Inclusion of Residual Tissue in Biobanks: Opt-In or Opt-Out?

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Abstract: Residual samples are an important source of tissue for biobanks. They refer to leftover tissue that is obtained in the course of clinical care. Residual samples can be included through an opt-in method—that is, a person explicitly expresses consent to include residual tissue—or an opt-out method—that is, the tissue is stored unless a person explicitly refuses. At the moment there is a renewed interest in the appropriate method for the inclusion of residual samples in biobanks. The expansion of biobanks and rapid developments in biomedical research underscore the need to evaluate the proper procedure. In this article we revisit the arguments in favor and against opt-in and opt-out methods for residual tissue research. We conclude firstly that an opt-out method is only justifiable when certain conditions are met: (1) awareness has to be raised, (2) sufficient information has to be provided, and (3) a genuine possibility to object has to be offered. An opt-out procedure that fulfills these conditions can be called a “thick” opt-out method. As a consequence, the dichotomy between opt-in and opt-out is less stark than usually suggested, as both methods require a certain amount of effort. Secondly, we conclude that because of the diversity of tissue and research, not every situation can be treated alike. There are at least four situations that require opt-in procedures: (1) research with higher risks or increased burdens, (2) the use of controversial or high-impact techniques, (3) research on sensitive tissue types, and (4) research involving vulnerable patients. We suggest that further interdisciplinary debate should answer the question when to opt-in or when to opt-out.

A biobank can be defined as a collection of human biological samples stored for medical-scientific research purposes, usually linked to phenotypic data [1,2]. To collect material, biobanks have different strategies: they may collect tissue specifically for research purposes, but often contain residual samples as well. Residual samples refer to tissue that was taken in the course of clinical care and is leftover (e.g., a diagnostic biopsy or therapeutic removal of tissue). In many cases, the stored tissue will be most valuable for research when it remains linked to information about the person [3–5]. Therefore, the included samples will often be stored coded and consequently will not be anonymous—if complete anonymization would be possible at all [6–8].

Regarding the inclusion of residual tissue, two predominant methods can be discerned: opting-in and opting-out. In an opt-in scheme, a person explicitly expresses his or her consent. Contrarily, in an opt-out scheme inaction is treated as a signal of consent [9]. A strong consensus exists that opting-in is the preferred method to include people in clinical research [10]. The same counts when tissue is collected specifically for research, since research is the only reason for taking the sample. However, at the moment, there is no consensus about the most appropriate procedure to include residual samples. Both opt-in and opt-out methods are practiced and advocated [11]; some even argue that there is no consent required at all [12,13].

The expansion of biobanks and the rapid developments in biomedical research (e.g., the emergence of whole genome sequencing (WGS) and the increase of personal information that can be derived from research [8]) emphasize the need to rethink the appropriate way to include residual tissue in biobanks [14,15]. Therefore, we sought the key arguments in favor and against opt-in and opt-out methods for residual tissue research in the literature. The aim of the article is to present an overview of the arguments and to discuss them briefly. We focus on new residual tissue that is stored coded and will not review the subject of archival residual tissue—residual tissue that is already stored at this moment. We will conclude by offering some brief comments in order to take the current debate a step forward.

Arguments in Favor of an Opt-Out Method for Inclusion of Residual Samples

Scientific Advantage

Opt-out procedures for the inclusion of residual tissue in biobanks are associated with low refusal rates and therefore high participation rates [16,17]. In order to generate scientifically valid results, sufficient numbers of samples are needed. People who are indifferent or do not mind participating in research, but are not willing to make an effort to explicitly consent, will be enrolled in an opt-out procedure. Conversely, they will not be included in an opt-in procedure.

However, it has been noticed that an opt-out method could, in theory, have a

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Abbreviations: IRB, Institutional Review Board; REC, research ethics committee; WGS, whole genome sequencing

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negative effect on participation rates as well. If people dislike the idea that their consent is not explicitly sought, it is possible they opt-out of participation because of public distrust or because their “gift” is taken for granted [9].

Lower Financial Costs

An opt-out procedure is associated with lower costs [18,19] compared to an opt-in procedure—which is generally costlier due to extensive procedures and lower participation rates [20,21]. Money spent on the recruitment of participants cannot be used for other purposes. As a result the quality of the research may decrease or some projects may not be able to start at all. However, whether an opt-out procedure indeed is considerably less costly depends on the way the formulated conditions are filled in. A very “thin” opt-out procedure, without adequate information provision or genuine possibilities to object, will certainly be less expensive. But when more demanding conditions are formulated, an opt-out procedure requires certain amounts of efforts and thus money as well [22].

Moral Duty to Participate

The aim of conducting biomedical research is to generate biomedical knowledge, which is a benefit as such [2,23,24] and may eventually also prevent serious harm [25,26]. Therefore, with an appeal to principles such as beneficence, solidarity, and reciprocity, participation in biomedical research can be considered a moral duty [25,27–29]. Solidarity calls for mutual support [30] and reciprocity appeals to a duty to contribute to the development of biomedical knowledge since we all benefit from it [25,31]. Although this duty would exist both with an opt-in and an opt-out procedure, it can nevertheless provide an argument for a less demanding procedure for the inclusion of residual tissue, like the opt-out procedure. After all, when there would be a moral duty to allow inclusion of residual tissue, it is reasonable to adopt a system where participation is the starting point or default position. Some even consider it an argument for not obtaining consent at all [12,27].

However, several important objections have been made against this duty [32,33]. For example, there are many actions that would benefit others or could rescue them (e.g., donate money for food). Priority or a special status for participation in biomedical research, compared to other goals, has not been shown. Another objection that has been made is that people already contribute to biomedical research by paying taxes and for treatments; therefore, they would not have a duty to participate based on reciprocity [32,33]. A complete overview of the extensive discussion on whether there is a moral duty to participate in biomedical research and if this duty would be strong enough is beyond the scope of this article. However, residual tissue research is considered to generate important biomedical knowledge and the association of the research with low risks and burdens would provide an additional argument for a moral duty [31].

Low Risks and Burdens

Research on tissue does usually not entail the same risks as research on persons. Moreover, residual samples are taken in the course of clinical care; therefore, there are no additional physical burdens involved. Consequently, many have estimated the risks of biobank research as low or even absent [3,5]. However, the precise consequences of biobank research are sometimes difficult to predict [34] and the accompanying risks may be less clear than they appear to be [35]. Particularly, the information derived from samples can harm people [36]. There are psychological and/or social risks (e.g., genetic discrimination or stigmatization of groups, possible implications for family members, and consequences for employment or insurance possibilities) [37–40].

It follows that the risks involved in biobank research are tightly connected to the type of research that will be carried out on the sample, as there will be certain studies that are associated with higher risks or burdens. For example, when a researcher intends to conduct WGS, the risk of disturbing information is present. The risks are also tightly connected to the governance policy of the biobank (e.g., how the confidentiality and security measures are regulated). For example, a well-functioning Institutional Review Board (IRB), known in the European Union as a Research Ethics Committee (REC), can minimize the chance of (excessive) risks by assessing the research protocols and applying ways of risk management [3,12].

Compatible with Autonomy

Usually, a distinction is made between negative and positive autonomy. Negative autonomy is commonly understood as the right of a person to make personal decisions without undue influence or coercion from others [41]. Positive autonomy refers to the more “thick” interpretation of autonomy and entails the ability to take control over one’s life and to live according to one’s values and beliefs. In a positive account, autonomy is associated with concepts like self-expression and self-determination [41].

Within an opt-out procedure potential participants can be sufficiently informed and they can still make a personal choice whether they want to participate or not [42,43]. Therefore, an opt-out method could be an adequate and sufficient way to respect autonomy [44]. However, this again depends on the exact implementation of the procedure. Firstly, people should be made aware of inclusion of their residual tissue as the default position. Secondly, they should receive adequate information about this and have easy access to additional information. Furthermore, they should have an accessible way to object to participation and this should be adequately registered [42,45,46]. For example, it is difficult to maintain that negative autonomy is respected when residual tissue is included without people knowing this. Also, when people do not receive understandable information, they will not be able to judge whether participation corresponds with the idea(ies) they have and positive autonomy will therefore not be fostered. It has been shown that, at present, there is (too) low awareness of people about the use of their residual tissue in research [47,48] and biobanks [49].

Positive Public Attitude

In general, people seem to have a positive attitude towards the use of their residual tissue for biomedical research, as they consider it to be an important goal [47,50–53]. Some argue that because of this, an opt-out method is best suited for biobank research [44].

However, a positive public attitude towards the use of residual tissue does not necessarily signify support for opt-out procedures. In addition, people themselves have expressed that although they emphasize participation, they expressed a preference for an opt-in procedure over an opt-out procedure [54,55].

Also, there is considerable variation in the views of the public [56]. It has been suggested that in general patients have a more positive attitude towards biobank research than the general public [57]. More specific, it has been shown that cancer patients preferred a thick opt-out procedure over an opt-in [38,59]. In addition, surgical waste was regarded very differently compared to healthy tissue. There was less concern about how unhealthy tissue was used after removal [48]. Therefore, although a positive attitude may be shared by many, it cannot be generalized [60]. The opinion of the
Fostering Positive Autonomy

Arguments in Favor of an Opt-In Method for Residual Samples Respect for Negative Autonomy

An opt-in procedure requires an act of consent from the individual before the proposed action will be carried out. Due to this requirement, respect for negative autonomy would be safeguarded. This will be of even greater importance when the participant can be considered the owner of the removed tissue—whether he or she can still be wronged when the decision about the inclusion of their residual tissue was taken from him or her [5, 65]. It would be misleading not to actively inform people about inclusion as the default position, as it would be reasonable for people to assume that residual tissue will be discarded. In an opt-out method it is assumed that people are aware of their inclusion, understand the information, and will take action if they do not want to participate [66]. As there is no evidence that people are willing to participate, it has been stated that opt-out, in principle, can never be considered as actual consent [67].

Fostering Positive Autonomy

To foster positive autonomy, non-interference is insufficient; one really needs to stimulate autonomous decision making. For example, when the research may generate relevant research results, mere non-interference is insufficient for adequate decision-making. Earlier we have defended a qualified disclosure policy, where different packages of individual research results are presented [68]. Opt-in will be a more suitable procedure to discuss such a policy.

Scientific Citizenship

Scientific citizenship is in line with the fostering of positive autonomy. It refers to a societal ideal where citizens are well informed and well-equipped to make decisions concerning scientific research. The engagement of citizens would lead to better protection and promotion of their interests. Providing participants with the opportunity to reflect on their participation and to act on that can be a way to stimulate scientific citizenship [69]. It has been noted that there are different levels of citizen participation—ranging from manipulation to actual citizen control [70]. Although an opt-in procedure seems to be more suited to stimulate citizen control (which is perceived as the highest level of participation), an opt-in method does not necessarily safeguard citizen participation as such.

Protection of Researcher

Consent is usually considered an instrument to protect the research participant and respect his or her autonomy. However, consent can also be viewed as a means to (legally) protect the researcher [60, 71]. By obtaining consent from the participant, the responsibility of the acceptance of the entailed risks and burdens shifts (partly) from the researcher towards the participant. This may limit the liability of the researcher. Since only the opt-in procedure provides proof of consent, this method is more suited to protect the researcher.

Public Trust

In order to conduct biomedical research public trust is indispensable. Public support is needed to facilitate research projects [72]. As noted before, distrust may result in high opt-out rates. Public distrust can be the result of people who are unaware of inclusion as the default position. Since people are not included without their explicit consent, an opt-in method is most likely to promote public trust. However, since within a thick opt-out procedure people are made aware of inclusion as the default position, public trust can be warranted as well.

Concluding Remarks

Taking stock of the arguments in favor and against opt-in and opt-out procedures for the inclusion of residual tissue in biobanks (see Table 1), we conclude that an opt-out procedure needs to fulfill certain conditions in order to be an appropriate method to include leftover material. Public trust and respect for negative autonomy can only be sufficiently protected and warranted within an opt-out procedure when (1) awareness is raised among people about inclusion of residual tissue as the default position, (2) adequate information is provided, and (3) a genuine possibility to object is presented and objections are adequately registered. In addition, although not a characteristic of the opt-out method, another condition that needs to be fulfilled is adequate governance of the biobank in order to protect participants (e.g., to ensure confidentiality). An IRB or equivalent committee should monitor the distribution of tissue by assessing research protocols. Adequate measures should be taken to fulfill these requirements. After all, an opt-out procedure should not result in the exploitation of people’s ignorance. Patients need to be actively, preferably personally, informed about the opt-out procedure [59]. Merely putting posters or leaflets in a waiting room will be insufficient. In this information there should be a description of the governance of the biobank (e.g., general information about the type of research, the identifiability of the tissue, etc.). Empirical research is needed to evaluate the implemented opt-out method.

An opt-out procedure that does not satisfy these conditions can be called a “thin” opt-out procedure and is clearly insufficient. An opt-out method that does fulfill the conditions can be classified as a “thick” opt-out procedure. In practice, the dichotomy between a thick opt-out and an opt-in procedure may be less stark than usually suggested. To our best knowledge, no studies have examined the exact financial differences between a thick opt-out and an opt-in procedure, but we expect this difference to be relatively small. However, it is also reasonable to assume that an opt-out will involve less administrative burden. Moreover, even if they may not differ that much in practice, they do differ in the underlying moral message. Opt-out as the default position sends the moral message that allowing your residual tissue to be used for research is the right thing to do. In contrast, with an opt-in procedure this appears more like an extraordinary act.

Secondly, we conclude that the question is not whether in general an opt-in or opt-out procedure is most suitable for residual tissue, but in which specific cases one or the other is appropriate. Residual tissue is a collective term for a diversity of samples. In addition, a wide variety of research types can be conducted on them. Hence, the appropriate method to include the tissue is context-specific and it would be too simplistic to treat all situations alike. We suggest at least four situations that would require an opt-in procedure. Firstly, there are certain types of research that are associated with increased burdens or higher risks (e.g., increased psychological or social risks associated with genetic information from WGS). When the risks or burdens of the proposed research increase, an opt-out method is no longer
sufficient. Secondly, in some studies controversial and/or high-impact techniques are involved (e.g., when an immortal cell line is derived or when chimaeras are created) [73]. As these types of research are sensitive and difficult to explain adequately in the general research information, an opt-out procedure would be insufficient. Thirdly, when sensitive cells or tissues are used (e.g., gametes), a more extensive consent procedure would be appropriate [74]. Lastly, for certain groups of vulnerable patients an opt-in method is required (e.g., psychiatric patients). For this group, the competency to understand the presented information needs to be evaluated before tissue can be included [75]. It should be the role of an independent IRB to determine when an opt-in procedure is required. Although a comprehensive overview of the situations that require an opt-in procedure has not been given, we submit that the type of tissue and research affect the appropriate consent procedure. Further discussion is needed to formulate the amount of risks and burdens, the nature of the techniques, the types of tissue, and the groups of vulnerable patients that would require an opt-in procedure. As the appropriate method is context-specific, the role of an opt-out procedure can differ between institutions and can change over time when developments in research alter the biomedical field. For instance, when a biobank intends to facilitate WGS for all samples, an opt-out method will be unfeasible. However, although the use of WGS is increasing, at the moment straightforward research still plays an important role in the scientific landscape and it seems reasonable to assume that this will continue to exist in the near future.

A third comment can be made about the consequence of the inclusion of residual tissue with a thick opt-out method. The drawback of this proposal is that researchers will have to re-contact participants when they want to conduct certain types of research (e.g., WGS, immortal cell lines) to ask additional consent. As there can be years between the inclusion of a residual sample and the actual research that will be conducted on them, it may be difficult to approach people. However, the distress that is caused to people by re-contacting them will probably decrease in a thick opt-out procedure as they will be aware of the inclusion of their residual tissue and the possibility that they will be contacted for specific research. In addition, introducing an opt-in procedure for all residual tissue research will not solve the dilemma of re-consent. Even within a broad opt-in consent procedure, it is impossible to discuss all the research possibilities that can be conducted on a sample. Previously described situations (i.e., high risks and controversial techniques) will therefore require a specific opt-in procedure as well. Hence, re-consent will also be necessary when an opt-in consent procedure is adopted for the inclusion of all residual tissue [9]. Moreover, introducing an opt-in procedure for all residual tissue research is at least at this moment overly restrictive and likely to hamper basic biomedical research unnecessarily.

In summary, an opt-out procedure is only appropriate when certain conditions are fulfilled; hence, we propose a thick opt-out method. The appropriateness of a thick opt-out method or an opt-in method is context specific. Further interdisciplinary debate is needed to determine when to opt-in or opt-out.

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Glossary

**Biobank**: a collection of human biological samples stored for medical-scientific research purposes, usually linked to phenotypic data

**Opt-in procedure**: a procedure where a person explicitly expresses his or her consent

**Opt-out procedure**: a procedure where inaction is treated as a signal of consent

**Residual tissue**: tissue that was taken in the course of clinical care and is leftover

**Thick opt-out procedure**: an opt-out procedure with the fulfillment of the following conditions: (1) awareness is raised about the opt-out procedure (2) adequate information is provided (3) a genuine possibility to object is presented and objections are adequately registered

**Thin opt-out procedure**: an opt-out procedure without the fulfillment of the three conditions
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