

# The Ethics of Repurposing Previously Collected Research Biospecimens in an Infectious Disease Pandemic

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**ABSTRACT** In the early days of a pandemic, repurposing biospecimens from established research projects could prove to be extraordinarily useful in achieving substantial and timely public health benefits. Nonetheless, there are potential ethical and regulatory uncertainties that may impede access to those valuable biospecimens. In this article, we argue that there should be a presumption in favor of using previously collected identifiable research biospecimens without re-consent to directly address an infectious disease pandemic, assuming certain conditions are met. This argument fills a unique yet critical gap in decision-making where the specific consent accompanying the identifiable biospecimens would not otherwise permit repurposing. Further, it suggests that even if gaining re-consent is feasible, doing so in a fast-moving crisis is not necessary. This analysis also attempts to address the ethical concerns of public health authorities who already may have the power to use such specimens but are reluctant to do so.

**KEYWORDS** human subjects research, human research ethics, pandemic, infectious disease pandemic, biospecimen research, identifiable research biospecimens, informed consent

Berkman, B. E., A. C. Mastroianni, L. Jamal, C. Solis, H. A. Taylor, and S. C. Hull, "The Ethics of Repurposing Previously Collected Research Biospecimens in an Infectious Disease Pandemic," *Ethics & Human Research* 43, no. 2 (2021) 2-18: DOI: 10.1002/eahr.500083

In an emerging infectious disease pandemic, time is of the essence. Rapid access to biospecimens obtained from people who have been exposed to a novel pathogen can be critical for facilitating effective public health responses. For example, early diagnostic testing can elucidate whether there has already been sustained community transmission<sup>1</sup> or whether multiple strains of the pathogen are circulating, and such testing can inform the development of strategies for implementing public health measures.<sup>2</sup> Rapid access to biospecimens can also lead to earlier evaluation of potential life-saving treatments and preventatives and can inform medical understanding of individual disease risk and outcomes<sup>3</sup> including identification of clinically relevant host factors.<sup>4</sup>

There are reasons to believe that in the early days of such an emergency, repurposing biospecimens from es-

established research projects could prove to be of extraordinary value in achieving substantial and timely public health benefits. Such biospecimens are often more valuable if they are linked to identifiable details about the patient. In some cases, these biospecimens were originally obtained without broad consent that covers repurposing for emergency (or any) purposes. Ethical and regulatory complexities, including considerations of consent, risk assessment, and regulatory interpretation, might thus impede access to these valuable biospecimens.

In this article, we argue that in an infectious disease pandemic, it is ethically appropriate for researchers and public health authorities to use previously collected identifiable research biospecimens<sup>5</sup> for a pandemic-related purpose even if the underlying consent would not otherwise permit that use, subject to certain conditions. For this analysis, pandemic-related purposes can

include any public health or clinical research activity that is undertaken for the direct purpose of mitigating the impact of the disease, such as disease surveillance, evaluation of treatments and vaccines, and development of clinical information about disease risk and outcomes. We use the term *pandemic* throughout, but our arguments can similarly apply (more locally and perhaps conservatively) to an emerging epidemic that has not yet reached pandemic status.

### BRIDGING PUBLIC HEALTH ETHICS AND RESEARCH ETHICS

Questions about the appropriateness of repurposing previously collected research biospecimens in this context surface a tension between the management of individual autonomy concerns and potential benefits that may accrue to the population. At its core, the tension is reflected in the bridging of two distinct but related ethical frameworks: public health ethics and research ethics.<sup>6</sup> The overarching goal of the former is to prevent disease and promote health by defining a range of ethically defensible activities and programs that can be implemented in communities; the goal of the latter is to ensure the ethical appropriateness of studies designed to generate knowledge that will prevent disease and promote health in the future. Each is guided by a set of ethical principles meant to maximize benefit and minimize harm; either may cause harm to individuals in pursuit of generating benefit to society.<sup>7</sup>

In routine public health practice, the state has the power to intervene when the action (or inaction) of an individual is causally related to a potential or actual harm to another individual and/or the larger community. Public health surveillance, for example, relies on reporting individual cases of disease to track and respond to morbidity and mortality trends in a given community.<sup>8</sup> This is considered to be ethically acceptable because there is broad agreement that the potential medical benefit to those exposed to the index patient outweighs the right to privacy of the individual who tested positive. In the midst of a serious pandemic, public health authorities are more likely to further restrict the liberty and override the autonomy of individuals to protect the health of the community.<sup>9</sup>

In an analogous but distinct way, much of research is conducted in a subset of individuals for the purpose

of generating knowledge to promote the health of others. In all human subjects research, there is a clear research question, the answer to which will be sought through the systematic collection and analysis of data. In exchange for access to otherwise private data (e.g., information generated from biological biospecimens), the investigator implements measures to keep the information gathered confidential. This exchange is described in the consent form, which is reviewed and signed by the prospective research subject in advance of enrollment.

This brings us to the question at hand: in an emerging infectious disease pandemic, is it ethically acceptable to repurpose research biospecimens for a reason other

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than the one that motivated their original collection? In essence, does an emergency justify prioritizing the benefit of advancing population health when weighed against autonomy concerns, including traditional approaches to informed consent and other protections for human research subjects? There has been no rigorous analysis of this question, although the public health community has recognized it as a potentially important issue.<sup>10</sup>

We argue for a presumption in favor of allowing use of previously collected identifiable research biospecimens without re-consent to directly address an infectious disease pandemic, assuming certain conditions are met, as further discussed below. Repurposing *deidentified* biospecimens is already permissible without re-consent, and repurposing *identifiable* biospecimens is similarly permissible provided that they are covered by broad consent. Our argument fills a unique yet critical gap in decision-making where the specific consent accompanying the biospecimens would not otherwise permit

repurposing. Further, this argument recommends that even if obtaining re-consent may be possible, doing so in a fast-moving crisis may not serve the interests of individuals or the population at risk. This analysis also attempts to address ethical concerns of public health authorities who already may have the power to use such biospecimens but are reluctant to do so, as was reported in a recent case (the Seattle Flu Study, discussed below). Our hope is that this analysis can serve as a framework for institutional review boards (IRBs), regulators, and researchers to think about how to make principled, ethically defensible decisions under the stressful and uncertain conditions of an urgent threat to the public's health.

We begin by discussing the potential value of repurposing research biospecimens in a pandemic, drawing on a real case and suggesting likely hypotheticals to provide an illustrative and timely starting point for a conceptual ethical analysis. We then present a series of analogous or related cases that can serve as reference points when grappling with this tension: (a) restrictions imposed during a public health emergency, (b) research in emergency settings, (c) emergency standards of care in the clinical setting, and (d) the public health emergency surveillance exception in U.S. federal human subjects protections regulations. We will use the ethical frameworks and lessons presented by each of these cases to argue for a presumption in favor of repurposing without explicit informed consent. We end with a discussion of the conditions under which such repurposing would not be acceptable and by exploring some of the policy implications of our view.

### THE VALUE OF REPURPOSING RESEARCH BIOSPECIMENS IN A PANDEMIC

The Covid-19 pandemic has already provided multiple examples of actual cases where questions about the acceptability of repurposing existing research biospecimens became urgently relevant. In Seattle, infectious disease researcher Helen Y. Chu had access to previously collected biospecimens from an ongoing seasonal influenza research project known as the Seattle Flu Study.<sup>11</sup> Since Seattle was one of the first areas in the United States to report Covid-19 cases in people who had been traveling, Chu had an opportunity to rapidly test these biospecimens (obtained from people in the region with flu-like symptoms) for Co-

vid-19 to ascertain whether community transmission had already begun.<sup>12</sup> Given lackluster federal surveillance efforts, repurposing these existing biospecimens would have provided a timely signal of the state of local disease spread, which could then have informed earlier adoption of targeted public health interventions to contain the outbreak. As Chu asserted, "Traditional approaches to respiratory virus surveillance may not identify novel pathogens in time to implement crucial public health interventions."<sup>13</sup> In fact, evidence has since emerged that encouraging physical distance in the communities where Covid-19 first appeared just two weeks earlier could have prevented the vast majority of Covid-related deaths.<sup>14</sup>

Despite the importance of this opportunity, Chu ran into bureaucratic resistance from federal and state officials who cited, among other concerns, worries about lack of explicit consent for the future research use of the biospecimens as a reason not to proceed.<sup>15</sup> After weeks of delays, she eventually ran the tests despite these objections and confirmed everyone's worst fears: that the disease had already been spreading for weeks.<sup>16</sup> Chu's decision was endorsed by the University of Washington's IRB, which reportedly agreed with Chu that it would be ethically acceptable to test these biospecimens in a pandemic, although no public health agency had authorized or requested those results.<sup>17</sup> The IRB separately determined that the additional testing met the regulatory and ethical requirements for granting a waiver of informed consent because it involved minimal risk, most people would be unlikely to object to the testing, and there was no risk of group stigmatization given the diversity of the individuals providing biospecimens.<sup>18</sup> Testing, in fact, revealed an actionable sentinel case of community transmission in the United States. The IRB decision that allowed release of this identifiable information to public health authorities required an urgently parsed application of the regulatory exception in the human subjects protection regulations for "public health surveillance" activities. Nonetheless, federal government officials ordered Chu to stop testing her previously collected biospecimens, although they eventually allowed her to test prospectively obtained biospecimens with explicit informed consent.<sup>19</sup>

In Chu's case, testing stored biospecimens without explicit consent informed urgent and valuable public

health action.<sup>20</sup> Previously collected research biospecimens can also be important tools in other areas of biomedical research that support responses to an emerging pandemic. Biospecimens from infected people are vital for conducting early-phase in vitro research about the effects of potential therapeutic or preventive agents, but obtaining these biospecimens has been exceedingly difficult.<sup>21</sup> While biospecimens for this kind of activity could come from a variety of prospectively collected clinical, research, or surveillance sources, there are several reasons to think that use of previously collected research biospecimens may be more feasible and efficient, less costly, and quicker.<sup>22</sup> First, there is a worry that clinical or surveillance biospecimens will be difficult to obtain in the midst of an emerging pandemic where medical and public health professionals will already be spread thin. Second, it may be difficult to transport biospecimens across international borders, meaning that countries might have access only to local cases.<sup>23</sup> Finally, since biospecimens can be most useful for such research when taken from infected patients who have fully recovered (a process that can take up to two months in the case of Covid-19), prospectively waiting for newly infected patients to convalesce would sacrifice valuable time.

Thus, previously collected research biospecimens offer unique value in combatting a public health threat in the early days of a pandemic. To be clear, our specific interest is in whether it is appropriate to repurpose research biospecimens that were obtained without broad consent for sharing and that remain identifiable. Maintaining identifiability can be important for maximizing the value of these samples for three reasons. First, there will be times that it is desirable or necessary to report a positive result to an individual patient so that they can take appropriate medical action or can be isolated. Second, maintaining identifiers can allow for contact tracing to mitigate the spread of the infection. Finally, identified biospecimens will allow for collection of linked clinical data (e.g., regarding the course or outcome of the patient's illness) that can be vital for understanding both the utility of early treatment attempts and individual disease risk and outcomes. It is possible in certain circumstances that the biospecimens could be deidentified and coded prior to testing, but for these three goals

to be addressed efficiently, the biospecimens must be identifiable or easily reidentifiable.

## RISKS AND HARMS OF REPURPOSING RESEARCH BIOSPECIMENS

Any analysis of how to address the tension between the respect we owe research participants and the potential for population benefit requires examination of the relevant risks. Participants in research initially consented to provide biospecimens for a particular research project with an associated set of risks and a defined set of protections designed to mitigate those risks. Repurposing biospecimens has the potential to change

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**If the group of participants whose biospecimens will be repurposed is drawn from a diverse cross-section of the population, group harms can be dismissed as a risk. But if the repurposed biospecimens come from an identifiable group, concern about group harms seems reasonable.**

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this risk profile by adding new risks or abandoning promised protections.

Our core argument is that in an emergent pandemic, IRBs, researchers, and others should be able to determine that it is ethically acceptable to repurpose research biospecimens for pandemic-related activities without research participants' explicit informed consent. This assertion relies on a careful evaluation of whether public health benefits of repurposing biospecimens outweigh corresponding risks and threats to participants' nonwelfare interests. These benefits, risks, and interests may apply to individuals or groups, which we analyze separately.

With respect to individuals, the relevant ethical concerns are grounded in the values of respect for persons and autonomy. This is because repurposing research

biospecimens may involve sharing biospecimens and related information among public health departments, academic research collaborators, and/or private companies. Without explicit authorization from research participants, expanded biospecimen and data sharing may undermine the confidentiality on which participants' initial research participation was premised. Depending on the extent and granularity of this additional sharing, it may also increase the risk that a research subject will be identified against his or her will. Harms that might result from this include embarrassment, stigma, and/or discrimination (e.g., loss of insurance or employment). Irrespective of any resulting harms, violations of confidentiality may be interpreted as breaches of respect for research participants. The unauthorized sharing of research biospecimens and data also raises the concern that research biospecimens will be used in a way that is not consistent with a participant's values, commonly characterized as a nonwelfare interest.

In a pandemic, where the goal of repurposing biospecimens is to respond to an urgent public health crisis using established methods without significantly altering the risk-benefit ratio of research, we see a strong case for allowing immediate and important public health benefit to justify a decision against reconsent. Survey and focus-group data show that most people generally support the majority of health-related purposes for which their biospecimens might be used.<sup>24</sup> That said, in situations where the goal of repurposing research biospecimens is to promote controversial, risky, or highly stigmatizing research, these individual-level concerns may provide sufficient reason not to repurpose biospecimens without the explicit informed consent of research subjects.

The ethical concerns about group harms, which involve justice and fairness, matter most when they adversely affect vulnerable or underserved groups disproportionately. In a pandemic, these concerns must be weighed against the social and public health benefits that would be impossible to realize without repurposing research biospecimens.

For example, using research biospecimens that are disproportionately drawn from vulnerable or underserved research subjects risks exploiting those groups to the unfair benefit of better-off groups in society. Also problematic is when previously collected biospecimens fail to represent the diversity<sup>25</sup> of the population expe-

riencing a pandemic, particularly those experiencing a disproportionate burden of disease, such that repurposing existing biospecimens to address justified pandemic research may not benefit the entire affected population. Repurposing biospecimens could inadvertently harm specific groups by imposing opportunity costs or creating negative social impacts. For example, if research biospecimens were previously collected to address a research question of special importance to a vulnerable or underserved group, repurposing the biospecimens could divert scarce resources from this goal.<sup>26</sup> Alternatively, repurposed biospecimens may reveal that a vulnerable or underserved group is one of the primary drivers of disease spread, thereby compounding the social stigma and discrimination directed toward them. Understanding from whom the biospecimens were collected and for what use is an important factor in considering whether repurposing the samples is ethically acceptable.

In an emergent pandemic, when both biospecimens and time are scarce resources, concerns about group harms are likely to be outweighed by the prospect that repurposing biospecimens will promote the public health by facilitating improved disease surveillance, treatment and preventives development, and research on clinical understanding of the emerging disease. Improved disease surveillance benefits all of society, including disadvantaged populations, although the opportunity costs of using scarce and precious resources collected for another purpose must be taken seriously and weighed carefully against those benefits,<sup>27</sup> and steps should be taken to minimize the risks of potential social stigma and discrimination associated with public health surveillance. Concerns related to the representativeness of research findings and potential lack of access to the benefits of such activities because of systematic disadvantages that some populations face, such as limited insurance coverage or the inability to access health care, are critical justice considerations that must be carefully examined.

### **AN ARGUMENT FOR REPURPOSING RESEARCH BIOSPECIMENS IN A PANDEMIC**

**A**s noted above, repurposing research biospecimens during public health crises generates an ethical conflict between the respect owed to research subjects

and the potential benefit that may accrue to the population. Promises made to individual research participants (e.g., to use the data for specific research purposes, keep their information confidential, and typically not return research results) are violated to potentially benefit the larger community (e.g., through better understanding how the disease spreads).

While repurposing biospecimens that have been previously collected for a specific research aim in a pandemic is a novel issue, analogous cases involving related ethical trade-offs can inform our analysis. In this section, we discuss a series of cases where there is already a well-developed literature about how nonideal circumstances can change the way we make trade-offs between the traditional, individual-focused principles of research ethics and the communitarian aims of public health ethics. Taken together, these cases suggest that there is broad ethical support for waiving consent in a range of situations where the public health benefit of doing so is sufficiently high. Arguably, many of the examples of infringement described below (concerning public health powers of the state, conducting research without prior consent, and overriding autonomous medical decisions) are of far greater magnitude than repurposing biospecimens that were legitimately collected for another research purpose. When these examples are juxtaposed against what we are advocating, the idea that there should be serious concerns about repurposing research biospecimens in a pandemic seems implausible on its face.

While we share this instinct, in this section, we present a more rigorous argument in support of the view that repurposing is ethically appropriate in a pandemic. We borrow from the frameworks used to analyze these analogous precedents to argue that almost all plausible reasons for repurposing research biospecimens in a pandemic will easily clear the bar for ethical appropriateness. In situations where the prospect of public benefit is high, alternatives are few, and the additional risks to human subjects are minimal, we believe that the opportunity cost of inaction outweighs the potential risks and harms we have outlined above.

**Public health emergency autonomy constraints.** In general, the ethics of public health practice allow for infringing on individuals to benefit the health of the community. For example, the freedom to smoke a cigarette

is restricted in public spaces to limit community exposure to tobacco smoke.<sup>28</sup> In the wake of an infectious disease outbreak such as Covid-19, the ethics of public health practice could justify even stricter limits on the liberty of individuals with the goal of reducing the further spread of the virus.<sup>29</sup> The types of restrictions of individual liberty that are permissible in a public health crisis depend on the magnitude of the public health threat and the range of available public health interventions.

Though public health officials clearly have the authority to implement interventions that impose privacy and autonomy burdens on individuals, such power has

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## Researchers should make clear why repurposing is scientifically necessary for answering an important question about a serious pandemic.

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to be carefully constrained. There is general agreement across various public health ethics frameworks about the principles one should use to assess whether a particular public health action is ethically acceptable.<sup>30</sup> A public health action should promote the health of the population; identify, consider, and equitably distribute its benefits and burdens; and respect the autonomy of those affected by the action to the extent possible.<sup>31</sup> On the final point, there is also agreement that actions taken that limit individual autonomy ought to be proportional to the public health threat and the least restrictive as possible to meet the public health goal.<sup>32</sup>

Taking the first criterion, there is no doubt that Covid-19 is a pandemic that demands interventions to protect the public's health. In the absence of a vaccine or an effective treatment, there are strong ethical justifications for restrictive measures such as physical distancing, isolation, and quarantine as means of reducing transmission on a population level. Repurposing biospecimens for pandemic-related activities can similarly be justified as important tools for protecting the public's health. While public health interventions are significantly more intrusive than mere repurposing of already-collected

biospecimens, the reasons for engaging in both kinds of activities are equally strong. Physical distancing, isolation, and quarantine are designed to limit the spread of disease, obviously a core goal in a pandemic. Repurposing biospecimens to facilitate early surveillance efforts can be equally important because it informs the strategies public health officials should use to limit transmission. Similarly, accelerating development of an effective treatment, even by just a few weeks, can mitigate substantial morbidity and mortality, which, in turn, can curtail the need for ongoing public health restrictions.

The question of equitable distribution of burdens and benefits is trickier. Repurposing necessarily involves imposing some additional privacy and autonomy violations on a defined set of research participants for the purpose of potentially producing knowledge that will help protect community health. Thinking first about the distribution of burdens, it is relevant to consider whether there is any way to spread the risks more broadly. Unfortunately, in the case at hand, there is no feasible way to redistribute the risks because the biospecimens under consideration for repurposing will have been taken from an already-defined set of people; one cannot retrospectively recruit a different group.

If the group of people who will bear the burden is fixed, this leaves us with a subsequent question about whether there is anything about that fixed group that is relevant to the analysis. Building on our discussion above about the risks of repurposing, we argue that the risks to any given individual are very low, but that more consideration should be given to the risk of group harms. If the group of research participants whose biospecimens will be repurposed is drawn from a diverse cross-section of the population, group harms can be dismissed as a risk. But if the repurposed biospecimens come from an identifiable group, there does seem to be a reasonable concern about the possibility of group harms (e.g., exploitation, stigma, and discrimination).

The analysis then would turn on whether the very low risk to individual research participants and the more substantial risk to identifiable groups are outweighed by the benefit to society (or to the individual or group itself). We believe that the very low risk to individuals is clearly outweighed by the possibility of generating almost any information that can be tangibly used to combat a pandemic. If there is an identifiable

group, however, the bar would be higher but not insurmountable. For example, both early detection of community spread and early contribution to treatment or preventive development could plausibly outweigh the possibility of group harms. Furthermore, as discussed below, there are strategies that can be used to mitigate the possibility and effect of group harms.

Thus far, we've focused on distribution of risks. Distribution of benefits is generally straightforward in public health surveillance cases because the public as a whole will stand to gain from more knowledge about how the disease spreads. Other contexts that support an urgent public health response, however, raise concerns when there is reason to believe that interventions, such as vaccines or treatments, might be accessible only to certain privileged groups. It would be problematic if biospecimens were repurposed largely from a group (e.g., people without health insurance) who would not be able to access the resulting intervention.

Finally, an analysis of the “least restrictive means” similarly suggests the appropriateness of repurposing. Generally, repurposing will be proposed only if there is no other choice. If the characteristics of the public health threat are known to be such that prospective collection of biospecimens is an option, obviously, this path should be taken. But since we typically will not know how serious the public health threat is at the outset, this will rarely be the case.

**The emergency research framework.** When questioning the appropriateness of repurposing biospecimens for use in research and surveillance during public health crises, we are largely concerned with the ethics of using information gathered from people in ways to which they have not prospectively agreed. Ordinarily, seeking informed consent before using biospecimens is ethically required—but pandemics and other public health crises are anything but ordinary. One critical difference between using biospecimens in ordinary and crisis circumstances is that the costs associated with lost time from obtaining informed consent are much higher than usual in a crisis. It will be instructive, then, to examine the ethics of obtaining informed consent in other exceptionally time-sensitive circumstances.

In emergency research—research on incapacitating conditions that arise without much warning and that necessitate immediate intervention—the informed

consent process can constitute a nearly insurmountable burden. When it does, we and others contend that informed consent need not necessarily be sought when recruiting research participants. In choosing between abandoning the enterprise of emergency research and forging ahead without informed consent, the exceptionally high social value of the enterprise justifies taking an alternate route. This position—that emergency trials need not necessarily seek informed consent—is supported by a wide consensus and is codified in U.S. regulations.<sup>33</sup> Strong support for it has been found in surveys of former participants as well as the wider public,<sup>34</sup> clinician groups,<sup>35</sup> and bioethicists.<sup>36</sup>

There is a general consensus that enrollment into clinical trials in emergency settings without prospective consent is, given certain conditions, morally acceptable. The first condition is that *the trial meets the ordinary standards for conducting biomedical research* (with the exception of those regarding informed consent). Waiving informed consent should not even be considered for trials that fall short of these other standards.

While all clinical trials should meet this first condition, the next criteria are unique to emergency trials that seek to waive the requirement for informed consent. Most critically, the second criterion is that *none of the possible methods for obtaining consent are practicable* (and therefore, obtaining consent threatens the completion of the trial).<sup>37</sup> A third condition is that *extra precautions should be put into place to protect emergency research participants* (e.g., using an independent data monitoring committee, attempting to quickly locate legally authorized representatives, and disclosing information about the trial to the relevant communities and consulting with them).<sup>38</sup> Others argue for an additional precaution: that *there should be no evidence that the intervention would go against the patients' preferences*.<sup>39</sup> These precautions may be stronger than those taken in nonemergency research, because of the vulnerability of individuals with emergency conditions.

When biomedical research is sufficiently valuable and obtaining consent represents a substantial barrier to completing the research, we make ethical allowances for enrolling participants without first obtaining their informed consent. This is the case not because informed consent is unimportant but, rather, because of the exceptional importance of some clinical research, includ-

ing much emergency research. Still, enrollment of research participants without prospective consent does not allow them to make an autonomous choice, which is certainly not a matter to be taken lightly. In the case of emergency research, then, we contend that social value can justify some rights violations.

By analogy, we can draw some lessons from the case of emergency research for our discussion of repurposing biospecimens. As we have seen, autonomy rights are not sacrosanct but, rather, one critically important aspect of the pursuit of rigorous, valuable, and ethical outcomes. In ordinary circumstances, it is necessary that these rights be respected. In exceptional circumstances—when a great deal of social good may be produced in violating these rights—we can, and should, consider proceeding. If we do so, then we should take care to minimize the harm we create in the process.

Most important for our repurposing analysis is the criterion that there are no other possible feasible methods available for obtaining consent.<sup>40</sup> Emergency research without prior consent is acceptable because certain important research questions cannot be answered without relaxing the normal informed consent requirement. The patients needed to study certain acute conditions will, by definition, not be capable of giving consent. In public health emergencies, a similar argument holds. Public health emergencies can emerge without much warning, limiting the ability to prospectively recruit research participants. The relevant questions about a pandemic that require early and expeditious analysis will almost always require access to biospecimens that were collected from patients before anyone would have known to get consent for such activities.

This parallel alone provides an argument for borrowing from emergency research ethics to justify the appropriateness of repurposing biospecimens in a pandemic. There are differences between the two cases, however, that provide further reason to support our view. In emergency research, the intervention can be relatively invasive (radiologic imaging, administration of experimental agents, etc.) and can present significant physical risks. In contrast, repurposing of biospecimens in a pandemic does not involve any further interaction with research participants; any potential harms will either be psychosocial or dignitary. It is not necessarily the case that physical risks are always more significant



than psychosocial or dignitary harms. But in this case, we argue that the magnitude and scope of the risks associated with repurposing are relatively minor compared to the kinds of risks we generally allow (without prospective consent) in emergency research.

As a final point, consider the emergency research criterion stating that there should be no positive evidence that the research activity would go against the patients' preferences (either individually or as a group). We believe that individual cases where such evidence exists will be extraordinarily rare, largely because research participants will usually not have had a chance to express such a view, but also because we have some evidence of their preferences vis-à-vis their prior agreement to have their biospecimens used in research. Even if such cases do arise, we do not think that repurposing should be precluded. We take up this argument later as part of our discussion of the absence of a requirement to obtain re-consent when feasible. If there is positive evidence of an identifiable group's concern about repurposing, transparency and consultation are indicated, as discussed in the next section.

**The crisis standard of care framework.** In conventional, nonemergency situations, respect for autonomy permeates standard approaches to delivering health care to individual patients. This is reflected in well-established patient consent processes, such as participation in decision-making about critical life-sustaining interventions, and in management and protection of private health information.

In a public health emergency, surge demand exceeds supply at some or all levels related to the provision of patient care services. In response, the traditional dominance of patient autonomy in informing care shifts as health systems strive to fairly address the necessity of rationing. Utilitarian decision-making and emphasis on maximizing community benefit compete with autonomous decision-making by patients and providers when crisis standards of care are triggered: the system must move from a primary focus on addressing the needs of individuals to addressing the needs of the community.<sup>41</sup>

Instead of decisions at the bedside, rationing decisions are made at the level of the health care system and de facto limit autonomous choices by patients and practitioners,<sup>42</sup> crisis standards of care are implemented at the macro level to address priority allocation of scarce

resources at the individual level (e.g., hospital beds and ventilators), organizational level (e.g., service priorities of trained workers), and the population level (e.g., access to vaccination)<sup>43</sup> and restrict opportunities for patient and provider input that are otherwise practicable in nonemergent settings.

An Institute of Medicine (IOM) committee articulated an oft-cited ethical framework to support the establishment and implementation of crisis standards of care.<sup>44</sup> Decision-making protocols are to be guided by the ethical values of "fairness and the professional duties to care and steward resources" and are implemented through procedures and processes that attend to "transparency, consistency, proportionality, and accountability."<sup>45</sup> To promote public acceptance of the implementation crisis standards of care, opportunities for community education and engagement ought to be established. The public ought to be aware of the fact that the standard approach to obtaining informed consent from each patient may be abandoned, and there should be opportunities for community engagement in pre-crisis times. The ethical principle of autonomy is cited only once in the three IOM consensus reports<sup>46</sup> addressing crisis standards of care, highlighting its tension with resource limitations: "Though patient autonomy is reduced by the circumstances of disaster, patients still deserve clear information about available choices, respect for preferences within resource constraints, and empathic acknowledgment of the sometimes-dire consequences of resource limitation."<sup>47</sup>

The above discussion established that, in an emergency, when there are scarce resources, it may be possible to abandon the standard practice of individual autonomous medical decision-making in favor of a systems-based approach. We highlight this case to illustrate that, in a crisis, radical departures from well-established norms can be ethically justified. The analysis here is straightforward: if we are willing to make scarce resource allocation decisions that disadvantage (perhaps fatally) specific people because of their medical or demographic profile, it does not seem like an unwarranted leap to argue that it is acceptable to impose relatively minor risks on research participants when their biospecimens could be productively repurposed to combat a pandemic.

The broader point to be taken from this case, however, is that process matters when norms will be temporarily relaxed. As discussed above, resource allocation decisions should be informed by the ethical values of “fairness and the professional duties to care and steward resources” with a procedural commitment to “transparency, consistency, proportionality, and accountability.”<sup>48</sup> When researchers propose to repurpose biospecimens in a pandemic, they should be transparent about such repurposing. This transparency does not necessarily mean that they need to reach out to research participants in real time (see policy implications below), but debriefing should be accomplished as soon as is reasonably feasible. This is particularly the case when there is evidence that an identifiable group may have concerns about repurposing of their samples. Consistency in implementation encourages trust in the system. Proportionality is important in the sense that the researchers should be clear about why repurposing is scientifically necessary for answering an important question about a serious pandemic. Finally, accountability means that researchers should try to anticipate, minimize, ameliorate, and make reparations for any potential harms that could flow from repurposing.

**The public health surveillance exception.** In 2018, the U.S. Office for Human Subjects Research Protections (OHRP) explicitly established that certain public health surveillance activities are not considered research under the federal regulations governing research with humans (the Common Rule).<sup>49</sup> Eligible activities, therefore, are not required to comply with the Common Rule’s provisions for IRB review and informed consent—even if they use identifiable private information or biospecimens. Although a formal definition of public health surveillance activities is not included, the recently updated Common Rule establishes three criteria for determining which activities in this category can be excluded from the definition of research:

- Must be a public health surveillance activity;
- [m]ust be conducted, supported, requested, ordered, required, or authorized by a public health authority; and
- [m]ust be limited to that necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets

of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products).<sup>50</sup>

Draft OHRP guidance issued in 2018 suggests that these criteria should be narrowly interpreted and are neither mandatory nor prescriptive.<sup>51</sup> The public health authority requirement constrains eligible activities to those that fall within the official mandate of agencies such as state, tribal, and local health departments or federal agencies (including the Department of Health and Human Services [DHHS], Centers for Disease Control and Prevention [CDC], and Occupational Safety and Health

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**Pandemics should prompt extraordinary flexibility. Decision-makers should draw upon existing ethical frameworks and regulatory guidance in creative ways to favor the conduct of research that is critical to the public’s health and safety.**

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Administration, among others) and that are linked to decision-making and actions that public health authorities must make. Importantly, the guidance clarifies that eligible surveillance activities may be carried out by other entities such as academic institutions or nonprofit organizations. More recent Covid-19-specific guidance issued by OHRP encourages researchers to “prioritize public health and safety,” promises to use available flexibilities in its own decision-making, and provides the following example to clarify the distinction between surveillance and research activities: “If a public health authority authorizes general screening for Covid-19 for public health surveillance purposes, and requests that test results be shared as necessary with a public health authority to allow the public health authority to identify, monitor, assess or investigate the Covid-19 outbreak, an investigator may incorporate these activities into an existing research study visit without prior IRB review and approval.”<sup>52</sup>

The 2018 guidance also expands upon streamlined language in the Common Rule about “the collection and testing of information or biospecimens,”<sup>53</sup> enumerating a variety of sources that may be used for public health surveillance, including “mandatory reporting of certain conditions, routine monitoring, vital records, medical records, medical billing records, clinical specimens, and public health investigations.”<sup>54</sup> However, both the regulations and associated guidance are silent on uses of existing identifiable research biospecimens for screening and other public health surveillance activities, which leaves open questions about how to interpret the new regulatory language in cases like the ones we have laid out above.

The sole mention of secondary analysis in OHRP’s 2018 draft guidance<sup>55</sup> is provided as a counterexample of an activity that does *not* constitute public health surveillance. Of the five specific examples of public health surveillance activities that OHRP considers not to involve research under the Common Rule described at the end of the guidance document, at least two are salient in relation to the emergence of the Covid-19 outbreak in Seattle:

- Surveillance activities designed to enable a public health authority to locate the range and source of a disease outbreak or to identify cases of a disease outbreak.
- Surveillance activities designed to enable a public health authority to detect the onset of disease outbreaks or provide timely situational awareness during the course of an event or crisis that threatens the public health.

In concept, these examples of scientific surveillance activities could be addressed rigorously using previously collected identifiable research biospecimens in much the same manner as stored clinical biospecimens have been used for infectious disease surveillance.<sup>56</sup> However, whether such activities would be deemed not to be research under the Common Rule is not a given; that determination requires both the authorization or request of a public health authority as well as an interpretation on the part of an IRB that the nature of the proposed activity is appropriately limited to the narrow public health goals defined in the Common Rule at 45 C.F.R. 46.102(l)(2).

The Common Rule public health surveillance exception reflects the paramount emphasis on population benefit offered by the use of biospecimens; qualifying activities require no research ethics committee review or consent. We think it is likely that Common Rule public health surveillance requirements would be interpreted *not* to apply to the use of previously collected identifiable research biospecimens in *in vitro* treatment-related research, even in the context of pandemic countermeasures, because such research goes beyond the mandate of a public health authority to identify, monitor, assess, or investigate an outbreak. For our purposes, the exception is quite narrow and does not address the full range of potential cases involving a real prospect of public health benefit that, in our view, would justify an argument against re-consent.

Further, the bureaucratic resistance that Chu appears to have faced from agencies such as the CDC and the U.S. Food and Drug Administration (FDA)<sup>57</sup> suggests that the Common Rule’s new public health authority requirement is not straightforwardly applied in such cases, even when the IRB overseeing her research determined that reporting positive Covid-19 results to public health authorities was not considered to be a research activity and that it instead met “the criteria for being a ‘Public Health Surveillance Exclusion’ from the federal human subjects research regulations.”<sup>58</sup> If the use of previously collected identifiable research biospecimens for public health surveillance is not considered to meet the requirements for a “not human subjects research” determination based on one or more of the criteria provided, then the activities default to being defined as research under the Common Rule, and IRB review is required to make a determination about issues like whether previous consent is adequate to address the proposed secondary uses and whether to disclose results either to public health authorities or participants themselves.

The Common Rule exclusion for public health surveillance activities will, at best, apply to a small subset of important cases and may be variably applied. Given the potential narrowness of this exception, IRBs and regulators will likely be called upon to make determinations about the appropriateness of repurposing biospecimens and the necessity of obtaining (or waiving the need for) new consent, whereas these determinations would not be needed in cases where the public health surveillance

exclusion is determined to apply. This gap between the regulatory exception and the practical reality underscores the need to explore other possible options for justifying the repurposing of identifiable research biospecimens, particularly when the original research consent was not broad enough to cover secondary use for public health emergencies.

### LIMITATIONS AND POLICY IMPLICATIONS

Allowing for relaxation of certain rules and norms in an emergent pandemic can often be ethically warranted, but society should not permit abuse of this flexibility. There should be limits on the ability to repurpose research biospecimens such that investigators are discouraged and prevented from taking advantage of an emergency to get research unrelated to the pandemic approved.<sup>59</sup>

One key limitation on the ability to ethically repurpose research biospecimens in a pandemic relates to the severity of the disease. Specifically, it is only appropriate to repurpose biospecimens when the threat of severe disease outcomes is sufficiently high, accounting for both the magnitude and probability of the potential harm. For example, it would be inappropriate to repurpose biospecimens to combat a disease with an extremely low incidence or where effective treatments are widely available. Similarly, it would be inappropriate to repurpose biospecimens to search for a novel yet undiscovered virus. A theoretical public health threat is an inadequate justification for repurposing biospecimens, as it would be practicable to collect biospecimens prospectively and with consent for this purpose and because the chance of actual harm from a theoretical public health infectious disease threat is very low.

A second limitation relates to the likelihood that the biospecimens in question would actually be a valuable tool to combat the pandemic. This again requires analysis of multiple criteria. First, it is important to interrogate whether testing available biospecimens would be a means of answering an urgently important scientific question about the pandemic. Repurposed biospecimens should be used only for projects that are immediately integral to reduction of the disease's spread or mitigation of the disease's effects. Second, one must ask whether the researchers are proposing a methodology that can feasibly answer that question using scientifically

valid methods. If it is not reasonably possible to obtain a clear result (positive or negative), it would be inappropriate to repurpose existing biospecimens. Finally, there is a question about whether the available biospecimens represent a rare or unique means of answering a pandemic-related question. If it is possible to obtain different biospecimens where broad consent has already been given, or if prospective biospecimens would suffice, repurposing biospecimens without consent is not appropriate. In addition to having IRB oversight, it might be necessary to take advantage of the expertise of institutional scientific review and prioritization processes to ensure that researchers' proposals satisfy these criteria.

Beyond these limitations, there are a number of questions about how best to implement repurposing. First, while the potential to maximize benefit and minimize harm to the public in a short-term emergency should supersede concerns about hypothetical group harms, plans to repurpose biospecimens should anticipate and mitigate group harms to the extent possible. In some cases, this might mean sharing data with public health authorities in aggregate, deidentified form, without the use of stigmatizing group identifiers, and/or engaging members of vulnerable and underserved communities in the implementation of culturally sensitive public health measures that are suggested by these data. In other cases, this would require researchers to seek input from vulnerable or underserved communities about study design, implementation, and the dissemination of results, particularly when there is prior knowledge, ideally attained through authentic and sustained engagement and relationship-building efforts, that marginalized groups have concerns about repurposing of their samples. Such consultation may reveal that benefits of rapid projects involving existing research samples are outweighed by risks to groups and should not proceed.<sup>60</sup> We acknowledge that it will not be possible to foresee and mitigate all potential group harms that might result from repurposing biospecimens in an emergency. However, investigators and public health authorities can and should monitor the impacts of repurposing biospecimens on specific groups and adjust their plans to mitigate group harms as they become apparent.

Second, IRBs might also be called upon to decide whether to require re-consent for repurposing research

biospecimens in a pandemic when feasible. Our view is that in most cases (with the possibility of group harms being a notable exception), researchers are not obligated to attempt to recontact participants to obtain new consent when there is an opportunity to conduct valuable research on their previously collected research specimens to investigate pandemic emergencies. As discussed above, not all such research is likely to be excluded from the Common Rule’s definition of research as public health surveillance activities.<sup>61</sup> Nonetheless, we argue that the pressing need for data in a pandemic will often outweigh the autonomy interests of research participants to give specific consent for ongoing use of their specimens in such circumstances. Taking the time to recontact participants to obtain their consent could undermine the ability to respond efficiently with data to inform a pandemic response.

Furthermore, repurposing specimens is not likely to conflict with participants’ expectations, particularly in cases when biospecimens were initially collected for research in similar categories (as when biospecimens collected for influenza research are being used for research about Covid-19). Consent forms are increasingly expected to include language about secondary use of biospecimens for a broad range of future uses<sup>62</sup> and expectations regarding potential public health reporting.<sup>63</sup> In addition, the majority of research participants who have provided “one-time general consent” for research uses of their biospecimens do not want to be recontacted about each subsequent use.<sup>64</sup> Even when ongoing secondary uses were not described in the original consent form, most proposals for secondary use of research biospecimens in emergency contexts should be eligible for a waiver of informed consent according to the criteria set forth in the Common Rule.<sup>65</sup>

Indeed, in the recent University of Washington case, the IRB determined that retesting biospecimens from the Seattle Flu Study for the presence of Covid-19 met these regulatory requirements for a waiver of consent.<sup>66</sup> Certainly, plans to repurpose existing identifiable research biospecimens should carefully consider confidentiality protections and other appropriate provisions to ensure that risks are minimized. For example, the Seattle Flu Study biospecimens were collected from diverse populations, which reduced the IRB’s concerns about the potential for stigmatizing a particular group.<sup>67</sup>

Finally, there will be practical questions about how much flexibility should be granted to interpret existing government regulations and institutional policies. Essential questions about repurposing will likely fall to IRBs, and although recent OHRP guidance helpfully endorses flexibility and prioritization of public health in the context of Covid-19 specifically,<sup>68</sup> decisions may involve other regulatory authorities (e.g., the FDA, Centers for Medicare & Medicaid Services, or Office for Civil Rights in the DHHS) and laws (e.g., the Clinical Laboratory Improvement Amendments [CLIA] and the privacy rule of the Health Information Portability and Accountability Act). This overlap of regulatory authorities can sometimes create tension between decision-makers with different views about ethics and/or distinct areas of bureaucratic orientation. For example, in the Seattle Flu Study case, it appeared that the IRB was comfortable with repurposing biospecimens but that regulatory agencies reportedly thought that both the lack of explicit consent as well as regulatory concerns about the laboratory’s lack of CLIA certification were problematic.<sup>69</sup> When confronted with powerful regulatory agencies that are expressing concern, institutions will be understandably worried about regulatory sanctions. Our view is that pandemics should prompt extraordinary flexibility, and we argue that decision-makers should draw upon existing ethical frameworks and regulatory guidance in creative ways to favor the conduct of research that is critical to the public’s health and safety.

## PREPARING FOR THE NEXT PUBLIC HEALTH EMERGENCY

Though there is already ethically and legally appropriate authorization for using certain biospecimens without consent (i.e., those that are deidentified, obtained with permission for broad sharing, and/or consistent with the public health exception), we believe that pandemics could uniquely require access to biospecimens that fall outside of these mechanisms. Here, we have argued for a presumption in favor of repurposing identifiable biospecimens collected for research purposes to conduct activities that will directly address a pandemic, even if the original consent would not have permitted such use, subject to some limitations. We have further argued that repurposing amidst a pan-

democratic crisis does not require an attempt to obtain new consent, even when feasible.

In any emergency, there will be a temptation to relax established rules and norms, as well as a countervailing worry about unjustified violation of vital protections.<sup>70</sup> A challenge of good governance in an emergency is navigating where to draw the line between creation of urgently needed flexibility, on the one hand, and, on the other hand, adherence to the rules as they are practiced under normal circumstances. Pandemics further complicate matters (perhaps not uniquely, but certainly acutely) by challenging autonomy rights in the pursuit of public health goals.

Under these difficult circumstances, it is important to have well-reasoned arguments about cases that will require IRBs and regulators to make a difficult choice between flexibility and strict adherence since there is possible harm associated with making a mistake in either direction. For high-profile problems like allocation of scarce life-saving resources (e.g., respirators) or the appropriateness of human vaccine challenge studies,<sup>71</sup> there will generally already be significant (albeit controversial and conflicting) guidance about how to proceed. Our motivation in writing this article was to explore the ethics of a Covid-19-related case that might reoccur in future public health emergencies. Our goal was to provide IRBs, regulators, and other decision-makers with a set of arguments to help better prepare them for making what we have argued should be an easy ethical decision to allow liberal repurposing of existing research biospecimens. In the stress of an emerging pandemic, ethical priorities will necessarily shift, and adherence to regulations that were designed primarily to protect individuals cannot be paramount when the public's health and safety are urgently at stake. ♦

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## DISCLAIMER AND ACKNOWLEDGMENTS

The views herein are our own and do not represent the views or policies of the Department of Health and Human Services or the National Institutes of Health. This research was supported in part by the NIH Clinical Center and the Intramural Research Program of the National Human Genome Research Institute. We would like to thank David Wendler and Michael Hahn for their valuable comments and suggestions.

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on Biological Samples,” *British Medical Journal* 332 (2006): 544-47.

65. Protection of Human Subjects, 45 C.F.R. 46.116(f)(3). Specifically, the Common Rule stipulates, “(i) The research involves no more than minimal risk to the subjects; (2) [t]he research could not practicably be carried out without the requested waiver or alteration; (iii) [i]f the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format; (iv) [t]he waiver or alteration will not adversely affect the rights and welfare of the subjects; and (v) [w]henever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

66. Moe, correspondence addressed to Helen Chu and Janet Englund.

67. Ibid.

68. “OHRP Guidance on Coronavirus,” Office for Human Research Protections.

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