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Pass the tissue: restoring researcher access to legal human donations

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ABSTRACT

The sensitivity of human tissue and previous instances of misuse have, rightfully, led to the introduction of far-reaching oversight and regulatory mechanisms for accessing, storing and sharing samples. However, these restrictions, in tandem with more broad-based privacy regulations, have had the unintended consequence of obstructing legitimate requests for medical materials. This is of real detriment to ambitions for biomedical research, most notably the precision medicine agenda. As such, this paper makes the case for facilitating authorised researcher access to human tissue and associated data along practical medical ethics lines, detailing how liberating samples from unfit regulations, re-evaluating biobanks, diversifying considerations for donor benefit-risk, future proofing donor consent and flattening hierarchies of donation acceptability equate to a more cohesive and respectful means of managing biological samples and information than is achieved at present.

Recognising the sensitivity of human tissue donation and the historical[1] and contemporary abuses[2] thereof, strict regulations now govern sample sourcing, supply, retention and destruction. European mandates, including the Tissue and Cells Directives (2004/23/EC[3] ; 2006/17/EC[4] ; 2006/86/EC[5]), have set standards for the quality, safe passage and testing protocols of human tissues intended for biomedical research while the Human Tissue Act of 2004[6] regulates the life cycle of these samples in the UK. However, the expansive nature of these legislative changes has often had the unintended consequence of obstructing researcher access to human samples via authorised pathways.[7] The scope of these restrictions, and their accompanying bureaucratic burden, has been criticised as stifling to scientific innovation and discovery.[8] This is especially apparent during times of public health emergency where inflexible regulations delay critical research.[9] Additionally, meeting broad consent and privacy requirements is challenging, especially when work leverages retrospective data or biobank stock. It may not be possible to confirm sample origins or previous terms of consent in these contexts.[10]

Consequently, this paper will make the case for improving researcher access to human tissue along practical medical ethics lines. It will demonstrate how streamlining regulations, reforming biobanking, diversifying donor benefit-risk, future-proofing donor consent and tackling hierarchies of donation acceptability represents a more cohesive and ethically rigorous approach to the access and appropriate use of human tissue than we are achieving at present.

A REGULATORY OVERSIGHT

Biological samples are best analysed in the context of the body they were extracted from. Doing so at scale not only reveals patterns of disease specific to the individual but those of potential relevance to entire populations. However, by labelling human tissues (annotating the gender, age, race, blood type or even lifestyle of the person they were extracted from) or providing researchers with wraparound access to relevant medical records, we increase the risk of donor reidentification during data security breaches.[11]

Efforts to mitigate this risk have produced a daunting regulatory environment, with legislation including General Data Protection Regulation,[12] the Oviedo Convention[13] and the US Health Insurance Portability and Accountability Act[14] enforcing levels of data accountability that our current research landscape is insufficiently resourced to meet in all instances. Inequalities emerge in laboratory capacity to take on the associated administrative burden or to plan for the retrospective, collaborative or longitudinal research efforts that present greater consent challenges: these barriers select for only the most established and well funded.[15] Meanwhile, inflexible, and sometimes incomprehensible, tissue and data sharing agreements are disincentivising to industry and academia and the time and expense taken to secure them can be financially prohibitive to both.[16] Worse still, while official channels of procuring tissue data remain this challenging, private or black market channels will continue to proliferate.[17]

As a collective, these obstacles carry substantial consequences for patient outcomes. The prioritisation of privacy over prognosis is especially poignant for those without the luxury of time. The concept of reciprocal altruism is a recurrent theme in research into patient motivations for donating biological samples: here the expectation, or at least hope, is that these donations lead to the discoveries that facilitate their recovery or that of patients just like them.[18] Though not strictly a violation of terms of consent, restricting researcher access in this way is arguably a violation of the spirit, or social contract, by which that consent was given.

While necessary, regulation also inhibits drug discovery and—with digital, cultured or synthetic tissue research in its infancy[19]—fosters an overreliance on animal samples[20] that are usually poorly generalisable to human outcomes[21] and ethically dubious.[22] As such, it is recommended that regulators pursue a more streamlined approach, ringfencing medical data and materials away from domain-general privacy regulations and constructing terms of access that can flex to patient preferences and prognoses.

THE BIOBANKING CRISIS

Red tape is far from the only bottleneck in biomedical research, however. The activities of biobanks, facilities dedicated to the processing, storage and onward distribution of biomedical donations, have also faced criticism. For example, the ways in which their performance is currently evaluated—most notably stocklist size and measures of capacity—can perversely incentivise donation hoarding.[23] This prolonged storage—and the destruction of expired samples that often occurs as a consequence[24]— is a direct violation of donor good faith and the aforementioned Oviedo Convention.[13] As per Article 22 ('*the use of parts of the human body must be restricted to that for which specific information and consent was given*'), the indefinite retention of samples invalidates consent taken from donors expecting them to be used for biomedical research.

As a bank, and not a vault, the health of these facilities must instead be appraised through metrics including collection-distribution turnaround time. Initiatives such as the Ethical Tissue Bank based out of University of Bradford[25] have been stood up to answer this call, countering the underutilisation of donations. Here, success is measured against the pace of sample churn, the breadth of sample distribution and the scale of research impact as access requests are trimmed down to a 3-week approval process. This is an asset for time-sensitive research; entire granting periods can expire in the time taken to secure samples from conventional biobanks, by comparison.[26] It is, therefore, recommended that this model of biobanking be considered best practice going forwards. As echoed in work by the European Commission[27] and Makhlouf and colleagues,[28] this will only be achieved if biobanking governance models and accreditation systems are aligned internationally—better coordinating access to donations and collaborations between entities in the process.

A NEW BENEFIT SYSTEM

At present, these opportunity costs of failing to use tissue samples for their donated purposes are poorly incorporated into the utilitarian benefit–risk calculations at the centre of medical ethics.[29] Moreover, while these concepts of benefit and risk should have parity, the legal protections associated with risk are far weightier in biomedical research than those associated with patient benefit: legal recourse can be sought for damages, but not so easily for lost opportunities.

There are multiple examples where this institutionalised risk-aversion has led to the termination of potentially high-reward investigations. Recent disruptions to the male contraceptive campaign are notable example—products that only spelled additional risk for its intended consumers (mild side effects) despite sizeable benefits for fertile partners who do not wish to conceive.[30] This conservative mindset has likewise undermined the use of human tissue and associated data as the hypothetical risks of reidentification or tissue misuse supersedes indirect, shared or other more distal forms of donor benefit. The sharp consequences of violating tissue protections only exacerbates the likelihood of their underuse and subsequent destruction. This, again, is in direct conflict with the tacit assumption or explicit assurance of onward usage that underpins donor consent. Failing to use what has been freely given out of fear of the ramifications that come with doing so improperly constitutes a violation of this consent.

Therefore, just as the advent of shared patient benefit–risk has seen the renewal of male contraceptive research,[31] this paper recommends that biomedical research stretch its own conceptualisation of the ways in which patients can benefit from donating their tissue and give even the most invisible positive externalities appropriate weighting in ethical evaluations in the process. The risk of sample expiration must also be fully costed, with biobanks reprimanded or fined when samples are stored indefinitely or data access is obstructed arbitrarily.

CONSENT À LA CARTE

This paper has evidenced the primacy of both obtaining and honouring donor consent for ethical conduct in the biomedical sciences. In this, a prospective donor must be fully aware of what their contribution to research amounts to and the way their data, or donations, will be stored. However, due to the aforementioned legalities around this process, consenting a patient can be a narrow exercise: patients are typically invited to support a specific research endeavour in a specific way with data retained for a specific time and purpose. Changes to a research protocol will, therefore, need to reconsent the original patient set to go ahead. This can be cumbersome, especially when aiming to reanalyse data from the now-deceased, and frustrating for living donors who are repeatedly contacted to update their permissions.[10]

Such 'single-use' consent conflicts with the experimental or expansive mindset that necessitates scientific discovery. It allows little room for nuance or conditionality, especially from the patient-side. This can be disempowering as individual patient preferences cannot be incorporated into standard legal documents. That said, obtaining broad or flexible consent at the point of extraction also poses problems: presenting patients with extensive lists of possible uses of their data, sometimes at the most stressful moment of their lives, can blur the line between consent and duress.[32]

To counter these opposing criticisms, this paper recommends a middle way be found between one-time and open-ended consenting. A menu-style approach could be a viable way forward, if presented in plain language. Here, donors would be at liberty to consent via standard text or, if preferable, use additional opt-in clauses to stretch their consent to broader research interests or make it conditional to specific time windows or use-cases (vetoing pluripotent stem cell use in animal research, eg). This enhanced consenting process could also include accelerated data-sharing agreements, providing those who value research participation above extensive privacy protections with a mechanism to fast-track their samples and associated data to researchers. This tailoring process future-proofs donor consent and elevates their wishes above overfitting bureaucracy. It is acknowledged that this will have implications for online tissue directories—platforms that, based on researcher specifications, collate decentralised samples and their associated data. They will be required to adjust cataloguing methods to indicate when donor consent is no longer harmonised across intended research cohorts.

EMOTIONAL HIERARCHIES

Beyond the structural, bureaucratic and legal challenges outlined, it is important to acknowledge the more psychological factors that influence tissue donation and the disparities in giving that these have engendered.

While strict rationalists are loathe to admit it, emotion plays a considerable role in the causes we prioritise and the way we legislate. Disgust is a key example: our aversion to pursuing urgent medical and moral agendas including tissue donation, abortion

and euthanasia sees simple squeamishness at its root as visibly as economics or religious difference.[33] However, this disgust is not elicited evenly, with hierarchies emerging in all areas cited. This is especially true within tissue donation.

Research has demonstrated how superficial tissues are donated far more readily than visceral or self-identified counterparts in the brain, heart or eyes.[34] Perhaps a human trait, this acceptability gradient is paralleled in *carnism* where the extent of our emotional distance from an animal—or our ability to personify it—determines our likelihood of consuming it.[35] Despite the recent change from opt-in to opt-out donation models,[36] the persistence of this cognitive bias undermines the biodiversity of our tissue pipeline and the quality of our research by extension. Tackling this uphill battle takes on Sisyphean qualities as patient mistrust in donation cannot be countered by the scientific success stories that encourage a culture of universal giving.

This is a catch-22 that our regulatory environment is enshrining, not dismantling. For example, abortive tissue is still far harder for researchers to access than its less value-laden alternatives despite the pluripotency it offers and the informed consent of its donors.[37] Its prevalence means that it is indeed its perceived sanctity, and not scarcity, that is responsible for this. This is a sanctimoniousness we can ill-afford given our designs for treating, preventing and even eliminating disease. It is also one that has historically amounted to white exceptionalism in practice. Such deference has not been extended to persons of colour (where the examples of Henrietta Lacks, Tuskegee and the use of enslaved bodies as 'anatomical materials' are top of mind[38]) or protected environments where our appetite for extraction goes far deeper than the topsoil we are willing to offer of ourselves.[39]

Unless biomedical materials are destigmatised wholesale, public trust will continue to collapse when 'undesirable tissues' are discovered in the products we benefit from—just as we saw when the use of fetal cells in certain COVID-19 vaccines was disclosed.[40] This paper calls for policymakers to combat these taboos head on—consciousness raising in close collaboration with aligned community leaders and educators to divorce legitimate donation from trafficking and promote the value of such altruism for population health. Meanwhile, our regulations and codes of ethical conduct cannot be permitted to continue to prop up or pander to our most irrational instincts.

UNDERUTILISED AND UNDERSERVED

To conclude, the consequences of failing to act on the recommendations proposed (table 1) are considerable. Until cloning, cultivation or digital twinning technologies reach maturity, the gap between the biomedical discoveries we are making and of those we are capable will only be closed by public engagement with donation drives. While their privacy and bodily autonomy are inalienable in this, patients will be underserved if legitimately acquired samples remain underutilised. Moreover, the inertia, overregulation and irrationalities that contribute to this will undermine the biomedical field's sincerity if widely publicised and disillusion patients from participating within it going forwards.

Table 1 Summary of problem areas discussed and solutions proposed

Problem area	Proposed solutions
Difficult regulatory landscape	► Consensus building on what regulations are strictly necessary and which only serve to disincentivise, or create inequalities within, biomedical research ► Ring-fencing tissue samples and associated data away from domain-general privacy restrictions ► Construct regulations, data sharing agreements or terms of access that are more flexible to use-cases for example, more liberal allowances during public health emergencies or when advancing the interests of patients with terminal illness
Biobank sample retention	► Evaluations to focus on throughput of samples and speed of researcher access rather than storage metrics or stocklist sizing
Risk aversion	► Consider applying lessons learnt from introduction of 'shared consent' to diversify the benefits considered when evaluating proposed research or donation drives for example, positive externalities, psychological benefits, long-term benefit to patients like the donor etc. ► Better incorporate the opportunity costs of failing to undertake research or use samples
Narrow consent	► Menu-style approaches be explored, allowing patients to have greater control over the breadth of their consent and its terms, conditionalities and non-negotiables
Selectively stigmatised donation	► Government-supported and subsidised awareness campaigns for the value of donating human tissue ► Universal promotion to address acceptability gaps between tissue donation types

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