Allocation of scarce biospecimens for use in research

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ABSTRACT

Hundreds of millions of rare biospecimens are stored in laboratories and biobanks around the world. Often, the researchers who possess these specimens do not plan to use them, while other researchers limit the scope of their work because they cannot acquire biospecimens that meet their needs. This situation raises an important and underexplored question: how should scientists allocate biospecimens that they do not intend to use? We argue that allocators should aim to maximise the social value of the research enterprise when allocating scarce biospecimens. We provide an ethical framework for assessing the social value of proposed research projects and describe how the framework could be implemented.

INTRODUCTION

A scientist has completed a research project that examined biospecimens from patients with rare neurodegenerative diseases. She has residual samples, which her laboratory's research will not exhaust, and which many other researchers would be interested in studying. Over the long term, research on these samples has the potential to lead to better treatments for devastating conditions. The scientist faces a challenge: how should she allocate these limited samples among researchers proposing valuable—but mutually exclusive—projects?[i]

When researchers, clinicians and biobanks ('allocators') have obtained consent to share biospecimens and do not intend to use them, they should distribute these samples to other researchers.[1] Though hundreds of millions of specimens are stored in laboratories, hospitals and biorepositories around the world,[2] certain samples are rare and in high demand. The pace of research has been impeded by lack of access to high-quality human biospecimens. For example, a 2011 survey found that 81% of cancer researchers have limited the scope of their work because they could not acquire samples that met their needs.[3 4] Similarly, a survey of asthma researchers found that 86% rely on human tissue in their research. Of those who use human tissue, nearly all use primary cells even though this is the preferred tissue type for only 13%.[5] In a study of biospecimen sharing, Pereira observes that the challenge of procuring samples has been called: 'the rate-limiting step' for some genomic research, 'a major roadblock to translational research and personalised medicine', and 'the number one roadblock to a cure (for cancer).'[6]

Given that a majority of researchers studying various disease processes rely on biospecimens, and given that insufficient access to biospecimens is a critical barrier to scientific progress, allocators should ensure that available biospecimens are distributed in the best possible ways. The scientific community agrees, and we affirm, that specimens must be allocated in ways that are consistent with the consent given by the donor. However, beyond this basic parameter, there is a lack of clarity regarding how samples ought to be distributed. Despite calls for guidance on the distribution of these research resources,[7] very little has been written about the ethics of allocating biospecimens among competing research programmes when demand exceeds supply. As a result, researchers and clinicians have minimal guidance on which to base allocation decisions.

Although biobanks have expertise in sharing samples, their policies are usually private, and the publicly available policies reveal disparate and in some cases dubious criteria. A 2017 study found that only 74 of 523 biobanks (14%) have publicly available access policies and that only 20 of these (27%) specify prioritisation criteria for allocating samples.[7] The most commonly cited criterion, 'priority for active members (contributing/collecting),' was cited in only four policies. Other policies include criteria that may lead to suboptimal allocation, such as 'first come, first served.' Providing scarce resources to the first researchers who request them without taking account of the importance of their research is likely to reduce the resources available to researchers whose projects would yield more social value. Even more concerning is evidence that confusion regarding how scarce samples ought to be distributed has a chilling effect on the sharing of samples, leading to their underuse.[6]

In this article, we present an ethical framework for researchers, clinicians and biobanks who have biospecimens they could share. We show how applying the framework would help maximise the social value of the research enterprise, and we offer guidance on the process by which allocation decisions should be made.

MAXIMISING THE SOCIAL VALUE OF RESEARCH

In distributing samples, allocators should aim to maximise the social value of the research enterprise. In this context, the term 'social value' refers to the importance of the expected benefits of allocating samples to a given research project.[8] Two components are widely considered relevant to assessing the importance of benefits: the magnitude of the benefits and the extent to which the beneficiaries deserve priority, where those who are worse off deserve higher priority.[9] The social value of allocating samples to a given research project is therefore a function of the magnitude of the benefits that this

[i]This example is modeled on a consultation that came to our Bioethics Consultation Service.

Table 1 A framework for allocating scarce biospecimens

Principle	Criterion	Key questions
Maximise social benefit	Necessity	How critical is it that the proposed research project uses these samples, rather than samples that are more widely available?
	Quantity	How much sample does the proposed project require?
	Plausibility	How likely is it that the project will meet its scientific aims?
	Prevalence	How many people are affected by the condition that the project will investigate?
	Magnitude	If the project succeeds, to what extent will it advance the scientific enterprise?
Prioritise disadvantaged populations	Disadvantage	How disadvantaged are the populations affected by the conditions that the research project targets?
Fair process	Transparency	Are allocation processes and decisions publicly available?
	Revisability	Can allocation decisions be appealed?
	Inclusion	Are stakeholders and experts appropriately included?

choice will yield and the degree of disadvantage of the choice's beneficiaries. All else being equal, it is more socially valuable to allocate resources to scientific projects that are expected to generate greater benefits. However, it matters how the benefits are distributed. It would be unfair if all biospecimens were used in research on conditions that mainly affect advantaged groups, even if using biospecimens in this way would maximise the total benefits generated by the research. Thus, all else being equal, it is more socially valuable to allocate samples to a scientific project that is likely to benefit more disadvantaged patients.

In practice, it is difficult to determine who will benefit, and how much, from health research. For example, in the development of new pharmaceutical treatments for a specific condition, there may be great uncertainty about whether an intervention will result from the research, the degree of effectiveness that any resulting intervention will have, who will have access to it and so forth. These problems are magnified for basic science research, where plausible interventions may not yet have been identified. However, this significant uncertainty does not entail complete ignorance about the magnitude of expected benefits or the identity of probable beneficiaries. Here, we propose six criteria that, taken together, can help allocators assess the expected social value of allocating scarce biospecimens to a proposed research project (table 1).

First, necessity: How critical is it that the proposed research project uses these samples, rather than samples that are more widely available? Some research projects rely on unique features of the samples they use. If those features cannot be found in alternative sample collections, the project cannot be carried out. Other research projects could be carried out with samples from various different sources and so are not reliant on any particular allocator. For example, a project studying a rare form of amyotrophic lateral sclerosis may require samples with a specific genetic mutation, while more general projects on neurological disease may be able to use a wider variety of samples. Allocators should give higher priority to projects insofar as the samples the project needs are rare. In so doing, they will facilitate more research, maximising the benefits produced by the research enterprise as a whole.

Second, quantity: How much sample does the proposed project require? Allocators should prioritise projects that require less material, as there is an opportunity cost associated with using up scarce samples. More resource-intensive projects should be more socially valuable.

Third, plausibility: How likely is it that the project will meet its scientific aims? Allocators should attempt to identify projects that will be successfully carried out. By this we do not mean projects that produce positive results, but rather ones that are expected to achieve their scientific aims within a reasonable timeframe. In assessing whether a project is likely to succeed, allocators should take into account its design and feasibility, as well as the research team's funding, qualifications, and track record. More risky research projects must be justified in terms of the other criteria—for example, on grounds that the reward in the event of success would be much greater than it would be for more conservative projects. Allocators may not always be in a position to assess the plausibility of proposed projects, especially when these projects fall outside their research area. When this is the case, it is reasonable for allocators to defer to previously conducted peer-review processes, operating on the assumption that projects which have passed peer review meet a threshold of plausibility.[ii] However, allocators with more resources and who allocate specimens more frequently should set up infrastructure to facilitate independent plausibility assessments.

Fourth, prevalence: How many people are affected by the condition that the project will investigate? All else being equal, projects targeting conditions that affect more people should receive higher priority because there are more potential beneficiaries. Frequently, competing projects will propose to study the same condition. For instance, multiple research teams may request to use glioblastoma tumour samples in studies expected to benefit glioblastoma patients. In such cases, allocators should consider whether the proposals investigate features of the disease that affect a larger or smaller proportion of patients. While this criterion favours more common conditions, it should not prevent research on rare conditions. Rare conditions will get higher priority for samples that are specific to those conditions (on necessity grounds), and research into health problems that are under-studied are likely to merit higher priority on grounds of magnitude.

Fifth, magnitude: If the project succeeds, to what extent will it advance the scientific enterprise? The ultimate goal of health research is to improve human health. It will sometimes be possible to estimate the type of health benefits that individuals would experience if a project succeeded. Projects that would yield larger health benefits for individual patients should then receive higher priority. However, it is often very difficult to anticipate the ultimate effects that research will have on individual patients, especially for basic science research. For such research, some sort of proxy indicator for magnitude should be sought. We suggest that allocators assess the magnitude of the expected benefits of such projects by considering the extent to which they will advance the scientific enterprise if they succeed. Which projects will advance the scientific enterprise more depends in large part on where researchers are in the life-cycle of investigating a disease. For example, if a disease has only recently been discovered, then projects studying its most fundamental pathways may

[ii] We are grateful to an anonymous reviewer for this suggestion.

be useful. If extensive research has already been done on a given disease process, allocators might instead prioritise projects that test promising drug targets.

Sixth, disadvantage: How disadvantaged are the populations affected by the conditions that the research project targets? Where possible, allocators should prioritise research that is expected to benefit disadvantaged populations. There is disagreement among scholars about whether those allocating resources should take into account forms of disadvantage other than medical disadvantage. However, we think that the reasons favour considering both medical and social disadvantage when evaluating how badly-off a population is.[10] In order to benefit medically disadvantaged patients, allocators should favour projects that investigate conditions that cause higher morbidity and mortality in the patients who have them. Socially disadvantaged populations include the medically underserved, people with low socioeconomic status, and otherwise marginalised groups. The medical disadvantage of a population can be assessed using familiar measures, such as years of life lost through premature mortality, quality of life assessments, and so forth. It will often be more difficult to ascertain whether a given research project is likely to benefit socially disadvantaged groups and to quantify their degree of disadvantage. However, allocators can ask questions like the following: is the condition that the researcher intends to study most prevalent in poorer or richer countries and communities? If the researcher plans to study a treatment, what are the chances that the treatment will be affordable and widely accessible? Have disadvantaged populations benefitted from similar research in the past?

IMPLEMENTATION OF THE CRITERIA

Allocators may face uncertainty in applying the aforementioned criteria, since there are rarely clear and determinate answers regarding the benefits that research will yield, who will benefit and how trade-offs should be made among valuable goals. As a result, it will be difficult to make direct comparisons between competing projects. Moreover, allocators do not typically receive requests for samples concurrently, so they may be unable to predict how much demand for a specimen there will be in the future or how valuable future proposed projects would be. The following suggestions for priority-setting processes may mitigate these sources of uncertainty, even if they cannot be eliminated.

First, we recommend that reviewers score incoming proposals on the six criteria. Samples can then be provided to those proposals that reach a threshold of social value. While this approach is distinct from an allocation process that relies solely on 'first come, first served,' it similarly eliminates the need to attempt head-to-head comparisons and prevents samples from going unused. The threshold that an allocator employs can and should vary according to factors such as the quantity of materials available, actual and projected demand for the samples and so forth. Thresholds can also be established for individual criteria, since a very poor score on one criterion may indicate that allocating samples to that project would yield little or no social value. For example, projects that lack plausibility will lack social value, no matter how important the health condition they propose to investigate.[iii]

[iii]Thank you to an anonymous reviewer for bringing this possibility to our attention.

There are two further sources of uncertainty that are not addressed by establishing a threshold. First, reasonable people may disagree about how a criterion should be interpreted. For instance, even if reviewers agree on what benefits will be generated by two different projects, they may disagree on which project will advance human health more. One might favour cure research, while another might prefer research on new diagnostics. Second, there may be uncertainty about how to balance different criteria. For example, one project might be expected to benefit patients who are very badly off, while a second might benefit more patients, but healthier ones.

These sources of uncertainty are unlikely to be eliminated, but they can be partially addressed through using a fair process to implement the framework. A fair process will ensure procedural fairness and can also promote fairer results by illuminating which benefits of research matter most to stakeholders. To realise these objectives, the process should be transparent, include a mechanism for appealing decisions and involve relevant stakeholders and experts.[11]

While all allocators should strive to be fair, the appropriate process for distributing samples will depend on the scale of specimen sharing. Allocators with more resources or who allocate specimens more frequently should set up structured processes that involve regular meetings between stakeholders and experts. Biobanks might consider the research priorities of specimen donors by including them on the panel that scores proposals and makes allocation decisions. For instance, the Mayo Clinic Biobank established a Community Advisory Board to work closely with biobank leadership in developing and implementing new policies.[12] By contrast, resource constraints would typically render it unrealistic and inefficient for individual researchers to institute separate processes and establish formal panels. These researchers can nonetheless realise some of the benefits of a fair process through less burdensome means. For instance, a researcher could determine stakeholders' preferences by consulting her patients or reviewing the literature on a patient population's priorities. Similarly, a formal appeals process may be feasible only for larger allocators, but smaller actors should remain open to having conversations with requestors whose requests for samples were denied when they have additional information to present.

FUTURE DIRECTIONS

Our framework does not resolve all uncertainty surrounding the distribution of scarce biospecimens. More empirical research is needed in order to elucidate best practices, and there remain several areas in which further normative work is warranted.

First, how the criteria in our framework should be weighted relative to one another depends on the answers to both normative and empirical questions. As far as we are aware, the data do not exist that would allow us to answer the relevant empirical questions, such as the extent to which plausibility matters vs prevalence in generating knowledge that ultimately benefits patients. Likewise, as we noted above, criteria such as magnitude surely matter, but it is an open question how they should be measured for the purposes of research priority setting, especially for basic science research. Given this empirical uncertainty, we would caution against putting too much weight on comparisons between research projects on criteria—like magnitude—that are hard to quantify. Allocating scarce biospecimens on the basis of a systematic framework, like the one we outline, is likely to result in a better distribution, but perfect precision is not to be expected. Over time, experimentation with different ways of evaluating and comparing research projects that request biospecimens may inform improved practices.

Second, we have not discussed when researchers are ethically required to share their samples or what duty they have to inform the research community about their collections. Allocators are bound by certain constraints—for instance, on their time, and by what donors have consented to. Their duty to distribute samples in a socially valuable way may sometimes be challenged or overridden by these other obligations. The nature of the obligation to promote socially valuable research may also be affected by who the allocator is. For example, actors within the private and public sectors may have obligations to different populations. Nevertheless, we think that almost all allocators will have some obligation to promote socially valuable research. For-profit organisations, for instance, benefit from government legal protections, taxation policies that incentivise research and federally funded basic science research. They, therefore, have obligations to the states in which they operate, and one way of discharging these obligations is by promoting socially valuable research.[13]

Third, the principles we propose govern the allocation of samples within the constraints of consent processes that are already in place. We have not addressed the question of how a consent process should be designed when researchers anticipate sharing their samples later on. Here, there may be a balance to strike between facilitating sample sharing, and so maximising the value of future research, and taking into account considerations such as increasing ease of recruitment and providing participants with greater control.

Last, allocators may have reason to prioritise researchers who have shared their own biospecimens in the past and who have a track record of collaborating with other teams conducting related research. Doing so may incentivise cooperative behaviours that can ultimately promote social value. However, it is unclear whether these considerations are ethically important, arising from duties of reciprocity, or whether they are merely instrumentally important, allowing for the continued existence of sample collections. Moreover, giving such considerations too much weight may disadvantage smaller or newer teams in ways that may fail to promote social value. This issue merits further thought.

CONCLUSION

Allocators distributing samples should aim to maximise the social value of the research enterprise. Social value is a function of the magnitude of the expected benefits and the degree of disadvantage of the beneficiaries. We have provided a framework that will help allocators make decisions in light of this goal.

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