from oppressed or disadvantaged communities, be predisposed to cooperate with a research enterprise that seems to systematically ignore their needs?

There are other ongoing controversies in the context of international research collaborations that involve analysis of human specimens. In collaborative studies involving resource-rich countries such as the US or European countries as research sponsors, conducted in low and middle income countries (LMIC), there are often challenges to the practice of shipment and analysis of specimens outside the host countries. For example, specimens collected during a clinical trial in sub-Saharan African countries may be shipped to the US for analysis in university research laboratories that have more sophisticated assays and tests available. Specimens might be stored in repositories in the US or other countries with more technologic capacity and experience in this area (Staunton and Moodley 2013). Often these practices have engendered resentment and backlash (Moodley et al 2014); government authorities, ethics committees and researchers in low and middle-income countries (LMIC) have claimed that removal of specimens is exploitative and unjust (Barchi et al 2015; Langat, 2005; Mduluza et al 2013; Ndebele and Musesengwa 2008; Muula and Mfutso-Bengo 2007). There are concerns that valuable scientific resources are not shared equitably with the host countries; that unethical research might take place; that research collaborators from LMIC are not given fair opportunities; and that intellectual property might be developed to benefit wealthier countries and the not the host countries in which the research took place. In these debates, the ethical and diplomatic issues regarding human specimens have moved significantly outside the traditional human subjects concerns about privacy and confidentiality of data pertaining to human subjects. Questions of distributive justice in international scientific collaborations, the legacy of colonial powers, and broader geopolitical issues often overshadow seemingly mundane questions about what specimens are stored in which

freezer.

Specimens differ from data yet another way: they are a finite resource, and unlike data, they are physically located in one place at a time, at least until they are subdivided into smaller units. These facts raise issues relating to distributive justice in access to scarce resources; to control and governance issues; and the need for priority setting about appropriate uses of the specimens for valid research projects. Many of these issues have been explored with relation to the establishment of biobanks, however these discussions have not necessarily extended to the use of specimens in diverse contexts outside of biobanks. As mentioned above, international collaborative research also raises issues relating to power and control within and across countries and research institutions, and several countries have enacted legislation that restricts or prohibits the shipment of specimens outside their borders (Nienaber 2011; Sathar and Dhai 2012).[8]

In these international research scenarios, specimen research garners yet another layer of meaning: representation of colonialism and extraction of resources from low and middle income countries (LMIC) to be used, historically at least, for the benefit and profit of those in high income countries (HIC). This significance may be layered on top of other more traditional research ethics concerns, such as informed consent, group harms or stigma. Cultural concerns about uses and meaning of blood and blood rituals may also be a widespread phenomenon.

[8] An additional issue that has been raised is intellectual property (IP). Some research leads to intellectual property gains for individuals, or more often, for institutions or companies that sponsor the research. Some challenge the notion that financial gains like IP could be derived from specimens without sharing the benefits with the individuals who contributed to the research. This concern, however, is not different in principle from the notion of benefit sharing in other research, like clinical research involving direct interventions on human subjects—which may lead to huge profits for drug companies conducting clinical trials—yet these benefits are never shared with participants in clinical studies. The question of whether or how financial benefits from research ought to be shared with those who contribute to the enterprise in some way will not be addressed in this work, given that it is not one of the unique aspects of specimen research that set it apart from other research activities. However, there is the question of power relationships between/among different countries participating in research, and specimen research has unique implications in these situations that need to be addressed in the context of an ethical framework for oversight of ownership, control and secondary use of specimens.

Both the Henrietta Lacks story and the international research scenarios described above raise questions about fair distribution of benefits from scientific investigation—benefits of improved medical care, or fair opportunities for benefits of professional development and success by researchers from the communities and countries where the specimens were obtained. These broader questions of distributive justice are not unique to specimen research (clinical trials can raise the same kinds of concerns) but somewhat ironically, the imposition of the informed consent requirement begs the question of whether the overall enterprise is ethically appropriate—even though the process of individual consent is in no way positioned to address claims of wide-scale economic and social injustice in distribution of health care or scientific opportunity. The existence of research oversight procedures simply raises questions that cannot be satisfactorily answered. A regression to consent forms to document acquiescence of individual donors skirts many of the most important and foundational issues at stake.

A challenge could be raised in cases in which specimen research leads to profits or benefits for certain parties. Should these benefits be shared with those individuals who donated specimens? Would it not be unfair or exploitative not to share the fruits of the enterprise with all those who contributed to it? This claim may have some appeal, but further analysis is needed to fully address a claim of distributive justice. First, the benefits of research findings should be socially valuable information, which in some cases has financial benefits to some parties, in some cases not. The question of distribution of benefits from pharmaceutical research, for example, is complex and goes well beyond the scope of this paper, since the question relates to the interplay of free market forces with cooperative structures for health research, and in some cases, the support and cooperation of public health authorities and funders to help advance the research; all this, in addition to the cooperation of individuals who either donate specimens or participate in clinical studies. A full unpacking of the distribution of burdens and benefits in commercial

research is a lengthy enterprise and will not be attempted here.

However, it is important to point out some limitations, briefly, on the claim that those who donate specimens must be compensated directly for profit arising from those ventures. The distribution of individuals who have access to research, are able to enroll in research (i.e. meet inclusion criteria) and by chance enroll in a project that results in a profitable outcome—the resulting distribution of benefits is non-random in particular ways that don't advance the cause of justice. For example, one might argue that a person's willingness to participate in research should lead to some reciprocity—researchers should compensate the donors due to the cooperation with the project. If, for example, 100 people volunteer for a research study and 50 of them are not eligible for some biological reason outside their control, are the other 50 more deserving of compensation? Also, the individuals who contribute to research that benefits public health, in publicly funded research that does not lead to commercial profit, arguably deserve reward just as much.

What might more sense from a distributive justice point of view would be that populations or communities who are being studied should benefit from the research, collectively—a claim that has frequently been advanced in the context of clinical research studies in LMIC. It should be noted that extraordinary cases, such as the acquisition of patentable information from a specific cell line which leads to huge financial gain—these unusual cases deserve some special attention. But the vast majority of research studies form just one step in a long pathway of scientific discovery, and the distribution of benefits and burdens must be seen in the context of a larger system of research, not an individual-to-individual transaction.

Legal questions: property rights and gifts

Several cases have arisen in the last decade in regard to legal ownership of human specimens as described by Glantz and Annas (2008). The legal landscape in the United States is relatively clear: the original donors of the specimens do not have property rights to the specimens, but neither do the researchers using them. The right to store and distribute specimens for research is held by institutions (such as universities or other research institutions), not individual researchers. Researchers may patent discoveries made from the use of the specimens, but do not have property rights to the specimens themselves. The ambiguity in questions of ownership echoes some of the ambiguities that have arisen in connection with rights to a dead body. In English common law and in the US, there is no legal right of ownership of a corpse, however there is a right of possession, which entails certain rights and responsibilities (Mason and Laurie 2001; Lawrence 1998).

Glantz and Annas (2008) argue that uses of specimens should be governed by a legal framework applicable to gifts, stating that "A piece of tissue, identifiable or not, constitutes neither research nor a research subject. At some point it may be used for research, at which time identifiable information might be derived about the donor, and it is the use of the tissue for research that requires human subject protection."

Beyleveld and Brownsword (2000) take a different approach. Their starting point is analysis of the existing policies requiring informed consent in the Council of Europe Convention on Human Rights and Biomedicine (Council of Europe 1997). Article 21 of the Convention prohibits commercial uses of human body parts, and Article 22 requires informed consent for any uses of body parts (including blood and tissue specimens) for a purpose other than that for which the specimen was originally taken.[9] Beyleveld concludes that the only rational explanation for these

[9] "When in the course of an intervention any part of a human body is removed, it may be stored and used for a purpose other than that for which it was removed, only if this is done in conformity with appropriate

consent requirements is that donors have a property interest in their specimens. He examines the claim that some donors may have religious beliefs that conflict with certain uses of specimens in research and that this would the basis for informed consent requirements. His first argument is that if a religious objection was the basis for the consent requirement, then the requirement should hold only in cases where religious objections in fact exist. To the contrary, the Convention requires informed consent in all cases. And in fact, the Convention does not justify its requirement in Article 22 with any mention of conscientious objection to research. Most importantly, the structure of Article 22 is inconsistent with claims about religious objections to research. The Article states that any use of specimens other than the original intended use requires consent. So in a case, for example, where a donor gives a specimen originally for research on condition Y, but objects to use of specimens for research on condition X, then researchers may quite reasonably use the specimen for research on condition Z (which is not the basis of religious objection). But the Convention prohibits such use, absent specific consent. There is, he argues, no basis for restriction on unrelated research if there is no religious or other conscientious objection, except for a property interest on the part of the original donor.

While the legal frameworks of gift giving and of property rights each have some appeal in addressing specimen research, neither captures the full range of concerns (privacy, advancement of science, human dignity, group interests) that have been expressed.

Specific group interests: ethnic identity, protection from stigma, religious beliefs.

Group interests are a real concern. Some examples are easy to envision. The first is the possibility of stigma being engendered by identification of certain biological traits or

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information and consent procedures."

characteristics in a specific population group. Granted, not all health-related findings create stigma. Members of the Pima tribe of Native Americans, for example, have been identified as likely to have a genetic predisposition to diabetes (Knowler et al 1990). It is not clear whether this finding has caused social harm or stigma. It is certainly true that some group findings can provide benefit to groups in that health screening and interventions can be targeted to groups where needed and appropriate. But some kinds of research findings may cause harm. For example, a finding that a specific population group was more susceptible to infectious disease might results in social segregation or discrimination.

Chapter 4: A New Ethical Framework is Needed

This ethical analysis has identified five types of non-privacy concerns that individual or groups might have regarding research with anonymized specimens. Specimens representing the person, human dignity, etc.; religious views; legal rights of ownership; exploitation; group interests/risks/harms. These concerns are not easily classified with regard to the degree of protection or deference that should be afforded to these views in specific situations. With regard to the views about conscientious objection to certain projects, biological specimens are not people, nor do they represent personal participation on the part of an individual donor. Thinking through it another way, if biological specimens are, for example, left over from medical procedures and are then used for research, the use of the specimens is not part of the original medical care delivered to that individual, but is part of a larger social enterprise of biomedical research which is designed to generally advance knowledge for human health. Biological specimens can contain information about people, and people have strong emotions, in some cases, about biological materials derived from the human body. But the specimens in and of themselves are not persons, nor do they represent participation by a person in an activity. In contrast, identifiable specimens raise concerns about privacy and about risks and benefits of individual findings in research, which clearly relates to the identity and welfare of individuals and could engender claims, for example, of a right to privacy.

For the case of group interests and protection from stigma or social harm, there is a true instrumental value to devising a protection scheme for groups. The nature of the concern about group harms is not symbolic but relates to actual outcomes. That said, group interests are not likely to be well protected by individual informed consent. For example, individuals within a group may not be aware of the implications of planned research, or may disagree amongst

themselves about the implications. Individual consent processes do not allow groups to deliberate and share views about potentially controversial research topics. Also, individual decisions not to participate in research may not ultimately be in the best interests of specific groups, since sometimes, all things considered, research on distinct population groups may be more beneficial than harmful. Absent an opportunity to hear all concerns and carefully weigh the pros and cons of research, decision-making by individuals, one by one, may not lead to outcomes that are optimal for group interests. In sum, group interests are better protected when groups have representatives who are able to gather information, create conditions for deliberation and debate, and consider varying points of view. And just as important, group representatives should be engaged with researchers and health authorities in determining how research findings can be brought to bear on current needs and realities of group members. In other words, research prioritization as well as dissemination of research findings should occur with active participation of group representatives. This process of stakeholder engagement holds the promise of advancing health sciences and health care for the benefit of the group and the larger population, rather than having individuals express reservations on a case-by-case basis that does nothing to address redirection of research, better management of research findings, or other aspects of research that might address group interests.

On a policy level, requirements of individual informed consent are unlikely to be effective in protecting group interests. A refusal to provide informed consent on the part of sufficient numbers of people in a defined group might make it impossible to conduct certain research projects on that group. But that would also preclude that group receiving the benefits of knowledge that might help advance health and health care. Rather than using individual informed consent for making policy decisions, it would be preferable to devise a comprehensive mechanism for eliciting group health needs and priorities for research, communicating amongst stakeholders, including funders, researchers and community representatives, and communicating

about and implementing research findings with affected communities, where appropriate.

The third general concern is respect for human dignity. The disposition of material taken from the human body raises a worry about disrespect of individual people, whether living or dead, or disrespect of the widespread views, across many cultures, that the remains of the human body are sacred. This concern, again, should be carefully considered, but is not well-addressed with an individual informed consent procedure. Consent for research does nothing to address human dignity directly, except that it gives a person an opportunity to decline to have specimens used. As with group interests, individual consent does not provide an opportunity for discourse and debate or to advance societal interests in scientific advances in a manner consistent with views about human dignity. In fact, a better goal would be to determine ways that researchers and members of the public can jointly address the disconnect between the scientific views of biological material and the quasi-religious views of the public with regard to the human body and its remains. A more profound synthesis of divergent meanings associated with human biological materials is needed.

The concept of syncretism describes the multiple overlaid meanings given to biological materials that may be used in research. Ancient traditions give way to modern medical practice, which in turn gives way to cutting edge research. Each of these activities carries a certain significance, but does not need to be viewed a conflicting with other meanings.

By analogy, consider another inanimate object: the table. The concept of "table" can have significant social and moral implications. Tables signify group events of a certain kind, as in the phrase, "having a seat at the table." Meetings conducted around tables may involve power, equality, or inequality (e.g. the head of the table versus the sides); may signify group membership or exclusion; may invoke certain processes (tabling a motion; putting one's cards on the table,

making a deal under the table). This is a rich array of culturally significant associations that exist in many historical and cultural settings. Another group of meaningful associations occurs in relation to family structure—the dinner table, the children's table in a large gathering, "dinner table conversation," and so on. When a physical table is used in such a situation, certain rules and norms apply. But the rules and norms are significant not because of the physical presence of the table, but because of the activity and cultural association connected with it. For example, when an old wooden table that is no longer functional is chopped up for firewood, this is not an affront to the whole concept of "table." Rather, it is the physical object that is no longer fulfilling that role.

In the case of biological specimens used in research, the concept that there are multiple uses and meanings, and that in some cases, a sample of tissue or blood may in fact have no intrinsic value or significance to the person from whom it was obtained—this statement runs counter to the currents of human subjects regulation over the last 30 years. But in principle, there is no reason that multiple meanings, or lack of meaning, must irrevocably be associated with a particular tiny tube of biological material stored in a freezer. In fact the construction of meaning is dynamic, and policies ought to reflect this. By analogy, the physical construction of tables is not highly regulated. However certain kinds of meetings and procedures occurring "around the table" may be quite formal and controlled, such as formal negotiations and meetings; and cultural norms regarding appropriate behavior in table-related may be stringent. By this logic, policies and regulation regarding uses of human tissue do not need to assume an immutable significance attached to each tissue or body part. The existing human subjects regulations attempted to strip the "human subjects" significance from data and specimens with the identifiable/non-identifiable distinction. But as this "workaround" solution appears to be breaking down, a more nuanced and refined sense of the purpose and function of regulation is required.

Given the commitment of modern liberal democracies to religious pluralism, it is desirable to have a mechanism for respecting religious traditions and the implications of religious views on scientific research. However, it is also true that members of the public, and society at large, have an interest in promoting efficient use of scientific resources, particularly those supported by public funds. Weighty bureaucratic processes and tracking systems for research with biological materials may detract from scientists' ability to conduct research efficiently. Some observers object to a consequentialist view about research—arguing that serious moral objections cannot be swept under the rug with worries about efficiency. As mentioned above, the question is exactly how serious the moral objections are, and in light of that assessment, determining the best way to address them. For example, there are serious questions about what kind of research ought to be supported with public funds and about whether some kinds of research cross a line into morally fraught territory. But one argument against deciding these questions with individual informed consent for use of specimens is that matters of general public interest, involving public funds and/or a large amount of social cooperation amongst institutions and individuals ought to be decided collectively and transparently after public deliberation and debate. Sometimes, after such a discussion, a policy decision is made that favors a majority view and does not allow opt-out decisions by individuals; in other cases the policy is set so that individuals are always free to choose. The point here is that for activities like use of specimens in research projects, in which actual burden on individuals is zero, and in which privacy risks should always be minimized, it is not obvious which of these policy solutions is optimal. Further analysis is needed.

Furthermore, scientific projects involving the use of specimens must pass other kinds of criteria for scientific merit and social value. In the public sector, there are checks and balances on research funding and there must be some rational basis for believing the research is worthwhile to advance an important scientific goal. In health research, the goal is ultimately to improve human health and reduce morbidity and mortality. Therefore the use of specimens is not, or should not

be, arbitrary or capricious. In the private sector, clearly there are market incentives at play in the use of biological materials to advance scientific research that can lead to successfully marketed products. But again, the regulatory apparatus that determines what products go to market entails some evaluation of risks and benefits of using products and in the end, there must be some efficacy and reasonable safety profile of a product for it to clear these hurdles. If companies seek to market products, there must be some demand for the products, regulatory approvals must be obtained, and there is arguably a good prospect of some social value to the enterprise. The question of what entities receive profit from these scientific investigations is a complex one and would entail a fairly detailed ethical analysis about risks, burden, benefits, investments, and social value. There are numerous critiques of the current system of research and development for pharmaceutical products and a full discussion of these issues is beyond the scope of this paper.

One might also argue that engagement in the health care system might create some level of obligation for cooperation with medical research that supports the effectiveness of health care, such as research uses of anonymized specimens, especially because such uses do not impose risks or burdens. If a general obligation to cooperate with non-harmful, non-risky research were recognized, the adjudication of which research projects are unacceptable or acceptable would be left to scientific authorities and the political apparatus that oversees them.

In sum, policies addressing use of specimens in scientific research must address an array of ethical concerns, above and beyond questions of individual privacy and confidentiality. Individual informed consent is insufficient to address all the relevant issues. Models of ethical oversight for specimen research could be drawn from governance and ethical standards for biobanks (UK Biobank 2007; Gottweis and Lauss, 2010); from international agreements and treaties regarding environmental resources; or from benefit sharing agreements for bioprospecting (Schuklenk and Kleinsmidt 2006) and intellectual property development. Each of these domains

has some ethical relevance for questions of specimen research. An additional concern related to the special significance of the human body and its remains must incorporate numerous cultural viewpoints, some of them vague and diffusely represented, lurking behind public discomfort about research with specimens. At the same time, scientific research can bring tremendous tangible benefits to populations through improve diagnosis, prevention and treatment of serious diseases and conditions. A robust ethical framework must be able to incorporate the multiple meanings of human specimens in a coherent and comprehensive way. A framework should address questions about subjects' interests in understanding and controlling use of their specimens; questions about human dignity and representation of the human body; distributive justice and fair terms of collaboration in research; and responsible and ethical use of scarce resources. Our current regulatory framework misses the mark. This outline below proposes a new model of ethical guidance for this critical area of research.

Outline of a new ethical framework for research with human specimens

A new ethical framework must be built on broadly accepted principles, must have procedures that reflect both principles and pragmatism, and must be able to be periodically evaluated for its effectiveness in addressing the ethical goals of the project.

The following principles must underlie the ethical framework for oversight and cooperation, and in some cases, must be balanced with each other and with pragmatic considerations.

- Research is a collective, cooperative endeavor designed fundamentally to advance knowledge and understanding. Health related research in particular should advance knowledge or practice related to human health and health care, which are societal goods that are widely valued across communities, countries and regions. Health research should

not be viewed as simply a market transaction between individuals, as the pursuit of collective good implies both a higher degree of altruism and cooperation, and also implies a higher degree of obligation for sharing of benefits and burdens. Research with human specimens as one form of this collective enterprise should be conducted with transparency and with adequate information for the public.

- The interests of individuals and groups whose specimens have been used in research should be protected. This entails consideration of privacy interests and group harms. All projects involving human specimens should entail appropriate confidentiality protections in cases in which personal information is associated with, or derived from, the specimens. In cases in which group interests may be affected, for example through the potential for stigmatizing findings, engagement with relevant stakeholders should take place before, during and after the research as appropriate to mitigate harms or make appropriate modifications to the research.

- The views of communities and groups regarding special spiritual significance of human biological materials should also be respected. The mechanisms for advancing respectful engagement should be developed through consultation with relevant communities.

- Research projects using human specimens should receive appropriate vetting with regard to scientific value and use of resources. As specimens often consist of finite and valuable resources, prioritization of different projects using stored specimens may entail another ethical analysis to determine best use of scarce resources amongst competing claims.

- Research involving human specimens that involves trans-national collaborations or other collaborations among multiple partners or countries must be planned and conducted with fair opportunities for research partners to access specimens and related research resources, to contribute to research prioritization and design, and to receive appropriate recognition for their contributions.

- Efficiency in research is also important, given the value of research for societal goals and the use of limited resources for its support. Therefore, unnecessary bureaucratic procedures should be reduced or eliminated.

Most of these concerns are not well addressed in the current Common Rule, with the exception of requirements for confidentiality of individual private information. A new ethical framework could advance these ethical goals, while eliminating individual informed consent and IRB review, and instead substituting procedures to address these broader ethical issues.

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