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Genomic Research with the Newly Dead: A Crossroads for Ethics and Policy

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Introduction

Research uses of human bodies maintained by mechanical ventilation after being declared dead by neurological criteria ("heart-beating cadavers"), were first published in the early 1980s with a renewed interest in research on the newly or nearly dead occurring in about last decade.[1] While this type of research may take many different forms, recent technologic advances in genomic sequencing along with high hopes for genomic medicine, have inspired interest in genomic research with the newly dead. For example, the Genotype-Tissue Expression (GTEx) program through the National Institutes of Health aims to collect large numbers of diverse human tissues with the eventual goal of elucidating the genetic bases of common diseases through a better understanding of the relationship between genetic variation and gene expression.[2] Ethical and policy assessments of such research projects are also evolving. In the U.S., Institutional Review Board (IRB) review is not required for research using deceased "subjects"[3] and, although the Uniform Anatomical Gift Act (UAGA) is applicable, it does not adequately address the ethical issues raised by genomic research with the newly dead.[4] Of particular relevance to these ethical and policy assessments is the, as yet unexplored, way in which genomic research with the newly dead is situated within a nexus of other more established clinical and research practices. In this paper we will consider how this crossroads of practices informed the ethical and policy issues raised by a particular research project within our institution.

Launched in 2010, the Comprehensive Individual Molecular Atlas (CIMA) studies gene expression across all the cell types in one human body.[5] Its Principal Investigator has described this genomic study as "a comprehensive molecular characterization of the genome and genomic output from essentially all tissues of an individual human, addressing a question fundamental to medical science: How does a single genome, importantly the exact same genome, generate all of the exquisitely differentiated cell types and tissues of an individual intact human body?"[6] To accomplish this study's innovative comparative analysis of gene expression in one person, investigators would have to permanently remove most of the organs from the body, along with other tissue and fluid samples. Such massively invasive research would, of course, require that the subject is deceased. Investigators would also request the medical record associated with the deceased individual, thus offering both phenotypic and genotypic data for the study. To ensure that the gene expression patterns they capture are like those in living individuals, samples would have to be acquired and immortalized cell lines created as soon after the person's death as possible. In order to proceed with dissection and genetic and medical record analysis of an individual's whole

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body in a high profile “N of 1” study, the CIMA investigators intended to turn to the decedent's family for permission to conduct the research.

What ethical frameworks and policy considerations should inform the design and conduct of a project like CIMA? There exist some recent ethical guidelines for research with the newly dead,[7] but the literature, though helpful, is sparse and does not address the ways in which the CIMA project seems to cut across multiple contexts of established biomedical practice, including human subjects research, organ transplantation, biobanking, and more traditional cadaveric donation. A challenge thus facing the CIMA project was where to turn to address the practical ethical and policy issues raised by the proposed research. In particular, where to turn for guidance regarding: the moral permissibility of proxy consent to research donation, recruitment of vulnerable populations, disclosure of potentially disturbing aspects of the research procedures, disclosure of findings, and the use of broad consent to research?

In this paper we appeal to the idea that genomic research with the newly dead stands at a crossroads between the other more established biomedical practices noted above. In addressing the ethical and policy issues raised by the CIMA project in particular, we aim to illustrate the moral significance of paying careful heed to how one formulates a response to ethical questions raised by a novel endeavor. For example, as we suggest below, it is important to be aware of the ways in which practical aspects of a novel endeavor can create an illusion of moral alignment with an established practice where the ethical issues may actually diverge. Similarly, applicable law may under determine appropriate standards for a novel endeavor that raises additional moral and policy issues. We conclude, indeed, that the appropriateness of looking to one particular established practice for addressing ethical questions in one context does not necessarily translate to appropriate reliance on that model in another context — and can even obscure important moral controversy.

Before moving on, we note that the CIMA project is currently on hold not having received a suitable body donation within the project's allotted time frame. The team originally hoped to collect tissues from the body of a patient who had been declared dead by neurological criteria while perfusion of the organs was maintained through ventilation. However, since organ procurement for transplantation is typically prioritized over research uses of bodies that meet this description,[8] the team developed a back-up recruitment strategy for “warm autopsy” of a terminally ill cancer patient who would like to donate his or her body to research but may die at home. In this scenario, the person could give an informed consent while still alive to the use of his or her body in the project after death. The person would be declared dead by cardiorespiratory criteria and so would not be a “heart-beating cadaver.” The team further agreed to consider donation of a body from which limited organ retrieval would also occur, thus limiting their access to all relevant organs and tissues of a single body. Although the CIMA project is not now active, ethical and policy issues similar to those raised by the project are currently faced by other genomic research with the newly dead and will continue to be relevant as this area of science develops. Further, the methodological ethical issues raised by the CIMA project are pertinent even in the hypothetical.

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1. Law and Policy Background for Research with the Newly Dead

Until relatively recently, declaration of death occurred after a patient's heart stopped beating, the body then prepared for release to family or friends for burial or cremation. A few people donated their own bodies for scientific research, following a long tradition of reliance on cadavers for medical training.[9] But in the latter half of the 20th century, interest in the newly dead human body turned to organ procurement with the first successful cadaveric kidney transplant in 1950.[10]

Two sets of laws subsequently emerged as legal platforms to support organ donation. By 1968, the UAGA offered state legislatures model language supporting the right of a person, or after his or her death, certain intimates of that person, to make a gift of the human body for organ donation, therapy, or "advancement of medical or dental science."[11] Then, in the early 1980s, the Uniform Determination of Death Act (UDDA) expanded the criteria for death to include the irreversible cessation of brain function,[12] thus creating the "heart-beating cadaver" – the body of a person whose brain has ceased functioning, but whose heart and other organs function via the circulatory perfusion provided through "life" support mechanisms. Currently in the U.S., all states and the District of Columbia acknowledge neurological (whole brain) criteria as a legitimate basis of death, and thus for organ procurement.[13]

The usual goal of physiologic maintenance of a body after death is to preserve the organs for transplant into a recipient patient; however, research goals may also be pursued under these conditions. As we have noted in the introduction, because the "subject" is deceased, research on the newly dead does not fall under the technical definition of human subjects research in the U.S.,[14] leaving the ethical issues raised by such research unsupervised by an IRB. The CIMA research team, recognizing that their project raised significant ethical issues without adequate policy guidance, thus turned for assistance to our research ethics group, of which the authors of this paper are a subset.

2. A Crossroads

When faced with sorting ethical issues relevant to a novel research or clinical endeavor, one important moral question is how this new endeavor fits with other more established practices that are relevantly similar. The appeal to standards of practice (or existing policy or law) is so pervasive in biomedical culture, that calling attention to this as a particular way of addressing ethical issues may seem odd. Of course, it is no novel ethical critique to point out that how things *are* done is not necessarily how they *ought* to be done. Perhaps that is why clinicians and researchers have moved to a language of best practices, thus building a normative recommendation into standardization.

Prior to vexing moral questions about whether established practices should be embraced, however, comes the casuistical question of which established practices the novel endeavor most resembles and in what regard.[15] The CIMA project falls at a crossroads between practices, each of which has a somewhat distinct set of ethical norms, guidelines and regulations. As noted in the introduction, these practices include (but are not limited to): organ donation for transplantation, human subjects research, human biological specimen

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research, and other body donation for research or educational purposes. Below we investigate relevant similarities and differences between these practices and the CIMA project regarding several ethical issues. Before engaging these issues in more detail, however, a few comments laying out the nature of the crossroads as well as previewing how these factors relate to the ethical analysis to follow are in order.

In our experience, particular practical and procedural aspects of the CIMA project illustrate the crossroads nature of this proposed research. For example, the similarity of the specimen retrieval process to organ procurement as well as the need to co-ordinate with the Organ Procurement Organization (OPO) to avoid conflicting donation requests, caused the CIMA researchers to contemplate using the OPO as their recruitment team. Indeed, integrating informed consent to genomic research on the newly dead into existing OPO solicitation processes is recommended by one group of ethics commentators.[16] This co-ordination, however, immediately created a context in which organ donation practices and procedures presented a ready to hand model for addressing the moral questions relevant to CIMA independently of whether the answers to those questions seemed aligned. And, as we shall see, particularly with regard to issues of disclosure, measures appropriate for the CIMA project seemed to differ from standard practices for organ donation.

Similarly, while the research subject would be deceased when the retrieval process began, consideration of the ethics and policies of human subject research seemed relevant because of two features of the project: circulation would still be taking place if death were declared by neurological criteria and, alternatively, the subject would actually still be alive when consent was sought if the warm autopsy model was used. Yet, as we shall discuss, the human subject model did not translate neatly regarding issues of vulnerability and inclusion particular to research on decedents, thus highlighting the need for considering multiple perspectives including specific histories as well as contemporary research inclusion rates.

The retrieval of multiple specimens from a single body and the potential for identification of the individual whose body had been donated, raised similar issues to those currently plaguing other genomic research with supposedly non-identifiable human biological samples, making those considerations relevant as well.[17] At the same time, the potential for identifiability was also inflated in this case independently of the genomic nature of the research. Additionally, any impetus to disclose incidental medically actionable findings was both muted by the fact that the subject would be deceased and also heightened by the fact that the family would be known to the researchers.

Finally, while all research on the newly dead legally falls under body donation for research purposes (and thus the UAGA), other commentators have already drawn attention to the ways in which this type of research in general seems morally distinct from other uses of donated bodies,[18] for example, as we shall discuss, in the need for consent specific to the research project at issue. Hence, as with lack of IRB review, the legal requirements envisioned by the UAGA seem to under determine appropriate policy guidance for genomic research with the newly dead and rather to offer only one set of relevant considerations to take into moral account.

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3. Proxy Consent

If death of the potential subject were declared by neurological criteria, first-person consent specific to participation in the CIMA project could not reasonably have been obtained. To make first-person consent possible, the CIMA team would have had to anticipate which critically ill, but still decisionally capable, patients would eventually be declared brain dead but not meet organ donation criteria. Since many who are eventually declared dead by neurological criteria have first suffered traumatic injury, this scenario for identifying likely subjects who could give first-person consent was highly impracticable.

For a living human subject's participation in research, if that person cannot consent to be part of the study because of age, cognitive capacity, or other mental or psychological status, another person (usually parents in the case of minor children and guardians for child or adult wards of the state) may consent to the participation. However, because of the possibility of harm to the subject, there are fairly strict regulatory limitations to the types of research that can go forward under a proxy consent model for children.[19] Further, there are important moral considerations regarding restrictions that should be in place for the inclusion of those who cannot consent to participation due to cognitive or other mental status issues as well as the general ethical requirement, in many situations, for “assent” of participants who are not legally able to consent to research participation.[20]

After death, if a person has not already consented to donation of his or her body (including for organ retrieval or for research or educational purposes generally), specific other intimates to that person may authorize these uses. Further, while the confidentiality of medical records survives the death of the patient, not even proxy authorization for review of a decedent's medical records is needed under the state's research exception.[21] Similarly, no consent is legally required in the U.S. for research uses of specimens left over from medical procedures or from other research, if the subject is not identified.[22]

In this law and policy landscape, requiring proxy consent for research use generally would be sufficient for the CIMA project to meet the entry level standards of practice consistent with these other established endeavors. After all, as it may be argued, the dead cannot be harmed, so the regulatory and moral restrictions in place regarding living human subjects who cannot themselves consent to research are not relevant to research on the newly dead. One might even argue that since the dead cannot be harmed, no consent at all is needed *morally* despite the legal requirements pertinent to body donation.

Importantly, however, the GTEx project, which arguably could seen as helping to set policy standards for genomic research on the newly dead given its public status, seeks consent from family members of the deceased for donation specific to that project.[23] At the same time, the brochure notes, “The family of a deceased person…can donate unneeded organs and tissues to benefit research studies *like* GTEx,”[24] thereby alluding that research uses of a deceased individual are generally not specified to the particular project. It appears then that the CIMA team's plan, which was to seek proxy consent *specific* to the CIMA research project for donation of a newly dead body and for review of the individual's medical records, meets reasonable policy expectations.

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And yet we may still ask whether proxy consent for a study like CIMA really is morally sufficient. Here the particularities of the CIMA research project become important, as do departures from other types of practices involving the dead or newly dead. The fact that a single individual would have been studied and given the genomic nature of the research (as discussed below in section 7), created a significant likelihood that the CIMA research subject would have been identified despite efforts on the part of researchers to keep that information out of reach. Furthermore, because of the in-depth nature of the study — involving both intensive genomic research as well as association with medical chart history — much would have been discovered and potentially made public about this individual that he or she may have preferred be kept private. These intimacies might relate to behavior, disease, habit, or disposition (e.g., as pregnant). Thus, if it is possible to harm a person posthumously, this study included risk of harm associated with the possibility of accidental (or even purposeful) identification of the study subject.[25] Given these risks, strict guidelines regarding the conditions under which proxy consent to research participation is permissible (such as in human subjects research) might then seem relevant.

Much in this argument seems to hinge, however, on whether posthumous harm of an individual is possible and, of course, we do not aim to resolve that question — a source of philosophical dispute at least since Aristotle's observation that “if a living person has good or evil of which he is not aware, then a dead person also, it seems, has good or evil when, e.g., he receives honours or dishonours, and his children, and descendants in general, do well or suffer misfortune.”[26] The problem with posthumous harms is that they are not actually experienced by the person to whom the harm allegedly accrues (in this case, the deceased person).

Nonetheless, whatever we think about the deeper philosophical question of non-experiential harm,[27] we can endorse the idea that we should not risk undermining the narrative given to a person's life, whether posthumously or not. It is easy to imagine situations in which posthumous accidental disclosure of a person's previously socially undisclosed substance use, mental health history, disease status, or pregnancy could “re-write” how that person's life is understood for loved ones, and their community at large. With regard to this type of narrative harm, the question of whether the person her- or himself is the subject of the harm seems somewhat misplaced since life stories are cultural and social projects involving irretrievably enmeshed relations between the person and their community. This concern persists, moreover, beyond the narrower worry about harming someone's reputation if that is understood as largely related to social prestige rather than the broader relational meaning of a person's life. Research uses of the dead that risk narrative harm seem to pose, at the very least, an extra burden of thoughtful deliberation on proxy decision-makers consenting to the donation of their loved one's body as well as on the researchers proposing such uses.

It is important to also note that, unlike for organ donation where a person is more likely to have discussed preferences or perspectives on donation with family members, for a research protocol as unique as the CIMA project such insight is unlikely. Family members would instead have to consider more remotely relevant aspects of a person's perspectives and preferences such as their views on participation in research generally or their attitudes towards privacy. Also unlike organ donation, the benefit to others stemming from the

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donation of a body to the CIMA project would be unclear at the point of donation even though the types of basic research that CIMA envisions are promising regarding eventual human health applications.

While the considerations of narrative harm are more significant for CIMA because of the N of 1 nature of the study, they may apply to other genomic research linking samples with medical records, depending on the risk of identifiability. The question of potential benefit to others and determination of donor preferences also apply widely to genomic research with the newly dead, at least at the present time.

Taken together, then, the likely identification of the subject, the concern about altering the story of a person's life posthumously, and a probable lack of evidence regarding preferences for post-mortem inclusion in such research, support the idea that first person consent (while the research subject is still alive) is morally preferable for research like CIMA. Yet, as we have noted, such first person consent would not simply be difficult when death of the individual is established by neurological criteria, but practicably impossible. Hence this research provides an interesting example where the scientifically best route for donation is in tension with the arguably morally best route.

As noted in the introduction, the CIMA team had considered expansion of its criteria to include gravely ill patients who could provide first person consent to inclusion in the study while still alive, but whose death would be declared by cardiorespiratory criteria. While this decision was made because of the difficulty of obtaining a body donation where death was declared by neurological criteria (due to prioritization of organ donation), and would not have been optimal from a scientific point of view, the warm autopsy recruitment model would arguably be preferable with respect to consent. Further complicating moral matters, however, is the fact that the potential for benefit to others from the research may be increased when death of the studied individual is declared by neurological criteria. In sum, given the legal landscape for research using decedents, the notion that GTEx could be seen as helping to set reasonable policy standards for consent in this research area, and the arguable moral value of doing the research in a way that will offer the best potential for future benefit, it may be hard to argue that proxy consent is not appropriate for this case. Yet the moral case, it seems to us, is still somewhat unsettled.

4. Vulnerable Populations

Research involving humans typically centers attention on the Common Rule for protection of human subjects.[28] Yet, as we have noted, research using deceased humans does not fall under the technical definition of human subject research in the U.S. The highly liminal nature of research on newly dead human beings is set in stark relief by the fact that a switch in means of determining death (from neurological to cardiorespiratory criteria) can mean that a research use of a newly dead individual is agreed to while that individual is still living. Somewhat surprisingly, however, even when the individual is not yet deceased at the time a request is made for research inclusion (which would include the warm autopsy model for CIMA or when a person is declared dead after a “controlled” cardiac cessation), the research use has been deemed by the U.S. Office for Human Research Protections (OHRP) not to fall under the Common Rule.[29]

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As we have already mentioned, research using certain de-identified human biological specimens may be done without any consent, and here it is important to note that research using these specimens also do not meet the definition of human subject research in the regulations.[30] However, the heavy emphasis on biospecimens and related research in the changes to the Common Rule proposed in 2011[31] illustrate the extent to which the use of "non-subject" human materials for research is an evolving area of concern. This point is further emphasized by the fact that the OHRP itself is divided regarding whether research uses of the newly dead agreed to while the subject was still alive meet the technical definition of human subject research.[32]

While the CIMA project thus did not fall under human subjects protection, two of the three populations deemed vulnerable in the regulations (pregnant women and prisoners) were potentially represented in the patient population of interest to the OPO and thus to CIMA given their need for alignment in the consent process (the CIMA team did not consider requesting donation of a child's body). Other potential populations of interest included vulnerable groups not explicitly protected by the regulations, including impoverished persons, uninsured persons, undocumented residents, racial and ethnic minority group members, those with diminished cognitive capacity, and socially marginalized persons.

Despite a long history of problematic donation, or simply appropriation, of deceased members of vulnerable populations — particularly those living in poverty and racial minorities — as cadavers for dissection and study,[33] the UAGA resolves the question of vulnerability only through a requirement for proxy consent. Similarly, despite the revelations regarding Henrietta Lacks' biospecimin "donation" (resulting in the HeLa immortal cell line[34] routinely used in scientific research), there are still no direct considerations of vulnerability in policies related to biospecimen retrieval. In organ donation, prisoners are not typically considered appropriate donors though there is no consideration of prisoner status in the organ allocation process. For undocumented immigrants, the opposite is often the case in practice (e.g., families of persons without legal residency may be approached for donation, but individuals meeting this description are often not allocated organs). These discordances in the organ donation case, however, are more due to practical hurdles regarding organ retrieval and risk status in the prisoner case and financing of follow-up care and medications in the case of undocumented immigrants than with specific policies regarding these groups.

The regulatory guidance for human subject research thus provides the only stable standard of practice available in helping frame an inquiry into the vulnerability of CIMA's potential research "subject." Subpart A of the federal regulations on human subject research gives IRBs discretion in accounting for subject vulnerabilities that they identify.[35] Controversial since their promulgation in the early 1990s, the additional subparts define entire populations (pregnant women and fetuses, prisoners, and children) as vulnerable in a research context. While multiple scholarly and commission group publications exist regarding the ethical treatment of other vulnerable groups, there is no particular set of standard practices (other than IRB discretion or a requirement for consent in whole body donation) to appeal to in carving out additional considerations for newly dead persons falling into one of the other groups identified as vulnerable.

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The issues for the donation of pregnant women's bodies concern in part post-mortem privacy and information disclosure, which we take up below in section 6. Important, too, is the potential for modification of a particular life narrative for the deceased individual, and, potentially, her family, as discussed in section 3. While the CIMA team did not consider requesting donation of a child's body, scandals such as that surrounding the unauthorized retention of organs from dead children from the late 1980s to mid-1990s at the Alder Hey Children's Hospital and other institutions in the U.K. and elsewhere[36] create part of the historical backdrop that must be taken into account when considering genomic research with newly dead children. In the U.K. this scandal led to an overhaul of organ and tissue retrieval regulation that also interestingly made illegal DNA analysis without specific consent (in most circumstances).[37] Further, the potentially disturbing procedures associated with the retrieval of the organs and tissues for such research (addressed in the next section) may be particularly salient in consideration of the child's body both culturally and because of the particular tragedy of childhood death.

With regard to other legally protected human subject groups, the prospect of using newly dead prisoners for genomic research, raises somewhat different concerns regarding the larger social implications of such use. Prisoners have historically been a source of human bodies for anatomical dissection and study, in part because of judgments about the social worth of prisoners that intervene in normal barriers of propriety in dealing with the dead. As Edward Halperin notes,

> When schools of anatomical instruction were established in England, Scotland and the American colonies in the 18th cen., it became customary to use the bodies of criminals for dissection. Dissection for murderers was mandated in England in 1752 as an alternative to postmortem gibbeting.… To be double-sentenced (i.e., to be hung and then dissected) was viewed as a sentence worse than execution alone.[38]

In an important sense, concerns about the potential use of prisoner populations for research on the newly dead go beyond the scope of the Common Rule's more proximal concerns with an individual prisoner's rights and interests, to the social and historical context of such use. These broader social concerns also apply to groups falling outside the Common Rule's list of vulnerable populations: the poor, racial minorities, and the socially marginalized, who were also historically disproportionately used for anatomical dissection.[39] In fact, early attempts to regulate anatomical dissection protected the bodies of the wealthy by legalizing the use of unclaimed bodies of the poor in certain circumstances.[40] To the extent that genomic research with the newly dead may involve individuals from these historically exploited populations, it risks reviving, or being perceived to revive, problematic value judgments about the people who lived and died within those social categories.

At the same time, concern for greater *inclusion* of vulnerable populations in research has also been a matter of growing concern in the past couple of decades, leading to the NIH Revitalization Act in 1993 and the issuance of guidelines for the inclusion of women and minorities as subjects in clinical research in 1994[41] and the inclusion of children in 1998.[42] This trend in human subject research may be somewhat at odds, then, with the cautionary note above about body donation for research or educational purposes. Perhaps in part due to

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the fact that whole body donation programs now take pains to insure that individuals intentionally seek out opportunities to donate their bodies, the trend for such donations may actually be away from minority participation. For example, of the 203 bodies donated to Duke University School of Medicine between 2003 and 2006, 97% were Caucasian and only 3% African American or bi-racial.[43] Similarly, while racial and ethnic diversity in body donation for genomic research with the newly dead generally is hard to estimate, publicly available data on rates of organ donation for different minority populations in the US give some reason to project that rates of participation may be low in these groups.[44]

Of course the racial and ethnic diversity of the decedents tracks just one factor of potential interest regarding the inclusion of vulnerable populations in genomic research with the newly dead. The important point is that addressing vulnerability in the context of these studies must involve not only consideration of the specific histories of various groups with respect to post mortem body use but also questions of potential group benefit from inclusion where donation rates are low. Further, while the Common Rule provides the only U.S. regulatory guidance regarding vulnerability and research inclusion, this guidance does not neatly track the particular histories relevant to research on the newly dead, nor does it adequately account for the unique assessment required in addressing potential benefits or harms of inclusion.

5. Disclosure of Disturbing Procedures

Family members considering donation of their newly deceased relative's body to the CIMA project may have found both the retrieval process (i.e., as involving a “heart-beating cadaver” in the case of death by neurological criteria) as well as the extent of dissection of the body and tissue removal disturbing to contemplate. How potentially disturbing procedures are disclosed or not both differs between, and may be ambiguous within, the various standards of practice relevant to research with the newly dead. Human subject research ethics typically requires that potentially disturbing procedures be disclosed to participants (and proxy decision makers). In transplant, the fact that organ retrieval (in the case of death by neurological criteria) is begun while a deceased person's heart is beating is not kept secret from donors and family; however, it also is not made explicit in the consent process. Indeed, news of this fact may come as a surprise to some who have donated the bodies of their loved ones for purposes of organ retrieval. Also in the practice of organ donation, alterations to the donor's body are both implied and mollified with the common refrain that open casket viewing is still possible after organ donation. In the donation of bodies to science, while a donor or family will typically seek out donation to a particular organization and thus be informed of the types of uses that are likely, specific protocols and research purposes may not be disclosed, and uses such as crash test “dummies,” body decay studies, and blast impact studies[45] may be disturbing to some potential donors and families.

Recent publications and news media coverage regarding organ donation have shifted from a narrow focus on issues of allocation to consideration of the less well known aspects of the organ procurement process, such as the extent of tissue procurement, the methods involved, and the economic aspects of organ transplant.[46] As perhaps surprising facets of the practices and procedures involved in use of the newly dead for transplant, study, or research purposes

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bubble up in the social consciousness of would be donors and their family members, the practice standards around disclosure of potentially disturbing procedures are likely to also evolve to keep pace.

In a changing set of practices, however, it is particularly important to be clear about the nature and scope of the moral issues involved. The issue in disclosure of potentially disturbing procedures is not the same as that of treating the dead with respect, which has been thoroughly discussed in other publications regarding research with the newly dead.[47] As Wicclair notes, treating the dead respectfully is attitudinal, at least in part, and thus depends to a large degree on the actor.[48] Hence a procedure that is potentially disturbing to a family or a donor may be carried out in a perfectly respectful manner. The issue is also not necessarily that of a potential moral objection to a research use. A family or donor may find a research use disturbing or unsettling, distressing even, but not necessarily *morally* objectionable.

Because potentially disturbing research procedures are often compatible with both respectful treatment and with objection to use not based on moral ideals or values, a question may arise as to whether disclosure of such procedures is morally required (or whether we can even guess ahead of time which procedures will be found disturbing). A researcher may reason that a family member may object to a procedure and refuse participation on the basis of distress, but that the objection is based on "mere" sentiment. If objection to body donation for research were held to some standard of ethical reasoning or if the default moral position was a requirement to donate one's body to research, this skeptical approach to objection based in a "creepiness factor" would become salient. However, since objection to research uses does not require independent justification or argument, but is based on the preferences of individuals and their family members, the mere fact that a procedure is disturbing can be reason enough not to participate or to donate the body of a loved one. Further, if we believe that *morally* such *mere preferences* ought to be abided by, then, barring overturn by persuasive utilitarian rationale, it would seem that procedures that researchers might reasonably guess could cause a family to decide against donation, ought also to be disclosed.

For those starting from a human subjects research model, the ethical requirement to disclose facets of genomic research with the newly dead that researchers reasonably believe may motivate a family member not to donate their loved one's body, will seem obvious. Importantly, however, the norms of other standards of practice with which the research is coordinated, for example by reliance on the OPO for donor procurement, may obscure this line of ethical reasoning. To the extent that first-person agreement to donate organs, which is then legally binding on family members,[49] may occur by mere agreement that is not *informed* consent, it is clear that the general norms of consent in this set of practices is divergent from what would be required in a research setting. Further, while agreement to body donation for research must be made explicitly and is not presumed by organ donor status,[50] we have already noted that this consent may be to research uses generally rather than for a particular study.

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6. Disclosure of Research Findings and Incidental Findings

One of the vigorously debated questions in human genomic research is whether and how to return the results of genomic studies to individual research participants, including incidental findings that were not anticipated in the consent process.[51] In the past, genetic researchers have generally warned prospective participants not to expect to learn any individual information, but have often reported their collective findings directly to a study cohort. As genomic research becomes more informative, however, the convention of not returning individual results is under increasing pressure from those concerned to warn individual research participants about genetic findings that predict risk for preventable and serious health problems. It is interesting in light of these debates that the GTEx project, which collects tissues from both live donors (as surgical waste) and deceased individuals, has elected to follow the traditional model of sharing general news about the types of studies being done using the GTEx tissue biobank, but not to share any individual results.[52] Perhaps relevant to this decision is the fact that GTEx is not a specific study, but rather creates a resource for many different researchers to utilize.

With a study like CIMA, researchers would be relieved of any obligation to warn the now deceased subject about his or her individual health risks or other incidental findings. Here, the situation resembles organ donation for transplant and cadaveric body donation, where incidental anatomical or medical findings are usually not disclosed, since they are irrelevant to the health of surviving family members. On the other hand, what genomic investigators learn about the genome and gene expression levels in a newly dead subject could have indirect implications for family members that share those genes. If a familial risk of preventable serious disease were identified, then genomic findings could indicate the potential benefit of wider screening within the family. While the CIMA researchers did not plan to share such incidental findings, because family members would know about the donation and could follow the study publications and results as they became public, this type of information might become available to them in ways that it would not with studies involving multiple decedents.

The CIMA project also faced the prospect of non-genomic incidental discoveries about its subject raising questions about disclosure. For example, as mentioned earlier, it is possible that researchers could discover that a female donor within a certain age range was pregnant when she died. In cadaveric donation for research or study purposes, pregnancy at time of death is typically not disclosed to donors' families. The relative anonymity of cadavers at the point of dissection, the complexity of re-contacting family members, and concerns for the deceased woman's privacy all weigh against such disclosure. In the transplant context, a discovered pregnancy in an organ donor may not be disclosed due to concerns over adding additional emotional burden to a family in knowing that the life of the (related) fetus had also ended with the death of the deceased woman, and, again, out of privacy concerns regarding the deceased. However, the issue is controversial since the family is typically at hand in the donation setting and the news may seem especially salient in the context of a new death.

In the CIMA case, the research team would have access to the family as with the organ donation case, but unlike in organ donation, disclosure may seem appropriate if that

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information were likely to emerge in project publications. On the other hand, pregnancy is considered a private matter in our society, and the 2005 “Consensus Panel on Research with the Recently Dead” echoes that sentiment in declaring “Respect for the dead, their legacy and their living relatives and friends require that information about them not be openly shared.”[53] That disclosure of a positive pregnancy status may be seen as necessary in light of future inevitable revelations itself gives some insight into the ethical conundrums particular to an N of 1 study like CIMA.

7. Broad Consent

The difficulty of maintaining anonymity for the CIMA research subject bears directly on another challenge: the scope of the research consent requested from family members. With the CIMA project itself, the study in question has a very broad but still delimited scope: to map variations in gene expression across all the major tissues. From one perspective, this comprehensive project requires consent to dissect and remove specimens from the body and to review the decedent's medical records. But in the process, the project would also create an archive of samples and data that could be extremely useful to researchers examining other questions in human genomics beyond the delimited scientific scope of CIMA. As a result, the CIMA organizers had planned to request permission from the family of the donor for unspecified future research uses of this archive, by having them consent to the wide sharing of data, samples, and immortalized cell lines with researchers around the world.

In the past, in both pre and post-mortem contexts, undertaking previously unspecified research on waste tissues from surgical procedures or on excess blood from a clinical draw has relied on such specimens being rendered untraceable to their individual human sources, effectively defusing any research risks.[54] For genomic research, however, the same kinds of individually unique genomic profiles that are used as reliable “genetic fingerprints” in the forensic setting are produced as part of the research analysis of each sample, making them inherently traceable to their human sources.[55] As a result, genomic research on bio-specimens is being nudged toward the practice standards used for identifiable human subjects research, including informing donors of the kinds of research that will be conducted with their materials.[56] For the GTEx study, for example, which also includes donation associated with surgical procedures on living persons, consent is sought that makes clear the wide sharing of data and samples, association with the medical record, and immortalization of cell lines.[57] Again, this consent, while specific to the GTEx project is also very broad in scope as the GTEx project creates a research resource rather than delimiting a particular study.

In the case of the CIMA study, the potential for identification through genomic analysis would be magnified by the fact that only one person's body is involved. Thus, leaving genomic identification aside, even family members of the donor may inadvertently (or purposively) make known the studied individual's identity. *If* anonymity is the prerequisite for the moral acceptability of broad consent to unspecified future research uses of collected biospecimens, requesting such consent for future research uses of the samples and derivative products originally provided for a study like CIMA may seem problematic.

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However, the traditional practice of donating one's body to science presents a somewhat more complex set of norms. As we have noted, body donation may be broad in not specifying a particular research or study use. At the same time, in a context in which the use is limited to anatomical dissection, cadavers may be explicitly identified in memorial services involving the donors' families. Thus, unlike the human subjects research context, in this set of practices it seems unproblematic for biomedicine to accept such open-ended and identified gifts, as praise-worthy and durable expressions of the donor's wishes and altruism. However, it is unclear whether this difference is due to the fact that the donor is deceased or due to the fact that the identified cadavers are typically used in a narrowly defined program whereas the cadavers used for more open-ended research may remain anonymous.

Conclusion

Donation of newly dead bodies for research is not itself new[58] and procedures involved in organ retrieval are well-honed. Genomics research involving human subjects as well as biological samples is also routinely engaged. The novel nature of the CIMA project comes from the overlap of these worlds in which practices have become relatively standardized, but differently so, along with the prospect of an individual research “subject.” Legal guidance has under determined appropriate moral responses to genomic research on the newly dead by excluding deceased persons from the category “human subject” and yet failing in the applicable UAGA to address relevant issues of informed consent, disclosure, and vulnerability. As we look to developing appropriate policy for the future of genomics research using newly dead individuals, we stand at a crossroads of practices, each of which bears some practical or conceptual allegiance to these new endeavors, yet each offering somewhat variable norms to guide the morally salient features of the research.

In this paper, we have explored some of these alignments and discordances in searching for an answer to the question of where a project like CIMA should look in modeling itself after a current standard of practice. We have noted, along the way, the importance of recognizing that the search for such alignment is itself morally fraught (since how we do things may not be how we should do them). Further, we have noted the ways in which a new endeavor may be influenced by practical alliances that should not necessarily be endorsed. For example, the CIMA study's pragmatic allegiance with the OPO may create an illusion that similar habits should be engaged not only regarding disclosure of a discovered pregnancy but also in neglecting to give specific disclosure of the potentially disturbing aspects of the retrieval process to those approached to donate their family member's body. Similarly, where guidance may be forthcoming on a particular issue from only one relevant practice, that guidance must be re-evaluated in the context of the new endeavor. For example, only human subjects regulations offer guidance on the complex issue of vulnerability, but neither the reasons for vulnerability in human subjects nor the particular history of vulnerability in that context translate neatly to research uses of newly deceased persons.

The lesson of our paper is not that CIMA should start anew in creating a moral framework for its research. Guidance can be drawn both from existing practices as well as overarching moral norms such as those of justice, respect, utility, and researcher virtue. Rather, the

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lesson is simply to choose practice allegiances carefully and with an eye to distinctions that may make a moral difference.

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