2022

A Mixed Methods Approach to Understanding Participant Perspectives on Return of Individual Research Results

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A MIXED-METHODS APPROACH TO UNDERSTANDING PARTICIPANT PERSPECTIVES ON RETURN OF INDIVIDUAL RESEARCH RESULTS

By

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M.P.H, San Jose State University, 2003

A Dissertation Submitted in Partial Fulfillment of
the Requirements for the Degree of Doctor of Philosophy

Department of Public Health and Health Sciences

School of Health Sciences
In the Graduate School
The University of South Dakota
August 2022

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Abstract

Provision of individual research results to participants is a critical component of the research process. While there is general interest amongst researchers in returning individual research results, a lack of understanding of the personal value of results for participants has hindered the return of individual results. This is especially true for non-genomic research results such as surveys, laboratory test results, or imaging results. This study examined the participant perspectives on the return of individual research results in a diverse cohort of 1587 mothers currently enrolled in the Environmental Child Health Outcomes (ECHO) program. A mixed-methods approach was used to delineate the influence of result type and standardization status (availability of normative data) on the perceived value of individual research results. Racial differences between American Indian and White participants with respect to perceived value of individual research results were examined. Additionally, the study explored the process by which participants make decisions regarding value of individual research results. Findings from this study indicate that irrespective of result type, participants attributed higher perceived value to individual research results that were framed within a normative context than those that were not framed within a normative context. No significant differences were found between American Indian and White participants with respect to perceived value of individual research results. Qualitative interviews showed that participants' process of attributing value to individual research results is influenced by others' experiences including advice from the researcher.

A. Elliott

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Amy Elliott, PhD

Acknowledgements

I would like to express my sincere appreciation to Dr. Amy Elliott, Committee Chair for her enthusiasm, guidance, and patience throughout the dissertation process. I am also grateful to the dissertation committee members, Dr. Barbara Brockevelt, Dr. Jean Caraway, and Dr. DenYelle Kenyon for their feedback and support for this dissertation work.

Research reported in this dissertation was supported by the Environmental Influences on Child Health Outcomes (ECHO) program, Office of the Director, National Institutes of Health under the awards UH3 OD023279 and UH3 OD023279-06S1.

I would like to acknowledge the staff at Avera Research Institute for their contribution to the data collection efforts for this research. Many thanks to Ms. Katherine Ziegler, Dr. Christine Hockett, and Dr. Lacey McCormack for their helpful comments and suggestions throughout the dissertation process.

Finally, special thanks to my family for their encouragement and support during my pursuit of the graduate program and the dissertation.

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Chapter 1. Introduction

Introduction and Background

This dissertation investigated participant perspectives on the return of individual research results (IRR). The overall intent of the dissertation was to address gaps in knowledge in participants' perceived value of IRR, with the ultimate goal to guide researchers in their efforts to return IRR. Participants are key stakeholders in the research process and their voice is crucial to identifying effective and sustainable strategies for the return of IRR. Return of individual results should be viewed as a voluntary process in which participants have the choice to opt-in or opt-out of receiving IRR. In general, return of research results may be divided into three categories: return of aggregate results, return of individual results, and return of incidental findings. Aggregate and individual results are directly related to the goals of the study. In contrast, incidental findings are findings discovered during the conduct of research, but unrelated to the goals of the study (SACHRP, 2016). Aggregate results provide overall information about the research, population demographics or research outcomes, but do not contain participant specific results. Aggregate results are typically disseminated through scholarly forms and publications but may also be returned to participants in the form of plain language summaries (MRCT, 2017). Individual research results contain participant-specific information and may be provided directly to the research participant (SACHRP, 2016).

Experts argue that the return of individual results is a matter of respect and reciprocity towards participants for their contribution to research (NASEM, 2018). In research, participants often receive financial incentives for their time in the study. Although financial incentive is a benefit, the provision of financial incentives alone may not recognize their full contribution to research. Advocates for patient engagement in research argue that patients must be treated as 'partners in research'; recognition of this partnership is multi-dimensional and may include financial rewards, personal recognition, increased knowledge or other non-tangible rewards (Smith et al., 2020). Return of individual results contributes to increased participant knowledge about their health and is a reciprocal gesture for their contribution to research. Many ethics experts believe that dissemination of results directly to participants and communities is an ethical obligation (Fernandez, 2003; Steinbekk & Solberg, 2012).

Scientific and technological developments have enhanced our ability to collect wide-ranging health data from individuals. In addition to traditional data collection formats such as surveys, laboratory tests or behavioral assessments, new imaging techniques or use of wearable devices have opened up new frontiers for data collection. This diversity in result types poses a challenge for developing universal guidelines for the return of IRR. Additionally, regulatory and ethical considerations add to the complexity of returning IRR.

Advisory groups such as the Secretary's Advisory Committee on Human Research Protections recommend returning individual results when they are more likely to inform clinical utility(SACHRP, 2016). The clinical utility of a result refers to its potential to inform clinical decision-making (Grosse & Khoury, 2006). Per existing regulations, research results used for clinical decision-making must conform to regulatory standards such as the CLIA certification for laboratory or genetics results (Sobel et al., 2020). CLIA or Clinical Laboratory Improvement Amendments is a regulation through which the Centers for Medicare and Medicaid oversees laboratory testing performed on humans for clinical purposes (CMS, 2021). In general, when research testing occurs in a non-CLIA laboratory, those tests need to be verified by a CLIA laboratory prior to returning them to the participant for clinical interpretation. The cost for additional testing is typically transferred to the participant. Thus, the existing regulatory framework governing use of research results for clinical decision-making creates inequitable access for participants who may not be able to afford additional testing and therefore are unable to derive benefit from their participation in research.

Arguably, not all individual research findings have the potential to inform clinical decision-making. Observational studies, in particular longitudinal studies that follow individuals over several years or decades have the potential to generate vast amounts of data (Sayeed et al., 2021).While results from these data may not always inform clinical decision-making, the results may contribute to personal value for participants in other ways. Exclusively focusing on clinical utility limits the type of results that may potentially be available for return.

Recent years have seen a growing consensus toward returning a broad range of IRR (Sabatello et al., 2020; Sayeed et al., 2021; Sobel et al., 2020). Studies by Wilkins et al., (2018) and Sayeed et al., (2021) have noted that participants are interested in receiving individual results that are also unrelated to clinical utility. In an attempt to facilitate the return of IRR, researchers are being encouraged to consider the personal value of individual results for participants rather than clinical utility alone (NASEM, 2018). Personal value for participants may come from the knowledge gained, clinical utility, or the feeling of appreciation by receiving their results. In fact, participants may see value in the act of receiving results regardless of type (NASEM, 2018). Research suggests that the return of IRR serves as a reciprocal act for the participants' contribution to research, and leads to increased participant trust in research, particularly in communities that have historically struggled with mistrust of scientific research and researchers such as American Indian and African American communities (Lewis et al., 2021; Portacolome, 2020).

Despite overall support for the return of IRR, barriers such as inadequate resources, disputes concerning investigator obligations for return of IRR, and a potential disconnect between investigator and participant perceptions of value have hindered efforts to return IRR (NASEM, 2018; Klitzman et al., 2013). Moreover, the return of IRR has largely been driven by clinical trials and genetic results, and information on return of other result types is lacking (Wong et al., 2018). There appears to be a lack of enthusiasm to return IRR when the results do not inform clinical utility or are not 'well understood' due to a lack of normative standards. For example, many environmental contaminants do not have normative standards or reference ranges, which makes interpretation of individual results for environmental contaminants challenging (NASEM 2018). Normative data refers to data from a reference population that can establish a benchmark against which an individual result may be compared (O'Connor, 1990). Researchers are concerned that provision of results of unknown certainty may not be useful to participants and may create additional stress or financial burden for them. As key stakeholders in the research process, participants may offer solutions to some of the barriers or concerns by identifying their perceived value of IRR based on result type or the ability to interpret the result. Therefore, it is critical to focus on participant views to help guide researchers in developing strategies that align resources with participant preferences.

Statement of Problem

A large body of work has shown that participants highly value genetic results (Bollinger et al., 2012; Miller et al., 2010; West et al., 2020). However, participant perceptions of value for other result types remained largely unexplored. Furthermore, it is unknown how the availability or lack thereof of normative data may influence participant perceptions of the value of an IRR. This dissertation examined participant perspectives on the value of diverse types of IRR and explored how participants made decisions regarding the value of IRR. Additionally, this dissertation explored racial differences between American Indian and White participants with regard to the perceived value of IRR. It is anticipated that the findings from this research will help inform best practice guidelines for returning individual research results.

Significance

Professional Significance

This dissertation investigated participant perspectives on the value of IRR in a prospective cohort of mother-child dyads currently enrolled in the PASS ECHO Environmental Child Health Outcomes study (5UH3OD023279-05). The PASS ECHO study is part of a national network of 31 grantees and 68 different cohorts that contribute to a unique national cohort of 50,000 children. Designed to explore the effects of prenatal and early life environmental exposures on long-term child development, the PASS ECHO study is a community-engaged effort involving multiple community organizations, hospitals, and clinic partners, to enroll approximately 4400 mother-child dyad participants from two sites in South Dakota – Sioux Falls and Rapid City. The cohort is a diverse mix of white, American Indian, and other races. Recruitment for this study began in 2016 and will continue through 2023.

The PASS ECHO cohort provided an unprecedented opportunity to explore the perspectives of participants currently enrolled in a research study. The PASS ECHO cohort is unique because it has the highest percentage of American Indian participants amongst all ECHO network sites. American Indians have been historically underrepresented in research and their inclusion in this research is a major strength of this dissertation. Additionally, the ability for participants to draw on their PASS ECHO experience and reflect on their perceived value of IRR makes this work highly impactful. This dissertation has a two-fold impact: First, findings from this work will specifically inform the return of IRR for PASS ECHO participants, and second, the findings will broadly inform strategies for the return of IRR from observational studies in future.

This dissertation is timely as it is responsive to the new paradigm of participant engagement in research where participants are not ‘mere subjects’, but equal partners in decision-making about their research participation and outcomes (Bromley et al., 2017). In many ways, the existing regulatory framework was not designed to include participants as equal partners. The Belmont report requires that researchers and regulatory groups such as institutional review boards estimate the risks and benefits on behalf of participants based on their (researcher) assessment of the proposed research (HHS, 2016). Given this regulatory charge, typically, researchers have unilaterally made assessments regarding the risks and benefits of research. The new paradigm of participant engagement calls for bidirectional communication between the researcher and the participant to facilitate participant input in all aspects of the research design.

It is time to examine the new paradigm with respect to the return of IRR. In general, researchers assume that results framed by normative context and incorporating reliable, published evidence are more meaningful to participants, as the results may inform behavior or health related decision-making. In contrast, results that cannot be framed by normative context are uncertain and therefore likely to be less meaningful to participants. There is also a long-held belief that the return of uncertain results may potentially lead to increased risk for participants (NASEM, 2018). In terms of risk, it is possible that participants will be willing to accept more risk than researchers believe is acceptable based on contemporary guidance for returning individual results. At least a few genetic studies have shown that some participants value results that may not be fully understood or directly applicable due to a lack of normative standards (Clift et al., 2020; Lewis, et al., 2021; Mollison et al., 2020). Yet, there is a gap in knowledge on participant perceptions about other types of results of unknown certainty. In this study, the investigator examined if PASS ECHO participants' perceived value of IRR was influenced by result type and the ability to interpret the results within a normative context.

The increased acceptance of genetic testing and models for health risk prediction is testimony to rapid scientific progress in genetics and widespread recognition of information that may not have been acceptable a decade ago (Brittain et al., 2017). It is possible that information that is presently ill defined could be framed within a normative context in the future. A restrictive view on the return of IRR may limit the possibilities for return of results that may be truly important and meaningful to the participants. It is important therefore, that researchers remain unprejudiced and willing to engage participants to gain insight into their beliefs about IRR.

The American Indian perspective

American Indians have historically remained an understudied population in research (Cole et al., 2020). Issues related to mistrust in research have been amplified in American Indian communities due to historical negative experiences including misrepresentation of research purpose, lack of adequate informed consent, and failure to return any information back to the participants resulting in a lack of engagement in research (Dillard et al., 2018). Approximately eight percent of the PASS ECHO mothers self-identified as American Indian, offering a unique prospect to include them in research and explore racial differences between White and American Indian participants on factors influencing the perceived value of IRR. Return of research results has been shown to increase trust in research and contribute to greater transparency in scientific research. According to Kirkness and Barnhardt (1991), the 4Rs - respect, relevance, responsibility and reciprocity are an important paradigm for defining relationships in many indigenous communities, including American Indian communities. The scientific research enterprise has struggled to meet the 4Rs standards due to its 'top down' approach, where participants are not treated as equal partners in research. Return of individual results is a path to creating a reciprocal relationship that contributes to sustained participant engagement in research (Hiratsuka et al., 2018)

This dissertation is significant due to the inclusion of American Indian participants in the study sample. To date, only a handful of studies have discussed the dissemination of results in American Indian communities; and these studies have focused on aggregate results, not IRR (Beans et al., 2018; Dillard et al., 2018). One other study by Wilkins et al., (2018) included a small number of American Indians, but the participants were identified through a database of research volunteers and were not part of an on-going research study. This dissertation is the first to examine the influence of result type and ability to frame the results in a normative context on the perceived value of IRR in a sample American Indian mothers participating in an ongoing research study.

Research Questions and Hypotheses

The overarching aim of this dissertation is to investigate participant perceptions of the value of the return of IRR and how a range of factors such as result type, availability of normative context, and timing of the return of results may influence the perceived value of IRR. A concurrent mixed methods approach was used to gather quantitative data and qualitative interviews to examine the participants' perceptions of value and the decision-making process.

Three result types analogous to data collected in the PASS ECHO study were included– survey result, biospecimen result, and physiology result. Each result type included a measure/assessment collected in the PASS ECHO study and corresponded with three domains respectively – sleep health (psychosocial domain), urine phthalate exposure (chemical domain), and sleep physiology assessment (physiology domain)

The dissertation study was guided by three aims:

1. To what extent do result type and standardization of results influence participant perceptions of value of receiving IRR?
2. Are there differences in participant responses regarding value of research results from psychosocial, chemical exposures, and physiology domains between American Indian and White participants?
3. How do participant perceptions of the value of the return of IRR differ based on when results are returned and the age of the affected individual?

Quantitative Study

In this dissertation, the term 'standardization' referred to whether or not a normative context was available for the IRR. An experimental factorial design was used to test whether the interaction between the two independent factors (result type and standardization status) influenced participant perceptions of the value of the IRR.

There were three experimental hypotheses corresponding to each of the main effects of the two factors and an interaction effect. The alternate hypotheses are as follows:

- There would be main effect for result type; participants would attribute higher value to result type, irrespective of standardization
- There would be a main effect for standardization type; participants would attribute higher personal value to standardized results
- There would be an interaction between result type and standardization such that for standardized results, the three types of results would be attributed equal value, but for non-standardized results, chemical assay results would be ranked higher in value than psychosocial results or physiological results.

Qualitative Study

Using semi-structured interviews, the qualitative study explored participants' views on decision-making regarding the value of the IRR, the influence of timing on the value of the IRR, and their preferences for communicating the results to them.

Conceptual Framework

The primary goal of the study was to assess the participants' perspectives on the value of IRR as defined by the 2018 National Academy of Sciences, Engineering and Medicine Consensus Study Report (NASEM, 2018). As such, gaining insight into participant perspectives of the value of IRR would allow for the harmonization of IRR guidelines with participant preferences. In clinical practice, 'values clarification methods' are used to assist with medical decision-making so that treatments align with patients' choices (Kong Lee et al., 2013). Witteman et al. (2016) define values clarification as 'the process of sorting out what matters to an individual relevant to a given health condition". Values clarification methods are "strategies that are intended to help patients evaluate the desirability of options or attributes of options within a specific decision context; in order to identify which option he/she prefers (p.2)".

There are several types of values clarification methods cited in the literature, but fundamentally, their goal is to help patients make health related decisions through the use of decision aids to align their values with options provided to them (Witteman, 2021). Some examples of use of values clarification methods are: choosing between various chemotherapy options for treatment of cancer, or choosing between five different types of treatments for knee pain (Fraenkel et al., 2007).

Most values clarification methods use Decision Process Theories to guide the process of decision-making (Fagerlin et al, 2013). Using an innovative approach, this study applied the Behavioral Decision Framework (one of the Decision Process Theories) to evaluate the process by which participants make decisions about their perceived value of individual research results. As described by Fagerlin (2013), the Behavioral Decision Framework has three basic tenets:

- Decision strategy that focuses on consequences based on others' experiences - For e.g., selecting a particular method of treatment because it was recommended by a friend or doctor;
- Structuring – logically evaluating each of the options and determining their value on a personal level
- Using compensatory decision rules – evaluating tradeoffs of selecting a certain option

In this study, we primarily examined the decision strategy component of the Behavioral Decision Framework by applying the framework to develop the qualitative interview questions and guide the inquiry into the process by which participants in the dissertation study were likely to attribute value to IRR. Understanding how participants make decisions about the value of IRR may provide clues to operationalize the return of results process and answer questions related to what, when and how to return IRR.

Summary

The purpose of this dissertation study is to identify gaps in knowledge regarding participant perspectives, and better understand the influence of result type and normative context on the perceived value of IRR in a diverse group of research participants from a large observational study. This study will be of interest for researchers, funders and policymakers as the outcomes are expected to underscore the need to incorporate participant opinions in the process of returning IRR and serve as an impetus for continued research related to the return of diverse types of research results. This dissertation was planned as a three-manuscript model. The four chapters following this introductory chapter include:

- Chapter 2 - Participant Perspectives on Return of Individual Research Results: A Review of Salient Topics, Trends, and Gaps
- Chapter 3 - Return of individual research results: A quantitative study of participant perspectives in the ECHO cohort in South Dakota
- Chapter 4 - Participants' perspectives on the return of individual research results: A qualitative study of participant perspectives in the ECHO cohort in South Dakota
- Chapter 5 – Conclusion including integration of the quantitative and qualitative results

Chapter 2. First Manuscript

Participant Perspectives on Return of Individual Research Results: A Review of Salient Topics, Trends, and Gaps

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Funding support: 3UH3OD023279-06S1 and 3UH3OD023279-06

Word Count: 2323

Key Words – Individual research results, American Indian, Cohort studies

Abstract

Return of individual research results is a critical component of the research process. Prior work in the field of return of individual research results suggests that both participants and researchers are interested in establishing a process for returning individual results. However, lack of empirical data on return of various types of results, including a gap in knowledge regarding participant preferences of the value of IRR continues to pose significant barriers to returning IRR. This manuscript provides a review of salient topics and emerging ideas related to return of IRR and provides recommendations for future research that could pave the way for developing best practices for return of all types of IRR.

Introduction

Broadly speaking, the ultimate goal of health-related research is to generate results that lead to improved health outcomes for individuals and/or benefit society as a whole. In order for research to achieve its desired goals, research results must be available to all, including the research participants. These results may be shared in an aggregate format or on an individual basis. By definition, the return of individual research results (IRR) relates to the return of information related to a specific participant (SACHRP, 2016). According to a 2016 report by the Secretary's Advisory Committee on Human Research Protections, the provision of individual research results to participants aligns with the principles of Respect for Persons and Beneficence as outlined in the Belmont Report and recognizes their valuable, often altruistic contribution to research (SACHRP, 2016). Sharing of IRR improves trust and willingness to participate in research (Kaufman et al., 2008).

Previous research suggests that study participants are interested in receiving IRR (Long et al., 2016; Shalowitz & Miller, 2008; Snowdon et al., 1998) and researchers are interested in providing results to participants (Sayeed et al., 2021). Despite the interest within the research community, overall the return of IRR remains "uncharted and untested' (Wong et al., 2018). The return of results process is complex and influenced by factors related to clinical utility, resources, and inadequate knowledge about participant preferences for IRR. Prior work from genetic studies shows that participant preferences for IRR are dynamic, and vary depending on individual experiences and cultural factors (Lakes et al., 2013). Some other studies exploring participant preferences for diverse types of IRR have found similar results (Hiratsuka et al., 2018; Sayeed et al., 2021; Wilkins et al., 2018). Clearly, diversity in participant preferences needs to be considered when developing a framework for the return of IRR. Continued examination of participant perspectives of personal value and meaningfulness of IRR is critical to developing best practices for the return of diverse types of research results. The purpose of this manuscript is to review the salient topics related to IRR and identify current trends and gaps in participant perspectives regarding the return of a broad spectrum of individual research results.

To inform the literature review, we consulted with a research librarian and conducted a search of two databases: MEDLINE and EMBASE. Using 'individual research results' as a preliminary search term, we identified the following MeSH terms: beneficence, cohort studies, ethics, genomics, moral obligation, personal satisfaction, patient preference, and researcher-subject relationship and biospecimens Due to limited published literature on researcher and/or participant perspectives across multiple types of studies, we kept the search criteria relatively broad. We excluded articles related to the IRB review of IRR, regulatory and legal framework, and incidental findings as these were not directly relevant to examining participant perspectives of return of IRR.

Return of Individual Research Results – An Ethical Obligation

Many ethics experts believe that the dissemination of results directly to participants and communities is an ethical obligation (Fernandez, 2003; Steinbekk & Solberg, 2012). The origins of this belief can be traced to the three key ethical principles outlined in the Belmont Report: individual autonomy, beneficence, and justice (Hintz &Dean, 2019). The idea here is of respect and reciprocity to those that have contributed data, time, and effort to research (Vaz et al., 2018). Fernandez et al., (2003) have supported providing participants with research results, irrespective of the prospect of direct benefit. Yet, many others in the field have opposed the idea of providing results as an ethical obligation, particularly when results, especially genetic results are of unknown significance and may be difficult to interpret (Knoppers et al., 2006; Miller et al., 2007). The concerns with returning results of unknown certainty may also stem from the belief that researchers must ‘first do no harm’. Many researchers believe returning results (even with participant consent) of unknown certainty may do more harm than good by putting the participant at additional physical, mental or financial risk. Additionally, results obtained in a research setting may not meet the same validity standards established for results used in clinical care, i.e. Clinical Laboratory Improvement Amendment (CMS, 2021). Yet, a few pragmatic researchers question the reluctance to return results based on insufficient scientific evidence. Biesecker (2013) calls out the ‘fallacy of Nirvana’ or the attempt to attain perfection. The author argues that participants and researchers do not live in an ideal world and clinicians make decisions based on less than perfect evidence each day. Thus, a real world approach is necessary to developing policies surrounding return of individual research results.

Research participants have expressed mixed feelings about the researcher’s obligation to return IRR. A study of pediatric oncology patients and their parents found that greater than 95% participants indicated they had a strong or very strong right to receive individual research results (Fernandez et al., 2007). In another qualitative study of 141 diverse adults, participants noted they have a right to obtain the results as they see themselves as ‘owners’ of the data (Murphy, 2008). Simultaneously, studies have noted that many participants do not consider return of IRR as a researcher obligation, primarily because participants do not strongly perceive individual results to be an incentive to participate in research. These individuals are motivated to participate for altruistic reasons and do not expect anything in return. Individual research results may be a motivating factor for some individuals but other factors such as trust and the ability to have a voice in the research process have also been shown to influence participant engagement in research (Lewis et al., 2021).

Participants in research should not be considered as ‘mere subjects’, but equal partners in decision-making about their research participation and outcomes (Bromley et al., 2017). In many ways, the existing regulatory framework was not designed to include participants as equal partners. The Belmont report requires that researchers and regulatory groups such as institutional review boards estimate the risks and benefits on behalf of participants based on their (researcher) assessment of the proposed research (HHS, 2016). Given this regulatory charge, typically, researchers have unilaterally made assessments regarding the risks and benefits of research. The new paradigm of participant engagement calls for bidirectional communication between the researcher and the participant to facilitate participant input in all aspects of the research design.

Beyond Genetics Results

In the past decade, rapid progress in genomic sequencing has made genetic testing more affordable resulting in increased interest in the diagnostic and predictive ability of genetic results. An abundant body of literature including systematic reviews and mixed-methods studies primarily in genetics exists on participant perspectives on IRR (Goodman et al., 2018; Joffee et al., 2019; Kaufman et al., 2008; Lewis et al., 2021; Mwaka et al.,2021 & Wong et al.,2018). These studies investigated participant preferences with respect to health conditions, the timing of return, comfort with results of unknown certainty and the potential cost or trade-offs for receiving the genetic results. Simultaneously, there exists a significant gap in knowledge with respect to other types of results, even as basic as survey results or laboratory results (Wong et al., 2018). It is time to look beyond genetic results. The emergence of new data collection techniques such as wearable devices or remote data collection creates an urgency to gather empirical data on participant preferences for other types of results to better inform ‘what, how, and when’ to return

IRR. Availability of empirical data may also help shape the regulatory guidance on return of IRR in the future allowing more flexibility in returning individual results.

Clinical Utility versus Personal Value

The concept of clinical utility has been the principal driver of existing overall guidance on when and what to return (Burke et al., 2014). The focus on clinical utility appears to create a discordance between the ethical perspective that promotes obligatory disclosure of results and contemporary scientific guidance which limits disclosure based on clinical utility. This disconnect may have resulted in confusion and/or lack of motivation for researchers to return to IRR. The rationale for withholding results based on unknown clinical utility may simply not be appropriate across the myriad of results that can potentially be returned.

In a 2018 report, the National Academies of Sciences Engineering and Medicine (NASEM) recommended that researchers consider the value of the result to the participant, along with the risk and feasibility of return (NASEM, 2018). Marking a shift in the conversation from 'clinical utility' to 'value' of results for participants, the report opened the door for a broader conversation surrounding the value-based return of results. The NASEM report advises against ranking personal utility lower than the clinical utility. In fact, the NASEM report expands the definition of 'value' to include personal and clinical utility. Essentially, participants' sense of a value of a research result may be derived from either personal utility, clinical utility, or both.

Previously published work in return of IRR has shown that participants found personal value in the negative, non-diagnostic genetic results or results of unknown clinical utility (Bollinger et al.,2020, Hoell et al., 2021 & Mollison et al.,2020). Mollison et al., (2020) examined parents' perceptions of the personal utility of exome sequencing results in a study of children with suspected genetic disorders. In these studies, parents found personal utility in negative as well as uncertain results. Personal utility was attributed to several reasons including, feeling empowered by the knowledge gained, feeling respected by researchers, and feeling more involved in the study.

Lack of Geographic and Racial Diversity

The literature review on the return of IRR showed a lack of adequate representation of geographically and racially diverse participants. Lewis et al., (2021) conducted a study with an African American genomic sequencing research cohort and found that participants valued engagement and the ability to share their views, particularly given the history of abuse and mistrust in research. Wilkins et al., (2018) queried participants from ResearchMatch, a research registry database to gather their perspectives on the personal value of a broad range of research results (Harris et al., 2012). The majority of the participants in this study were white (40.8%), followed by Hispanic, Latino or Spanish (12.8%), Black, African American or African (27.3%), Asian (12%), and American Indian or Alaska Native (1.6%). This study also found that the perceived value of results differed across demographic groups and educational achievement.

American Indian/Alaska Native Perspectives

Wilkins et al., (2019) is important because it explored participant perspectives on topics beyond genetics and clinical utility. Yet the study was limited due to the lack of representation of American Indian/Alaska Native populations. The history of research with American Indian/Alaska Native populations is complicated. Dillard et al., (2018) have noted that American Indian or Alaska Native people have had negative research experiences, including a lack of for their participation in research. According to Kirkness and Barnhardt (1991), the 4Rs - respect, relevance, responsibility and reciprocity are an important paradigm for defining relationships in many indigenous communities, including American Indian communities. The scientific research enterprise has struggled to meet the 4Rs standards due to its ‘top down’ approach, where participants are not treated as equal partners in research. Return of individual results is a path to creating a reciprocal relationship that contributes to sustained participant engagement in research (Hiratsuka et al., 2018)

Furthermore, a lack of respect in communicating research findings, as in the case of the Barrow Alcohol study has further diminished trust in research and researchers (Foulks, 1989). The American Indian/Alaska Native population is the smallest racial minority group in the United States, comprising approximately 1.3% of the country’s population, and yet they bear the greatest burden of chronic disease (IHS, n.d.). Many of health challenges arise from preventable/modifiable factors such as dietary and lifestyle changes including avoidance of substance use. Engaging American Indians in research and providing information from research back to them is critical to improving health through enhancing health promotion and disease prevention. We know that participant interests vary significantly across gender, race/ethnicity (Sabetello et al., 2020; Sayeed et al., 2021). Yet, there is very little information on American Indian participants’ perceived value of IRR and preferences for communication of results.

Beans et al. (2018) used a mixed methods approach to obtain quantitative and qualitative feedback from Southcentral Foundation, a tribal health organization serving Alaska Native and American Indian people in southcentral Alaska. The researchers convened a Health Research Forum with community members and solicited responses on questions such as how, when or where should results be shared. Notably, these questions did not distinguish between individual and aggregate results.

The Beans et al. (2018) study was one of the first attempts at understanding American Indian perspectives on the return of results. Participants in the study recommended the use of multimodal communication strategies such as mail, email, and the development of patient portals. Similar to Wilkins et al., (2019) this study was also limited in that participants were not research study participants. Rather, they were members of the community. While community member perspectives are important, responses regarding the personal values of those enrolled in research may differ from general community members. Evidently, there is a compelling argument for the inclusion of American Indian participants in the examination of return of IRR to help inform culturally tailored strategies for returning results.

Moving the Field Forward

Interest in the return of individual genetic results has failed to relay to other types of results. The relative streamlining of the return of individual genetics results that we see today is the product of several years of research. In order to develop a robust knowledge base for the return of other types of results, it is necessary to collect data from on-going research studies (Wong et al., 2018). Large network studies such as the Environmental Child Health Outcomes Study, the *All of Us* Research Program, or the HEALthy Brain Child Development Study are poised to generate a tremendous amount of diverse types of data and are well placed to gather participant perspectives to inform meaningful return of IRR (Blaisdell et al., 2021; HBCD, 2022). The Environmental Child Health Outcomes study is a nationwide effort to collect longitudinal information from 50,000 children and their parents on exposures that affect child health and development. The HEALthy Brain Child Development study examines the long-term effects of perinatal exposure to opioids on infant and child development in a sample of 10,000 children and their parents. These two studies combined collect a wide variety of data including structural and functional imaging, biospecimens, data on social, emotional and cognitive development, and physiology data through wearable devices and many more components of family, medical and social history. Another longitudinal research endeavor is the All of Us Research Program - a national effort to collect information on the relationship between environment, lifestyle and genetics from at least one million people to advance scientific research and discovery for years to come (Mapes et al., 2020).

These large studies exemplify the potential for in-depth examination of participant preferences of IRR across a wide variety of data. The large community based sample and longitudinal study design for these studies provides an opportunity to capture changes in participant preferences for IRR over time. It is important that attention and resources be dedicated towards collecting information on participant preferences and processes for return of IRR within these studies.

In order to move the field forward, it is imperative to define and qualify participant interest with respect to result type, timing of return and feasibility of return. Finally, understanding racial and geographic differences in participant perception are critical to developing culturally appropriate strategies and long-term engagement in research.

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Chapter 3. Second Manuscript

Return of individual research results: Participant perspectives in a longitudinal community-based sample

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Funding support: (3UH3OD023279-06S1 and 3UH3OD023279-06).

Word Count – 2984

Number of figures and tables: 3

Key Words - Individual research results, American Indian, Cohort, results of unknown significance

Abstract

The last decade has witnessed growing calls for the return of individual research results. Prior work in genetic studies shows that participants' preferences for individual research results are dynamic and influenced by individual contextual and cultural factors. There exists a gap in knowledge about participants' views about other types of results. This study investigates the perspectives of 1587 mothers enrolled in the Environmental Influences on Child Health Outcomes (ECHO) Program. Participants were presented with hypothetical scenarios to determine their perceived value of individual research results based on result type and the ability to interpret the result within a normative context. Irrespective of the result type, participants attributed higher perceived value to results that were well understood than results of unknown certainty.

Introduction

The return of individual research results (IRR) to participants is a complex process due to the diversity of research results, regulatory and ethical considerations, and resources essential for the return of results. Individual results returned to participants may include but are not limited to, survey results, laboratory test results, genetic test results, socio-behavioral test results, or biospecimen analyses. The framework for the return of IRR has largely been guided by genomic results and the utility of results for clinical decision-making (Wilkins et al., 2018). Yet, not all research findings may inform clinical decision-making. Within the scientific community, there is a growing consensus toward returning a broader range of individual results (Sabatello et al., 2020; Sobel et al., 2020). It is widely acknowledged that the return of individual and/or aggregate research results leads to increased participant trust, particularly in communities that have historically struggled with mistrust of scientific research and researchers such as the American Indian and African American communities (Hiratsuka et al., 2019; Lewis et al., 2021; Portacolome, 2020).

More recently, researchers are encouraged to consider the personal value of individual results and not be encumbered by the clinical utility of results (NASEM, 2018). The personal value of individual results may vary from one participant to another. For some, the personal value may be derived from the clinical significance, result type, or actionability of the result; for others, the personal value may result from the reciprocal act of receiving results in exchange for research participation (NASEM, 2018).

Background

Despite the interest in the return of IRR, concerns surrounding utility, cost, and lack of operational clarity have stymied the return of IRR (Bollinger et al., 2014; Brody et al., 2014; Klitzman et al., 2013; Murphy et al., 2008). Thus, researchers have typically not returned IRR unless they were relevant to clinical decision-making (Wilkins et al., 2018). Recently, the Multi-Regional Clinical Trials Center (MRCT) released a new website with resources for the return of IRR from clinical trials (MRCT, 2022). Some of the resources include how to categorize individual clinical trial results, how to create a plan for IRR, who to involve, and how to return IRR. These resources were created through the engagement of diverse stakeholders including participant advocates, researchers, and regulatory entities.

Arguably, a comparable effort is essential to optimize the return of IRR in studies other than clinical trials such as observational studies, in particular longitudinal studies. These studies follow individuals over several years or decades and have the potential to generate vast amounts of data (Sayeed et al., 2021). While these data may not always be used for clinical decision-making, they may have personal value for participants in other ways. In this study, we investigated the perspectives of a cohort of mothers enrolled in the Environmental Child Health Outcomes (ECHO) program – a National Institutes of Health initiative to study the long-term effects of early-life environmental exposures on child health outcomes (Blaisdell et al., 2021; Gillman & Blaisdell, 2018).

Using a mixed-methods design, we examined participant perspectives of the value of varied types of individual results and explored how participants make decisions concerning the personal value of the individual research results. Specifically, we investigated participant perspectives of the value of an IRR based on result type (survey result, biospecimen result, or physiology assessment result) and ability to interpret the result within a normative context (standardized). An additional purpose of this research was to delineate racial differences in participant perspectives between American Indian and White participants. This manuscript describes the methods, analytic strategies, and results from the quantitative component of the study. The qualitative component is described in a separate manuscript.

Methods

Participants

Participants were sampled from mothers enrolled in the ECHO program in South Dakota. At the time of enrollment, participants were either pregnant or had a child currently enrolled in ECHO. Mothers greater than 18 years of age, currently enrolled in ECHO, able to understand English, and provide informed consent were eligible to participate. Mothers with multiple children enrolled in ECHO received only one instance of the survey. We excluded children where someone other than the mother provided the original parent/guardian consent. Participants enrolled in this study represent two prominent racial populations in South Dakota: White and American Indian.

Randomized Factorial Design

The study design utilized a 2x3 randomized factorial design (independent samples) that included two levels for standardization status (standardized and non-standardized) and three levels for result type - survey result, biospecimen result, and physiology assessment (Table 1). We hypothesized that there would be an interaction between result type and standardization status such that for standardized results, the three types of results would be attributed equal value. For unstandardized results, biospecimen results would be attributed higher value than survey results or physiology assessment results. In this study, the term ‘standardized results’ refers to IRR that can be compared to population normative standards such as data on Body Mass

Index (CDC, 2020). In contrast, 'non-standardized' results are stand-alone results for which normative comparisons are not available.

Each participant was randomly assigned to one of the six groups and was asked to respond to one hypothetical scenario that correlated with one of the six groups (Table 1). A copy of the questionnaire is included in Appendix A. In general, scenarios allow participants to analyze a given situation by placing themselves within a specific context (Pinto & Pinto, 2019).

Evidence from previous studies in genetics suggests the personal value of individual results is influenced by several factors, including clinical significance, result type, actionability, or personal value (NASEM, 2018). For this study, we chose two factors to investigate - result type and standardization status. To create an engaging experience for participants, we used result types from actual assessments collected in the ECHO program. Each result type included a hypothetical scenario pertaining to data on an environmental exposure collected in ECHO. For example, the biospecimen result type included a scenario related to phthalate exposure in urine. Participants were asked to attribute the perceived value (outcome variable) of each result based on the result type and standardization status (independent variables). Because clinical decision-making was not the focus of this research, hypothetical scenarios focused on results that would not inform clinical decision-making.

Data Collection

The study protocol was approved by the Avera Health Institutional Review Board. All participants provided written consent prior to research participation. Survey readability was assessed using the Flesch Reading Ease and Flesch –Kincaide Grade level scores. All scenarios used in the survey scored greater than 60 for the Flesch Reading Ease, and between 8th and 9th-grade reading levels for the Flesch-Kincaid Grade Level. The survey was pilot tested to ensure clarity of scenarios, and to identify challenges with the use of the online survey platform. The survey was administered using the Research Electronic Data Capture (REDCap) system. Participants were randomized to receive one of the six scenarios using the 'randomization module' in REDCap. Participants received a URL via their preferred email prompting them to respond to the survey. A two-week reminder was sent to non-respondents. In REDCap, participant responses were recorded via a slider with a response range from 0 to 50, with 0 being 'least valuable and 50 being 'most valuable' (Appendix A). The slider was set up such that the default position was in the middle of the sliding scale as shown in Appendix A. Participants were asked to drag the slider to a position that aligned with their value for the scenario (low value to high value). The REDCap system recorded a response only if the slider was moved from its default location. A $25 gift card was provided for participation.

Measures

In addition to the outcome measures, demographic data including age, race, ethnicity, and maternal education were collected (Table 1). Participants were also queried about years of participation in research.

Data Analysis

Descriptive analyses were conducted on all variables to assess the homogeneity of variances, normality of distribution, skewness/kurtosis, and total missingness. We used Pearson's chi-square to test whether the standardized and non-standardized groups within each result type were different. To determine if there was a response bias, we examined the differences in the sociodemographic characteristics of participants who recorded a response (moved the slider) and those missing a response (did not move the slider) using Pearson's chi-squared test. We conducted a factorial analysis of variance followed by Tukey's test to understand differences between results and to test for significant main effects, (result type and standardization status), and an interaction effect. Finally, we conducted a multivariate general linear model analysis to identify racial differences in the influence of result type on the value of results between White and American Indian participants, while adjusting for covariates such as maternal age, education, and years of research experience. Descriptive analyses were conducted in SAS OnDemand for Academics.

Results

Between December 2021 and January 2022, electronic surveys were sent out to 2536 eligible participants. Of these, 1676 surveys were returned with a response rate of 66%. From these, we excluded 89 duplicate responses resulting in a final sample of 1587 adult, female respondents (Appendix B). For duplicate responses, we kept the first response and excluded the duplicate. The mean maternal age was 35.3 years (*SD*=6.3) years at the time of survey completion. Ninety-one percent of the participants were White (n=1409), followed by 8.2% American Indian (n=127) and 1.3% from Other races (n=20). Participants identifying as American Indian plus another race were considered American Indian, while all other races such as African American, Asian, Native Hawaiian and those identifying as White plus another race, were considered 'Other'. There were no statistically significant differences in maternal age, race, or education amongst standardized and non-standardized groups for each result type. Table 2 describes the sociodemographic characteristics of the mothers included in the analytic sample. Additional descriptive statistics are presented in Appendix C.

During analysis, we discovered that 149 participants submitted the survey, but the slider remained at the default midpoint of the sliding scale and the response to the scenario was recorded as 'missing'. It is not possible to discern whether these participants (n=149) neglected to move the slider or intended to keep it at the midpoint on the scale. Participants that moved the slider were more likely to be White and more likely to have a college degree ($p<0.001$). In the primary analysis for the question - "To what extent do type and standardization of results influence participant perceptions of value the of IRR", we ran a factorial analysis of variance to test for main and interaction effects for result type and standardization status. Results for the interaction were not statistically significant; therefore, we ran the factorial analysis for the variance for main effects alone which were significant for result type [$F_{(5, 1432)}$ =10.92, p<.0001] and standardization status [$F_{(5, 1432)}$ =278.30, p<.0001], (Table 3). We found that the standardization status and result type were independently associated with the perceived value of the result. Result type was associated with the perceived value of the result where the mean difference in the perceived value of biospecimen results was higher than physiology assessment results (M_D =3.36 [CI-1.37-5.35]) and survey result (M_D =3.55 [CI – 1.58 – 5.53]). Standardization status was associated with the perceived value of result where the mean difference in the perceived value of the result of standardized results was higher than non-standardized results ($M_{D=}$11.48 [CI - 10.13-12.83]).

Sensitivity Analysis

To understand the influence of missing data (n=149), we conducted a two-step analysis. As described above, we ran the analysis excluding the missing data (n=149) and then conducted a posthoc sensitivity analysis including the missing data (n=149) by assigning a score of 25 for the missing values assuming participants intended to choose the midpoint response on the sliding scale (Appendix D). Based on the results of the sensitivity analysis we observed no difference in the overall results, therefore chose to include all participants.

To identify racial differences between White and American Indian participants in the association of result type with perceived value, we conducted separate multivariate general linear models for standardized and non-standardized scenarios. Overall the model accounts for a statistically significant variation in the outcome (p<.001) adjusting for the following covariates, maternal age, race, and education. No statistically significant interaction between race and result type was observed. After adjusting for maternal education, age, and years of research experience in the unstandardized group, we observed both race (p=.0302) and result type (p<.0001) were significantly associated with perceived value (Appendix E). We ran a contrast statement to test whether the racial groups were significantly different from one another and found a significant difference in the perceived value of the result between American Indian and the Other racial groups, where American Indian participants had a higher perceived value of IRR based on result type than participants in the Other racial group (p<0.0057).

Discussion

In this study of a racially diverse sample of mothers from South Dakota, we found no influence of result type (e.g., biospecimen result or physiology result) as a function of standardization status on the perceived value of the result. The result type had an effect on perceived value irrespective of the standardization status, and participants attributed higher value to standardized results than unstandardized results across all result types. To our knowledge, this is the first study examining the influence of these two factors on the perceived value of individual results in a diverse sample of American Indian and White participants. The role of other potential influencers of the perceived value of results such as the timing of the return of results, along with the participant's approach to value-based decision making is described in the accompanying qualitative manuscript.

Thus far, discussions surrounding the return of IRR have focused on genetic results and clinical utility. Yet, the formation of large, observational adult and pediatric cohorts such as All of Us, ECHO, and the HEAlthy Brain and Child Development (*All of Us*, 2021; ECHO, n.d.;

HBCD, 2022) provides a compelling argument to look beyond clinical trials and genomic results, and direct attention to other types of individual research results.

Our study highlights the need and interest in the return of IRR from observational studies. Our study found that participants attribute a higher value to different result types where results from biospecimens were valued higher compared to surveys. Our findings are similar to those from the Project Baseline Health Study, a prospective cohort study (n=1890) that showed participants' preferences differed across results types (Sayeed at al., 2021). Evidently, the diversity in participant preferences warrants more attention and needs to be explored across various populations and study types.

Participants in our study overwhelmingly attributed higher value to standardized results or results that can be interpreted within a normative context. This is an important finding given that results from many observational measures may not have existing normative standards, thereby potentially limiting the return of results. Yet, this finding may help investigators in identifying priorities and managing available resources for the return of IRR.

As noted previously, a major strength of our study was the inclusion of a large number of American Indian participants. One hundred and twenty-seven (8.1%) participants in our study self-identified as American Indian. We know from previous studies that participant preferences for return of IRR vary based on race and sociodemographic characteristics (Sayeed et al., 2021; Wilkins et al. 2018). No study to date has explored American Indian perspectives on the return of IRR for subjects currently enrolled in research. Hiratsuka et al. (2020) explored opinions of Alaska Native community members on broad dissemination of research results, not IRR. The Wilkins et al., (2018) study included only 42 (1.6%) American Indian participants. Neither of these studies included subjects currently enrolled in research. Our study is novel because participants were able to draw on their experience from participating in ECHO to provide feedback on their perceived value of IRR. We hypothesized there would be racial differences between American Indian and White participants regarding value attributed to IRR such that American Indians would attribute a higher value to results irrespective of the standardization status due to underlying cultural beliefs about reciprocity in research. Several studies have shown that reciprocity and respect is an important paradigm of relationships in American Indian communities (Hiratsuka et al., 2020; Around Him et al., 2020). Given this notion, we hypothesized that American Indian participants would attribute a higher value to results, irrespective of whether they were standardized. However, we did not find a statistically significant difference between American Indian and White groups with respect to the perceived value of results. Statistically significant differences were found between American Indian and Other groups where American Indian participants had a higher perceived value of IRR than participants in the Other group. However, this finding should be interpreted with caution due to the relatively broad definition of the "Other group" and difference in sample size between the groups.

There were several limitations to this study. The study may not be generalizable across varying geographic locations due to its focus on women enrolled from a specific region. Two of the three scenarios used in the study were related to sleep data and may not have been adequately distinguishable. Even with these limitations, the study provides valuable knowledge to further research into return of IRR for cohort studies.

Conclusion

Our study supports the growing call for patient-centered research where participants contribute to all aspects of research – from design to dissemination. Participants in our study attributed higher value to IRR when provided within a normative context. This is interesting because even in the current research climate that supports greater transparency through increased data sharing, participants only want data that can provide meaningful comparisons, presumably to inform health related behavior changes. In our study, we only queried about the value of results in the presence or absence of population normative standards. We did not inquire about their perceived value of results if comparisons were available with others within the cohort. Further research in this area may be highly beneficial as many observational data do not have established normative standards, but may be able to provide individual comparisons within the cohort. In order to align resources with participant preferences, researchers may want to focus their efforts on results with normative standards, but continue to gather participant perspectives on other factors that influence perceived value of IRR.

Table 1

Experimental Factorial Design

		Factor B (Result Type)		
		Level 1 Survey Results (Sleep Health)	**Level 2 Biospecimen Results (Urine Phthalate)**	**Level 3 Physiology Assessment (Sleep Physiology)**
Factor A (Standardization)	**Level 1 Standardized**	Sleep Health /std.	Urine Phthalate/Std.	Sleep Physiology/Std.
	Level 2 Non-Standardized	Sleep Health/Non-std.	Urine Phthalate/Non-std.	Sleep Physiology/Non-Std.

Table 2

Participant characteristics

	Total (n=1587)	**Survey Result Sleep Health**			**Biospecimen Result Urine Phthalate**			**Physiology Assessment Sleep Physiology**		
		Standardized (n=252)	Non-standardized (n=284)	p-value	Standardized (n=246)	Non-standardized (n=264)	p-value	Standardized (n=271)	Non-standardized (n=270)	p-value
Maternal Age [mean(std)]	1586 (35.3) (6.3) [a]	36 (6.3)	35 (5.9)	0.15	35.6 (6.6) [a]	35.6 (6.0)	0.9	35 (6.6)	35 (6.2)	0.52
Maternal Race, n (%)				0.88			0.87			0.86
Caucasian	1409 (90.55)	232 (92.06)	254 (91.04)		220 (91.67)	235 (92.16)		236 (88.72)	232 (87.88)	
American Indian	127 (8.16)	18 (7.14)	23 (8.24)		17 (7.08)	18 (7.06)		24 (9.02)	27 (10.23)	
Other	20 (1.29)	2(0.79)	2 (0.72)		3 (1.25)	2 (0.78)		6 (2.26)	5 (1.89)	
Missing	31(1.9)	0	5 (1.7)		6 (2.4)	9 (3.4)		5 (1.8)	6 (2.2)	
Maternal Education, n (%)										
Less than HS	57 (3.64)	8 (3.17)	8(3.17)	0.73	7 (2.90)	9 (3.45)	0.76	9 (3.35)	16 (6.02)	0.45
HS or GED	110 (7.02)	16 (6.35)	18(6.45)		18 (7.47)	14 (5.36)		23 (8.55)	21(7.89)	
Some college/no degree	203 (12.95)	32(12.70)	27(9.68)		30 (12.45)	36 (13.79)		37 (13.75)	41(15.41)	
College degree	1198 (76.40)	196 (77.78)	226 (81.00)		186 (77.18)	202 (77.39)		200 (74.35)	188 (70.68)	
Missing	19 (1.1)	0	5 (1.7)		5 (2.0)	3 (1.1)		2 (0.7)	4	
Years of research experience, n (%)										
Less than 1 year	502 (31.63)	81 (31.24)	91 (32.04)	0.05	85 (34.55)	78 (29.66)	0.34	88 (32.59)	79 (29.26)	0.43
2-5 years	380 (23.94)	45 (17.86)	67 (23.59)		53 (21.54)	74 (28.14)		63 (23.33)	78 (28.89)	
6-10 years	379 (23.88)	59 (23.14)	76 (26.76)		57 (23.17)	57 (21.67)		64 (23.70)	66 (24.44)	
Greater than 10 years	324 (20.42)	67 (26.59)	50 (17.61)		51 (20.73)	54 (20.53)		55 (20.37)	47 (17.41)	
Missing	2 (0.13)	0	0		0	1		1	0	

[a] one participant was missing age information

Table 3

Factorial Analysis of Variance

Source	DF	Type III SS	Mean square	F Value	Pr>F
Result type	2	3600.95	1800.47	11.37	<.0001
Standardization status	1	43115.99	43115.99	272.20	<.0001

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Chapter 4. Third Manuscript

Participants' perspectives on the return of individual research results: A qualitative study of longitudinal cohort study participants in South Dakota

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Funding support: 3UH3OD023279-06S1 and 3UH3OD023279-06

Word Count – 2997

Number of figures and tables: 2

Abstract

In general, qualitative studies are an important tool to explore participant opinions and perspectives on issues of personal importance. This manuscript explores participant perspectives on the return of individual research results in a cohort of mothers from South Dakota. Participants were queried on their process of attributing value to individual research results and the factors that would influence their decision making regarding value of individual research results. Additional information gathered included influence of timing on return of results and communication preferences for individual results. Understanding the decision making process and other preferences will help harmonize participant opinions with available resources and improve researcher- participant communication during the return of results process. The outcomes of this research will help inform work on developing best practice guidelines for return of individual research results.

Background

Return of individual research results (IRR) remains central to the discussion on ways to maximize the value of research for participants (Sayeed et al., 2021; NASEM, 2018). Recent commentaries suggest that participants are interested in receiving IRR; many ethicists believe that researchers may be ethically obligated to offer IRR to participants (Bollinger et al., 2012, Burke et al., 2014). While several studies have explored participant and researcher perspectives on the return of IRR, those studies have focused on certain results from specific types of data such as genetic data or biospecimens (Kohler et al., 2017; Lewis et al.,2021; Sobel et al.,2020). Recently the *All of Us* Research Program successfully returned individual genetic results to participants who had donated biospecimens for research (NIH, 2020). This milestone is reflective of the progress made in establishing systematic guidelines for the return of individual genetic results.

While genetic results have served as a catalyst for conversations surrounding the return of other types of results, efforts to develop guidelines for other types of results remain rudimentary (Sayeed et al., 2021). Prior research from genetics studies shows that participant preferences for the return of IRR are heterogeneous; therefore, guidelines must reflect participant opinions across a diverse racial, geographic and sociodemographic spectrum. To that end, our study aims to gather perspectives from participants enrolled in the Environmental Child Health Outcomes Program (ECHO) – a large cohort study of diverse mother-child dyads enrolled in two locations in South Dakota. The goal of the ECHO program is to examine the effects of a broad range of early-life environmental exposures on long-term child development (Blaisdell et al., 2021; Gillman & Blaisdell, 2018). ECHO collects diverse types of participant data including survey data, biospecimens, physical and cognitive assessments, and wearable device data.

Given the diversity in data collection, ECHO presents a unique opportunity to collect participant opinions to inform future work for the return of IRR.. This qualitative study was based on the Behavioral Decision Framework, as recommended by Fagerlin et al (2013), to evaluate the process by which participants make decisions about their perceived value of individual research results. As described by Fagerlin (2013), the Behavioral Decision Framework has three basic tenets:

- Decision strategy that focuses on consequences based on others' experiences - For e.g., selecting a particular method of treatment because it was recommended by a friend or doctor;
- Structuring – logically evaluating each of the options and determining their value on a personal level
- Using compensatory decision rules – evaluating tradeoffs of selecting a certain option

The objective of the current study was to explore participant opinions and beliefs about the value of IRR and the process by which participants made decisions about value. Understanding the process by which participants make decisions about value will allow for a patient-centered approach to the return of IRR

Methods

Participants

Participants were selected using random sampling stratified by race (White or American Indian) and maternal education (with or without a college degree). ECHO participants 18 years or older who identified as females, were able to understand English, and provide informed consent, were eligible to participate in the current study. In ECHO, American Indian participants represent eight percent of the cohort. We oversampled American Indian participants (four times) with the goal of allowing for adequate representation of participants who self-identified as American Indian.

Twenty–two participants were approached with a goal to enroll 12-15 participants. Eligible participants received a phone call inquiring about their interest in participating in the study. Of the participants approached, nine did not return the phone calls; two participants did not keep their scheduled appointments. There was one refusal. Ten participants completed the interview. The mean age was 37 years (*SD* =9.5) Ninety percent (n=9) of the participants were White and 10% (n=1) identified as 'Other'. Despite oversampling, we did not enroll American Indian participants. Eighty percent of the participants had a college degree (n=8). Twenty percent (n=2) of participants did not have a college degree.

Data Collection

The Avera Health Institutional Review Board (IRB # 2020.073) approved all study materials. We conducted ten in-depth semi-structured interviews that lasted approximately 35-45 minutes. The study procedures were guided by the four tenets of trustworthiness in qualitative research as described by Lincoln and Guba (1986). Interviews were conducted via Zoom videoconferencing, recorded and transcribed with participant permission.

Pilot testing. The interview guide was pilot tested with three individuals who were not part of the study. Of these, two were researchers and the third was a community member with prior experience as a research participant. Pilot testing offered an opportunity to revise the questions, identify potential follow-up questions or probes, and establish a cadence for the interview.

Interviews. To ensure consistency, the lead author (Angal) conducted all interviews. Ms. Angal has experience with conducting qualitative interviews and is knowledgeable about the issues related to the return of IRR. Interviews were conducted until thematic saturation. All women provided verbal consent and received a $25 gift card for their participation. The final interview guide is presented in Table 1. At the beginning of each interview, the interviewer presented a brief overview of the ECHO assessments and potentially available results (Appendix F). Participants were encouraged to leverage their ECHO experience while responding to the questions.

Analysis

Using generic qualitative approach, we conducted a thematic analysis in which a priori and emergent themes were assessed (Braun & Clarke, 2008; Percy et al., 2015). Two coders independently read and coded the transcripts line by line. Primary data coding was done by the lead author and was guided by the research protocol and interview questions. The second coder independently identified themes and subthemes. Inter-coder agreement was achieved through multiple rounds of coding during which the two coders discussed the themes and subthemes, identified areas of discordance, and resolved coding discrepancies through consensus (Forero, et al. 2018). Minimum kappa was set at .40. Individual kappa coefficients for each of the coding categories ranged from .41 to .76, which is deemed as acceptable ((NVivo, 2020).

Results

We identified six themes and subthemes. Table 2 shows the themes and corresponding key findings for each one of them.

Theme 1: Determining Value

Participants were asked to describe factors they would consider when attributing value to IRR. Initially, some participants struggled with this question. However, the use of probes and examples helped elicit insightful responses. Several participants revealed that the experiences of family members or friends and information on how the research assessments were used would inform their decision-making about the value of IRR.

Participant EPSF-1723-A (age 46) noted the following, " I mean I always take into consideration when I read other people's experiences, obviously is it always going to be exactly the same, no, but yes, I would, I would. I guess it would be of some value to me."

Advice from the researcher was an important contributor to decisions about the value of an individual research result. Participants felt that researchers should provide more information about the purpose of the research assessments and expectations regarding follow-up from the individual results.

Maybe like what certain things that you are looking for or how like maybe let's say anxiety plays into the role of child development or something like that. May be giving more information about what you're looking at and why exactly (EPSF-00693-A, age 48)

I think because the researchers would know a little bit more about it than I would know. I think hearing it from them would be, I think the first step and then maybe chatting with my doctor or something like that, going from there (EPSF-00693-A, age 48)

Theme II: Inherent Value of Result

Inherent value of results emerged as a strong theme as participants began to describe factors that would make IRR inherently valuable for them. For many, the result type, future impact of the result, and personal knowledge gained were significant contributors to the inherent value of the result.

This was particularly true for participants with a medical background or interest in scientific research who had a strong desire to learn about their health or the health of their children.

As a nurse, I think it would be interesting just to see and just to find out just you know, am I normal compared to other people? I don't know. I think it is interesting just because of my medical history and medical background. So I think it would be fun (EPRC-00366-A, age 39)

Other participants thought that results that are likely to impact future outcomes or behavior would inherently be valuable. For example, many participants expressed that results from pregnancy-related assessments may be of value only if they were planning to have more children. Participant EPSF-00084-A (age, 52) said " well, as I won't be having any more children, that example doesn't necessarily hold but of course, it would have been better if I were going to have more children to be told word if it could impact. ....Yeah, I'd love to know about it, you know, I mean, absolutely, if I can help my kids or their offspring or their siblings."

Finally, interviewees felt that in certain cases result type would influence the inherent value of the result. Results from genetic testing, incidental findings, and fetal and child development assessments were noted as valuable.

> *I mean I would be interested in like how maybe height and weight. Like especially like my weight I guess affected development, fetal development, and then it would also be interesting to know, maybe like how nutrition and stuff affects him and probably like sleep too would be interesting. Yeah, I think, like how you parent especially like with nutrition and how you help your child, develop like mentally and I think that would be good to see to help my parenting.*
> (EPSF-00916-A, age 30)

Theme III: Participation Motivations

Participation for altruistic reasons and advancing science emerged as important sub-themes in the study. Several participants noted that they were participating in research for the greater good and did not expect to receive individual results. Nevertheless, they were appreciative of the possibility of receiving IRR. For example, participant EPSF-00916-A mentioned, "I think it's important to have to participate just to help the greater good I think that that's important." Similarly, participant (EPSF-00084-A) noted the following, "It's more like I hope that the information is helpful for the science. So from my perspective I wasn't really looking for anything, I was looking to give things. Does that make sense?

I know when they came to me when I was pregnant with her and asked me to do this, it was more or less just to help you guys out as far as for your studies for as far as for me there wasn't much that I thought that I could take away from it, it was more just to help your study (EPSF-01723-A, age 46)

Theme IV: Payment for Results

Participants were asked about their attitudes towards payment for additional testing often required for confirmation of clinically significant results identified during research testing. Participants suggested they would evaluate their willingness to pay on a case-by-case basis depending on the cost and perceived risk or value of the finding.

I think it would just depend on the cost of it. You know, genetic testing can be expensive and you know, I don't know how in depth of the genetics that you guys go and things like that. So I guess it would just depend on the cost of it, honestly (EPRC-00366-A, age 39).

I think it would depend on what the test was. If it was something that could be harmful or something that would make a difference in my child's health then I would be willing to pay for it, but if it was more just interesting information then I don't know that I would see the value of paying a cost for it (EPSF-01612-A, age 40)

Two participants noted they did not see an issue with paying for additional testing as they are going to be the beneficiary of the results and see it as a preventive measure. *EPSF-01723-A* said “I wouldn't see any harm in having; I mean I probably would pay the additional costs just to make sure. I mean if it's a preventative then yeah.”

Theme V: Timing of Return of Results

Participants were asked if the timing of the return of the result would influence their perceived value of the result. Many participants indicated that they would like to receive the results irrespective of the timing of return.

I think more information is better no matter when, even if it is delayed by, you know, I mean at the very least if there's some new finding, pregnant women talk to other pregnant women and that might help somebody else. So why wouldn't it? More information, more adequate, logical appropriate information is better than no information would be my take. So yes. (EPSF-00084, age 52).

For others, specific conditions such as pregnancy influenced their opinions about timing.

Well, for me I'm not having any more babies, so I guess like in that aspect like I wouldn't be able to use that information to like improve how I am during pregnancy I guess. So, like in that way it wouldn't, but I think anything after like the pregnancy information would be valuable no matter the time frame I guess (EPSF-00916-A, age 30).

Theme VI: Communication of Results

Participants were asked about their preferred mode of communication of results, namely: (1) in person or phone and/or (2) letter or email. In general, communication preferences were equally divided between in-person or phone, and letter or email. For some participants, the mode of communication was result-dependent.

Initially, I lean towards a letter would be fine. But then, if you're going to tell me something serious, then I'd probably rather it be in person. So, if I could pick two, I'd say in person or a letter. (EPSF-03485-A, age 28)

Many participants emphasized the importance of providing context for the results that were communicated back to them. This view was also expressed in relation to results that increase personal knowledge.

*Just a… you know, I mean, I don't know if you're throwing this at me and I haven't thought it all the way through. There could be good and bad. I don't know. I think I would want the ability to have someone provide context for me. I wouldn't just want to be thrown to the walls (*EPSF-00084, age 52)

One participant only wanted aggregate results due to anxiety associated with potentially negative individual results. This participant categorically refused IRR due to increased risk and preferred to get aggregate results (EPSF-03217-A, age 32).

Discussion

In this study, we examined participant perspectives on wide-ranging topics related to IRR such as the process of attributing value to research results, factors determining the inherent value of results, and the influence of timing on the value of IRR.

Return of IRR has widely been acknowledged as a means to reciprocate participants' contribution to research. In our study, a faction of the participants had no expectation of reciprocity from research with respect to the return of IRR. These participants were motivated by altruism and the desire to contribute to 'the greater good'. Return of IRR was not a priority unless the results informed clinical decision-making. Our findings are similar to those found by Bollinger et al., (2012) which showed at least a few participants did not consider IRR as a pre-requisite for study participation, but considered it as a form of compensation.

To our knowledge, our study represents the first attempt to elucidate the process by which participants make decisions about the perceived value of an IRR. In our study, several participants noted that they would consider the experiences of others, such as friends and family when making decisions about the value of an IRR. Participants expected the researcher to help guide the decision-making process by providing information on the study purpose, information regarding the assessments, and results that may be available to them. We were not able to identify other studies in the literature with explicit mention of the role of the researcher in assisting with determining value of IRR.

Most participants found value in results that provide context about their individual health and behavior. We did not specifically query participants on their beliefs about receiving results of unknown significance. However, a small group of the participants expressed a strong interest in receiving everything the study was able to offer. In contrast to previous studies, this desire to receive everything was not related to data ownership or reciprocity (Sayeed et al., 2021) – it was simply because they were curious to find out about themselves. This pattern of results has been seen in other studies and highlights the diversity in participant preferences based on individual experiences and sociodemographic characteristics (Bollinger et al., 2012; Sayeed et al., 2021).

We opted to conduct interviews via Zoom Videoconferencing because the participants were located at two sites across the state of South Dakota. Although in-person interviews are believed to be the 'gold standard' for qualitative research, web-based interviews were not expected to diminish the quality of interaction or data. A recent study has shown that there is only a marginal difference in the quality of data collected from in-person versus video conferencing, with in-person interviews providing slightly superior data (Krowell et al., 2019). A major strength of this manuscript is its qualitative rigor. We used recommendations by Shenton (2004) to strengthen four aspects of trustworthiness in this study: 1) credibility (peer scrutiny, qualified investigators, iterative questioning and examination of previous research findings); 2) transferability (providing the reader contextual information to determine level of transferability); 3) dependability (sufficient description of the research design and operational details of data collection); and 4) confirmability through an audit trail.

Conclusion

This study has increased our understanding of participants' decision-making process and preferences for the return of IRR. Participants in this study preferred results provided with context and follow up plans. Results were inherently valuable if they increased personal knowledge. Participants also noted that the decisions of determining value were difficult and could not be made in isolation. They acknowledged that the opinions of others (family, friends or researcher) influenced their value of IRR. The variability in participant responses demonstrates the challenges in the pathway to developing systematic guidelines for multiple types of results. Participants in our study acknowledged the complexities involved in the return of IRR and seemed to be willing to negotiate the challenges encountered during the return of IRR. It is up to the researchers to engage participants as partners to create a mutually agreeable and meaningful process for the return of IRR.

Table 1.
Interview Questions

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1. As you heard me summarize this study, what first came to mind? (Lakes et al.,2013)

2. The value of an individual result may differ from one person to another. Can you describe the things you would consider when thinking about whether a research result would be of value to you?

    a. PROMPT: Some people may consider whether the result means anything, others may want to know if their doctor can do something about the result. Some people may consider what their friends or relatives have found valuable. Yet others may consider every result from the study important.

3. Is there information the researcher could give that would help you determine the value of the result?

4. Are there any personal or social beliefs that may influence your personal value of an individual research result?

5. In many instances, tests done for research have to be repeated in a clinical lab before the results can be given to you (for example genetic testing or lab tests). How do you feel about having to pay an additional cost of testing in order to receive the results?

6. Let's talk about the timing for when results are returned. Would the value of the result differ depending on whether you are getting them during or after your study participation?

    a. PROMPT: Let us say you were offered results about data collected from you during pregnancy after the birth of your child.
7. If some of the results are from stored samples that are analyzed in the future, would those be valuable to you?

8. How would you prefer the results be returned? Would you be more comfortable receiving the result in person, or through a letter, phone call or some other form of communication?

9. Is there anything else you would like to tell me?

Table 2.
Themes and key findings

Themes	Key Findings
Communication of result	• Participants preferred results with context and an action plan for follow-up as needed • The mode of communication varied with result type and perceived level of risk/value
Determining Value	• Opinions of others (family, friends and researchers) contributed to the process of determining the value of an individual research result
Inherent Value of result	• Results were inherently valuable if they increased personal knowledge • Value of result was influenced by result type and potential for future impact
Participation motivations	• Altruism and scientific benefit were identified as reasons for participating in research • No expectation of receiving individual results as a matter of reciprocity
Payment of results	• Willingness to pay was dependent on cost and perceived value or risk of the result
Timing	• Timing of result mattered based on result type and future childbearing decisions

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Chapter 5. General Conclusion/Discussion

Introduction

This study employed a mixed-methods design to examine participant perspectives of the value of individual research results and the process by which they attribute value to IRR. The research study gathered the opinions of participants currently enrolled in the ECHO program – an observational cohort study designed to examine the effects of a variety of early life environmental exposures on long-term child development (Blaisdell et al., 2021; Gillman & Blaisdell, 2018). The ECHO cohort provided a unique opportunity to examine previously unexplored perspectives of participants enrolled in a diverse longitudinal cohort. This chapter includes a description of the main research findings and their implications for the field of individual research results. Also included is a review of the limitations, delimitations, and potential direction for future research.

Discussion

The return of individual research results remains a topic of great interest and debate within the research community. Growing calls for greater transparency in research through data sharing and increased participant involvement in the research process have accentuated the focus on this topic. Yet, a lack of a comprehensive framework for the return of varied types of IRR has thwarted efforts to return IRR. In particular, there is a lack of knowledge on participant perspectives on the return of individual results beyond genetics results (Wong et al., 2018). As recipients of research results, participant perspectives are critical to determining what, when, where, and how should IRR be returned. Historically, an unequal balance of power has existed between researchers and participants. Researchers have driven most scientific and operational decisions of research including potential risks and benefits of research. In doing so, researchers have often made assumptions about participant preferences such as motivations to participate in research or willingness to accept results of unknown certainty. The National Academy of Medicine and Sciences Report on return of individual results cautions researchers against making assumptions about participant preferences and encourages them to seek input from the participants directly (NASEM, 2018). Return of individual results is a resource intensive process (MRCT, 2017; NASEM, 2018); understanding participant perspectives will help align resources with participant choices creating a cost-effective process for returning results.

Recognizing the need to examine participant opinions, extensive research has been conducted on participant perspectives on return of genetic results, including return of genetic results of unknown certainty. These studies show that participant opinions vary by race and sociodemographic characteristics. While many participants value results that are clinically meaningful, several others find results of unknown significance also valuable. Researchers have been hesitant to return the latter due to potential risk of anxiety or stress for the participant. Prior research in genetics has paved the way for return of genetics results as demonstrated by the return of individual genetics results in the All of Us Research Program (NIH, 2020).

Arguably, there is a need to collect similar data on other types of results such as survey results, laboratory results, biospecimen results, or physiology assessments. Observational cohort studies such as the ECHO program have the potential to generate a wide variety of results. Therefore, exploring perspectives of ECHO participants may inform the return of results process in the ECHO program as well as other studies in the future.

Analytic Strategy

Mixed-method designs draw on the strengths of quantitative and qualitative research to gain deeper knowledge about complex research questions that may be difficult to answer using a single method (Doyle et al., 2009; Ivankova et al., 2006). For this study, a concurrent mixed methods design (QUAN + QUAL) was used in which the quantitative and qualitative data was collected and analyzed simultaneously (as opposed to sequentially), with equal importance given to both types of data (Schoonenboom & Johnson, 2017). Sequential mixed methods designs work well for research questions where results from the first phase of data (quantitative or qualitative) help inform the next phase of data collection and the two phases are connected during this transition (Ivankova et al., 2006). For instance, in sequential explanatory designs, the quantitative results may help inform the interview guides for the qualitative phase,

For this dissertation study, the overall goal was to 1) examine participant perceptions of value of IRR with respect to result type (survey result, biospecimen result, physiology assessment) and standardization status (ability to interpret the result in a normative context), and 2) understand the process by which participants attributed value to individual research results. While these two questions were topically related, the activities for each question were not dependent on each other. Thus, a concurrent-independent design was most suitable to answer the questions of the dissertation (Schoonenboom &Johnson, 2017). In this approach, the quantitative and qualitative data were analyzed separately and results were compared during the interpretation and integration phase.

Integration of Results

Results from the quantitative data showed no interaction between standardization status and result type on the perceived value of the result. By itself, the result type was significantly associated with perceived value of IRR, irrespective of the standardization status. The mean difference in the perceived value of biospecimen results was higher than physiology assessment results (M_D =3.36 [CI-1.37-5.35]) and survey result (M_D =3.55 [CI – 1.58 – 5.53]). Standardized results were attributed higher value than non-standardized research results irrespective of the result type ($M_{D=}$11.48 [CI - 10.13-12.83]).

Results of quantitative data were supported by the qualitative interviews in which participants noted they find individual results more valuable if the results could be interpreted within a normative context. Several participants noted that they would want context for the results to compare themselves to other people and make decisions about their health and the health of their children. The preference for contextual results came through in themes such as 'communication of result and 'inherent value of result'. The main conclusion to be drawn here is overall, for participants enrolled in the dissertation, IRR were valuable when participants could make meaningful comparisons. Still, a few participants in the qualitative study found all results valuable – they wanted all results out of curiosity or to increase personal knowledge. Additionally, one person wanted aggregate results only due to potential anxiety associated unfavorable individual results.

In the quantitative analysis, result type was significantly associated with perceived value of IRR such that biospecimen results had a higher perceived value than survey results or physiology results. In the qualitative study, participants were not directly queried on the influence of result type on perceived value of IRR. Nonetheless, during the course of the interview participants described how result type may influence their perceived value of IRR. For example, participants noted that results related to maternal behaviors during pregnancy or childhood development assessments would be valuable. Notably, participants intending to have additional children in future had a higher perceived value of individual results pertaining to maternal behaviors during pregnancy than those that did not intend to have additional children. Clearly, influence of result type on personal value of IRR differed based on individual experiences and circumstantial factors. This diversity in participant opinion is consistent with findings from other studies (Sayeed, 2021; Terry, 2016).

Results from the quantitative data did not demonstrate statistically significant racial differences between American Indian and White participants regarding the influence of result type on their perceived value of IRR. The influence of American Indian cultural beliefs on decisions regarding perceived value of IRR could not be explored due to the lack of enrollment of American Indian participants in the qualitative study. The findings from the dissertation will help guide the return of results in the ECHO program and serve as a base for expanding and refining the return of results process in ECHO and other studies.

Conceptual Framework

The primary goal of the qualitative study was to explore participants' decision-making process for evaluating the personal value of IRR. Understanding the process by which participants make decisions about value will help inform the guidelines for return on individual research results to optimize the resources available for the return of IRR. In clinical practice, decision-making frameworks help guide patients through the process of selecting an appropriate treatment option. This dissertation adapted the Behavior Decision Framework used in clinical practice to explore participants' strategies for decision making about the personal value of IRR, including any trade-offs they were willing to accept for their choices (Fagerlin et al., 2013).There are three basic tenets in the Behavior Decision Framework as described by Fagerlin (2013):

- Decision strategy that focusses on consequences based on others' experiences – For example, selecting a particular method of treatment because it was recommended by a friend or doctor.
- Structuring – logically evaluating each of the options and determining their value on a personal level

- Using compensatory decision rules – evaluating tradeoffs of selecting a certain option

The qualitative interviews helped explore the decision strategy component of the Behavior Decision Framework. In response to question on how others' experience influenced decision making regarding value of IRR, participants indicated they would likely be influenced by others' experiences, including friends or family or recommendation from the researcher. Several participants acknowledged that while their experiences may not identical as their friends or family, experiences of others would definitely help with making decisions about value of an IRR. Participants also noted that researcher recommendations would influence their decision strategy regarding perceived value of IRR. The inclusion of the researcher in the decision strategy may be an indication of participants' desire for a shared decision making process regarding IRR and underscores the need for open communication between researcher and participants regarding research results.

This dissertation did not explore all aspect of the Behavior Decision Framework. However, the information gathered regarding the decision strategy may serve as preliminary finding for future research. Given the diversity of research results, the decision process for attributing value should allow for a dynamic process where participants are able to evaluate their options and tradeoffs based on their personal value and guidance from the investigator.

Implications and Recommendations

Overall, participants in the dissertation study attributed higher personal value to IRR when normative comparisons were available. These comparisons would allow them to make decisions regarding the health of themselves or their loved ones. This finding is in line with the current guidance on return of IRR. However, the diversity in participant opinion with respect to personal value of result type underscores the need for researchers to be mindful of these differences. The findings from this dissertation contribute to the existing literature by highlighting the opinions of mothers enrolled in the ECHO longitudinal study. Additional studies are necessary to get a more comprehensive understanding of participant preferences, with respect to other types of results and across diverse populations and racial groups.

We know from previous studies that participant preferences are associated with racial and demographic differences and that IRR are associated with increased motivation to participate in research. In minority communities, lack of participation in research is a persistent concern and deprives them of the benefits of effective prevention and treatment strategies (George et al., 2014). Return of IRR could serve as an important tool to increase motivation for research participation. More research with diverse populations and studies may help provide additional data about participant preferences with respect to individual and cultural contexts.

Until more data is available on participant opinions across a broad range of results, developing uniform guidelines may be challenging. It may be necessary to evaluate the return of IRR on a study-by-study basis. For instance, the findings from the dissertation suggest that the ECHO program should identify and prioritize the return of IRR framed within a normative context. It may also be possible to provide a comparison with other participants within the same cohort.

Return of individual research results takes time and resources. While investigators have an ethical obligation to return results, funding agencies must also demonstrate their commitment and support for the return of IRR. In recent years, the National Institutes of Health (NIH) has demonstrated their commitment to broad data sharing by requiring investigators to share de-identified data through a centralized resource such as the NICHD Data and Specimen Hub (DASH) repository. NIH also requires investigators to commit to data sharing early on in the grant application process and holds them accountable for non-compliance with previously agreed on terms of the grant. A comparable effort/policy may be necessary to motivate investigators to return IRR. It may not be unreasonable for NIH to require investigators to submit a plan for return of IRR with their grant application. Additionally, NIH should consider provision of additional resources when return of results need extensive time/content experts.

Limitations and Delimitations

This dissertation is limited by its lack of generalizability due to its focus on mothers enrolled from a certain geographic location. In addition, participant perspectives were limited to three result types – survey result, biospecimen result, and physiology assessment result. While the sample in the quantitative study was diverse, the recruitment of American Indian participants in the qualitative study was a challenge. The sampling strategy was followed as planned to ensure a representative sample based on race and maternal education, and interviews were conducted until thematic saturation. Yet, the qualitative study lacked representation of American Indian participants. Due to this limitation future research may need to exclusively focus on American Indian participants. The delimitations of the study include restricting the investigation to results pertaining to the mother's health. This was done to avoid confounding of responses in relation to results about their child.

Summary

The study provides vital data on participant perspectives regarding return of results beyond genetics results. The strengths of the study include a geographically and racially diverse sample of participants that were able to reflect on their participation in research through the ECHO program. Return of IRR is a complex endeavor and a concerted effort at multiple levels of the research enterprise including sponsors and investigators will facilitate return of IRR of personal value to participants. To make the process of return of IRR truly participant oriented, IRR should not be returned as an afterthought. Starting at the study design phase, researchers must proactively work on creating a plan with input from participants for return of IRR and effectively communicate the plan with the participants during the informed consent process. Return of individual research results should be a voluntary process and participants must choose if they get their results.

Mainstream research is often criticized for its inability to incorporate individual cultural and contextual factors especially in relation to minority communities. In order to promote fair research practices, researchers need to ensure adequate representation of racial minorities in efforts to understand participant preferences regarding result type and the modality of return of IRR.

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Appendices

Appendix A: Return of Results Survey

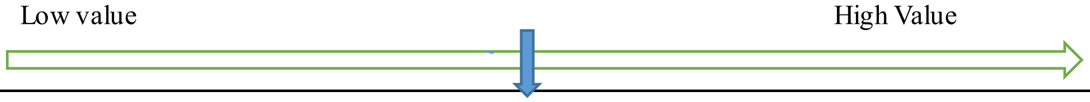
Avera Research Institute Center for Pediatric and Community Research ECHO Environmental influences on Child Health Outcomes		**Return of Results Survey** Site Protocol | 210602			Form : Return of Results Survey Page **85** of **101**
Cohort ID:	Site ID:	Participant ID:	PIN	Cohort Visit ID:	Form Completed:
					__ __ / __ __ / __ __ __ __ *mm* *dd* *yyyy*

Scenario – Sleep Health -Standardized

Ms. J is a 25-year-old pregnant woman. She took part in a research study to look at the sleep quality in pregnant women. Researchers know that poor sleep during pregnancy may affect the health the mother or her child. As part of the study, Ms. J was asked to complete a survey about her sleep habits including, her sleep duration and how well she slept in the past 7 days. This survey was given three times during her pregnancy.

At the end of the study, researchers analyzed her responses and provided Mrs. J with her pregnancy sleep health score, along with information on whether her score would be considered an adequate or an inadequate sleep health score for pregnant women of her age.

Using the sliding scale below, please indicate how valuable these results would be for Ms. J

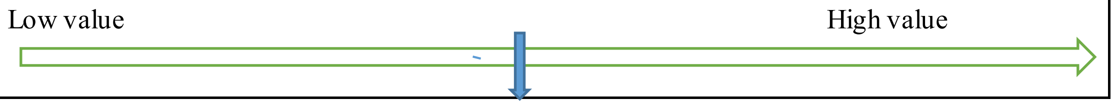


Scenario – Sleep Health – Non- standardized

Ms. J is a 25-year-old pregnant woman. She took part in a research study to look at the sleep quality in pregnant women. Researchers know that poor sleep during pregnancy may affect the health the mother or her child. As part of the study, Ms. J was asked to complete a survey about her sleep habits including, her sleep duration and how well she slept in the past 7 days. This survey was given three times during her pregnancy.

At the end of the study, researchers analyzed her responses and provided Mrs. J with her pregnancy sleep health score. Ms. J was told that at this time researchers do not information on whether her score would be considered an adequate or an inadequate sleep health score for pregnant women of her age.

Using the sliding scale below, please indicate how valuable these results would be for Ms. J

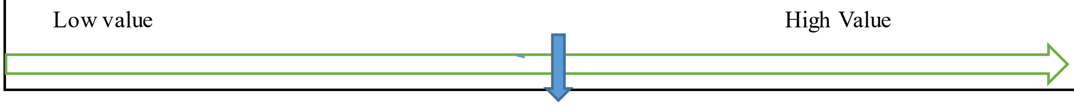


Scenario – Urine Phthalate- Standardized

Ms. J is a 25-year-old pregnant woman. She took part in a research study to look at the effect of various chemicals on the health of individuals. Ms. J gave a urine sample to look for a chemical called phthalate. There are many types of phthalates. Phthalates are used in personal care products such as make up products, perfumes, nail polish. Phthalates are also used in home floors and panels. Phthalates are known to have negative effects on health but we do not have enough information on all the types of phthalates that we may be exposed to in daily life.

At the end of the study, researchers analyzed Ms. J's urine sample and told her that it tested positive for a certain kind of phthalate. Mrs. J was told whether her results would be considered acceptable or not acceptable based on results from other pregnant women of her age.

Using the sliding scale below, please indicate how valuable these results would be for Ms. J

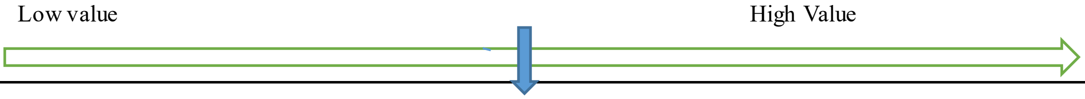


Scenario – Urine Phthalate- Non- Standardized

Ms. J is a 25-year-old pregnant woman taking part in a research study to look at the effect of various chemicals on the health of individuals. Ms. J gave a urine sample to look for a chemical called phthalate. There are many types of phthalates. Phthalates are used in personal care products such as make up products, perfumes, nail polish. Phthalates are also used in home floors and panels. Phthalates are known to have negative effects on health but we do not have enough information on all the types of phthalates that we may be exposed to in daily life.

At the end of the study, researchers analyzed Ms. J's urine sample and told her that it tested positive for a certain kind of phthalate. Mrs. J was told that at this time researchers do not have information on what would be considered an acceptable or not acceptable level of phthalate exposure for pregnant women of her age.

Using the sliding scale below, please indicate how valuable these results would be for Ms. J



Scenario – Sleep physiology- Standardized

Ms. J is a 25-year-old pregnant woman. She took part in a research study to look at how sleep affects health during pregnancy. As part of her study, her sleep pattern and heart rate were monitored during an overnight sleep recording using a small device that she could wear while she slept. The recording from the device was analyzed to look at the quality of her sleep.

At the end of the study, researchers provided Ms. J information on changes to her heart rate pattern during sleep. Ms. J was told whether her results would be considered acceptable or not acceptable based on results from other pregnant women of her age

Using the sliding scale below, please indicate how valuable these results would be for Ms. J

Low value High Value

Scenario- sleep physiology- Non- Standardized

Ms. J is a 25-year-old pregnant woman. She took part in a research study to look at how sleep affects health during pregnancy. As part of her study, her sleep pattern and heart rate were monitored during an overnight sleep recording using a small device that she could wear while she slept. The recording from the device was analyzed to look at the quality of her sleep.

At the end of the study, researchers provided Ms. J information on changes to her heart rate pattern during sleep. Ms. J was told that at this time researchers do not have information on what would be considered an adequate or inadequate level of heart rate activity during sleep for pregnant women of her age.

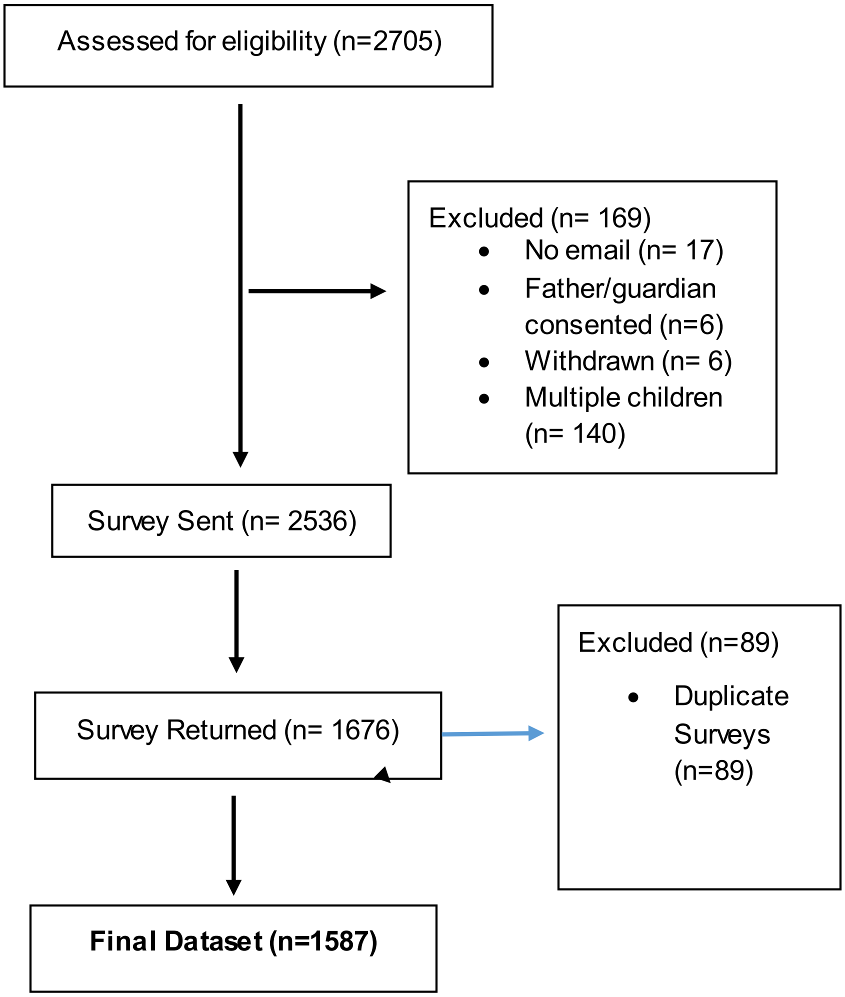
Using the sliding scale below, please indicate how valuable these results would be for Ms.

Low value High Value

How many years have you participated in research?

- ○ Less than 1 year
- ○ 2- 5 years
- ○ 6 - 10 years
- ○ Greater than 10 years

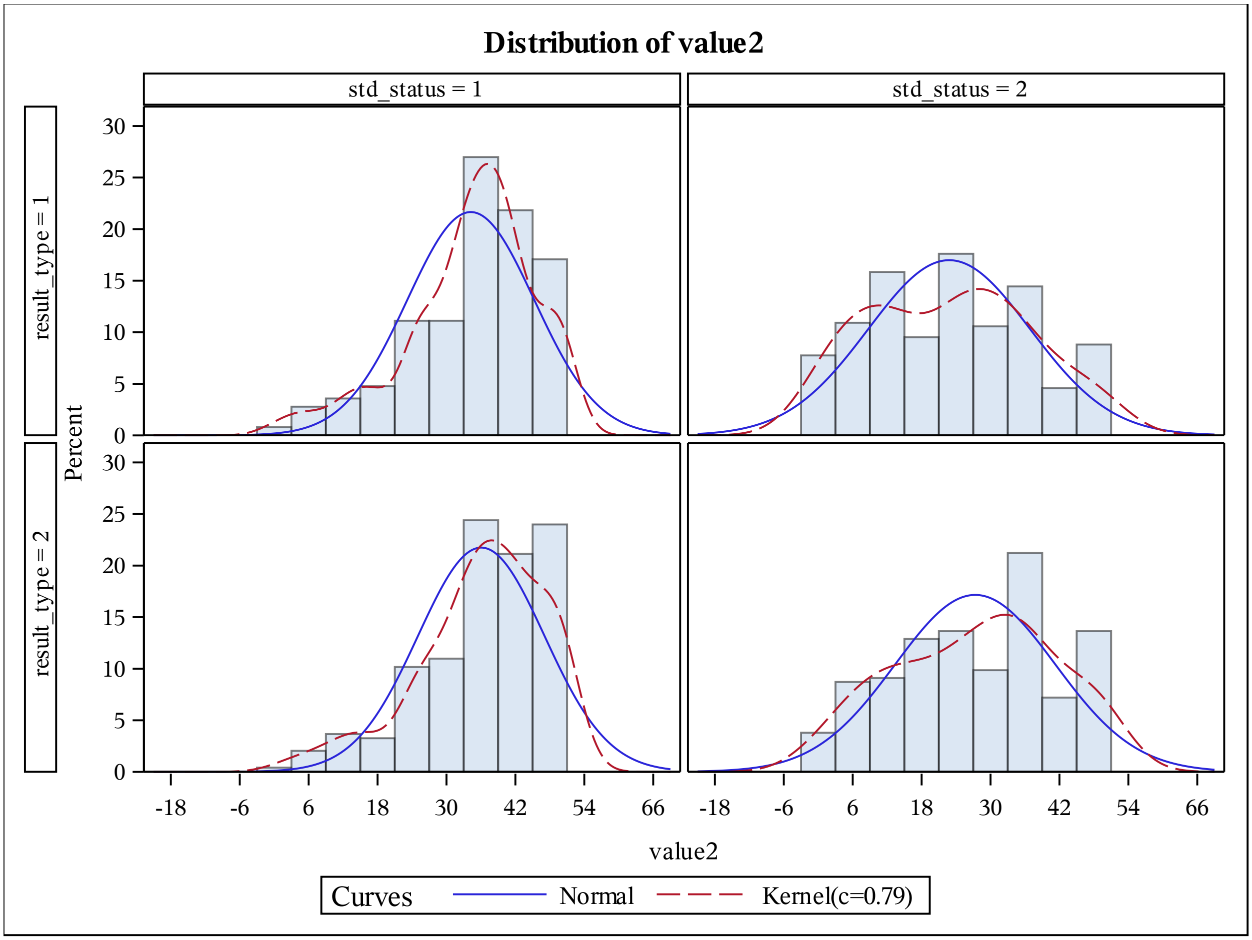
Appendix B: Consort Chart



Appendix C: Descriptive Statistics

Figure 1.

Histogram of value by result type and standardization status



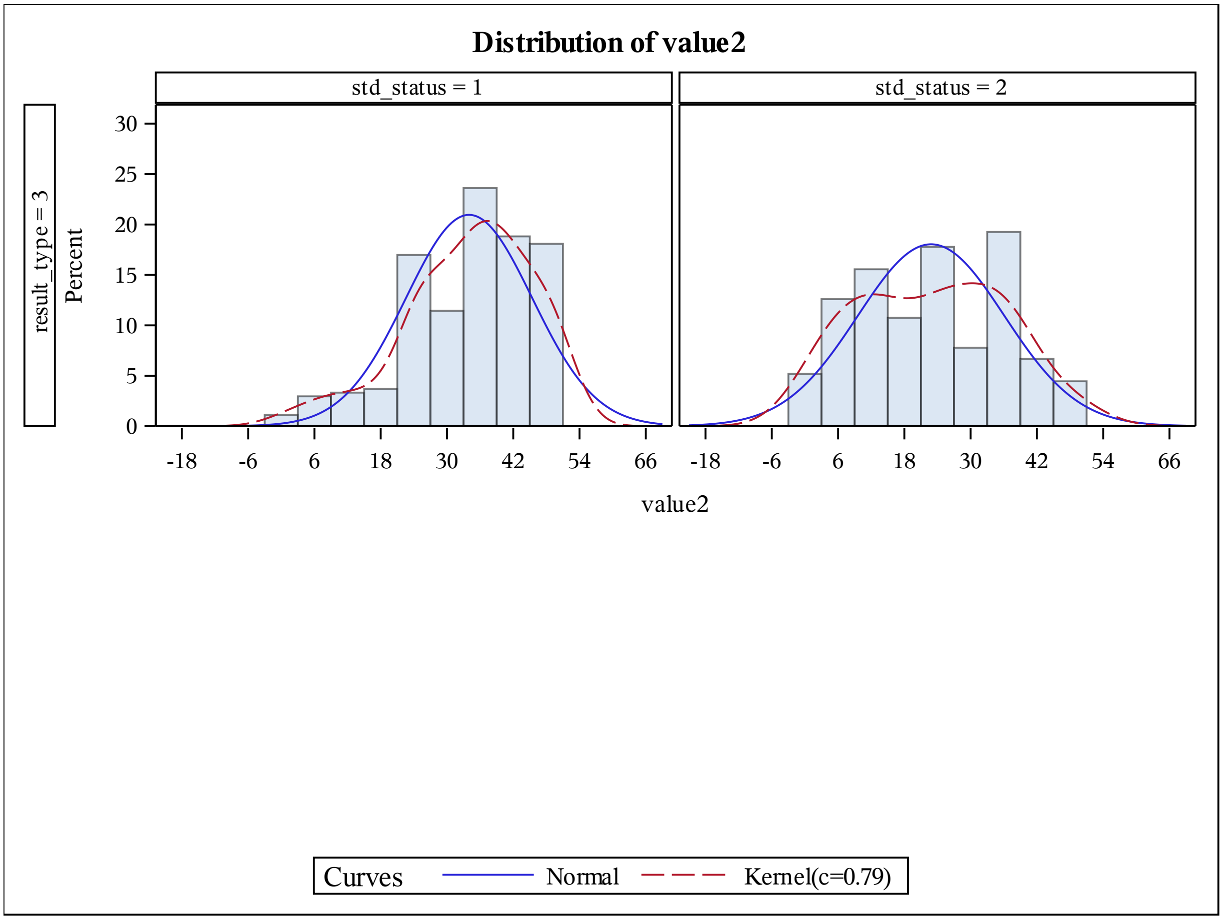
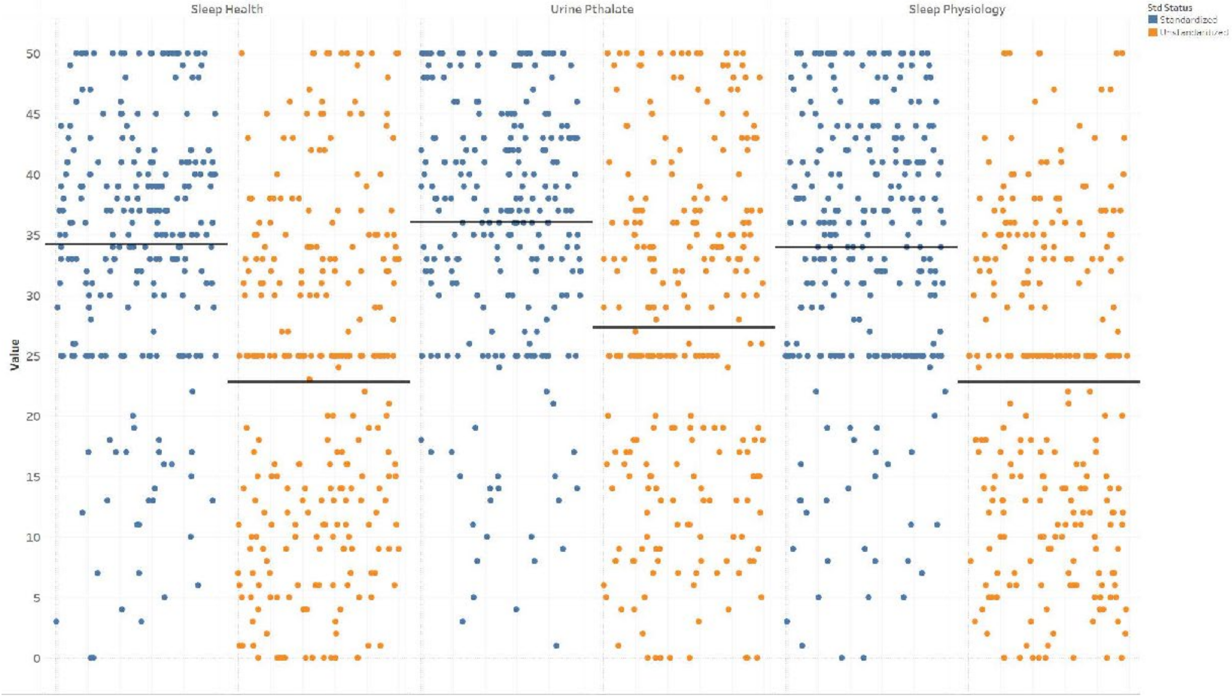

Distribution of value2
std_status = 1
std_status = 2
result_type = 3
Percent
30
25
20
15
10
5
0
-18
-6
6
18
30
42
54
66
value2
Curves
Normal
Kernel(c=0.79)

Figure 2.

Jitter plot of the relationship between value by result type and standardization status



Appendix D: Sensitivity Analysis

Sensitivity Analysis including all (n=1587) participants

Research Question 1: To what extent do type and standardization status influence participant perceptions of value of receiving individual research results?

Number of Observations Read	1587
Number of Observations Used	1587

Source	**DF**	**Type III SS**	**Mean Square**	**F Value**	**Pr > F**
result_type	2	3705.58411	1852.79205	11.68	<.0001
std_status	1	43393.51342	43393.51342	273.66	<.0001

Least Squares Means for Effect result_type				
i	**j**	**Difference Between Means**	**Simultaneous 95% Confidence Limits for LSMean(i)-LSMean(j)**	
[a]1	**[b]2**	-3.239939	-5.067346	-1.412531
1	**[c]3**	0.063082	-1.737787	1.863952
2	**3**	3.303021	1.479617	5.126425

- [a] **Result_ type 1 = Sleep Health Survey**
- [b] **Result_type 2 = Urine Pthalate (Biospecimen)**
- [c] **Result_type 3 = Sleep Physiology (Physiology assessment)**

Appendix E: Multivariate General Linear Model

Multivariate General Linear Model in the Non-standardized scenarios

Research Question 2: To identify racial differences between White and American Indian participants in the association of result type with perceived value.

Number of Observations Read	818
Number of Observations Used	791

Source	DF	Type III SS	Mean Square	F Value	Pr > F
result_type	2	3712.691596	1856.345798	9.80	**<.0001**
race	2	1331.505336	665.752668	3.51	**0.0302**
Years of research experience	3	211.340665	70.446888	0.37	0.7733
Maternal education	3	439.438012	146.479337	0.77	0.5092
age	1	236.286153	236.286153	1.25	0.2644

Appendix F: Qualitative Interview Script and Materials

The ECHO research team is looking for identify best ways to return individual results to our research participants. The purpose of this interview is to explore your opinions, ideas and expectation on how valuable it would be for you to receive these results.

I would like to remind you that as a participant in this study you can choose to not answer a question or to stop the interview for any reason.

These interviews will be video recorded. You can stop your video recording at any time, if you would like to. Recordings will be transcribed by a third party. However, we will only share the audio file with the transcription company. We will not share your name, video or any other identifiable information. This interview should last for about 60 minutes. If you need to take a break, please let me know. You will receive $25 for participating in the interview.

Do you consent to participate in this interview? Let's begin by reviewing this PowerPoint about types of data collected in the ECHO study (see table).

Types of data collected in ECHO from mothers and/or children

Survey Data	Specimens	Physiology Recordings	Physical Measurements
Pregnancy health, sleep, nutrition	Urine sample Blood sample, hair saliva and toenail clippings from child and mother.	Maternal and fetal heart rate recordings	Height/ weight
Family relationships, emotional support and parenting techniques		Child EEG recordings	Child breathing tests
Mental health/ anxiety depression	Home dust collection		
Chemical Exposures			