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The Ethics of Repurposing Research Samples in a Pandemic

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Seattle Flu Study Controversy

- Seattle Flu Study (SFS) – collected samples from people in the region with flu-like symptoms
- Since Seattle was an early area to report cases in travelers, SFS had an opportunity to rapidly test these biospecimens for COVID-19 to ascertain whether community transmission had already begun

Seattle Flu Study Controversy

- Bureaucratic resistance from federal and state officials (e.g., FDA)
 - A primary worry: lack of explicit consent for the future research use of the specimens
- Ran the tests anyway and found sustained community transmission (but could have found this weeks earlier)
- IRB endorsed their decision, but officials ordered them to stop testing
 - Eventually allowed to test prospectively obtained samples with specific consent

Introduction

- In a pandemic, time is of the essence
 - “Traditional approaches to respiratory virus surveillance may not identify novel pathogens in time to implement crucial public health interventions.” (Chu et al., NEJM)
- Rapid access to previously obtained samples will be a vital tool
 - Sustained community transmission
 - Multiple strains of the organism
 - Evaluation of treatments
 - Understanding of individual disease risk and outcomes
 - Genetic host factors
- There has been no rigorous analysis of this question, although the public health community has recognized it as a potentially important issue (WHO 2015)

Some questions

- In an emerging infectious disease pandemic, is it ethically acceptable to repurpose research biospecimens for a reason other than the one that motivated their original collection?
- Does an emergency situation justify prioritizing the benefit of advancing population health at the expense of protections for human research subjects?

Our argument

- It is ethically appropriate for researchers and public health authorities to use previously collected identifiable research biospecimens for a pandemic-related purpose even if the underlying consent would not otherwise permit that use, subject to certain conditions

Situating our argument

- Existing repurposing of biospecimens
 - Repurposing of deidentified biospecimens is already permissible without re-consent
 - Repurposing of 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 **identifiable** research biospecimens would not otherwise permit repurposing

Why identifiability is important

- Reporting a positive result to an individual patient so that they can take appropriate medical action or can be placed into isolation
- Allow for contact tracing to mitigate the spread of the infection
- Link specimen to clinical data (e.g., regarding the course or outcome of the patient's illness) to better understand both the utility of early treatment attempts and individual disease risk and outcomes

Roadmap

- Value of repurposing
- Harms associated with repurposing
- Five analogous cases (where rules/norms have been altered)
 - Public health restrictions
 - Emergency research
 - Crisis standard of care
 - Public health surveillance exception
- Limitations and policy implications

Risks and harms of repurposing Biospecimens

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- Individuals
 - Unauthorized data sharing can undermine confidentiality on which participation was premised
 - Increased risk of reidentification
 - Embarrassment, stigma, discrimination
 - Non-welfare harms
 - Specimens used in a way not consistent with subject's values
- Minimal weight given to these concerns
 - Risk of tangible harm is tiny
 - Data suggests most people support most health-related research purposes for their samples
 - COVID-19 isn't controversial like cloning or reproductive research

Risks and harms of repurposing Biospecimens

- Groups

- Justice and fairness concerns, particularly when burdens would disproportionately fall on underserved or vulnerable groups
 - Exploitation – if samples taken from at-risk groups are used to primarily benefit well-off groups
 - Opportunity costs – if biospecimens were repurposed from research questions of particular importance to a particular group
 - Stigmatization – if research identifies a particular group as a driver of disease spread

Five Analogous Cases

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- Goal:
 - Borrow from cases where there is a well-developed literature about how non-ideal circumstances can change the way we make tradeoffs between the traditional, individual-focused principles of research ethics and the communitarian aims of public health ethics



Autonomy Constraints Imposed in a Public Health Emergency

- In general, the ethics of public health practice allow for the infringement on the autonomy of individuals in order to benefit the health of the community
 - Mandatory vaccination
 - Quarantine/isolation/stay-at-home orders
 - Location/contact tracing

Autonomy Constraints Imposed in a Public Health Emergency

- Public Health Ethics Framework
 - Action taken must be intended to promote the health of the population
 - Identify, consider, and equitably distribute its benefits and burdens
 - Respect the autonomy of those affected by the action to the extent possible
 - Actions taken that limit individual autonomy ought to be proportional to the public health threat and the **least restrictive** to meet the public health goal

Autonomy Constraints Imposed in a Public Health Emergency – promoting public health

- Physical distancing, isolation, and quarantine are designed to limit the spread of disease
- 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 just by a few weeks, can mitigate substantial morbidity and mortality, which in turn can curtail the need for ongoing public health restrictions

Autonomy Constraints Imposed in a Public Health Emergency – burdens

- Individuals/diverse groups – Benefits > Risks
 - Very low risk is outweighed by almost any tangible prospect of combatting a pandemic
- Identifiable groups
 - Higher bar, but not insurmountable
 - Given the magnitude of benefit early detection of community spread and early contribution to treatment or preventive development would plausibly outweigh the possibility of group harms
 - Furthermore, elsewhere in the paper we outline strategies that can be used to mitigate the possibility and effect of group harms

Autonomy Constraints Imposed in a Public Health Emergency – benefits

- Surveillance case is straightforward – everyone benefits from knowledge about disease spread
- Interventions, such as vaccines or treatments, might only be accessible 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

Autonomy Constraints Imposed in a Public Health Emergency – least restrictive means

- Generally, repurposing will only be proposed 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

Emergency Research

- Repurposing biospecimens is largely concerned with the ethics of using information gathered from people in ways to which they have not prospectively agreed
- 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
- Emergency research: research on incapacitating conditions which arise without much warning, and which necessitate immediate intervention
 - Informed consent can be a nearly insurmountable burden, justifying enrollment without prospective consent

Emergency Research Framework

- [Trial meets the ordinary standards for conducting biomedical research]
- None of the possible methods for obtaining consent are practicable
- [Extra precautions should be put into place to protect emergency research participants]
- No evidence that the research would go against the patients' preferences

Emergency Research – no other way to obtain consent

- Public health emergencies can emerge without much warning, limiting the ability to prospectively recruit subjects
- The relevant questions about a pandemic that require early and expeditious analysis will almost always require access to biospecimens taken from patients that were collected before anyone would have known to get consent for such activities

Emergency Research – no evidence that repurposing would be against preferences

- Very rare
 - Subjects will usually not have had a chance to express such a view
 - 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
- If there is positive evidence of an identifiable group's concern about repurposing, transparency and consultation are indicated

Crisis standards of care

- 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 more holistic, systems-based approach
 - In a crisis, radical departures from well-established norms can be ethically justified
- Crisis standard of care vs. repurposing
 - If we are willing to make scarce resource allocation decisions that disadvantage (perhaps fatally) specific people because of their medical or demographic profile, it seems acceptable to impose relatively minor risks on research subjects by productively repurposing samples to combat a pandemic

Crisis standards of care

- Process matters when norms will be temporarily relaxed
 - 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**”
- When researchers propose to repurpose biospecimens, they should be **transparent** about having done so
 - Not in real time, but debriefing ASARF
 - Particularly in cases of identifiable groups who may have concerns about repurposing
- **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
- **Accountability** means that researchers should try to anticipate, minimize, ameliorate, and make reparations for any potential harms that could flow from repurposing

Public Health Surveillance Exception to the Common Rule

- Revisions to the Common Rule allow some regulatory flexibility for using research biospecimens for public health surveillance purposes
 - Public health surveillance activities are not considered research
 - Not required to comply with requirements for IRB review and informed consent -- even if they utilize identifiable private information or biospecimens

Public Health Surveillance Exception to the Common Rule

- Many problems with this exception
 - Only applies to public health surveillance activities
 - Not treatment research, natural history, etc.
 - Needs a public health agency to authorize
 - Broad discretion, orientation towards risk-minimization (e.g., FDA)
 - Guidance focuses on prospective activities; no mention of repurposing existing samples

Limitations

- Severity
 - Repurposing is appropriate only when the magnitude of the threat is sufficiently high, accounting for both the magnitude of the potential harm and the probability of that harm manifesting
- Not appropriate when:
 - Low incidence/infection rates
 - Existing effective treatments
 - Searching for novel, theoretical pandemic threats

Limitations

- Effective tool for combating a pandemic
 - Repurposed samples must help answer an urgently important scientific question
 - Methodology must be sound, capable of producing data that can answer the question
 - Uniqueness



Policy Implications

- No need to obtain new consent, even if feasible
- Decision-makers should draw upon existing ethical frameworks and regulatory flexibilities in creative ways to favor the conduct of research that is critical to the public's health and safety
- Mitigate group harms, to the extent possible

Conclusion

- Though there is already ethically and legally appropriate authorization for using certain samples without consent, pandemics could uniquely require access to specimens that fall outside of these mechanisms
- We argue for a presumption in favor of repurposing identifiable research specimens to conduct activities that will directly address a pandemic, even if the original consent would not have permitted such use

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