Patient awareness and approval for an opt-out genomic biorepository

Aim: In this study, we sought to assess patient awareness and perceptions of an opt-out biorepository. **Materials & methods:** We conducted exit interviews with adult patients and parents of pediatric patients having their blood drawn as part of their clinical care at Vanderbilt University Medical Center (TN, USA). **Results:** 32.9% of all patients and parents of pediatric patients report having heard of the opt-out biorepository, while 92.4% approve of this research effort based on a brief description. Awareness that leftover blood could be used for research increased among adult patients during the study period, from 34.3 to 50.0%. **Conclusion:** These findings will inform ongoing assessments of the suitability of opt-out and opt-in methods as alternatives to written informed consent for inclusion in a biorepository.

KEYWORDS: biorepository ■ exit interviews ■ human nonsubjects biorepository ■ opt-out research ■ research ethics

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A value core to all modern statements on the ethics of human research is that participation in research should be fully voluntary [1–3]. In practice, the value of voluntariness is often associated with the assumption of risk. For example, US regulations on research with human subjects require that participants be provided with detailed information on relevant risks and benefits, and signal their willingness to take on risk by signing an informed consent document. Researchers conducting studies involving very limited risks (such as epidemiological research using existing data) need not seek written consent.

There are, however, other reasons to ensure that participation in research is voluntary. The principle of respect for persons, in particular, implies that the wishes of humans contributing samples and data should be respected even when they are not engaging in research as human subjects [4]. Failure to show this form of respect threatens public support for research [5]. We have previously coined the term 'human nonsubjects research' to highlight the respect that is due to persons who donate samples for research, even when those persons are not engaged in research as research subjects [6,7].

The availability of new technologies such as next-generation sequencing and advanced computational approaches create opportunities to conduct research in new ways, which in turn create the need to re-examine how voluntary participation can be obtained within the scope of existing research regulations and ethical values. Recent innovations, for example, have made it possible to generate useful health-related findings using large data sets that contain medical record data and biosamples. These collections may be referred to as biorepositories or biobanks. This type of research can be conducted using only de-identified data and thus may be considered to involve risk similar to epidemiological research. In fact, US human research protections regulations define research on de-identified information and biosamples from humans as exempt from the requirements of the Common Rule, including those for informed consent [101]. These regulations do not require complete anonymization of information. Indeed, it may not even be possible to obtain complete anonymization [8,9]. Current regulations instead provide guidance on the information that must be removed or altered in order for data to be considered deidentified [102].

Given that written informed consent may not be required by regulations, but that respect for research participants remains important, several institutions have begun to explore whether opt-in and opt-out approaches can be used effectively to obtain permission from participants to use their medical record information and leftover biosamples for biorepository research [10,11]. Opt-in and opt-out methods are designed to minimize the burdens of eliciting voluntary participation from a large number of patients while providing those who do not wish to contribute the opportunity to exercise that preference. Such opportunities for participants to have a say are especially important in research involving next-generation sequencing, since some patients will

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have concerns about the private or potentially stigmatizing information that may be revealed through sequencing technologies.

Unlike informed consent methods, opt-in and opt-out approaches assume that any decision not to participate is likely to be based on a patient's general disposition toward the idea of research on their biosamples and that participants can usually make this decision with a simple overview of what is involved in the research. The primary aim is to ensure that any decisions about participation or nonparticipation authentically reflect a person's preferences. Comprehensive information about the research is not always needed to attain that end. It has been argued that providing comprehensive information to research participants is more relevant to the aim of protection against liability and that providing participants with relatively brief information about research studies may actually improve their ability to make effective decisions [12]. In this spirit, opt-in and opt-out documents are usually provided as short permission forms focused on notifying patients that samples are being collected for research and that patients have a choice about whether their sample will be included.

If opt-in or opt-out approaches are to be considered as suitable alternatives to obtaining written informed consent, the forms and other notification efforts they utilize must be effective with respect to making potential participants aware of the research and providing them with enough information to make an effective decision. Since the default for opt-out methods is inclusion in research, biorepositories utilizing this approach must additionally ensure that participants recognize that they have the opportunity to opt-out of participation.

In this article we report the findings of an exit interview study conducted with patients at Vanderbilt University Medical Center (TN, USA) on BioVU, an opt-out biorepository composed of leftover clinical blood samples and de-identified medical record information. At the time this study was conducted, patients were asked to sign a two-page 'consent for treatment' form at the time of their first visit to an outpatient clinic and then once every 12 months. A description of BioVU along with an opt-out checkbox were included in this "consent for treatment" form just above the signature line. Patients wishing to opt-out of inclusion of their biosample in BioVU were prompted to check the box indicating this preference. The language used in this form is provided in Supplementary Figure 1A (see online www.future-medicine.com/doi/suppl/10.2217/PME.13.34). Through this form, all patients receiving care at a Vanderbilt outpatient facility were notified of BioVU and their opportunity to opt-out. In order to supplement this form, patients were also notified of BioVU through posters and pamphlets in clinical areas, and advertisements in local publications. The interview study reported here was intended to evaluate whether the procedures adopted by BioVU were adequate in terms of informing patients of this research and making them aware that opportunities to opt-out are provided. We explore here the implications of these findings for the policies that should be adopted by individual opt-out biorepositories, as well as their implications for the larger debate on alternative methods for ensuring voluntary participation in research.

Materials & methods

Survey overview

From 2009 to 2012, we conducted exit interviews with adult patients and parents of pediatric patients who were having their blood drawn at outpatient phlebotomy areas. This study involved three distinct cohorts. First, we conducted interviews in 2009 with adult patients having blood drawn at the two busiest adult outpatient phlebotomy areas in Vanderbilt University Medical Center (Adult time point 1 or Adult 1 cohort). During this period, the biorepository was relatively new and collected samples from adult patients only. In 2010, immediately following expansion of the biorepository to include pediatric patients, we began interviewing the parents of pediatric patients who were having their blood drawn at the two busiest outpatient phlebotomy areas in the Monroe Carell Jr. Children's Hospital at Vanderbilt (Nashville, TN, USA; Pediatric cohort [Peds cohort]). Finally, in 2011, we began a second round of exit interviews at the same adult phlebotomy areas where the Adult 1 cohort sample was collected. This second sample was obtained to determine whether awareness and approval for the opt-out biorepository had changed as the biorepository became better established and public notification efforts continued (Adult time point 2 or Adult 2 cohort).

No identifiable information about respondents was viewed or recorded at any time. The Vanderbilt Institutional Review Board reviewed this study and approved its classification as an exempt study.

Survey design

The survey instruments used for each of the three cohorts were similar. The instrument

used for the Adult 1 cohort was designed collaboratively by two pediatricians with expertise in research ethics issues (KB Brothers and EW Clayton) and a sociologist with experience in survey design (DR Morrison). The instrument used for the Peds cohort was designed by the same team. It was modified from the Adult 1 cohort instrument to account for pediatric-specific issues (i.e., the possibility that respondents might view the collection of their child's sample differently from the collection of their own sample) and based on feedback from the study personnel who fielded the Adult 1 cohort survey. Revisions incorporated into the design of the Adult 2 cohort instrument were intentionally minimized in order to facilitate comparisons with the earlier adult cohort. The Adult 2 cohort instrument was identical to the Adult 1 cohort with the exception of one additional question. As shown in Supplementary Figures 2–4, all three instruments were designed with branching logic; the questions asked of each participant were determined by his or her earlier responses. For this reason, several questions were posed to only a subset of respondents.

Survey administration

All three cohorts were collected in clinical practice settings where information about the opt-out biorepository was communicated through posters, pamphlets and consent-for-treatment forms. In order to increase the number of exit interviews conducted, interviewers coordinated with staff at each phlebotomy area to identify the periods each week when the most clinical blood samples were typically drawn. During these times, an interviewer was stationed outside the phlebotomy area and attempted to approach every patient (or pediatric patient's parent) as they entered or exited the phlebotomy area. The interviewer identified qualified participants by asking "[Did you/will you] have your blood drawn today?" Only potential participants who answered affirmatively were invited to complete the survey. The interviewer explained that the survey would take about two minutes and would be completed anonymously. Interviewers also explained that respondents could choose to end the survey at any time.

Otherwise qualified patients were excluded from our study if they declined participation or were unable to complete the survey in English. In addition, when more than one patient entered or exited the phlebotomy area at the same time, the single interviewer was only able to approach one. Interviewers tallied the number of potential respondents who were not included in our study for each of these reasons. Potential respondents who exited the phlebotomy area at a time when the interviewer was busy were counted based on the observations of the interviewer; it is possible that some patients exited the phlebotomy area but were not noticed by the interviewer.

After obtaining agreement to participate, interviewers verbally administered the survey and recorded participant responses. As demonstrated on the provided interview guides (Supplementary Figures 2–4), some questions required interviewers to code open-ended participant responses. Interviews with adult patients included the collection of participant demographics, including age, gender and self-identified ethnicity. Interviews with the parents of pediatric patients involved collection of demographics for both the adult participant and the child having his or her blood drawn.

Statistical analysis

The primary outcomes for this study were:

- Awareness of the Vanderbilt DNA databank;
- Awareness that leftover blood could be used for research;
- Support for the biorepository.

An analysis of the two adult groups (Adult 1 cohort vs Adult 2 cohort) allowed us to investigate changes over time. Inclusion of the Peds cohort allowed us to explore whether differences existed between adult patients and parents of pediatric patients. Initially, chi-squared techniques were used to test for differences in gender and ethnicity between the two adult groups in order to reveal potential confounders for changes over time; an independent samples t-test was performed to test for differences in age. Similarly, χ^2 and analysis of variance techniques were used to test whether parents of pediatric patients differed from the two adult groups. χ^2 techniques were used to test whether surveyed participants differed significantly in age, gender or ethnicity from the total patient population being seen in the medical center during that time period.

χ^2 techniques were used to test (unadjusted) for differences in the proportions of individuals in each group who:

- Had heard of the Vanderbilt DNA databank;
- Understood that leftover blood could be used for research;
- Supported the DNA databank.

Similarly, χ^2 techniques were used to test for differences in the proportion of adults who recalled or preferred to opt-out of the DNA databank between the two time points. Multivariable logistic regression techniques were used to test (adjusted for age, ethnicity and gender) whether inclusion in the Adult 1, Adult 2 and Peds cohorts predicted responses to questions related to the four primary outcomes. We performed a descriptive analysis of the reasons patients and parents of pediatric patients gave for supporting or opposing the DNA databank.

Results

Demographics & participation rates

Our adult participants at Adult time point 1 were significantly more likely to be black compared with the total population of adult outpatients seen in 2009 (19.5 vs 7.3%; p < 0.001). The adult cohort interviewed at Adult time point 2 was significantly more likely to be white (87.5 vs 61.9%; p < 0.001) when compared with the total population of adult patients seen in 2011 and 2012 (Table 1). Mean age differed significantly between the two adult cohorts (57.8 vs 52.1 years; p = 0.038). Respondents in adult 2 cohort were significantly less likely to be black (19.5 vs 6.3%; p = 0.010) and significantly less likely to be other (2.6 vs 6.3%; p < 0.001) when compared with adult 1 cohort (Table 1).

As expected, parents of pediatric patients who we interviewed were significantly different from adult patient participants. Parents were significantly more likely to be female (83.8 vs 58.4% and 55.0%; p < 0.001), younger (29.3 vs 57.8 years and 52.1 years; p < 0.001) and more likely to be a member of a minority racial/ethnic group (41.2 vs 22.1% and 12.5%; p < 0.001). The children whose parents were interviewed for our study were fairly representative of all pediatric patients seen in outpatient areas of the children's hospital, with the exception of age; the children of respondents were younger compared with the general pediatric patient population (p < 0.001) (Table 2).

As a result of differences in patient populations, parents of pediatric patients were more likely to be unable to participate because they were non-English speaking compared with adult patients (Tables 3 & 4). In addition, more potential participants refused participation in the Adult 2 cohort as compared with the other cohorts. Overall response rates were robust across all three cohorts (>60%).

Primary outcomes

Unadjusted, as seen in Table 5, respondents in the Peds (18.8 vs 48.1% and 32.5%; p < 0.001) and Adult 2 cohorts (32.5 vs 48.1%; p = 0.047) were significantly less likely to have heard of the DNA databank. On the other hand, respondents in the Adult 1 cohort were significantly less likely to understand that leftover biospecimens could be used for research (34.3 vs 50.0% and 46.3%; p = 0.040).

Despite relatively low awareness, a large majority of all three cohorts supported the DNA databank after a brief explanation (n = 219, 92.5%), and parents of pediatric patients supported a DNA databank for children (n = 71, 88.8%).

As seen in Table 6, the logistic regression models fit the data well, as indicated by Hosmer–Lemeshow p-values greater than 0.05. Following adjustment, adult patients at Adult time point 2 remained significantly more likely to recall signing a consent for treatment form (overall response [OR]: 2.10; 95% CI: 1.02–4.32; p = 0.042) and to understand that their leftover specimens could be used for research (OR: 1.91; 95% CI: 1.07–3.73; p = 0.041) when compared with adult patients at Adult time point 1. The decrease from Adult time point 1 to Adult

Table 1. Adult demographics stratified by time point.

Demographic		Adult 1 cohort (n = 77) (%)	All adult outpatients in 2009 (n = 222,304) (%)	p-value cohort versus all	Adult 2 cohort (n = 80) (%)	All adult outpatients 2011–2012 (n = 207,646) (%)	p-value cohort versus all	p-value Adult 1 versus 2 cohort
Female		45 (58.4)	128,085 (57.6)	0.884	44 (55)	119,356 (57.5)	0.654	0.664
Ethnicity	White	60 (77.9)	155,339 (69.9)	0.124	70 (87.5)	128,442 (61.9)	<0.001*	0.112
	Black	15 (19.5)	16,291 (7.3)	<0.001*	5 (6.3)	15,274 (7.4)	0.705	0.010*
	Other	2 (2.6)	50,674 (22.8)	<0.001*	5 (6.3)	63,930 (30.7)	<0.001*	<0.001*
Age (SD)		57.8 (1.74)	65.0 (0.91)	0.095	52.1 (1.64)	52.1 (0.88)	0.914	0.038*

**Significant at the 0.05 level.*
SD: Standard deviation.

Table 2. Demographic variables of pediatric patients whose parents participated in our study in comparison with all pediatric patients with outpatient visits during the study period.

Demographic		Peds cohort (n = 80) (%)	All pediatric outpatients (n = 63,199) (%)	p-value
Age of child (SD)		4.4 (0.53)	8.04 (5.31)	<0.001*
Female (child)		36 (45.0)	29,782 (47.1)	0.704
Child ethnicity	White	45 (56.3)	30,806 (48.7)	0.180
	Black	19 (23.8)	8309 (13.1)	0.005*
	Other	16 (20.0)	24,084 (38.2)	0.001*
Location	Multispecialty clinic	32 (40.0)	–	–
	Primary care clinic	48 (60.0)	–	–

*Significant at the 0.05 level.
Peds cohort: Pediatric cohort; SD: Standard deviation.

time point 2 in the proportion of respondents who reported having heard of the DNA databank remained following adjustment (OR: 0.51; 95% CI: 0.26–1.01; p = 0.054), although this change became nonsignificant. Females were more likely to have heard of the DNA databank (OR = 2.34; 95% CI: 1.23–4.44; p = 0.009) and older individuals were more likely to support the DNA databank (OR: 1.10; 95% CI: 1.02–1.18; p = 0.016).

As seen in Table 7, the most common reason provided by adult patients for supporting the biorepository was the potential for it to support research that improves understanding of diseases (coded by interviewers as "doctors will study diseases"). As seen in Table 8, parents of pediatric patients most often reported the potential for the biorepository to benefit others as a reason that they support the biorepository. Among those respondents who reported that they oppose the biorepository, two out of seven adult patients and two out of four parents of pediatric patients cited privacy concerns.

Discussion

Awareness of the DNA databank & use of leftover blood for research

We found that adult patients surveyed in 2009 were more likely to report having heard of the DNA databank in comparison to adult patients surveyed from 2011 to 2012 (48.1 and 32.5%, respectively), even though awareness that leftover blood could be used for research increased during this period, from 34.3 to 50.0%. We theorize that even though patients were increasingly aware that leftover blood could be used for research, they became less likely to recognize the name 'DNA databank', in part because program literature increasingly used the name 'BioVU' to describe this resource. However, convenience-based samples in pragmatic settings are sensitive to a range of procedures throughout a program. Thus, our data are best suited to provide both a benchmark and tracking for key measures, such as awareness and perceptions of the biorepository. This methodology does not facilitate attribution of trends to specific causes.

Although patients may not have been able to recognize that 'DNA databank' and 'BioVU' refer to the same research resource, the concept that leftover blood could be used for research is a consistent concept across all patient notification efforts. For this reason, we believe it is the more accurate surrogate for awareness of this program. In an earlier study, we demonstrated that only 32% of patients recalled seeing posters intended to notify them about BioVU [13]. Based on these data, notification efforts were

Table 3. Reasons for noninclusion.

Cohort	Reason for noninclusion		
	Patient/parent refused, n (%)	*Staff busy, n (%)*	*Non-English speaking, n (%)*
Adult 1 (n = 35)	17 (48.6)	17 (48.6)	1 (3.8)
Adult 2 (n = 48)	34 (70.8)	14 (29.2)	0 (0.0)
Peds (n = 35)	8 (22.9)	4 (11.5)	23 (65.6)

Peds: Pediatric.

Table 4. Response rates.

Cohort	Total potential respondents (included and not included)	
	Response rate† (%)	*Refusal rate† (%)*
Adult 1 (n = 112)	68.8	15.2
Adult 2 (n = 128)	62.5	26.6
Peds (n = 115)	69.6	7.0

†Rates are calculated according to the American Association for Public Opinion Research guidelines and assume that all nonparticipants would have been eligible [23].
Peds: Pediatric.

markedly expanded, including handing pamphlets to all new patients, expanding posters to both phlebotomy and clinic areas and placing advertisements in local publications. Based on the findings of this study, these efforts seem to have been somewhat successful.

Although this increase in awareness is heartening, it is not clear what an appropriate goal should be for this value. Even research participants who complete an informed consent process are not always aware that they are engaged in research. The percentage of participants in prior studies who are able to correctly identify that they are participating in research ranges from 56.4 to 92.2% [14–18]. Even those who recognize that they consented to research often do not recall the aims of that research; the proportion who do ranges from 33.3 to 55.2% [14,19]. Despite these findings, at least one study has indicated that as much as 100% of biorepository participants are able to identify this activity as research [20].

By comparing these previous findings with the results reported here, we believe that the opt-out procedures utilized by BioVU are not yet optimal. Informed by these data and due to unrelated institutional interest in improving the quality of the outpatient consent to receive treatment process, the entire medical center is currently transitioning from the paper-based process described above to a kiosk-based consent process. Instead of signing a two-page paper form every twelve months, patients will now be asked to acknowledge each screen of information one-at-a-time. This includes a dedicated screen that includes a description of BioVU using language that has been rewritten for clarity and simplicity. The new language used in the kiosk-based consent is provided in Supplementary Figure 1B. We hypothesize that, since this new process requires an explicit acknowledgement from patients that they have read the presented information, patient awareness of BioVU will improve.

We have also implemented ongoing exit interviews with patients based on the methods described in this report. These interviews will provide critical information in ongoing quality assurance efforts and will allow evaluation of whether the expanded notification methods will result in a higher level of awareness among our patient population.

Approval of the opt-out approach to biobanking

Following a description of the biorepository, the vast majority of respondents report approval for this approach to sample collection for research on human health. This finding has been remarkably consistent across a range of populations and survey approaches. We recently reported on

Table 5. Outcomes studied stratified by cohort.

Variable	Adult 1 cohort (n = 77) (%)	Adult 2 cohort (n = 80) (%)	p-value Adult 2 vs Adult 1 cohort	Peds cohort (n = 80) (%)	p-value Peds vs Adult 1 & 2 cohorts
Previously heard of DNA databank	37 (48.1)	26 (32.5)	0.047*	15 (18.8)	<0.001*
Understood leftover specimens could be used for research	25 (34.3)	40 (50.0)	0.026*	37 (46.3)	0.475
Recall previously choosing to opt-out of the DNA databank	2 (2.6)	2 (2.5)	0.969	–	–
Support DNA databank	68 (88.3)	76 (95.0)	0.129	75 (93.8)	0.245
Support DNA databank for children	–	–	–	71 (88.8)	–

**Significant at the 0.05 level.*
Peds cohort: Pediatric cohort.

Table 6. The multivariable logistic regression models predicting primary outcomes.

Outcome (Hosmer–Lemeshow p-value)	Predictor	OR	95% CI of OR	p-value
Recognize consent for treatment form (p = 0.575)	Adult 1 cohort	Ref.	–	–
	Adult 2 cohort	2.10	1.02–4.32	0.042*
	Peds cohort	1.68	0.69–4.10	0.178
	White	0.67	0.35–1.31	0.676
	Female	1.03	0.55–1.91	0.931
	Age	1.00	0.98–1.02	0.963
Have heard of DNA databank (p = 0.635)	Adult 1 cohort	Ref.	–	–
	Adult 2 cohort	0.51	0.26–1.01	0.054
	Peds cohort	0.21	0.08–0.51	0.001*
	White	1.15	0.57–2.35	0.692
	Female	2.34	1.23–4.44	0.009*
	Age	1.00	0.98–1.02	0.953
Understand leftover blood could be used for research (p = 0.125)	Adult 1 cohort	Ref.	–	–
	Adult 2 cohort	1.91	1.07–3.73	0.041*
	Peds cohort	1.10	0.48–2.50	0.821
	White	1.08	0.57–2.04	0.822
	Female	1.76	0.97–3.18	0.061
	Age	0.99	0.97–1.01	0.248
Support DNA databank (p = 0.875)	Adult 1 cohort	Ref.	–	–
	Adult 2 cohort	2.44	0.74–8.53	0.147
	Peds cohort	2.25	0.72–7.32	0.204
	White	2.08	0.58–3.62	0.182
	Female	1.60	0.48–2.57	0.697
	Age	1.10	1.02–1.18	0.016*

A Hosmer–Lemeshow p-value greater than 0.05 suggests the model fits the data well.
**Significant at the 0.05 level.*
OR: Overall response; Peds cohort: Pediatric cohort; Ref.: Reference.

large-scale surveys with members of the Nashville community and employees of Vanderbilt University (TN, USA) demonstrating rates of approval (93.9 and 94.6%, respectively) nearly identical to those identified in this study [21]. Although we did interview a small number of adult patients who reported previously opting out of BioVU (2.5%) and a small number who opposed the biobank (7.6%), this sample was inadequate to conclusively identify the reasons that usually motivate this decision.

Voluntariness of participation

We believe there are at least three empirical questions relevant to assessing whether the opt-out approach to building biorepositories can effectively ensure that inclusion of biosamples is voluntary:

- Are patients made aware of the research through notification efforts and the opt-out form?
- Are patients provided with enough information to make an effective decision?
- Are patients aware of not only the research, but also of their opportunity to opt-out?

The present study addresses only the first empirical question, although our answer is an incomplete one. Even though we were able to determine that roughly half of patients report that they are not aware that their leftover blood could be used for research, we are not able to discriminate among the possible explanations for this finding. It is likely that some patients have simply never noticed the posters in clinic areas,

Table 7. Reasons given by adult patients for supporting or opposing the DNA databank.

Response	Number of respondents (%)	
	Adult 1 cohort	***Adult 2 cohort***
Reasons for supporting†:	n = 68	n = 77
Research might benefit me or my family	11 (16.2)	17 (22.4)
Research is being done at Vanderbilt	4 (5.9)	3 (3.9)
Collection of samples is helpful to scientists	21 (30.9)	5 (6.6)
Doctors will study diseases	31 (45.6)	36 (47.4)
Other	4 (5.9)	47 (61.8)
Reasons for opposing†:	n = 6	n = 1
I do not know how my DNA will be used	2 (33.3)	0 (0)
I do not believe my information is safe	1 (16.7)	1 (100)
Other	3 (3)	1 (100)

†Respondents were permitted to provide multiple reasons.

pamphlets handed out in clinics and opt-out language included on the consent for treatment form. Other patients may have seen one or more of these notifications, but did not understand its content. These are the causes that we are most interested in eliminating, since they are particularly relevant to the question of voluntariness of inclusion in BioVU. However, there are certainly other possible reasons that patients report not being aware of the DNA databank. For example, previous research on participant recall in the setting of informed consent to research participation, as described above, indicates that even individuals who undergo a detailed informed consent process do not recall the key elements of that information.

Indeed, our results indicate that even though we can assume that every patient has signed a consent for treatment form in the past and therefore has had an opportunity to read information pertaining to BioVU (since medical center policies require that a signed copy of the consent for treatment form must be in the electronic medical record in order for an outpatient to receive treatment), 23.8% of parents either report that they have never seen the form or that they are not sure whether they have seen the form. Since we do not have access to respondents' administrative records, we are unable to infer what has caused this lack of recall (i.e., parents who signed these forms recently yet report they have never seen them may not have been attentive to what they were signing; parents who signed the forms months ago may have just forgotten about them). However, it does appear that recognition of the form is a relatively strong predictor of awareness that leftover blood could be used for research; those patients who report signing the consent for treatment form on the day they responded to the survey are significantly more likely to be aware that leftover blood could be used for research compared with those who do not recall signing the form (61 vs 37%; p = 0.0007).

Limitations

This study has a number of limitations, several of which have been mentioned above. Perhaps the most significant limitation of this study is that all variables are based on patient recall. We did not seek permission from respondents to access their administrative records, so we do not know which of them had opted out of the biorepository

Table 8. Reasons given by parents of pediatric patients for supporting or opposing including children in the DNA databank.

Response	Number of respondents (%)
Reasons for supporting†:	n = 71
Benefit other people	60 (89.6)
Benefit me or my family	6 (9.0)
Benefit people with same disease	4 (6.0)
I don't see a reason not to support it	11 (16.4)
Reasons for opposing†:	n = 4
Concerned about privacy of DNA information	1 (25.0)
Concerned about privacy of health information	1 (25.0)
Other	2 (50.0)

†Respondents were permitted to provide multiple reasons.

in the past or when each last viewed and signed the 'consent for treatment' form. We also do not know who is actually included in the biorepository, since all data in the biorepository is de-identified.

An additional limitation is that all three cohorts were collected as convenience samples. In order to maximize the number of patients who could be surveyed, interviewers focused on the busiest phlebotomy areas on their busiest days of the week. However, all four of the phlebotomy areas where patients were interviewed (two adult, two pediatric) serve multiple clinics. One of the pediatric locations and one of the adult locations serve primarily subspecialty clinics, while the remaining two locations serve primarily primary care patients. Interviewers were intentional in balancing interviews conducted at each location. We have assessed selection bias in two ways: by tallying the patients who were not included in our study (Tables 3 & 4) and by comparing our sample with the total outpatient population (Tables 1 & 2). The former method indicates a strong response rate for this survey and the latter method demonstrates that our sample is reasonably representative of the patient population of interest.

The absence of comparison groups also significantly limits our ability to interpret the findings of this study. We have identified only one previous study evaluating awareness of an ongoing research project involving an opt-out dimension, although the research involved – a study of resuscitation algorithms in a pediatric intensive care unit – is significantly different from that performed using a genomic biorepository [22]. As other institutions develop biorepositories based on opt-in and opt-out models, patient awareness and approval should be evaluated. This experience across settings will help establish best practices for patient notification and meaningful benchmarks for awareness of opt-in and opt-out approaches to biorepository research.

Conclusion

We found that many patients and parents of pediatric patients having blood drawn as a part of their medical care were not aware of our opt-out biorepository that collects leftover clinical samples to be used for research on health, although the vast majority approved of this research effort. While recognition of the 'DNA databank' decreased over time among adult patients, awareness that leftover blood could be used for research increased. We attribute this increase to ongoing patient notification efforts, although the relatively low level of awareness in our sample indicates that additional improvements in these efforts are needed. Additional empirical research will be needed to inform a thorough analysis of the suitability of opt-out methods to ensure voluntary participation in research.

Future perspective

In future work we hope to conduct interviews with patients who have given us consent to access their electronic administrative record. This approach will not only allow us to assess whether patients who recently signed consent for treatment forms are more likely to be aware of BioVU, but also to assess whether patients who report a desire to opt-out of inclusion have successfully opted out in the past. These additional data will help us address our overarching aim of examining the effectiveness of opt-out procedures for ensuring voluntary participation in research.

We hope other biorepositories utilizing opt-out and opt-in methods will conduct similar empirical research in their own research settings. These new empirical findings will help inform the follow-on ethical and policy analysis that will be needed to determine the appropriateness of opt-in and opt-out methods, since, in certain circumstances, traditional informed consent can be impractical or can pose a significant barrier to answering important research questions.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Background

- 'Human nonsubjects' approaches to research, including opt-in and opt-out methods, represent attempts to respect the preferences of individuals on the research uses of their biosamples and/or medical information, even though they are not engaging in research as subjects.
- Empirical data is needed in order to assess whether the opt-out approach to building a biorepositories can effectively ensure that inclusion of biosamples is voluntary.

Materials & methods

- In this manuscript, we report on exit interviews we conducted to assess patient awareness of one particular opt-out biorepository.
- The primary outcomes for this study were:
  - Patient awareness of the Vanderbilt DNA databank;
  - Patient awareness that leftover blood could be used for research;
  - Patient support for the biorepository.

Results

- Adult patients surveyed in 2009, less than 2 years after the biorepository started, were more likely to report having heard of the DNA databank in comparison with adult patients surveyed from 2011 to 2012. At the same time, awareness that leftover blood could be used for research increased during this period.
- Parents of pediatric patients were less likely than adult patients to have heard of the DNA databank. However, a comparatively large number of them were aware that leftover blood could be used for research.
- Despite relatively low awareness, a large majority of patients and parents of pediatric patients supported the DNA databank after a brief explanation and a comparable majority of parents supported a DNA databank for children.

Discussion

- Additional research is needed to determine whether high levels of awareness can be obtained through patient notification efforts, including opt-out forms, posters and brochures.
- Additional research is also needed to assess whether opt-out approaches can be effective at making patients aware of the opportunity to opt out and providing them with enough information to make an effective choice.

References

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.* US Government Printing Office, Washington, DC, USA (1979).

2 *Trials of War Criminals Before the Nuernburg Miltary Tribunals Under Control Council Law No. 10, Volume II: Nuernburg, October 1946–April 1949.* US Government Printing Office, DC, USA, 181–182 (1946).

3 *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.* World Medical Association, Ferney-Voltaire, France (2008).

▪▪ **This document, with its continuing periodic revisions, is treated worldwide as the definitive statement of the principles of research with human subjects.**

4 Pulley J, Clayton E, Bernard GR, Roden DM, Masys DR. Principles of human subjects protections applied in an opt-out, de-identified biobank. *Clin. Transl. Sci.* 3(1), 42–48 (2010).

5 Trinidad S, Fullerton S, Ludman E, Jarvik G, Larson E, Burke W. Research practice and participant preferences: the growing gulf. *Science* 331(6015), 287 (2011).

6 Brothers KB. Biobanking in pediatrics: the human nonsubjects approach. *Per. Med.* 8(1), 71–79 (2011).

7 Brothers KB, Clayton EW. 'Human non-subjects research': privacy and compliance. *Am. J. Bioethics* 10(9), 15–17 (2010).

▪ **Two authors of the present publication introduce and discuss the concept of 'human non-subjects research,' that is, research on materials and information obtained from humans that does not involve interaction with these persons as research subjects.**

8 Gymrek M, McGuire AL, Golan D, Halperin E, Erlich Y. Identifying personal genomes by surname inference. *Science* 339(6117), 321–324 (2013).

9 Homer N, Szelinger S, Redman M *et al.* Resolving individuals contributing trace amounts of DNA to highly complex mixtures using high-density SNP genotyping microarrays. *PLoS Genet.* 4(8), e1000167 (2008).

10 Marsolo K, Corsmo J, Barnes MG *et al.* Challenges in creating an opt-in biobank with a registrar-based consent process and a commercial EHR. *J. Am. Med. Inform. Assoc.* 19(6), 1115–1118 (2012).

11 Roden DM, Pulley JM, Basford MA *et al.* Development of a large-scale de-identified DNA biobank to enable personalized medicine. *Clin. Pharmacol. Therapeut.* 84(3), 362–369 (2008).

▪ **Describes the design of the BioVU resource, the biorepository whose opt-out approach is examined in this manuscript.**

12 Lantos J. Informed consent the whole truth for patients? *Cancer* 72(Suppl. 9), 2811–2815 (2006).

▪ **In this well-reasoned article, the author examines the rationale for treating research consent and clinical consent differently. Several helpful observations of general ways consent for both could be improved are made.**

13 Pulley JM, Brace M, Bernard GR, Masys D. Evaluation of the effectiveness of posters to provide information to patients about a DNA database and their opportunity to opt out. *Cell Tissue Bank.* 8(3), 233–241 (2007).

14 Fortney JA. Assessing recall and understanding of informed consent in a contraceptive clinical trial. *Stud. Fam. Plann.* 30(4), 339–346 (1999).

15 Howard JM, Demets D. How informed is informed consent? The BHAT experience. *Control. Clin. Trials* 2(4), 287–303 (1981).

16 Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent in cancer clinical trials: a cross-sectional survey. *Lancet* 358(9295), 1772–1777 (2001).

17 Mccollum AT, Schwartz AH. Pediatric research hospitalization: its meaning to parents. *Pediatric Res.* 3(3), 199–204 (1969).

18 Riecken HW, Ravich R. Informed consent to biomedical research in Veterans Administration hospitals. *JAMA* 248(3), 344–348 (1982).

19 Toccaceli V, Fagnani C, Nisticò L *et al.* Research understanding, attitude and awareness towards biobanking: a survey among Italian twin participants to a genetic epidemiological study. *BMC Med. Ethics* 10(1), 4 (2009).

20 Ormond K, Cirino A, Helenowski I, Chisholm R, Wolf W. Assessing the understanding of biobank participants. *Am. J. Med. Gen.*149(2), 188–198 (2009).

21 Brothers KB, Morrison DR, Clayton EW. Two large-scale surveys on community attitudes toward an opt-out biobank. *Am. J. Med. Gen.* 155(12), 2982–2990 (2011).

22 Raymond TT, Carroll TG, Sales G, Morris MC. Effectiveness of the informed consent process for a pediatric resuscitation trial. *Pediatrics* 125(4), e866-e875 (2010).

▪ **Reports on work to assess the effectiveness of efforts to notify parents that an opt-out research effort is underway. Although the issues relevant to resuscitation trials differ significantly from those relevant to biorepositories, this study provides important insights into the effectiveness of opt-out methods for ensuring voluntary research participation.**

23 *Standard Definitions: Final Dispositions of Case Codes and Outcome Rates for Surveys.* The American Association for Public Opinion Research, IL, USA (2011).

Websites

101 OHRP: Guidance on Research Involving Coded Private Information or Biological Specimens (2008). www.hhs.gov/ohrp/policy/cdebiol.html

▪ **This guidance document provides the regulatory rationale for utilizing opt-out or opt-in methods to elicit permission for inclusion in research in the USA.**

102 45 CFR 164.514 – Other Requirements Relating to Uses and Disclosures of Protected Health Information (2002). www.law.cornell.edu/cfr/text/45/164.514