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The MICHR Genomic DNA BioLibrary: An Empirical Study of the Ethics of Biorepository Development

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Abstract

In this article, we report on an effort to study the development and usefulness of a large, broad-use, opt-in biorepository for genomic research, focusing on three ethical issues: providing appropriate understanding, recruiting in ways that do not comprise autonomous decisions, and assessing costs vs. benefits. We conclude: 1) Understanding can be improved by separating the task of informing subjects from documenting informed consent (Common Rule) and permission to use personal health information and samples for research (HIPAA); however, regulations might have to be changed to accommodate this approach. 2) Changing recruiting methods increases efficiency but can interfere with subject autonomy. 3) Finally, we propose a framework for the objective evaluation of the utility of biorepositories and suggest that more attention needs to be paid to use and sustainability.

Keywords

biorepository; biobank; ethics; autonomy; understanding; informed consent; genomic research; cost-benefit analysis

Biorepositories – collections of biospecimens gathered for research – have become important tools for biomedical research over the last 10-20 years. Although there are no authoritative listings, it is probably safe to say that they number in the thousands and cumulatively house tens of millions of samples. Their growth, however, has not been centrally planned, resulting in major differences in size, purpose, organization, support and use. There are also no general frameworks for assessing their contributions to research (Gottweis & Zatloukal, 2007; Henderson et al., 2013; Shickle, Griffin, & El-Arifi, 2010;

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Zika et al., 2011). Since biological materials collected from research subjects are an essential element of biomedical research, it is generally assumed that banking samples for widespread use is an efficient way to conduct research and therefore worth funding. But banking samples is also expensive and raises policy and ethical issues that should be addressed before materials are stored away with promises of future benefits.

The research reported below was initiated as an ongoing discussion of opt-in vs. opt-out approaches to collecting biorepository materials attracted some national attention. The 2010 publication of *The Immortal Life of Henrietta Lacks* (Skloot, 2010) raised widespread public concern about the use of human tissue without the consent of the donor, even if the samples are not identified. A year later, the Office for Human Research Protection raised a series of questions about strengthening consent protections in an *Advance Notice of Proposed Rule Making*, specifically asking whether the policy of using leftover samples without permission should be continued (Office for Human Research Protection & Public Health Service, 2011).

Requiring biorepositories to obtain active consent for de-identified, excess materials could increase development costs and slow research. Major biorepositories, such as Vanderbilt University's BioVU, have relied on an opt-out approach to build collections with $>10^5$ samples (Pulley, Clayton, Bernard, Roden, & Masys, 2010). If the opt-out process is abandoned, are there ways to efficiently and effectively obtain active consent? And how should efficiencies and inefficiencies be addressed as biorepositories are planned?

Between 1 April 2011 and 15 November 2012, the Michigan Institute for Clinical and Health Research (MICHHR) Genomic DNA BioLibraryⁱ recruited 480 subjects to implement and assess a different opt-in approach to establishing and evaluating the usefulness of a large, broad-use biorepository for genomic research. Biorepositories were not new to the University of Michigan campus and other researchers were already exploring ways to collect and store DNA for broad use. However, different views existed about the best way to obtain consent and then store and share samples. With this project we therefore decided to begin from the ground up and question every aspect of biorepository development before we made decisions and offered recommendations. We are also interested in practical day-to-day issues, with the long-term goal of basing decisions about the ethics and usefulness of biorepositories on empirical evidence.

In this article, we report our findings on three practical ethical issues associated with biorepository development: 1) providing appropriate understanding, 2) recruiting in ways that do not compromise autonomous decisions about participation, and 3) assessing whether the benefits of biorepositories justify the cost of establishing them.

Background: Ethical Issues

Understanding

As biomedical research has become more complex, relying on long, complex consent forms has been shown to reduce understanding (Behrendt, Golz, Roessler, Bertz, & Wunsch, 2011;

ⁱThe term “biolibrary” was chosen to emphasize the importance of housing information in one place and then sharing that information so others could learn from it.

Kass, Chaisson, Taylor, & Lohse, 2011; Koh, Goh, Yu, Cho, & Yang, 2012; Mancini et al., 2011; Pilegaard & Ravn, 2012; Stunkel et al., 2010; Taylor & Bramley, 2012; Beskow, Dombeck, Thompson, Watson-Ormond, & Weinfurt, 2014). In response, efforts have been made to reduce the length and complexity of informed consent forms (Beskow, Friedman, Hardy, Lin, & Weinfurt, 2010; Matsui, Lie, Turin, & Kita, 2012; Stunkel et al., 2010) but left open the question whether shorter forms provide adequate understanding. While too much information may be confusing, too little information could leave key questions unaddressed, putting researchers and review committee in the difficult position of weighing the importance of information, particularly presumed required regulatory language, vs. understanding.

As a solution to this problem, we experimented with a different approach to providing information and fostering understanding. Rather than attempting to design one streamlined and more understandable form, we separated the information material for this project from the official, signed consent form. This allowed us to design information materials that maximized understanding and to focus the consent form on clearly identifying the basic elements of consent (Common Rule) (Office for Human Research Protection. Public Health Service, 2011a) and authorization (HIPAA) (Department of Health and Human Services, 2002). This approach followed the general recommendations of an Association of American Medical Colleges committee to disaggregate the informed consent tool kit, but carried disaggregation one step further by separating “informing” from “consent documentation.” (Association of American Medical Colleges & Division of Biomedical and Health Sciences Research, 2007) One goal of this project was to test whether this approach, which has been used by others (Benatar, McKibbin, & Stewart, 2012), provided adequate understanding. If it does, it offers a different and potentially more ethical way to provide informed consent.

Autonomous decisions

The Belmont Report explains autonomous decisions as follows:

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979, p. 40)

There are inherent in this explanation two contrasting way to interpret autonomy, sometimes referred to a “negative” and “positive” autonomy. (Giesbertz, Bredenoord, & van Delden, 2012, p. 2) Negative autonomy frames the discussion of opt-out/opt-in in the context of subject's general attitudes toward participation in research, or as one study defined this issue: “on a patient's general disposition toward the idea of research on their biosamples.” (Brothers et al., 2013, p. 350) Positive autonomy places more emphasis on making an active decision based on specific information and understanding.

A second goal of this project was to learn more about factors that influence a subject's decision to contribute a sample to a biorepository. There are different ways to recruit subjects. Information material can be mailed or handed out in person in a clinic. Recruiting

can take place at check in or check out. By looking at the impact of different recruiting strategies and comparing our results with other work on this topic, we are endeavoring to bring additional information to bear on the opt-in/opt-out debate. As with information vs. understanding, finding the right balance between the efficiency of opt-out and positive autonomy inherent in opt-in requires an understanding of how and why subjects make decisions about research participation.

Costs and benefits

Government and others have gone to great lengths to provide objective evidence of the benefits of biomedical research. A 2011 Battelle report estimated a return of \$141 for every dollar invested in the human genome project between 1998 and 2010 (Gitlin & National Human Genome Research Institute, 2013; Tripp & Grueber, 2011). Rogers et al. estimated that centralized biorepositories could save \$188.4 million/year in research funding (Rogers, Carolin, Vaught, & Compton, 2011). The main shortcoming of these studies is their focus on financial rather than research benefits. The human genome project may have benefitted the economy but has it been the most cost-effective way to use research "... to enhance health, lengthen life, and reduce illness and disability" (National Institutes of Health)? Centralized biorepositories may reduce the cost of using them for research but are biorepositories a cost-effective tool for research in comparison to other ways to advance health research?

Assessing the costs and benefits of biorepositories is not a simple task. We believe, however, that it is an essential task that should be factored into biorepository planning, if not for other, for ethical reasons. Seventy-two percent of the facilities in Henderson's recent survey of major U.S. biorepositories reported that economic sustainability was either a major or moderate concern; 41% listed underutilization as a major or moderate concern (Henderson et al., 2013). It is neither sound economic policy nor ethical to invest funds in biorepositories without some prior cost-benefit analysis and assurance that they will be both sustainable and used. Our final goal for this project was to begin the process of developing a framework for estimating the costs and benefits of biorepositories.

Methods

The investigative team recruited, informed, consented, validated consent, and enrolled 480 subjects using five recruiting strategies (See Table 1). The University of Michigan Medical School Institutional Review Board approved the research and informed consent was obtained in writing from all participants.

Recruiting and sample collection

All recruiting was conducted within the University of Michigan Health System (UMHS), focusing on two populations:

Research Volunteers—6,498 individuals registered in a UMHS web-based portal for clinical research volunteers (UMClinicalStudies.org) (University of Michigan) were notified that they qualified for a new study that had recently been posted--the MICH BioLibrary. To get information about the study, volunteers went to their personal account and looked for

new studies. If they were interested in the BioLibrary, they could ask for more information by clicking a button or directly emailing the study coordinator (SC). The SC followed up with an email that included the BioLibrary Pamphlet (BLP, discussed below) and an Informed Consent document (IC, discussed below). Those who were still interested after reviewing the email and additional information were scheduled for a visit to enroll in the BioLibrary. To increase enrollment, the SC sent follow-up emails to 1,088 individuals within the study population and continued to enroll subjects until we reached our final goal of 230.

Ambulatory care patients—An additional 250 subjects were recruited in two ambulatory care settings to study the impact of clinic workflow on recruiting times and rates. Four placement strategies were tested, two at check-in and two at check-out.

- Check-in. Recruiting during check-in was essentially passive. Potential subjects were either handed a BLP when they checked in and told to contact the SC if they were interested or made aware of the BioLibrary project by a prominent sign at a recruiting table. In each case, potential subjects had to approach the SC to get more information and enroll.
- Check-out. Recruiting during check-out was more active. The SC approached subjects as they were checking out. The SC was located near but not with the normal check-out personnel so that recruiting was not seen as part of the check-out process. During the first phase of testing, only potential subjects with a blood draw order were approached. During the second phase, all subjects checking out were asked if they might be interested in learning about the BioLibrary.

Through all recruiting rounds, the SC tracked total recruiting time (H) as well as the time needed to enroll subjects (E). This information was used to calculate the relative cost/sample and efficiency of different recruiting methods. The SC also tracked total contacts as well as the numbers enrolled to allow estimates of enrollment rates.

Informing and consenting

To streamline the consent process and improve understanding, the materials used to inform subjects were separated from the materials used to document consent. The University of Michigan Center for Health Communication Research provided initial guidance for the text-only version of the information materials. Later a graphic artist working with the research team and an academic-community advisory committee developed the graphic version of the BLP. (See supplemental materials)

BioLibrary Pamphlet (BLP)—The BLP described the study and elements of consent at a level and in terms subjects could presumably understand. We began with a text-only pamphlet and then added illustrations during the ambulatory care phase to improve understanding of important points and concepts. (Supporting Information, Appendices A and B).

Informed Consent document (IC)—The one-page IC used throughout this study summarized three key aspects of consent: 1) IRB approval, 2) the essential elements of

consent, and 3) HIPAA authorization. Additional information about HIPAA was provided on the back of the IC. (Supporting Information, Appendix C) Subjects were asked to sign the consent form to donate to the BioLibrary and to participate in our study of the development of the biorepository before their understanding was validated and then verbally agreed again to contribute a sample once their understanding had been validated.

Validating understanding

Understanding was validated using a 14-question quiz (first 30 subjects) or semi-structured interview (remaining 450 subjects). Understanding was judged on a five-point scale (1 = “doesn’t make any sense at all” and 5 = “makes perfect sense”). Any items rated less than 5 were fully explained by the SC before subjects were enrolled. (Supporting Information, Appendix D)

Sample collection

Once final consent was obtained, subjects provided a 10 ml sample of blood, which was labeled with their name, date of birth, and medical record number and then sent to a processing laboratory. In the processing laboratory, blood samples were verified, coded, entered into the Freezerworks[®] specimen management software system and stored at 4°C for no more than 10 days. DNA was then extracted using Autogen FlexSTAR[®] and Qiagen Flexigene[®] technology, placed in pre-labeled 2 ml rubber-gasketed cryovials and stored at -80°C. The same basic procedure for collection and processing was used throughout the study on all samples.

Data validation and population phenotype

To assess whether the collected samples could be used for research, the SC: 1) confirmed that the IC and IRB approval number had been properly entered into the medical record of each subject, and 2) requested a search for basic information to characterize the study population, including age, gender, race, ethnicity, medical insurance, and smoking history. We selected these fields to provide a basic characterization (clinical phenotype) of our population. The search was approved by the IRB and conducted by the Medical School Honest Broker Office.

Results

Distribution of effort

It took 1,177 hours of SC time to collect 480 samples for an average of 2.5 hours/sample. Most of this time (~90%) was spent recruiting subjects. Once a subject read the BLP and agreed to participate, obtaining consent, validating understanding, answering questions, enrolling and collecting a blood sample averaged about 14 minutes/sample or less than 10% of total time/sample. (Table 1).

Recruiting strategies

None of the recruiting approaches provided a quick, inexpensive way to enroll large numbers of subjects. However, the different recruiting strategies had some impact on efficiency.

Volunteer population—From the initial population of 6,498, 1,047 (16%) individuals responded and 230 (4%) eventually enrolled. The response and enrollment rates to the personal email (62% and 9%) were higher than to the general announcement (6% and 2%), suggesting that personal contact is important. (Table 2) Since we stopped recruitment at 230 subjects, we do not have a final recruiting rate. If the response to the SC follow-up emails (only 1,088 were sent) continued at the same rate, the final recruiting rate would have been about 10%. The recruiting time for this population (2.3 hrs./subject) was in line with average recruiting time for all subjects (2.5 hrs./subject). (Table 1)

Ambulatory care population, passive recruiting—Handing out BLPs at check-in was the least efficient way to recruit (5 hrs./subject, 2.8% enrollment). Establishing a recruiting table in the waiting area was more efficient (2.8 hrs/subject) and resulted in our highest recruiting rate (21.1% of those who approached the recruiting table). (Table 3)

Ambulatory care population, active recruiting—Active intervention by the SC during check-out proved to be the most efficient way to recruit (2.5 and 2.1 hrs./subject). Approaching subjects who had a blood draw order was not more efficient than approaching all subjects and resulted in a slightly lower recruiting rate (11.3% vs. 14.1%). (Table 3)

Cost

Total cost/sample was estimated using the following formula.

$$(H_{sample} \times \$_{study\ coordinator}) + \$_{information\ pamphlet} + \$_{processing} = Cost/sample$$

We estimated SC salary at \$20/hour. The BLP cost \$1,250 to print (\$2.60/sample). The University of Michigan charges \$16.78/sample for extracting and storing the DNA. Adding these figures together, the average cost/sample comes to \$69.38 ([2.5 hours × \$20] + \$2.60 + \$16.78 = \$69.38). A full cost assessment would include the expense of purchasing storage space as well as management and research support staff effort. (See discussion below)

Consent and understanding

89% of the subjects enrolled rated their understanding of the 14 validation questions as 5 after reading the BLP (Table 4). The remaining 11% rated their understanding as 3 or 4. Doubts about understanding varied slightly from question to question, but overall general understanding was high and there were no major differences between the text and graphic versions of the BLP. All doubts and questions were answered before subjects confirmed their consent to enroll and blood was subsequently drawn.

Search results

With two exceptions, our population closely mirrored the general population of the University of Michigan Health System. Disproportionately more women enrolled than are represented in the general patient population (63.9% vs. 51.8%), and few Medicaid recipients enrolled compared to the general population (1.3% vs. 13.0%) (Table 5). Other apparent differences can either be accounted for (e.g., age, the BioLibrary did not take anyone under age 18) or are not significantly different due to subjects not providing information.

Discussion

The different approaches used in this project for recruiting and enrolling subjects in a genomic biorepository would be expensive if scaled to large collections. At roughly \$60/sample, a modest collection of 10,000 samples would cost \$600K, a large collection of 100,000 samples \$6M. While there could be some economies of scale, they would probably not impact our major cost, namely recruiting time. If anything, getting large numbers of donations from a limited population could become more expensive as the most willing subjects enrolled. Therefore, more efficient approaches probably need to be used. But greater efficiency usually comes with a price. In the case of biorepositories, the price could be lower ethical standards for research and less human subject protection, as explored in the following discussion of our results.

Understanding

Separating the complex information in a typical informed consent form into a subject-friendly information pamphlet and short, to-the-point consent form provides a simple and practical way to foster understanding. The cost of designing effective information materials is not prohibitive. Validation does not take a great deal of time and is only needed until confidence in the information materials is established. As an added benefit, validation also provides evidence that the subjects have been properly informed and that researchers and research institutions take their responsibility to inform subjects seriously. Based on these findings, we agree with the AAMC's recommendation to disaggregate the informed consent process and offer the user-friendly pamphlet coupled with a checklist consent form as an example of how this could be accomplished.

This approach to informed consent poses a potential dilemma for IRBs. IRBs are responsible for the dual tasks of protecting human subjects and assuring that their institution meets Federal regulations. (Klitzman, 2012) In principle, these tasks should be in harmony with one another but in practice conflicts arise. In our case, the key question is whether our practical approach to *providing understanding*—a universally agreed to and essential element of human subjects protection—satisfies the Common Rule and HIPAA requirements.

Setting aside exemptions, the Common Rule requires documentation of consent through “a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative.” (45 CFR 46 § 46.117 (a)) As long as our short consent form was approved by an IRB, which it was, it should meet the basic requirement for documentation.

However, the Common Rule goes on to state that the consent form must be: “A written consent document that *embodies* the elements of informed consent required by § 46.116.” (45 CFR 46 § 46.117 (a)(1), emphasis added) Depending on how “embodies” is interpreted, an IRB could view a summary of essential information provided elsewhere as adequate or require that the information be included in the signed consent form, thereby defeating the purpose of the simplified form.

HIPAA (45 CFR Part 160) is not as flexible as the Common Rule and adds additional complications. It describes “valid authorization” as “a document,” (45 CFR 164.508 (b) (1)), not a process. (In its explanation of the Common Rule, OHRP stresses that informed consent is a process, not a document: “...even if a signed consent form is required, it alone does not constitute an adequate consent process.”(Office for Human Research Protection. Public Health Service, 2011b)) HIPAA documentation, moreover, must include specific information, names, addresses, and other details (164.508 (c) (1) and (c) (2)). As a result, even if adding words reduces understanding, IRBs are compelled to do so to meet HIPAA requirements. As an example, in order to meet HIPAA requirements, a newly established UMHS Biorepository, which modeled its consent process and documents on the MICHHR BioLibrary project, felt compelled to move away from our validated checklist IC to a longer (200 words longer), reorganized IC, which has not been validated. (University of Michigan Medical School, n.d.) This change gives reassurance of compliance but not understanding, placing compliance above human protection.

Autonomy

When left to act on their own, only 2% (Table 2) of our volunteer population actively made the decision to donate blood to the MICHHR BioLibrary. With follow up emails, we increased the enrollment rate in this population to 4%, with a projected maximum rate of about 10% if the SC had personally contacted every potential subject. (Table 2) Recruiting in the check-in area of an ambulatory care clinic increased the recruiting rate to over 20% of patients who approached SC for information about the BioLibrary. (The rate for the entire clinic population on any day would have been lower.) The most efficient way to recruit in terms of SC time/subject was to approach all patients at check-out. However, even in this setting, recruiting rates remained low. (Table 3).

With more time and publicity, there are undoubtedly ways we could improve the efficiency of our recruiting process. The Mayo Clinic achieved an enrollment rate of 28% when they sent two rounds of invitations to patients who were scheduled for a clinic visit. (15% of the Mayo population declined to participate and the rest did not respond.) (Olson et al., 2013) But overall, our evidence suggests that on their own and in relatively neutral settings, well under 50% of potential subjects make an autonomous decision to contribute an identified sample to a general-purpose biorepository.

These low recruiting numbers stand in marked contrast the high levels of public support and actual enrollment reported in other biorepositories studies. Vanderbilt's BioVU has reported more than a 90% approval rate and similarly high enrollment rates for a de-identified biorepository using an opt-out recruiting process. (Brothers, Morrison, & Clayton, 2011) Similarly high acceptance (Brothers et al., 2011; Goldman et al., 2008; Kaufman, Murphy,

Erby, Hudson, & Scott, 2009; Ma et al., 2012; Mezuk, Eaton, & Zandi, 2008; Pulley et al., 2010) and enrollment rates (Johnsson et al., 2010; Joseph, Neidich, Ober, & Ross, 2008) have been reported in other studies. There clearly are ways to increase both support for and enrollment in biorepositories. What is less clear is the impact of different approaches to biorepository development on the autonomy of subjects.

Research suggests that personal interests play an important role in decisions to participate in research. (Goldman et al., 2008; McCarty, Garber, Reeser, & Fost, 2011; Wendler & Emanuel, 2002) We started with research volunteers because we knew they were already interested in participating in a research study. Participation rates increased when we moved into clinical settings, where potential subjects were actively engaged in confronting health issues and making medical decisions. Some of the most successful biorepositories are ones focused on specific populations and/or diseases, thereby closely aligning the subject's personal interests with researchers' interests. (Johnsson et al., 2010)

But can this alignment get too close? Can a subject's personal health interests or connection with their research professional compromise their ability to make a more detached or more informed decision about participation in a biorepository? One comparative study of enrollment vs. support rates suggests that this might be the case and explain why across most of the comparison groups used for the study actual enrollment rates were higher than hypothetical support rates.

Patients may be more inclined to participate in research than the general public, possibly from a sense of duty to reciprocate or because they find themselves part of a social agreement, community, or alliance. Potential research subjects may find it easier to trust researchers whom they meet face-to-face, and so may be more likely to agree to participate. (Johnsson et al., 2010)

In other words, in medical setting, trust and a sense of responsibility may outweigh the reasoned decision subjects might make in other settings.

The impact of setting on decision-making may be reflected in our enrollment times. (Table 1) It took on average 18 minutes to enroll subjects in our volunteer population compared to only 12 minutes in the clinic population. Why? Some of the difference could be explained by text-only BLP used for the volunteer population vs. the graphic BLP used in the ambulatory care setting. But both populations had basically the same level of understanding/lack of understanding after reading the BLP (89% vs. 88% had a basic understanding of all of the essential points the SC raised). (Table 4) However, the volunteer population was not pressed for time and therefore spent longer talking with the SC. They were there to enroll in the BioLibrary, not to attend to other health issues. They were interested in our project and wanted to know more about it. They took the time to understand what we were asking and to make an informed decision about participation. When we approached them during clinic visits, they had less time and took less time to make decisions. For some, a general commitment to help others was enough to justify enrollment.

With this analysis, we are not suggesting that it is unethical to recruit subjects for biorepositories or other research in clinical settings. Recruiting in these settings goes on all

the time and in many cases is the only or best place to recruit. We are suggesting, however, that when recruiting for research that is not directly related to the clinic visit, such as a general-purpose biorepository, it is essential for subjects to get the same information and time to think as they would if they were approached in some other setting. It is also important to make sure that other factors, such as general trust for a researcher, research program or research institution, do not unduly influence the decisions subjects might otherwise make. An autonomous decision to contribute material to a biorepository is one made on its own, apart from other influences and with a full understanding of risks and possible outcomes. Trust in an institution or researcher by itself should not be a primary reason for participation.

Beneficence

In their article urging support for centralized human biorepositories, Rogers et al. note: “Because grant applications do not typically require a cost-benefit or cost-effectiveness analysis with submission and the government rarely performs such studies on grant research retrospectively,” assertions about the value and benefits of biorepositories “must be accepted at face value, absent objective supporting evidence.” (Rogers et al., 2011) Our goal in tracking time and expense is to begin the process of gathering “objective supporting evidence” to support more reasoned decisions about the resources allocated to biorepository development. In return for their time and personal materials, subjects are being promised great strides in the advance of medicine. Will this promise be realized? How much funding should be devoted to storing human materials? How many samples are needed? What is the best way to store and share samples? Will they be used and if so, for how long? Is it ethical to encourage public support for biorepositories when their short- and long-term utility has not been assessed?

Our estimate of \$65.58 to recruit and enroll a single subject is obviously only a partial estimate of the cost of making samples available for general research purposes. Turning the collected samples into a fully functioning biorepository will add: 1) storage costs, 2) biorepository management costs, including the cost of reviewing requests to use samples, and 3) the actual cost of sharing samples. There are also optional costs, such as public communication and engagement. Although the public generally understands the concept of “no personal benefit,” support for biorepositories is stronger when subjects feel personally involved and are kept abreast of research results. (Gottweis, Gaskell, & Starkbaum, 2011; Lemke, Wolf, Hebert-Beirne, & Smith, 2010; McCarty et al., 2011) It also increases when compensation is increased. (Kaufman, Murphy, Scott, & Hudson, 2008) These additional costs could easily increase the cost per sample into the \$100s and place the total investment in biorepository collections in the \$100s of million.

A research investment of this magnitude should be based on more than a “face-value” justification of benefits, particularly since under utilization and uncertain future support have been identified as potential problems. (Henderson et al., 2013) Need and potential uses should be addressed before any samples are collected. Strategies of local, regional, national and international collaboration should be compared, looking at both development and use. Others have called for better advanced planning (Vaught, Rogers, Carolin, & Compton,

2011) but for the most part the major strategy seems to be to develop and hope beneficial research will follow.

In setting out how the principle of beneficence should be interpreted, the Belmont Commission stressed the need to consider research as a whole and not just specific projects, noting:

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979)

Waste is now recognized as a significant risk in research. (Al-Shahi Salman et al., 2014; Chalmers et al., 2014; Chan et al., 2014; Ioannidis et al., 2014) The costs of developing biorepositories can be established. Further work is needed to assess whether anticipated benefits satisfy the principle of beneficence.

Best practices

The logic of storing excess or purposeful biological materials for research is clear. However, the practical details of collecting and using these materials present significant ethical challenges for researchers and IRBs. It is universally agreed that understanding and autonomous decision-making are key elements of ethical research. It is also clear that strict institutional adherence to regulations can compromise subject understanding and that autonomous decision making can be influenced by factors unrelated to the research itself. The short- and long-term benefits of stored samples are uncertain and undoubtedly vary from collection to collection, making it difficult to assess the beneficence of biorepositories. In short, the ethics of biorepositories is complex and needs to take into account some practical issues that have to date not received a great deal of attention.

Understanding—We have taken steps toward demonstrating that understanding can be improved if it is seen as a unique task, separate from documenting informed consent (Common Rule) and permission to use personal health information and samples for research (HIPAA). If this approach does not comply with current research regulations, then we would suggest that the regulations ought to be changed rather than compromising subject understanding. It is unethical to continue with a system that places regulatory compliance before human protection by allowing the continued use of complex and difficult-to-understand consent and permission forms, particularly when there are better ways to provide understanding.

Autonomy—We have shown that recruiting efficiency can be improved by changing approaches to recruiting and suggest that care needs to be taken to avoid approaches to biorepository development that could interfere with subject autonomy. The fact that a number of studies have shown that a majority of the public agrees in principle with the

purpose of biorepositories and even expresses a willingness to donate samples does not mean they will actually follow through when asked to do so. Willingness to participate can be influenced. If the results of a study of the attitudes of veterans applied to our population, we could have increased participation by adding a \$200 payment to our \$68.00 recruiting cost. (Kaufman et al., 2008) Recruiting in medical settings, adopting an opt-out approach and de-identification also appear to increase participation. It is important for IRBs to look at all of these incentives and ask whether they improperly influence subject autonomy.

Beneficence—Finally, we have begun the process of developing a framework for the objective evaluation of the utility of biorepositories and suggest that more attention needs to be paid to use and sustainability. This is particular important for genomic biorepositories since the rapid evolution of the genomic sciences may short make de-identification a promise that cannot be guaranteed. The needs of biomedical research also change rapidly and could render many samples stored today of limited use in the near future. We have not addressed use and sharing cost estimates in this study but suggest that the same framework we used for costing development can be and should be applied to use.

We have approached each of these issues from an empirical perspective, focusing on data that is designed to assist practical decision-making. Our goal was to point the way toward the types of studies needed before conclusions are drawn about best practices for the development of biorepositories. Our study could be extended to a larger population to allow estimates of the statistical significance of some of our observations, such as lower enrollment rates when we approached only potential subjects scheduled for a blood draw. More use could be made of validated instruments for assessing understanding (Joffe, Cook, Cleary, Clark, & Weeks, 2001; Ormond, Cirino, Helenowski, Chisholm, & Wolf, 2009) rather than relying on the open-ended semi-structured interview used in our pilot to minimize impact on recruiting times. And, of course, accurate cost-benefit analyses need to be based on more detailed studies of the actual use of biorepositories over an extended period of time. As an overall best practice at this stage in the study of biorepositories, we would recommend that before large collections are developed for future use, it is important to have evidence that the samples in these collections were freely donated by understanding subjects and stored in a way that will assure reasonable and productive use in the future.

Future Research

In addition to the need for more research on the costs associated with storing and sharing samples and on realistic-use projections, discussions about the funding and development of biorepositories would benefit from a detailed meta-analysis of the attitudes and recruitment literature. There currently is no standard instrument for measuring public attitudes toward biorepository participation. There is, therefore, no way to assess whether the numbers in one study can be compared with the numbers in another study. Moreover, some of the literature on attitudes is potentially biased by the fact that it has been gathered in preparation for establishing or to justify a particular biorepository project. A careful and independent study of the attitudes and recruitment literature would produce a more solid empirical foundation on which to based policy decisions about biorepository development and IRB decisions about the ethics of new biorepository initiatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Recruiting strategies and times to enroll 480 BioLibrary subjects

Population	Strategy	Enrolled	Recruit (Hrs.)	Hrs./sub	Enroll (Min.)
Volunteers	Electronic		535	2.3	18
Clinic	Personal		30	5.0	13
Check in	(1) Notice & email	230	535	2.3	18
	(2) Handout	6	30	5.0	13
	(3) Table	100	284	2.8	11
Check out	(4) Patients undergoing blood draw	69	172	2.5	14
	(5) All patients	75	156	2.1	11
Summary		480	1177	2.5	14

Table 2

Recruiting numbers and percentages, volunteer population

Volunteer	Total population		Response to general announcement		Response to SC email	
Contacted	6,498	100%	6,498		1,088	
Responded	1,047	16%	372	6%	675	62%
Enrolled	230	4%	127	2%	103	9%

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Table 3

Ambulatory care population

	Total	Recruited	Time	Hr/sub	% Enroll
Check in					
Handout	216	6	30	5.0	2.8%
Table	474	100	284	2.8	21.1%
Check out					
Blood draw	612	69	172	2.5	11.3%
All	531	75	156	2.1	14.1%
Total	1833	250	642		13.6%

Table 4
Validation of understanding by recruiting rounds

Validation responses	Text (230)		Graphic (250)	
5 = Makes perfect sense	204	89%	221	88%
3 or 4 =	26	11%	29	12%
a. The main purpose of the BioLibrary is to store and share genetic samples with linked health information for research.	1	0%	6	2%
b. Your blood sample and health information will be used for research if you participate.	1	0%	3	1%
c. You will not get any information or health benefit if you donate to the BioLibrary.	6	3%	6	2%
d. There might be better ways for you to help with health research. Like enrolling in other research studies.	10	4%	8	3%
e. An Institutional Review Board and the MICHHR BioLibrary will approve any studies that use your "Book."	4	2%	6	2%
f. Your personal identity will be protected through a something called "deidentification."	3	1%	10	4%
g. "Deidentification" will not provide total protection from your being identified.	8	3%	7	3%
h. You may restrict how your "Book" is used for research.	3	1%	3	1%
i. Your "Book" will be used as long as the BioLibrary is active or until you request that it be removed.	2	1%	3	1%
j. If you withdraw your "Book," DNA and health information that have already been shared with researchers cannot be taken back.	5	2%	2	1%
k. There is a small risk that you could feel some discomfort from the blood draw.	0	0%	4	2%
l. You are not required to participate in the BioLibrary.	2	1%	0	0%
m. You will only be paid for travel to provide a blood sample.	0	0%	0	0%
n. More information about the BioLibrary can be found in the Information Pamphlet.	0	0%	0	0%
1 or 2 =	0	0.00%	0	0.00%

Table 5
Population characterization, BioLibrary compared to total University of Michigan Health System patient population

Total population	BioLibrary	UMHS
Age		
average	53.3	50.6
Race		
American Indian & Alaska Native	0.2% (1)	0.23%
Asian	4.0% (19)	3.43%
Black or African American	6.7% (32)	7.75%
Native Hawaiian/Pacific Islander	0.2% (1)	0.04%
White or Caucasian	86.0% (413)	73.21%
Unknown, other, no data	2.7% (13)	15.34%
Patient Refused	0.2% (1)	0.18%
Gender		
Female	306 (63.8%)	51.76%
Male	174 (36.3%)	46.38%
Not recorded		1.85%
Insurance		
BCBS	53.1% (225)	41%
Commercial	12.5% (60)	13%
Medicaid	1.3% (6)	13%
Medicare	22.9% (110)	28%
Other	10.2% (49)	5%

Data is as self-reported by participants.