Informed Choices in Biobanking: An Examination of Participants' Understanding and Congruence between Knowledge, Values, and Decisions

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Nursing)
in the University of Michigan
2018

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Dedication

Ad Majorem Dei Gloriam

(All for the greater glory of God)

----St. Ignatius of Loyola 1491-1556

To my loving husband, Joe--- your love, inspiration, patience, emotional, and yes, financial support made this work possible. Also to three other academic role models: my late father, and two early research mentors, Dr. David E. Uddin and Mrs. Diane G. Schwartz, thank you.

Acknowledgements

I am grateful for the expertise of my dissertation committee and their guidance on this work. A special thank you to my Chair, Dr. Arslanian-Engoren, for encouraging me to publish my work, repeatedly, while in the PhD program. To Dr. Marcelline Harris, my advisor, confidant, and friend during the process, thank you so much! To my husband, Joe, thank you so much for your love and support through this arduous process. Many thanks to my sister, Sara---especially during the last two most difficult last two years, as you have remembered every medical appointment and been a great support to me. To other friends and family who have seen me through: Maxine and Mark Galloway, and Glenn Diamond and Laura Kibrick; what would I do without you? I thank the U-M School of Nursing, the Jonas Foundation, and Rackham for their generous financial support; it really made a huge difference in pursuing this dream. Sometimes important work is tangential to the goal; therefore, I thank Dr. Barbara A. Carper and the family of Dr. Philip H. Phenix. I also thank the University of Michigan library system---the best thing about U-M! Finally, thank you to all the staff at UMHS and MDHHS and the mothers who participated in my research projects.

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Abstract

The ethical foundation of clinical research is informed consent. Biobanking has added to the complexity of the informed consent process. Biomedical research with human biospecimens often occurs without any consent or with inadequately understood consent information. Yet, the use of biospecimens in research is not without controversy.

One abundant source of biospecimens for research is residual dried blood spots (rDBS) from newborn screenings. Approximately 4 million infants are born annually in the United States (U.S.) and most have mandatory newborn screening. In 2010, the state of Michigan implemented a process of written parental consent for donating newborns' residual dried blood spots to the Michigan BioTrust for research. Thus, biobanking of newborn rDBS in Michigan presented a prime opportunity to study mothers' level of knowledge, attitudes, values, and decision-making after a broad consent process for donating their newborn's rDBS for research.

Therefore, the purposes of this dissertation research are to a) describe the current state of the science regarding participants' understanding of informed consent for biobanking; b) describe the influence of mothers' knowledge (understanding of biobanking), values (personal and religious), and perceptions of the informed consent process (content and context) on their decisions to donate their newborn's rDBS for research purposes; c) compare and contrast mothers' knowledge of and attitudes towards biobanking, socio-demographics, and personal and religious values with their decisions (yes or no) to donate their newborn's rDBs for research purposes and determine the proportion of informed choices.

A qualitative descriptive design, a non-experimental survey, and methodological triangulation are used in this three-paper style dissertation. The first of the three papers (Chapter 2) is a systematic review to evaluate participants' level of understanding of the information presented during the consent process for donation of biological specimens for research purposes (i.e., for biobanking or genetic epidemiological studies). Results indicated many elements of informed consent unique to biobanking were inadequately understood by potential participants. Next, semi-structured interviews (Chapter 3) were used to describe mothers' understanding of biobanking, attitudes about rDBS research, and the influence of personal values on the decision-making process. Findings indicated that while most mothers agreed (14/20; 70%) to donate the rDBS and expressed favorable attitudes about research, most decisions (16/20; 80%) were determined to be uniformed choices due to inadequate knowledge of the Michigan BioTrust and biobanking. A non-experimental, descriptive and correlational survey was randomly distributed to 500 mothers in the state of Michigan with a newborn age 0-3 months (Chapter 4) to examine knowledge, attitudes and values, and the proportion of informed choices in a larger sample using standardized instruments. Just over half of the mothers (55%) in this study were deemed to have made an informed choice; however, knowledge scores were still low. On average, respondents were only able to correctly answer approximately 8/16 biobanking questions.

With 4 million American newborns having blood spots each year there are significant policy implications to this research (Chapter 5). Three recommendations are put forth: include the ethical implications of biobanking in educational materials, enhance consenters' knowledge about rDBS research and their communication skills for conducting informed consent processes, and move the educational content about rDBS research to the prenatal setting (Chapter 5).

Chapter 1 Introduction

Informed consent is a central tenet of the bioethical principles governing both medical treatment and clinical research. There are similarities in informed consent for medical treatment (e.g. surgery) and research including the obligation of the provider or researcher to disclose to the patient or potential participant the risks, benefits, nature of the procedure and alternatives (Levine, 1983; Beauchamp, 2011). However, while standard medical treatment is believed to be in the patient's best interest, research may involve risks without any intended or direct benefit to the participant. Thus, informed consent in clinical research often involves more information and formality, and is highly regulated by the government (Levine, 1983; Beauchamp, 2011). In clinical research, informed consent is an ongoing, interactive process in which an individual is given important information about voluntary participation in the research project (e.g. risks, benefits, and the right to withdraw at any time) before deciding whether or not to participate (National Cancer Institute [NCI], 2018). For informed consent to be considered valid, adequate information must be provided by researchers. In addition, efforts must be made to ensure the potential participants understand the information provided (Faden & Beauchamp, 1986). However, as clinical research is becoming increasingly complex many individuals do not understand the informed consent information (Cohn & Larson, 2007; Falagas et al., 2009; Flory & Emanuel, 2004; Nishimura et al., 2013).

This dissertation focuses on the concept of informed consent for clinical research, specifically, biobanking research. Biobanking, defined as the collection, storage, and management of human biological specimens (e.g. tissue, cells, blood) and/or associated personal

health information for future and often unspecified research activities (Biobanking and Biomolecular Resources Research Infrastructure [BBMRI], 2012; Henderson et al., 2013) has further added to the complexity of the informed consent process (Brothers, 2013; Rothstein, 2005). Since the completion of the Human Genome Project, millions of biospecimens have been preserved in private and public biobanking repositories (Collins, Green, Guttmacher, & Guyer, 2003; Henderson et al., 2013). Biobanks vary greatly in their administrative governance (e.g. public, non-profit, academic, private, or for profit companies) and purpose (e.g. to conduct disease-focused research, and/or to facilitate research for other scientists by providing biospecimens; Henderson et al., 2013).

Biospecimens are useful in research for at least two reasons. First, they contain deoxyribonucleic acid (DNA), the molecule that constitutes genes and chromosomes and contains the unique genetic code of each individual. DNA determines the expression of human physical traits, (e.g. eye color) and susceptibility to certain diseases (e.g. Alzheimer's disease). Genomic sequencing provides information about an individual's complete set of genes and important insights about individual and population health and human disease (Collins et al., 2003; Rédei, 2008; International Human Genome Sequencing Consortium, 2004; NHGRI, 2010; Seemungal & Carr, 2001).

The second reason biospecimens are useful in research is because they are considered "naturally occurring raw materials" (*Moore v. Regents of the University of California*, 1990, 793 P.2d at pp. 492-93; Rao, 2000) for use in the creation of genetically-engineered animals, cell lines, and embryos, increasingly used for scientific experimentation (Jones & MacKellar, 2009; *Moore v. Regents of the University of California*, 1990; Salvi, 2001). Biobanks frequently supply scientists with biospecimens including specific human cells (e.g. fibroblasts, leukocytes)

and DNA for incorporation into these genetically-modified creations. While the wealth of knowledge gleaned from this research has led to medical advances, the use of biospecimens in research is not without controversy.

Statement of the Problem

Biobanking has become an important part of scientific research and millions of biospecimens are collected for research each year. If, however, relevant consent information is omitted, inadequately provided, or inadequately understood, then individuals may make uninformed biobanking decisions (Eisenhauer, Tait, Rieh, & Arslanian-Engoren, 2017; Lewis, Goldenberg, Anderson, Rothwell, & Botkin, 2011; Wertz, 1999). The era of genetics and genomics has ushered in new types of biomedical research, bringing forth concerns about genetic privacy and the ethical use of human biospecimens (Brothers, 2013; Rothstein, 2005, 2010). Increasingly, empirical research describes the importance of personal, religious, and moral values regarding the use of biospecimens (Eisenhauer & Arslanian-Engoren, 2016; Modell, Citrin, King, & Kardia, 2014; Tomlinson, Kaplowitz, & Faulkner, 2014; Tomlinson, De Vries, Ryan, Kim, Lehpamer, & Kim, 2015). Whether, and how, individuals incorporate their personal, religious, and moral values when making decisions about biobanking participation is an understudied, but important area of research that warrants further investigation, as uninformed choices may lead to decisional regret and moral distress.

Significance of the Research

While an abundance of evidence exists describing attitudes toward biobanking and preferences for type of consent (e.g. opt-in, opt-out, specific, tiered, or broad; Botkin et al., 2012; Brothers, Morrison, & Clayton, 2011; Hull et al.,2008; Igbe & Adebamowo, 2012; Murphy et al., 2009; Simon, et al. 2011; Tarini et al., 2009; Thiel et al., 2014; Wong et al., 2004), there is a

paucity of empirical evidence that has evaluated whether decisions that result from the informed consent process for biobanking meet the standard of informed decisions. Informed decision-making requires adequate knowledge and consistency with one's values (Marteau et al., 2001; O'Connor, Llewellyn-Thomas, & Flood, 2004). Inadequate information, knowledge, and understanding may lead to biobanking participation decisions that are inconsistent with personal values, beliefs, and preferences (Tomlinson et al., 2014; Tomlinson, et al., 2015) and may result in dissatisfaction, decisional regret, moral distress, and a lack of trust and participation in future research (Modell et al., 2014; Rothstein, 2005; Tomlinson et al., 2014).

This also has implications for personalized medicine, as it depends on a large, diverse quantity of biobanked specimens to establish generalizability of results. Finding the right balance and best method for biobanking consent requires empirical results describing how individuals make actual biobanking decisions, in their natural settings, and in real-time. It also requires examining the role of personal and religious values and the diversity of beliefs. Two recent literature reviews revealed few studies have addressed the influence of personal and religious values at the point of actual biobank specimen donation decisions (Eisenhauer et al., 2017; Eisenhauer & Arslanian-Engoren, 2016).

Informed consent for genetics, genomics, and biobanking requires frank, open discussions with potential participants that include their values and explicit examples of various types of research for which biospecimens may be used (e.g. animal research, behavioral genetic research, creation of immortalized cell lines, embryonic stem cell research, germ-line gene therapy (GLGT), in vitro fertilization, preimplantation genetic diagnosis, prenatal genetic screening, and somatic nuclear cell transfer). Providing accurate and balanced information is necessary, so participants can develop an informed understanding of biobanking research to

make decisions in alignment with their values. By doing so, the informed consent process may be transformed from a perfunctory, rote process to one that provides meaningful information to participants, from which they can then consider whether or not to participate in the proposed research guided by their understanding (e.g. of risks and benefits) and their personal values.

In addition to a lack of research on concerns about moral risk, studies that seek to determine participants' understanding of informed consent information also often lack the use of standardized measures (Cohn & Larson, 2007; Falagas et al., 2009; Flory & Emanuel, 2004; Nishimura et al., 2013). This dissertation begins to address these gaps by examining the influence of personal and religious values in biobanking decision-making, using standardized measures of knowledge, attitudes, informed choice, and biobanking consent information, during actual decision-making, in real-time and natural settings. Analysis resulting from this work will provide the foundation for tailored interventions to facilitate informed choices in biobanking, and continued development of an emerging middle-range nursing theory of informed consent for clinical research (Eisenhauer & Arslanian-Engoren, 2016).

Background

Biobanking and Informed Consent

Currently, in the United States (U.S.) a national policy debate is occurring regarding the consent requirements for the use of human biospecimens (Federal Policy for the Protection of Human Subjects, 2015; 2017; 2018). Differing views among stakeholders include some believing that asking for consent will hinder the pace of biomedical research (Forsberg, Hansson, & Eriksson, 2011), while others believe it is an ethical requirement (Greely, 1999; Hofmann, 2009; Rothstein, 2005). Residual, non-identified biospecimens from clinical care (e.g. venipuncture, surgery), previous research studies, or currently existing in biobanks can be used

for research without informed consent. However, the use of identifiable biospecimens or biospecimens obtained specifically for research purposes requires written informed consent (United States [U.S.] Department of Health & Human Services [DHHS]. Office for Human Research Protections [OHRP], 2008). Survey research shows most individuals support the goals of biomedical research, while at the same time many individuals want control over the use of their biological specimens and want to be asked permission for their research use (Botkin et al., 2012; Brothers, Morrison, & Clayton, 2011; Hull et al.,2008; Igbe & Adebamowo, 2012; Murphy et al., 2009; Simon, et al. 2011; Tarini et al., 2009; Thiel et al., 2014; Wong et al., 2004). As a result, some agencies are now asking for consent to use biospecimens in research, even when it may not be required (Langbo, Bach, Kleyn, & Downes, 2013; Tarini & Lantos, 2013).

Biobanking informed consent documents vary widely on the amount and type of information provided to potential participants (Master, Nelson, Murdoch, & Caulfield, 2012). Three common types of biobanking consent documents are study-specific, categorical (or tiered), and broad consent forms. Study-specific consent forms clearly describe the details of a single, specified study and allow the use of the participant's biospecimen for a specified purpose and time frame. A categorical consent document allows a participant to grant permission for specific categories of research activities. Broad consent forms allow researchers to use participants' biospecimens often for indefinite periods of time and for unspecified research purposes (Master et al., 2012). Broad consent forms are often favored by researchers for their latitude, and are also frequently acceptable to participants as they provide some degree of choice and control (Grady et al., 2015). However broad consent forms often lack specific details and may not be adequately understood by participants, raising ethical issues about its acceptability (Hofman, 2009). Despite these concerns, the use of broad consent for the use of identified biospecimens in research was

recently approved by the U.S. federal government (Federal Policy for the Protection of Human Subjects, 2017).

Genetic Privacy

Genetic privacy is a risk of biobanking participation. Some ethicists argue this is more than minimal risk, especially when it involves proxy consent for minors because minors have a right to their own values that may not align with the values of the surrogate (Baumann, 2001; Caulfield & Weijer, 2009; Hens, Cassiman, Nys, & Dierickx, 2011; Hofmann, 2009). Donated biospecimens provide researchers access to individuals' genetic fingerprint. Sequencing DNA reveals the donor's genetic susceptibility to disease and potentially even adverse behavioral traits (Andrews, 2005; Rothstein, 2005). Analyzing the DNA of one family member can provide information about and create risks for other family members or an entire race, ethnicity, or religious group (Andrews, 2005; Rothstein, 2005), as it is now possible to definitively identify an individual using relatively little genetic material (Lin et al., 2004). Further, biospecimens in biobanks are often linked to medical data or information in public health registries, creating additional privacy and discrimination concerns (Andrews, 2005). Other concerns include linking specific genetic traits, especially those that hold social stigma (e.g. alcoholism, mental illness, criminality) to specific racial populations or religious groups, that may contribute to pervasive discrimination (Andrews, 2005; Rothstein, 2005; Wertz, 1999).

Moral Risks

Additional risks include moral risks: the possibility that biospecimens and the knowledge they generate may be used in research activities or procedures that are misaligned with the donor's (or surrogate's) personal, religious, or cultural values (Modell et al., 2014; Rothstein, 2005; Tomlinson et al., 2014; 2015). Compared to privacy concerns, the threat to individuals'

moral values is less understood as it relates to personal values, expectations, and human rights regarding stewardship or jurisdiction over one's body and the right to bodily integrity in life and even after death (Young, 2012).

Concerns include: religious prohibitions against blood storage, cloning, predicting the future, and trying to "play God" by analyzing and /or manipulating genetics (Eisenhauer & Arslanian-Engoren, 2016). Because future research use of biospecimens is often unspecified, alignment with personal values may not always be clear and should be explored during the informed consent process. Therefore, it is necessary to know if individuals considering biobank donation are given balanced information, presented with examples of various types of experiments conducted with biospecimens, and to determine how (or whether) individuals' incorporate their values into the reasoning and decision-making processes. This requires eliciting and clarifying participants' values during a consent process, and encouraging them to weigh the risks and benefits in light of their values.

Newborns' Blood Spots

One abundant source of biospecimens for research is residual dried blood spots (rDBS) from newborn screenings. Approximately 4 million infants are born annually in the U.S and most have mandatory newborn screening tests (American Academy of Pediatrics, 2000; Hamilton et al., 2015). Newborn screening programs, under the administration of state health departments, that choose to retain, store, and distribute rDBS for research purposes have become blood spot biobanks (Tarini & Lantos, 2013), with 20 states retaining rDBS for over one year (Olney, Moore, Ojodu, Lindegren, & Hannon, 2006). Laws and policies about the storage, retention, and parental consent for research use of rDBS vary widely across states (Lewis et al., 2011). Biobanks created without parental consent in Minnesota and Texas have resulted in lawsuits

(*Bearder et al. v State of Minnesota et al.,* 2010; *Beleno et al v. Texas Department of State Health Services et al.* 2009). In Texas, rDBS were sent to the military to create a forensic database and traded for laboratory equipment; state officials attempted to cover-up these activities (Ramshaw, 2010). Eventually, Texas was required to destroy more than 5 million blood spot cards and parental concerns resulted in changes to state policies in both Texas and Minnesota (Carmichael, 2011).

Michigan

In 2009, Michigan Department of Health and Human Services (MDHHS) proactively created the Michigan BioTrust for Health (i.e. the "BioTrust") to operationalize policies regarding the storage and research use of the newborn rDBS (Langbo et al., 2013). The BioTrust has three advisory boards to help inform policy development: a Community Values Advisory Board (CVAB), the Scientific Advisory Board (SAB), and the physical repository for the residual dried blood spots, the Michigan Neonatal Biobank (MNB) has its own board of directors (Langbo et al.). In 2010 MDHHS implemented a process of written parental consent (broad consent) for donating newborns' residual dried blood spots to the BioTrust for research (Langbo et al.). Thus, biobanking of newborn rDBS in Michigan presented a prime opportunity to study mothers' level of knowledge, attitudes and values, decision-making and the proportion of informed choices, after a broad consent process for donating their newborn's rDBS for research. While it is laudable to ask for consent, even broad consent, it is also important to determine if the information is understood and being used to make an informed choice: a choice consistent with adequate knowledge and the decision maker's values (Marteau, et al., 2001).

Specific Aims

The aims of this dissertation research are to:

1) Describe the current state of the science regarding participants' understanding of informed consent for biobanking.

2) Describe the influence of mothers' knowledge (understanding of biobanking), values (personal and religious), and perceptions of the informed consent process (content and context) on their decisions to donate their newborn's rDBS for research purposes.

3) Compare and contrast mothers' knowledge of and attitudes towards biobanking, socio-demographics, and personal and religious values with their decisions (yes or no) to donate their newborn's rDBs for research purposes and to determine the proportion of these decisions that are deemed informed.

Theoretical Framework

The theoretical framework for this study was The Marteau et al. (2001) Multidimensional Measure of Informed Choice (hereafter: MMIC; Figure 1). The main concepts are knowledge, attitudes, and the participation decision. Knowledge is defined as participants' understanding of key information about a topic, including risks, deemed essential by professional consensus for making an informed choice. Attitudes are value-judgements about facts and information. In this model, each concept has two possible dichotomous outcomes; knowledge may be good or poor; attitudes may be positive or negative, and the participation decision may be yes or no. According to the Marteau et al. (2001, p. 100) informed choice is defined as "one that is based on relevant knowledge, consistent with the decision-maker's values and behaviourally implemented". Using this definition, only two different combinations of knowledge, attitudes and participation decisions are considered informed choices (Figure 1). Thus, if the participation decision is both based on a good level of knowledge and consistent with attitudes and values, the decision is classified as an informed choice. However, if the participation decision is based on a

poor level of knowledge and/or inconsistent with the participant's values the decision is classified as an uninformed choice. All other outcomes are uninformed choices (Figure 1). While the MMIC has been used to study prenatal testing decisions (Marteau et al. 2001; Piechan et al. 2016; van den Berg, Timmermans, ten Kate, van Vugt, & van der Wal, 2006), to the best of knowledge, this is the first study that uses it to frame choices about biobanking research.

Figure 1. Informed Choices per Marteau et al. 2001

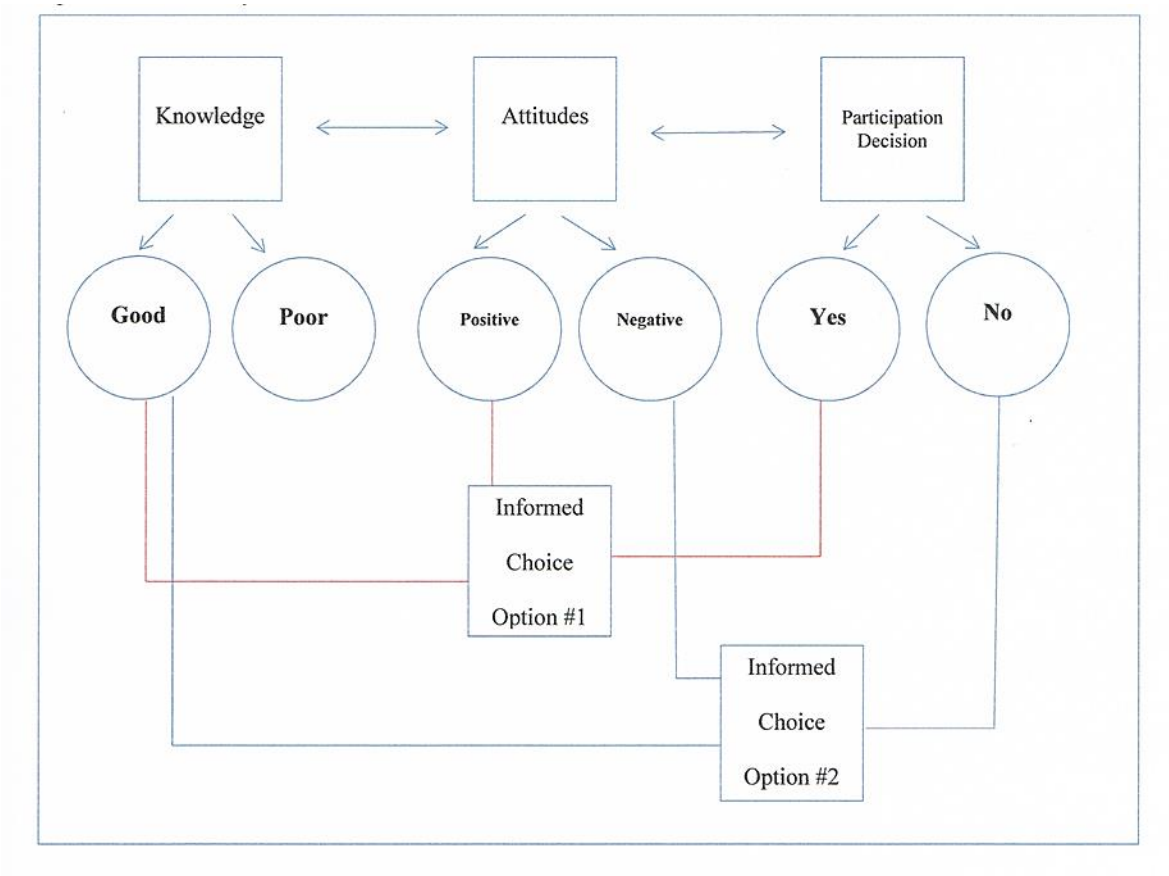


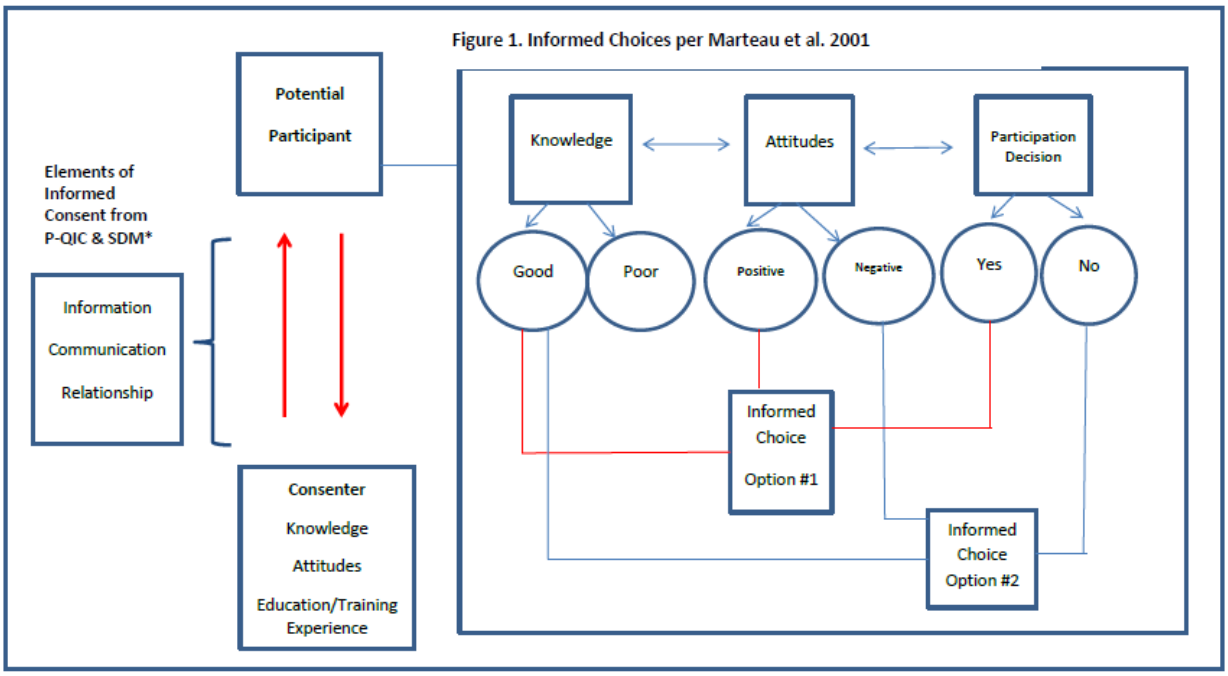
Figure 2 depicts the Marteau et al. (2001) model of informed choice in the context of an informed consent process. The Information-Motivation and Behavioral Skills Model (IMB) (Fisher & Fisher, 2000) and the Process and Quality of Informed Consent (P-QIC) tool designed by Cohn, Jia, Smith, Erwin, & Larson (2011) also influenced the development of this synthesized model. Information is transmitted through a communication process that requires specialized training and skills and feedback should be elicited from the participant to ensure understanding (Cohn et al., 2011). The quality of this process is dependent in part on the educational level and training of the consenter, who is also influenced by his/her own knowledge and attitudes and needs to know how to manage them in the context of a consent relationship. Moreover, the potential participant's knowledge and attitudes are related and informed by each other (Fisher & Fisher, 2000). Individuals apply value judgements to factual information and contextual situations, and values are often combinations of knowledge and beliefs (Fisher & Fisher, 2000; Rokeach, 1979).

Research Design

This dissertation used a non-experimental, descriptive design with methodological triangulation. Triangulation is a study design that includes qualitative and quantitative methods that complement each other to provide a more comprehensive understanding of the construct's dimensions compared to one method alone (Polit & Hungler, 1999). Each component had distinct sampling, data collection, analysis, and results; findings were subsequently combined in an overall discussion and interpretation of the study. Further, this dissertation followed a three paper manuscript-style format. The first chapter is the introduction, followed by three papers that present a comprehensive and cohesive report on a completed research project, and a

discussion chapter synthesizing the three papers and presenting directions for future research (School of Nursing, University of Michigan, 2015).

Figure 2. Synthesized Model of Informed Consent for Biobanking with Informed Choices



P-QIC= Process and Quality of Informed Consent. See: Cohn, E. G., Jia, H., Smith, W. C., Erwin, K., & Larson, E. L. (2011). Measuring the process and quality of informed consent for clinical research: development and testing. *Oncology Nursing Forum 38*(4), 417-422. Elwyn, G., Frosch, D., Thomson, R., Joseph-Williams, N., Lloyd, A., Kinnersley, P., ... & Edwards, A. (2012). Shared decision making: a model for clinical practice. *Journal of General Internal Medicine, 27*(10), 1361-1367.

One advantage of this dissertation format is rapid dissemination of results for publication, which is consistent with the intention that the results of this dissertation research to improve and protect informed consent.

The first of the three papers (Chapter 2) is a manuscript entitled, *Participants' Understanding of Informed Consent for Biobanking: A Systematic Review.* It was completed as part of preliminary study work, co-authored, and is currently an online publication in *Clinical Nursing Research* (Eisenhauer et al., 2017). The purpose of the systematic review was to evaluate participants' level of understanding of the information presented during the consent

process for donation of biological specimens for research purposes (i.e., for biobanking or genetic epidemiological studies). It included 34 studies: nine qualitative; 21 quantitative; and four mixed-method studies. Results indicated that many elements of informed consent unique to biobanking (e.g. risks of biobanking, access to specimens, the role of genetics, and the return of genetic results) were inadequately understood by potential participants. A possible source of bias was uncovered in that 30 studies (88%) had an author associated with a biobank or biobank-related funding. In addition, there was substantial variation in the elements of informed consent assessed for understanding and the measurement of understanding across the studies. Only one study explicitly disclosed and assessed understanding of the moral risks associated with biospecimen donation (and understanding was inadequate). A number of contextual factors were found to influence understanding and included (a) circumstances of recruitment (e.g. member of the public approaches researcher; researcher approaches a patient); (b) education, literacy, and reading; (c) consent modalities (e.g. paper/reading, computer module, human/verbal interaction); (d) locality; (e) other demographics (e.g., age, gender, and income) (f) consenters (e.g. nurses, physicians); and (g) amount of time spent explaining consent information. Recommendations based on the review included incorporating updated health literacy recommendations that do not rely solely on patient education, but also emphasize improving healthcare provider communication skills and re-designing institutional processes to facilitate informed choices.

The focus of the qualitative component of this dissertation research was to describe mothers' understanding of biobanking, attitudes about rDBS research, and the influence of personal values on the decision-making process. This was accomplished in two ways: 1) by conducting passive participant observation of the consent process and 2) by conducting semi-structured interviews with postpartum mothers, immediately after they decided whether or not to

donate their newborn's rDBS for research. Findings indicated that while most mothers agreed (14/20; 70%) to donate the rDBS and expressed favorable attitudes about research, most decisions (16/20; 80%) were determined to be uniformed choices due to inadequate knowledge of the Michigan BioTrust and biobanking. The study is presented in Chapter 3.

The focus of the quantitative component of this dissertation research was to examine knowledge, attitudes and values, and the proportion of informed biobanking choices in a larger sample using standardized instruments. A non-experimental, descriptive and correlational survey was randomly distributed to 500 mothers in the state of Michigan with a newborn age 0-3 months. Standardized measures were used to measure key variables including biobanking knowledge and attitudes, intrinsic religiosity and other personal values (Wells et al., 2014; Hoge, 1972; Lindeman & Verkasalo, 2005), an element often lacking in other studies on participants' understanding of informed consent (Cohn & Larson, 2007; Eisenhauer et al., 2017; Falagas et al., 2009; Flory & Emanuel, 2004; Nishimura et al., 2013). While the number of respondents was small (N=80), the study generated insightful empirical data on the proportion of mothers' informed choices about the BioTrust. Findings from this study indicate that knowledge and experience contribute to making an informed choice about biobanking. Results are presented in Chapter 4.

The results of both components are examined, compared, and contrasted with existing literature, and implications for policy recommendations and future work are discussed in Chapter 5.

Implications for Nursing

Nurses play an integral role in care and patient education along the entire continuum of maternal–child care from early pre-natal care to delivery and beyond. As such, nurses should

have knowledge of the fundamental values of the nursing discipline: altruism, autonomy, human dignity, integrity, and social justice and professionalism. Because of this special preparation they are in a position to assume roles in which they conduct the consent process. Nurses play a central role in clinical research, often employed as clinical research coordinators (Hastings, Fisher, McCabe, & National Clinical Research Nursing Consortium, 2012). Thus, nurses need to be aware of the potential issues that patients and other biobanking participants may consider and/or that influence the decision-making process (Eisenhauer et al., 2017). Indeed, the American Nurses Association (ANA) recently endorsed clinical research nursing as a specialty nursing practice (Zaparoni, 2016).

This phenomenon has further implications for nursing. Definitions of evidence based nursing (DiCenso, Guyatt, & Ciliska, 2005), patient–centered care (Berwick, 2009), and shared decision-making (Elwyn et al., 2012) promote the inclusion of patients' values in decision-making. As healthcare professionals, nurses are expected to advocate for the value-based decisions of their patients. Baccalaureate nursing graduates are taught to practice from a holistic, caring framework, and provide patient-centered care that identifies, respects, and advocates for patients' values and preferences (AACN, 2008). Care is a foundational concept for nursing and involves veracity, trust, and the skillful application of specific measures (Carper, 1979; Watson, 1988/2007).

The use of the MMIC (Marteau et al. 2001) contributes to nursing practice by providing guidance on factors that influence patients' decision-making. This theory emphasizes knowledge, attitudes, and choice and highlights the importance of discussing these elements with patients. Nurses have not just a social mandate, but a covenant with the public (Fowler, 2017) and a responsibility to uphold and advocate for the true meaning of informed consent. Moving beyond

autonomy alone, facilitating a truly informed choice demonstrates respects for the dignity, worth, values, and moral agency of each human being.

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Chapter 2 Participants' understanding of informed consent for biobanking: A systematic review

Acknowledgement

Chapter 2 is a published article in *Clinical Nursing Research* (SAGE) by Eisenhauer, Tait, Rieh, and Arslanian-Engoren (2017). The table and figure numbers have been updated here to correspond with the rest of this dissertation. The caption in each table and figure at the end of Chapter 2 indicates if numbering has been revised. I acknowledge the assistance of my co-authors on this published manuscript: Dr. Alan R. Tait, Dr. Soo Young Rieh, and Dr. Cynthia M. Arslanian-Engoren. As noted in the publication, I thank Dr. Bonnie M. Hagerty for her comments on an earlier draft and the anonymous referees for their valuable comments and suggestions. I also thank Nai-Wei Shih, Editorial Assistant at Clinical Nursing Research for her editorial assistance.

The citation for the published article is as follows:

Eisenhauer, E. R., Tait, A. R., Rieh, S. Y., & Arslanian-Engoren, C. M. (2017). Participants' Understanding of Informed Consent for Biobanking: A Systematic Review. *Clinical Nursing Research*, [Advance online publication]. doi:10.1177/1054773817722690.

Abstract

Nurses are increasingly asked to obtain consent from participants for biobanking studies. Biobanking has added unique complexities to informed consent. The purpose of this systematic review was to evaluate participants' level of understanding of the information presented during the informed consent process unique to the donation of biological specimens for research. PRISMA guidelines were utilized to conduct the review. PubMed, EMBASE, CINAHL, PsycINFO, Scopus, Web of Science, and ProQuest bibliographic databases were searched. Results indicated that elements of informed consent unique to biobanking were poorly understood. Most studies had authors or funding associated with a biobank. Only one study disclosed and assessed participants' understanding of moral risks. Increased disclosures, values-clarification, and presenting information via multiple modalities may facilitate understanding. There is a need to improve the quality of informed consent for biobanking studies by utilizing standardized instruments, definitions, and encouraging research about informed choice outside the biobanking industry.

Keywords

Biological specimen banks, Biobanking, Informed consent, Moral risks, Understanding

Introduction

Clinical research increasingly involves biobanking, the collection of human biological specimens (e.g. tissue, cells, blood, DNA) and related clinical data for future, often unspecified, research activities (Biobanking and Biomolecular Resources Research Infrastructure [BBMRI], 2012; Henderson et al., 2013). The mapping of the human genome and genetic-engineering have revolutionized the use of biospecimens. However, this scientific progress has made understanding informed consent information more difficult. In part, this difficulty is because biobanking research includes social and moral issues that distinguish it from participation in traditional clinical trials that do not involve a biobanking component (i.e. those without biospecimen collection) (Rothstein, 2005). Nurses play a central role in clinical research, often employed as clinical research study coordinators (Hastings et al., 2012), and may be responsible for obtaining consent from participants for biobanking studies. Thus, nurses may need to be aware of the unique difficulties patients may face during the decision-making process.

Privacy and Dignitary Risks

Consent for biobanking differs from consent for participation in traditional clinical trials in several important ways. First, genetic research, noted to be one of the most frequently conducted biobanking activities (Henderson et al., 2013), carries unique privacy risks to the participant and extended family members, as genetic analysis may reveal susceptibility to a host of diseases and potentially even personal behavioral traits (Rothstein, 2005). Beyond genetic privacy, however, there is a relationship between biobanking and associated biotechnological procedures that may not align with some participants' religious or personal values. Such procedures may include: animal research, creation of immortalized cell lines, embryonic stem cell research, germ-line gene therapy (GLGT), in-vitro fertilization, pre-implantation genetic

diagnosis, prenatal genetic screening, and somatic nuclear cell transfer (i.e. research cloning) (Modell, Citrin, King, & Kardia, 2014; Rothstein, 2005, Tomlinson, Kaplowitz, & Faulkner, 2014). Ethicists have labelled the moral, religious, or cultural concerns of potential biobank participants as "dignitary risks" (Rothstein, 2005) or more recently as "non-welfare interests" (Tomlinson et al., 2014). Indeed, potential biobank participants have expressed concerns about biobanking violating tenets of their religion. Concerns include religious prohibitions against blood storage, cloning, predicting the future, and trying to "play God" by analyzing and /or manipulating genetics (Eisenhauer & Arslanian-Engoren, 2016). If individuals participating in biobanking research were to discover that they had inadvertently contributed to applications, procedures, or research to which they hold moral reservations, they may suffer decisional regret or moral distress, and may eventually distrust medical researchers (Modell, et al. 2014; Rothstein, 2005, Tomlinson et al., 2014).

Information and Consent

Biobanking informed consent documents can vary widely on how much information about the research is given to potential participants. There are three common types of biobanking consent documents in use today: study-specific (or classical or traditional), tiered (or menu or line item), and broad (or blanket) consent forms (ISBER, 2012; Master et al., 2012; Weir, 2000; Wertz, 1999). Study-specific consent forms clearly describe the details of a single, specified study and allow the use of the participant's biospecimen only for this specified purpose and time frame. A tiered informed consent document allows a participant to grant permission for some portion(s) of the research project, but not necessary all portions, as determined by the participant. Choices may include the research purposes for which the biospecimen may be used, who has access to the biospecimen or associated data, and permission for use of the biospecimen

in future research projects. Broad consent forms allow researchers substantial latitude in the use of participants' biospecimens, often for indefinite periods of time and with few details of future use. Broad consent forms may inadequately inform participants of their choices and the consequences of their decisions (ISBER, 2012; Master et al., 2012; Weir, 2000; Wertz, 1999). For example, specimens originally collected for diabetes research could later be used for researching alcoholism or addiction, ancestral origins, aggressiveness or criminality, mental illness, reproduction, and sexual orientation, and this may offend biospecimen donors' values (Harmon, 2010; Weir, 2000; Wertz, 1999).

Presenting patients with different types, levels, and amounts of information may result in disparate understanding of biobanking research, and different decisions about participation (Abhyankar, Summers, Velikova, & Bekker, 2014; Tomlinson et al., 2014). Tomlinson et al. (2014) compared the biobanking donation decisions of individuals presented with either a brief or expanded description of a biobanking research project. For example, when the possibility of contributing to an increase in abortions was described in a biobanking project for creating a prenatal genetic test for cystic fibrosis, the number of pro-life participants willing to donate a biospecimen dropped from 87.5% to 61.7% (Tomlinson et al., 2014). This result indicates that when provided explicit information about the use of biospecimens, potential participants are able to assess the personal, moral implications of biobanking, which may enhance their understanding and affect their donation decisions. Thus, biobanking has unique characteristics that increase the complexity of the informed consent process, and the understanding thereof.

The purpose of this systematic review, therefore, was to evaluate participants' level of understanding of the information presented during the informed consent process unique to the

donation of biological specimens for research purposes (i.e. for biobanking or genetic epidemiological studies). Specific research questions were:

Research Question 1: What types of information are presented to prospective biobanking participants?

Research Question 2: What specific elements of informed consent are assessed for understanding?

Research Question 3: How is participants' understanding of informed consent measured?

Research Question 4: What types of contextual factors influence understanding of informed consent for biobanking?

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (i.e. The PRISMA Statement) was used as a guide to conduct this systematic review (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). In January 2015, a protocol for this review was registered on PROSPERO (registration number: PROSPERO 2015:CRD42015015649). The protocol can be accessed from the following link: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015649

Systematic searches of the PubMed, EMBASE, CINAHL, PsycINFO, Scopus, Web of Science, and ProQuest databases were conducted during November, 2014-March, 2015. The searches were updated in November, 2016; three new, relevant studies were identified and incorporated into the results.

Eligibility Criteria

Studies included in this review were (1) written in English; and (2) included healthy or ill adults (≥18 years of age), volunteers or surrogates (for children or incapacitated adults), who

participated in an informed consent process for donating biospecimen(s) to an actual or hypothetical biobank for research purposes. Further, included studies needed to contain a qualitative or quantitative assessment of participants' understanding of the information presented during the informed consent process. Studies were excluded that (1) only presented results about attitudes, preferences, willingness to donate to, or general knowledge of biobanking, without assessing understanding of informed consent, and/or (2) focused on the donation of biospecimens for clinical, diagnostic, or therapeutic purposes (i.e. non-research purposes) or biospecimens from fetal tissue or deceased donors. Conference abstracts, duplicate publications, editorials, essays, literature reviews, master's theses, newspaper articles, opinion pieces, philosophical articles, posters, secondary analyses, and theoretical papers were also excluded.

Search Strategy and Study Selection

The search strategies included controlled vocabulary terms (i.e. Medical Subject Headings [MeSH®]), keywords, and synonyms for the concepts of informed consent, biobanking, and understanding/comprehension including: informed consent, consent forms, consent, biological specimen banks, genetic databases, biobank, comprehension, and understanding. Searches were adapted as necessary based on the controlled vocabulary terms and functions of each database. Although theses and abstracts were excluded, relevant dissertations were mapped to published articles. Reference lists of included studies were searched for additional relevant citations. Titles and/or abstracts of studies retrieved during the search phase were screened for inclusion by two authors (EE, CAE). If relevancy could not be determined from the title or abstract, the full-text was skimmed. Screened studies that addressed the inclusion criteria were retrieved and read in full. Search and selection processes are presented in Figure 3.

Data Extraction and Synthesis

A data extraction form was designed by (EE) and refined by (CAE) to capture 14 pertinent outcome and contextual variables from each included study (data available upon request). A table (Table 1) was created delineating key elements of informed consent for biobanking (Beskow, Dombeck, Thompson, Watson-Ormond, & Weinfurt, 2015; Joffe, Cook, Cleary, Clark, & Weeks, 2001; Protection of Human Subjects, 2009). Studies varied by the number of elements of informed consent measured for understanding (Table 2), thus data were further organized by the elements of informed consent and the level of understanding for that element as measured in each study (data available upon request). We then categorized these measurements using a modified version of the method used by Falagas et al. (2009), using a threshold of ≥80% participant understanding to define adequate understanding. Qualitative studies were synthesized separately from the quantitative studies. Key words describing the level of understanding in qualitative studies were analyzed. This was done to reflect understanding of informed consent using narrative descriptions and to compare the outcome of understanding between the quantitative and qualitative studies.

Risk of Bias and Quality Assessment

The Johns Hopkins Nursing Evidence-Based Practice Research Evidence Appraisal Tool was used to evaluate the quality of included studies (Dearholt & Dang, 2012). However, because this tool did not capture the critical elements of quality and bias in informed consent studies, we also used a modified checklist of additional items based on the work of Edwards, Lilford, Thornton and Hewison (1998) and Cohn and Larson (2007) (Appendix A). The Cochrane Collaboration recommends assessing other sources of bias (Higgins et al., 2011); thus, we added an item that assessed the risk of bias in biobanking studies: author or funding source associated with a biobank, as discussed by Master et al. (2012) and Roessler, Steneck, and Connally (2015). Study

quality and risk of bias was initially assessed by one author (EE) and 11 studies were randomly assessed for accuracy (using every third included study in alphabetical order) by a second author (CAE). Quality rating disputes were reconciled by discussion until 100% consensus was reached on the final quality and bias assessments (Table 3).

Results

Study Characteristics

A total of 34 studies were included in this review (Table 4): nine were qualitative (26%), 21 were quantitative (62%), and four used a mixed-method approach (12%). Sample sizes ranged from as few as nine to as many as 2,192 participants. Nine studies involved hypothetical decision-making, while 25 involved actual decisions to biobank specimens (Table 4). Additional variables describing the included studies are presented in Table 4.

Risk of Bias and Quality Assessment

Using the Johns Hopkins Nursing Evidence-Based Practice Research Evidence Appraisal Tool (Dearholt & Dang, 2012) two studies (6%) received a low rating. However, 24 studies (71%) received a low (0-2 out of 6 possible points) rating using the tool specific to informed consent studies (Table 3). Yet, the decision was made to include all of the studies in the review in order to better reflect the state of the science of participants' understanding of informed consent for biobanking. Most notably, 30 studies (88%) had an author associated with a biobank or biobank related funding (Table 3). Four studies were related to a single biobank (Mahnke et al., 2014; McCarty et al., 2007, 2008, 2015). Detailed results of the quality assessment are presented in Table 3.

Information Presented

Per our inclusion criteria, all participants had undergone an informed consent process for biobanking. Only one study explicitly disclosed and assessed understanding of moral risks associated with biobanking and reported inadequate understanding of these issues (McCaughey et al., 2016). However, it is difficult to truly ascertain what specific or additional information was provided to participants as only 11 studies actually provided the biobanking informed consent document (whole or partially) (Table 3). Thus, it is difficult to truly ascertain what specific or additional information was provided to participants. This frequent lack of disclosure raises a concern about transparency in studies of participant understanding of informed consent information for biobanking.

Understanding: Assessed and Reported

Across the 25 studies reporting quantitative results, understanding of the selected elements of informed consent was most frequently measured at < 80% (Table 2). Generally, participants understood their participation was voluntary and that they would not be paid for commercial products that could result from their donated biospecimens. Participants showed highly variable rates of understanding in their awareness of participating in a research project, benefits to self and others, who to contact with questions about the study, procedures, purposes, and that they could withdraw from a study. Understanding of the risks of biobanking and the experimental nature of research were particularly poor. Inadequate understanding was especially prevalent in the following elements of informed consent: alternatives to participation, access to study records/specimens, collection data from personal medical records, confidentiality, injury compensation, the role of genetics including DNA banking & storage, study duration, and return of genetic results (data available upon request). Many poorly understood elements are unique to biobanking. Participants' self-rating of their understanding was usually higher than

understanding scored on objective measures (Klima et al., 2014; McCarty et al., 2007; McCaughey et al., 2016; Ormond et al., 2009).

Qualitative studies also frequently described participants' understanding as inadequate. Four of the nine (44%) qualitative studies clearly reported participants' understanding as inadequate (Barr, 2006; Dixon-Woods et al. 2007; Ducournau et al., 2009; Hoeyer, 2003). Four other (44%) studies described participants' understanding as riddled with "ambiguity" (Busby, 2004, p.46), "confused" (McCarty et al., 2008, p.3030; McGraw et al. 2012, p. 16), or "debatable" (Allen et al., 2011, p.159). Beskow and Dean (2008) reported that participants "seemed to understand" (p. 1447) the information provided.

Studies varied widely on the number of elements of informed consent assessed for understanding (Range 2-16) (Table 2). Studies that used the Quality of Informed Consent (QuIC) instrument were most comprehensive in their assessments, assessing an average of 15 elements of informed consent for biobanking (Klima et al., 2014; McCarty et al., 2007, 2015; Ormond et al., 2009; Simon et al., 2015). Originally designed for use in cancer clinical trials, the QuIC is a standardized instrument, with published reliability and validity data, that assesses both objective and subjective understanding about specific elements of informed consent using 20-detailed true/false and 14-Likert scale questions (Joffe et al. 2001). The QuIC has been adapted and used in several studies (noted above) for assessment of understanding of informed consent in biobanking studies.

Measurement of Understanding

The methods and instruments used to assess understanding varied widely among studies. Methods included: in-person interviews (nine studies), telephone interviews (one study), verbally administered surveys (five studies), and self-administered surveys (16 studies), including some

that were mailed (six studies) or electronic (four studies) (Table 4). Twenty-three of the 34 studies (68%) included some validation of their instrument or interview guide, while 11 studies (32%) did not address validity (Table 3). Only six studies used a previously validated instrument to assess understanding (Bickmore et al., 2009; Klima et al., 2014; McCarty et al., 2007, 2015; Ormond et al., 2009; Simon et al., 2015). Five studies used the QuIC instrument (Klima et al., 2014; McCarty et al., 2007, 2015; Ormond et al., 2009; Simon et al., 2015) and one used the Brief Informed Consent Evaluation Protocol (BICEP) (Bickmore et al., 2009). One of the studies that used a self-administered survey also reported the initial reliability (Cronbach alpha of 0.73) and validity data (content validity) for a newly developed instrument to measure surrogate consent for genetic studies (Shelton et al., 2015).

Contextual Factors

Contextual factors found to influence understanding included: (1) circumstances of recruitment; (2) education, literacy, and reading; (3) consent modalities; (4) locality; (5) other demographics (e.g. age, gender, & income) (6) consenters; and (7) amount of time spent explaining consent information.

Health status and the setting in which participants were recruited (e.g. patient versus non-patient; healthcare versus community) varied across the studies, affecting the understanding of informed consent information. Differences in understanding (Ormond et al., 2009; Toccaceli et al. 2009) or in the amount of time spent considering information (Roessler et al., 2015) were reported when participants were self-referred versus recruited in the healthcare setting.

Understanding differed based on level of education in 9 studies (Beskow et al. 2017; Cervo et al., 2013; Joseph et al., 2008; Marshall et al., 2006; Merz & Sankar, 1998; Ormond et al., 2009; Panoyan et al., 2008; Petersen et al., 2014; Toccaceli et al. 2009). Two studies identified better

literacy (or health literacy) as a factor associated with increased understanding (Bickmore et al., 2009; Marshall et al., 2006). The extent to which participants actually read study materials (i.e. all, part of, or none) was examined in two studies by Matsui et al. (2007, 2012). Reading more of the informed consent document was associated with higher rates of self-perceived understanding. However, no significant difference in reading amount was noted when given a shorter informed consent document (five pages) or a traditional longer document (11 pages) (Matsui et al., 2012) . Likewise, in a study by Beskow et al (2017), shorter documents did not improve understanding. Education was not a statistically significant factor for increased understanding in the study by McCaughey et al. (2016), and despite the fact that 81.6% of their sample reported reading the information pamphlet at least once, understanding was still poor on objectives measures.

Studies about computer-based informed consent often involved hypothetical biobanking decisions (Beskow et al., 2017; Bickmore et al., 2009; Mahnke et al., 2014; McGraw et al., 2012; Shelton et al., 2015). While computer modules may occasionally lead to small gains in understanding, two authors cautioned that technology should be used as an adjunct to more traditional methods of informed consent including human interaction and reading of paper documents (McGraw et al., 2012; Shelton et al., 2015). Interactivity, in the form of comprehension checks or quizzes, provided an important opportunity to review consent information, clarify confusion, and improve understanding (Beskow et al., 2017; Bickmore et al., 2009; Simon et al., 2015). Two computer studies involved actual biobanking decisions (McCarty et al., 2015; Simon et al., 2015): McCarty et al. conducted a randomized controlled trial of traditional versus computer-based consent found no major differences in understanding. Simon et al. reported small gains in understanding in multimedia groups, but emphasized the

importance of interactivity across modalities. Comparably, another study involving an actual biobank found repetition of consent information and presenting the information via multiple modalities (e.g. paper, media, humans) to be important factors in facilitating adequate understanding (Cervo et al., 2013).

Locality, the cultural and sociopolitical environment of the participants, influenced their understanding of biobanking informed consent information (Hoeyer, 2003; Marshall et al., 2006; Petersen et al. 2014). For example, Hoeyer (2003) noted that in countries where the government finances health care, citizens may have a sense of wanting to give back to the government and therefore may be more likely to donate biospecimens to government-run research biobanks. Petersen et al. (2014) found perceptions of medical research and data protection standards varied in breast cancer patients from three European countries, and these varied perceptions influenced patients' understanding of informed consent for biospecimen donation.

Demographic (e.g. age, gender, income) composition of participants and reporting of these variables varied across studies. Notably, younger age was usually (Beskow et al., 2017; Robinson et al., 2013; McCarty et al., 2007), but not always (Klima et al., 2014), associated with better understanding. Females were more likely than males to demonstrate correct understanding (Klima et al., 2014; McCarty et al., 2007; Toccaceli et al. 2009), as were individuals with or of higher levels of household income (Beskow et al., 2017; Joseph et al., 2008; Panoyan et al., 2008). Yet, Klima et al. (2014) found participants with higher levels of household income were less likely to correctly answer the question of who would pay for a research related injury than those with incomes <$35,000.

Variability in the qualifications (e.g. physicians versus research assistants) and actions of the consenter may have influenced participants' understanding of informed consent in ways that

have yet to be determined. In eight studies (Beskow et al., 2017; Beskow & Dean, 2008; Mahnke et al., 2014; McCarty et al., 2008; McGraw et al., 2012; Merz & Sankar, 1998; Rahm et al., 2013; Shelton et al., 2015) participants only read a consent document and/or viewed a computerized version of the consent, with no human leading a consent discussion. Finally, estimated time to explain consent information varied across included studies, ranging from less than one minute to one hour.

Discussion and Application

This systematic review indicates many elements of informed consent for biobanking are inadequately understood by participants. These findings are consistent with research on understanding informed consent for traditional clinical trials and treatments (Cohn & Larson, 2007; Falagas et al., 2009; Flory & Emanuel, 2004; Nishimura et al., 2013). Our appraisal of the biobanking literature also revealed a unique finding of concern: the vast majority (88%) of the included studies involving understanding of informed consent for biobanking had either an author associated with a biobank, genetic epidemiological study, or funding associated with these entities. While these associations are not evidence of wrongdoing, they may pose a risk of bias analogous to pharmaceutical funding of drug studies (Stelfox, Chua, O'Rourke, & Detsky, 1998) or the beverage industry sponsoring research on the health effects of soft drinks (Schillinger, Tran, Mangurian, & Kearns, 2016).

It was striking that only one study disclosed and assessed understanding of moral risks (McCaughey et al., 2016). McCaughey et al. (2016) reported inadequate understanding of these moral risks to biobanking. Most participants, however, could not consider this undisclosed information. This placed prospective biobank participants at a disadvantage, unable to evaluate all pertinent information when key aspects of moral controversy are omitted (Tomlinson et al.,

2014). A Notice of Proposed Rulemaking (NPRM) suggested strengthening human subject protection by requiring consent for the use of biospecimens in research (Federal Policy for the Protection of Human Subjects, 2015). However, the final rule did not adopt the proposed requirement for consent involving non-identified biospecimens (Federal Policy for the Protection of Human Subjects, 2017). As such, it remains to be seen whether there will be sufficient discussion of moral risks in the future to facilitate truly informed decisions (Marteau, Dormandy, & Michie, 2001).

Evidence from this review indicates the need for caution when recruiting in healthcare settings. Contradictions were evident in participants' understanding of the benefits of biobanking. For example, even when they recognized that biobanking research was intended to help others, many participants still held expectations of benefits to themselves or their immediate loved ones (Barr, 2006; Busby, 2004;Dixon-Woods et al., 2007; Joseph et al., 2008;Klima et al., 2014; McCarty et al., 2007, 2015; Ormond et al., 2009; Petersen et al., 2014). These incongruencies may indicate therapeutic misconception, defined as when a research participant expects personal benefit, even when the goal of the study to benefit only future patients has been explained (Appelbaum, Roth, Lidz, Benson, & Winslade, 1987).

The emphasis on utilizing computers to deliver informed consent information may be a reflection of U.S. researchers' increasing concerns about cost, time-savings, and efficiency (McCarty et al., 2015; Roessler et al., 2015). However, this may also be indicative of an ethically detached approach to obtaining informed consent, typical in western countries (Carper, 1979). This approach may not be realistic when dealing with biobanking research involving value-laden, moral risks.

Strengths and Limitations

The strengths of this review include: (a) the use of the PRISMA guidelines (Moher et al., 2009), including the online publication of a protocol; (b) exposing a risk of bias in research about participants' understanding of biobank informed consent; and (c) revealing the lack of disclosure and assessment of understanding regarding moral risks in biobanking.

Four limitations to this research are noted: (a) Included studies demonstrated vast heterogeneity in key characteristics: study designs, participant populations, interventions, and, especially, the definitions and measurements of understanding and the delivery of informed consent information. Problems with such heterogeneity have been previously recognized in the literature as a limitation of studying understanding of informed consent (Cohn & Larson, 2007; Falagas et al., 2009; Flory & Emanuel, 2004; Nishimura et al., 2013; Sand, Kaasa, & Loge, 2010). The heterogeneity of measures in the included studies made accurate comparisons difficult. (b) Moreover, the quality of included studies was lacking. There was frequent reliance on homogeneous convenience samples. Outcome measurements rarely involved the use of an instrument with published reliability and validity data. Several studies were based on hypothetical decision-making, and many demonstrated a lack of transparency in reporting what information was disclosed to participants. There was immense variability and selectivity involving which elements of informed consent were assessed for understanding. (c) In addition, only studies written in English were included, and (d) most studies were from the U.S. or Western Europe.

Nursing Implications

This review demonstrates that participants' biobanking decisions are not always truly informed; instead decisions may be based on limited understanding, values, trust, or even time constraints. An uniformed participant may be at risk for decisional regret. Nurses can help

guard against such potential errors in judgment by taking advantage of educational opportunities on genetics and genomic science, such as the Summer Genetics Institute (SGI) sponsored by the National Institute of Nursing Research (NINR) (NINR, 2017). Nurses need to know, that without explicit explanations, patients may not understand the connections between donating biospecimens for research and controversial biotechnological procedures (Tomlinson et al., 2014). To do so, nurses must first understand these distinctions in order to accurately convey this information to patients. Next, nurses must be diligent not to exploit the strong trust of their patients (Hoeyer, 2003; Norman, 2016). Obtaining consent from patients for biobanking without providing adequate information and consideration for individual patient's values is inconsistent with professional nursing values of respect for human dignity and the right to self-determination (American Nurses Association, 2015). Assessing patients' motivation for study participation and assessing their comprehension of biobanking and its implications are ways in which nurses can advocate for their patients (Penckofer, Byrn, Mumby, & Ferrans, 2011). Further, to help patients make decisions more congruent with their personal values, and thereby avoid decisional regret, it may be helpful for nurses to describe some of the potential morally controversial uses of biospecimens (e.g. animal research, the creation of immortalized cell lines, and stem cell research) and include a disclaimer such as: "If any of these make you uncomfortable, you might not want to participate in this [biobank]" (University of Michigan, 2016).

Recommendations for Practice and Future Research

Biobanking research involves presenting complex information to potential participants as they decide whether or not to grant their permission to participate in the research. Principles of health literacy apply to imparting such information. Health literacy is defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information

and services needed to make appropriate health decisions" (Ratzan & Parker, 2000, p.vi). The field of health literacy has evolved from solely emphasizing patient education to focusing on provider communication skills, and more recently calling for an increase in transparent, patient-friendly healthcare environments (Rudd, 2014). For biobanking research, this three-fold approach to aid participants' understanding of complex information includes: (a) increasing curriculum on genetics and biotechnology in secondary education, (b) emphasizing human-to-human dialogue in the informed consent process, and (c) encouraging a more transparent research enterprise; one that encourages participants to make a truly informed choice (Marteau et al., 2001). Recommendations for future research include improving the quality of studies on understanding informed consent for biobanking by utilizing standardized instruments, controlling for contextual variables, and establishing a common threshold for defining adequate understanding. In addition, future work should include studies conducted by non-biobank associated researchers, with demographically diverse samples, and examine actual (not hypothetical) informed choices in real-time. Future systematic reviews examining participant understanding of informed consent for biobanking should also examine these specific attributes.

Figure 3. Flow chart and study selection Moher et al., 2009.
Note: This is Figure 1 in published article.

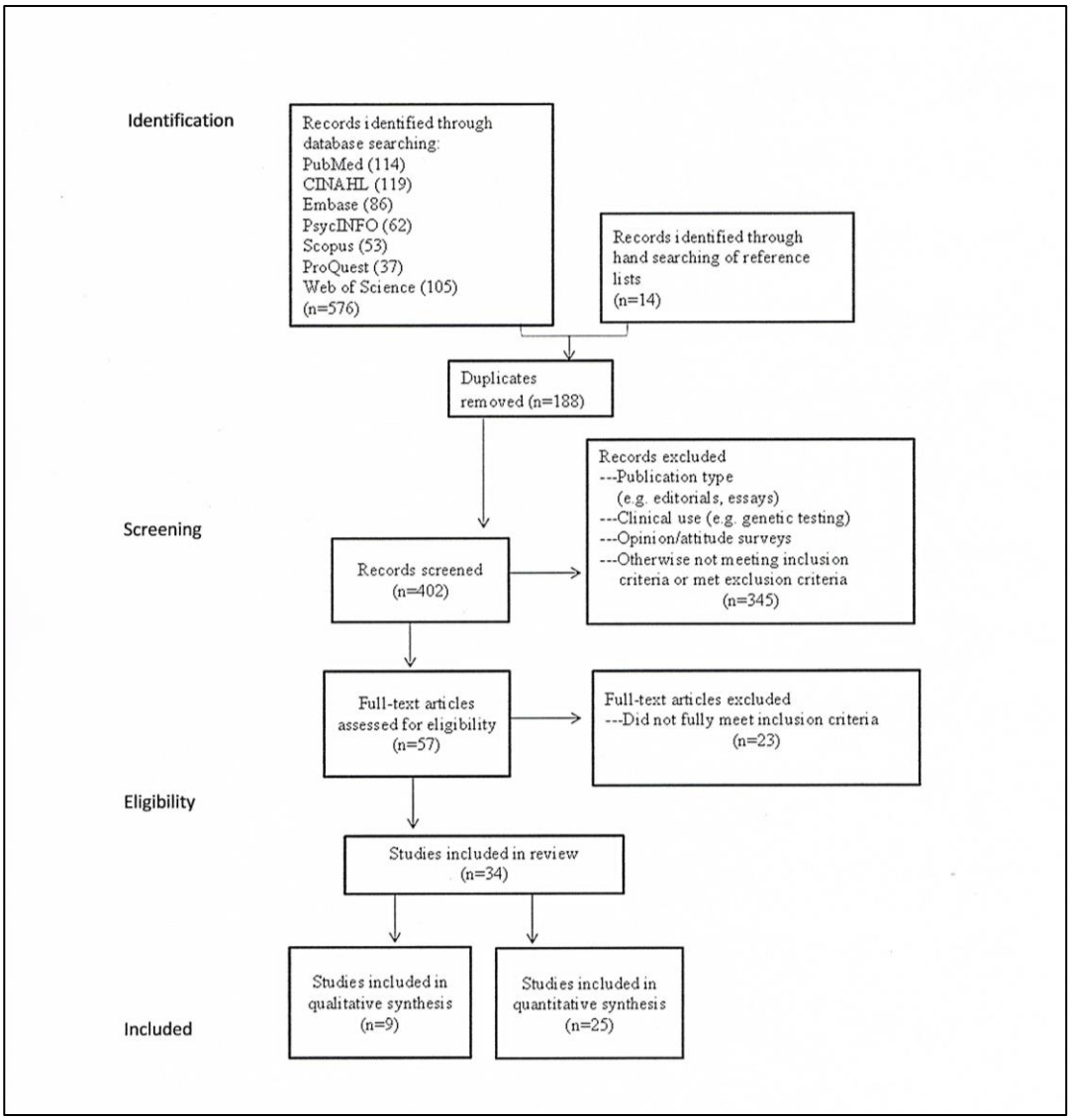

Table 1. Elements of informed consent for biobanking

Access to Specimens or Data (Data Sharing)
Alternatives
Benefits
Collect Data from Medical Record
Confidentiality
Contact Person
Experimental Procedures
Injury
No Penalty
Payment/Commercial Use
Purpose
Research (Awareness of Participation)
Re-contact
Return of Results
Risks
Role/Knowledge of Genetics, Cells, DNA
Study Duration
Study Procedures
Voluntary
Withdrawal

Table 2. Understanding in included studies with quantitative results
Exp=experimental group

Included studies	No. of key elements of informed consent for biobanking (Table 1) assessed for understanding	**Most elements <80%** Yes/No
1. Beskow et al., 2017	13	No
2. Bickmore et al., 2009	Categories not provided---**all mean scores <80%**	
3. Cervo et al., 2013	2	No
4. Joseph et al., 2008	7	No
5. Klima et al., 2014	14	**Yes**
6. Mahnke et al., 2014	7	No
7. Mancini et al., 2011	3	**Yes**
8. Marshall et al. 2006	2	**Yes**
9. Marshall et al. 2014	6	No
10. Matsui et al., 2012	3	No
11. Matsui et al., 2007	N/A---Categories not provided	
12. McCarty et al., 2015	16	**Yes**
13. McCarty et al., 2007	16	**Yes**
14. McCaughey et al., 2016	6	**Yes**
15. Merz & Sankar, 1998	6	**Yes**
16. Moutel et al., 2001	3	**Yes**
17. Ormond et al., 2009	15	**Yes**
18. Panoyan et al., 2008	3	**Yes**
19. Petersen et al., 2014	2	**Yes**

20. Rahm et al., 2013	5	**Yes**
21. Robinson et al., 2013	2	**Yes**
22. Roessler et al., 2015	89% self-rated their understanding at the highest level	
23. Shelton et al., 2015	9	Control: **Yes**; Exp: No
24. Simon et al., 2015	16	No
25. Toccaceli et al., 2009	3	**Yes**

Table 3. Quality Assessment of Included Studies

Citation	level/ grade[b]	Quality of Evidence and Risk of Bias Checklist for Studies of Informed Consent Item: Point(s)[a] sampling hierarchy	outcome measure	response rate	info supplied	biobank affiliation
Beskow et al., 2017	I/B	0	1	0	1	0
Bickmore et al., 2009	I/B	0	2	0	1	1
Matsui et al., 2012	I/B	1	0	1	1	0
McCarty et al., 2015	I/B	1	2	1	0	0
McGraw et al., 2012	I/B	0	1	0	0	0
Robinson et al., 2013	I/B	1	1	1	0	0
Shelton, et al., 2015	I/B	0	2	0	0	1
Simon et al., 2015	I/B	1	2	0	0	0
Matsui et al., 2007	II/C	1	0	1	0	0
Allen et al., 2011	III/B	0	0	0	0	1
Barr, 2006	III/B	0	0	0	0	0
Beskow et al., 2008	III/B	0	1	0	1	0
Busby, 2004	III/B	0	0	0	0	0
Cervo et al., 2013	III/A	1	1	1	0	0
Dixon-Woods et al., 2007	III/B	0	1	0	1	0
Ducournau et al., 2009	III/C	1	0	0	0	0
Hoeyer, 2003	III/B	0	0	1	0	0
Joseph et al., 2008	III/B	0	1	0	0	0
Klima et al., 2014	III/A	1	2	0	1	0

Mahnke et al., 2014	III/B	0	1	0	0	0
Mancini et al., 2011	III/A	1	1	1	1	0
Marshall et al., 2014	III/B	0	1	0	0	0
Marshall et al., 2006	III/B	0	1	1	0	0
McCarty et al., 2007	III/B	1	2	0	1	0
McCarty et al., 2008	III/B	0	0	0	0	0
McCaughey et al., 2016	III/A	0	1	0	1	0
Merz & Sankar, 1998	III/B	0	1	0	1	0
Moutel et al., 2001	III/B	0	0	0	0	1
Ormond et al., 2009	III/A	0	2	0	0	0
Panoyan et al., 2008	III/A	1	1	0	0	0
Petersen et al., 2014	III/A	0	1	1	0	0
Rahm et al., 2013	III/B	0	0	1	0	0
Roessler et al., 2015	III/B	0	0	0	1	0
Toccaceli et al., 2009	III/A	1	1	0	0	0

[a]See the Appendix A. Higher score indicates less risk of potential bias/higher quality.[b]Based on Dearholt and Dang (2012, Appendix E: Research Evidence Appraisal Tool, pp. 238-240). Quality rating based on quality appraisal: A = high quality; B = good quality; C = low quality; I = experimental study; II = quasi-experimental; III = descriptive or qualitative.

Table 4. Characteristics of Included Studies
BICEP=Brief Informed Consent Evaluation Protocol instrument; QuIC= Quality of Informed Consent instrument

Citation, Year, Country	Design/Method	Sample Information
Allen et al., 2011, Australia	Qualitative; semi-structured interviews	Healthy cohort of participants (n=24) in actual biobank
Barr, 2006, England	Qualitative; semi-structured interviews	Female patients (n=43) who donated to actual biobank
Beskow et al., 2017, U.S.	National online survey; randomized experiment	Hypothetical decision-makers (n=1916)
Beskow et al., 2008, U.S.	Qualitative; cognitive interviews	Hypothetical decision-makers (n-40)
Bickmore et al., 2009, U.S.	Randomized experiment using BICEP	Hypothetical decision-makers (n=29)
Busby, 2004, England	Qualitative/ interviews	Donors (n=27) to an actual genetic research project
Cervo et al., 2013, Italy	Descriptive; self- administered questionnaire	Patients (n=430) enrolled in actual biobank studies
Dixon-Woods et al., 2007, England	Qualitative; semi-structured interviews	Healthy volunteers (n=29) in an actual genetic study
Ducournau et al., 2009, France	Qualitative; observation & interviews	Men (n=60) offered a check-up & asked to participate in actual biobank
Hoeyer, 2003, Sweden	Qualitative; observation & interviews	Donors and refusers (n=29) recruited as participants in actual program offering check -ups
Joseph et al., 2008, U.S.	Survey; verbally administered, in-person	Female donors and refusers (n=93) to an actual biobank
Klima et al., 2014, U.S.	Survey; mailed, self- administered QuIC	Parents (n=252) who actually enrolled their children to participate in congenital cardiovascular malformation research that included biobanking
Mahnke et al., 2014, U.S.	Proof of concept study testing hypothetical computer-based consent	Community members (n=9) representative of potential biobank participants
Mancini et al., 2011, France	Mailed, self-administered, 12- page questionnaire	Patients (n=574) treated for cancer and actually asked to donate tumor samples for research
Marshall et al., 2006, Nigeria & U.S.	Qualitative & Quantitative; survey & interviews	Clinic patients and controls (n=655) actually enrolled in genetic hypertension study in Nigeria & U.S.
Marshall et al., 2014, Nigeria	Qualitative & Quantitative; survey & interviews	Female cases and controls (n=215) enrolled in an actual genetic epidemiological study on breast cancer
Matsui et al., 2012, Japan	Intervention study; add-on cluster, randomized controlled trial	Patients (n=336) actually consenting to genetic cohort study

Citation, Year, Country	Design/Method	Sample Information
Matsui et al., 2007, Japan	Descriptive study of intervention using a 2-question, in-person questionnaire	Patients (n=2192) being asked to participate in actual genetic cohort study
McCarty et al., 2015, U.S.	Randomized controlled trial; mailed, self-administered QuIC	Men with prostate cancer (n=71) willing to enroll in actual biobank
McCarty et al., 2008, U.S.	Qualitative; focus group (Focus Group Series 3)	Potentially eligible biobank subjects (n=21)
McCarty et al., 2007, U.S.	Mailed, self- administered QuIC	Random sample of actual biobank participants (n=924)
McCaughey et al., 2016, Australia	Retrospective survey: mailed/ e-mailed, 35-item questionnaire with 14 questions re: understanding	Patients and controls (n=141) who actually donated a biospecimen for ophthalmic research
McGraw et al., 2012, U.S.	Qualitative; cognitive interviews evaluating written versus video informed consent	Patients and community members (n=43) making hypothetical biobanking decision
Merz & Sankar, 1998, U.S.	Descriptive survey	Prospective jurors (n=99) making hypothetical decision
Moutel et al., 2001, France	Self-administered questionnaire	Patients (n=51) enrolled in actual biobanking study
Ormond et al., 2009, U.S.	Qualitative & Quantitative; interviews & QuIC	Actual biobank participants (n=200)
Panoyan et al., 2008, U.S.	Survey; self-administered questionnaire	Participants (n=151) in actual genetic study
Petersen et al., 2014 Belgium, Germany, & UK	Self-administered questionnaire	Female breast cancer patients in Belgium (n=152), Germany (n=122), and UK (n=122)
Rahm et al., 2013, U.S.	Self-administered questionnaire	Donors and refusers (n=203) to hypothetical biobank
Robinson et al., 2013, U.S.	Randomized trial; interview & questionnaire	Individuals (n=229) recruited into actual studies
Roessler et al., 2015, U.S.	14 question quiz or semi-structured interview (self-rated understanding only)	Research volunteers and patients (n=480) being asked to enroll in actual biobank
Shelton, et al., 2015, U.S.	Intervention study; experimental post-test only; in person, self-administered questionnaire	Visitors (n=134) in waiting rooms; hypothetical decision to donate biospecimen of family member
Simon et al., 2015, U.S.	2 x2 experimental design; prospective randomized study /online survey, QuIC	Patients (n=200) approached for enrollment into an actual biobank
Toccaceli et al., 2009, Italy	Mailed, self-administered survey	Participants (n=99) recruited from a twin registry and radio ads for actual genetic study

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***References marked with an asterisk indicate studies included in the systematic review.**

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Chapter 3 A qualitative study examining mothers' decisions to donate their newborns' blood spots for research

Introduction

Residual dried blood spots (rDBS) are blood specimens that remain after legally required newborn screening (NBS) is completed on the nearly 4 million infants born annually in the United States. The rDBS are frequently stored and used for research, often without parental consent (Lewis, Goldenberg, Anderson, Rothwell, & Botkin, 2011). The collection of human biological specimens for future, unspecified, research (i.e. biobanking) has become a widespread practice (Henderson et al., 2013). By retaining, storing, and distributing rDBS, newborn screening programs, managed by state departments of health, are a major source of pediatric biospecimens for research. This research has led to important medical advancements, for example, in pediatric cancer research (Zhang et al., 2015), however, with these advancements come new ethical issues (e.g. genetic privacy and moral risk) (Hens, Nys, Cassiman, & Dierickx, 2009).

Taking note of ethical concerns, in 2010, the Michigan Department of Health and Human Services (MDHHS) was the first to adopt a broad research consent process as part of NBS that occurs about 24 hours after birth (Langbo, Bach, Kleyn, & Downes, 2013). However, because broad consent provides few details about future research it may not provide adequate information for informed decision-making (Hofmann, 2009) and thereby could contribute to decisional regret and moral distress (Harmon, 2010). While obtaining permission to use rDBS for research is laudable and congruent with ethical principles, it is also essential to determine whether mothers have adequate information, knowledge, and understanding of biobanking to make an informed

choice. As NBS and rDBS research occurs globally, this concern has international implications (Therrell et al. 2015).

Background

Genetic Privacy

It is important that individuals considering a donation to a biobank understand the potential risk of a breach of genetic privacy. Deoxyribonucleic acid or "DNA" in biospecimens reveals individuals' unique attributes and genetic predispositions to a host of diseases, including many that carry potential, social stigmas (e.g. schizophrenia, alcoholism) (Rothstein, 2010). Unwanted exposure of private genetic information may cause personal embarrassment, distress, or discrimination (e.g. employment, insurance, or social) despite partial protective legislation (Genetic Information Nondiscrimination Act of 2008; Rothstein, 2010). Because DNA is unique to each human, removing identifiers may not fully protect genetic privacy (Rothstein, 2010).

Moral risk

Because the intended research uses of rDBS are often unspecified, alignment with personal values may be unclear. This lack of clarity may precipitate a moral risk, defined as the possibility that biospecimens may be used in research activities misaligned with the parents' (or donors') personal, religious, or cultural values (Rothstein, 2010; Tomlinson, Kaplowitz, & Faulkner, 2014). Without specific (or in some cases any) consent, rDBS have been used to study issues such as maternal cocaine and tobacco use (Henderson et al., 1997; Spector, Murphy, Wickham, Lindgren, & Joseph, 2014). A recent literature review (Eisenhauer & Arslanian-Engoren, 2016) examining religious values and biobanking decisions identified several religious concerns related to biobanking including blood storage, cloning and genetic analysis.

Further, rDBS have been used to study birth defects and to develop new techniques for prenatal genetic diagnoses (MDHHS, 2017; Nelson et al., 2001). Research from Canada and the United Kingdom demonstrates that advances in prenatal genetic testing have contributed to an increase in abortions due to the presence of fetal anomalies (Liu et al., 2002; Wyldes & Tonks, 2007). While some may view such testing as promoting parental choice, others view abortion as morally inconsistent with their personal and religious values (Pew Research Center, 2014).

Theoretical Framework

Marteau et al.'s (2001) Multidimensional Measure of Informed Choice (hereafter: MMIC) was the theoretical framework for this study (Figure 1). The main concepts are knowledge, attitudes, and the participation decisions (i.e. agree or decline). Knowledge is defined as participants' understanding of key information about a topic, including risks, deemed essential by professional consensus for making an informed choice. Attitudes are value-based judgements about facts and information. In this model, each concept has two possible dichotomous outcomes; knowledge may be good or poor; attitudes may be positive or negative, and the participation decision may be yes or no. According to the Marteau et al. (2001, p. 100) definition of informed choice "one that is based on relevant knowledge, consistent with the decision-maker's values and behaviourally implemented" only two different combinations of knowledge, attitudes and participation decisions are considered informed choices. All other outcomes are uninformed choices (Table 5). While the MMIC has often been used in studies about prenatal testing decisions (Marteau et al. 2001; Piechan et al. 2016; van den Berg, Timmermans, ten Kate, van Vugt, & van der Wal, 2006), this is the first study, to our knowledge, to use it to guide the examination of mothers' decisions about donating newborns' blood spots.

Aim

This paper presents the qualitative component of a larger triangulated study (Eisenhauer, 2018) conducted to investigate factors influencing mothers' decisions to donate their newborn's rDBS to the Michigan BioTrust for Health, the program of MDHHS charged with oversight of the research use of rDBS (Langbo et al., 2013). The primary aims of this study were to describe mothers' knowledge and values and experience of the consent process and examine how they influenced the decision. The specific research questions were:

1. What do mothers know about biobanking at the time of the consent process for the BioTrust?

2. How do personal and religious values influence mothers' decisions to donate their newborn's blood spots for research?

3. Does the current consent process for the BioTrust provide adequate information and opportunity for mothers to make an informed choice?

Design

A qualitative descriptive design (Sandelowski, 2010) was used to identify factors that influence mothers' decisions regarding donating their newborn's rDBS for research. Factors included the mothers' knowledge and values, the context of the post-partum unit, and their overall experience with the consent process.

Ethical considerations

Approval to conduct the study was obtained from the university institutional review board (IRB). Mothers were free to stop the interview at any point or not answer particular interview questions. No names were included on audiotapes or transcripts to ensure complete confidentiality of the participants. No incentives were offered for participating in the interviews

Participants

Potential participants were recruited using a convenience sample of mothers who had given birth within the previous 24-hours and had not yet been approached regarding NBS. The PI (EE) shadowed the staff member responsible for obtaining BioTrust consent (i.e. "the consenter") on the mother/baby unit. The same consenter was observed for all 29 consent interactions. When the consenter approached each mother to explain NBS and the BioTrust, she also explained the PI's presence. Verbal permission from each mother was obtained for observation of the BioTrust consent process. After the mother rendered a decision about the BioTrust, the mother was asked to participate in a brief semi-structured interview regarding her decision. To be eligible to participate in the semi-structured interview, mothers had to be: (1) ≥18 years of age, (2) able to speak English, (3) seen within a 24-hour window of rendering the decision of interest, and (4) willing to be audiotape recorded. Once eligibility was determined, the study was explained in detail and written informed consent was obtained. Interviews were conducted in the mother's hospital room at that time or later the same day. Family members (e.g. newborn's father) who were present were allowed to stay with participant permission and were made aware the interview would be audiotaped.

Data Collection

Observations

Passive participant observation was used to collect data on (1) the physical setting in which the consent discussion occurred, (2) informational materials provided, (3) individuals present in the room during the consent and interviews, (4) activities and interactions, and (5) non-verbal behaviors to emphasize the importance of contextual factors of the post-partum period during the BioTrust consent process.

Semi-structured interviews

An interview guide was developed (Table 6) using information in the BioTrust brochure (MDHHS, 2015), essential biobanking informed consent topics (Beskow, Dombeck, Thompson, Watson-Ormond, & Weinfurt, 2015) and concepts in the MMIC. Content validity was established by team members with expertise in informed consent (ART) and maternity care (i.e., certified nurse midwife [LKL]). The interview guide was pilot tested with five mothers. Additional questions were asked at the completion of the five interviews to elicit feedback about the interview process and to assess if anything asked was unclear. As no suggestions for change were provided, these five interviews were included in the final sample.

Following the consent process mothers were interviewed to examine their understanding of the biobanking information provided and experience with the consent process. Knowledge was assessed by asking each participant to describe her understanding of the blood spots, newborn screening, the BioTrust, and biobanking. Next, each mother was asked to describe the informed consent process that had just occurred (e.g. who came in the room? what were you told?). Each mother was asked to reflect on questions or concerns she may have had during the decision-making process, whether her questions were answered, and if any additional information may have been helpful. Each mother was then asked to repeat her decision and describe why she agreed or declined to donate her newborn's blood spots for research and what was important to her in making the decision. Lastly, each mother was asked to describe any personal experiences or personal or religious values she thought may have influenced her decision (Table 6). At the end of each interview, each mother was given an opportunity to provide any additional thoughts or descriptions of their experience. Demographic data including age, education, race, religion, insurance status and parity were also collected. After confirmation

with the mother that she had no additional information to share, the interview was considered complete. The observations and interviews were conducted over four days from October to November 2016.

Data Analysis

The data were analyzed using qualitative content analysis as described by Elo & Kyngäs, (2008). Steps included: (1) preparation, (2) organizing, and (3) reporting the results. First, preparation included verbatim transcription of the audiotaped interviews (EE)**.** This involved dwelling with and scrutinizing the data, accomplished by listening multiple times to each interview as part of the transcription process, and then by reading, re-reading, and abstracting the interview transcripts (EE and CAE). Next, initial codes were developed based on categories in the MMIC framework and interview questions (e.g. knowledge, attitudes, and decisions), and keywords and phrases. Narrative data were extracted from the transcripts, organized in tables, reviewed, and iteratively compared. The unit of analysis was the collective experiences of the 20 mothers who participated in the qualitative interviews. Data matrices were then created to compare and contrast responses and demographics of mothers who decided to donate or not donate their newborn blood spots.

Responses to knowledge questions were classified as either good (+) or poor (-) by two coders (EE and CAE). Responses consistent with factual materials (e.g. per the BioTrust brochure) were classified as good knowledge whereas, inconsistent responses or statements such as, "I do not know" were classified as poor knowledge. Similarly, attitudes were classified into positive and negative categories. Favorable, optimistic thoughts or feelings toward blood spot research were characterized as positive attitudes, while negative attitudes were marked by suspicious thoughts or feelings toward such research. Using the MMIC definition of an informed

choice, there were only two possible combinations of knowledge, attitude and donation decisions that would constitute an informed choice. Option one was when a mother had: a) good knowledge about the BioTrust and biobanking, b) a positive attitude toward rDBS research, and c) agreed to donate her newborn's rDBS. The other option was when a mother had: a) good knowledge about the BioTrust and biobanking, b) a negative attitude toward rDBS research, and c) declined to donate her newborn's rDBS (Figure 1). Choices based on poor knowledge and/or attitudes incongruent with decision-making, were classified as uninformed choices per the Marteau et al. (2001) framework (Table 5).

Rigor

Trustworthiness of the data was reinforced by the use of audiotape and subsequent verbatim transcription of the interviews. Participants' views were confirmed through informal member checking and probes used during the interviews to clarify statements (Polit & Hungler, 1999). The sample size was deemed adequate after the fourteenth interview as determined by data saturation, the point when new themes stop occurring and established themes continue to repeat (Guest, Bunce & Johnson, 2006; Polit & Hungler, 1999). Inter-rater reliability was established using the approach of Miles and Huberman (1994) (number of agreements divided by total number of agreements and disagreements). Codes and themes were iteratively discussed, defined, and revised as needed between two coders (EE and CAE). Two evaluations of biobanking knowledge were changed from good to poor. Themes of "altruism" and a "pro-research attitude" were merged into "beneficence" and "perception of limited risk" and "concerns about use and privacy" were changed to "level of perceived risk". Discordance was reconciled by further discussion and 100% consensus was reached.

Results

Observation of BioTrust Consent

The BioTrust consent process was observed 29 times and was estimated to be, on average, 5 minutes in length.

Physical setting. The physical setting for the BioTrust consent process was private rooms on the mother/baby unit of a large, urban, academic medical center; the mother/baby unit has 50 private maternity rooms and delivers nearly 4,000 newborns each year.

Informational materials. At our institution, mothers are given a folder of information at admission, including brochures on NBS (MDHHS, 2015b) and the BioTrust (MDHHS, 2015). These folders were observed to be present in the mother's room during the consent process. A detailed review of the brochure materials with the mother during the consent process was not observed; however, the consenter did verbally reference them by saying "there's a pamphlet in your folder…" during the observation period. Prior to checking a yes or no box to indicate a participation choice, each mother looked at the BioTrust consent form (MDHHS, n.d.), that summarizes key information on the back of the newborn screening blood spot card. However, it is unknown the extent to which mothers actually read or understood the information. A detailed comparison of elements of informed consent for biobanking (Beskow et al., 2015, Joffe, Cook, Cleary, Clark, & Weeks, 2001, and Protection of Human Subjects, 2009) and information on the blood spot card consent form (MDHHS, n. d.) is presented (Table 7). No in-depth discussions with the consenter were observed, nor were informational materials used that explained potential moral risks, controversial types of research, or associated biomedical technologies.

Individuals present in the room. Family members, especially fathers and newborns, were frequently observed in the room with the mother (e.g. fathers were present in 15/20 (75%)

interviews). Mothers identified others present at the time of the BioTrust consent and/or the interviews as an aunt, a sister-in-law, and as grandparents.

Activities and interactions. Mothers who had given birth the previous day were identified from a list, and approached regarding NBS education and potential rDBS donation. The consenter arranged her visits with mothers according to time of delivery and approached mothers before the heel stick procedure occurred. While the consenter strived to give each mother as much time to rest after birth as possible time constraints existed, as NBS must be conducted after the newborn is at least 24 hours old, but before leaving the hospital.

The same consenter, an unlicensed member of the ancillary staff, was observed for all consent interactions. She respectfully introduced herself to the mother by name and job title, and explained she was there to talk about NBS. Next, the consenter asked each mother if she was familiar with the newborn heel stick and described the process. She explained six blood spots would be collected to screen for over 50 metabolic diseases, often briefly describing examples (e.g. PKU and Cystic Fibrosis). Next, the consenter described the difference between screening and research by stating: "The state also wants me to ask if they can use the leftover blood for anonymous medical research. The screening is required, but you can say yes or no to the research." The manner used to present the information and the language used was the same at each encounter. Discussions of risks were not observed. Mothers tended not to ask questions during the BioTrust consent process. Mothers (or fathers) verbally expressed a choice and then signed the blood spot card accordingly.

Non-verbal behavior. Eye contact, looks, and glances were observed between mothers and fathers before responding to the consent question. If silence was prolonged, the consenter prompted the mother by stating, "the blood spots either go to the biobank for research or sit with

the state. It's up to you". During one observation, parents contradicted each other's decision to donate: the mother stated she wanted to agree and the father stated he wanted to decline donation. Subsequently, the mother declined.

Semi-Structured Interviews

Participant characteristics. Twenty mothers (20/29; 69%) participated in the semi-structured interviews and nine mothers declined (9/29; 31%). Interviews lasted between 6 to 20 minutes (median: 8 minutes). The median age of participants was 32 years old (range 23-42 years), most were multiparous (n=15), with this birth most often being their second child (n=10). Three-quarters (n=15) had at least some college or a college degree. Sixty-three percent of the mothers identified a religious affiliation and indicated the practice of their faith was important (n=12/19, 63%). Of those mothers who identified a religion, the importance of the practice of their faith was rated highly (average 8.75 on a 10-point scale; King, Speck, & Thomas, 1995). Characteristics of the participants are presented in Table 8.

Knowledge. Fourteen (70%) mothers were able to correctly describe knowledge of the newborn screening by stating: "…screening for these different diseases and they will tell us if our child has them and what we need to do to treat them to prevent certain symptoms" and "…check[ing] for different diseases or illnesses that babies could have." Conversely, when asked to describe the Michigan BioTrust, most mothers' (16/20; 80%) stated, "I don't know anything about it" or "nothing" about it. Similar responses were noted when asked to describe biobanking. Most mothers (16/20; 80%) indicated they did not have any knowledge of it and stating, "Biobanking? I don't know" and "Sorry, I don't know."

Lack of Knowledge and Misunderstandings. Five mothers who declined to donate their newborns' rDBS for research purposes described a "lack of information around the process" and

clearly stated “I just really didn’t know anything…about the research part of it so that’s why my answer was no”. Mothers described “the inability to get clear information” and their unwillingness to “put my child out there” because “I just don’t know a lot of information”. One mother perceived that donation options were not “presented equally”, and described the BioTrust brochure as “definitely geared toward you saying yes.” She stated, “making certain options harder…becomes alienating”.

In addition, four types of misunderstandings emerged from the narrative data, involving 11 of the mothers. One mother who declined donation, misunderstood the procedure and said, “I just don’t want him to be more uncomfortable”, believing donation would require the newborn to have a second heel stick. Two other mothers agreed to donate because they perceived “it’s [the university hospital] asking me” and felt “[the university hospital] does a lot of good research…I am happy to participate”. Four other mothers who agreed to donate stated since “…it’s totally anonymous” and one said, “if it wasn’t anonymous I probably wouldn’t do it…” Five mothers indicated a “nurse” entered the room to ask for consent.

Attitudes. All of the mothers who agreed to donate their newborn’s blood spots (n=14) had attitudes about blood spot research classified as positive. The six mothers who decided not to donate had attitudes classified as negative. No choice was inconsistent with the stated attitudes about the blood spot research.

Personal value of beneficence. Mothers who agreed to donate their newborn’s blood spots (n=14; 70%) overwhelmingly described wanting to do “good” and to “help” others. One mother said donating blood spots was about “Helping, helping others, finding cure, helping finding cure, hopefully”. Mothers described blood spot donation as a way “… to be socially responsible…” and “…advance medical care…” Mothers frequently (n=12; 60%) expressed the

perception of research as a benevolent act. One mother said "…research is good. Let's do that!" and two other mothers stated they were "always pro-research". Six of these mothers described their "love of science" and perception of "research is good" as related to occupational experiences (their own or those of newborn's father) in education, nursing, medicine, and public health.

Personal assessment of level of perceived risk. Three mothers who agreed to donate blood spots perceived no risk with the blood spot research. One participant stated "They're not… to harm my child, so, why not [participate]!" Nine others who agreed to donate perceived "little" or "small" risks and expressed that the research was "low enough risk that I'm not too worried about it". The perception of low risk was often linked to the fact the bloodspots were "leftover" and there would not be "an extra prick" for the newborn.

However, mothers who declined to donate perceived more risk and stated "… it's private information. I don't want it to go out in public" and expressed concerns the blood spots would be used for "commercial reasons…for profit". Additional concerns included "any negative research" and "uncertainty about how it's going to be used."

Religious Values. Six mothers (30%) described religious, spiritual, or moral issues that influenced their donation decisions. Two mothers, who agreed to donate, associated "trying to help each other" with their religious beliefs. They stated "[my congregation] really believe in the inner connectedness of all livings beings" and **"**I hope to God they find cures for illnesses." Two other mothers, who agreed to donate, said: "just don't clone them" or use the blood spots for "anything like immoral, like…abortion". A mother who declined to donate stated "…I believe in certain things like being Christian for one, and in Christ and all that" and she feared the blood

spots may be used for "witchcraft". Another mother denied that "visions", (i.e. religious or spiritual entities), led her to say no, but stated she declined based on her lack of knowledge.

Mothers' descriptions of consent process. The majority of mothers (12/20; 60%) were able to describe the difference between NBS and the request to use rDBS for research. One mother stated:

> "She came she came in and …described… the state requires six bloodspots and they do some testing for children…and then…she asked… if we would be willing to…use the leftover blood spots for research."

However, eight mothers were unable to describe the difference clearly. One mother stated, "She just really just asked me if I … want to it get a researched *[sic]* and I said yes, but I don't want those remaining blood kept".

Four mothers characterized the consent process as "straight forward" or "no big deal" and as an "easy decision". Two of these mothers reported "details" were not provided, nor were they always perceived as necessary. One mother stated,

> "…I think she didn't specify more details just because I didn't ask for them ….

Two mothers stated the speed at which the decision was made was "… like a one second decision!" and "…I made it on the fly!" A third mother stated, "I didn't think twice of it".

Two mothers specifically reported the brief explanation provided by the consenter to be "helpful" in making the decision and that the consenter "kind of went over it a little bit with us." Two other mothers stated they appreciated "having a choice" about donation (one said yes and one said no to donation) and three mothers explicitly denied feeling any pressure imposed by the consenter to influence their decisions. One said it was "very low pressure… like it was okay

either way." Another one stated she felt "no pressure at all" and the third mother said "it felt normal." However, another mother described that she did not find the process helpful stating:

> …how can we give informed consent when you're getting patients who a couple of hours, couple of hours after a birth, when they've had all kind of narcotics and drugs, and trauma? And there is somebody in the room every half hour performing some sort of test, and this is just one more test, and again, you are not really informed about your choices."

When asked, "If you were to change your mind about donating what would you have to do?" Four mothers were able to described the process to withdraw from the BioTrust stating they would "[use] the internet", "read the pamphlet", or "contact the state". Eight other mothers described it as "telling the lady" or "telling you guys", while others stated they did not know (n=5) or did not understand the question (n=3).

Demographics and Decisions. A total of 14 mothers agreed to donate their newborn's blood spots to the BioTrust and six declined. Mothers who self-identified as of white race tended to agree to donate, while mothers who self-identified as of a non-white race were split in their decisions (Table 8). Additionally, mothers who declined to donate tended to be of younger age, (in their twenties), compared to mothers who agreed to donate rDBS, who were mostly in their thirties or over forty years of age. Twelve mothers (12/19; 63% of those who answered demographic questions) reported a religious affiliation (i.e. Christian, Muslim, or Unitarian). Five out of twelve (42%) mothers who indicated a religious affiliation declined to donate their newborn's rDBS, whereas all of the seven mothers who indicated no religious affiliation agreed to donate their newborn's rDBS. Education, insurance status, and number of births did not seem to be exclusively associated with any particular donation decisions (Table 8**).**

Classification of choices. Based on the MMIC four mothers (20%) made an informed choice: a choice congruent with both (a) possessing relevant knowledge and (b) consistent with personal attitudes toward blood spot research. Sixteen mothers (80%) lacked the relevant knowledge to make an informed choice (Table 9 & 10). Informed choices included three mothers who agreed to donate and one who declined. Only three of the four mothers who made an informed choice were willing to answer demographic questions. All three of these mothers were in their 30s, had at least some college education, and identified a religious affiliation. Two had private insurance and one had public insurance (i.e. Medicaid). Two mothers were multiparous and one a first time mother; fathers were present in two out of four instances of informed choice. All mothers indicated they were fairly confident with their decisions (Table 8).

Discussion

This study provides insight into the knowledge, attitudes, and decision-making of mothers faced with the choice of whether or not to donate their newborn's blood spots for research purposes. The majority of mothers (n=16, 80%) made the decision without adequate knowledge of the Michigan BioTrust or biobanking. These decisions failed to reach the threshold of an informed choice. Findings were consistent with the current literature indicating biobanking participants lack understanding of key elements of informed consent (Eisenhauer, Tait, Rieh, & Arslanian-Engoren, 2017) and that low knowledge scores contribute to uninformed decisions about prenatal testing (Marteau et al. 2001; Piechan et al. 2016; van den Berg et al. 2006), and declining vaccinations for children (Lehmann, de Melker, Timmermans, & Mollema, 2017). This lack of knowledge was also exhibited in the form of misunderstandings. Of concern, 11 mothers made decisions influenced by one or more of four different misunderstandings, one of which was perceived use of rDBS as anonymous. When used for

research, rDBS are de-identified and coded (MDHHS, 2015); but do not meet the Food and Drug Administration's (2008) definition of anonymous biospecimens as "never labeled with personal identifiers when originally collected, neither is a coding key generated" (p.6). While the consent form states the rDBS are coded, the consenter incorrectly characterized the identifiability of the rDBS as anonymous, which may have contributed to this misunderstanding.

Information & Attitudes

Decisions about donating blood spots were often based on attitudes toward biomedical research in general. Many of the mothers interviewed in this study expressed a belief that all research was good and beneficial. This may have influenced their decision to donate, a finding that calls for further research to evaluate how mothers' assess the credibility of the presented information (Rieh, 2002). However, two mothers who agreed to donate rDBS expressed moral caveats on research involving abortion and cloning, indicating perceptions of moral risk. One held the misperception that the request for rDBS was emanating from the hospital, a trusted institution in the community, even though the request was not from the hospital. Thus, it will be important to clarify in the written material and during verbal discussions that the request for rDBS is coming from MDHHS, and not the hospital, so that mothers have accurate information on which to base their donation decision. The six mothers who declined to donate perceived higher risks to personal values (e.g. privacy and uses). Consistent with other research, religious values were found to both encourage and discourage donation (Eisenhauer & Arslannian-Engoren, 2016; Hassona, Ahram, Odeh, Gosh, & Scully, 2016). When a religious influence was present, those who agreed to donate tended to link altruism and the pursuit of health with their religious beliefs, and those who declined tended to link moral concerns to religious prohibitions.

Process and Context

Five mothers in this study perceived the consenter to be a nurse, even though she was an ancillary staff member and she did not introduce herself as a nurse. The credentials (or the perception of credentials), communication skills, and actions of the consenter may influence understanding and decision-making about biobanking research participation (Eisenhauer et al., 2017). Because of the high degree of public trust in nurses (Norman, 2016), perceiving the consenter to be a nurse may have influenced mothers' decisions to donate their newborn's rDBS for research purposes. While trust in the consenter may be a motivating factor and lead an individual to participate in biobanking, trust should not be conflated with objective understanding of information (e.g. risks and benefits) (Fisher & Fisher, 2000). Hoeyer (2003) showed that patients' trust in nurses is so strong that it may impede rational deliberation during biobanking consent. However, in contrast, Cervo et al. (2013) found participants to have a good understanding of biobanking after initially speaking with a physician, and then a biobank nurse or biologist; adequate levels of understanding of the informed consent information were reported among participants.

Further, the manner in which the consenter presented the choice may also have influenced mothers' decision-making. While her approach was friendly, it was also routine, brief, and observed to elicit only a yes or no response, as opposed to asking in a manner to create an opportunity for a more open discussion. During the observed consent process, no examples of specific types of research were provided during the interactions and no values-clarification techniques were observed being used (e.g. asking: how do you feel about biobanking?). Instead, it appeared that the choice relied on a consumer information model of consent in which basic information is provided and the individual is left alone to make an autonomous choice (Gadow, 1990). A better approach might be to follow a model of shared decision-making and existential

advocacy (Gadow, 1990) where evidence and information is openly shared, participant values are clarified, and the participant "is supported to consider options, to achieve informed preferences" (Elwyn et al. 2012, p.1361). Extended discussion with a knowledgeable person is the most efficacious intervention to aid understanding of consent information (Flory & Emanuel, 2004; Nishimura et al., 2013).

One possible explanation for the observations may be that while the MDHHS provides some in-person and online BioTrust consent training to birth hospital personnel (Langbo et al., 2013), it appears to be minimal. An online flyer (MDHHS, 2018) lists only eight brief steps for obtaining consent (i.e. "Provide BioTrust consent brochure. Ask parent to read. Answer any questions. If a parent has more questions, contact BioTrust Coordinator. Ask parent to mark their decision. Collect parent signature. Return white copy to state lab. Give pink copy to parent.") Additional educational efforts include an online video training describing the process of obtaining consent that includes a certificate of completion option for the consenter (MDHHS, 2016). While this is commendable, it raises many concerns. In particular, it remains unclear if this training is optional or required, how compliance is monitored, how evaluation is conducted, or if there are minimum educational requirements for consenters.

Although the blood spot card consent form was created by MDHHS in collaboration with the Office of Human Research Protections (OHRP) to address all required elements of the consent process (Rothwell et al., 2017), it appears the card was written in a generic manner without attention to the specifics of biobanking or donating rDBS. The form does not clearly explain that newborn screening will still be conducted, and that the pediatrician will still receive results, even if parent(s) decline research participation. As such, the distinction between newborn screening and experimental blood spot research may not be clear. The card does not address any

medical or lifestyle information about the parents or the newborns that may be linked to the rDBS from other state databases or registries (e.g. birth certificates; see Korzeniewski et al., 2010). The only risk listed is that the blood spot could be identified. The card does not address the risk of participating in research that may be incongruent with personal or religious values (i.e. moral risks). The issue of using rDBS to develop commercial for profit products is not addressed on the blood spot card, although identified frequently as a value-based concern of biobank participants (Eisenhauer et al. 2017; Eisenhauer & Arslanian-Engoren, 2016) and mothers in this study. Comparisons are considered essential pieces of information to aid understanding (Brehaut, 2012). Key terms (e.g. DNA, low risk) are not explained or defined and the word "experimental" is not used.

A recent focus group study of 69 participants in three states reported individuals found information on the blood spot card confusing (Rothwell et al., 2017). The lack of understanding among participants in this study about the level of identifiability of the blood spots was similar to findings of Rothwell et al. (2107) where focus group participants were also confused about the level of identifiability of the blood spots after reading the information on the consent card. Participants in Rothwell et al. (2017) wondered why the benefit section does not mention any possible benefits of the rDBS to society as a whole. In addition, although possible injury is not listed as a risk of participation, the card oddly mentions a number to call in case of a research related injury (Rothwell et al., 2017). Without comparisons or specific research examples participants had difficulty understanding what types of research may be conducted on blood spots. Specific examples were desired by mothers in this study and are requested by the general public (Rothwell et al, 2017). Other common elements of biobanking consent (Beskow et al., 2015) such as return or research results, re-contact for future studies, and the role of cells, DNA

and/or genetics are not addressed on the consent card. While key elements are further explained in the BioTrust brochure, several mothers in our study reported not having read it; nor was information from it discussed with the mother by the consenter.

The context of the postpartum period also influenced information use and decision-making as described by participants in this study. Fathers were an important influence on mother's decisions to donate their newborn's blood spots for research. During the interviews, fathers frequently asked or answered questions, even though research questions were intended for and directed to the mother. It was observed that decision-making about blood spot donation was often a joint decision between the parents of the newborn. While fathers' level of biobanking knowledge and involvement in this decision was not specifically assessed in this study, it should be required, as they both have contributed to a newborn's DNA (Baumann, 2001).

Mothers described being sleep-deprived, fatigued, under the effect of medication or in pain, and were observed to be preoccupied with their new baby. There are a myriad of decisions that need to be made during the postpartum period, including decisions about newborn care, pain medication, breastfeeding, and male circumcision (Torres & De Vries, 2009). Others have found the routinizations of consent for such decisions may impede informed consent (Lowe, 2004; Press & Browner, 1997). Patients' values and ethical dilemmas are often overlooked during consent for these procedures, and the potential emotional consequences of the decisions are often not fully explained (Lowe, 2004; Press & Browner, 1997). It seems the same may hold true for the BioTrust decision, in this often physically and emotionally overwhelming context. This provides support for moving information and education about rDBS research out of the postpartum environment and into the prenatal setting (American College of Obstetricians and

Gynecologists, 2015; American Academy of Pediatrics, Newborn Screening Authoring Committee, 2008).

Limitations and Strengths

There were three limitations to this study: (1) the small sample size at a single institution (2) adaptations and limitations of the MMIC, and (3) the potential for the Hawthorne effect. The study sample was a small, convenience sample derived from a single data collection site, where only one consenter was observed which limits the generalizability of results to the larger population. However, data saturation was achieved, adding strength to its adequacy and validity (Guest, Bunce & Johnson, 2006; Polit & Hungler, 1999). The novel application of MMIC to data on mothers' decisions about donating their newborns' blood spots for research was a strength of the study. However, the MMIC attributes an informed choice to only three categories: knowledge, attitudes, and participation. An informed choice may be more complex and involve a component of deliberation (van den Berg et al. 2006), not captured in the MMIC. In addition, dichotomized categories likely reduced the granularity in the interview data. Further, the MMIC was originally used with quantitative scale data and verified with qualitative responses. However, our qualitative interviews produced rich, detailed data that captured the mothers' decision-making process as it occurred. The examination of actual, real-time decisions that occurred in their natural environment on the post-partum unit was a noted strength of the study, as was the ability to observe the effects of context on decision-making. Lastly, despite efforts by the PI to be as unobtrusive as possible during the observations of the consent process, one cannot rule out the potential for a Hawthorne effect. The consenter knew she was being observed which may have influenced her behavior during the consent the process (Polit & Hungler, 1999).

Policy Implications

Based on findings from this study, four policy recommendations are put forth: (1) Information provided to parents about research on rDBS must be accurate, comprehensive, and include ethical implications of biobanking. Positive and potentially controversial research examples must be provided; (2) Evidence-based decision-aids should be developed to supplement verbal interaction between the consenter and the potential participant in biobanking consent discussions. (3) The consenter should be required to annually complete and document appropriate training to conduct informed consent discussions including training form MDHHS on rDBS research, communication skills training, and formal human subjects' training, such as that provided by the National Institutes of Health (NIH, 2018). (4) Education about NBS and rDBS research should begin at the time of the prenatal visits.

Provision of information about the moral implications of biobanking has been found to influence decisions (Tomlinson, Kaplowitz, & Faulkner, 2014; Tomlinson, De Vries, Ryan, Kim, Lehpamer, & Kim, 2015). Implementing standardized tools designed to elicit and clarify values to aid decision making will help to provide value-based, tailored information to each potential participant. Decision aids are effective in improving the quality of other preference-based healthcare decisions (Stacey et al., 2017). The delivery of complex consent information requires advanced communication skills, comparisons, and value-clarification techniques (Brehaut et al., 2012). These are skills many nurses possess or could enhance via continuing education. Furthermore, the application of nursing theory has been useful in the care and recruitment of research subjects (Penckofer, Byrn, Mumby, & Ferrans, 2011). Studies need to be conducted to assess differences in participant understanding based on the credential of the consenter to improve the informed consent process. In the meantime, all consenters should at least have

training form MDHHS on rDBS research, communication skills training, and human subject protection training Moreover, leading organizations have called for moving these educational activities form the postpartum environment to the prenatal setting to provide more time, in a less stressful environment for the consideration of complex information (American College of Obstetricians and Gynecologists, 2015; American Academy of Pediatrics, Newborn Screening Authoring Committee, 2008). While individual level knowledge may be difficult to improve, the process and context of the BioTrust consent process may be more amenable to change.

Conclusion

This study examined donation decisions of mothers asked donate their newborn's rDBS for research purposes to the Michigan BioTrust. While most mothers agreed to donate the blood spots, many decisions were based on inadequate knowledge and misunderstandings. Therefore, policy changes are needed to re-structure the informed consent process to promote knowledge, understanding and to explicate values. Consenter certification, value clarification techniques, and changing the context in which education about NBS and rDBS research occurs, will facilitate informed choices. To facilitate a more meaningful informed consent process for biobanking decision making, additional research is needed to more fully understand optimal content, timing, and delivery of education about NBS and rDBS.

Table 5. Marteau et al. (2001) Choice Classifications

	Good Knowledge	Positive Attitude	Donation Decision
Informed Choices	✓	✓	✓
	✓	X	X
Uninformed Choices	✓	X	✓
	✓	✓	X
	X	✓	✓
	X	X	✓
	X	✓	X
	X	X	X

✓=Yes/X=No. Good knowledge=responses consistent with factual materials (e.g. the NBS and BioTrust brochures). Poor knowledge=inconsistent responses or "I do not know". Positive attitude= favorable, optimistic thoughts or feelings toward blood spot research. Negative attitude = suspicion or opposition toward such research.

Table 6. Examples of interview questions, probes, and categories

Interview Questions	Probes	Category
First, please describe to me what you know about the blood spots from the newborn screening test?	What do you understand about the blood spots from the newborn screening test?	NBS Knowledge
Please tell me what you know about the Michigan BioTrust.		BioTrust Knowledge
Next, please describe how you were asked for permission to donate the leftover blood spots to the BioTrust as you experienced it.	Who asked for your permission? What did s/he tell you? What happened? What kind of information were you given?	Informed Consent
What was your decision about the donating your baby's blood spots to the biobank?	Did you agree or not agree to donate your baby's blood spot to the biobank?	Donation Decision[1]
What kinds of thoughts, questions, or concerns were in your mind as you made your decision?		Values/ Attitudes
Do you think your questions answered? How was this done?	By whom or by what information?	Informed Consent
Do you think you were you able to get the information that you needed to make the decision?		Informed Consent
Is there any additional information that would have been helpful to you in making this decision?		Informed Consent
If you had more time, would you be willing to find more information?		Informed Consent
What did you find helpful or unhelpful to you to make the decision to donate your baby's blood spot to the MI BioTrust?		Informed Consent
Please tell me about how you chose (yes/no)?	What was important to you in making the decision?	Values/ Attitudes
What personal experiences, values, opinions or religious beliefs of yours do you think may have influenced your decision?	How did _____affect your decision? Can you give me an example?	Values/ Attitudes
What have you heard about biobanking?	Can you please describe biobanking in your own words?	Biobanking Knowledge
What is the purpose of the Michigan BioTrust?		Knowledge Informed Consent
Next, please describe your expectations about medical research involving your child's genetic information/bloodspots.		Attitudes/ Values
Do you have any concerns about medical research involving your child's genetic information/bloodspots? If yes, please explain.		Attitudes/ Values
Are there things you would want or would not want the blood spots used for?	Like what? Can you please give me an example?	Attitudes/ Values
On a scale of 1-5 (rating decribed) how would you rate your confidence in your decision?		Confidence
If you were to change your mind about donating what would you have to do?		Informed Consent
*Please complete the following sentence: For me, personally, donating (or not donating) my newborn's blood spots for research is_(fill in the blank)____.		Attitude
Anything you would like to add about your experience and decision regarding the BioTrust?		Summation

* Question adapted from Marteau et al.; 2001 NBS=newborn screening; 1. 19/20 decisions were observed as they were made.

Table 7. Comparison between Elements of Informed Consent for Biobanking and MDHHS NBS Blood Spot Consent Card

	Consent Element	MDHHS NBS Blood Spot Card Consent
1	Access to Specimens	"the state lab and research approved by MDHHS" & "researchers"
2	Alternatives	Blood spots "may or may not be used for health research."
3	Benefits	"Most likely you or your child will not benefit from blood spot research."
4	Data from Medical Record(s)	Not addressed on card.
5	Confidentiality	"Unused blood spots are stored using a code and not your child's name." "Many steps are taken to protect privacy. Details that could identify your child or family are removed before your child's blood spots are given to a researcher."
6	Contact Person	"If you still have questions, please call the Michigan Department of Health and Human Services (MDHHS) toll free at 1-866-673-9939."
7	Experimental Procedures	"Many types of laboratory methods are used to study biological factors like DNA or environmental factors like metals and toxins."
8	Injury	States "For questions about your research rights or whom to contact in case of a research-related injury, please call the MDHHS IRB at 517-241-1928."
9	No Penalty	"There is no penalty or loss of benefits for saying no or changing your mind."
10	Payment/Commercial Use	Not addressed on card.
11	Purpose	"Stored blood spots may be used by the state lab to help ensure that newborn screening detects those at risk. Stored blood spots may also be used for research approved by MDHHS. Blood spots can only be used for studies to better understand disease or improve the public's health."
12	Research (Awareness)	"My baby's blood spots may be used for health research through the BioTrust" or "My baby's blood spots may not be used for health research."
13	Re-contact	Not addressed on card.
14	Return of Results	Not addressed on card.

15	Risks	"The risk for using your baby's blood spots in research is that it could be identified. This risk is very low. Many steps are taken to protect privacy. Details that could identify your child or family are removed before your child's blood spots are given to a researcher."
16	Role of Cells, DNA, Genetics	Not addressed on card.
17	Study Duration	"The spots are stored forever at a secure site (Biobank) unless you, or your grown child, change your mind."
18	Study Procedures	"Your choice applies to all blood spots collected for newborn screening."
19	Voluntary	"Participation is voluntary."
20	Withdrawal	"You can call MDHHS at any time if you change your mind."

Sources: Elements of informed consent for biobanking synthesized from: Beskow, Dombeck, Thompson, Watson-Ormond, & Weinfurt, 2015, Joffe, Cook, Cleary, Clark, & Weeks, 2001, and Protection of Human Subjects, 2009. MDHHS NBS blood spot card consent form (MDHHS, n. d.).

Table 8. Characteristics of interviewed mothers

Age, years		Donation Decision	
		Yes (n=14)	No (n=6)*(%)
Median	32	34	24
Range	23-42	25-42	23-29
Race	n (%)	n (%)	n (%)
Asian	1 (5)	0 (0)	1 (17)
Black or African American	2 (11)	0 (0)	2 (33)
White or Caucasian	12 (63)	11 (79)	1 (17)
Other (Arabic, mixed-race, other)	4 (21)	3 (21)	1 (17)
Unknown	0 (0)	0 (0)	1 (17)
Religion			
Christian	6 (32)	3 (21)	3 (50)
Muslim	5 (26)	3 (21)	2 (33)
None	7 (37)	7 (50)	0 (0)
Unitarian	1 (5)	1 (7)	0 (0)
Unknown	0 (0)	0 (0)	1 (17)
Highest level of education completed			
High School	4 (21)	1 (7)	3 (50)
Some College	6 (32)	5 (36)	1 (17)
Bachelor's	4 (21)	4 (29)	0 (0)
Master's	4 (21)	3 (21)	1 (17)
Professional Degree (PhD, MD)	1 (5)	1 (7)	0 (0)
Unknown	0 (0)	0 (0)	1 (17)
Insurance coverage			
Public (Medicaid)	8 (42)	5 (36)	3 (50)
Private (Employer sponsored /Self-insured)	10 (53)	9 (64)	1 (17)
Both	1 (5)	0 (0)	1 (17)
Unknown	0 (0)	0 (0)	1 (17)
# of live births (including this baby)			
1	4 (21)	3 (21)	1 (17)
2	10 (53)	7 (50)	3 (50)
≥ 3	5 (26)	4 (29)	1 (17)
Unknown	0 (0)	0 (0)	1 (17)
Confidence in Decision -Average (1 uncertain- 5 very confident)			
Overall	4.4	4.5	4.2

*NOTE: n = 19/20; 1 mother declined to answer demographic questions---donation decision=no; informed choice=yes. Columns may not total 100% due to rounding.

Table 9. Examples of mothers' responses to questions eliciting knowledge about biobanking, the MI BioTrust, and attitudes towards the donation of the newborn's blood spots for research.

Knowledge Questions	**Responses classified as indicating good knowledge**	**Responses classified as indicating poor knowledge**
Please tell me what you know about the Michigan BioTrust.	…there is a Detroit BioTrust so I read a little bit about the Detroit BioTrust and the fact that it provides anonymous samples…of… the Michigan bloodspots for various types of research projects and they have to be approved for them to get access…	I actually don't know anything about it [laughs].
What have you heard about biobanking? Probe: Can you please describe biobanking in your own words.	….Biobanking isn't that where they take samples of ah blood, hold them over and they study it? And I think they save it forever or something like that?	Biobanking? I don't know. Sorry, I don't know.
(What is or) Do you know the purpose of the Michigan BioTrust?	…other than just research and to study the different, different genetic diseases that are present. That's about what I know.	I don't [know].
Attitude Questions	**Responses indicating positive attitudes towards blood spot biobanking research**	**Responses indicating negative attitudes towards blood spot biobanking research**
For me, personally, donating my newborn's blood spots for research is _____.	Rewarding.	Not going to happen!
What kinds of thoughts, questions, or concerns were in your mind as you made your decision?	…I'm always pro research so… Yeah. And I knew that it's totally anonymous kind of thing too, so it's not it's like anybody knows whose is whose….	…it's just that I don't know much about it, so well I didn't …want to put something out there and I didn't understand it too.

Table 10. Biobanking Choice Classifications based on Marteau et al. (2001).

	Good Knowledge	Positive Attitude	Donation Decision	# of Mothers
Informed Choices				
	✓	✓	✓	3
	✓	X	X	1
Uninformed Choices				
	✓	X	✓	0
	✓	✓	X	0
	X	✓	✓	11
	X	X	✓	0
	X	✓	X	0
	X	X	X	5

✓=Yes/X=No. Good knowledge=responses consistent with factual materials (e.g. the NBS and BioTrust brochures). Poor knowledge=inconsistent responses or "I do not know". Positive attitude= favorable, optimistic thoughts or feelings toward blood spot research. Negative attitude = suspicion or opposition toward such research. Adapted from Marteau et al. (2001) p. 104.

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Chapter 4 Measuring mothers' choices about blood spot donation for research

Introduction

Due to the rapid evolution of genetic and genomic science, it is likely that every individual living today will, at some point, be asked to donate biospecimens for research (Wells et al., 2014). However, in order to make an informed choice regarding donation of biospecimens for research there must be an understanding of the potential risks and benefits, including threats to genetic privacy and personal values and the possibility of life-saving medical advancements (Rothstein, 2005). An informed choice also requires adequate knowledge and consideration of personal values relative to the consequences of the decision (Marteau, Dormandy, & Michie, 2001). When biobanking consent is obtained, potential participants may be provided with minimal information and a consent form that grants research broad latitude for future research (i.e. broad consent) (Hofmann, 2009). However, the provision of basic biobanking information alone may not be enough and often fails to satisfy the foundational ethical mandate of informed consent. Instead, it is the responsibility of those requesting biospecimen donations to ensure that potential participants have sufficient knowledge to make an informed choice (Protection of Human Subjects, 2009).

A recent literature review revealed that many individuals have difficulty understanding biobanking information (Eisenhauer, Tait, Rieh, & Arslanian-Engoren, 2017). To date, it has been difficult to develop effective interventions to facilitate informed choices, in part because of empirical research related to participants' understanding of informed consent for biobanking lacks standard definitions, instruments, and theoretical frameworks, making comparison across

studies difficult (Eisenhauer et al., 2017; Sand, Kaasa, & Loge, 2010). Therefore, this study was designed to begin to address these deficits by (1) defining and measuring key variables (i.e. knowledge, attitudes, and informed choice) with standardized instruments and (2) using an established framework--- the multidimensional measure of informed choice (Marteau et al. 2001) to assess participant understanding of biobanking and determine the proportion of informed choices made. The findings will be used to inform future interventions aimed at improving the informed consent process for biobanking.

Background

Newborns' blood spots

Newborn screening (NBS) programs administered by state departments of health have become "huge biorepositories [biobanks] of blood samples from all newborns in the USA" (Tarini & Lantos, 2013, p. 82). Unless a parent objects for religious reasons, all newborns in the United States (U.S.) (approximately 4 million annually) are required to undergo newborn screening (NBS). This involves blood drawn from a newborn's heel and collected on filter paper to screen for treatable metabolic and genetic disorders, which if left undiagnosed or untreated can cause permanent disability (Baby's First Test, 2017). While few doubt the importance of early detection of treatable diseases, some question whether NBS screening programs have expanded too far beyond their original mission (Botkin & Rothwell, 2016; Lewis, Goldenberg, Anderson, Rothwell, & Botkin, 2011). Many states now retain, store, and distribute the residual dried blood spots (rDBS) for research after NBS has been completed, often without parental consent (Botkin & Rothwell, 2016; Lewis et al. 2011; Olney et al. 2006). As such, these biobanks have become one of the largest sources of pediatric biospecimens available for research

purposes; California has 16 million specimens and Michigan 5 million specimens, dating back to the 1980s (McGreevy, 2015; MNB: Michigan Neonatal Biobank, n.d.).

State policies vary about whether parental permission is required to use newborns' rDBS for research (Lewis et al., 2011). Because rDBS contain deoxyribonucleic acid (DNA) and because the sequencing of DNA reveals the unique genetic pattern of each newborn, the storage, retention, and research practices that use rDBS raise ethical concerns about privacy and values (Hens, Nys, Cassiman, & Dierickx, 2009). Studies show that parents want to be asked permission for, and feel they have the right to decline the use of their newborn's biological material for research purposes (Tarini et al., 2009; Botkin et al., 2012; Thiel et al., 2014). Lawsuits filed over parents' privacy concerns have resulted in changes in state policies and the subsequent destruction of millions of blood spot cards (Carmichael, 2011; Couzin-Frankel, 2009; Cohen et al., 2010).

Michigan

In 2009, the Michigan Department of Health and Human Services (MDHHS) proactively created the Michigan BioTrust for Health (i.e. the "BioTrust") to operationalize policies regarding the storage and research use of newborn rDBS leftover from state mandated, newborn screening programs (Langbo et al., 2013). Currently, three advisory boards inform policy development: Community Values Advisory Board (CVAB), Scientific Advisory Board (SAB), and the board of directors of Michigan Neonatal Biobank (MNB) (Langbo et al., 2013). In 2010, MDHHS implemented an opt-in parental consent process, conducted within 24-hours of birth in connection with NBS, for parents considering donation of their newborns' rDBS to the BioTrust for research purposes (Langbo et al., 2013).

Areas of Consensus

While there is much debate about the type and scope of consent for biobanking (Hofmann, 2009), two areas of consensus exist: (1) Individuals should have sufficient knowledge and understanding of biobanking in order to voluntarily donate their (or their newborn's) biospecimens for research purposes (Greely, 1999; Hofmann, 2009; Sheehan, 2011); and (2) there are specific elements of biobanking, including risks, vetted by experts, that a person should understand in order to participate (Beskow, Dombeck, Thompson, Watson-Ormond, & Weinfurt, 2015; Wells et al., 2014).

A consent procedure should facilitate knowledge and understanding to help a person make an informed, voluntary choice, and not simply provide legal protection to the state or convince a person to participate (Marteau et al., 2001; Raffle, 2001; Roth, Meisel, & Lidz, 1977). Without accurate knowledge and information, it may be difficult for an individual to deduce alignment with their values and rendered decisions may be misaligned. While the state of Michigan's early adoption of an opt-in consent process for storage and research use of the blood spots is commendable, it is remains unknown if these biobanking decisions are informed choices (Marteau et al., 2001).

Theoretical Framework

The theoretical framework for this study was the Multidimensional Measure of Informed Choice (MMIC) by Marteau et al. (2001) (Figure 1). The principal concepts of this framework are knowledge, attitudes, and the participation decision. In the framework, knowledge is defined as participants' understanding of key information about a topic, including risks, deemed essential by professional consensus for making an informed choice. Attitudes are value judgements about facts and information. In this model, each concept has two possible dichotomous outcomes; knowledge may be good or poor; attitudes may be positive or negative, and the participation

decision may be to agree or decline to participate. According to the Marteau et al. (2001, p. 100) informed choice is defined as "one that is based on relevant knowledge, consistent with the decision-maker's values and behaviourally implemented" only two different combinations of knowledge, attitudes and participation decisions are considered informed choices (Figure 1). All other outcomes are uninformed choices (Table 5).

Aims

The purposes of this study were to: (1) describe mothers' of newborns level of biobanking knowledge, attitudes, and personal and religious values, using established measures; (2) determine the influence of these factors on mother's decisions to donate their child's residual blood spots for research purposes; and (3) evaluate the proportion of mothers' who make an informed choice.

Design

A larger methodologically triangulated study was conducted to describe the influence of mothers' biobanking knowledge, personal values, and perceptions of the consent process on their decisions to donate their newborn's rDBS for research purposes and determine the proportion of informed choices (Eisenhauer, 2018). A qualitative descriptive study was conducted and found participants (n = 20) lacked knowledge of the BioTrust and biobanking and that most decisions failed to meet the criteria of an informed decision (Chapter 3). The results of the non-experimental, descriptive and correlational survey are presented in this paper.

Participants

Five hundred surveys were mailed by the MDHHS to mothers who gave birth within the last three months in the state of Michigan. The initial sample was randomly selected by MDHHS using a random number generator. The Newborn Screening Follow-up Program database by

MDHHS was used to select the sample. The final study sample consisted of respondents to the survey. Eligibility criteria for the quantitative portion of the study included the mother of the newborn in the household: 1) was ≥18 years of age and 2) had a newborn 0-3 months of age. Exclusion criteria included subjects with no BioTrust parental consent decision (yes or no) on file with MDHHS or evidence of an infant death in the state database.

Data collection

Five hundred survey packets were prepared, each containing: (a) an invitation letter, (b) an informed consent form, (c) a letter from MDHHS explaining the project (d) study instruments (i.e. Biobanking Attitudes and Knowledge Survey [BANKS] (Wells et al., 2014); 10-Item Hoge Intrinsic Religiosity Motivation Scale (Hoge, 1972); Short Schwarz's Value Survey (Lindeman & Verkasalo, 2005), and a brief investigator developed demographic questionnaire (Appendices B-H). The invitation letter and informed consent form described the research project. A PI-addressed stamped envelope was included for participants to return the materials within one month of receipt. A two-dollar bill was also included in the packet as an honorarium to thank participants for their time and effort. Survey packet envelopes were sealed and hand-delivered to MDHHS in Lansing, MI, whose staff then added the mailing address of potential participants. This was done to safeguard the protected health information (e.g. names, addresses) of potential participants. The study team was not aware of the names or mailing addresses of potential participants.

A modified Dillman approach (Dillman, Smyth, & Christian, 2009) was used that included one initial mailing and one reminder postcard mailed seven days later. Reminder postcards were mailed by MDHSS, to the same 500 potential participants, to thank those who completed the survey and to remind those who had not yet done so to complete and return the

survey. Survey responses were completely anonymous, as no identifying links or codes were collected or maintained. The IRB granted a signature waiver on the consent form to maintain anonymity of the respondents. Return of the completed survey was considered evidence of consent to participate.

Measures

Measure of Informed Choice. Marteau et al. (2001) categorical rubric of knowledge, attitudes, and decisions was used to measure informed choices. This 8-cell typology classifies knowledge as good or poor and attitudes as positive or negative and examines the congruency of the health decision (yes or no) with attitudes. The MMIC requires dichotomization of knowledge and attitude data from continuous scales using an absolute score, the sample mean, or the scale mid-point. Choices are considered informed when individuals demonstrate good knowledge and positive attitudes that result in participation, and also when individuals demonstrate good knowledge and negative attitudes that result in a decision not to participate. All other possible combinations of knowledge (good/poor), attitudes (positive/negative), and decision (yes/no) are considered uninformed choices (Marteau et al., 2001). The rubric was applied to the knowledge, attitude, and participation decision data to evaluate the proportion of informed choices among mothers regarding MI BioTrust donation decisions.

Standardized instruments. Three standardized instruments with sound reliability and validity measures were used in this study (Table 11). A description of each follows.

Biobanking attitudes, knowledge, self-efficacy. The Biobanking Attitudes and Knowledge Survey (BANKS) tool includes three, self-contained, multiple-item scales to measure biobanking- related constructs: attitudes, knowledge, and self-efficacy (Wells et al., 2014). The attitude scale consists of 14 items using a 5-point Likert-type scale (*Strongly Agree, Agree,*

Neither Agree nor Disagree, *Disagree*, *Strongly Disagree*) to measure attitudes about biobanking. An example of a question is: "People who give biospecimens help prevent diseases". Ratings are summed for a final attitude score. The scale includes both positively and negatively worded items. Positively worded items are reverse coded, as higher scores indicated more positive attitudes (Wells et al., 2014).

The knowledge scale consists of 16 items with categorical responses (*yes, no, don't know*). Many questions represent elements of informed consent for biobanking. For example, the item, "A person can stop being in a research study after giving a biospecimen", reflects the element of informed consent concerning the right to withdraw from a study. A knowledge score is obtained by counting the number of correct responses (raw score) and dividing the number of correct responses by the total number of items (% correct). "Don't know" responses are counted as incorrect. A higher number/percentage of correct responses indicates more knowledge about biobanking.

The 12-item self-efficiency scale uses a horizontal, segmented, numeric rating scale (*0 = Cannot Do to 10 = Highly Certain I Can Do*) to determine a participants' confidence in donating biospecimens under certain conditions. For example, "I think I could give a biospecimen to a biobank even if it is against my religious beliefs". Ratings are summed to create a self-efficacy score, with higher scores representing more confidence about donating biospecimens.

The remaining 3-single items in the BANKS tool ask about intentions to donate and receptivity to more information. As mothers had already made the decision about donation, these were not applicable to this study, and therefore were not included.

Influence of religious values on biobanking decisions. The Hoge Intrinsic Religiosity Motivation Scale (1972) was used to measure the influence of religious values on biobanking

decisions. It is a 10-item, 4 point Likert scale questionnaire that measures underlying religious motivations for behavior. Ratings are summed and averaged for a total intrinsic religiosity score. Negatively worded items are reversed scored so that a lower score is indicative of more intrinsic religious motivation (Hoge, 1972).

Personal Values. The Short Schwartz' Value Survey (SSVS) is a 10-item questionnaire that asks respondents to rate the importance of specific values as life-guiding principles using a Likert-like scale of 0-8 (*0= opposed to my principles, 8= of supreme importance*). This shortened version of the Schwartz's Value Survey (Schwartz 1992, 2012) was used to reduce participant burden, and has acceptable correlations values among similarly aged participants (e.g. college students) (correlations ranged from 0.45 to 0.70 across items; all p values < .001) (Lindeman & Verkasalo, 2005). The SSVS was used as a measure of the personal values that may be motivating respondents.

Ethical considerations

Approval to conduct this study was obtained from the institutional review boards (IRBs) of the university and MDHHS.

Data Analysis

Each returned survey was scored per the respective measurement tool instructions. Data were entered, checked for accuracy, and analyzed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA). First, descriptive statistics were used to analyze data from questions on the BANKS scales of knowledge, attitudes, and self-efficacy, the Hoge IRM scale, the SSVS and the demographic questionnaire. Normality of these continuous variables (i.e. knowledge, attitudes, self-efficacy, and religiosity scores) was assessed by visual inspection of histograms and the Shapiro-Wilk test. Attitude and religiosity scores differed

significantly from the normal distribution. Thus, t-tests were used to identify any significant differences between means for knowledge and self-efficacy scores and the Mann-Whitney U test was used to compare distributions of attitude and religiosity scores between mothers who agreed and those who declined. Chi Square tests were used to assess significant associations among categorical variables (e.g. demographics). Multivariate linear regression was conducted to identify significant factors contributing to increased knowledge.

The primary outcome variable was making an informed choice. The analysis of informed choice involved three variables (a) a decision (i.e. yes or no) about donating the rDBS (b) a knowledge scale score and (c) an attitude scale score. Only scales that were 100% complete were used in this analysis. Therefore, most analyses were run on a subset of data which required that each respondent had: (a) remembered her decision about donating the bloodspots (i.e. yes or no) and (b) completed the knowledge and (c) completed the attitude scale. A flow chart of survey respondents in the analysis of informed choices is presented (Figure 4). Next, knowledge and attitude scores were dichotomized to classify choices as informed or uninformed. The scale mid-point (i.e. 50%) for knowledge was used as the cutoff for adequate or inadequate knowledge and the mid-point of the attitude scale (range 14-70; mid-point 42) was used as the cut-off for positive or negative attitudes. Attitudes were then compared to the biobanking decision of the respondent for value consistency; positive attitudes with a decision to donate and negative attitudes with a decision not to donate were labelled as value consistent. Lastly, a forward logistic regression was performed to identify other factors such as age, education, parity, race, and religion that may have contributed to making an informed or uninformed choice. Missing values were reported (and not included) as indicated; no data were imputed. All tests are two-tailed, using $p = < 0.05$ to denote statistical significance.

Results

Of the 500 surveys, 16 were returned to MDHHS as undeliverable and 83 were returned to the PI, for an initial response rate of 17.2% (83/484). However, three envelopes were returned without any responses, for a useable returned sample of 80. Of these, 63 mothers (78.75%) reported having agreed to donate their newborn's blood spots for research; 9 (11.25%) declined; 8 (10.0%) did not recall their decision. The study sample mostly self-identified as of white race, with at least a high school education and between the ages of 26-45 years of age. More than three-quarter of the respondents had private insurance. The representation of primiparous and multiparous mothers in the study sample closely mirrored Michigan data (Table 12).

There were no significant differences in the demographic characteristics of mothers who agreed or declined to donate rDBS, likely due to the small number of decliners in the sample (n=9; 11.25%) (Table 13). Because of the small number of decliners, logistic regression was not able to be conducted to analyze the outcome of agree or disagree, which would have required a larger sample size for robust results (Peduzzi, Concato, Kemper, Holford, Feinstein, 1996). No significant differences in mean scores were noted on the knowledge and intrinsic religiosity scales between mothers who agreed or declined to donate their newborn blood spots for research purposes. However, there were significant differences in mean scores for attitudes (55 vs. 48, p=.036) and self-efficacy (72 vs. 40, p=.002), with decliners having lower scores (Table 14).

Knowledge

Overall, knowledge scores were low with a mean of 47% (i.e. fewer than 8/16 questions answered correctly). No significant difference was noted in the mean knowledge score between mothers who agreed or declined to donate (Table 14). However, mean knowledge scores were significantly higher among the 71 mothers' who remembered their donation decision (and

completed the knowledge scale; M= .49, SD.22) than among the seven mothers who did not remember their donation decisions (M=.22, SD.08) (degrees of freedom adjusted for unequal variances; *t* (17.25) = -6.91, p= <. 001, 95% confidence interval [-.36, -.19], *d*=.6).

Eighty percent of participants (n=64/78) correctly answered questions about not having to spend money to donate biospecimens and 82.5% (n=66) correctly answered the item that scientists must keep a person's information private when doing research. However, only 10% of the mothers' (n=8) knew that profit can potentially result from donated biospecimens, 21% (n=17) correctly indicated they would not necessarily be contacted about the risk of a disease, and approximately 1 in 5 (n=17; 21.3%) knew they could withdraw from a study after donating a biospecimen (Table 15). A backward elimination multiple regression revealed the two variables education (p=.002) and parity (p=.002) that best predicted knowledge scores (Table 16).

Attitudes and Values

Attitude data (Table 17) from mothers who agreed and mothers who did not agree to donate did not meet the assumption of normality and homogeneity of variances (Table 14). As such, a Mann-Whitney U test comparing rank order was conducted. Results indicated attitudes were significantly higher for mothers who agreed to donate blood spots compared to mothers who declined donation (U = 152.5, *p*=.036).

Self-efficacy scores also varied significantly between mothers who agreed to donate blood spots and those who declined (Table 14). Among participants who agreed to donate their newborn's blood spots, self-efficacy ratings were lowest on the item related to donating biospecimens even if it was against religious beliefs (Table 18). No relationships were noted between identifying a religious affiliation, or intrinsic religiously scores and agreeing or declining to donate blood spots (X^2= 0.571 (1) p=.708; X^2= 32.0 (34) p=.566, Fisher's Exact test

p= .741) or between personal values on the SSVS between those who agreed or declined to donate blood spots (Figure 5; Table 19). Achievement was rated as more important among those mothers who declined to donate their newborn's rDBS than among mothers who agreed to donate their newborn's rDBS (t (68) =1.996, p= .05, 95% confidence interval [.00, 2.2], d=.9 ; U = 160.0, p = .039).

Informed Choice

Using the MMIC, 55% (38/69) of mothers made an informed choice about rDBS donation and 45% made an uninformed choice (31/69). Six decisions (8.7%) were not consistent with positive attitudes toward biobanking, such that attitudes were classified as positive yet resulted in the mother declining to donate blood spots.

To ascertain effects of demographic characteristics on making an informed choice a forward selection logistic regression was performed (Table 20). Insurance status (a proxy for socioeconomic status) was not included due to the small sample size and collinearity with education (χ 2(1) = 24.514, p =< .001; r=.609, p= < .001). Six insurance responses were missing and cross tabulation showed no one with ≤ high school education had private insurance (i.e. data separation). All variables included in the logistic regression were categorical. The final logistic regression was statistically significant, χ2 (2) = 15.886, p= < .001 and included parity and education (Table 9) as factors influencing an informed choice. While statistically significant, (χ2 (2) = 15.886, p= < .001) the model only explained 21-28% of the variance (Peng, Lee, & Ingersoll, 2002) and correctly classified 71.0% of cases. Mothers with > high school education were 8.47 times (95% confidence interval [1.484, 48.302]) more likely to make an informed choice than those with ≤high school education. Multiparous mothers were 5.35 times more

likely to make an informed choice than were primiparous mothers (95% confidence interval [1.786,16.027]) (Table 20).

Discussion

This study provides a cross-sectional view of the biobanking knowledge, attitudes, and values of mothers who made a decision about donating their newborn's blood spots for research. Low knowledge scores were associated with nearly half of the participants making uniformed decisions. The knowledge scores are comparable to results from other studies on understanding informed consent for biobanking where low knowledge scores were found (Eisenhauer et al., 2017; Falagas, Korbila, Giannopoulou, Kondilis, & Peppas, 2009), and to prenatal screening studies that used the MMIC and found low knowledge to be a factor in uninformed choices (Gourounti, & Sandall, 2008; Marteau et al. 2001; Piechan et al. 2016; van den Berg et al., 2006). Similarly, Lehmann, de Melker, Timmermans, & Mollema (2017) found low knowledge scores among parents of at least one child between 3 months and 3.5 years of age who decided not to vaccinate their children.

While there is no gold standard of a passing score or cut-off for good knowledge of informed consent information, ideally, the participant should know all of the information pertaining to the required elements of informed consent (e.g. risk and benefits). However, due in part to a lack of information provided and limitations in the cognitive abilities or in attention, this is rarely the case (Sand et al., 2010). Nonetheless, participants should be able to demonstrate a good level of gist understanding, the understanding of risks and benefits of participation given one's personal values in real-life contexts (Reyna, 2008). Moreover, a minimal passing score for knowledge tests is needed to compare scores across studies (Eisenhauer et al., 2017). The field of education often uses an absolute score of 80% as passing on tests of mastery for subject-

matter, appropriate to demonstrate competence for a particular purpose (Guskey & Anderman, 2013; Norcini, 2003). Using the same educational standard of 80% only five mothers (7%) would have been be classified as having made an informed choice in the current study.

It is also important that potential participants have prerequisite knowledge to make an informed choice because this is the threshold set for participation in clinical research by the Nuremberg Code and the Declaration of Helsinki (Trials of War Criminals, 1949; World Medical Association, 2013). While setting a standard score always involves an element of judgement (Zieky, 2001), it reflects researchers' values and represents the level of knowledge that is deemed important for participants to be well informed before agreeing to participate in biobanking research. Low expectations of participant understanding may precipitate decisional regret (Wiggins, 2013). The BANKS knowledge test represents common elements of informed consent for biobanking, upon which experts have agreed are minimally required for participation (Beskow et al., 2015; Wells et al., 2014). Indeed, when elements are considered essential, scores of 100% are expected (Beskow, Lin, Dombeck, Gao, & Weinfurt, 2017) potentially making a minimal expectation of 80% unacceptable. Likewise, setting a passing rate for study participants (e.g. 80% of a sample answered the question correctly or passed the comprehension test) provides a similar benchmark that has been used in studies of informed consent (Falagas et al., 2009).

Gaps have been identified in the information about biobanking presented to potential research participants and to the public via the media and frequently involve the lack of disclosure about controversial uses for rDBS and other biospecimens (Caulfield, 2005; Eisenhauer et al., 2017; Ogbogu et al., 2014; Tomlinson et al., 2014). The focus of biobanking information is often on possible benefits to society, with a lack of focus on personal risks (Caulfield, 2005;

Eisenhauer et al., 2017; Ogbogu et al., 2014; Tomlinson et al., 2014). To be more balanced, information about biobanking should present both positive and potentially negative controversial outcomes. Given the insights provided by this research, potential research uses for rDBS, including potential threats to personal or religious values (e.g. exposure of private genetic data, prenatal genetic testing, predicting the future), should be described.

Limitations and Strengths

There were four primary limitations to this study: (1) a low response rate; (2) data obtained from only the state of Michigan, with a provision for opt-in consent; and (3) measurement limitations and (4) the use of categorical variables. The low response rate (17%) occurred despite sending a reminder postcard one week after the initial survey mailing and including a $2 honorarium. Because of financial limitations, larger incentives and repeated mailings were not feasible. Surveys were mailed to mothers who gave birth within the last 3 months in order to minimize recall bias. However, as new mothers are often tired and stressed, this may also have contributed to the low response rate. Moreover, only scales that were 100% complete were used in the analysis of informed choice further reducing the sample size. The response rate, however, is not unlike that in similar studies. Lehmann et al. (2017) for example, sent letters to 8000 parents inviting them to answer an online survey. Although these authors had a greater number of responses (1615 parents), their overall response rate was similar to that experienced in the current study (16.2%). The response rate from mothers who declined to participate in the BioTrust was also small. This small sample may represent a response bias and because survey was anonymous, data on non-respondents was not able to be collected. Further, the study sample was mostly White, and did not include responses from African Americans mothers. African Americans frequently decline to participate in research based on fear and

distrust given the history of past research abuses (Shavers-Hornaday, Lynch, Burmeister, & Torner, 1997). The sample was older, more educated, and somewhat less religious in comparison to state level data. Demographic differences may affect the generalizability of the data. A larger sample size would have also allowed for the creation of a neutral attitude category that may have more accurately reflected values (van den Berg, Timmermans, ten Kate, van Vugt, & van der Wal, 2005). While the results may not be generalizable the larger population, the findings provide insight on the knowledge, attitudes, and proportion of informed choices, especially among White mothers in Michigan who agreed to donate rDBS to the BioTrust. Moreover, the similarity of parity between the study data and the Michigan population give credence to the observation that parity influences knowledge and informed choices, suggesting that experience in making this decision matters.

Second, surveys were only mailed to mothers in Michigan. Fathers were not included and may have had different responses if surveyed. However, because Michigan is one of few states that offer an opt-in consent process for use of rDBS, this also a strength of the research, as it provides data on a unique situation.

Lastly, the MMIC required dichotomization of knowledge and attitude data and such classifications may have overlooked important gradations within the data (Dawson & Weiss, 2012). In an effort to make the demographic sheet easy for respondents to complete, check boxes were used and age was collected as a categorical variable which did not allow for analysis of it as continuous variable and, as such, differences may have been missed. A noted limitation of a quantitative approach is that the reasons for donating or declining to donate rDBS are not always obtainable from the survey questions asked. As such, a qualitative semi-structured interview study was also conducted and provides a source of rich detailed data for comparison

(Eisenhauer et al., 2018 unpublished data). Furthermore, while the MMIC is a reliable and valid rubric for informed choice, it is limited to the categories of knowledge, attitudes, and the participation decision, it may not have adequately captured the complexities of an informed choice, involving components such as appreciation, deliberation, and reasoning (Appelbaum & Grisso, 2001; Lehmann et al., 2017; Roth et al., 1977; van den Berg, et al., 2006). The use of standardized measures to assess biobanking knowledge, attitudes, self-efficacy, intrinsic religiosity, and personal values was an additional strength of the study as they make comparisons across studies more feasible, and have been under-utilized in studies on understanding informed consent for biobanking (Eisenhauer et al., 2017).

Recommendations and Future Work

Findings from this study indicate that low biobanking knowledge scores, the importance of values in biobanking decisions, and education and experience (i.e. parity) of the participants contribute to making an informed choice about biobanking. Therefore, the following recommendations are put forth**:**

1. Education about NBS and research use of rDBS along with the consent request should be moved to the prenatal environment. This would provide parents more time to consider biobanking information, deliberate, and discuss their decision, which may aid in making informed choices, based on our data, especially, for first time mothers (American College of Obstetricians and Gynecologists, 2015; American Academy of Pediatrics, 2000, 2008; Botkin et al., 2016; van den Berg et al., 2006). There are a host of distractions and other important decisions to make in the postpartum environment (Lowe, 2004; Torres & De Vries, 2009) that may impede informed consent for biobanking.

2. Evidence-based decision aids that include more balanced information and value-clarification exercises (Stacey et al., 2017) should be developed and certified using International Patient Decision Aid standards (IPDAS, 2013), and evaluated by third parties, not invested in recruiting biobank participants, to help ensure that information provided is not biased. Currently, consent forms, information brochures, and educational materials are written by MDHHS and may be biased in favor of biobanking because the state government has decided biobanking is a good investment in public health. Implementing standardized tools designed to elicit and clarify values will help to provide appropriate, tailored information to each potential participant. Decision aids have been shown to be effective in improving informed choices other preference-based healthcare decisions (Stacey et al., 2017).

3. A standardized assessment of participant understanding needs to be implemented at each biobanking consent encounter. While there are a plethora of instruments available to assess individual understanding, they are rarely used in clinical settings (Dunn, Nowrangi, Palmer, Jeste, & Saks, 2006). If an instrument is not used, understanding may not be ensured.

4. A standard passing score for knowledge tests needs to be agreed upon for studies of understanding informed consent in order to make accurate comparisons across studies. While we used a passing score of 50% to classify informed choices for this study based on instrument scoring instructions, we also offered support from the literature for using 80% as the cut-off which would have dramatically reduced the proportion of informed choices.

Future work should include follow-up studies to examine the effects of content and context of biobanking education on informed choices. Additional research on the role of values in decision-making about biobanking is also needed. Likewise, the credentials, education, and training of consenters need further study as the skills and perceptions of the person obtaining

consent influences biobanking decisions (Eisenhauer et al., 2017; Hoeyer, 2003). Valid and reliable instruments are needed to assess consenters' skills, and the degree to which organizations, including state health departments, facilitate informed choices by structuring processes in a truly patient centered fashion (Rudd, 2014). Finally, different analytic approaches of passing scores requires further psychometric testing, including exploring alternative scoring methods such as formula scoring (Nunnally & Bernstein, 1994), receiver operating characteristic curve analysis, sensitivity and specificity testing (see e.g. Jeste et al., 2007), and other techniques comparing test scores against the judgment of human experts such as the Angoff method (1971). While these techniques are beyond the scope of the current manuscript, they are essential for further research on creating a standard of study knowledge for informed consent.

Conclusion

This study examined mothers' of newborns level of biobanking knowledge, attitudes, and personal and religious values, and determined the proportion of informed choices using established standardized measures. Findings indicated that knowledge scores were low, attitudes toward rDBS were positive, and just over half of the mothers' decisions were classified as informed choices. Given the widespread lack of knowledge, it is important to examine the process of biobanking education and make procedural changes to facilitate informed choice. Effective interventions such as transferring education about research on rDBS from the postpartum period to the prenatal period, and the use of decision aids that incorporate value-based information, must be developed and implemented.

Table 11. Psychometric characteristics of measures

Citation	Instrument	Variables	#/Items	Reliability & Validity
Wells et al., 2014	Biobanking attitudes and knowledge survey (BANKS)	Biobanking Knowledge Attitudes Behavioral skills (Self-Efficacy)	45 items total (42 included) (3 additional single-item measures not applicable to current study)	Cronbach's alpha Attitudes= 0.88 Self-efficacy=0.95
Hoge, 1972	Intrinsic Religious Motivation Scale	Religious values	10-items Intrinsic Religious Motivation Scale	Kuder-Richardson formula 20 =0.901
Lindeman & Verkasalo, 2005	Short Schwartz's Value Survey – SSVS	Personal values	10-items about personal values	Intraclass correlations 0.34-0.77

Table 12. Demographic Characteristics of All Survey Respondents (n=80) and Michigan Comparison Data

Variable	n (%)	Michigan Comparison Data [e]	
Donation Decision		Donation Decision	
No	9 (11.3)	No	19%
Yes	63 (78.8)	Yes	66%
Don't Remember	8 (10.0)	No Signature	14%
Age		Age	
18-25	10 (12.5)	18-24	27.7%
26-45	70 (87.5)	25-40+	70.6%
Level of Education [a]		Level of Education	
4th-12 Grade	3 (3.8)	<HS	11.7%
HS or GED	9 (11.3)	HS Grad/GED	24.1%
Some College or Vocational School	11 (13.8)	Some College	33.5%
Associate's Degree	11 (13.8)	College Degree +	30.7%
Bachelor's Degree	32 (40.0)		
Master's Degree	8 (10.0)		
PhD/ Professional	6 (7.5)		
Insurance Status [c]		Insurance Status	
Public	16 (20.0)	Public	29.5%
Private	58 (72.5)	Private	54.2%
Religiously Affiliated [d]		Religiously Affiliated	
No	26 (32.5)	No	24%
Yes	54 (67.5)	Yes	75%
Race [b]		Race	
Asian	2 (2.5)	Asian	2.4%
African American/ Black	2 (2.5)	African American/Black	17.8%
Hispanic or Latino	5 (6.3)	Hispanic or Latino	5.6%
White	69 (86.3)	White	70.2%
Other	2 (2.5)	Other	3.9%
Number of Births			
Primiparous	33 (41.3)		41.2%
Multiparous	47 (58.8)		58.8%

[a, b] Variables were collapsed for further analysis due to small cell counts (i.e. race: non-white or white; education: ≤ high school (HS) or > HS). [c] insurance: proxy for socioeconomic status; n=74; three missing responses and 3 responses of "both" (not included in analysis). [d] Identified religions: Catholic (n=16) or Protestant (n=31) Christians; Other (n=2); Not Specified (n=5). Total percentages may not equal 100 due to rounding. [e] Michigan Comparison Data sources: MDHHS, 2016 as cited by Rothwell et al., 2017 ; Haak, Paciorek,,Sauter, (2017). Michigan PRAMS Data Tables 2014; Pew Research Center: Religion & Public Life. (2017). Religious Landscape Study: Adults in Michigan. Retrieved from http://www.pewforum.org/religious-landscape-study/state/michigan/#

Table 13. Demographics and decisions to donate blood spots (n=72)

Variable	Agreed n=63 n (%)	Declined n=9 n (%)	Test*
Age			
18-25	10 (15.9)	0 (0)	
26-45	53 (84.1)	9 (100.0)	*p*=.343
Level of Education			
≤HS	11 (15.3)	0 (0)	
>HS	52 (84.7)	9 (100.0)	*p*=.337
Insurance Status (n=66) [c]			
Public	12 (21.1)	2 (22.2)	
Private	45 (78.9)	7 (77.8)	*p*=1.0
Religious Affiliation [d]			
No	22 (34.9)	2 (22.2)	
Yes	41 (65.1)	7 (77.8)	*p*=.708
Race [b]			
White (only)	54 (85.7)	8(88.9)	
Other	9 (14.3)	1(11.1)	*p*=1.0
Number of Births (includes current birth)			
Primiparous	27 (42.9)	2 (22.2)	
Multiparous	36 (57.1)	7 (78.8)	*p*=.297

*All 2x2 chi squared tests p values are based on Fisher's Exact test due to some cells with counts < 5.
[c]Insurance status: proxy for socioeconomic status; n=66 (8.3% missing data): 3 missing responses and 3 responses of "both" not included in analysis.

Table 14. Mean differences in continuous scored variables according to mothers' decision to donate blood spots

Variable		Overall (N=80)		Shapiro -Wilk	Donation Decision						Test			95% Confidence Interval of the Difference	
					Agreed (N=63)			Declined (N=9)							
	n	Mean	SD	Sig.	*n*	Mean	SD	*n*	Mean	SD	t	df	Sig. (2-tailed)	Lower	Upper
BK %	78	0.47	0.22	.068	62	0.49	0.22	*9*	0.49	0.19	-0.061	69	.951	-0.16	0.15
BK # correct	78	7.45	3.56	.067	62	7.85	3.55	9	7.78	3.07	-0.062	69	.951	-2.57	2.41
*BA score	75	53.83	7.36	.012	60	55.13	5.92	9	47.67	10.95	-2.002	8.71	.077*	-15.95	1.02
BSE score	74	67.31	30.41	.132	58	72.00	26.93	9	39.56	33.53	-3.254	65	.002	-52.36	-12.53
**HIR score	72	2.85	1.17	.007	56	2.93	1.191	8	2.40	1.36	-1.158	62	.251	-1.45	0.39

Note: BK=BANKS Knowledge scale; potential range 0-100% or 0-16 correct questions. BA=BANKS attitude scale; potential range 14-70; higher score =more positive attitude toward biobanking. BSE= BANKS Self-efficacy scale potential range 0-100 higher score=more self-efficacy in donating biospecimens. HIR= Hoge (1972) intrinsic religiosity scale; potential range 1-5; lower score =more intrinsic religiosity. * Banks Attitude score is ordinal, Likert scale data. Levene's Test for Equality of Variances: F=7.679 p=.007, thus table reports equal variances not assumed; if assumed: *t* (67) = -3.109, p=.003, 95% confidence interval [-12.261, -2.673]; Mann Whitney U test for ranks significant for attitudes: U = 152.5, *p* = .036. **Mann Whitney U test not significant for HIR: U=165.00 p=.231.

Table 15. BANKS (Wells et al. 2014), knowledge scores by item.

BANKS-knowledge scale (*N*=78) Mean 46.5% SD 0.22 Range 0-94%				
Item	Yes, *n* (%)	No, *n* (%)	Do not know, *n* (%)	Missing *n* (%)
1. A person has to spend money to give a biospecimen	2 (2.5)	**64 (80.0)**	14 (17.5)	0 (0.0)
2. Anyone can access the biospecimens people give	1 (1.3)	**52 (65.0)**	27 (33.8)	0 (0.0)
3. Research results from biospecimens will show up in medical records	4 (5.0)	**39 (48.8)**	37 (46.3)	0 (0.0)
4. Biospecimens given to a biobank will be sold to drug companies	5 (6.3)	**22 (27.5)**	53 (66.3)	0 (0.0)
5. A scientist must keep a person's information private when doing research	**66 (82.5)**	0 (0.0)	14 (17.5)	0 (0.0)
6. The biospecimens people give can be sent to any organization that requests them	13 (16.3)	**34 (42.5)**	33 (41.3)	0 (0.0)
7. Police departments can legally get the biospecimens a person gives	10 (12.5)	**25 (31.3)**	45 (56.3)	0 (0.0)
8. Biospecimens given to a biobank can be sold to anyone	4 (5.0)	**49 (61.3)**	27 (33.8)	0 (0.0)
9. Insurance companies can legally get the biospecimens a person gives	1 (1.3)	**41 (51.3)**	38 (47.5)	0 (0.0)
10. Researchers will always contact people if their biospecimens show risk for a disease	17 (21.3)	**17 (21.3)**	46 (57.5)	0 (0.0)
11. A person's family can get information about the biospecimens a person gives	5 (6.3)	**34 (42.5)**	41 (51.3)	0 (0.0)
12. People can make money from donated biospecimens	**8 (10.0)**	33 (41.3)	39 (48.8)	0 (0.0)
13. People no longer own their biospecimens after they give them to a biobank	**31 (38.8)**	7 (8.8)	42 (52.5)	0 (0.0)
14. After a person gives a biospecimen to a biobank, she/he can get it back	5 (6.3)	**39 (48.8)**	36 (45.0)	0 (0.0)
15. A person might be cloned if he/she donates a biospecimen to a biobank	2 (2.5)	**52 (65.0)**	25 (31.3)	1 (1.3)
16. A person can stop being in a research study after giving a biospecimen	**17 (21.3)**	18 (22.5)	44(55.0)	1 (1.3)

Note: Correct answers in **Bold** font

Table 16. Multiple linear regression model of on outcome of biobanking knowledge scores[a]

Model	Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B		Collinearity Statistics	
	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound	Tolerance	VIF
(Constant)	.226	.065		3.465	.001	.096	.357		
Education	.205	.063	.344	3.239	.002	.079	.331	.998	1.002
Parity	.153	.047	.350	3.292	.002	.060	.246	.998	1.002

a Non-significant variables included age, race, and religion. Model fit: F(2, 68) = 10.262, p= < .001, R=.481, R2 = .232, Adjusted R 2=.209

Table 17. BANKS (Wells et al., 2014) attitude results by item. (Most frequent response in **bold**)

BANKS-Attitude scale (*N*=75) Mean 53.8 SD 7.4 Range 31-70						
Item	Strongly Agree *n* (%)	Agree *n* (%)	Neither Agree nor Disagree *n* (%)	Disagree *n* (%)	Strongly Disagree *n* (%)	Missing *n* (%)
1. Giving a biospecimen is for the greater good of society	29 (36.3)	**30 (37.5)**	18 (22.5)	2 (2.5)	0 (0.0)	1 (1.3)
2. People who give biospecimens help prevent diseases	25 (31.3)	**41 (51.3)**	12 (15.0)	1 (1.3)	0 (0.0)	1 (1.3)
3. People who give biospecimens help cure diseases	23 (28.8)	**36 (45.0)**	19 (23.8)	2 (2.5)	0 (0.0)	0 (0.0)
4. Giving a biospecimen is a waste of a person's time	1 (1.3)	1 (1.3)	6 (7.5)	**40 (50.0)**	32 (40.0)	0 (0.0)
5. Giving a biospecimen will help future generations	29 (36.3)	**41 (51.3)**	9 (11.3)	0 (0.0)	1 (1.3)	0 (0.0)
6. Giving a biospecimen gets in the way of a person's medical care	5 (6.3)	0 (0.0)	10 (12.5)	28 (35.0)	**37 (46.3)**	0 (0.0)
7. Giving a biospecimen will help a person's family	11 (13.8)	**34 (42.5)**	30 (37.5)	5 (6.3)	0 (0.0)	0 (0.0)
8. Medical information is unlikely to be stolen from a biobank	7 (8.8)	**33 (41.3)**	26 (32.5)	7 (8.8)	5 (6.3)	2 (2.5)
9. Giving blood to a biobank is a good way to help cancer research	18 (22.5)	**53 (65.0)**	8 (10.0)	2 (2.5)	0 (0.0)	0 (0.0)
10. Personal information is unlikely to be stolen from a biobank	9 (11.3)	**35 (43.8)**	24 (30.0)	6 (7.5)	6 (7.5)	0 (0.0)
11. A person's family medical information is safe in a biobank	8 (10.0)	**38 (47.5)**	27 (33.8)	6 (7.5)	1 (1.3)	0 (0.0)
12. Biospecimens that people donate might be used for purposes they do not want	7 (8.8)	18 (22.5)	**28 (35.0)**	22 (27.5)	4 (5.0)	1 (1.3)
13. A person should not donate biospecimens because it may identify health problems	0 (0.0)	2 (2.5)	7 (8.8)	**44 (55.0)**	25 (31.3)	2 (2.5)
14. Giving biospecimens to a biobank may lead to more health care costs	3 (3.8)	4 (5.0)	20 (25.0)	**40 (50.0)**	11 (13.8)	0 (0.0)

Table 18. BANKS (Wells et al., 2014) self-efficacy results related to values according to mothers decision to donate blood spots

Question	Agreed			Declined			Test		95% CI		
	n[1]	Mean	SD	*n*	Mean	SD	*t* (df)	*p*	*LL*	*UL*	*d*
6. I think I could give a biospecimen to a biobank even if it is against my cultural beliefs	63	4.95	3.37	9	1.22	3.31	-3.11 (70)	.003	-6.12	-1.34	2.04
8. I think I could give a biospecimen to a biobank even if I am worried about how it will be used	62	4.74	2.98	9	1.22	1.99	-3.43 (69)	.001	-5.57	-1.47	2.08
11. I think I could give a biospecimen to a biobank even if it is against my religious beliefs	62	4.10	3.39	9	1.33	3.32	-2.29 (69)	.025	-5.17	-.360	1.5

BANKS self-efficacy scale ranges from 0 (*low self-efficacy*) to 10 (*high self-efficacy*). Data drawn from subset of mothers who recalled their donation decision (*n*=72). [1]*n* varies due to missing responses. SD=Standard Deviation. CI=Confidence Interval. LL=Lower Limit, UL= Upper Limit. Levine tests for homogeneity of the variance were non-significant; accordingly, table reports *p* values for equal variances assumed. Because data for each question failed to meet assumption of normality, non-parametric test (Mann Whitney U) was also conducted: question 6: U=97.5, p=.001; question 8: U=88.0, p=.001; question 11: U=126.0, p=.007.

Table 19. Ratings of personal values using The Short Schwartz Value Survey [SSVS] (Lindeman & Verkasalo, 2005)

	Declined Mean (n=9)	SD	Agreed Mean (n=62)	SD	t-test
Power	3.33	1.225	3.53	1.576	t=-.362(69) p=.718
Achievement*	6.44	1.13	5.34*	1.59	t=1.996 (68) p=.050
Hedonism	4.89	2.522	4.13	2.012	t= 1.025(69) p=.309
Stimulation	5.11	1.764	4.31	1.896	t=1.199(69) p=.234
Self-Direction	6.56	0.882	5.97	1.679	t=1.026 (69) p=.309
Universalism	6.56	1.236	5.56	2.046	t=1.411(69) p=.163
Benevolence	7.78	0.441	6.98	1.732	t=1.361(69)p= .178
Tradition	6.11	2.522	5.66	1.708	t=.693 (69) p=.491
Conformity	5.78	2.279	5.21	2.136	t= .740 (69)p= .462
Security	6.00	2.179	5.69	1.77	t=.471 (69)p=.639

SD=Std. Deviation * 61 valid responses for Agreed and Achievement, p=0.05.
Total n= 71/72 mothers who remembered donation decision (yes/no) and completed the Short Schwartz Value Survey (one person left entire scale blank).

Table 20. Final forward logistic regression model of age, education, number of births, race, and religion on outcome of informed choice[a]

Variables[b]		B	S.E.	Wald	df	*p*	Odds Ratio (OR)	95% C.I. for OR	
								Lower	Upper
	Education	2.136	.888	5.781	1	.016	8.467	1.484	48.302
	Parity	1.677	.560	8.978	1	.003	5.351	1.786	16.027
	Constant	-2.588	.941	7.564	1	.006	.075		

[a]Not significant/Not included in model: age (0=18-25; 1=26-45) religion (0=no affiliation; 1=identified affiliation), race (0= non-White; 1=White). [b]Education (0= ≤high school; 1=>high school), Parity 0= primiparous; 1= multiparous.

Figure 4. Flow chart of survey respondents and subset of data for analysis of informed choice (based on Moher et al., 2010)

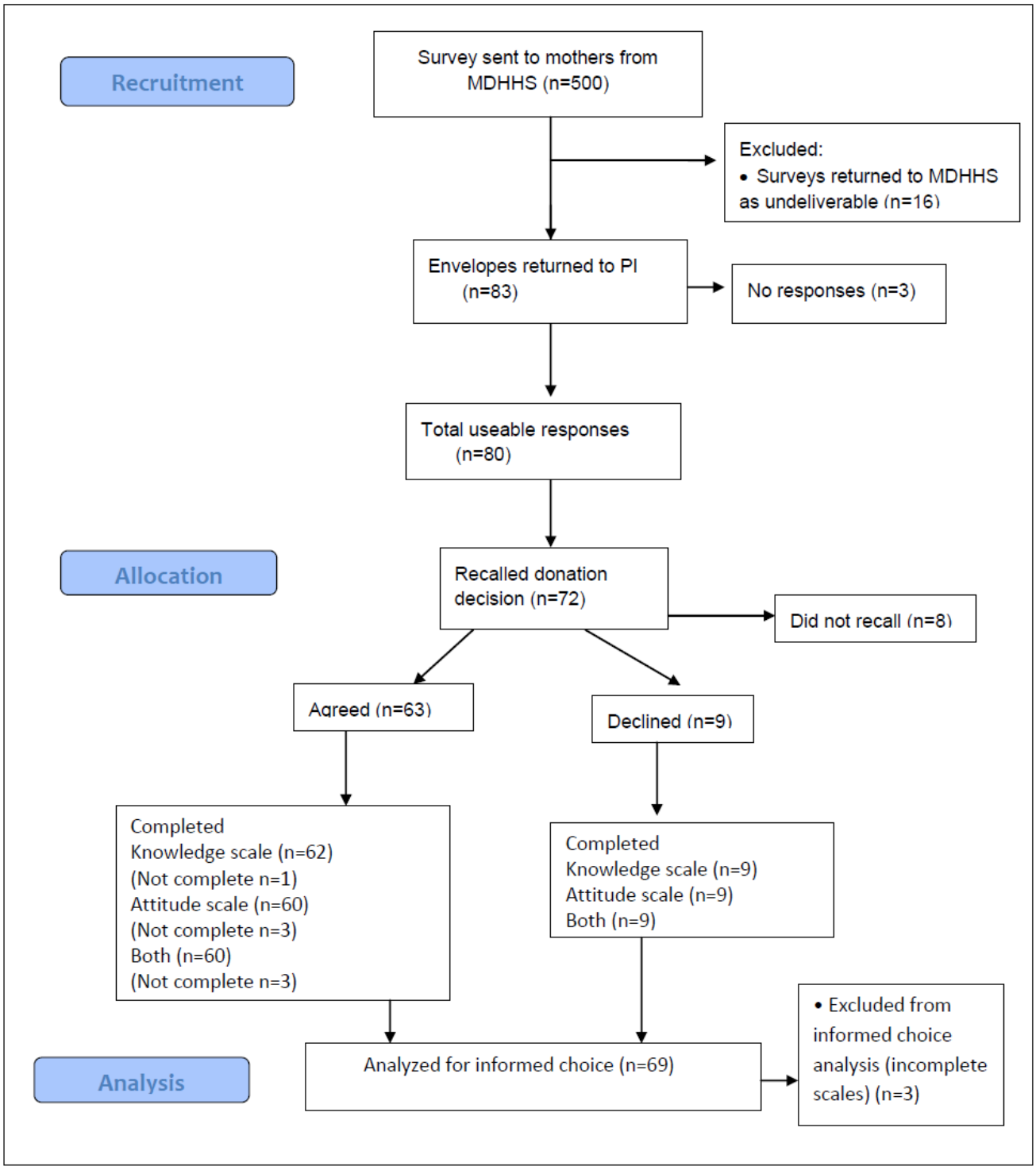
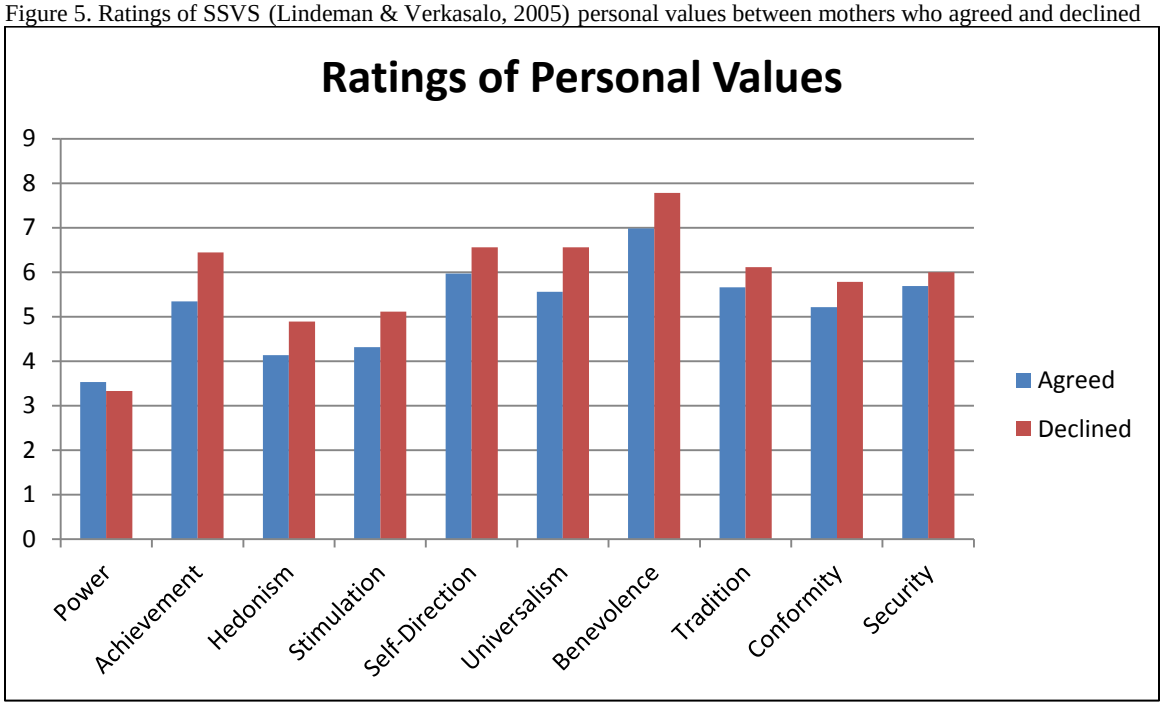


Figure 5. Ratings of SSVS (Lindeman & Verkasalo, 2005) personal values between mothers who agreed and declined



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Chapter 5 Discussion

This dissertation examined the understanding of information presented to mothers who made a decision about donating their newborn's rDBS for research and the influence of knowledge, attitudes, and values on making an informed decision about participation in biobanking. The study designs used in Chapters 3 and 4 built on recommendations from the literature review that studies on understanding informed consent a) be conducted by non-biobank associated researchers, b) examine actual choices in real-time, c) use standardized instruments, and d) establish a threshold for defining adequate understanding and informed choice.

Current Federal Policy

In 2011 the Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) reviewed issues involving the use of rDBS and aimed to lay the foundation for national guidelines (Therrell et al., 2011). Policy recommendations have fallen short (Tarini, 2011) and have not yet adequately addressed the issue. Arguably, the quandaries have only increased since the SACHDNC recommendations. To date, state laws about the storage and parental consent for research use of rDBS, remain inadequate, fragmented, and confusing (Genetic Alliance, 2018; Lewis, Goldenberg, Anderson, Rothwell, & Botkin, 2011). Furthermore, federal legislation, The Newborn Screening Saves Lives Reauthorization Act of 2014, required parental consent for federally funded research with newborn rDBS and prohibited IRBs from waiving consent. However, the protections under this law will no longer be effective if recent changes to the Common Rule are implemented as

planned (Federal Policy for the Protection of Human Subjects, 2017, 2018). With 4 million American newborns having blood spots collected each year, this as an important issue to address.

Policy Implications and Recommendations

If changes in the federal laws reverse previous policy protections, parents may lose trust in the research enterprise, and this may also potentially jeopardize trust in related the newborn screening process (Institute of Medicine Roundtable on Translating Genomic-Based Research for Health, 2010). Parental concerns regarding rDBS being collected, stored, and distributed for research have already resulted in litigation in Minnesota and Texas (Carmichael, 2011) and more recently in Indiana (Stafford, 2017) and Michigan (Reynolds, 2018).

This dissertation research provides evidence that the current consent process is inadequate, as it does not always facilitate making informed decisions about donating rDBS for research. Yet, it is known that parents want to be asked permission before their newborns' rDBS are used for research (Tarini et al., 2009). Therefore, a meaningful consent process that facilitates informed decision-making must be developed that takes into account participants' knowledge, attitudes, values, and the context of decision-making. Findings from this research support the need to enhance the type, depth and clarity of information provided to participants, the process of consent and context in which the consent occurs, as well as, the training of the consenter. As such, three specific recommendations are put forth: a) biobanking educational materials need to be more comprehensive, tailored to individuals' needs and values, and include the ethical implications of the research; b) consenters' knowledge about rDBS research and their communication skills for conducting informed consent processes must be enhanced, and c) the educational content about rDBS research should be moved from the postpartum unit into the prenatal setting. Each recommendation is discussed further below.

Recommendation: Tailored Biobanking Educational Materials

An overarching finding from this dissertation research was lack of knowledge and understanding about biobanking among many of the participants. The systematic review of the literature examining participants' understanding of informed consent for biobanking revealed that elements of informed consent, especially those unique to biobanking (e.g., the genetic nature of the research, storage of DNA, and the risks associated with such research) were often poorly understood. These findings are consistent with research examining understanding of informed consent for traditional clinical trials and treatments that have shown many participants have difficulty understanding consent information (Cohn & Larson, 2007; Falagas et al., 2009; Flory & Emanuel, 2004; Nishimura et al., 2013). Because attitudes, beliefs, and values interact with knowledge (Rokeach, 1979) and participant knowledge about biobanking was poor overall, the full extent of the influence from values remains unclear. Inasmuch as value-based information is not often provided to or discussed with individuals considering biobanking (Eisenhauer et al., 2017), some individuals may not make important associations between research uses for biospecimens and personal values (Tomlinson et al., 2015), consistent with qualitative findings from this dissertation research.

Likewise, knowledge of the Michigan BioTrust for Health and biobanking was poor among many the participants in the qualitative and quantitative components of this dissertation research study. When mothers were asked in semi-structured interviews to describe the Michigan BioTrust the majority indicated they did not know anything about it. Similar responses were noted when asked to describe biobanking. Lack of knowledge was also exhibited in the form of misunderstandings about the credentials of the consenter, the identifiability of the

biospecimens, the entity conducting the research, and the need for an additional heel stick for the biospecimen.

Gaps in information provided to mothers' were noted. First, while the blood spot card was created by MDHHS in collaboration with the Office of Human Research Protections (OHRP) and reportedly contains all eight required elements of informed consent (Rothwell et al., 2017), it did not include value-based guidelines or ethical comparisons for types of research to be conducted or laboratory methods used, even though comparisons and value-based information are relevant to understanding (Brehaut, 2012; Tomlinson et al., 2014; 2015). Definitions and explanations of key terms were also absent (e.g. DNA, low risk). Further the distinction between newborn screening and experimental blood spot research was not made clear. A recent focus group study (N=69) spanning three states indicated individuals found information on the blood spot card confusing (Rothwell et al., 2017). While these elements are further explained in the MDHHS brochure, several mothers in this dissertation study reported not having read it. During the observations of the consent process, the brochure was not observed being used by the consenter in the discussion with the mothers.

No information on potentially controversial research was observed being provided to individuals at the time of decision-making. This gap in the process is consistent with studies of informed consent that do not report disclosing controversial ethical information to potential participants, and therefore, do not assess understanding of it (Eisenhauer et al., 2017). If individuals are given clear examples of both non-controversial (e.g. advancing cancer treatment) and controversial research (e.g. substance abuse surveillance, advancing prenatal genetic testing), it may be found that biobanking decisions will be more congruent with personal values, and therefore decisions are more informed. In turn, there may be less decisional regret and moral

distress, increased trust in research, and the information disclosed would convey a respect for human dignity, by providing information to allow each individual to make an informed decision. Knowing this will guide the development of interventions to improve understanding, facilitate informed choices, uphold values, and preserve the public's trust. A recent study by Tomlinson et al., (2015) showed that when U.S. adults (aged ≥18 years) were first asked if they would donate biospecimens to a hypothetical biobank and permit the biobank to "use [their biospecimens] for any research study that it allows, without further consent" (p. 417); 68% of individuals agreed. However, when they were given explicit examples about biospecimen use for abortion research, patents and profits, and genetic links to violence, significantly fewer individuals were willing to donate (49.5 %, 55.2%, 58.1% respectively, p=. <001), indicating this information was important for many individuals and influenced their decisions. Decisions may be made differently in different contexts; based solely on knowledge or attitudes alone, or by a complex combination of both; value tradeoffs may be necessary (Graham & Wiener, 1995). However, even if ethical information does not determine the participation decision, it may be germane to informed decision-making for a substantial number of individuals (Tomlinson et al., 2014, 2015).

Tailoring information refers to delivering specific information to each person, based on his or her unique characteristics (e.g. age, cognitive capacity, educational level, religion, values) related to the outcome of interest, and derived from an individual level assessment (Kreuter & Skinner, 2000) and may help to increase informed decision-making. Li et al. (2016) demonstrated that values, beliefs, context, and personality influenced the types and amounts of information parents need to make informed decision about genetic sequencing for their children. One way to tailor informed consent information to the values and needs of individuals is through the use of evidence based decision aids (Stacey et al., 2017). Decision aids, based on

standardized criteria, emphasize the importance of patient values in making health related decision. Paradoxically, implementing such a standardized decision aid may facilitate the provision of tailored information based on what is meaningful to the patient via the use of an explicit value-elicitation and clarification process, and result in personalized recommendations based on expressed preferences (Stacey et al., 2017).

Evidence-based decision-aids for donation of rDBS and other biobanking research need to be developed, endorsed, tested and nationally standardized. Currently, consent forms and information brochures are written by MDHHS and may be biased in favor of biobanking because the state government has deemed this is a good investment in public health. To help ensure that information provided is accurate, objective and unbiased, decision aids should be developed using International Patient Decision Aid Standards (IPDAS, 2013) and evaluated by third parties, who are not involved with recruiting potential biobank participants. Evidence-based decision-aids have been shown to be effective in improving the quality of other preference-based healthcare decisions (Stacey et al., 2017). While decision aids (Stacey et al., 2017) and other multimedia (e.g. DVDs, computer modules; Henry et al., 2009) may help deliver personal and relevant biobanking information, multimedia aids should only be used as an adjunct to personal communication, as extended discussion with a knowledgeable person has been found to be the most efficacious intervention to aid understanding of consent information (Flory & Emanuel, 2004; Nishimura et al., 2013).

The overall results regarding biobanking knowledge indicate additional education about genetics, genomics, and biobanking is necessary for parents and consenters. However, while knowledge is an important prerequisite for understanding, increasing individual knowledge alone may not increase the proportion of individuals making informed decisions. Increasing individual

level knowledge via traditional patient education is only one piece of current health literacy recommendations (Rudd, 2014).

Recommendation: Enhanced Consenter Training

Education, training, and communication skills of the consenter are crucial elements of the consent process (Cohn et al., 2011). The consenter observed in this research possessed misunderstandings. For example, the consenter used the word anonymous to describe blood spot research. Blood spots are de-identified and coded when distributed to researchers, but can be identified by MDHHS, and therefore are not anonymous, thereby indicating a need for additional training.

While the MDHHS does provide periodic training to personnel at birth hospitals (Langbo et al., 2013; including at the hospital where consent was observed), the extent and frequency of this training is unknown. Educational efforts have evolved to include an online module with an optional certificate of completion (MDHHS, 2016), however it remains unclear whether these trainings are required, how compliance is monitored, how evaluation of consenters' skills is conducted, or if there are minimum educational requirements for consenters. The consenter in this study was a member of the ancillary nursing support staff. The job posting indicates the minimum requirement for this role is a high school diploma with an associate's degree preferred. Formal human subjects' training, such as that provided by the National Institutes of Health (NIH, 2016) should certainly be required before any healthcare personnel conduct an informed consent process, and updated annually. However, beyond the basic ethical principles of informed consent, consenters need on-going training and up-to-date knowledge of biobanking and rDBS research. In addition, the delivery of consent information requires assessment skills, advanced communication skills, provisions of comparisons, and value-clarification techniques (Brehaut et

al., 2012). Therefore, content of training for consenters needs to include information about the nuanced complexities of genetics and genomic science and not only general elements of informed consent, but those ethical, legal, and social issues unique to biobanking and rDBS research including (e.g. the return of results, the difference between newborn screening results and research results, coded versus anonymous research, genetic privacy and moral risks). Consenters' knowledge in these areas should be tested and competency demonstrated before conducting consent for rDBS research with patients.

Consenters need also need communication skills including decision support skills and values clarification techniques; they need to be able to engage the potential participant in dialogue, help them ask questions, answer their questions, and provide empathetic and non-judgmental support, and respect for a diversity of values and beliefs. These skills need to be practiced in role-playing scenarios and simulation activities in order to be well developed. The informational brochure may need to be read aloud to the potential participant to ensure adequate information is provided and discussed. The Ottawa Decision Support Tutorial (O'Connor, Stacey, & Boland, 2015) has been used as a guide in shared decision-making for patients' making decisions about genomic sequencing for their children (Li et al., 2016). The guide was designed to be used in skill-building workshops to improve healthcare providers' knowledge of decision support and shared decision-making techniques including provider communication and value clarification techniques (O'Connor et al., 2015). This guide may be a useful tool in training consenter for rDBS research. However, many licensed health-care providers lack knowledge of and confidence in communicating genetic information (Guttmacher, Porteous, & McInerney, 2007). Thus, expecting unlicensed personnel to conduct meaningful informed consent processes for complex genetic and genomic research including rDBS research without additional focused

training in the aforementioned areas may be unrealistic. If the consenter is not adequately informed, this person will be poorly equipped to answer questions and engage in knowledge based discussions with potential participants.

Recommendation: Employing Nurses as Consenters

While the consenter in the qualitative study was not a nurse and did not introduce herself as a nurse, the credentials (or the perception of credentials), communication skills, and actions of the consenter may have influenced understanding and decision-making about biobanking research participation (Eisenhauer et al., 2017). Further, because of the high degree of public trust in nurses (Norman, 2016), perceiving the consenter to be a nurse may have influenced mothers' decisions to donate their newborn's rDBS for research purposes (Hoeyer, 2003). While trust in the consenter or institution conducting the research may motivate an individual to participate in biobanking, trust should not be conflated with objective understanding of information (e.g. risks and benefits) (Fisher & Fisher, 2000).

Because of their special preparation and knowledge nurses are in a position to assume roles in which they conduct the consent process (Hastings et al. 2012). However, some nurses may also lack adequate knowledge and understanding of biobanking, genetics and genomics and the ethical implications involved (Badzek, Henaghan, Turner & Monsen, 2013; Sanner, Yu, Udtha, & Williams, 2013). As the field of genetics and genomics continues to grow, nurses are obtaining more education on these issues through nursing schools, continuing education, and other national opportunities (e.g., Summer Genetics Institute (SGI) sponsored by the National Institute of Nursing Research [NINR, 2017]). Biobanking and genetic research is an important area of science where nursing can and should lead as patient advocates. This needs to occur at the individual, organizational, and governmental policy level (Badzek et al., 2013).

There are several reasons to promote nurses to act as consenters. Nurses are educated in therapeutic communication techniques, know how to assess patients' values, attitudes and understanding, and advocate for patients prior to health related decisions (Bu & Jezewski, 2007). While it may be difficult to ensure decisions are not based on trust alone, asking potential study participants to articulate their reasons for participation can help clarify motivations and patient needs (Penckofer, Byrn, Mumby, & Ferrans, 2011). Tools developed by nurses to assist in providing clear communication and adequate information should be used in the informed consent process (Cohn et al., 2011). To advocate for consumers, in 2018 the American Academy of Nursing issued a policy brief calling for an increase in government oversight of private profit companies that offer direct-to consumer (DTC) genetic testing (Starkweather et al., 2018). In addition, the American Academy of Nursing warned of exploitation of consumers by these companies due to use of uncertified laboratories, lack of appropriate information about the meaning of test results, and the risk of genetic privacy violations and discrimination because DTC companies may sell consumers' genetic data (Starkweather et al., 2018).

Process

A very brief consent process was observed for the donation of rDBS to the BioTrust; limited information was provided and decisions were rendered quickly, often without much deliberation. This likely contributed to several misunderstandings including who was conducting the research and the level of identifiability of the rDBS. Importantly, it was the MDHHS asking to collect, store, and distribute the rDBS for research, not the hospital or the university. Mothers may have had different levels of trust for the MDHHS than for the hospital or its associated university. Moreover, informed decisions are not made solely based on trust, but rather with adequate knowledge and consistent with personal values (Marteau et al., 2001). In addition,

because rDBS are de-identified and coded (MDHHS, 2015), they do not meet the standard definitions of anonymous biospecimens: "never labeled with personal identifiers when originally collected, neither is a coding key generated" (Food and Drug Administration, 2008, p.6). As such, mothers who expressed a willingness to donate newborn's rDBS based on the perception of anonymity may not have been fully aware of the implications of their decision. Different perceptions and information about the degree of identifiability of biospecimens are known to affect donation decisions (Hull et al., 2008; Robinson, Slashinski, Wang, Hilsenbeck, & McGuire, 2013).

To this end and to uphold the principle of veracity, it is imperative that this information be stated clearly and that accurate participant understanding be confirmed by the consenter through a validated comprehension check methods such as teach- back (i.e., the participant repeats back key information in their own words; Rudd, 2014). The National Quality Forum recommends the use of teach-back as a standard element of the informed consent process (National Quality Forum, 2005). Importantly, teach-back should be not an ad hoc practice, but rather endorsed by the institution as a standard practice and documented. Participants may need clarifications on some points and the teach-back process can be repeated two or three times until understanding is evident. If, however, understanding cannot be achieved after couple of iterations the participant should not be consent to the research study. In addition, there are a plethora of other instruments available to assess individual understanding; often they are used for research on understanding and rarely used in clinical settings (Dunn, Nowrangi, Palmer, Jeste, & Saks, 2006). While some clinicians may believe such tools are too time consuming for clinical practice, several actually only take a few minutes to complete (Dunn, et al., 2006; Jeste et al., 2007). Other tools to facilitate the informed consent process include standard communication

checklists; components of the communication process such as value clarification and teach-back are listed on a standard form to ensure they are incorporated into the process, but the content of communication is expected to be tailored to individual participants' needs (Ripley, Tiffany, Lehmann, & Silverman, 2015). These instruments and tools could be adapted for use in the consent process for rDBS research and for other biobanking activities.

Context

The context of the post-partum environment also influenced information use and decision-making by participants in this study. Mothers in the post-partum unit described being sleep-deprived, fatigued, under the effect of medication or in pain, and were observed to be preoccupied with their newborn during the consent process. There are numerous decisions that need to be made during the post-partum period, including decisions about newborn care, pain medication, breastfeeding, and male circumcision (Torres & De Vries, 2009). Routinization of consent for such decisions may impede informed consent (Lowe, 2004; Press & Browner, 1997), making the process superficial. Patients' values and ethical dilemmas are often overlooked during consent for these procedures and the potential emotional consequences of the decisions are often not always fully explained (Lowe, 2004; Press & Browner, 1997). It appears the same may hold true for the BioTrust decision, in this often physically and emotionally overwhelming context, where values and long-term implications of biobanking were not observed to be discussed during the observations of the consent process of this dissertation research. Findings from this study suggest that the postpartum environment is not the opportune time or context for this important decision.

In addition, the post-partum environment may mitigate the perception of risks in that it may make information presented about the BioTrust seem less important than the myriad other

activities occurring in the post-partum period. Salience refers to the importance of something (e.g. information about biobanking) relative to the surrounding environment (the postpartum unit) and competing demands for attention (e.g. the baby, the hospital staff, relatives and visitors, mothers' post-partum emotional and physiological state) (Günther, Müller, & Geyer, 2016). It is possible that information about an optional decision without immediate consequences is simply not important given the environment. Yet, some ethicists consider biobanking more than minimal risk especially when it involves surrogate consent for minors (Baumann, 2001; Caulfield & Weijer, 2009; Hens, Cassiman, Nys, & Dierickx, 2011; Hofmann, 2009). Multiple leading maternal-child health organizations and researchers have called for moving education about NBS and the use of rDBS to the prenatal setting (American College of Obstetricians and Gynecologists, 2015; American Academy of Pediatrics, Newborn Screening Authoring Committee, 2008). In contrast to stakeholders' concerns that education will lead to more refusals to participate, evidence shows that educational efforts actually increase support for NBS and rDBS research (Botkin et al., 2016). In addition, the healthcare system and research enterprise should allow new parents to attend to the birth experience without having to make these decisions during the post-partum period. Other points in time, ideally early in the prenatal setting, would better allow time for discussion and further deliberation.

Fathers were important influence on mother's decisions to donate their newborn's blood spots for research. During the interviews, fathers were observed to ask or answer questions, even though research questions were intended for and directed to the mother. It was observed that decision-making about blood spot donation was often a joint decision between the parents of the newborn. While fathers' level of biobanking knowledge and involvement in this decision was not specifically assessed in this study, from interactions observed during the consent process it

appeared that they wanted to be engaged in the education and decision-making process. Further exploration is needed on the father's decision-making relative to rDBS research and biobanking.

Limitations and Strengths

There were three primary limitations to the empirical research in this dissertation. First, the qualitative and quantitative studies of this research had small samples of participants from only one state, which limits the generalizability of study findings. While the qualitative sample of 20 mothers was a convenience sample from a single data collection site, data saturation was achieved, adding strength to its adequacy and validity (Guest, Bunce & Johnson, 2006; Polit & Hungler, 1999). Despite sending a reminder postcard one week after the initial survey mailing, and a $2 honorarium included in the mailing, the response rate for the survey was only 17% (N=80). Larger incentives and repeated mailings were simply not financially feasible and therefore results should be interpreted with caution. This small sample may represent a response bias and because the survey was anonymous, data on non-respondents was not able to be collected. Surveys were mailed to mothers who gave birth within the last 3 months in order to minimize recall bias. However, as new mothers are often tired and stressed, this may have contributed to the low response rate.

Second, the MMIC (Marteau et al., 2001) restricts the definition an informed choice to the categories of knowledge, attitudes, and participation decisions, and an informed choice may be more complex and involve a component of deliberation, not captured in the MMIC (van den Berg et al. 2006). However, the novel application of MMIC to data on mothers' decisions about donating their newborns' blood spots for research was a strength of the study. Findings from the qualitative study indicated many mothers who agreed to donate had poor knowledge and were often unaware of their knowledge gaps and misinformation. Similar findings of poor knowledge

have been reported in individuals with diabetes making health related decisions in that individuals who lack knowledge of diabetes may fail to recognize the relevance of important health information, impacting health related decision-making (St. Jean, 2017). In contrast, five of the six mothers who declined to donate did recognize the inadequacy of their own knowledge of biobanking and declined to participate. Declining to participate in a study when one recognizes that he or she possess poor knowledge is viewed as a rational decision, but does not constitute an informed choice according to Marteau et al. (2001). Increased knowledge and understanding may increase participation (Jallo et al., 2013; Quinn et al., 2012). It has been suggested that individuals who agree to participate in clinical research or biobanking may need to demonstrate higher knowledge scores than decliners because they are exposing themselves (or their newborns) to additional risks (Roth, Meisel, & Lidz, 1977). In addition, dichotomized categories may have overlooked gradations in the interview data. This is perhaps especially true in the quantitative research, where dichotomizing continuous data is often considered controversial (Dawson & Weiss, 2012). Lastly, only one consenter at a single institution was observed in the qualitative interviews. Variations in organizational policies, level of training, and individual differences may exist at other institutions and in other consenters. Nevertheless, this does not negate the need for consistent training for all consenters and observing only one consenter provided a degree of consistency in the study.

There are several strengths to the study. The qualitative interviews produced rich, detailed data and captured the mothers' decision-making process as it occurred. The examination of actual, real-time decisions that occurred in their natural environment on the post-partum unit was a noted strength of the study, as was the ability to observe the effects of context on decision-making. Additional strengths included the use of standardized measures to assess biobanking

knowledge, attitudes, self-efficacy, intrinsic religiosity, and personal values. Standardized measures make comparisons across studies more feasible and have been under-utilized in studies on understanding informed consent for biobanking (Eisenhauer et al., 2017).

Future Research

Findings from this study indicate that knowledge and experience contribute to making an informed choice about biobanking. Introducing information and education about NBS and research use of rDBS, and perhaps even the consent request, in the prenatal environment would provide more exposure to biobanking information, allow parents time to deliberate, and may aid informed choices especially for first time parents (American College of Obstetricians and Gynecologists, 2015; American Academy of Pediatrics, 2008; Botkin et al., 2016; van den Berg et al., 2006). Follow-up studies should be conducted to determine if this change improves understanding and ultimately the proportion of mothers making informed choices.

Additional research on the role of values in decision-making about biobanking is needed. The use of decision aids that include more balanced information and value clarification exercises may aid informed choice (Stacey et al., 2017). Likewise, the role of nurses in explaining and obtaining consent need further study. Nurses possess key communication skills to aid values-clarification and hold ethical discussions, at the same time the public's trust in nurses must not be exploited or misused. Research on the basic competencies of informed consent and best practices for teaching these skills needs is urgently needed (Gaeta, Torres, Kotamraju, Seidman, & Yarmush, 2007; McClean & Card, 2004; Sherman, McGaghie, Unti, & Thomas, 2005). Necessary competencies for informed consent include communication skills, value-clarification techniques, and principles of shared decision-making. Methods of teaching these skills may include the use of case studies, simulation and role-playing, and educational videos (Gaeta et al.,

2007; McClean & Card, 2004; Sherman, et al., 2005). Once such competencies and best practices are determined, policies need to be implemented to require that these competencies are met by all consenters and skills maintained by annual training sessions across organizations and state lines to uphold the federal regulations on protecting human subjects.

Conclusion

This dissertation research provides valuable insight into informed choices being made about biobanking participation, specifically in regard to biobanking newborn rDBS. Future work is needed to more fully understand the content, context, and delivery of education about NBS and research use of rDBS. Practicability, administrative convenience, and efficacy of biospecimens accrual should not override ethics (Baumann, 2001). Nurses need to advocate for biobanking decisions to be informed choices, based on adequate knowledge and in accordance with personal values, to uphold the true meaning and spirit of informed consent and to respect the dignity, worth, and moral agency of all individuals.

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Appendices

Appendix A

Quality of evidence checklist for studies of informed consent:

Adapted from: Edwards, S. J., Lilford, R. J., Thornton, J., & Hewison, J. (1998). Informed consent for clinical trials: in search of the "best" method. Social Science & *Medicine*, 47(11), 1825-1840 and Cohn, E., & Larson, E. (2007). Improving participant comprehension in the informed consent process. *Journal of Nursing Scholarship*, 39(3), 273-280.

(A) sampling hierarchy: sampling (0) not stated or convenience; (1) all biobank participants offered entry in a study on understanding informed consent or random sample of all biobanking participants. (B) outcome measurement: (0) reliability/validity not addressed; (1) reliability/validity addressed in study (some validity /reliability testing, content validity testing by experts, piloting, inter-rater reliability testing) but no statistical measures reported or available (i.e. no published reliability/validity data on the instrument); (2) use of a an instrument with published reliability and validity data (e.g. test–retest reliability intra-class correlation coefficients, Cronbach's alpha, Q-Kappa). (C) response rate: response rate to outcome measure must be given and acceptable at 70% or above (0) not given or < 70% (1) ≥70% (D) actual information given at consent (i.e. informed consent document) and questionnaire (or interview guide) should be supplied in the study (including made available online as supplemental material) (0) not supplied (1) supplied *(E) study includes an author affiliated with a biobank or funding associated with biobanking: (0) yes/(1) no/unknown.

Possible 6 points Total

*This source of bias has been discussed in the work of Master et al., 2012 and Roessler et al. 2015.

Appendix B BANKS

Biobanking Attitudes and Knowledge Survey (BANKS)

Please circle your response

Please note: The term "biospecimen" refers to substances taken from the human body, such as tissue, blood, plasma, and urine. For this survey, please think about biospecimens as the leftover dried bloodspots from your newborn's screening tests.

BANKS – Attitudes

Response scale: *Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree*

1. Giving a biospecimen is for the greater good of society
   Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

2. People who give biospecimens help prevent diseases
   Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

3. People who give biospecimens help cure diseases
   Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

4. Giving a biospecimen is a waste of a person's time
   Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

5. Giving a biospecimen will help future generations
   Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

6. Giving a biospecimen gets in the way of a person's medical care
   Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

7. Giving a biospecimen will help a person's family
   Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

8. Medical information is unlikely to be stolen from a biobank
   Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

9. Giving blood to a biobank is a good way to help cancer research
   Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

10. Personal information is unlikely to be stolen from a biobank
    Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

11. A person's family medical information is safe in a biobank
Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

12. Biospecimens that people donate might be used for purposes they do not want
Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

13. A person should not donate biospecimens because it may identify health problems
Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

14. Giving biospecimens to a biobank may lead to more health care costs
Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree

BANKS – Knowledge

Response scale: *Yes, No, Don't Know*

1. A person has to spend money to give a biospecimen
   Yes, No, Don't Know
2. Anyone can access the biospecimens people give
   Yes, No, Don't Know
3. Research results from biospecimens will show up in medical records
   Yes, No, Don't Know
4. Biospecimens given to a biobank will be sold to drug companies
   Yes, No, Don't Know

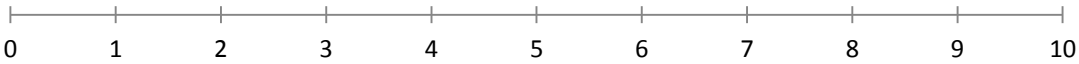
5. A scientist must keep a person's information private when doing research
   Yes, No, Don't Know
6. The biospecimens people give can be sent to any organization that requests them
   Yes, No, Don't Know
7. Police departments can legally get the biospecimens a person gives
   Yes, No, Don't Know
8. Biospecimens given to a biobank can be sold to anyone
   Yes, No, Don't Know
9. Insurance companies can legally get the biospecimens a person gives
   Yes, No, Don't Know
10. Researchers will always contact people if their biospecimens show risk for a disease
    Yes, No, Don't Know
11. A person's family can get information about the biospecimens a person gives
    Yes, No, Don't Know
12. People can make money from donated biospecimens
    Yes, No, Don't Know
13. People no longer own their biospecimens after they give them to a biobank
    Yes, No, Don't Know
14. After a person gives a biospecimen to a biobank, she/he can get it back
    Yes, No, Don't Know
15. A person might be cloned if he/she donates a biospecimen to a biobank
    Yes, No, Don't Know
16. A person can stop being in a research study after giving a biospecimen
    Yes, No, Don't Know

BANKS – Self-Efficacy

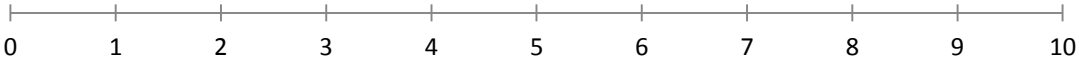
<u>Response scale</u>: *0= cannot do to . . . . . 10* = highly, certainly can do

(0= Cannot do, 5= Moderately, Certain Can Do, 10= Highly, Certain Can Do).

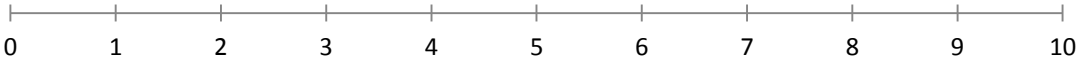
1. I think I could give a biospecimen to a biobank even if I have not donated a biospecimen before



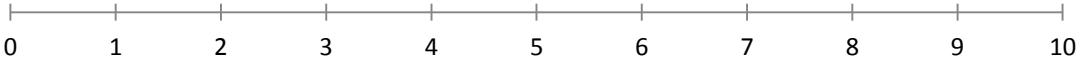
2. I think I could give a biospecimen to a biobank even if I had to travel far to do so



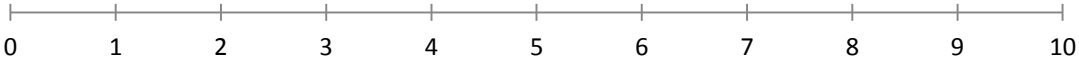
3. I think I could give a biospecimen to a biobank even if it hurts



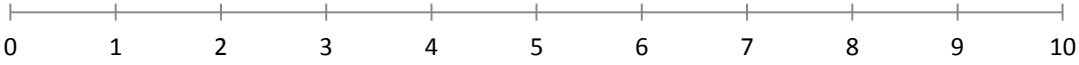
4. I think I could give blood to a biobank even if I feel weak



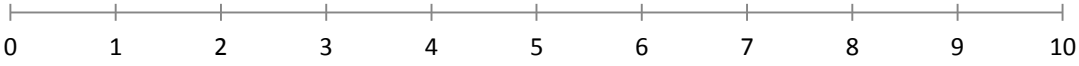
5. I think I could give a biospecimen to a biobank even if my family does not want me to



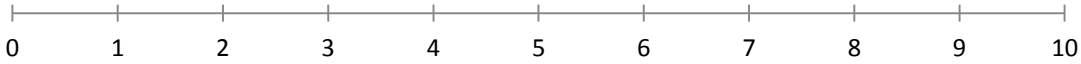
6. I think I could give a biospecimen to a biobank even if it is against my cultural beliefs



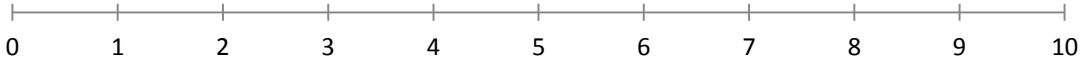
7. I think I could give blood to a biobank even if it hurts



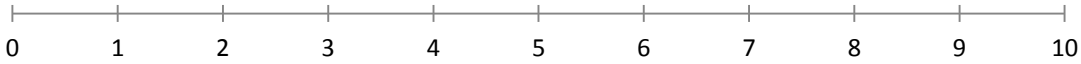
8. I think I could give a biospecimen to a biobank even if I am worried about how it will be used



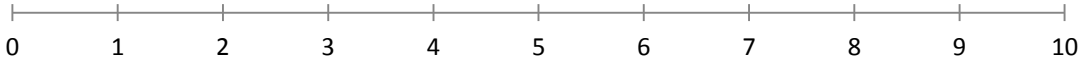
9. I think I could give a biospecimen to a biobank even if I am not feeling well



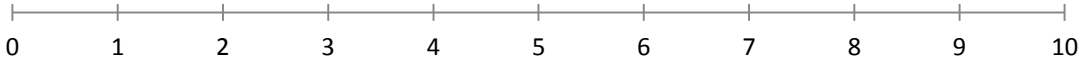
10. I think I could give a biospecimen to a biobank even if I am afraid of needles



11. I think I could give a biospecimen to a biobank even if it is against my religious beliefs



12. I think I could give a biospecimen to a biobank even if I have to spend more time at a doctor's office



Source: Wells, K.J., Arevalo, M., Meade, C.D., Gwede, C.K., Quinn, G.P., Luque, J.S., San Miguel, G.,Watson, D., Phillips, R., Reyes, C., Romo, M., West, J., Jacobsen, P.B. (2014). Development and validation of the biobanking attitudes and knowledge survey (BANKS). ***Cancer Epidemiology, Biomarkers & Prevention, 23*****(3), 374-82.**

Appendix C Hoge intrinsic religiosity motivation scale

Note: There is no agreement about right or wrong attitudes on these questions.

1. My faith involves all of my life

1-strongly agree 2- agree 3-disagree 4-strongly disagree

2. In my life, I experience the presence of the Divine (i.e., God)

1-strongly agree 2- agree 3-disagree 4-strongly disagree

3. Although I am a religious person, I refuse to let religious considerations influence my everyday affairs

1-strongly agree 2- agree 3-disagree 4-strongly disagree

4. Nothing is as important to me as serving God as best as I know how

1-strongly agree 2- agree 3-disagree 4-strongly disagree

5. My faith sometimes restricts my actions

1-strongly agree 2- agree 3-disagree 4-strongly disagree

6. My religious beliefs are what really lie behind my whole approach to life

1-strongly agree 2- agree 3-disagree 4-strongly disagree

7. I try hard to carry my religion over into all my other dealings in life

1-strongly agree 2- agree 3-disagree 4-strongly disagree

8. One should seek God's guidance when making every important decision

1-strongly agree 2- agree 3-disagree 4-strongly disagree

9. Although I believe in religion, I feel there are many more important things in life

1-strongly agree 2- agree 3-disagree 4-strongly disagree

10. It does not matter so much what I believe as long as I lead a moral life

1-strongly agree 2- agree 3-disagree 4-strongly disagree

Source: Hoge, R. (1972). A validated intrinsic religious motivation scale. *Journal for the Scientific Study of Religion, 11*(4), 369–376. http://doi.org/10.2307/1384677.

Appendix D The Short Schwartz's Value Survey

Rate the importance of the following values as a life-guiding principle for you
Use the following scale for rating each value using scale: 0 1 2 3 4 5 6 7 8
in which: 0= opposed to my principles, 1= not important, 4= important, 8= of supreme importance.

	opposed to my principles	not important			Important				of supreme importance
1. POWER (social power, authority, wealth)	0	1	2	3	4	5	6	7	8
2. ACHIEVEMENT (success, capability, ambition, influence on people and events)	0	1	2	3	4	5	6	7	8
3. HEDONISM (gratification of desires, enjoyment in life, self-indulgence)	0	1	2	3	4	5	6	7	8
4. STIMULATION (daring, a varied and challenging life, an exciting life)	0	1	2	3	4	5	6	7	8
5. SELF-DIRECTION (creativity, freedom, curiosity, independence, choosing one's own goals)	0	1	2	3	4	5	6	7	8
6. UNIVERSALISM (broad-mindedness, beauty of nature and arts, social justice, a world at peace, equality, wisdom, unity with nature,environmental protection)	0	1	2	3	4	5	6	7	8
7. BENEVOLENCE (helpfulness, honesty, forgiveness, loyalty, responsibility)	0	1	2	3	4	5	6	7	8
8. TRADITION (respect for tradition, humbleness, accepting one's portion in life, devotion, modesty)	0	1	2	3	4	5	6	7	8
9. CONFORMITY (obedience, honoring parents and elders, self-discipline, politeness)	0	1	2	3	4	5	6	7	8
10. SECURITY (national	0	1	2	3	4	5	6	7	8

security, family security, social
order, cleanliness, reciprocation
of favors)

Source:Lindeman, M. & Verkasalo, M. (2005). Measuring values with the short Schwart'z value survey. *Journal of Personality Assessment, 85*(2),170-178.

Appendix E Demographic Data

1. Did you agree to give permission for this baby's leftover blood spots to be used for research through the Michigan BioTrust?

____Yes

____No

____I don't remember

2. Please indicate your race.

____American Indian or Alaska Native

____Asian

____Black or African American

____Hispanic or Latino

____Native Hawaiian or Other Pacific Islander

____White

3. What is your current age?

____18-25

____26-45

____46+

4. What is the highest level of education you completed?

_____4^{th}-8^{th} grade_____9^{th} -12^{th} grade

_____Graduated from High School/GED

_____Some College or vocational school

_____Associate's Degree

_____Bachelor's Degree

_____Master's Degree

_____PhD or professional degree

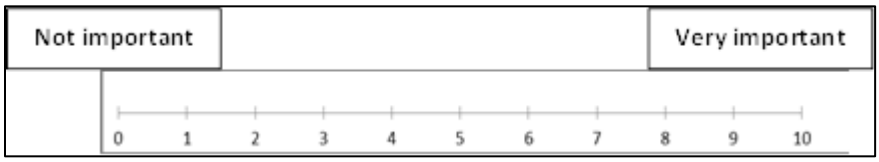
5. a) Do you identify with any specific religion?

_____Yes _____No

b) If yes, what religion?

6. (If yes to #5) Please circle the number on the line which is closest to your view.

How important to you is the actual practice of your faith?



#6. Adapted From King, M., Speck, P., & Thomas, A. (1995). The Royal Free interview for religious and spiritual beliefs: development and standardization. *Psychological Medicine*, *25*(6), 1125-1134.

7. What type of health insurance do you have?

(For example: Blue Cross or Medicaid)

____Public coverage (Medicaid)

____Private coverage (Employer sponsored or directly purchased)

8. a) How many live births have you had?

b) This is your ____ live birth.

9. How many of your children were born in MI?

10. In what years were they born in MI?

11. Have you donated any other newborn's leftover blood spots to a biobank?

_____Yes _____ No _____ Unknown

Appendix F MDHHS Invitation Letter

STATE OF MICHIGAN
DEPARTMENT OF HEALTH AND HUMAN SERVICES
LANSING

RICK SNYDER
GOVERNOR

NICK LYON
DIRECTOR

January 2017

Dear Parent:

The Michigan Newborn Screening Program is working with Elizabeth Eisenhauer and her research team on a study called **"Informed choices in biobanking: An examination of congruence between knowledge, personal & religious values, and decisions."** Ms. Eisenhauer is a doctoral candidate and researcher at the University of Michigan. The goal of this study is to explore mothers' knowledge of and attitudes towards biobanking and their socio-demographics, personal and religious values in relation to their decisions to donate their newborn's residual blood spots to a biobank for research purposes. This study may help improve informed consent processes in the future. You are receiving this letter because our records show that you recently made a decision about allowing your baby's newborn screening blood spots to be used in health research through the Michigan BioTrust for Health. Please note:

- The enclosed letter and consent document explain more about the study, so you can decide whether you might want to participate.
- We have not given any identifying information about you to the research team. They prepared the envelope, but we addressed and mailed it.
- If you want to be in this study, please complete the enclosed surveys and return them to the research team using the enclosed pre-addressed envelope. *In order to protect your confidentiality, please do not place your address or a return address label on this envelope.*
- You may decide at any time not to be in this study.

If you have any questions about the study, please contact the University of Michigan researchers directly at eeisen@umich.edu or call 1-937-266-9135. If you do not wish to be contacted again about this study or have any questions about the Michigan BioTrust for Health or Newborn Screening Program, please call the Michigan Department of Health and Human Services at 1-866-673-9939.

Sincerely,

Janice Bach, MS
Manager,
Genomics and Genetic Disorders Section

333 SOUTH GRAND AVENUE • LANSING, MICHIGAN 48913
www.michigan.gov/mdhhs • 517-373-3740

Appendix G Informed Consent

Study ID: HUM00116895 IRB: IRBMED Date Approved: 9/1/2016 Expiration Date: 8/31/2017

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

NAME OF STUDY AND RESEARCHERS

Title of Project: Informed choices in biobanking: An examination of congruence between knowledge, personal & religious values, and decisions

Principal Investigator: Elizabeth Eisenhauer, R.N., M.L.S., Doctoral Candidate, School of Nursing University of Michigan

GENERAL INFORMATION

We're doing a study to learn more about how mothers make the decision to donate or not to donate their baby's blood spots to the Michigan (MI) BioTrust for research. To get information, we'd like 500 mothers to answer a survey. We expect it to take you about 20 minutes to complete the survey. We are asking you to participate because you just had a new baby. We would like to speak with you whether your decision to donate was "yes" or "no". There is no wrong choice.

Answering this survey is voluntary. You don't have to answer it if you'd rather not. You can skip any questions that you don't want to answer, whatever the reason, and you don't have to tell us why. Choosing not to answer our survey won't affect the medical care you might receive at the University of Michigan Health System. If you agree to be part of the research study, please fill out and return the survey in the stamped envelope provided. The survey topics include your knowledge and understanding of biobanking and your personal and religious values. It's possible that some of the questions may make you feel uncomfortable. If a question makes you uncomfortable, you can just skip it and go to the next question.

To keep your information confidential, your survey responses will be completely anonymous. No one, including members of our study team, will know which subjects gave which answers. The State of Michigan did not give your address to us. The State is helping the researchers by mailing the surveys out, while keeping your name and address private. The State of Michigan will not have the results of your survey. Please send your survey results to the researcher at School of Nursing using the stamped envelope provided. The survey does not have your name or address on it. Please do not include your name or address on the survey materials

Answering our survey won't benefit you directly. We hope what we learn will help other people in the future.

To thank you for taking part in our study, we have included $2.00 in the survey packet. You may keep the $2.00 enclosed in the packet even if you choose not to return the survey.

We plan to publish the results of this study, but will not include any information that would identify you. The researchers plan to keep this study data forever for future research about decision-making.

Consent subtitle_____
Consent version _____

Groups of people, whose job it is to make sure research is done safely, may need to see the study data. These groups may include the University of Michigan and other government research offices.

CONTACT INFORMATION

To find out more about the study, to ask a question or express a concern about the study, or to talk about any problems you may have as a study subject, you may contact:

Principal Investigator: Elizabeth Eisenhauer
Mailing Address: University of Michigan, School of Nursing, 400 North Ingalls Street, Ann Arbor, MI 48104
Telephone: 1-937-266-9135
Email: eeisen@umich.edu

You may also express a concern about a study by contacting the Institutional Review Board:

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
734-763-4768
E-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study, you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

Appendix H Eisenhauer Invitation

Study ID: HUM00116895 IRB: IRBMED Date Approved: 3/26/2017 Expiration Date: 8/31/2017

Date

Dear New Mom,

I am a student at the University of Michigan School of Nursing. I am writing to ask for your help in a research study. The purpose of the study is to help researchers understand how moms make the important decision to donate or not to donate their baby's leftover blood spots to the Michigan (MI) BioTrust for research.

You are being asked to take part in this survey because you just had a new baby in Michigan. I am asking you to please complete the enclosed survey whether your decision to donate was "yes" or "no". There is no wrong choice!

To make sure the research is done right, only the new mom in this household should respond to the survey. Whether or not you choose to answer the survey is totally up to you.

If you agree to be part of the research study, please fill out and return the survey in the stamped envelope provided. The questions should only take about 20 minutes for you to answer. The questions are about your knowledge of biobanking and your personal and religious values. I have enclosed $2.00 as a small thank you for your time. Answering questions about your experiences, values, and religion can sometimes be difficult. If you are uncomfortable answering any questions you may skip them. You may choose not to answer any question for any reason. You will not receive a direct personal benefit from participating in this research. You may keep the $2.00 enclosed whether or not you return the survey. I hope that this study will help researchers better understand how new moms make the decision to donate (or not donate) to a biobank. This knowledge may help improve the process in the future.

I respect your privacy and will protect your information. This survey is anonymous. The State of Michigan is helping me by mailing the surveys out, while keeping your name and address private. The State of Michigan did not give me your address. Please do not include your name or address on the survey materials or return envelope. The State of Michigan will not have the results of your survey. Please send your survey results to me at the School of Nursing, using the stamped envelope provided. There is no way to link the survey to you and your family. Study data will be put into a password–protected computer. I plan to keep this study data forever for future research about decision-making. I plan to publish the results of this study, but will not include any information that would identify you.

Sometimes groups of people, whose job it is to make sure research is done safely, may need to see the study data. These groups may be at the University of Michigan and other government research offices.

To find out more about the study, to ask a question or express a concern about the study, or to talk about any problems you may have as a study subject, you may contact:

HUM00116895

Principal Investigator: Elizabeth Eisenhauer
Mailing Address: University of Michigan, School of Nursing, 400 North Ingalls Street, Ann Arbor, MI 48109
Telephone: 1-937-266-9135
Email: eeisen@umich.edu

You may also express a concern about a study by contacting the Institutional Review Board:
University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
734-763-4768
E-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study, you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

Many Thanks,

Elizabeth Eisenhauer, RN, MLS

Appendix I Published article
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Article

Clinical Nursing Research
1–29

DOI: 10.1177/1054773817722690
journals.sagepub.com/home/cnr
SAGE

Participants' Understanding of Informed Consent for Biobanking: A Systematic Review

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Abstract

Nurses are increasingly asked to obtain consent from participants for biobanking studies. Biobanking has added unique complexities to informed consent. The purpose of this systematic review was to evaluate participants' level of understanding of the information presented during the informed consent process unique to the donation of biological specimens for research. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were utilized to conduct the review. PubMed, EMBASE, CINAHL, PsycINFO, Scopus, Web of Science, and ProQuest bibliographic databases were searched. Results indicated that elements of informed consent unique to biobanking were poorly understood. Most studies had authors or funding associated with a biobank. Only one study disclosed and assessed participants' understanding of moral risks. Increased disclosures, values-clarification, and presenting information via multiple modalities may facilitate understanding. There is a need to improve the quality of informed consent for biobanking studies by utilizing standardized instruments,

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definitions, and encouraging research about informed choice outside the biobanking industry.

Keywords
biological specimen banks, biobanking, informed consent, moral risks, understanding

Introduction

Clinical research increasingly involves biobanking, the collection of human biological specimens (e.g., tissue, cells, blood, DNA) and related clinical data for future, often unspecified, research activities (Biobanking and Biomolecular Resources Research Infrastructure [BBMRI], 2012; Henderson et al., 2013). The mapping of the human genome and genetic-engineering have revolutionized the use of biospecimens. However, this scientific progress has made understanding informed consent information more difficult. In part, this difficulty is because biobanking research includes social and moral issues that distinguish it from participation in traditional clinical trials that do not involve a biobanking component (i.e., those without biospecimen collection; Rothstein, 2005). Nurses play a central role in clinical research, often employed as clinical research study coordinators (Hastings, Fisher, McCabe, & National Clinical Research Nursing Consortium, 2012) and may be responsible for obtaining consent from participants for biobanking studies. Thus, nurses may need to be aware of the unique difficulties patients may face during the decision-making process.

Privacy and Dignitary Risks

Consent for biobanking differs from consent for participation in traditional clinical trials in several important ways. First, genetic research, noted to be one of the most frequently conducted biobanking activities (Henderson et al., 2013), carries unique privacy risks to the participant and extended family members, as genetic analysis may reveal susceptibility to a host of diseases and potentially even personal behavioral traits (Rothstein, 2005). Beyond genetic privacy, however, there is a relationship between biobanking and associated biotechnological procedures that may not align with some participants' religious or personal values. Such procedures may include animal research, creation of immortalized cell lines, embryonic stem cell research, germ-line gene therapy (GLGT), in vitro fertilization, preimplantation genetic diagnosis, prenatal genetic screening, and somatic nuclear cell transfer (i.e.,

research cloning) (Modell, Citrin, King, & Kardia, 2014; Rothstein, 2005; Tomlinson, Kaplowitz, & Faulkner, 2014). Ethicists have labeled the moral, religious, or cultural concerns of potential biobank participants as "dignitary risks" (Rothstein, 2005) or more recently as "non-welfare interests" (Tomlinson et al., 2014). Indeed, potential biobank participants have expressed concerns about biobanking violating tenets of their religion. Concerns include religious prohibitions against blood storage, cloning, predicting the future, and trying to "play God" by analyzing and/or manipulating genetics (Eisenhauer & Arslanian-Engoren, 2016). If individuals participating in biobanking research were to discover that they had inadvertently contributed to applications, procedures, or research to which they hold moral reservations, they may suffer decisional regret or moral distress, and may eventually distrust medical researchers (Modell et al., 2014; Rothstein, 2005; Tomlinson et al., 2014).

Information and Consent

Biobanking informed consent documents can vary widely on how much information about the research is given to potential participants. There are three common types of biobanking consent documents in use today: study-specific (or classical or traditional), tiered (or menu or line item), and broad (or blanket) consent forms (International Society for Biological and Environmental Repositories [ISBER], 2012; Master, Nelson, Murdoch, & Caulfield, 2012; Weir, 2000; Wertz, 1999). Study-specific consent forms clearly describe the details of a single, specified study and allow the use of the participant's biospecimen only for this specified purpose and time frame. A tiered informed consent document allows a participant to grant permission for some portion(s) of the research project, but not necessary all portions, as determined by the participant. Choices may include the research purposes for which the biospecimen may be used, who has access to the biospecimen or associated data, and permission for use of the biospecimen in future research projects. Broad consent forms allow researchers substantial latitude in the use of participants' biospecimens, often for indefinite periods of time and with few details of future use. Broad consent forms may inadequately inform participants of their choices and the consequences of their decisions (ISBER, 2012; Master et al., 2012; Weir, 2000; Wertz, 1999). For example, specimens originally collected for diabetes research could later be used for researching alcoholism or addiction, ancestral origins, aggressiveness or criminality, mental illness, reproduction, and sexual orientation, and this may offend biospecimen donors' values (Harmon, 2010; Weir, 2000; Wertz, 1999).

Presenting patients with different types, levels, and amounts of information may result in disparate understanding of biobanking research, and different decisions about participation (Abhyankar, Summers, Velikova, & Bekker, 2014; Tomlinson et al., 2014). Tomlinson et al. (2014) compared the biobanking donation decisions of individuals presented with either a brief or expanded description of a biobanking research project. For example, when the possibility of contributing to an increase in abortions was described in a biobanking project for creating a prenatal genetic test for cystic fibrosis, the number of pro-life participants willing to donate a biospecimen dropped from 87.5% to 61.7% (Tomlinson et al., 2014). This result indicates that when provided explicit information about the use of biospecimens, potential participants are able to assess the personal, moral implications of biobanking, which may enhance their understanding and affect their donation decisions. Thus, biobanking has unique characteristics that increase the complexity of the informed consent process, and the understanding thereof.

The purpose of this systematic review, therefore, was to evaluate participants' level of understanding of the information presented during the informed consent process unique to the donation of biological specimens for research purposes (i.e., for biobanking or genetic epidemiological studies). Specific research questions were as follows:

Research Question 1: What types of information are presented to prospective biobanking participants?
Research Question 2: What specific elements of informed consent are assessed for understanding?
Research Question 3: How is participants' understanding of informed consent measured?
Research Question 4: What types of contextual factors influence understanding of informed consent for biobanking?

Method

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (i.e., The PRISMA Statement) was used as a guide to conduct this systematic review (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). In January 2015, a protocol for this review was registered on PROSPERO (registration number: PROSPERO 2015:CRD42015015649). The protocol can be accessed from the following link: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015649

Systematic searches of the PubMed, EMBASE, CINAHL, PsycINFO, Scopus, Web of Science, and ProQuest databases were conducted during

November 2014 to March 2015. The searches were updated in November 2016; three new, relevant studies were identified and incorporated into the results.

Eligibility Criteria

Studies included in this review were (a) written in English and (b) included healthy or ill adults (≥18 years of age), volunteers or surrogates (for children or incapacitated adults), who participated in an informed consent process for donating biospecimen(s) to an actual or hypothetical biobank for research purposes. Furthermore, included studies needed to contain a qualitative or quantitative assessment of participants' understanding of the information presented during the informed consent process. Studies were excluded that (a) only presented results about attitudes, preferences, willingness to donate to, or general knowledge of biobanking, without assessing understanding of informed consent, and/or (b) focused on the donation of biospecimens for clinical, diagnostic, or therapeutic purposes (i.e., nonresearch purposes) or biospecimens from fetal tissue or deceased donors. Conference abstracts, duplicate publications, editorials, essays, literature reviews, master's theses, newspaper articles, opinion pieces, philosophical articles, posters, secondary analyses, and theoretical papers were also excluded.

Search Strategy and Study Selection

The search strategies included controlled vocabulary terms (i.e., Medical Subject Headings [MeSH®]), keywords, and synonyms for the concepts of informed consent, biobanking, and understanding/comprehension including informed consent, consent forms, consent, biological specimen banks, genetic databases, biobank, comprehension, and understanding. Searches were adapted as necessary based on the controlled vocabulary terms and functions of each database. Although theses and abstracts were excluded, relevant dissertations were mapped to published articles. Reference lists of included studies were searched for additional relevant citations. Titles and/or abstracts of studies retrieved during the search phase were screened for inclusion by two authors (EE, CAE). If relevancy could not be determined from the title or abstract, the full-text was skimmed. Screened studies that addressed the inclusion criteria were retrieved and read in full. Search and selection processes are presented in Figure 1.

Data Extraction and Synthesis

A data extraction form was designed by (EE) and refined by (CAE) to capture 14 pertinent outcome and contextual variables from each included study

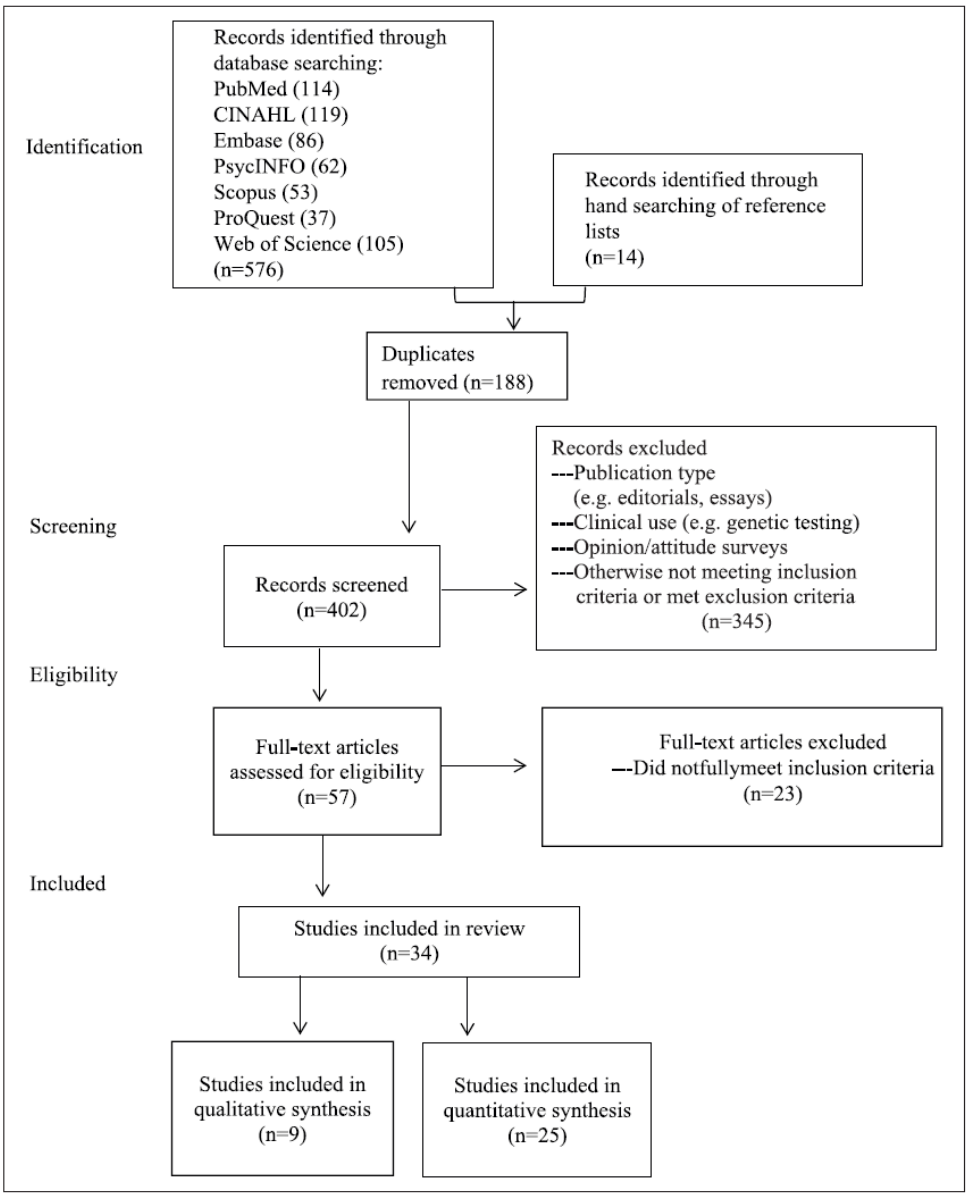

Figure 1. Flow chart of search and study selection.
Source. Moher, Liberati, Tetzlaff, Altman, and The PRISMA Group (2009).

(data available upon request). A table (Table 1) was created delineating key elements of informed consent for biobanking (Beskow, Dombeck, Thompson, Watson-Ormond, & Weinfurt, 2015; Joffe, Cook, Cleary, Clark, & Weeks, 2001; Protection of Human Subjects, 2009). Studies varied by the number of elements of informed consent measured for understanding (Table 2); thus

Table 1. Elements of Informed Consent for Biobanking.

Access to specimens or data (data sharing)
Alternatives
Benefits
Collect data from medical record
Confidentiality
Contact person
Experimental procedures
Injury
No penalty
Payment/commercial use
Purpose
Research (awareness of participation)
Re-contact
Return of results
Risks
Role/knowledge of genetics, cells, DNA
Study duration
Study procedures
Voluntary
Withdrawal

data were further organized by the elements of informed consent and the level of understanding for that element as measured in each study (data available upon request). We then categorized these measurements using a modified version of the method used by Falagas, Korbila, Giannopoulou, Kondilis, and Peppas (2009) using a threshold of ≥80% participant understanding to define adequate understanding. Qualitative studies were synthesized separately from the quantitative studies. Key words describing the level of understanding in qualitative studies were analyzed. This was done to reflect understanding of informed consent using narrative descriptions and to compare the outcome of understanding between the quantitative and qualitative studies.

Risk of Bias and Quality Assessment

The Johns Hopkins Nursing Evidence-Based Practice Research Evidence Appraisal Tool was used to evaluate the quality of included studies (Dearholt & Dang, 2012). However, because this tool did not capture the critical elements of quality and bias in informed consent studies, we also used a modified checklist of additional items based on the work of Edwards, Lilford,

Table 2. Understanding in Included Studies With Quantitative Results.

Included studies		No. of key elements of informed consent for biobanking (Table 1) assessed for understanding	Most elements <80% Yes/no
1.	Beskow, Lin, Dombeck, Gao, and Weinfurt (2017)	13	No
2.	Bickmore, Pfeifer, and Paasche-Orlow (2009)	Categories not provided—all mean scores < 80%	
3.	Cervo et al. (2013)	2	No
4.	Joseph, Neidich, Ober, and Ross (2008)	7	No
5.	Klima et al. (2014)	14	Yes
6.	Mahnke et al. (2014)	7	No
7.	Mancini et al. (2011)	3	Yes
8.	Marshall, Adebamowo, Adeyemo, Ogundiran, Vekich, et al. (2006)	2	Yes
9.	Marshall, Adebamowo, Adeyemo, Ogundiran, Strenski, et al. (2014)	6	No
10.	Matsui, Lie, Turin, and Kita (2012)	3	No
11.	Matsui, Lie, and Kita (2007)	NA—Categories not provided	
12.	McCarty et al. (2015)	16	Yes
13.	McCarty, Nair, Austin, and Giampietro (2007)	16	Yes
14.	McCaughey et al. (2016)	6	Yes
15.	Merz and Sankar (1998)	6	Yes
16.	Moutel, de Montgolfier, Meningaud, and Herve (2001)	3	Yes
17.	Ormond, Cirino, Helenowski, Chisholm, and Wolf (2009)	15	Yes
18.	Panoyan, Lee, Arar, Abboud, and Arar (2008)	3	Yes
19.	Petersen, Desmedt, Harris, Buffa, and Kollek (2014)	2	Yes
20.	Rahm, Wrenn, Carroll, and Feigelson (2013)	5	Yes
21.	Robinson, Slashinski, Wang, Hilsenbeck, and McGuire (2013)	2	Yes
22.	Roessler, Steneck, and Connally (2015)	89% self-rated their understanding at the highest level	
23.	Shelton, Freeman, Fish, Bachman, and Richardson (2015)	9	Control Yes / Exp No
24.	Simon, Klein, and Schartz (2015)	16	No
25.	Toccaceli et al. (2009)	3	Yes

Exp=experimental group.

Thornton, and Hewison (1998) and Cohn and Larson (2007; see the appendix). The Cochrane Collaboration recommends assessing other sources of bias (Higgins et al., 2011); thus, we added an item that assessed the risk of bias in biobanking studies: author or funding source associated with a biobank, as discussed by Master et al. (2012) and Roessler, Steneck, and Connally (2015). Study quality and risk of bias was initially assessed by one author (EE) and 11 studies were randomly assessed for accuracy (using every third included study in alphabetical order) by a second author (CAE). Quality rating disputes were reconciled by discussion until 100% consensus was reached on the final quality and bias assessments (Table 3).

Results

Study Characteristics

A total of 34 studies were included in this review (Table 4): nine were qualitative (26%), 21 were quantitative (62%), and four used a mixed-method approach (12%). Sample sizes ranged from as few as nine to as many as 2,192 participants. Nine studies involved hypothetical decision-making, while 25 involved actual decisions to biobank specimens (Table 4). Additional variables describing the included studies are presented in Table 4.

Risk of Bias and Quality Assessment

Using the Johns Hopkins Nursing Evidence-Based Practice Research Evidence Appraisal Tool (Dearholt & Dang, 2012), two studies (6%) received a low rating. However, 24 studies (71%) received a low (0-2 out of 6 possible points) rating using the tool specific to informed consent studies (Table 3). Yet, the decision was made to include all the studies in the review to better reflect the state of the science of participants' understanding of informed consent for biobanking. Most notably, 30 studies (88%) had an author associated with a biobank or biobank-related funding (Table 3). Four studies were related to a single biobank (Mahnke et al., 2014; McCarty et al., 2015; McCarty, Chapman-Stone, Derfus, Giampietro, & Fost, 2008; McCarty, Nair, Austin, & Giampietro, 2007). Detailed results of the quality assessment are presented in Table 3.

Information Presented

Per our inclusion criteria, all participants had undergone an informed consent process for biobanking. Only one study explicitly disclosed and assessed

Table 3. Quality Assessment of Included Studies.

Citation	Quality of evidence and risk of bias					
	Checklist for studies of informed consent item: Point(s)[a]					
	Level/ grade[b]	Sampling hierarchy	Outcome measure	Response rate	Info supplied	Biobank affiliation
Beskow, Lin, Dombeck, Gao, and Weinfurt (2017)	I/B	0	1	0	1	0
Bickmore, Pfeifer, and Paasche-Orlow (2009)	I/B	0	2	0	1	1
Matsui, Lie, Turin, and Kita (2012)	I/B	1	0	1	1	0
McCarty et al. (2015)	I/B	1	2	1	0	0
McGraw et al. (2012)	I/B	0	1	0	0	0
Robinson, Slashinski, Wang, Hilsenbeck, and McGuire (2013)	I/B	1	1	1	0	0
Shelton, Freeman, Fish, Bachman, and Richardson (2015)	I/B	0	2	0	0	1
Simon, Klein, and Schartz (2015)	I/B	1	2	0	0	0
Matsui, Lie, and Kita (2007)	II/C	1	0	1	0	0
Allen and McNamara (2011)	III/B	0	0	0	0	1
Barr (2006)	III/B	0	0	0	0	0
Beskow and Dean (2008)	III/B	0	1	0	1	0
Busby (2004)	III/B	0	0	0	0	0
Cervo et al. (2013)	III/A	1	1	1	0	0
Dixon-Woods et al. (2007)	III/B	0	1	0	1	0
Ducournau and Cambon-Thomsen (2009)	III/C	1	0	0	0	0
Hoeyer (2003)	III/B	0	0	1	0	0
Joseph, Neidich, Ober, and Ross (2008)	III/B	0	1	0	0	0
Klima et al. (2014)	III/A	1	2	0	1	0

(continued)

Table 3. (continued)

Citation	Quality of evidence and risk of bias					
	Checklist for studies of informed consent item: Point(s)[a]					
	Level/ grade[b]	Sampling hierarchy	Outcome measure	Response rate	Info supplied	Biobank affiliation
Mahnke et al. (2014)	III/B	0	1	0	0	0
Mancini et al. (2011)	III/A	1	1	1	1	0
Marshall, Adebamowo, Adeyemo, Ogundiran, Strenski, et al. (2014)	III/B	0	1	0	0	0
Marshall, Adebamowo, Adeyemo, Ogundiran, Vekich, et al. (2006)	III/B	0	1	1	0	0
McCarty, Nair, Austin, and Giampietro (2007)	III/B	1	2	0	1	0
McCarty, Chapman-Stone, Derfus, Giampietro, and Fost (2008)	III/B	0	0	0	0	0
McCaughey et al. (2016)	III/A	0	1	0	1	0
Merz and Sankar (1998)	III/B	0	1	0	1	0
Moutel, de Montgolfier, Meningaud, and Herve (2001)	III/B	0	0	0	0	1
Ormond, Cirino, Helenowski, Chisholm, and Wolf (2009)	III/A	0	2	0	0	0
Panoyan, Lee, Arar, Abboud, and Arar (2008)	III/A	1	1	0	0	0
Petersen, Desmedt, Harris, Buffa, and Kollek (2014)	III/A	0	1	1	0	0
Rahm, Wrenn, Carroll, and Feigelson (2013)	III/B	0	0	1	0	0
Roessler, Steneck, and Connally (2015)	III/B	0	0	0	1	0
Toccaceli et al. (2009)	III/A	1	1	0	0	0

[a]See the appendix. Higher score indicates less risk of potential bias/higher quality.

[b]Based on Dearholt and Dang (2012, Appendix E: Research Evidence Appraisal Tool, pp. 238-240). Quality rating based on quality appraisal: A = high quality; B = good quality; C = low quality; I = experimental study; II = quasi-experimental; III = descriptive or qualitative.

Table 4. Characteristics of Included Studies.

Citation, year, country	Design/method	Sample information
Allen and McNamara (2011), Australia	Qualitative; semistructured interviews	Healthy cohort of participants (n = 24) in actual biobank
Barr (2006), England	Qualitative; semistructured interviews	Female patients (n = 43) who donated to actual biobank
Beskow, Lin, Dombeck, Gao, and (2017), the United States	National online survey; randomized experiment	Hypothetical decision-makers (n = 1,916)
Beskow and Dean (2008), the United States	Qualitative; cognitive interviews	Hypothetical decision-makers (n = 40)
Bickmore, Pfeifer, and Paasche-Orlow (2009), the United States	Randomized experiment using BICEP	Hypothetical decision-makers (n = 29)
Busby (2004), England	Qualitative/interviews	Donors (n = 27) to an actual genetic research project
Cervo et al. (2013), Italy	Descriptive; self-administered questionnaire	Patients (n = 430) enrolled in actual biobank studies
Dixon-Woods et al. (2007), England	Qualitative; semistructured interviews	Healthy volunteers (n = 29) in an actual genetic study
Ducournau and Cambon-Thomsen (2009), France	Qualitative; observation and interviews	Men (n = 60) offered a check-up and asked to participate in actual biobank
Hoeyer (2003), Sweden	Qualitative; observation and interviews	Donors and refusers (n = 29) recruited as participants in actual program offering check–ups
Joseph, Neidich, Ober, and Ross (2008), the United States	Survey; verbally administered, in-person	Female donors and refusers (n = 93) to an actual biobank

(continued)

Table 4. (continued)

Citation, year, country	Design/method	Sample information
Klima et al., 2014, the United States	Survey; mailed, self-administered QuIC	Parents (n = 252) who actually enrolled their children to participate in congenital cardiovascular malformation research that included biobanking
Mahnke et al. (2014), the United States	Proof of concept study testing hypothetical computer-based consent	Community members (n = 9) representative of potential biobank participants
Mancini et al. (2011), France	Mailed, self-administered, 12-page questionnaire	Patients (n = 574) treated for cancer and actually asked to donate tumor samples for research
Marshall, Adebamowo, Adeyemo, Ogundiran, Vekich, et al. (2006), Nigeria and the United States	Qualitative and Quantitative; survey and interviews	Clinic patients and controls (n = 655) actually enrolled in genetic hypertension study in Nigeria and the United States
Marshall, Adebamowo, Adeyemo, Ogundiran, Strenski, et al. (2014), Nigeria	Qualitative and Quantitative; survey and interviews	Female cases and controls (n = 215) enrolled in an actual genetic epidemiological study on breast cancer
Matsui, Lie, Turin, and Kita (2012), Japan	Intervention study; add-on cluster, randomized controlled trial	Patients (n = 336) actually consenting to genetic cohort study
Matsui, Lie, and Kita (2007), Japan	Descriptive study of intervention using a two-question, in-person questionnaire	Patients (n = 2,192) being asked to participate in actual genetic cohort study
McCarty et al. (2015), the United States	Randomized controlled trial; mailed, self-administered QuIC	Men with prostate cancer (n = 71) willing to enroll in actual biobank

(continued)

Table 4. (continued)

Citation, year, country	Design/method	Sample information
McCarty, Chapman-Stone, Derfus, Giampietro, and Fost (2008), the United States	Qualitative; focus group (Focus Group Series 3)	Potentially eligible biobank subjects (*n* = 21)
McCarty, Nair, Austin, and Giampietro (2007), the United States	Mailed, self-administered QuIC	Random sample of actual biobank participants (*n* = 924)
McCaughey et al. (2016), Australia	Retrospective survey: mailed/emailed, 35-item questionnaire with 14 questions re: understanding	Patients and controls (*n* = 141) who actually donated a biospecimen for ophthalmic research
McGraw et al. (2012), the United States	Qualitative; cognitive interviews evaluating written vs. video informed consent	Patients and community members (*n* = 43) making hypothetical biobanking decision
Merz and Sankar (1998), the United States	Descriptive survey	Prospective jurors (*n* = 99) making hypothetical decision
Moutel, de Montgolfier, Meningaud, and Herve (2001), France	Self-administered questionnaire	Patients (*n* = 51) enrolled in actual biobanking study
Ormond, Cirino, Helenowski, Chisholm, and Wolf (2009), the United States	Qualitative and Quantitative; interviews and QuIC	Actual biobank participants (*n* = 200)
Panoyan, Lee, Arar, Abboud, and Arar (2008), the United States	Survey; self-administered questionnaire	Participants (*n* = 151) in actual genetic study

(continued)

Table 4. (continued)

Citation, year, country	Design/method	Sample information
Petersen, Desmedt, Harris, Buffa, and Kollek (2014) Belgium, Germany, and the United Kingdom	Self-administered questionnaire	Female breast cancer patients in Belgium (n = 152), Germany (n = 122), and the United Kingdom (n = 122)
Rahm, Wrenn, Carroll, and Feigelson (2013), the United States	Self-administered questionnaire	Donors and refusers (n = 203) to hypothetical biobank
Robinson, Slashinski, Wang, Hilsenbeck, and McGuire (2013), the United States	Randomized trial; interview and questionnaire	Individuals (n = 229) recruited into actual studies
Roessler, Steneck, and Connally (2015), the United States	14 question quiz or semi-structured interview (self-rated understanding only)	Research volunteers and patients (n = 480) being asked to enroll in actual biobank
Shelton, Freeman, Fish, Bachman, and Richardson (2015), the United States	Intervention study; experimental posttest only; in person, self-administered questionnaire	Visitors (n = 134) in waiting rooms; hypothetical decision to donate biospecimen of family member
Simon, Klein, and Schartz (2015), the United States	2 × 2 experimental design; prospective randomized study/online survey, QuIC	Patients (n = 200) approached for enrollment into an actual biobank
Toccaceli et al. (2009), Italy	Mailed, self-administered survey	Participants (n = 99) recruited from a twin registry and radio ads for actual genetic study

Note. BICEP = Brief Informed Consent Evaluation Protocol instrument; QuIC = Quality of Informed Consent instrument.

understanding of moral risks associated with biobanking and reported inadequate understanding of these issues (McCaughey et al., 2016). However, it is difficult to truly ascertain what specific or additional information was provided to participants as only 11 studies actually provided the biobanking informed consent document (whole or partially; Table 3). Thus, it is difficult to truly ascertain what specific or additional information was provided to participants. This frequent lack of disclosure raises a concern about transparency in studies of participant understanding of informed consent information for biobanking.

Understanding: Assessed and Reported

Across the 25 studies reporting quantitative results, understanding of the selected elements of informed consent was most frequently measured at < 80% (Table 2). Generally, participants understood their participation was voluntary and that they would not be paid for commercial products that could result from their donated biospecimens. Participants showed highly variable rates of understanding in their awareness of participating in a research project, benefits to self and others, who to contact with questions about the study, procedures, purposes, and that they could withdraw from a study. Understanding of the risks of biobanking and the experimental nature of research were particularly poor. Inadequate understanding was especially prevalent in the following elements of informed consent: alternatives to participation, access to study records/specimens, collection data from personal medical records, confidentiality, injury compensation, the role of genetics including DNA banking and storage, study duration, and return of genetic results (data available upon request). Many poorly understood elements are unique to biobanking. Participants' self-rating of their understanding was usually higher than understanding scored on objective measures (Klima et al., 2014; McCarty et al., 2007; McCaughey et al., 2016; Ormond, Cirino, Helenowski, Chisholm, & Wolf, 2009).

Qualitative studies also frequently described participants' understanding as inadequate. Four of the nine (44%) qualitative studies clearly reported participants' understanding as inadequate (Barr, 2006; Dixon-Woods et al., 2007; Ducournau & Cambon-Thomsen, 2009; Hoeyer, 2003). Four other (44%) studies described participants' understanding as riddled with "ambiguity" (Busby, 2004, p. 46), "confused" (McCarty et al., 2008, p. 3030; McGraw et al., 2012, p. 16), or "debatable" (Allen & McNamara, 2011, p. 159). Beskow and Dean (2008) reported that participants "seemed to understand" (p. 1447) the information provided.

Studies varied widely on the number of elements of informed consent assessed for understanding (range = 2-16; Table 2). Studies that used the Quality of Informed Consent (QuIC) instrument were most comprehensive in their assessments, assessing an average of 15 elements of informed consent for biobanking (Klima et al., 2014; McCarty et al., 2015; McCarty et al., 2007; Ormond et al., 2009; Simon, Klein, & Schartz, 2015). Originally designed for use in cancer clinical trials, the QuIC is a standardized instrument, with published reliability and validity data, that assesses both objective and subjective understanding about specific elements of informed consent using 20-detailed true/false and 14-Likert-type scale questions (Joffe et al., 2001). The QuIC has been adapted and used in several studies (noted above) for assessment of understanding of informed consent in biobanking studies.

Measurement of Understanding

The methods and instruments used to assess understanding varied widely among studies. Methods included in-person interviews (nine studies), telephone interviews (one study), verbally administered surveys (five studies), and self-administered surveys (16 studies), including some that were mailed (six studies) or electronic (four studies; Table 4). Twenty-three of the 34 studies (68%) included some validation of their instrument or interview guide, while 11 studies (32%) did not address validity (Table 3). Only six studies used a previously validated instrument to assess understanding (Bickmore, Pfeifer, & Paasche-Orlow, 2009; Klima et al., 2014; McCarty et al., 2015; McCarty et al., 2007; Ormond et al., 2009; Simon et al., 2015). Five studies used the QuIC instrument (Klima et al., 2014; McCarty et al., 2015; McCarty et al., 2007; Ormond et al., 2009; Simon et al., 2015) and one used the Brief Informed Consent Evaluation Protocol (BICEP; Bickmore et al., 2009). One of the studies that used a self-administered survey also reported the initial reliability (Cronbach's α of .73) and validity data (content validity) for a newly developed instrument to measure surrogate consent for genetic studies (Shelton, Freeman, Fish, Bachman, & Richardson, 2015).

Contextual Factors

Contextual factors found to influence understanding included (a) circumstances of recruitment; (b) education, literacy, and reading; (c) consent modalities; (d) locality; (e) other demographics (e.g., age, gender, and income) (f) consenters; and (g) amount of time spent explaining consent information.

Health status and the setting in which participants were recruited (e.g., patient vs. nonpatient; health care vs. community) varied across the studies, affecting the understanding of informed consent information. Differences in understanding (Ormond et al., 2009; Toccaceli et al., 2009) or in the amount of time spent considering information (Roessler et al., 2015) were reported when participants were self-referred versus recruited in the health care setting.

Understanding differed based on level of education in nine studies (Beskow, Lin, Dombeck, Gao, & Weinfurt, 2017; Cervo et al., 2013; Joseph, Neidich, Ober, & Ross, 2008; Marshall, Adebamowo, Adeyemo, Ogundiran, Vekich, et al., 2006; Merz & Sankar, 1998; Ormond et al., 2009; Panoyan, Lee, Arar, Abboud, & Arar, 2008; Petersen et al., 2014; Toccaceli et al., 2009). Two studies identified better literacy (or health literacy) as a factor associated with increased understanding (Bickmore et al., 2009; Marshall, Adebamowo, Adeyemo, Ogundiran, Vekich, et al., 2006). The extent to which participants actually read study materials (i.e., all, part of, or none) was examined in two studies by Matsui, Lie, and Kita (2007) and Matsui, Lie, Turin, and Kita (2012). Reading more of the informed consent document was associated with higher rates of self-perceived understanding. However, no significant difference in reading amount was noted when given a shorter informed consent document (five pages) or a traditional longer document (11 pages; Matsui, Lie, Turin, & Kita, 2012). Likewise, in a study by Beskow, Lin, et al. (2017), shorter documents did not improve understanding. Education was not a statistically significant factor for increased understanding in the study by McCaughey et al. (2016), and despite the fact that 81.6% of their sample reported reading the information pamphlet at least once, understanding was still poor on objectives measures.

Studies about computer-based informed consent often involved hypothetical biobanking decisions (Beskow, Lin, et al., 2017; Bickmore et al., 2009; Mahnke et al., 2014; McGraw et al., 2012; Shelton et al., 2015). While computer modules may occasionally lead to small gains in understanding, two authors cautioned that technology should be used as an adjunct to more traditional methods of informed consent including human interaction and reading of paper documents (McGraw et al., 2012; Shelton et al., 2015). Interactivity, in the form of comprehension checks or quizzes, provided an important opportunity to review consent information, clarify confusion, and improve understanding (Beskow, Lin, et al., 2017; Bickmore et al., 2009; Simon et al., 2015). Two computer studies involved actual biobanking decisions (McCarty et al., 2015; Simon et al., 2015): McCarty et al. (2015) conducted a randomized controlled trial of traditional versus computer-based consent and found no major differences in understanding. Simon et al. (2015) reported small

gains in understanding in multimedia groups, but emphasized the importance of interactivity across modalities. Comparably, another study involving an actual biobank found repetition of consent information and presenting the information via multiple modalities (e.g., paper, media, humans) to be important factors in facilitating adequate understanding (Cervo et al., 2013).

Locality, the cultural and sociopolitical environment of the participants, influenced their understanding of biobanking informed consent information (Hoeyer, 2003; Marshall, Adebamowo, Adeyemo, Ogundiran, Vekich, et al., 2006; Petersen, Desmedt, Harris, Buffa, & Kollek, 2014). For example, Hoeyer (2003) noted that in countries where the government finances health care, citizens may have a sense of wanting to give back to the government and therefore may be more likely to donate biospecimens to government-run research biobanks. Petersen et al. (2014) found perceptions of medical research and data protection standards varied in breast cancer patients from three European countries, and these varied perceptions influenced patients' understanding of informed consent for biospecimen donation.

Demographic (e.g., age, gender, income) composition of participants and reporting of these variables varied across studies. Notably, younger age was usually (Beskow, Lin, et al., 2017; McCarty et al., 2007; Robinson, Slashinski, Wang, Hilsenbeck, & McGuire, 2013) but not always (Klima et al., 2014), associated with better understanding. Females were more likely than males to demonstrate correct understanding (Klima et al., 2014; McCarty et al., 2007; Toccaceli et al., 2009), as were individuals with or of higher levels of household income (Beskow, Lin, et al., 2017; Joseph et al., 2008; Panoyan et al., 2008). Yet, Klima et al. (2014) found participants with higher levels of household income were less likely to correctly answer the question of who would pay for a research-related injury than those with incomes <$35,000.

Variability in the qualifications (e.g., physicians vs. research assistants) and actions of the consenter may have influenced participants' understanding of informed consent in ways that have yet to be determined. In eight studies (Beskow & Dean, 2008; Beskow, Lin, et al., 2017; Mahnke et al., 2014; McCarty et al., 2008; McGraw et al., 2012; Merz & Sankar, 1998; Rahm, Wrenn, Carroll, & Feigelson, 2013; Shelton et al., 2015), participants only read a consent document and/or viewed a computerized version of the consent, with no human leading a consent discussion. Finally, estimated time to explain consent information varied across included studies, ranging from less than 1 min to 1 hr.

Discussion and Application

This systematic review indicates many elements of informed consent for biobanking are inadequately understood by participants. These findings are

consistent with research on understanding informed consent for traditional clinical trials and treatments (Cohn & Larson, 2007; Falagas et al., 2009; Flory & Emanuel, 2004; Nishimura et al., 2013). Our appraisal of the biobanking literature also revealed a unique finding of concern: the vast majority (88%) of the included studies involving understanding of informed consent for biobanking had either an author associated with a biobank, genetic epidemiological study, or funding associated with these entities. While these associations are not evidence of wrongdoing, they may pose a risk of bias analogous to pharmaceutical funding of drug studies (Stelfox, Chua, O'Rourke, & Detsky, 1998) or the beverage industry sponsoring research on the health effects of soft drinks (Schillinger, Tran, Mangurian, & Kearns, 2016).

It was striking that only one study disclosed and assessed understanding of moral risks (McCaughey et al., 2016). McCaughey et al. (2016) reported inadequate understanding of these moral risks to biobanking. Most participants, however, could not consider this undisclosed information. This placed prospective biobank participants at a disadvantage, unable to evaluate all pertinent information when key aspects of moral controversy are omitted (Tomlinson et al., 2014). A Notice of Proposed Rulemaking (NPRM) suggested strengthening human subject protection by requiring consent for the use of biospecimens in research (Federal Policy for the Protection of Human Subjects, 2015). However, the final rule did not adopt the proposed requirement for consent involving nonidentified biospecimens (Federal Policy for the Protection of Human Subjects, 2017). As such, it remains to be seen whether there will be sufficient discussion of moral risks in the future to facilitate truly informed decisions (Marteau, Dormandy, & Michie, 2001).

Evidence from this review indicates the need for caution when recruiting in health care settings. Contradictions were evident in participants' understanding of the benefits of biobanking. For example, even when they recognized that biobanking research was intended to help others, many participants still held expectations of benefits to themselves or their immediate loved ones (Barr, 2006; Busby, 2004; Dixon-Woods et al., 2007; Joseph et al., 2008; Klima et al., 2014; McCarty et al., 2015; McCarty et al., 2007; Ormond et al., 2009; Petersen et al., 2014). These incongruencies may indicate therapeutic misconception, defined as when a research participant expects personal benefit, even when the goal of the study to benefit only future patients has been explained (Appelbaum, Roth, Lidz, Benson, & Winslade, 1987).

The emphasis on utilizing computers to deliver informed consent information may be a reflection of U.S. researchers' increasing concerns about cost, time-savings, and efficiency (McCarty et al., 2015; Roessler et al., 2015). However, this may also be indicative of an ethically detached approach to obtaining informed consent, typical in Western countries (Carper, 1979). This

approach may not be realistic when dealing with biobanking research involving value-laden, moral risks.

Strengths and Limitations

The strengths of this review include (a) the use of the PRISMA guidelines (Moher et al., 2009), including the online publication of a protocol; (b) exposing a risk of bias in research about participants' understanding of biobank informed consent; and (c) revealing the lack of disclosure and assessment of understanding regarding moral risks in biobanking.

Four limitations to this research are noted: (a) Included studies demonstrated vast heterogeneity in key characteristics: study designs, participant populations, interventions, and, especially, the definitions and measurements of understanding and the delivery of informed consent information. Problems with such heterogeneity have been previously recognized in the literature as a limitation of studying understanding of informed consent (Cohn & Larson, 2007; Falagas et al., 2009; Flory & Emanuel, 2004; Nishimura et al., 2013; Sand, Kaasa, & Loge, 2010). The heterogeneity of measures in the included studies made accurate comparisons difficult. (b) Moreover, the quality of included studies was lacking. There was frequent reliance on homogeneous convenience samples. Outcome measurements rarely involved the use of an instrument with published reliability and validity data. Several studies were based on hypothetical decision-making, and many demonstrated a lack of transparency in reporting what information was disclosed to participants. There was immense variability and selectivity involving which elements of informed consent were assessed for understanding. (c) In addition, only studies written in English were included, and (d) most studies were from the United States or Western Europe.

Nursing Implications

This review demonstrates that participants' biobanking decisions are not always truly informed; instead decisions may be based on limited understanding, values, trust, or even time constraints. An uniformed participant may be at risk for decisional regret. Nurses can help guard against such potential errors in judgment by taking advantage of educational opportunities on genetics and genomic science, such as the Summer Genetics Institute (SGI) sponsored by the National Institute of Nursing Research (NINR; 2017). Nurses need to know, that without explicit explanations, patients may not understand the connections between donating biospecimens for research and controversial biotechnological procedures

(Tomlinson et al., 2014). To do so, nurses must first understand these distinctions to accurately convey this information to patients. Next, nurses must be diligent not to exploit the strong trust of their patients (Hoeyer, 2003; Norman, 2016). Obtaining consent from patients for biobanking without providing adequate information and consideration for individual patient's values is inconsistent with professional nursing values of respect for human dignity and the right to self-determination (American Nurses Association, 2015). Assessing patients' motivation for study participation and assessing their comprehension of biobanking and its implications are ways in which nurses can advocate for their patients (Penckofer, Byrn, Mumby, & Ferrans, 2011). Furthermore, to help patients make decisions more congruent with their personal values, and thereby avoid decisional regret, it may be helpful for nurses to describe some of the potential morally controversial uses of biospecimens (e.g., animal research, the creation of immortalized cell lines, and stem cell research) and include a disclaimer such as, "If any of these make you uncomfortable, you might not want to participate in this [biobank]" (University of Michigan, 2016).

Recommendations for Practice and Future Research

Biobanking research involves presenting complex information to potential participants as they decide whether or not to grant their permission to participate in the research. Principles of health literacy apply to imparting such information. Health literacy is defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" (Ratzan & Parker, 2000, p.vi) . The field of health literacy has evolved from solely emphasizing patient education to focusing on provider communication skills, and more recently calling for an increase in transparent, patient-friendly health care environments (Rudd, 2014). For biobanking research, this threefold approach to aid participants' understanding of complex information includes (a) increasing curriculum on genetics and biotechnology in secondary education, (b) emphasizing human-to-human dialogue in the informed consent process, and (c) encouraging a more transparent research enterprise, one that encourages participants to make a truly informed choice (Marteau et al., 2001). Recommendations for future research include improving the quality of studies on understanding informed consent for biobanking by utilizing standardized instruments, controlling for contextual variables, and establishing a common threshold for defining adequate understanding. In addition, future work should include studies conducted by non-biobank associated researchers, with demographically diverse

samples, and examine actual (not hypothetical) informed choices in real time. Future systematic reviews examining participant understanding of informed consent for biobanking should also examine these specific attributes.

Appendix

Quality of Evidence Checklist for Studies of Informed Consent

Adapted from Edwards, Lilford, Thornton, and Hewison (1998) and Cohn and Larson (2007).

(A) sampling hierarchy: sampling (0) not stated or convenience; (1) all biobank participants offered entry in a study on understanding informed consent or random sample of all biobanking participants. (B) outcome measurement: (0) reliability/validity not addressed; (1) reliability/validity addressed in study (some validity/reliability testing, content validity testing by experts, piloting, interrater reliability testing) but no statistical measures reported or available (i.e., no published reliability/validity data on the instrument); (2) use of an instrument with published reliability and validity data (e.g., test–retest reliability intraclass correlation coefficients, Cronbach's alpha, Q-Kappa). (C) response rate: response rate to outcome measure must be given and acceptable at 70% or above (0) not given or < 70% (1) ≥70% (D) actual information given at consent (i.e., informed consent document) and questionnaire (or interview guide) should be supplied in the study (including made available online as supplemental material) (0) not supplied (1) supplied.[1] (E) study includes an author affiliated with a biobank or funding associated with biobanking: (0) yes/(1) no/unknown. Possible 6 points Total.

Author's Note

Elizabeth Eisenhauer is a recipient of the 2014-2016 Jonas Nurse Leader Scholar Award.

Acknowledgments

The authors wish to thank Dr. Bonnie M. Hagerty for her comments on an earlier draft of this manuscript. They also thank the anonymous referees for their valuable comments and suggestions.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Note

1. This source of bias has been discussed in the works of Master et al. (2012) and Roessler et al. (2015).

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