Parental Perspectives Regarding the Return of Genomic Findings in NeuroDevelopmental Disorders – A South African Study

By

ANGELIQUE DIEDERICKS

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Supervisor:

Associate Professor Jantina De Vries, PhD

Department of Medicine, University of Cape Town

jantina.devries@uct.ac.za

Tel: (021) 650 5716

Co-Supervisors:

Professor Kirsten Donald

Department of Paediatrics & Child Health, Red Cross War Memorial Children's Hospital and University of Cape Town

kirsty.donald@uct.ac.za

Nakita Laing

Division of Human Genetics, Department of Pathology, University of Cape Town

n.verkijk@uct.ac.za

Tel: (021) 406 6373

ABSTRACT

Title: PARENTAL PERSPECTIVES REGARDING THE RETURN OF GENOMIC FINDINGS IN NEURODEVELOPMENTAL DISORDERS – A SOUTH AFRICAN STUDY

Authors: Diedericks, A.
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Introduction: There is a lack of policies and research regarding the disclosure of results in genomic research, especially in South Africa. Challenges remain regarding the disclosure of genomic research results to research participants and their families, which may partly be addressed by considering parental and participants' preferences. This study serves as a sub-study to the NeuroDev study which is performing genotyping and exome sequencing on children with NeuroDevelopmental disorders in the Western Cape; and will investigate a feedback of findings method pertaining to the needs and preferences of the patient community.

Aims: To investigate parents' understanding of the genomic research study they are participating in as well as their preferences regarding the feedback process and anticipated contributions of significant genetic findings generated by the NeuroDev study. This study further hopes to inform a tailored feedback policy reflecting the needs of this South African population.

Research Design: A pragmatic qualitative approach was used by conducting 12 semi-structured interviews with 17 parents of children participating in the NeuroDev study. Purposive sampling was used, selecting retrospectively from patients recruited for the NeuroDev study in which findings of *de novo*, significant mutations are more likely expected. Interviews were conducted in English, in a private setting at Red Cross War Memorial Children's Hospital (RCWMCH), and were audio-recorded by the researcher; observations and field notes were documented. Generated data was analyzed using thematic analysis to generate themes and transcripts were imported into NVivo 12 to assist with managing and organizing the data for analysis. Ethical approval was been obtained from the University of Cape Town (UCT) (HREC 784/2018).

Results: Empiric data collection ran from May to July 2019 and preliminary data was presented at the NeuroDev AGM and on a poster at the SASHG conference, RCWMCH research open day and UCT postgraduate research day. Findings were that the parents of the participants understood the study they were participating in as well as basic concepts of genetics, however, parental understanding over the cause of their child's condition remains a source of confusion when pertaining to their understanding of genetics being 'passed down the family lineage' and how that integrates with *de novo* mutations. Furthermore, there is potential for it to impact on feelings of guilt. Parents have a need for information, discovering the cause of their child's condition and to be involved in the research process with full disclosure as events unfold. Altruism seems to be a major motivator for participating in genomics research but personal and family benefit also served to be a key driver in that research results could potentially provide awareness and information regarding their child's condition, the management thereof and recurrence risk in future. Participants in this study want pertinent research results which could offer closure, acceptance and relief, however, differences over the meaning of such results were observed between those whose child already had a diagnosis versus those whose child remained undiagnosed. Furthermore, receiving non-pertinent and negative result was still perceived to be meaningful for some. Further diversity was observed in parental preferences for the explanation of preliminary results.

Discussion: Given that non-pertinent results still hold value for participants, consideration should be given as to more extensive ways of communicating this if such results are not to be returned since results are generally viewed as a point of access to information or relating to their child's condition. Diverse preferences regarding when and what participants want to know for results feedback needs to be addressed in order to facilitate a guidance framework for the delivery of genomic research results and can perhaps take the form of a tiered-consent model for feedback of incidental findings. As such, genetic counsellors may have a valuable role to play in facilitating participant satisfaction and bridging the gap between researchers and public expectations.

Ethical considerations: Consent was taken before commencement of the study. There were no risks with regards to participating in this study and participants had the freedom to withdraw at any time and at their own discretion.

DECLARATION

I, *Angelique Diedericks*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature:

Signed by candidate

Date: 10 February 2020

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To my family, you are my rock and my reason for being. I could not have done this without you.

To my two boys, Louka (6) and Giordano (3), thank you for sacrificing our time together and for being so understanding through it all. I have seen you grow during this time and I am so proud of who you are becoming. You are my whole heart and I am so blessed to have you in my life. May all the hours we spent apart be reflected in this work. You have been my light in the darkness and my biggest motivation. Most of all, may I have been an example for you to never give up on your dreams, you are never too old to chase them. Spread your wings and fly, always.

To my husband, Amilcare, thank you for your commitment to our family and for taking on all the extra load at home whilst I was busy writing. For sitting up with me on those long nights because you didn't want me to do it alone. Even through the loss you were suffering, you were my pillar of strength and have helped make this dream possible… for us.

To my parents, Con and Janet… What would I have done without you?! Thank you for carrying all of us through this and for standing in with our amazing little boys. You have been my biggest support and encouragement since I can remember. Thank you for encouraging me to finally chase my dream of becoming a genetic counsellor, for teaching me to get up when I fall and to never give up. Your belief in me has made me a better person. Thank you for all your sacrifices you have made to help get me through this. You have studied just as hard on all my degrees, all my achievements are ours.

Last but not least, thanks be to God for carrying all of us through an overburdened time. His Grace has been ever-present and all glory be to Him.

DEDICATION

I would like to dedicate this dissertation to my parents Con and Janet, my husband Amilcare and most of all my two amazing boys, Louka and Giordano. I love you to the moon and back. We did it!

"Love is the only way to grasp another human being in the innermost core of his personality. No one can become fully aware of the very essence of another human being unless he loves him. By his love he is enabled to see the essential traits and features in the beloved person; and even more, he sees that which is potential in him, which is not yet actualized but yet ought to be actualized. Furthermore, by his love, the loving person enables the beloved person to actualize these potentialities. By making him aware of what he can be and of what he should become, he makes these potentialities come true."

– Viktor E. Frankl, Man's Search for Meaning

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LIST OF ABBREVIATIONS

ACMG - American College of Medical Genetics

ADHD - Attention Deficit Hyperactivity Disorder

AMP - Association for Molecular Pathology

ASD - Autism Spectrum Disorders

CAP - College of American Pathologists

CLIA - The Clinical Laboratory Improvement Amendments

CNV - Copy Number Variants

CP - Cerebral Palsy

DDD - Deciphering Developmental Disorders

DSM-V - Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

FIF – Feedback of Incidental Findings

FoF – Feedback of Findings

GC - Genetic Counsellor

GDD – Global Developmental Disorders

GWAS - Genome-wide Association Studies

H3Africa - Human Heredity and Health in Africa

ID - Intellectual Disability

IF - Incidental findings

MLPA - Multiplex-ligation probe amplification

NDDs - NeuroDevelopmental disorders

NeuroDev - Genetic Characterization of NeuroDevelopmental Disorders

NGS - Next Generation Sequencing

RCWMCH - Red Cross War Memorial Children's Hospital

RoR – Return of Results

SA - South Africa

UCT - University of Cape Town

UK10K - 100 000 Genomes Project UK

U.S. - United States

VUS - Variants of uncertain significance

WC - Western Cape

WES - Whole Exome Sequencing

WGS - Whole Genome Sequencing

3V Framework - tripartite framework which is a disclosure framework incorporating the concepts of validity, volition and value

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1 CHAPTER 1 INTRODUCTION

Genomics research on mental health conditions and NeuroDevelopmental disorders (NDDs) is gaining traction in South Africa (SA) with various projects being conducted at University of Cape Town (UCT) such as the Genetic Characterization of Neuro-Developmental Disorders in South African Populations (NeuroDev) study and projects falling under the Human Heredity and Health in Africa (H3Africa) Consortium.

One pertinent challenge in genomics research relates to questions about what to do with research results that are relevant to the health of the participant. Deciding whether to disclose individual genomic research results, and the researcher's obligations in this regard, has been the topic of much controversy nationally and internationally, particularly where minors are concerned.
With the advent of whole-exome and whole-genome sequencing technologies, the identification of unintended, incidental findings (IF) as well as variants of uncertain significance (VUS) is inevitable. In many cases, determining what results mean for the patients and whether they are actionable remains a formidable task.

With the exception of the H3Africa feedback of findings (FoF) guidelines, few other policies and little research exists regarding the disclosure of research results to research participants in SA. The goal of this study was to investigate preferences for the FoF pertaining and tailored to the needs of a South African (SA) patient community. In the context of ongoing genomics research being conducted through the NeuroDev study at the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, there would then be potential for such needs to be recognized and policies to be informed.

The NeuroDev study is a large-scale, international collaborative study which aims to map genetic variation amongst children with NDDs by performing genotyping and exome sequencing on children aged 2 – 17 years old, with NDD. Although a lot has been written about the return of incidental or secondary findings in genomics research, in this research I will focus only on the

disclosure of pertinent genomic research results (ACMG, 2013a; Ortiz-Osorno, Ehler & Brooks, 2015). The NeuroDev study will be returning results that are currently known to be pathogenic and associated with ASD and ID and as such, with the child's condition. In other words, these are findings that are currently included in existing, validated diagnostic tests. In the empirical work for this thesis, I sought to understand better how and when these results ought to be fed back.

To assist in examining the role of the genetic counsellor (GC) and achieve the above-mentioned goals, this study will present findings of a qualitative research study conducted in the Western Cape (WC) on NDDs that focused on how to map participants' expectations and preferences for feedback. Insights gained in the research project will be used to explore the role that GCs could play in the return of pertinent genetic research results in genomics research and suggest elements of best practice for consideration. It will do so by engaging with enrolled participants to explore how this component of the study is explained and understood, and what patient preferences are for the return of results (RoR).The overall aim of this proposed study is to support the design of a returns policy for pertinent genomic research results for the NeuroDev study, which could possibly be of wider use to other genomic research being conducted at UCT.

1.1 DISSERTATION CHAPTER OUTLINE

I have thus far provided a brief introduction to my dissertation in "Chapter 1" above. As a guide to the reader, I provide the following as an outline to the chapters that will commence.
To start off, this project aimed to investigate parents' perspectives and preferences regarding the feedback process of genomic research results obtained during the NeuroDev study and the anticipated contributions of such findings and as such, focuses on three main research questions, namely, what NeuroDev research participants consenting to the return of positive individual NDD-related genetic results understand from the study to which they have consented, their reasons for agreeing to the return of positive individual NDD-related genetic results, and recommendations for how positive NDD-related individual genetic research results can best be fed back to research participants. These question have been used to guide my search for empiric data and to frame

my literature review, and I have aimed to structure my findings accordingly in order to answer these questions.

"Chapter 2 – Literature Review". In this chapter I will look at the key features and considerations for the return of genomics research results as well as how this relates to paediatric research and existing empirical. I provide an overview of international and SA-specific guidelines for the return of genomic research results and sketch a background on NDDs and the current clinical practice employed in diagnosing or testing for this group of disorders. I then focus on the NeuroDev study, providing insights into their feedback policy, aims, rationale and questions outstanding.

"Chapter 3 – Research Methodology". In this chapter I provide you with the study design used to conduct this qualitative research study, participant background, the recruitment process and the research procedure, data collection and analysis methods. Furthermore, ethical considerations are discussed with respect to informed consent, privacy and confidentiality and risks and benefits to participants.

The next three chapters (4, 5, and 6) will focus on the results of this study. The first of three findings chapters is "Chapter 4" which informs my first research question of how participants consenting to the return of individual pertinent research results understand what they have consented to.

"Chapter 4 – Participant understanding, expectations and reasons for partaking in genomic research". In this chapter I also provide the sociodemographic data of my study participants and what people want to know on a generic level.

"Chapter 5 – Pertinent Results is the second of three findings chapters". This aims to answer my research question regarding why participants agree to the return of pertinent research results.

The last of three findings is "Chapter 6 - Preference to feedback". Here I explore participant preferences to the feedback of genomic research results and recommendations on how best to feedback such results, informing my last research question.

The final chapter of the dissertation is "Chapter 7 – Discussion". This chapter will provide a landscape of findings from this study, highlighting prominent concepts pertaining to participant preferences in the return of genomic research results and how it can inform such disclosure as it relates to current literature. It will also discuss future recommendations and study limitations.

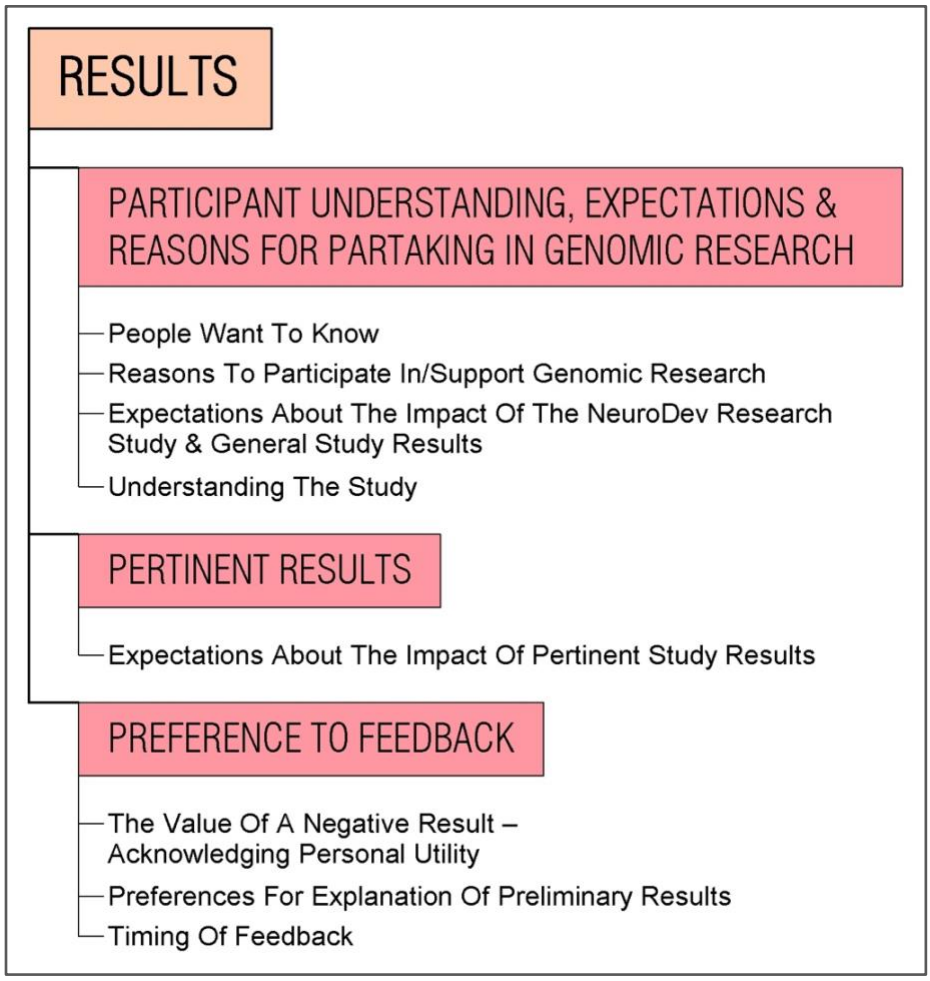

Figure 1. 'Roadmap' of Findings Informing Research Questions.

2 CHAPTER 2 LITERATURE REVIEW

2.1 RETURN OF INDIVIDUAL GENETIC RESEARCH RESULTS IN GENOMICS

Next generation sequencing (NGS) has become cost-effective and accessible in the field of genomic research, allowing for its use in research to extend from testing preselected genetic sequences to testing the entire genome. Whole exome sequencing (WES) and whole genome sequencing (WGS) are two methods that employ NGS. Whilst WGS analyzes the entire genome of an individual, WES allows for only the protein coding region of the genome to be analyzed and is less costly and time-consuming. WES detects rare protein truncating (loss of function) variants, found to be strongly associated with intellectual disability (ID) and autism spectrum disorders (ASD) in which the variant may be inherited or have arisen *de novo*. Such variants are reported to be present in at least 13% of cases with ASD and severe NDD phenotypes (Kosmicki et al., 2017). WES/WGS offer the potential to change clinical management and intervention strategies should an underlying genetic causative variant for NDDs be found. Furthermore, microarray analysis may be employed and is often used for genotyping in genomic research, allowing for the examination of the distribution and effects of risk conferring rare copy number variants (CNV) such as deletions or duplications that are often strongly associated with NDDs (Miller, David et al., 2010; Schaefer & Lutz, 2006).

However, with the increased use of NGS in research as well as clinical practice, IF and VUS are inevitable and interpretation of pathogenicity remains difficult and uncertain, complicating the process of returning results to research participants. This has fostered ethical debate worldwide regarding which results should be returned, when they should be returned, and by whom.

2.1.1. KEY FEATURES OF THIS DEBATE

A vast amount of genetic data is being generated using NGS technologies, emphasizing the need for clearly established policies about the disclosure of individual genetic research results. An intricate debate centres primarily around the nature of the result and the ensuing genetic information, with numerous terms and concepts used to define the nature of results with the aim of eliminating confusion and providing guidance for disclosure to researchers (Eckstein, Garrett & Berkman, 2014). Further adding to researcher confusion, dispute continues over the extent of researcher obligations in disclosing genetic research results.

Researchers are expected to classify between IF/secondary findings, ensure analytic validity and determine the clinical validity of a result which is complicated by phenotypic heterogeneity, gene penetrance, small study populations, and phenotypic modifiers (to name a few). Additionally, varying interpretations of a result may ensue depending on the reference system used by the researcher, which elicits differing views/opinions regarding the clinical utility of a result.

Disclosure should include results which are 1) *clinically significant* which improve treatment, prevention, or understanding of a disease for a participant or their relatives (Miller et al., 2008; Shalowitz, David & Miller, Franklin, 2008; Shalowitz & Miller, 2008) – these are suggested to be linked to the preferences of patients given that the benefits of knowledge, albeit painful, are shaped by personal views and values; and 2) *clinically relevant,* a concept which closely resembles clinical significance, but Kohane and Taylor suggest a greater knowledge of the participants' history, family and environment may help distinguish results and their associations from "interesting" variants (Kohane & Taylor, 2010). Pullman and Hodgkinson note that factors such as age, gender, medical history and the health behaviours of participants may influence which results are assigned clinically relevant (Pullman & Hodgkinson, 2006). Furthermore, the variety of genomic research being conducted, the types of participants contracted (for example, patients and healthy volunteers), the scope of genetic information (being validated or non-

validated, highly or poorly predictive, more or less probabilistic genetic data), and of the research add further complexity (Bredenoord et al., 2011).

Further distinction needs to be made between findings that are pertinent, IF and VUS when considering results disclosure. Pertinent findings are those which answer particular clinical or research questions and have been purposefully sought by genotyping specific areas of the genome or by specifically interrogating specific areas previously generated by WGS. These are primary findings/mutations, known to be pathogenic in origin and recognized to cause the disorder under investigation (Hall, Hallowell & Zimmern, 2013). IF relate to those unexpected, additional findings discovered during clinical or research investigations which have potential health implications and clinical significance. These findings are beyond the scope and aims of the research or requested test, were not actively sought during the research process (Hall, Hallowell & Zimmern, 2013) and are usually not disclosed to the participant or related clinician. VUS results relates to those in which a genotype-phenotype relationship cannot be statistically and scientifically established and there is a paucity of evidence to support the relationship between the variant and the phenotype (Hall, Hallowell & Zimmern, 2013).

Dispute concerning definitional/terminological uncertainty arises possibly due to varied beliefs regarding the distinction between research and clinical care, thereby impeding the formulation of a disclosure framework (Eckstein, Garrett & Berkman, 2014). The differences between the return of individual research results and the RoR in the clinical setting lie in the curatorship of samples (ensuring the sample belongs to the correct participant) as well as the obligations towards participants and their families. There is still much uncertainty regarding how the preferences of participants and their families are taken into account (during and after consent); to whom the results should be disclosed; and when and what the extent of researcher obligations are in terms of disclosure (Harris, Erin et al., 2012; IRCM Working Group, September 2015). Researchers need to fulfill their obligations for the disclosure of pertinent individual research findings but the need to protect participants and their parents from undue related harm (such as anxiety and privacy) remains a priority. This is challenging in the research setting, especially concerning paediatric research where the parents and the minors' right-to-know or not know about findings must be respected and remains a topic of controversy (IRCM Working Group, September 2015). Furthermore, results obtained in a research setting need to be validated by an accredited or certified laboratory before being returned to research participants. This may be costly, return may

require extra skills and more man-power, and an infrastructure and tight budget may not allow for individual RoR in a research setting. Clinical genetic results are obtained from an accredited laboratory and the medical professionals who deliver these results to their patients ideally have expertise in their field with access to multidisciplinary teams. These medical professionals have an obligation to return clinical results to their patients and have the means and access to implement management and/or therapeutic interventions. Whilst formal consent for testing is taken in such a setting and testing is done specifically to give results if there are any, the preference of the participants may not always play a role after consenting as the medical professional has a duty to disclose results, especially those which are believed to be clinically actionable, regardless of the individual's choice not to know (Harris, Erin et al., 2012; IRCM Working Group, September 2015).

All-embracing, three common concepts are identified in all ethical disagreements regarding the disclosure of individual genetic research results. These are validity, value and volition which form part of a tripartite framework (3V framework), which Eckstein et al. suggest as a disclosure framework to a general application of research findings without the distinction between primary and secondary findings (Eckstein, Garrett & Berkman, 2014). While validity and value focus primarily on the nature of the information, volition pertains to the individual to whom such information will be disclosed and whether they want the information or not.

2.1.1.1 WHY IS THIS AN ISSUE

Genomic research results are predictive of participants' future health, could impact on their reproductive choices, and may have implications for their family members as well. Notably, disclosure can influence the individual's ability to obtain health insurance and may expose him/her to stigmatisation or ostracisation from family or society. This is to say that the individual's genomic information may affect their self-related or perceived personal identity and they may further experience being dissociated from a cultural/ethnic group or other inclusion group with which they previously identified with.

Furthermore, participants entrust their health to the researchers during the time research is conducted and hence the nature of researcher-participant relationship is influenced by the duration and intensity of such research, which in turn may influence the extent of the duty to offer results. Offering results could foster productive partnerships between researchers and participants such as evoking long-standing commitment to the research study. This being said, questions of fairness and discrimination may be raised when participants find themselves taking part in a study where they feel they have no relationship or contact with the researchers and that they may not have equal treatment or consideration (Bredenoord et al., 2011).

Apart from the impact on the individual participant, disclosing research results to individuals may place burden on the research enterprise. It requires expertise and skills that may not be feasible within a particular research setting and lack of infrastructure may limit the range of actionability from one research setting to the next. This remains evident in an African research setting (Rotimi et al., 2014).

Genomic research results have implications for society as a whole since people have the opportunity to understand genomic contribution to disease and health, thereby being better placed to gain relevant skills and knowledge relating to conditions. Disclosure can support public understanding of the importance of research in healthcare, provide education regarding the complexity of genetic findings, and offer more involvement through offering a more active engagement in biomedical research.

The inevitability of IF can exacerbate issues of privacy and confidentiality, personal decision-making, and ethical obligations of researchers and clinicians (Sapp et al., 2014) and disclosure remains somewhat of an ethical controversy. It is clear, however, that consensus should be reached regarding the RoR and guidelines/policies implemented to guide healthcare professionals with such interpretation and disclosure (Holm et al., 2014; Sapp et al., 2014). A balance between showing respect for participant preferences, maximizing potential benefits from the knowledge, determining and reducing medical and psychosocial harm to participants,

ensuring accurate and comprehensible results, and burdens on the research enterprise needs to exist. Participant autonomy should be permitted, allowing individuals to indicate and exercise their preference for which results they would want to receive about their children and themselves (Holm et al., 2014).

2.1.2 KEY CONSIDERATIONS

2.1.2.1 PATHOGENICITY AND SCIENTIFIC EVIDENCE

Determining pathogenicity of a finding can be complex and relies on scientific, robust statistical evidence of what the function of the gene is (genomic characteristic) and how it links to a particular phenotype, and genomic databases produced from previous investigations and literature. Known pathogenic variants are those previously reported on and recognized to be the cause of a condition. However, if the representativeness of the sample on which those databases are based is too small or inadequately representative of different groups of people, these "lists" are likely to be incomplete. That is to say, pathogenicity is often based on a judgement which includes understanding what the gene may do, where it is positioned, whether it has been described before, the child's phenotype and so forth. The degree of certainty is assessed through the availability of such above-mentioned scientific evidence before reporting on such findings (Hall, Hallowell & Zimmern, 2013). VUS' are generally not reported on as these are deemed not clinically actionable since their relevance is uncertain and the course of clinical management of the patient is unlikely to change. The meaning of a VUS may change in the future as new data emerges, however, most research studies are under no obligation to continue interrogation of a VUS' relevance (Mark et al., 2017).

2.1.2.2 AUTONOMY AND CONSENT (VOLITION)

Autonomy relates to the participant's ability to decide for themselves about whether to participate in a research study. The issues that are faced nowadays pertain to the right of the participant to exercise their autonomy and state their preference regarding which findings resulting from the research study they would like to receive, which can only be appropriately decided if information is clearly conveyed to them and well-understood, and should be established during the process of a well-executed informed consent.

Ortiz-Osorno et al., McGuire and Beskow propose that a tiered approach re-contacting participants for consent to receive feedback on certain findings can promote autonomy and well-being of participants, can permit participants to set their preferences with regards to which type of results they would want to receive, and can be useful in informed consent in genomics and genetic research (McGuire & Beskow, 2010; Ortiz-Osorno, Ehler & Brooks, 2015). Ortiz-Osorno and colleagues feel that a participant's choice should be respected and that their decision bears weight and importance, regardless of the nature of the research finding. The actionability versus the non-actionability of the result impacts on the weight of the participant's decision and hence their preference to know or not know about the finding. They further state that, in accordance with Helgesson, with the concept of autonomy being a continuum of information a participant chooses to know or not know about, a participant has the right through autonomy to choose what findings they want to know or not know about (Helgesson, 2014). Knoppers and colleagues (2014) state that research findings that relate to the current or future health or quality of life of the participant should be offered to participants and their wish to not receive information should be respected (Knoppers, 2014). Others argue that researchers' obligations of a 'duty to warn' and a 'duty to rescue' precede the concept of autonomy and that participants should be re-contacted with research results that carry implications in lieu of their decision to opt-out of feedback (ACMG, 2013b; Presidential Commission for the Study of Bioethical Issues, 2013).

2.1.2.3 PARTICIPANT SATISFACTION

Novel genetic information is a constant discovery in genomic research, but such research now offers individuals the opportunity to receive results which may have meaning to them and thus receiving such results may be desirable to research participants. In studies conducted by Harris et al. and Kauffman et al. (Harris, et al., 2012; Kaufman et al., 2009), participants express their desire to receive research results, and Wolf et al. found that they feel they have a right to information generated by such research, which may have implications for their health (Wolf, 2012; Wolf et al., 2012).

In a research setting, unlike a clinical one, researchers have no duty to return research results. If such return is offered, guidelines by the Presidential Commission for the Study of Bioethical Issues (2013) suggest that the investigators should allow participants the option of opting out of receiving results (Presidential Commission for the Study of Bioethical Issues, 2013). Many different models have since been developed in an attempt to generate participant satisfaction (Bacon et al., 2015; Holm et al., 2015).

Incorporating preferences into the strategy for the return of research results remains a challenge and in doing so the participant's true desires regarding the information they want to receive needs to be reflected. It is evident from the literature that participants want to have a choice, but how granular must these choices be, and is just having a choice – any choice – the salient factor? It is unclear from the literature whether participants truly understand the implications of their choice regarding which results to receive and whether these choices are lucid and valid (Wolf, 2012). Of course, implementing preference-based models is costly and not always feasible given that participants need to be adequately educated about the types of results they could receive to enable informed choices.

Holm et al. (2015) and Christensen et al. (2017) described that greater participant satisfaction concerning the process of feedback of results may be achieved by 'allowing research participants to set preferences about the kinds of conditions they would want disclosed' rather than simply providing no options or binary options about whether disclosure *should* even occur (Holm et al., 2015; Christensen et al., 2017). They further argue that this may not necessarily require the

infrastructure needed to explain the different types of results to participants. Participants may have different perspectives to researchers and healthcare practitioners and may classify disease characteristics such as actionability and severity differently. According to Holm (2015) and Christensen et al. (2017), satisfaction appeared to be associated with benefits of information (i.e. participant reasons for wanting information) rather than harms (reasons for not wanting information). Benefits of knowing, as described by the participants included preparing for the future, having more control over the future, preventing worry, and seeking medical treatments (Holm et al., 2017). Participants' expectations about disclosure may be better met by matching preference-setting options with examples of conditions (Christensen et al., 2017). Studies have shown that research participants are more concerned about results that are important and health-relevant being withheld than they are about receiving unexpected, unsolicited information and its potential harms. When deliberating results disclosure approaches, satisfaction is only one component amongst many that needs consideration when evaluating the potential benefits and harms to participants (Wolf, 2012) and ethical arguments considering the implementation of participant preferences may carry much weight (Kollek & Petersen, 2011).

2.1.2.4 CONTEXT OR SETTING

Genomic research results cannot always be generalized from one context to another. As such, researchers need to be aware of the environmental context of their research setting, the culture influenced by such research and the availability of resources such as time and finances. Researchers may find the need to collaborate with international partners in order to finance the study or attain access to technologies or develop genomic databases. Besides infrastructure, researchers need to be cognisant of the community and participants' colloquialism, beliefs, education levels and personal circumstances which may serve as barriers to accessing healthcare or conducting research (Faure et al., 2019; Rutakumwa et al., 2019).

2.1.2.5 ETHNOCULTURAL LENS

Contextualization in disclosing genomic research results remains fundamental, even more so in a community like SA that is linguistically and culturally diverse (Munung et al., 2016; Nembaware et al., 2019; Tekola et al., 2009b). Understanding of genetics and concepts of heredity may be challenged by cultural beliefs and may require adjustment to means of communicating such information, especially since equivalent terms or concepts are often not available colloquially. Awareness of individual/community background or circumstance can ensure sound understanding and acceptance and promotes emotional well-being of participants and adaptation to genetic information (Tekola et al., 2009b).

2.1.2.6 ROLE OF THE GENETIC COUNSELLOR

The role of the GC in the feedback of genomic research results is particularly important, especially in the interpretation of the data and where unexpected findings are revealed. The GC is trained in the capacity to discuss risks, expectations, benefits and limitations of testing and has the skills to communicate the implications of this information to clinicians and their participants in ways that positively affect adaptation and behaviours to receiving genetic information (Joseph, 2018). A GC can assess risk to the participant and their family members, including risk of inheriting the condition and the risks to future pregnancies. They can assist with pregnancy planning options and help implement and coordinate appropriate management and surveillance plans for those at risk.

GC's have a sound background knowledge in genetics, work closely with clinical geneticists and a multidisciplinary team, and have the experience of dealing with genetic/genomic results and conditions. Furthermore, GCs understand the importance of 'wearing an ethnocultural lens' when dealing with a multitude of cultures such as that found in SA.

2.2 CONSIDERATIONS FOR THE RETURN OF PAEDIATRIC RESEARCH RESULTS

2.2.1 EMPIRICAL STUDIES ABOUT PARENTAL PREFERENCES

Participant preferences are subject to change as their personal or family circumstances influence these choices and are intimately linked to the values and norms of the participant, the nature of which may change as the information a participant has at hand changes at any given time (Harris et al., 2012). This leaves researchers with the difficult task of attempting to deal with participant future preferences. The importance of effective communication between researcher and participant could alleviate some of the complications that may arise from this uncertain changeable factor that could influence research (Eckstein, Garrett & Berkman, 2014; Kohane & Taylor, 2010). Matsui et al. hence suggest that proper procedures be put in place at the beginning of the research, to ascertain and secure participant preferences for future contact and disclosure (Matsui et al., 2008).

Eckstein and colleagues (2014), suggest that volition serves a gate-keeping role in decisions regarding disclosure of results. So while a participant might decide that he/she wants to receive feedback on research findings, the validity and value of these findings first need to be assessed before the participant's preference is adhered to (Eckstein, Garrett & Berkman, 2014).

Unique to a paediatric setting, is that parents are faced with difficult decisions as to whether they would want to receive secondary, unanticipated findings that could be predictive of adult-onset conditions, in addition to the other questions already raised.

In a study investigating the preferences, attitudes, values and beliefs of parents of children with undiagnosed, rare conditions undergoing exome sequencing, Sapp et al. (2014) found that parents are willing to 'learn and assimilate' new information such as secondary findings, regardless of its relationship to the condition. There were, however, limitations to what they wanted to learn and not all attitudes were positive to receiving any and all information (Sapp et

al., 2014). Additional studies have shown a generally positive attitude regarding the receipt of all types of information generated, however, the values and beliefs that inform participants' attitude, as well as whether these pertain to parents of affected children undergoing exome sequencing to identify a possible genetic cause contributing to their child's condition, remains to be studied (Harris et al., 2012; Ziniel et al., 2014). By understanding parental preferences, and their underlying beliefs and values, informed choice can be facilitated through 'designed intervention' (Sapp et al., 2014). The study conducted by Sapp et al. found that parents seemed to want actionable results and weighed the benefits of learning secondary results against the consequences of knowing. *Actionability* is the potential for knowledge of the finding to lead to some kind of action and controversies arise regarding its definition. Terry (2012) defines actionability in relation to the availability of treatment or prevention, whereas others take a participant-centered approach including into the definition the possibility for an improved health outcome (NHLBI Working Group; 2010) and the need to understand actionability from the participant's perspective (Wolf et al., 2015). Results from focus group discussions in the United States (U.S.) reported the following inclusions by members of the public: '1) getting treatment and prevention, 2) informing family members of their risk, 3) making reproductive decisions, 4) working for environmental action or remediation, 5) life and financial planning, and 6) participating in further research' (Sapp et al., 2014). Parents valued the importance of knowing but wished to preserve their child's autonomy in situations where few available treatments or prevention existed. Parents felt they had managed to adapt and cope with the uncertainty of their child's condition and were not intimidated by unexpected information. This was due to personal lived experience of having a child with a rare and undiagnosed condition. The parents from this study valued choice – being able to convey their preference regarding what information they wanted to learn about themselves and their child – and embraced the opportunity to consider their options and the implications (Sapp et al., 2014). Similarly, research conducted by Ziniel et al. (2014) showed that most parents wanted to receive individual research results but some were more selective and wanted a choice over which types of results they would receive, demonstrating a desire for control. These findings were reiterated in study findings by Harris et al. (2012) who additionally observed that participants expected to receive contextual information along with their child's research

results to assist them in the interpretation of the results and direct them to appropriate resources which would aid in gathering more information, especially when these findings are of unclear significance. Such contextual information includes resources which explain the results in detail, links to relevant literature, and recommended future direction, experts who could help interpret results or support groups. Tabor and colleagues (2011) found that parents of children with autism and diabetes who were participating in research were interested in receiving results for their children related to adult-onset conditions, regardless of the potential for negative psychological impact. Their reasons for this stemmed beyond the clinical utility of such results, including an explanation of disease etiology and psychological benefits. Interestingly, only parents of children with autism included reasons of reproductive decision-making for themselves, their unaffected children and extended family. They desired an explanation as to the cause of their child's autism and an answer to why it happened. These reasons related to their personal utility of results information (Tabor et al., 2011). As such, the perceptions of parents regarding the risks and benefits of receiving research results may differ amongst parents in different research contexts, i.e. where different conditions are being investigated (Tabor et al., 2011). For this reason, Miller et al. (2010) suggest that disclosure standards remain specific to disease contexts, giving consideration to the position of concurrent debates centering around the nature and cause of a given disorder as well as justifying such results with clarity regarding the appropriate standards of evidence because the meaning of the results to research participants differ across these contexts (Miller et al., 2010).

A study conducted by Christensen et al., (2017) found that parents of potential research participants show 'greater likelihood of having more nuanced preferences about genetic information disclosure than those patients who undergo clinical sequencing personally'. In this study, there appeared to be an overall trend for more information. Furthermore, it was also noted that research participants are more likely and willing to defer to experts (such as doctors) when the value of results is not well-understood and when facing the uncertainty and limited utility of disclosed results and under the circumstances of results uncertainty, their preferences for RoR are likely to change (Christensen et al., 2017).

When dealing with complex disorders such as autism where the epistemology of the disorder (i.e. the nature and way in which it may be regarded as genetic) is not well-understood, much controversy exists amongst researchers and further differences may arise concerning the validity of research findings (Miller et al., 2010). Miller and colleagues (2010) suggest that in order to honour research participants' desires for meaningful results information, a few things need to happen. 1) Studies will have to 'contend' over time in order to establish or contest the true nature or etiology of disease, 2) researchers will need to remain clear and transparent regarding their disagreements, and 3) research participants will need to be engaged at a level of meaning of results and what kind of results they would like to receive, at the level of validity of results as well as the level of epistemology (Miller et al., 2010).

Currently, there has been limited research and no publications conducted in SA on this topic to date that the researcher is aware of. This study serves to be a first of its kind locally.

2.2.2 CHILD'S AUTONOMY

Research involving children has the potential to hold benefit for everyone since many adult-onset as well as complex diseases/disorders have their antecedents in childhood. However, a fundamental difference in paediatric compared to adult research is the inclusion of a third party into the decision-making/consent process for the return of genetic research results, namely the parent. This parent-child-researcher triangulation adds complexity to the research process, especially with the need to consider the child's evolving capacity to make decisions that reflect the child's preferences regarding the RoR.

Ethical frameworks for the RoR in children have been proposed by a few (Avard, Denise et al., 2011; Holm, 2017; Holm et al., 2014; Knoppers, 2014); and the Presidential Commission for the Study of Bioethical Issues (2013) states that policy and options for this purpose be clearly outlined in the consent form.

Important ethical principles which arise during the consideration of returning genomic information include that of beneficence (acting in a person's best interests) and autonomy (respect for persons and their right to self-determination), both of which can be complex when it comes to decision-making regarding children, particularly vulnerable groups such as those with NDDs. Researchers have a duty to act in the best interests of the research participant and must uphold professional standards; parents have a duty to make decisions that are in the best interests of their child and they have the authority to do so; children have an evolving capacity 1) to make decisions for themselves, 2) for autonomy given that they will have full autonomy as future adults. The child has a right to an open future and parents have a duty to preserve that opportunity in a manner of decision-making on behalf of the child that will afford the child the opportunity to make his/her own decisions as adults. Adding to possible conflict, beneficence and autonomy are person-dependent in that the parent has a view of what is in the best interests of their child and themselves and they have the autonomy and authority to make these decisions for their child; the researcher's view is to protect the best interests of the child and family and to uphold professional standards and obligations to their research; and the child has a growing and future autonomy (Holm, 2017). Even more so, research has the ability to contribute to the greater good of the community. This is to say, doing the research may help a group of people in determining causal pathways, best treatments and so forth, though it may not necessarily be beneficial to the individual family who is involved in the research process.

During the consent process, a clear explanation of the policy and procedures of the research being conducted should be provided, and if return of research results is feasible, should give participants the option of receiving their results and should consider their preferences regarding the types of results they would want to receive (Holm, 2017; Kohane & Taylor, 2010; Sapp et al., 2014; Ziniel et al., 2014). In other words, participant choices are made during this time of consent, however, in paediatric research, the parents of the child provide "proxy" consent and the child participates through an assenting process fit for his/her age-appropriate capacity but engaging the child participant as much as possible in the research process is an important aspect. During the consent/assent process, explaining to the family where and what choices they may have, that

results for highly actionable childhood onset conditions will be returned and results for non-treatable adult-onset conditions will not be returned, may result in a truly informed consent process and overcome many ethical challenges. Prior to consenting to participation, individuals should be made aware that their preferences may be set aside in certain instances (Holm et al., 2014).

Consensus seems to be that only certain results – namely, those likely to be acutely important for the health of the child before adulthood - should be offered to the parents and their families under certain conditions (IRCM Working Group, September 2015). Results of an adult-onset or carrier status nature are generally not revealed and only results that are actionable are disclosed at the preference and consent of the parents (Holm et al., 2014).

2.2.3 BLAME

Issues of blame may arise in the event that a research discovery reveals causative mutations which appear to be inherited from one parent. These mutations are passed down from the parental lineage to the offspring, who is then a carrier of the same mutation and who is then also at risk of passing the mutation on to her children in the same manner. In such situations, it may be easy to assign blame to the partner for passing the condition on to the child. Amidst this blame, feelings of guilt or shame may also ensue as the individual may deem themselves as 'broken' or unfit to reproduce or blame themselves for their child's condition. In certain cultures these feelings may even be exaggerated by a partner choosing to take a new partner in order to have more, unaffected children. The psychological well-being of the research participants should always be in the forefront of a researcher's responsibility and it is thus of utmost importance to clarify the preference of participants when partaking in research as to which results they would want to receive, as well as educating them on the possibility of such an outcome.

2.3 INTERNATIONAL GUIDELINES AND SA-SPECIFIC GUIDELINES

General guidelines for the return of genomic research results traditionally focused on analytic validity, clinical validity, actionability and severity of the outcome (i.e. the nature of the result itself), however, studies have shown that parents of paediatric participants often desire to receive all research results, regardless of clinical utility or actionability, and indeed they do have a right to know information that may be important to their child's medical care (Harris, et al., 2012; Holm et al., 2014).

Albeit wide variability regarding the return of individual research results, several international policies recommend that the return of IF be obligatorily disclosed when relevant to health or quality of life (IRCM Working Group, September 2015).

2.3.1 INTERNATIONAL GUIDELINES

The American College of Medical Genetics (ACMG) and 100,000 Genomes Project (UK10K) guidelines stipulate that pertinent findings directly related to the cause of the condition must be fed back to participants and consent obtained from the participants as a prerequisite for participation in the study. They further state that secondary findings that fall within their list of recommended genes meeting their threshold of clinical significance be returned to participants. The ACMG list comprises of 59 recommended genes and includes IF (Green et al., 2013), whereas the UK10K has a more limited list of secondary findings of high clinical relevance to which the participant may have the option of opting out from receiving, however, IF will not be returned (Mark et al., 2017).

Other policies take participant preferences into account:

World Health Organization (WHO) guidelines and The Canadian Tri-Council Policy Statement (2018) stipulate that 'disclosure be made on the basis of a clear demonstration of clinical benefit and communicated in a way that averts or minimizes harm so long as there is evidence that the individual would *prefer* to know' (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, 2018; Council for International Organizations of Medical Sciences [CIOMS], 2014).

According to The Network of Applied Genetic Medicine international research ethics guidance for policies and practices relevant to children, ways in which researchers acknowledge and balance the rights of parents and children not to know about genetic findings should be included. These include 'respecting parents and children when they indicate not wanting to know about results; overriding preferences not to know when the results have significant health implications for the child; and extending the right not to know to relatives' (Avard et al., 2012). These guidelines leave room for the RoR to be an option rather than an obligation according to Lévesque, Joly & Simard (2011).

2.3.2 SOUTH AFRICA

H3Africa guidelines state that findings that are pertinent to the original research project will be returned to participants once the evidence base (analytic validity and validation by a certified diagnostic laboratory) has been assessed for potentially pathogenic variants in relation to the population being investigated, the value of the finding to the participant has been assessed, and participants have been appropriately informed of the implications of the findings for disease and treatment and follow-up care has been established (Rotimi et al., 2014).

However, SA and Africa as a whole, is lacking in legal and ethical guidelines/policies relating to the feedback of genomic research results, and ethical challenges are compounded by low literacy, poverty and socio-economic barriers (Masiye, Mayosi & de Vries, 2017). Gornick et al. (2017) found that research participants in the U.S. were less concerned about which policies were in place regarding the return of IF than they were about having the choice to decide which findings they wanted to receive. SA is a country that places high value on choice, which needs to be considered in ensuring harmony between research participants and researchers, before setting up any guidelines and policies. Participants need to be educated on possible research findings and their implications before consenting to participate in the research (Gornick et al., 2017). Public opinion, participant preferences and tailored FoF is pivotal to the success of the feedback process, especially in SA due to our cultural/demographic and linguistic diversity. The lack of such guidelines leave essential questions about how best to feedback research results to the SA population.

2.4 NEURODEVELOPMENTAL DISORDERS (NDDS)

2.4.1 WHAT ARE THEY

NDDs are a group of complex disorders characterised by developmental deficits such as impaired functioning on a social, personal, academic or occupational level. These disorders typically manifest in early development and according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), can include disorders like autism spectrum disorders (ASD), attention-deficit hyperactivity disorders (ADHD), intellectual disability (ID), global developmental delay (GDD), communication disorders and specific learning disorders (e.g. dyslexia) (American Psychiatric Association [APA], 2013). There is considerable co-morbidity between some of the disorders, which complicates the process of determining the burden of these conditions.

2.4.2 BURDEN IN SA

There is an overall lack of recent population-based data on NDD prevalence in SA. The only SA data emanates from a study conducted in a rural region of Mpumalanga (Bushbuckridge) where researchers diagnosed 3.56% of the children they examined with ID (Christianson et al., 2002).
A study conducted in Uganda found the prevalence of NDDs to be 12.7% (Namazzi et al., 2019). To put this into perspective, the reported global prevalence of NDDs is 8.4% (Olusanya et al., 2018), and Bitta et al. (2017) conducted a systematic review of reported prevalence and incidence of NDD, determining a minimum-pooled prevalence of 7.5 per 1000.
Other than the co-morbidity between some NDDs, reasons for complicating burden estimation also include 1) the age of the child, because some NDD only manifest later in life and tools used to detect these disorders may not be sensitive enough at such a young age; and 2) difficulties in diagnosing most NDDs, especially those which affect intellectual compared to physical functioning (Bitta et al., 2017).

2.4.3 GENETICS AND NDDS

NDDs are a group of complex disorders and can exist alone or be syndrome-related. A considerable proportion of NDDs – about 15-20% (Urban, 2015) – are due to small deletions/duplications that can typically be detected by microarray testing with the diagnostic yield increasing by 12-30% amongst those 40-60% of cases where the diagnosis remains unclear using conventional karyotyping, which only detects 3-5% (Rawal, 2019, Xu et al., 2018).

There are some variants that have been associated with ASDs and internationally-based diagnostic panels for testing do exist. However, due to the complexities of NDDs it is generally difficult to pinpoint specific variants as a single underlying cause for these conditions and individual variants may not necessarily be pathogenic in themselves as is the case in monogenic disorders. This is due to considerable overlap with individual phenotype, interaction with other variants, as well as gene-environment interactions that may contribute to the development of the disorder. A particular challenge is that many of the variations associated with NDDs appear to be *de novo* significant variants rather than familial in origin. The findings from studies such as the NeuroDev study may hence be difficult to interpret and not necessarily identify single mutations explaining the genetic cause.

Greater understanding is needed of the genetic contribution of NDD causation in Africa, as well as the gene-environment interactions and their resultant expressivity or phenotypic effects in individuals. This may assist in developing better diagnostic, treatment and management tools in Africa. Another requirement is to increase community education regarding these conditions (de Vries, Petrus et al., 2013).

2.4.4 CURRENT CLINICAL PRACTICE IN GENETIC TESTING FOR NDDS

Technologies employed to test for NDDs and the availability of skilled health professionals to analyze and interpret findings is abundant and cost-effective internationally. However, SA faces many challenges and inequities related to being a third world country and as such, the practise of genomics and genetic testing is influenced by an overall lack of resources, whether it be of skilled health professionals or equipment, infrastructure or financial limitations.

In certain public clinical settings in the WC, current methods often employed for the diagnosis of NDDs are microarray and multiplex-ligation probe amplification (MLPA) analysis, nonetheless, due to resource constraints, these are not always routinely available for all patients (Urban, 2015) and NGS is used sparingly; restricted access to such testing may particularly occur in the public sector where use needs to be made of external laboratories for testing, resources are limited and the health sector is overburdened.

2.5 THE NEURODEV STUDY

The NeuroDev study is a large-scale, international collaborative study which aims to contribute to mapping the genetic variation amongst children with NDDs in Africa by performing genotyping and exome sequencing on children, aged 2 – 17 years old, with NDDs in SA and Kenya. Genotyping will allow for differences in the genetic make-up of an individual to be determined by comparing the individual's DNA sequence to a reference sequence (control group), thereby revealing the alleles the individual has inherited from their parents. Current study sites are located in SA where 1,100 children will be recruited in the WC and will be matched against ancestral and geographically similar case controls. The study aims to phenotype these children comprehensively and to perform genetic testing via exome sequencing of both affected children and one or both parents where available. Expected findings include *de novo* significant variants, meaning that they will be relevant to the child's clinical condition. If the study identifies common, known genetic causes of NDDs, then researchers will take a second sample for confirmatory

diagnostic testing. Positive results (clinically confirmed by microarray testing for known genetic diagnosis of NDDs) will be fed back to individual research participants or their parents.

2.5.1 THE NEURODEV FEEDBACK POLICY

2.5.1.1 THE POLICY

The NeuroDev study requires consent from the parents and assent from the child (where appropriate) for the child to participate in the study. Parents also need to consent to their own personal participation should they wish to participate whereupon personal refusal will not hinder the child's ability to participate in the research.

The feedback of results process will involve re-contacting the participant after identifying a genetic variant at research level sequencing which may potentially be causative of the child's condition. At this time, they will be reconsented, a new blood/saliva sample will be taken and confirmatory clinical sequencing will be performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory in the U.S. to confirm the finding and whether it meets criteria for returning to the participant.

The NeuroDev study will only be returning primary research findings of variants in known pathogenic genes that have been associated with ID or ASD. At variant-level, pathogenicity will be determined by following the ACMG, Association for Molecular Pathology (AMP) and College of American Pathologists (CAP) guidelines to classify the variant's role in disease. The parents of participants in this larger study are informed at the time of consent for participation that they may not receive any clinically meaningful results from this study and of the possibility that no results may be generated. No adult-onset conditions but only findings relevant to the child's clinical condition which are the primary focus of the study will be returned, and no IF will be returned due to lack of validation in the African context and budget restraints.

2.5.1.2 SPECIFIC NDD CONDITIONS BEING TESTED

Structured according to the DSM-V, the group of NDDs being tested within the NeuroDev study will include ID, GDD, communication disorders, ASD, ADHD, and specific learning disorders (e.g. dyslexia) with the exclusion of Cerebral Palsy (CP) and motor disorders.

2.5.1.3 QUESTIONS OUTSTANDING FOR NEURODEV TO INFORM APPROPRIATE FEEDBACK

1) Why do people consent to receiving results?
2) What do they expect from the results?
3) How best to return these results?

2.6 STUDY AIMS AND RATIONALE

2.6.1 RATIONALE

Previously, I described that there is little empirical evidence in SA about FoF. I also described that there is no current practice for returning results from research studies. Against that background, I described that the NeuroDev project has a very detailed feedback policy that is already being implemented. In that study, participants are already consented to receive results when they enroll in the study. However, a key question remains as to participant expectations and how to feedback results. There is an opportunity for GCs to impact on this field but before this is implemented, it is important to know more about what participants understand regarding the genomic studies in which they participate and consent processes through which they may have been taken, their understanding of the impact of results and uncertainty which may arise as a result, understanding of scientific terms, personal meaning of results, as well as what they expect in return for participating in such genomic studies. Therefore, this study specifically set out to investigate participant experiences, understanding, recall and preferences for feedback of genomic research results.

Africa is the cradle of humankind and serves to be a valuable resource of genetic information in terms of its immensely diverse population, however, limited knowledge exists on African-specific variants (Campbell & Tishkoff, 2008). Furthermore, between 2000 – 3000 languages are spoken here (de Vries et al., 2013), and difficulties in explaining scientific methods and concepts in local languages have been described frequently (Masiye, Mayosi & de Vries, 2017). These dynamics make the nature of potential services challenging; however, with expanding knowledge and understanding of complex disorders generated by genomic studies such as the large-scale studies being conducted on NDDs in Africa namely, NeuroDev and the Deciphering Developmental Disorders (DDD) project in Johannesburg, it is pertinent to ensure that our method of communicating complex results (which may not necessarily translate into a single mutation explaining the genetic cause) is conducted in a comprehensible and harmless manner.

Against this backdrop, we proposed to conduct a study pertaining to the manner in which sensitive, pertinent, genomic research results derived from a SA NDD paediatric cohort may be communicated to this diverse population in a way that is demographically and linguistically appropriate, comprehensible, culturally respectful, empowering, and dignified. This study set out to specifically explore how these pertinent, individual results relating to NDD causation can best be fed back in the SA context. The approach was to engage with enrolled participants to explore how this component of the study was explained and understood, and what patient preferences were for the RoR .

2.6.2 SPECIFIC AIMS

This project aimed to investigate parents' understanding of the NeuroDev study and preferences regarding the feedback process of genomic research results obtained during the NeuroDev study and the anticipated contributions of such findings. Results from this study may inform a return policy for pertinent genomic research results for the NeuroDev study which is demographic-appropriate, sensitive and tailored to the SA population and could possibly be of wider use to other genomic research being conducted at UCT.

2.6.3 STUDY QUESTIONS

To determine:

1. What do NeuroDev research participants consenting to the return of positive individual NDD-related genetic results understand from the study to which they have consented?
2. What reasons NeuroDev participants give for their decision to agree to the return of positive individual NDD-related genetic results?
3. Recommendations for how positive NDD-related individual genetic research results can best be fed back to research participants

3 CHAPTER 3 RESEARCH METHODOLOGY

CHAPTER INTRODUCTION

The previous chapter outlined the current literature available on current policies/guidelines concerning genomic research and participant preferences regarding the return of individual results. It serves as a background to this study and describes how feedback of genomic research results may be successfully implemented by adhering to ethical guidelines for informed consent and considering participant perspectives and preferences. It also introduced the NeuroDev study, outlines the rationale for the current study and introduced the aims. This chapter describes the methodological framework employed to conduct this study, participant recruitment and sampling, an explanation of the research procedure, data collection and analysis as well as ethical considerations undertaken.

3.1 STUDY DESIGN

This study was conducted using a pragmatic qualitative approach, which allows a researcher to study the lived experiences of individuals and to derive in-depth, descriptive information from study participants (Savin-Baden & Major, 2013). A pragmatic approach provides descriptive information and believes that the worldviews and perspectives of research participants, phenomena and processes can be understood by careful qualitative interrogation (Savin-Baden & Major, 2013). Qualitative research seeks to understand human behaviour. According to Kumar (2014), it is a 'holistic approach built around the premise that as a multiplicity of factors interact in our lives, we cannot understand a phenomenon from just one or two perspectives'. In order to understand a situation or phenomenon, it needs to be looked at it in its totality and from every perspective, i.e. holistically (Kumar, 2014). It holds the view that reality can be interpreted in multiple ways and that the goal of research is to understand how individuals construct reality within their natural context. A 'thick description' of these contexts will render their behaviour,

experiences, perceptions and feelings meaningful and will allow for transferability (Korstjens & Moser, 2017). Due to the limited amount of research conducted on this topic in SA, a qualitative research approach appeared best suited to unpack parental preferences regarding the return of research results, since such an approach can pay equal attention to rare or complex phenomena and allow an insider point of view as experienced by the participant. In addition, quantity does not bear weight of importance but rather, the focus is on painting a wider picture (landscaping) to investigate concepts such as emotions, understanding or preferences which are hard to measure (Atieno, 2009; Wu et al., 2016).

3.2PARTICIPANTS

This project was specifically interested in determining the preferences of existing research participants to the return of individual causative genomic results to inform a feedback policy for the NeuroDev study, a large-scale genomic research study in which participants have already consented to receive pertinent results.

Therefore this study made use of purposive sampling to recruit parents of children who participated in the NeuroDev study. NeuroDev staff pre-screened their participant recruitment database for those willing to be re-contacted for secondary research and gave a list of participants that could be contacted for this study.

Inclusion criteria for participating in this sub-study were:

1) Biological parent or primary caregiver of a participant in the NeuroDev study
2) Cognitive capacity to consent, as assessed in the NeuroDev study procedure
3) Parents/caregivers consenting to be contacted for further research

No minor assent was required for this sub-study since it only focused on parental perspectives and no interviews were conducted with the children who had participated in the NeuroDev study.

3.3RECRUITMENT

Participants were selected based on the study purpose to provide unique and rich information of value to the study. As such, participants were recruited from the NeuroDev study cohort who were well-informed about the NeuroDev study's return of results policy and were thus able to provide information regarding their preferences for the return of their child's genomic research results. These participants were available, willing to participate, and able to communicate their experiences and opinions. The limitations of such non-random (i.e. purposive) sampling is that the researcher is subjective and bias in selecting participants for the study and gathered information cannot be generalized to the larger population (Etikan, Musa & Alkassim; 2016). However, the researcher's aim was to achieve a greater understanding of the preferences to the return of results of parents whose children are enrolled in a genomic research study as opposed to a breadth of understanding regarding public preferences.

The NeuroDev study retains the contact details of all participants within its cohort. The researcher of this study provided a list of criteria (mentioned above) for participants that she wanted to interview for this study and based on these criteria, the NeuroDev PI/study staff provided the researcher with a selection of people within the NeuroDev study eligible to participate in this study. This list comprised of 20 prospective families eligible for recruitment, who had been asked if they were willing to be contacted about further research by the PI/study staff working on the NeuroDev study at the time of recruitment into the NeuroDev study. Those who had consented to be contacted were approached telephonically by the researcher of this study and informed about the aims and objectives of this sub-study. For those who then gave verbal permission to participate, a date and time for the in-person interview was set up telephonically, via WhatsApp, text message or email. Of these 20 families, 13 families were contacted, 12 families consented to participation and only one family declined.

3.4RESEARCH PROCEDURE & DATA COLLECTION

Twelve in-depth, semi-structured interviews were conducted in English at a time convenient to participants and took place in private rooms at RCWMCH.

The interview guide was structured around the following themes: participant understanding of the genetic research study they are participating in, their reasons for participating and their preference for the FoF. The themes were identified based on the literature review, examining previously developed guides from similar research conducted in other settings and questions were adapted to suit our setting, aligning them with this study's objectives. Keyword prompts/phrases were used to guide the researcher and to allow for adaptation into relevant open-ended questions during the interview process, allowing for flexibility (Korstjens & Moser, 2017; Korstjens & Moser, 2018). Test interviews were conducted with three GC students to explore the utility and structure of the interview guide. Following revision the interview guide was piloted with two NeuroDev participants before final revision and implementation. Given the quality of the pilot interviews, these pilot interviews were analyzed together with the main data. A final interview guide can be found in Appendix A.

Interviews lasted for approximately one hour and were audio-recorded. Throughout the face-to-face interviews, shorthand notes were recorded and field notes written immediately following interviews to capture any elements and observations relevant to the research and data analysis. Field notes assisted the researcher in the process of recording and analyzing and proved an essential opportunity for reflection and data contextualization. On the same day, following the interviews, the researcher listened to the recordings and captured any observations and emerging insights in the field notes. These were then integrated into subsequent interviews. By interview ten, similar concepts and themes arose in the interview data which led the researcher to believe that data saturation may have been reached. This was tested by interviewing one more parent with a child with an undiagnosed condition and one more couple with a child diagnosed with ASD.

Transcription was done by a dedicated transcription company. Recordings were transcribed verbatim and the researcher listened to recordings to check the accuracy of transcriptions. Field notes taken during the interviews provided a summary of the interviews and informed transcripts. Transcripts were imported into NVivo 12 (QSR International data analysis software) to assist with managing and organizing the data for analysis.

3.5DATA ANALYSIS

Interview data and observational notes were analyzed using thematic analysis and framework matrices. Themes were extracted from the data, a process which commenced immediately following transcription of initial interviews. Thematic analysis assisted the researcher in understanding the meaning the participants were communicating (Kumar, 2014). Through using framework analysis, robustness and rigour was attained by allowing for clear audit trails of cases and for others to be able to follow the researcher's process (Gale et al., 2013). Framework analysis organizes and reduces the large amounts of data in qualitative research and allows for better understanding of participant perceptions and experiences by enabling the researcher to be fully immersed in the data (Gale et al., 2013; Hackett & Strickland, 2019). This was achieved by manually analyzing the first three interview transcripts through use of an open coding strategy which assigned open codes to relevant or interesting text excerpts. These codes were descriptive of the content of the quotes and were checked by one project supervisor to ensure reliability of code application over transcripts. Drawing on the list of open codes, a mind map was compiled with preliminary themes and both themes and coded text was imported into Excel and there re-organized into sub-themes/categories. In this way a hierarchical coding scheme was developed. The hierarchical coding scheme was reviewed by two of the project supervisors independently. In addition, one of the supervisors also used the hierarchical coding scheme in one transcript to ensure that it covered the data appropriately. Following that, all the coding was done by one individual and as such, the issue of inter-coder reliability was not of concern. Following this, the transcripts were then imported into a new NVivo 12 (QSR International data analysis software) project and the pre-determined code-set was applied in the software. Using the coded dataset, data summaries were generated using the framework matrice option in NVivo 12. Emerging insights (i.e. patterns in the data) were recorded in field notes and were further probed in subsequent interviews.

The researcher incorporated quotes from research participants into text excerpts which assisted with providing thick descriptions and context of participant meaning and experiences. To ensure credibility, the original data drawn from participant responses were incorporated to represent the correct interpretation of participants' views (Korstjens & Moser, 2018).

3.6ETHICAL CONSIDERATIONS

Information sheets and consent forms were explained and read to participants on the day of the interview to ensure that they were fully informed. Only one participant received the forms via email but forms were read through and signatures obtained on the day of face-to-face interview.

Respect for the individual, the individual's right to autonomy and their right to make informed decisions with regards to participating in research are fundamental principles for medical research involving human subjects (CIOMS, 2016; Declaration of Helsinski, 2014). The researcher has to be cognisant of the fact that 'the subject's well-being should always take priority over the interests of science and society and ethical considerations must always take priority over laws and regulations' (General Assembly of the World Medical Association [WMA], 2014). Ethical approval for this study was obtained from the UCT HREC (HREC 784/2018) as well as Institutional approval from RCWMCH.

3.6.1 INFORMED CONSENT

Research participants were informed verbally and in writing (see Appendix B) about their enrollment in this qualitative sub-study and written consent was obtained in English (see Appendix C). Participants were informed that their participation in the study was completely voluntary and that they were able to withdraw from the study at any given time should they wish to do so, without consequences to their current and future medical care.

Prior to obtaining written consent, participants were informed that a suitable translator previously used by UCT Department of Human Genetics could be made available, should they experience a language barrier, to ensure participant understanding of the information. All participants felt comfortable conducting the interview in English and none requested the translator to be present during the consent process and interview. All participants received a copy of the information form and the researcher kept the signed forms for her records.

3.6.2 PRIVACY AND CONFIDENTIALITY

Participants were advised that interviews would be audio-recorded and transcribed. They were informed that a code would be assigned and that names and any identifying information would not appear in the data. The researcher would be the only one with access to their personal information. Participants were informed that all audio recordings and written data obtained from the study would be locked away in a cupboard or stored on a password-protected computer. They were informed that upon completion of the research, hard copies of data will be shredded and disposed of.

The participants were advised that the data obtained during the research process would only be made available to the researcher and supervisors directly involved in the study and will be written up in a dissertation and possibly a publication, without any identifying information. They were also informed that all the information obtained will remain confidential and will be used for the sole purpose of conducting research.

3.6.3 RISKS AND BENEFITS TO PARTICIPANTS

There were no identified direct risks associated with the interview process for this study. During the consent process, the participant(s) were informed that they had the option to opt out of the study at any given time should they feel uncomfortable with continuing.

Given the sensitive and personal nature of the information, some emotional difficulties were experienced during the interviews. The participants were given the option to refrain from answering certain questions or even withdraw from the study if they felt upset or unable to continue and designated support and/or counselling would be assigned to the participant if needed. One participant was flagged due to concerns over extreme emotional difficulty caused by her circumstances and difficulty coping with her child's condition. A psychology referral was offered to the participant but she declined the offer. Following discussion with supervisors, it was decided not to follow-up for now.

Benefits of this study included that participants were able to share their stories and make sense of their child's condition. Storytelling is seen to have therapeutic benefits and has allowed for groups of individuals, with similar conditions or situations, to be heard (Koch, 1998). Some participants did seem to experience therapeutic benefit and thanked the researcher for "just listening" to their story. Another potential benefit is increased awareness amongst participants of the research being conducted and of what to expect from the NeuroDev study since the researcher offered to answer questions participants may have following the interviews.

Participants were offered compensation for their time and travel expenses to the value of R100 – R250 in keeping with compensation offered in the parent NeuroDev study.

Information obtained during the interview process may aid in improving our understanding of participant preferences and experiences regarding the return of their child's genomic result, as well as the underlying beliefs and attitudes that shape these preferences. This information is

beneficial for health care practitioners, including GCs, to understand and assess the efficacy of currently employed feedback methods and to establish more effective, preference-based methods which will guide healthcare professionals during the feedback process and minimize the gap between researcher obligations and participant expectations.

CHAPTER SUMMARY

This research project focuses on the perspectives and preferences of parents whose children are recruited into a genomic research study regarding the feedback of individual pertinent results. This chapter has provided insight into the methods employed to conduct this study that would help achieve the aims of this study. The next three chapters will focus on the results of this analysis, categorizing it into three sections, namely participant understanding, expectations and reasons for partaking in genomic research, their reasons for wanting/consenting to the return of pertinent results and participant preferences to results.

4 CHAPTER 4 RESULTS – PARTICIPANT UNDERSTANDING, EXPECTATIONS & REASONS FOR PARTAKING IN GENOMIC RESEARCH

CHAPTER INTRODUCTION

In 'Chapter 3' I described the study methods and research objectives. In this chapter I start with a brief summary of participant sociodemographic information then explore the broad context of what participants want to know, their reasons for participating in genomic research, as well as desired outcomes from genomic research, aiming to address the research question regarding what participants in the NeuroDev study who consented to the return of positive individual results understand.

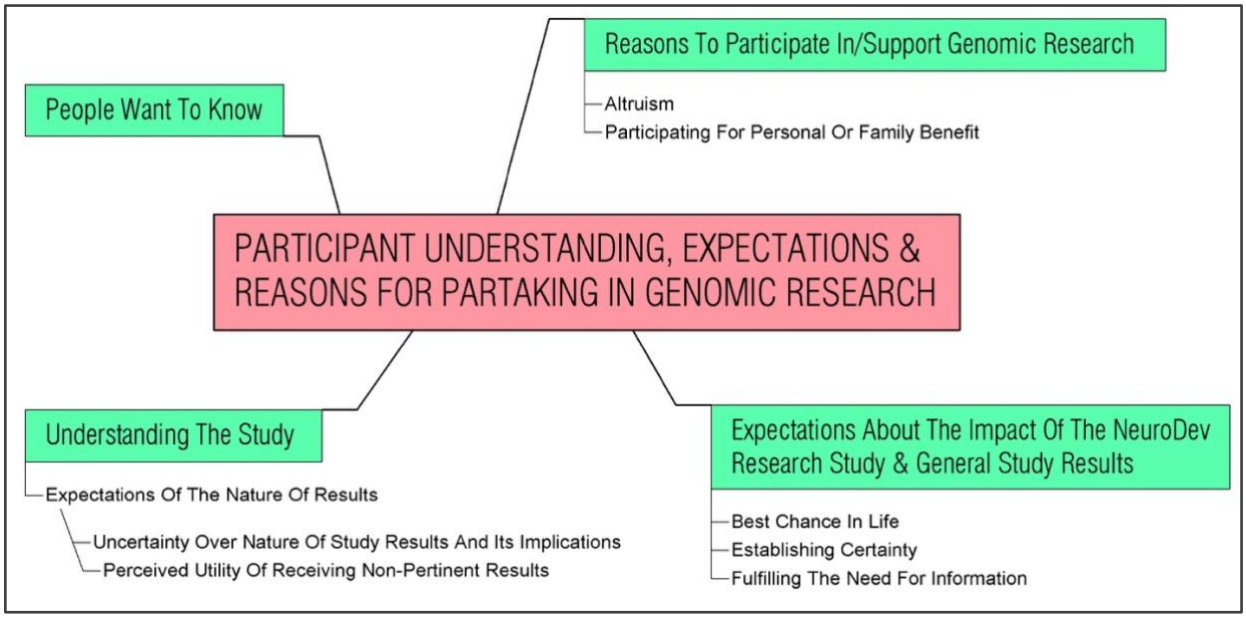

Figure 2. Theme Breakdown for Participant Understanding, Expectations and Reasons for Partaking in Genomic Research.

4.1SOCIODEMOGRAPHIC DATA

The table below depicts the sociodemographic data of the research participants involved in this study.

Total number of participants	17
Gender	12 females 5 males
Number interviewed individually	7
Number interviewed in couples	5
Number of parents with child with ASD	15
Number of parents with child undiagnosed	2
Ethnicity/cultural background Mixed ancestry Xhosa	 12 5

Table 1. Sociodemographic Data.

A total of seventeen participants were recruited, of which twelve were female. Seven individual and five couple interviews were conducted with the parents of children enrolled in the NeuroDev study. Of these, fifteen parents had a child diagnosed with autism whilst two parents had a child with an undiagnosed NDD-related condition. All participants were from Mixed Ancestry and the Xhosa ethnic groups reflecting the demographic of the patient population of the hospital. Translation services were offered prior to obtaining consent but participants declined the use of a translator.

4.2THEME 1 | PEOPLE WANT TO KNOW

As described in section 2.5.1.1, the NeuroDev policy is to return pertinent results only. However, it is evident from this study that participants want to be informed of findings that have preventable implications for their child's health. Such findings may be inclusive of all results which are medically actionable and have clinical utility, whether it be pertinent results or incidental findings.

P16: "Yes. Like I mean, if they found something that is, like I've said, of importance, they found that he has something that could be treatable, or that if we leave it it's going to cause harm or whatever, then yes, I would expect them to come back to us and let us know."

This desire is consistent with evolving consensus in ethics literature around RoR which seems to indicate that individual genetic findings be returned to participants if they are 1) medically actionable or have clinical utility, 2) can be associated with disease causation, and 3) can offer a diagnosis which may not have been made without such a finding (de Vries & Munung, 2019; Eckstein, Garrett & Berkman, 2014).

4.3THEME 2 | REASONS TO PARTICIPATE IN/SUPPORT GENOMIC RESEARCH

Altruism and personal/family benefit seem to be the primary reasons individuals decide to participate in genomic research overall. In the section below, I elaborate on each of these two reasons motivating participation in the NeuroDev study.

4.3.1 ALTRUISM

Altruism was a major motivator for most of the research participants interviewed for this study who described that they participated in NeuroDev because it could 'help others'. For instance,

P8: "So that once they find out what the cause is of it, it can help many other parents that struggle to accept their children's diagnosis. Before he was diagnosed, I was already told that it could be that. And I accepted it. When he got diagnosed, I cried, and then I just spoke up and told myself that he's still my child. Nothing is going to change. And from there onwards I've been doing so much to help other parents. I've created my own WhatsApp group and we have a support group and when it's awareness stuff we participate in it…Because I know my husband in the beginning was in denial and I know how hard it is to do it, accept it only on your own."

Specifically, participants expressed that they hoped the research could motivate institutions to increase access to resources.

P17: I'd like to do more, I mean, I'd like to do more for other people...I'd like to see that research motivating government, the health department. I hope that's going to happen…After the research, I mean, that for me, that there's more support for people that just don't have the resources to do anything.

Previous studies conducted have also identified altruism to be a motivating factor for participating in research, defining it as a 'prosocial behavior' which includes a desire to help others or to advance research in genetics or health (Facio et al., 2011; Gollust et al., 2012; Halverson, Clift & McCormick, 2016; Kauffman et al., 2017; Sanderson et al., 2016; Scherr et al., 2018).

When interviewed for this study, participants expressed their desire to help other families accept the condition by increasing support and offering a place of belonging for those experiencing difficulties in coping with a child with Neuro-Developmental abnormalities but they also hoped that information gathered through research would lead to prevention of these conditions in future.
Unexpectedly, many of the interview participants indicated that one of the unforeseen side-effects of participation in the NeuroDev study was that they met other parents of children with NDD conditions. Because many of the interview participants struggled to cope with their children and indicated feeling isolated, meeting other parents facing similar challenges was really important. After meeting, participants described that they had exchanged numbers, started their own support groups and were trying to raise awareness in their communities. This concept of finding comfort through connections and self-advocacy was also noted by Halverson, Clift & McCormick (2016).

P15: "To be honest with you, when I started this I knew it wasn't about her. It was basically about future children and helping future children not to be … not, not to be, but to just eliminate the amount of these types of abnormalities, basically. And also to gather a way of actually having a support for parents who do have children this way. Because I was one of a few until I came to NeuroDev for example, and I actually got to meet other parents. Not the same type of eye disorder, but also visually impaired. So it's a lonely journey until you find a community that shares the same. So that's the only thing that was very hard in the beginning. It's not knowing anybody that also understands or has a similar idea of what you are experiencing."

Importantly, for some participants altruistic intentions were more important than the possibility that they could receive some genetic results. These individuals felt that having a result would not change anything and were determined not to 'dwell in the past' with questions of 'where' and 'what'.

"P8: "I'm not really worried even. I'm not. Like I said, I partook in it so that it can help many other people. For me on my level that I am at now I fully accept it like it is. There are tough days, there's going to be that. But like for me I'm not worried if it's me, if it's my husband, whoever is the cause of it, where it comes in the genetics."

4.3.2 PARTICIPATING FOR PERSONAL OR FAMILY BENEFIT

Alongside altruism, and as noted in various studies (Allen et al., 2014; Biesecker et al., 2009; Kauffman et al., 2017; Sanderson et al., 2016), personal and family benefits were also strong motivators for participating in the NeuroDev study. Individuals expressed hope that genetic results could help reduce risks of developing a condition or identify ways to prevent them from happening. They also indicated that they hope results may help them prepare or plan for the future (Scherr et al., 2018). In this study, some participants felt that recognizing the condition or becoming aware of genetic status earlier may increase intervention for those affected individuals and/or their families and possibly prevent these conditions from occurring in others. Interestingly, participants also described that they were motivated to participate in the NeuroDev study in the hope of finding a cure/treatment, despite simultaneously describing that they knew that this is not what the study set out to do.

P7: "You see, there's many … I don't know if I can make it, like condition, there's many conditions out there and people who don't know about it, and others know, but others they don't care. And sometimes you'll find if they could have found it earlier maybe by now there is supposed to be a cure for it. Or there could've been something that they can do to help those people who suffer with this condition. Or something to prevent it so that there mustn't be many people suffering with this."

4.4 THEME 3 | EXPECTATIONS ABOUT THE IMPACT OF THE NEURODEV RESEARCH STUDY & GENERAL STUDY RESULTS

Some of the results discussed in this section show some overlap with what people expect individual (not generic) study results to illustrate. For this study, it was sometimes difficult to disentangle these as concepts. For example, the participants' need for information served multiple purposes on an individual and broader level for some individuals. This included that the information could help with management of their child and lead to self-empowerment, it could assist with gaining some form of acceptance of their child's condition through diagnostic closure, and help reducing the recurrence of these conditions.

Participants felt that the study could offer them the opportunity to give their child the best chance in life with a more favourable outcome and could potentially fulfill their need for information. They hoped that results could help establish the course of the condition and options for treatment.

4.4.1 BEST CHANCE IN LIFE

Overlapping with altruistic motivations for research participation, interviewees expressed the hope that results could educate and help people understand and recognize the signs of ASD, thereby enabling the diagnostic process for other children.

P13: It will teach us something, like if you see … because we didn't know that … the first we know that he has autism it was 2017. Because since when he was young we didn't know that he has got autism. So if we got the result and then they explain us, maybe lead us to the grain of this we know that the signs of this if you see something like this, we know, oh, they teach us that autism children are like that, like that, and like that. So it will help us to understand and then to know if your child looks like this, he's got autism.

Expectations varied from finding a cure for autism (as mentioned previously) to wanting an improved outcome for their child, with the opportunity of giving their child the best chance in life. This referred also to means of helping their child interact with others and acquiring developmental and social skills.

Some parents desired broader outcomes from general study results, describing that they were less interested in receiving a positive result and more interested in results that could help them understand their child's prognosis and how best to support them.

P9: "I would like something positive, but if not, I'll accept anything that's coming out of that. I know he's been diagnosed with autism. So it's not like it's going to just disappear overnight. I know that there's no medication also that can cure it. So it's something that we need to live with. It's just I would say that to better our situation."

Participants hoped that the NeuroDev study could offer them the opportunity to learn more about their child's condition and to support them by providing the best chance in life for their child by being a means of support on their journey, emphasizing the need that research participants have for information and support.

4.4.2 ESTABLISHING CERTAINTY

Many participants seemed to express the need to establish certainty amidst all the unknown factors associated with NDD disorders and long-term prospects. They hoped to reduce uncertainty over their child's future by obtaining direction about future treatment and management.

P5: "it's very difficult for me with handling him at home. It's very difficult. So he gets occupational therapy and he gets speech therapy…But the last appointment that I was here they explained to me they haven't seen this type of autism yet, that he has. So now I don't have any appointments as yet until they have a meeting and discuss how they can handle him."
INTERVIEWER: "Okay. And do you think this study is going to help with that?"
P5: "I hope so, because I need the help. I need the help with him… the last people that we saw they didn't say they can give me a result, but tell me this is the reason why he has autism. So I don't expect… like they explained to me they can't say it's genetically positive because they must first send the results away, or environmentally, so I'm passed that stage already to be honest, where I want to know. It's my last child. So … I just want help for the future. I'm saying that right now."
INTERVIEWER: So the cause is not that important to you?
P5: "It's not important to me…But I'm saying I need like … like some sense of direction. Like I told them also, no offense of their profession, they know what they're doing, but I don't see a result in the sense where there's help. Do you understand what I mean?"

On the other hand, participants whose child remains undiagnosed experienced diagnostic *and* prognostic uncertainty and indicated that they consented to participate in the NeuroDev study partly because they were hoping the study could help them attain a diagnosis, thereby establishing a management plan.

P15: "There was quite a lot happening with regards to my daughter. There were multiple abnormalities which we aware of before giving birth to her, but the uncertainty of not knowing what is going to happen. So a lot of emotions. Still is, but now and then, but we manage to get through it because we actually came to understand that no matter what tests are being done nothing is going to change. So I think the hope we have is just basically her vision. We're hoping her vision will just be better one day, or that there's something we can maybe do to just assist her with her vision to prevent her on doing braille full time."

Interviewees expressed the hope that participating in the NeuroDev study would offer a way to obtain more future certainty for participants through obtaining a diagnosis and through guidance in optimum management of their child.

4.4.3 FULFILLING THE NEED FOR INFORMATION

Participants were eager to learn more about their child's condition – where it came from and how best to support their child – and expressed feeling unsupported by the healthcare system. Participants seem to express an expectation that the results from the NeuroDev study will fill these gaps.

P2: "We'd really like to get to know the basics and details because not everyone goes in depth with this autism things. Like, here's pages, read it, that's what it's all about, do timetables, schedules and stuff. So, I really like, want to know the whole details of autism, can it be cured, genetic-wise, how and where did it come from. Like if could just get a little more information about the spectrum…No. Like I'm just at peace I think, like I wouldn't want … like, I mean, parents shouldn't say I wouldn't want a cure, but like it is what it is and he's been diagnosed with this so, for me on the whole I would want like to find out information and genetic-wise plays a big role in this so. Like genetic-wise I would want to have more information of - to find out different things, but for now I quite know that there won't be a cure. Because the only reason based on why this whole assessment that they're doing is to find the reason why too much kids are being diagnosed with autism."

Some wanted to know what 'conditions' cause Autism, questioning whether factors such as obesity (i.e. maternal health) could cause their child to be affected from birth; or if some environmental exposure triggered the condition (e.g. vaccinations).

P1: "Just basically where it stems from. Like what conditions bring it on. Like I want to know if it was my obesity that caused this. Because you know, like you just … you read a lot of things and nobody really has any concrete evidence to say where this comes from, so I'd just be interested to know where it comes from. So if it is something from birth or if it's something that happens afterwards, if it's something that is activated by vaccinations. I'd just like to know just for interest's sake, even if it turns out that there's something wrong with my husband, and that it isn't genetic. I would just like to know where it comes from. So whether it comes from vaccination. Anything that can help me in the future or help me to, you know, maybe navigate this better, or … like my main is just what caused it."

There was an obvious need for understanding their child's condition and the reasons for the cause of it; and participants felt that through their participation in the NeuroDev study, these questions could hopefully be addressed.

4.5THEME 4 | UNDERSTANDING THE STUDY

In this section I present a brief description and explore the understanding and recall of participants interviewed for this sub-study regarding which results the NeuroDev study would return, as explained to them during enrollment.

Overall, people remembered the NeuroDev study and seemed to understand that they would only get results back if there were positive results. There appeared to be some confusion over which results were considered positive, with some referring to individual genetic findings (pertinent or incidental) and their role in the onset of the condition whilst others referred to a positive outcome which could mean a negative result (i.e. an issue of terminology over the use of the word positive). During this interview process, the interviewer did not set out to clarify such misconceptions at the start of the interview in order to gain an overall insight into participant understanding from the enrollment process, however, these misconceptions were corrected following the interview. The purpose of the NeuroDev study was aimed at a better understanding of the genetic architecture

of NDD disorders. Whilst most participants understood this, they still felt conflicted as to *their* beliefs over the possibility of specific causes such as an environmental cause, which added to the uncertainty mentioned above.

P11: *"Because I don't know. That time when I came I didn't think about the vaccine. I didn't think about that. But when times goes on I was trying to figure out, you know, if you are a parent you are trying to think what went wrong and what … Sometimes you come out to say, no man, it's not that, but some people, there are people from another country they don't vaccine their children, especially in our country, there is a religion, they don't vaccine, but there are some people with autism."*

Participants generally understood that genetics and DNA is something that 'runs in families' but found it confusing that the condition of their children did not obviously run in their family. Only a few understood that changes in DNA (mutations) could occur in an affected individual for the first time and under those circumstances, they would not carry this mutation. Some carried a simplistic view; relating the condition to a single cause being either environmental or genetic; whilst many had some understanding of the concept of multifactorial inheritance, describing it as 'many little things that come together at one point to cause the condition' in their child or as cells that get activated.

P12: "I look at it as, how I look at bipolar also. Like everybody has cancer cells. It's just whether it gets activated. So maybe in that sense they're looking at autism. Is it maybe a cell that lies dormant, that's my understanding, as well as if it is a cell that lies dormant, what is it that maybe causes it to activate or something to that effect."

4.5.1 EXPECTATIONS OF NATURE OF RESULTS

When asked what results these parents are expecting to receive, some felt it would be causative results explaining what the change in their child's genetics is or 'how it came in their genes'; others felt the results would confirm an inherited genetic cause; whilst yet others continued to believe results would show an environmental cause only such as environmental exposure.

4.5.1.1 UNCERTAINTY OVER NATURE OF STUDY RESULTS AND ITS IMPLICATIONS

Some participants indicated that they were anxious about the nature of the results they could receive and felt the meaning of the result would be dependent on the kind of result they would receive.

P6: "It depends on what kind of result we're talking about. If it's like something to … what the cause is. Basically, there's nothing we can do about it."

Because there was uncertainty over what the meaning and implications of possible results would be, participants were unable to speculate how those results would make them feel.

P7: "I'm not sure. I'm not sure if it's not going to help me with anything. Because I'm not sure … I don't know if it's going to be good or it's going to be bad, or how I'm going to take it"

Conversely, others were not expecting to receive any results, understanding that the NeuroDev study was for data collection purposes only. It is also noteworthy that participants observed that a long time has passed since they enrolled in that study and since any researcher contact has been made, leading to decreased expectations of receiving any results.

INTERVIEWER: "Okay. What kind of result are you expecting?"
P9: "Nothing. [Laughing]…It's been a while now already and it's not even saying … we haven't forgotten about you or something. So, yes, that's why I feel … and I was actually surprised when you called. Okay, there is somebody still remembering us."

Uncertainty over the meaning of results and their implications created anxiety in participants that may have been caused by a lack of understanding which results would be fed back by NeuroDev. Whilst participants reiterated that only pertinent results would be returned, they continued to discuss the likely implications of non-causative or uncertain results. This is explored further in the following section.

4.5.1.2 PERCEIVED UTILITY OF RECEIVING *NON-PERTINENT RESULTS*

The majority of participants expressed their wish to receive all types of results, good or bad, including individual genetic research results that are of significance to the health of their child; and the confusion over the nature of results that the NeuroDev may return and the potential implications of their preference to IF was evident. Some believed that results could warn them of their child's potential health risks.

P5: "If it's something that can affect him, then yes, we would want to know about it…And they pick up something else that's not related, yes."

A few parents believed results would be indicative of their own personal health, also referring to incidental findings, mentioning that those findings could then be used to help others and inform future intervention strategies.

P7: "Any. I can't say I'm hoping for this, but any result that comes. Anything that they can find maybe some sicknesses in me or something maybe can … so that they can prevent it to other people…But if they can say the result is coming like this, this is something that we found that may cause your child to be like this, then I will accept it. The moment that they come with the result that says this is a condition we found but it's not what caused this on your child. That will be fine too. And then I'm going to look forward to see how they're going to maybe help it or treat it…Everything they find. Everything."

Others felt it would enable them to provide a better quality of life by being prepared and planning for their family's future. The latter was also described by a participant in terms of his own health, possibly driven by personal fears of having passed the condition to his child or another possibility being the confusion over the nature of the result he can receive, in other words an IF.

P17: "Look, I mean if there is a result there's a result. Obviously we have to know that. I've got dependents, five of them you know, so I would want to ... if I'm going to die tomorrow or in a few years' time I would like to have that quality of life. I don't just want to leave them behind or whatever.

Some participants seemed to prefer to receive information about all kind of results, including ones that do not yet have clinical significance (results that are normally referred to as 'variants of unknown significance'). They expressed the hope that those results could lead to further research that they could participate in.

P1: "Maybe then someone else would come and try to take that further and then we can be involved in that study."

These findings resonate with the reported results of published studies. For instance, the HealthSeq study (Sanderson et al., 2016) found that participants did not expect genetic testing information to be immediately available or beneficial, but hoped that continued research would provide more information in future. Furthermore, Halverson, Clift & McCormick (2016) and Miller, et al. (2008) found that participants found meaning in results of uncertainty and believed that knowledge about such results and analysis would grow, yielding answers in the future.

On the contrary, some were unsure about the usefulness of VUS information and expressed concern over the possibility of discovering new/other information, indicating a preference not to know about VUS results.

P16: "I don't know if I would want to know that part, because now you're going to be sitting with this information and you're thinking what could this be."

Reasons for wanting all generated results stemmed from a need to plan for the future, to provide quality of life, to inform personal health risks and to promote future research and information discovery.

However, some felt that receiving negative rather than all types of results (i.e. receiving feedback from researchers that no results were generated through the study) could reassure them that researchers tried their best to find answers, referring to closure and perhaps somewhat reducing anxiety, serving as confirmation of acknowledgement from the healthcare system and relieving their personal turmoil over having done all they could.

P1: "Just to let the whole thing come to fruition, I mean like, just have it being done and we… not that I would feel like this has all been for nothing. I mean, I've been educated about some subjects with regards to this, and I know what you [researchers] do. And ja, I just think that I would be okay with even if they didn't know anything, then at least I know that it's over and that they've done all they could and that it's still a mystery."

Others alluded to such findings having the potential to generate anxiety, representing new information and adding to existing uncertainty.

CHAPTER SUMMARY

In this chapter I presented a brief overview of participant sociodemographic data and explored what participants understood regarding the NeuroDev study returns policy (Section 2.5.1.1) and their expectations of the impact results may have, aiming to address research question 1. Whilst a level of confusion was observed with participants taking a broader perspective on likely implications of all types of results, there remained understanding that pertinent results explaining the cause of their child's condition would be returned. I explore the personal utility of receiving pertinent results in the following chapter.

5 CHAPTER 5 PERTINENT RESULTS

CHAPTER INTRODUCTION

In the previous chapter I discussed the understanding of research participants with regards to the nature of results the NeuroDev study would return. As mentioned, there appeared to be some confusion over the implications of results, with participants linking ideas over likely implications to not only pertinent results, but more broadly to all results that may be generated through a genomic research study. In this chapter I focus on participant perspective of the likely impact of *pertinent* results specifically – i.e. a diagnostic genetic result for their child's condition – and their reasons for wanting to receive such results, since this is what the NeuroDev study will be returning. This chapter ties in with research question 2: Why participants agree to the return of pertinent research results.

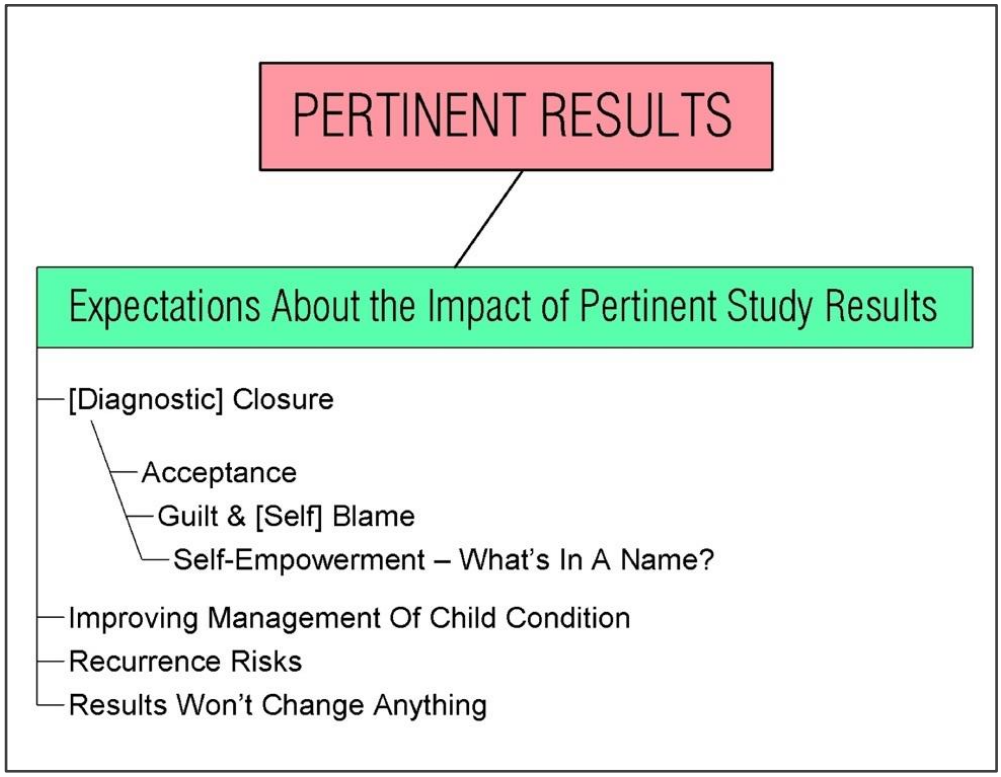

Figure 3. Theme Breakdown for the Return of Pertinent Results.

5.1 THEME 5 | EXPECTATIONS ABOUT THE IMPACT OF PERTINENT STUDY RESULTS

As previously discussed, overall participants expected the NeuroDev study to return results that explains the cause of their child's condition (i.e. pertinent results), with the majority expecting a genetic association (see table 2 below).

Expected Results	**Reasons for Wanting Pertinent Results (Results Explaining the Cause)**
Causative • Cause for Autism Genetic • Confirming it's from husband • Confirming it's from the father or mother's genetics • What the genetic change is and how it happened Environmental Exposure • Something that happened – being in the wrong place at the wrong time	A name for condition An answer 'why' For their children's future offspring Information To educate self To help navigate the condition better Better quality of life To not have future offspring

Table 2. Types of Results Expected from Parents Whose Children are Participating in the NeuroDev Study and Reasons for Wanting Pertinent Results.

Participants clearly linked their own meaning to results and perceived them as useful for reasons other than just clinical utility. Such personal value included closure, whether overall closure or diagnostic, improved management of their child's condition and information regarding recurrence risks.

5.1.1 [DIAGNOSTIC] CLOSURE

For participants, diagnostic closure was a major finding regarding their expectations. This encompassed acceptance of their child/situation, addressing guilt and blame and that it would aid in empowerment, discussed in the sub-themes below.

5.1.1.1 ACCEPTANCE

Many participants expressed that whilst the unknown brings fear, results would bring awareness and acceptance - some form of peace.

P16: "Awareness and being able to accept whatever it is and ... being able to accept something and being aware of it, it just makes you feel more at peace about whatever, you know, whatever the result is. But not knowing is scary. You don't know how to deal with things and, I mean, we used to think that [child's name] is just being naughty, you know, and sometimes you feel bad because we used to scold him and give him a spanking whatever, and in the meanwhile he had this problem. So ja, I'd rather be aware and know, and then know how to treat it."

P10: "If it's for example, a negative result we'll work towards a solution and move on…Because looking back and moaning about it, is not going to help anyone."

An observation was made that for some participants, answers would bring relief regardless of the meaning of the result or the cause of their child's condition.

P11: "It would be a relief. Because now we're just saying, okay, maybe ja, it's the vaccine. But maybe it's not. Maybe there's something wrong with me and [husband's name]…So you know, if they come and say we found something on [name of child], yo, it will be … it doesn't matter if it's bad or wrong but it will be a relief."

As noted in a study conducted by Halverson, Clift & McCormick (2016), participants who had exome sequencing done in a clinical setting perceived it as valuable to have a name for the condition or to know the cause. This could offer a sense of closure and relief by knowing that they have done all they can to ensure their health.

5.1.1.2 GUILT AND (SELF-)BLAME

Participants felt that results would resolve feelings of guilt and self-blame by offering an understanding of why this happened and where it stems from. Having answers would put the unknown to rest such as not knowing what it [the condition or the cause] could be, and they would be able to work towards a solution and move on by knowing that they did not do anything to cause their child's condition.

P15: "It will just be like closure. It will be … I did nothing wrong, my husband did nothing wrong. We didn't bring it upon her."

Many parents battled with questions as to why this may have happened and described being overcome with feelings of grief and guilt, which may have been somewhat relieved through participation in the study, either by the knowledge inferred upon them regarding their child's condition or by the comfort of knowing that help is available.

P13: "Yes, because, it's just like a miracle because in my mind I was thinking, oh, maybe one day I can find some people who's going to help me to understand about the situation with the baby. But God made a miracle, I met them [the NeuroDev staff] … after that I was very happy because I was always crying, oh God, what have I done. So there was time when I met them, so now I saw, oh no, it's not mine. It's not my fault. It's God and he knows what he's doing. But I was very happy because God gave us a healthy boy, never mind if he's not talking. But it will come one day."

It seemed that internal guilt may be exacerbated for some when the condition is not seen in other family members, possibly relating to the fact that they might have done something wrong to solely carry this flaw that they passed on to their child and also feeling guilt that their child expresses this condition which they too, carry.

P7: "If it's something that is in his DNA, it's not something that comes from me, then I'm not going to be worried because I'm not going to feel guilty like I'm the cause of him being like that. I'm going to know that it's naturally comes like that. But if it's going to come like something that he get from me I'm going to feel guilty on the other side, because even when I look at him suffering or it's difficult to do something I'm going to be like … you are like this because of me. But on the other side, I'm going to be glad that I give back to him so that I can know also that I have this condition, maybe I could've … maybe there was no chance that I can know what condition do I have there. Maybe this was a channel to give me the … to tell me about my body also."

For some, knowing that this is a spontaneous mutation, occurring in the child for the first time and not carried by them, may resolve such feelings of guilt albeit sharing the same DNA. On the contrary, for some results would not take such feelings away and the guilt affected extended family members as well, knowing that they had shared DNA and perhaps all carry this 'flaw'.

P4: "Since I hear that she is autistic I'm not well and if I can have a result now I think it's going to be the same. My sisters and my brother also, they'll feel bad but not as much as me … because I'm the mother. I'm the one who carried nine months in my tummy, so I will always feel bad."

Some were searching for confirmation that they were not to blame to assist in the process of guilt resolution. They felt they had done everything right during this pregnancy, whereas they had engaged in more risky behaviours during previous pregnancies and their other children were healthy.

P15: "At the same time you're a mother, you are human. You still want to know why. Even though a name is not going to change it, but it's also, you want … what is that word? It's just a need to know. Because when I, like in the beginning when we found out … the first thing we did we stopped smoking. That's the first thing we did. So we did everything right. We didn't do unnecessary going out. We just took it easy. In fact, I was more healthy with her to what I was with him [sibling] in my pregnancy. So I would like to know how and why."

The desire for answers as to the cause of their child's condition and a basic need to know, was fuelled by various reasons and agendas. Participants described the need to know if it [the condition] is genetic, linking this to their decision-making over having another child (discussed in greater detail below). It is possible that participants may also have been searching for someone to blame or were looking for ways to resolve feelings of self-blame.

P1: "So I definitely think - and this isn't to just like prove a point then oh my God, you have ADHD, I'm going to leave you because I want more children. I just … I need to know. And this for me was the perfect opportunity to …I do believe that there is a deeper cause and I do believe that it stems from my husband's side of the family and I do need to know."

5.1.1.3 SELF-EMPOWERMENT – WHAT'S IN A NAME?

For those whose child remains undiagnosed, hopes were that results would bring a name for their child's condition, thereby providing means for defined management and treatment of their child.

P15: "I haven't thought of it actually. For me any result … it's like I said before, the results that I'm going to get are not going to change anything. So it's just about knowing. It will be nice to have a name for her disorder because currently each department is just basically assisting her as per organ. She doesn't have a place to go to. She's all over at the hospital basically because she's being treated per organ."

A name for their child's condition would guide them in conducting their own research and foster self-empowerment.

P15: "In a category. And it will also make things easier for research, for me. When I … like when we discovered when she was born this was wrong … it's easy to Google once you have a name to something. But before they could tell me what was wrong with her eyes I was laying in the bed after giving birth and was trying to Google, born without a right eye, what does it mean. And ten thousand stuff came up and I'm like, now which one of these does she have. So, it would be nice to know."

5.1.2 IMPROVING THE MANAGEMENT OF CHILD'S CONDITION

For many becoming as educated as possible about their child's condition meant that they would have greater understanding and be better able to manage their child.

P1: "I mean, I just want to be like as educated as I can on the subject. Because I mean, it's part of my life now."

P7: "I think it's going to teach me something also so that I can know how to handle him, all that. Because if you know what is wrong with this person then you know what to do when you are around this person."

Having results could make things easier, raising hopes for treatment, medicines and an improved life for their child.

P6: "Like maybe what medication he can use, or something. I've seen a video of a … I think the girl is 24 and she's got autism, can speak and everything. She's got her own school for autistic children that actually helps them, but it's not here. It's overseas. Basically just to help him to improve his life."

However, interviewees also expressed that nothing could be done about the fact that the child has the condition and that a genetic diagnosis would not change this.

P6: “Basically we just want to know what the cause of Autism is and what we can do to make it better … you can’t do much about it.”

5.1.3 RECURRENCE RISKS

Receiving pertinent results can inform participants of their personal reproductive potential or that of their children. Some wanted to find out if they could have more children who would be unaffected,

P1: “I remember like the main reason why we did it, was so that we could find out if we could have more children without the child having some type of neurological issue”

while others more broadly wanted to help the next generation of their family.

P7: “So I said I understand. I don’t mind no matter it’s not going to help me now, maybe it’s going to help my grandchild in the future.”

Some wanted to know the likelihood of their child’s condition being genetic (referring to the likelihood of it being inherited) and what the recurrence risks are to the affected child’s future offspring.

P1: “Maybe also just to know if it is genetic and she has it would her offspring then also have it. That would also be interesting to know.”

This is consistent with findings in the literature which note that for some healthy participants, expectations of research study results involved a desire for health risk information for their children or grandchildren which tied in with reproductive planning (Allen et al., 2014; Biesecker et al., 2009; Kauffman et al., 2017; Sanderson et al., 2016).

5.1.4 RESULTS WON'T CHANGE ANYTHING

Contrary to all of the above-mentioned reasons for receiving pertinent results, some participants felt that receiving a genetic result would be unlikely to change how they relate to their child and the condition.

P12: "In all honesty, I … especially in the beginning when [name of child] was diagnosed, it's … I would like to know why, would be fantastic. I can honestly say I haven't come hundred percent to deal with the fact that my son has autism, but I can say that no matter the results, as to why … it's not going to change the way I feel towards my son, it's not going to change the things that I do for him, what I do or sacrifice. I feel with my family and myself, we would still have done everything that we did we would do again. It wouldn't change it. So as to why he has autism, I just it's just a bonus to know, but it won't make or break anything…It won't tell who my son is because I already know."

P15: "…it's not like she has an illness and she has a thing where she's getting worse. So anything they're going to find is not going to change or make her worse. She is who she is, she has what she has and we're administering it accordingly."

These individuals continued to hope for an answer but did not feel it would add further value other than knowing what the cause is, which is valuable information in itself.

CHAPTER SUMMARY

In this chapter I aimed to address the research question concerning participant reasons for agreeing to the return of positive NDD-related research results. I described how pertinent results has the potential to impact in a positive way for many participants who hope it could bring closure by bringing acceptance of their child's condition, dissipate feelings of (self-)blame or guilt and offer means of self-empowerment. Furthermore it is meaningful in the sense that it could offer information regarding improved management for their child and inform risks for future offspring. Some felt however that although receiving pertinent results would be valuable in offering a reason for the cause, it wasn't likely to change the outlook of their child's condition or the management thereof.

6 CHAPTER 6 PREFERENCE TO FEEDBACK

CHAPTER INTRODUCTION

The previous chapter focused on the meaning of pertinent results and why participants want such results returned. The chapter that ensues deals with participant preferences to the logistics of feedback of results, broadly presenting the how, where, what, why and whom questions often debated in literature concerning the return of genomic research findings.

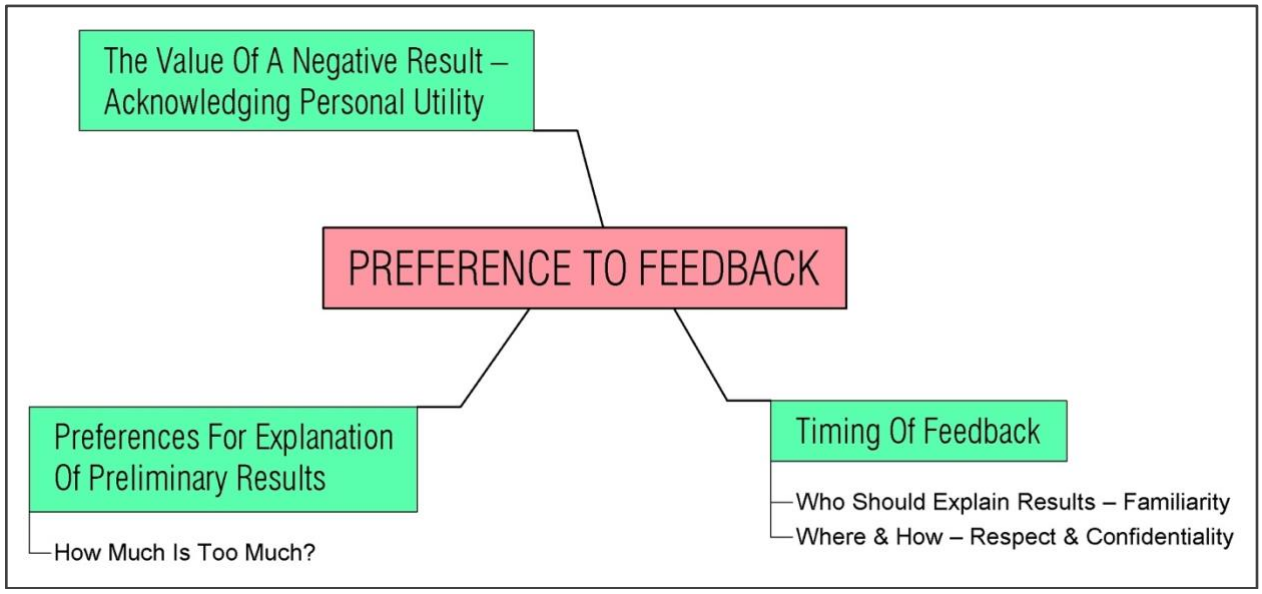

Figure 4. Theme Breakdown for Participant Preference to Feedback of Results.

6.1 THEME 6 | THE VALUE OF A NEGATIVE RESULT – ACKNOWLEDGING PERSONAL UTILITY

Participant motivation for their decision to receive pertinent study results was to gain information and to find a reason for what is going on with their child, however, they felt that they would want to know if there was no genetic result as this would also guide their future planning.

P2: "I'm quite fine. I'd also like to get information, but however they also mentioned that if they don't find anything in our blood which means like, although they won't contact us but it would also be nice if they could just say like your blood test came back, we're going to have to work on something else and see whether the next step will be better. Because currently we find nothing. So that only would be appreciated a lot, then we can follow next procedures and stuff and wait for something else to come."

P12: "I mean, I would like to believe that everybody in that position would, you know, say something … the main thing to do, not just about ethics or anything, it's just …"
INTERVIEWER: "But that's what you would want. You want all kinds of results back, it doesn't matter what they've found?"
P12: "Yes. I mean … anything's better than nothing. Even if it's just to say that look, we haven't, you know, found … the study was inconclusive. I would also like to know that."

Regardless of their understanding of the NeuroDev feedback policy which stipulates that only pertinent findings will be returned (Section 2.5.1.1), the majority of participants wanted to be contacted with a negative result for various reasons, including getting closure, for peace of mind, keeping calm, and to stay informed of research progress.

P12: "Yes. I think that is as important. I think it's more for peace of mind and also to … it's just about us being included. Keep updated. A negative result is still a result."

For some individuals, receiving a negative result would bring reassurance that they and the researchers did the best they could, despite a lack of answers over what the meaning of the result may be or the lack of clinical utility.

P1: "Just to let this whole thing come to fruition, I mean like, just have it being done and we … not that I would feel like this has all been for nothing. I mean, I've been educated about some subjects with regards to this, and I know what you do. And, ja I just think that I would be okay with even if they didn't know anything, then at least I know that it's over and that they've done all they could and that it's still a mystery."

A sense of entitlement over their blood and thus their results was apparent in a few individuals.

P7: "I prefer they must call me to tell me that. Because I'm going to sit like now, that year in Red Cross they take my blood and they say I didn't know what they're checking, I didn't know if there's anything that they found in my blood, but that is quiet. Nothing happen after that. I would like to … because it's my blood, I would like to contact me and tell me even if they didn't find anything."

Whilst many understood that researcher constraints, such as budget restrictions and the large number of participants enrolled in the study, may not allow for the feedback of negative results, they expressed their appreciation for such feedback.

P16: "Yes, I would appreciate that. I do know however that there is a budget for all of this and that, I mean, there's probably hundreds if not thousands of people enrolled in this thing, so it's not imperative that they have to call if they don't find a result. But if they are able to do so then, yes, I would appreciate getting a phone call."

Religion formed a strong foundation for some when it came to acceptance of the lack of results or answers for their child and served as an answer in itself.

P13: "Even if they didn't find anything, if God is fine, so we've got no problem. Because some things only comes from God. So even you can test and do your things, but if they comes from God there's nothing we can do. We can accept it as we say. And then they gonna help us with, if they find another thing they can call us and help us. We've got no problem about that."

Participants seemed to feel a sense of ownership over their blood or their contribution to the research study, finding meaning even in negative results. In other words, a negative result would be a meaningful return for being part of the NeuroDev study albeit the lack of an answer as to the cause of their child's condition. They viewed such a result as an answer in itself, with the potential to bring closure, peace and acceptance, perhaps through the knowledge of having done all they could.

6.2THEME 7 | PREFERENCES FOR EXPLANATION OF PRELIMINARY RESULTS

In investigating participant preferences for the RoR, it became apparent that tailoring such information to a standard guideline would be complex given the vast diversity in preferences of which results should be returned. Adding to the importance of resolving this dilemma would be considerations of what participants consider appropriate timing of feedback.

6.2.1 HOW MUCH IS TOO MUCH?

Information-load preferences for second sample contact varied from wanting a broad explanation/generic information as to why a second sample was needed to wanting a detailed explanation of preliminary results (See Section 2.5.1 in Chapter 2).

A broad explanation included the reason for wanting a second sample and what it would be for, i.e. was the first sample tainted or did the researchers just need more information. In order to eliminate worry and anxiety, some felt a need to not know what was found at this stage and only required generic information, being told that there is a likely result which needs to be verified.

Others however, wanted all information and detailed explanations at the time the second sample was obtained, including what the preliminary result is that requires verification and to have it explained in a comprehensible manner. Some alluded to expecting transparency with regards to researcher uncertainty over the meaning of results. Reasons for this was to be aware of findings and the process, to see which tests were done and what treatment is available. Others wanted to be a part of the process, to be kept informed as to the progression of the study and to understand the process of testing as well as how researchers came to the results.

P15: "Just basically why and what they found out. At what point are they at and how they actually came to that conclusion, or, yes, it's a test but what made you to actually do that particular test, to go that route."

However, it is of importance to remember that participants would automatically assume a genetic pertinent variant was found if second sample contact is made and that the impact of such knowledge should not be underestimated.

P1: "Obviously I would know then that it's got something to do with our genetics. So I'd probably wouldn't want to know because then I'm going to mull over it for the next couple of months while they do the second sample. So I would just assume that something is up with one of us and that they will have to verify it. So I'd prefer to get like actual information rather than this could be and that could be and we're still busy with that."

It is evident from the above that participants have diverse preferences and that such diversity complicates standardizing the process of the RoR.

6.3THEME 8 | TIMING OF FEEDBACK

When asked whether participants would want to be told of the preliminary result when the second blood sample was taken, preferences seemed to vary once again. As previously described, participants understood that the NeuroDev study would not feedback preliminary results (see NeuroDev policy, section 2.5.1.1).

Almost half preferred to only be told of the result after verification. The most prominent reasons for wanting to be told only after verification included avoiding unnecessary stress and worry over an inconclusive result, the need for certainty and to maintain peace of mind.

P3: "But it has to be something that they're certain about, like, okay we found this, like they know they found and let us know what the … not something that they're not sure about. Like if they don't know yet if it is that, so, they just need to be certain that they found this in the blood…"

Participants were happy to wait longer for results if waiting would assist in maintaining peace of mind.

P1: "Because I want like solid evidence that this is what they've found. I don't like this could be and that could be and then take the second sample and then it's like a totally different ballgame and that's why I'd prefer end results and in fact we're willing to wait longer for that."

However, others expressed their desire for receiving preliminary results, indicating a need for study involvement and to be prepared for the possible outcome.

P15: "I would like to know that yes. Like what is it and why? What did you pick up that you just want to verify. Yes, I know maybe it's not it, but just so I know exactly where they are heading."

P11: "A lot of reasons. Because sometimes I want to know what they found and why they are taking another sample. Maybe they found something good or bad, so I want to know. And then if I do the next step I will be knowing what they found."
INTERVIEWER: "So you'd be prepared for the next step going forward?"
P11: "Yes. And I don't mind if they come again like now, oh, we lost or we need some more, we want some more blood, or we want you again, I don't mind. I want to come."

Further reasons included wanting to know if they needed to be concerned, the desire to assist in the research being conducted but expecting researcher transparency throughout, the right to know and be informed.

P15: "I would like to know that yes. Like what is it and why? What did you pick up that you just want to verify. Yes, I know maybe it's not it, but just so I know exactly where they are heading. It's also the need to understand how they got to the point. So yes, they found something they're not sure and they need to double check it. But it would be nice to know that you guys actually … there's some type of progress. Because it's going somewhere and not just, we're back here again."

There was a perceived potential for preliminary results to cure or treat their child, possibly referring to the timeous receipt of results and early intervention.

P14: "In case there's something maybe we can fix."

As can be seen, the timing of feedback may have a degree of psychosocial impact for some or even influence participant trust in researchers or the research enterprise and should as such, be managed appropriately.

6.3.1 WHO SHOULD EXPLAIN RESULTS - FAMILIARITY

While some participants felt that they had no preference about who returned their results, most preferred the news to come from the original study researchers. Expectations were that it be a professional capable of explaining everything to participants in an understandable manner, someone the participant is familiar with and who listens, and someone who is familiar with their child, knows their child's background and who participants feel comfortable with asking questions. Some mentioned that they would be comfortable hearing results from other doctors or general practitioners known to them if the researchers on the NeuroDev study experienced time or resource constraints. At the time of feedback, participants expected thorough explanations and reassurance from the person who would be giving the feedback.

P12: "Hmm. But it also depends on how it's explained. Like how you explained, you are part of the feedback, etc., and that made me feel at ease when I speak to you. So if everybody has their different roles to play in that way I can understand speaking to somebody completely different. But if it's … I think the way you guys have done it overall, it's fine how it is. You guys explain yourself very well and make it clear. So …"

Many wanted to be told by a doctor who is involved in their child's management and placed their trust in the doctors at RCWMCH.[1]

P13: "Yes. Or even the doctor because this child is going to Dr [name]. Even the doctor explain us it will be fine. I would be happy with that. Because the doctor knows everything of the child."
INTERVIEWER: "And how would you feel if it was some other doctor?"
P13: "No problem…. No, I'm very happy with the doctors at Red Cross. I'm very happy. Because the first time when I came to Red Cross I met different doctors. So all of them I was very happy."

[1] In the NeuroDev study, the PI's are part of the clinical team overseeing the participants' children and the study is based at Red Cross War Memorial Hospital in Cape Town.

Overall the feeling seemed to be that researchers involved in the NeuroDev study would foster feelings of ease, could answer whichever questions arose with the results, have knowledge and insight of the individual's medical background and journey and are well-suited to explain the necessary information to participants. Familiarity was a key factor influencing preferences regarding who should deliver results.

6.3.2 WHERE & HOW – RESPECT & CONFIDENTIALITY

When participants were asked where they would like to receive feedback regarding their results after verification, consensus was that they should be called to come in to RCWMCH and be told in person. Many felt a WhatsApp or text message to set an appointment would be fine, although one participant was concerned that a text message could be missed and preferred a phone call to schedule the appointment. While some felt it would be alright to be given a negative result over the phone, it was thought that a face-to-face encounter, even with negative results, would alleviate anxiety and worry that 'something bad' was found. A few participants stated not wanting to be told telephonically, with one reason being a distrust of technology and fear of breach of security.

P10: "The lines are never secured. You can't say something is secured because even computers, cyber security, that's big."

One participant who had a child with an undiagnosed condition stated that results would not change anything for her child in terms of management or treatment and therefore a letter or email explaining results would suffice.

P15: "It can be a letter, it can be e-mail as well. I'm okay with that. Like I said, it's not like I'm going to need counselling because whatever diagnosis and treatment … there is a treatment for her, as basically if her kidneys are acting up it's antibiotic, it's normal. Her eyes, it would be her eye-drop, because she has an eye infection. So it's not like she actually needs to go … like you know, you get very sick children. For us she's not sick. You see, there's a difference. So it doesn't … It's not going to change her life for the worst…There won't be counselling needed. [Laughing]."

Overall, most mentioned that their/their child's private information would only be shared amongst researchers involved in the NeuroDev study, however, participants seemed to value confidentiality with some seemingly anxious about sharing private information on public databases or telephonically as described by P10 above and P16 below.

P16: "They [NeuroDev researchers] also asked us if we would mind having [child's name] picture online, which we did not agree to and so we didn't have to do that."

CHAPTER CONCLUSION

This chapter aimed to address the research question related to participant preferences for the feedback of positive NDD-related research results. Clearly, it remains essential to foster an open, trusting relationship with research participants and to protect them as far as the application of ethical principles in research allow. The desire for study involvement in the research process and the need for information as research evolves is consistently reiterated by study participants; offering such information may promote or maintain participant emotional wellbeing by creating more certainty for them and foster a sense of not being forgotten. Interestingly, research participants appear to be more resilient than we may expect and seemingly have greater understanding of the resource constraints researchers may experience. Transparency may be key in fostering researcher-participant relationships and even in considering guideline policies.

7 CHAPTER 7 DISCUSSION

CHAPTER INTRODUCTION

In this dissertation I presented the results of an empirical study that aimed to explore what NeuroDev research participants understood regarding the study they consented to participating in, their reasons for wanting to receive positive individual NDD-related genetic results, and recommendations for how best to return such results. In this chapter, I will discuss the research findings and their implications for informing a feedback policy which takes research participants' preferences and understanding into account.

Participant understanding of the cause of their child's condition

In this study, I enrolled the parents of children with neurodevelopmental conditions who had enrolled in a NeuroDev study. For these parents their understanding about the cause of their child's condition extended to their beliefs of maternal health or environmental factors playing a role. Health was also at times related to genetic inheritance insofar as having inherited the genes causing their (participant parents') ill-health from their parents. Some expressed that a multifactorial element to disease causation may exist such as cells being activated by 'triggers', which were possibly of a genetic nature.

One important observation of this study is that there is a tension between how genetics is explained to participants in the consent process – namely, 'as something that runs in the blood' – and their own observations that the condition affecting their children did not affect other family members. This intersects with confusion, expressed by many of the participants, about the concept of a *de novo* mutation which could lie at the basis of their condition. This is consistent with findings by Faure et al. (2019) who described that participants living with Rheumatic Heart Disease in the WC also described genetics as 'something passed down in the blood' but had difficulty explaining how these genes may be passed on through the family lineage.

In this study, I found that once participants started to engage with the idea of a *de novo* mutation, this impacted on feelings of internal guilt, exacerbated by the lack of expression of the condition in their family, leaving these parents feeling solely to blame for the condition in their child either through carrying this 'flaw' themselves, feeling that their personal health was the cause, or that they may have done something or been exposed to something which caused the condition.

Furthermore, whilst only a few alluded to the concept of multifactorial inheritance of NDDs, this was only vaguely understood by some. Whilst there is a dearth of empirical data exploring how genetic attribution impacts on perceptions about illness on the African continent, what little evidence there is has focused either on broad 'genetic knowledge' (Faure et al., 2019) or on monogenic conditions (Marsh, Kamuya & Molyneux, 2011; Meilleur et al., 2011). The observation in this study suggests that there is an equally important question about how people engage with and understand *de novo* mutations playing a role in disease causation.

- *Terminology differences*

Interestingly, distinctive terminology was observed as participants referred to positive results as something which has a good outcome without implications and negative results as a 'bad' outcome. This is contradictory to the medical use of the terms positive results, meaning a pertinent/clinically significant result was identified, and negative results, meaning there were no results. It is imperative that researchers remain aware of this difference in description as this may need to be addressed and clarified either during the consent process or during results delivery.

What motivates people to participate in research

Participants described two reasons for their participation in the NeuroDev study which are in direct tension with each other, namely altruism and the expectation of personal benefit.

Amongst these, the motivation that was most frequently mentioned by research participants was altruism. Participants discussed their challenges and being willing to go through great lengths to save others from the same fate. Research formed part of this altruistic act in that participants seemed to conceptualize it as the one thing they could do to make a difference by contributing to information and awareness about such conditions, thus reducing or prevent NDD-related conditions from occurring. This was also observed in a study by Sanderson et al. (2013) where participants expressed their willingness to participate in genomics research to help society understand and improve their health and to help others in general to 'not go through what they're going through'. Similar findings by Masiye, Mayosi & de Vries (2017) in a study in the WC also suggest that altruism is a strong motivator for participation in genomics research. In my study, they hoped that their participation would result in a better understanding of their child's condition and could lead to an increase in resources.

The second motivation for research participation was for personal and family benefit. Participants hoped that, through their participation in the study, they would gain more information regarding NDDs which would result in the development of better strategies in managing NDDs. They further hoped that the study would generate genetic information that could inform recurrence risk for their family and could offer them the chance to plan for their family's future .

Obviously, there is a careful balance between participants expecting some personal benefit from research participation, and the challenge of therapeutic misconception, where people do not meaningfully distinguish between healthcare and research and think that their research participation is part of their healthcare (Tindana & de Vries, 2016). In this study, participants did seem to know and recognize that the NeuroDev study was a research study, offering no personal/family benefit, and was not part of the routine healthcare of their children, as they reiterated what was relayed to them during the consent process about it being to help future generations and understood the possibility of the study not finding genetic answers, but some still held hope for a cure/treatment, even if this was a distant future outlook made possible through many studies to come, of which NeuroDev may only be the start.

Overall, perceived benefits to participating in the NeuroDev study included self-organization into advocacy as participants used the NeuroDev enrolment experience as an opportunity to link to other parents, forming their own support groups and taking personal control by conducting their own research using the knowledge they had gained in the process.

Return of research results and participant preferences to receiving results

In this study, it was apparent that the majority of participants wanted results of clinical significance related to the health of their child or their personal health and not a 'data dump' which they would struggle to make sense of and which they felt could have the potential to aggravate anxiety.

With regards to the return of pertinent findings (i.e. findings related to their child's condition), participants were keen to receive such results in order to help them understand their child's prognosis and enable the best management strategy. Participants in this study group generally expressed different reasons as to why they would want pertinent results which included the need for help in 'navigating' the condition and bettering their situation; the need for more information as to the cause; help in understanding the condition and the difficulties the child faces; and being able to manage their child best and better the health/outcome for their child.

They also described the expectation that pertinent results could offer closure, bringing personal acceptance, relief and the ability to move on. There was a notable difference regarding the meaning of results between those whose child already had a diagnosis and those who didn't.
For those whose children had a diagnosis of autism, receiving pertinent results could potentially impact on reproductive planning for individuals and hence lead to the prevention of such NDD conditions from occurring.
Participants whose child remained undiagnosed faced the emotional trauma and challenges associated with unanswered questions regarding their child's diagnosis, what they could do to help their child, and what the future could bring. Overall, results related to their child's condition, was hoped to impact positively on attaining answers for those with undiagnosed NDD-related conditions and to reduce uncertainty over the future.

The return on non-pertinent findings (i.e. findings not related to their child's condition) still held value for some participants as they perceived it as a result which may provide answers to issues relating to future health, either of themselves or their children, and could offer them a chance to prepare or plan for their future. Furthermore, for those whose children remained undiagnosed, a non-pertinent result still held the potential for answers as to their child's medical challenges and the prospect that future research may bring answers, regardless of the meaning or cause identified.

Generally, the RoR was seen by many as a point of access, either to information regarding their child's condition or concerning help with the management of their child. This was not particularly related to direct benefits from participating in the NeuroDev study, but rather related to increasing knowledge surrounding these conditions which could lead to better management strategies. This finding is consistent with findings in the literature regarding participant perspectives over the utility of participating and receiving genomic information being a means of gaining information about their health or the cause of their condition and accessing quality care (Hall, Michael et al., 2015; Hylind et al., 2018; Traore et al., 2015). As mentioned previously, in this study, motivations for participating in research and reasons for wanting research results overlap as they are both influenced by participant need for information and understanding the cause.

Given that there is this overlap between what drives participants to participate in research and the reasons and expectations participants assign to receiving various kinds of research results, it may be important to consider the perceived value and meaning participants attribute to results in addition to assessments of clinical utility or medical actionability, as participants may classify these concepts differently to researchers (Holm et al., 2015). For instance, participants in this study clearly described that negative results would also be a valuable return for their participation in the NeuroDev study and would confirm that they themselves and researchers had done all they could to discover the cause. Such results have the potential to bring closure, peace and acceptance. Taking participant preferences concerning results disclosure into account has the potential to lead to greater participant satisfaction as well as increase public uptake of genomic research participation (Holm et al., 2015), improve participant heterogeneity and improve adherence to the research program (Scherr et al., 2018).

- *What they want to know and when – Results feedback process*

Participants gave diverse preferences concerning the results feedback process, however, overall perspectives were the desire for certainty over the cause and course of their child's condition, familiarity with the person(s) delivering the results, researcher transparency, and the call for respect and confidentiality from those feeding back the results and concerning the sharing of results. Furthermore, amidst the preferences, participants held conflicting views regarding the best timing for delivering results but voiced the need for study involvement throughout the research process with some even expressing a desire to continue on a future research journey.
One important observation relates to the need to take a second sample to confirm the original test result – which is a question raised by the NeuroDev study team and described in the literature review chapter. Namely, the issue is that pertinent results cannot be fed back to research participants unless it has been verified by a CLIA-certified laboratory but such further testing may require an additional blood sample to be taken. Participants in our study described that they would automatically assume a pertinent variant is found at the time of contact for a second sample since this was explained during the consent process; and it has the potential to create anxiety for some individuals. Whilst some welcomed the opportunity to prepare for the possibility of a positive result and perceived a potential for preliminary results to offer a chance for early intervention, others preferred to receive no explanations; researchers face the challenge of dealing with managing participant anxieties during this process. Another consideration is that participant expectation of

receiving results from the study was influenced by the time since last contact with researchers, where a greater time lapse since contact seemed to lower any expectation of receiving results.

- *Stigma*

A topic raised above is the common challenge in genomics research that relates to the potential for it to cause or aggravate stigma. As described by de Vries et al. (2013) and Tekola et al. (2009a), genomic research has the potential to reinforce pre-existing forms of stigma which may be attached to certain conditions. Whilst stigma is a complex concept that is the result of political and social processes and not just of attribution (Link & Phelan, 2001), this study did reveal that this could be a factor to consider in the conduct of genomics research on NDDs. For instance, some participants in this study mentioned the possibility of being personally responsible, experiencing a lack of understanding from family and friends, denial over their child's condition either by close relationships or in the form of self-denial, and feelings of being judged. Whilst none of these constitute stigma, they involve feelings of guilt, denial, lack of understanding, or blame. In a study conducted by Oti-Boadi, Dankyi & Kwakye-Nuako (2020), it was clear that the mothers of children with ASDs experienced negative feelings towards themselves and God and were treated differently by family and friends. Whilst I did not specifically probe experiences of stigma in the interviews, participants did relate feelings of guilt or blame which, according to Selman et al. (2018), may possibly be related to felt stigma. Namely, some participants in my study described that finding answers as to the cause of their child's condition would inform them that they are not to blame and could assist in creating awareness about the condition. This is consistent with findings from Selman et al. (2018) that parents resist and counter the stigma they experience by learning and educating themselves about their child's autism and according to Broady, Stoyles & Morse (2017), such knowledge could also be used to educate the public about the cause of such conditions, leading to diminished stigma. Other participants in this study describe initially blaming themselves for their child's condition but through knowledge inferred during the NeuroDev study have come to realize that it's not through their actions nor that they are personally 'flawed', but rather expressed it positively as the will of God.

The emphasis of an (inherited) genetic link may create anxiety for biological relatives in that they may personally feel responsible for child's condition, potentially exacerbating feelings of being 'flawed' and at fault and can in such a manner be related to stigma, termed associative stigma (Faure et al., 2019). Often such feelings are heightened by the individual's community beliefs or values regarding the cause of such conditions (Faure et al., 2019).

Interestingly, Faure et al. describes how genetic information also has the potential to reduce stigma, since knowing the cause can decrease (self-)blame in an individual by allowing that individual to feel less responsible for the condition given that it was not under their control (Faure et al., 2019). In other words, genetic information can reduce blame but increase the sense of loss of control and feelings of hopelessness in these individuals, all of which relates to internalized stigma.

In a nutshell, whilst not the same as stigma, feelings of guilt and (self-)blame relate to stigma in that the caregivers of children with NDDs, particularly ASDs, often experience stigma (felt stigma) from family, friends, the child's school or the public in numerous ways namely, through lack of knowledge, judgement, lack of support and rejection (Broady, Stoyles & Morse, 2017). These parents internalize these feelings, blaming themselves for their child's condition, or feel responsible (guilt) and ultimately experience shame (Oti-Boadi, Dankyi & Kwakye-Nuako, 2020). From this study, there was some expectation that the RoR would impact on resolving feelings of guilt and sometimes (self-)blame as many participants alluded to seeking confirmation or validation that they were not responsible.

IN SUMMARY

This dissertation aimed to explore what research participants partaking in the NeuroDev study understood about the study, what their reasons were for partaking in this research and for wanting pertinent results returned, and recommendations for informing the feedback of results.

The empirical work conducted for this thesis suggests that it is essential to consider the following pertaining to participant preferences, 1) the personal utility of results and that there may still be value in knowing a negative result; 2) preferences remain diverse and tailoring information for a set guidance policy will be complex; 3) participant need for certainty of results may contrast the need for study involvement and participant thoughts on appropriate timing of feedback may vary; 4) familiarity is important for participants when considering who should communicate results, where it should be done, and who should be involved in the process; 5) participants have a need to maintain their dignity and should be shown respect when determining means of contact and methods employed to return results. In-person contact and the time afforded them may still be viewed as an acknowledgement of their circumstances and can reduce pre-existing anxiety.

Through embarking on genomic research results delivery, many challenges continue to surface when considering research participants' perspectives and preferences. Such challenges need to be addressed in order to facilitate a guidance framework for delivering genomic research results. Perhaps a GC has a valuable role to play in these situations and it has been well documented that it would be appropriate for a GC to be part of such a process (Middleton et al., 2017; Wonkam & de Vries, 2020). GCs may add value and are trained to address issues of uncertainty as well as psychosocial issues of guilt and blame, thereby enabling individual/parent adaptation to circumstances compounded by a medical condition and laying out a management plan going forward (Joseph, 2018). They can tailor the delivery of information to participants and have the appropriate set of communication skills and the ability to explain genetic concepts in a comprehensible manner, which may alleviate confusion regarding such concepts and their inheritance (Accreditation Council for Genetic Counselors [ACGC], 2013; Berrios et al., 2018). GCs can link participants to external resources such as appropriate healthcare professionals or support teams and to the latest developments in research information as well as possible projects or therapies (Joseph, 2018). Overall, GC's can act to bridge the gap between researcher and participant by being available to address concerns and through following up with participants regarding the progress and stance of the research (Benjamin et al., 2020), and can in such a manner meet the desires of participants (ACGC, 2013).

7.1RECOMMENDATIONS

Given the diversity in participant preferences, understanding of genomic results and individual circumstances, it remains important for researchers to understand the psychosocial impact of genetic testing and that findings cannot be generalized from one context to another. Adding to this, it is vital that the consent process incorporates an understandable and culturally appropriate 'framework' (Munung et al., 2016). As such, I propose the following recommendations.

1. VUS and IF appear to be important additional aspects to consider in the feedback of IF (FIF) debate and bodies considering FIF guidelines should consider ways of addressing these issues in a manner that support researchers that are planning to do FIF to navigate this ethically and medically complex area. As such, a tiered-consent model may need to be considered with options for which kinds of findings participants would like to receive; and
2. This tiered-consent could be supported by a follow-up information session describing what these results could mean and giving examples of related conditions, how people could use these results and whether they have the potential for clinical therapeutic benefits locally. Such an information session may not need to be a) done at the same time as the primary consent, and b) does not need to be individual but could be group-based. Addressing the genomics research challenges that arise in the SA context with regards to diagnostic and therapeutic benefits versus the potential harms and providing adequate information to participants remains an essential component in supporting the right of the participant to accept or decline participation in genomics research studies (Nembaware et al., 2019).

Furthermore, given the delay in return of genomic research results due to samples being processed in large batches, it may be useful to discuss participant preferences regarding the timing of receiving information about results. In cases where the participant cannot be accommodated, it may be useful to have a discussion where reasons for this could be explained. The following may be helpful suggestions for a practical approach, namely WhatsApp information

to give participants an idea of when the batch of their sample is likely to be processed, reassuring them that negative findings will be fed back via their main care provider or information sessions with the doctors that care for these families so they are also able to give families updates at their clinic visits. In this way, the researcher fulfills their obligation of communicating the planned process for disclosing results and is better able to manage any anxiety or 'unhappiness' and in so doing, maintain the trust of the participant and promote their psychosocial health and well-being.

Whilst serious effort has been put into ensuring that participants understand what they are consenting to, an interactive process may be necessary and this information could certainly assist treating clinicians in answering the questions as well. This will allow the research to play an appropriately supportive integrated role with clinical interface for these families. Clarifying confusion over participant understanding of heredity or genetic concepts and addressing terminology discrepancies between the participants and medical community can eliminate the possibility of confusion. Remaining aware of such discrepancies, some of which may be colloquially-based, and explaining any differences can aid in unifying language and communication, helpful in the goal to attaining standardized guidelines in future. Whilst this may be particularly helpful to address in the beginning stages of consent, it is suffice to say that such differences and confusions may likely need to be corrected throughout the research process as they arise.

Finally, given that participants find personal meaning in negative results and generally seem to want such 'answers', the absence of a positive pertinent result may also need to be communicated during the initial stages of consent. In the event that a participant desires such results, any limitations in being able to deliver it should be openly communicated. In the even that no result has been found yet, perhaps a newsletter or an informative event could facilitate in keeping participants abreast of research progress in the event that they haven't been individually contacted. This could provide participant satisfaction of being involved in the study process/progress and illustrate researcher transparency.

A tiered-consent model focusing on participant perspectives regarding FIF and clearly establishing understanding of the implications of such findings could facilitate the development of a context-appropriate results delivery system, thereby protecting participants from potential exploitation and supporting their rights and wellbeing, thus leading to greater satisfaction for

participants and a positive relationship between the research industry and participants (Harris, Erin et al., 2012; IRCM Working Group, September 2015).

Beyond this, the scope of GC roles could also include adequate, African-centric explanations of genetic concepts and inheritance (including multifactorial heredity), aid in addressing and clarifying issues of terminology, and could assist in easing the burden of researchers who may face time and resource constraints when attempting to 'revisit' participants. Addressing all the above issues of confusion over heredity and the nature/implications of results, issues over appropriate timing of delivery and personal preferences over extent of information wanted, preferences to receiving negative results or other kinds of results, as well as the continued contact and in-person discussions has the potential to alleviate participant anxiety and foster stable researcher-participant relationships.

7.2STUDY LIMITATIONS

Influence from the researcher is inevitable due to the researcher and participant interacting in a social process (Korstjens & Moser, 2017), so it was essential for the researcher to be aware of personal bias, idiosyncrasies, values and beliefs whilst conducting the research so as not to influence the results in any manner. The researcher took field and observational notes, practiced reflective techniques and discussed any arising personal opinions/issues with a supervisor in order to maintain objectivity. As a GC student, it was also important for the researcher to be aware of the influence that her role as a student-clinician had on the research process. This was managed through creating rapport with research participants using the researcher's own role as a mother, through continuous reflection and through continuous learning processes about cultural awareness, for example reading about the topic.

Given that the researcher is at a novice level within the qualitative research field, initial interviews may not have been as well performed compared to later interviews in that certain cues or important concepts may have been missed or not explored initially, which became apparent later.

Data may be slightly skewed by the limitations of recruiting subjects from a purposive sample obtained from the NeuroDev study and by participants who agreed to come versus those who could not be reached or who declined. This work is the first study that explored participant expectations for the return of pertinent individual genetic research results. Whilst it has shed some insights into what NeuroDev participants would like to know, the sample was small and narrowly tied for a particular condition.

Although it was believed that data saturation was reached for this study given that similar themes and concepts surfaced across interview data, the researcher acknowledges that there is always a possibility that data saturation was not reached. Furthermore, although sample size was sufficient for this method of research, a number of participants could not be reached for interviewing, rendering the sample size smaller than the anticipated number of twenty participants.

Given that sociodemographic data was not obtained by the researcher, certain aspects cannot be represented. These may include social circumstance, financial stance/household income, parental ages and demographic location. While these are important influences on the way individuals cope, these data were not considered essential to this study and so from a perspective of “data minimization” the researcher decided not to collect it. The only information included was the gender of the parents being interviewed, the condition of the affected child and their ethnic background.

Couple interviews were conducted in some instances which may have influenced the researcher-participant communication process of personal thoughts or beliefs of some individuals. This did not seem to impact substantially on the overall outcome however.

A final limitation to some of the interviews was that some research participants unexpectedly brought their children along to the interview. This made the interviewing process difficult as it was constantly interrupted and at times not focused. The recordings in these sessions were difficult to transcribe due to the background noise and some sections were too unclear to analyze.

REFERENCES

Accreditation Council for Genetic Counseling, 2013. Practice-based competencies for genetic counselors. *Accreditation council for genetic counseling.* Available: http://gceducation.org/Documents/ACGC%20Practice%20Based%20Competencies_13-Final-Web.pdf [2020, February 6].

ACMG. 2013a. *Recommendations for reporting of incidental findings in clinical exome and genome sequencing.*

ACMG. 2013b. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet. Med.* 15:565. Available: http://dx.doi.org/10.1038/gim.2013.73.

Allen, N.L., Karlson, E.W., Malspeis, S., Lu, B., Seidman, C.E. & Lehmann, L.S. Eds. 2014. Biobank participants' preferences for disclosure of genetic research results: perspectives from the OurGenes, OurHealth, OurCommunity project. Elsevier. 738-746.

American Psychiatric Association. 2013. *Diagnostic and statistical manual of mental disorders (DSM-5®).* American Psychiatric Pub.

Atieno, O.P. 2009. An analysis of the strengths and limitation of qualitative and quantitative research paradigms. *Problems of Education in the 21st Century.* 13:13-18. Available: http://ezproxy.deakin.edu.au/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=eue&AN=43917788&site=ehost-live&scope=site.

Avard, D., Sénécal, K., Madadi, P. & Sinnett, D. 2011. Pediatric research and the return of individual research results. *The Journal of Law, Medicine & Ethics.* 39(4):593-604.

Avard, D., Black, L., Samuël, J., Griener, G. & Knoppers, B.M. 2012. Best Practices for Health Research Involving Children and Adolescents, Centre of Genomics and Policy (CGP), Maternal Infant Child and Youth Research Network (MICYRN).

Bacon, P.L., Harris, E.D., Ziniel, S.I., Savage, S.K., Weitzman, E.R., Green, R.C., Huntington, N.L. & Holm, I.A. 2015. The development of a preference-setting model for the return of

individual genomic research results. *Journal of empirical research on human research ethics : JERHRE.* 10(2):107-120. DOI:10.1177/1556264615572092.

Benjamin, C., Phillips, A., Finch, J., Dubois, L., McGrath, L., Kulke, C., Brooks, C., Harris, P. et al. 2020. Exploring professional issues: the psychosocial component of genetic counseling in genomic healthcare. *Personalized Medicine.* 17(1):55-65. DOI:10.2217/pme-2019-0048.

Berrios, C., James, C.A., Raraigh, K., Bollinger, J., Murray, B., Tichnell, C., Applegate, C.D. & Bergner, A.L. 2018. Enrolling Genomics Research Participants through a Clinical Setting: the Impact of Existing Clinical Relationships on Informed Consent and Expectations for Return of Research Results. *J Genet Couns.* 27(1):263-273. DOI:10.1007/s10897-017-0143-2.

Biesecker, L.G., Mullikin, J.C., Facio, F.M., Turner, C., Cherukuri, P.F., Blakesley, R.W., Bouffard, G.G., Chines, P.S. et al. 2009. The ClinSeq Project: piloting large-scale genome sequencing for research in genomic medicine. *Genome Research.* 19(9):1665-1674.

Bitta, M., Kariuki, S.M., Abubakar, A. & Newton, C.R.J.C. 2017. Burden of neurodevelopmental disorders in low and middle-income countries: A systematic review and meta-analysis. *Wellcome Open Research.* 2:121-121. DOI:10.12688/wellcomeopenres.13540.3.

Bookman, E., Langehorne, A., Eckfeldt, J. Glass, K., Jarvik, G., Klag, M., Koski, G., Motulsky, A., Wilfond, B., Manolio, T., Fabsitz, R., Luepker, R.V.. Reporting Genetic Results in Research Studies: Summary and Recommendations of an NHLBI Working Group. *Am J Med Genet A.* 2006;140(10):1033-1040.

Bredenoord, A.L., Kroes, H.Y., Cuppen, E., Parker, M. & van Delden, J.J. 2011. Disclosure of individual genetic data to research participants: the debate reconsidered. *Trends Genet.* 27(2):41-47. DOI:10.1016/j.tig.2010.11.004.

Broady, T.R., Stoyles, G.J. & Morse, C. 2017. Understanding carers' lived experience of stigma: the voice of families with a child on the autism spectrum. *Health & Social Care in the Community.* 25(1):224-233. DOI:10.1111/hsc.12297.

Campbell, M.C. & Tishkoff, S.A. 2008. African genetic diversity: implications for human demographic history, modern human origins, and complex disease mapping. *Annual Review of Genomics and Human Genetics.* 9:403-433. DOI:10.1146/annurev.genom.9.081307.164258.

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, December 2018.

Christianson, A.L., Zwane, M.E., Manga, P., Rosen, E., Venter, A., Downs, D. & Kromberg, J.G. 2002. Children with intellectual disability in rural South Africa: prevalence and associated disability. *J Intellect Disabil Res.* 46(Pt 2):179-186. DOI:10.1046/j.1365-2788.2002.00390.x.

Christensen, K.D., Savage, S.K., Huntington, N.L., Weltzman, E.R., Ziniel, S.I., Bacon, P.L., Cacioppo, C.N., Green, R.C., Holm, I.A. 2017. Preferences for the return of individual results from research on pediatric biobank samples. *Journal of Empirical Research on Human Research Ethics.* 12(2):97-106. DOI:10.1177/1556264617697839.

Council of International Organizations of Medical Sciences (CIOMS). *International Ethical Guidelines For Health-Related Research Involving Humans*. Geneva: CIOMS; 2016. Available: http://cioms.ch/ethical-guidelines-2016/WEB-CIOMS-EthicalGuidelines.pdf [2020, February 6].

de Vries, J. & Munung, N.S. 2019. *Ethical considerations in genomic research in South Africa.* Available: http://www.samj.org.za/index.php/samj/article/view/12629.

de Vries, P.J., Venter, A., Jacklin, L. & Oliver, C. 2013. Behavioural phenotypes and neurodevelopmental disorders in Africa. *Journal of Intellectual Disability Research.* 57(9):793-795. DOI:10.1111/jir.12070.

Eckstein, L., Garrett, J.R. & Berkman, B.E. 2014. A Framework for Analyzing the Ethics of Disclosing Genetic Research Findings. *The Journal of Law, Medicine & Ethics.* 42(2):190-207. DOI:10.1111/jlme.12135.

Ellen Selman, L., Fox, F., Aabe, N., Turner, K., Rai, D. & Redwood, S. 2018. 'You are labelled by your children's disability' – A community-based, participatory study of stigma among Somali

parents of children with autism living in the United Kingdom. *Ethnicity & Health.* 23(7):781-796. DOI:10.1080/13557858.2017.1294663.

Etikan, I., Musa, S.A., Alkassim, R.S. 2016. Comparison of Convenience Sampling and Purposive Sampling. *American Journal of Theoretical and Applied Statistics.* 5. 1. 10.11648/j.ajtas.20160501.11.

Facio, F.M., Brooks, S., Loewenstein, J., Green, S., Biesecker, L.G. & Biesecker, B.B. 2011. Motivators for participation in a whole-genome sequencing study: implications for translational genomics research. *European Journal of Human Genetics : EJHG.* 19(12):1213-1217. DOI:10.1038/ejhg.2011.123.

Faure, M.C., Matshabane, O.P., Marshall, P., Appelbaum, P.S., Stein, D.J., Engel, M.E. & de Vries, J. 2019. Does genetics matter for disease-related stigma? The impact of genetic attribution on stigma associated with rheumatic heart disease in the Western Cape, South Africa. *Soc Sci Med.* 243:112619. DOI:10.1016/j.socscimed.2019.112619.

Gale, N.K., Heath, G., Cameron, E., Rashid, S. & Redwood, S. 2013. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology.* 13(1):117. DOI:10.1186/1471-2288-13-117.

Gollust, S.E., Gordon, E.S., Zayac, C., Griffin, G., Christman, M.F., Pyeritz, R.E., Wawak, L. & Bernhardt, B.A. 2012. Motivations and perceptions of early adopters of personalized genomics: perspectives from research participants. *Public Health Genomics.* 15(1):22-30. DOI:10.1159/000327296.

Gornick, M.C., Scherer, A.M., Sutton, E.J., Ryan, K.A., Exe, N.L., Li, M., Uhlmann, W.R., Kim, S.Y.H. et al. 2017. Effect of Public Deliberation on Attitudes toward Return of Secondary Results in Genomic Sequencing. *Journal of Genetic Counseling.* 26(1):122-132. DOI:10.1007/s10897-016-9987-0.

Green, R.C., Berg, J.S., Grody, W.W., Kalia, S.S., Korf, B.R., Martin, C.L., McGuire, A.L., Nussbaum, R.L. et al. 2013. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genetics in Medicine : Official Journal of the American College of Medical Genetics.* 15(7):565-574. DOI:10.1038/gim.2013.73.

Hackett, A. & Strickland, K. 2019. Using the framework approach to analyse qualitative data: a worked example. *Nurse Res.* 26(2):8-13. DOI:10.7748/nr.2018.e1580.

Hall, A., Hallowell, N. & Zimmern, R. 2013. Managing incidental and pertinent findings from WGS in the 100,000 Genomes Project. *Cambridge: PHG Foundation.*

Hall, M.J., Forman, A.D., Montgomery, S.V., Rainey, K.L. & Daly, M.B. 2015. Understanding patient and provider perceptions and expectations of genomic medicine. *Journal of Surgical Oncology.* 111(1):9-17. DOI:10.1002/jso.23712.

Halverson, C.M., Clift, K.E. & McCormick, J.B. 2016. Was it worth it? Patients' perspectives on the perceived value of genomic-based individualized medicine. *J Community Genet.* 7(2):145-152. DOI:10.1007/s12687-016-0260-x.

Harris, E.D., Ziniel, S.I., Amatruda, J.G., Clinton, C.M., Savage, S.K., Taylor, P.L., Huntington, N.L., Green, R.C. et al. 2012. The beliefs, motivations, and expectations of parents who have enrolled their children in a genetic biorepository. *Genetics in Medicine : Official Journal of the American College of Medical Genetics.* 14(3):330-337. DOI:10.1038/gim.2011.25.

Helgesson, G. 2014. Autonomy, the Right Not to Know, and the Right to Know Personal Research Results: What Rights Are There, and Who Should Decide about Exceptions? *Journal of Law, Medicine and Ethics.* 42(1):28-37.

Holm, I.A. 2017. Pediatric Issues in Return of Results and Incidental Findings: Weighing Autonomy and Best Interests. *Genetic Testing and Molecular Biomarkers.* 21(3):155-158. DOI:10.1089/gtmb.2016.0414.

Holm, I.A., Savage, S.K., Green, R.C., Juengst, E., McGuire, A., Kornetsky, S., Brewster, S.J., Joffe, S. et al. 2014. Guidelines for return of research results from pediatric genomic studies: deliberations of the Boston Children's Hospital Gene Partnership Informed Cohort Oversight Board. *Genetics in Medicine.* 16(7):547-552. DOI:10.1038/gim.2013.190.

Holm, I.A., Iles, B.R., Ziniel, S.I., Bacon, P.L., Savage, S.K., Christensen, K.D., Weitzman, E.R., Green, R.C. et al. 2015. Participant Satisfaction With a Preference-Setting Tool for the Return of

Individual Research Results in Pediatric Genomic Research. *Journal of Empirical Research on Human Research Ethics : JERHRE.* 10(4):414-426. DOI:10.1177/1556264615599620.

Hylind, R., Smith, M., Rasmussen-Torvik, L. & Aufox, S. 2018. Great expectations: patient perspectives and anticipated utility of non-diagnostic genomic-sequencing results. *Journal of Community Genetics.* 9(1):19-26. DOI:10.1007/s12687-017-0314-8.

IRCM Working Group, ASD and return of results. September 2015. *Returning genetic research results in neurodevelopmental disorders: Report and review.* Available: http://med-fom-neuroethics.sites.olt.ubc.ca/files/2017/02/IRCM-Returning-Genetic-Research-Results-in-NDD.pdf.

Joseph, F.M. 2018. A Key Role for the Genetic Counsellor in the Genomics Era. *F1000Research.* 7:420-420. DOI:10.12688/f1000research.14222.2.

Kauffman, T.L., Irving, S.A., Leo, M.C., Gilmore, M.J., Himes, P., McMullen, C.K., Morris, E., Schneider, J. et al. 2017. The NextGen Study: patient motivation for participation in genome sequencing for carrier status. *Molecular Genetics & Genomic Medicine.* 5(5):508-515. DOI:10.1002/mgg3.306.

Kaufman, D.J., Murphy-Bollinger, J., Scott, J. & Hudson, K.L. 2009. Public opinion about the importance of privacy in biobank research. *American Journal of Human Genetics.* 85(5):643-654. DOI:10.1016/j.ajhg.2009.10.002.

Knoppers, B.M. 2014. INTRODUCTION: From the Right to Know to the Right Not to Know. *The Journal of Law, Medicine & Ethics.* 42(1):6-10. DOI:10.1111/jlme.12113.

Koch, T. 1998. Story telling: is it really research? *Journal of Advanced Nursing.* 28(6):1182-1190. DOI:10.1046/j.1365-2648.1998.00853.x.

Kohane, I.S. & Taylor, P.L. 2010. Multidimensional results reporting to participants in genomic studies: getting it right. *Science Translational Medicine.* 2(37):37cm19-37cm19.

Kollek, R. & Petersen, I. 2011. Disclosure of individual research results in clinico-genomic trials: challenges, classification and criteria for decision-making. *Journal of Medical Ethics.* 37(5):271-275. DOI:10.1136/jme.2009.034041.

Korstjens, I. & Moser, A. 2017. Series: Practical guidance to qualitative research. Part 2: Context, research questions and designs. *European Journal of General Practice.* 23(1):274-279. DOI:10.1080/13814788.2017.1375090.

Korstjens, I. & Moser, A. 2018. Series: Practical guidance to qualitative research. Part 4: Trustworthiness and publishing. *European Journal of General Practice.* 24(1):120-124. DOI:10.1080/13814788.2017.1375092.

Kosmicki, J.A., Samocha, K.E., Howrigan, D.P., Sanders, S.J., Slowikowski, K., Lek, M., Karczewski, K.J., Cutler, D.J. et al. 2017. Refining the role of *de novo* protein truncating variants in neurodevelopmental disorders using population reference samples. *bioRxiv.* 10.1101/052886:052886. DOI:10.1101/052886.

Kumar, R. 2014. *Research Methodology : a Step-by-Step Guide for Beginners.* London: SAGE Publications.

Lévesque, E., Joly, Y. & Simard, J. 2011. Return of Research Results: General Principles and International Perspectives. *The Journal of Law, Medicine & Ethics.* 39(4):583-592. DOI:10.1111/j.1748-720X.2011.00625.x.

Link, B.G. & Phelan, J.C. 2001. Conceptualizing Stigma. *Annual Review of Sociology.* 27(1):363-385. DOI:10.1146/annurev.soc.27.1.363.

Mark, C., Jim, D., Martin, D., Leila, E., Tom, F., Sue, H., Tim, H., Luke, J. et al. 2017. *The 100,000 Genomes Project Protocol.* DOI:10.6084/m9.figshare.4530893.v4.

Marsh, V., Kamuya, D. & Molyneux, S. 2011. 'All her children are born that way': gendered experiences of stigma in families affected by sickle cell disorder in rural Kenya. *Ethnicity and Health.* 16(4-5):343-359.

Masiye, F., Mayosi, B. & de Vries, J. 2017. “I passed the test!” Evidence of diagnostic misconception in the recruitment of population controls for an H3Africa genomic study in Cape Town, South Africa. *BMC Medical Ethics.* 18(1):12. DOI:10.1186/s12910-017-0175-z.

Matsui, K., Lie, R.K., Kita, Y. & Ueshima, H. 2008. Ethics of future disclosure of individual risk information in a genetic cohort study: a survey of donor preferences. *Journal of Epidemiology.* 18(5):217-224. DOI:10.2188/jea.je2007425.

McGuire, A.L. & Beskow, L.M. 2010. Informed consent in genomics and genetic research. *Annual Review of Genomics and Human Genetics.* 11:361-381. DOI:10.1146/annurev-genom-082509-141711.

Meilleur, K.G., Coulibaly, S., Traore, M., Landoure, G., La Pean, A., Sangare, M., Mochel, F., Traore, S. et al. 2011. Genetic testing and counseling for hereditary neurological diseases in Mali. *J Community Genet.* 2(1):33-42. DOI:10.1007/s12687-011-0038-0.

Middleton, A., Marks, P., Bruce, A., Protheroe-Davies, L.K., King, C., Claber, O., Houghton, C., Giffney, C. et al. 2017. The role of genetic counsellors in genomic healthcare in the United Kingdom: a statement by the Association of Genetic Nurses and Counsellors. *European Journal of Human Genetics.* 25(6):659-661. DOI:10.1038/ejhg.2017.28.

Miller, D.T., Adam, M.P., Aradhya, S., Biesecker, L.G., Brothman, A.R., Carter, N.P., Church, D.M., Crolla, J.A. et al. 2010. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *The American Journal of Human Genetics.* 86(5):749-764.

Miller, F.A., Christensen, R., Giacomini, M. & Robert, J.S. 2008. Duty to disclose what? Querying the putative obligation to return research results to participants. *Journal of Medical Ethics.* 34(3):210-213.

Miller, F., Hayeems, R. & Bytautas, J. 2010. What is a meaningful result? Disclosing the results of genomic research in autism to research participants. *Eur J Hum Genet.* 18, 867–871. https://doi.org/10.1038/ejhg.2010.34.

Munung, N.S., Marshall, P., Campbell, M., Littler, K., Masiye, F., Ouwe-Missi-Oukem-Boyer, O., Seeley, J., Stein, D.J. et al. 2016. Obtaining informed consent for genomics research in Africa: analysis of H3Africa consent documents. *J Med Ethics.* 42(2):132-137. DOI:10.1136/medethics-2015-102796.

Murphy, J., Scott, J., Kaufman, D., Geller, G., LeRoy, L. & Hudson, K. 2008. Public expectations for return of results from large-cohort genetic research. *The American Journal of Bioethics : AJOB.* 8(11):36-43. DOI:10.1080/15265160802513093.

Namazzi, G., Hildenwall, H., Mubiri, P., Hanson, C., Nalwadda, C., Nampijja, M., Kakooza-Mwesige, A., Waiswa, P. et al. 2019. Prevalence and associated factors of neurodevelopmental disability among infants in eastern Uganda: a population based study. *BMC Pediatrics.* 19(1):379. DOI:10.1186/s12887-019-1769-z.

Nembaware, V., Johnston, K., Diallo, A.A., Kotze, M.J., Matimba, A., Moodley, K., Tangwa, G.B., Torrorey-Sawe, R. et al. 2019. A framework for tiered informed consent for health genomic research in Africa. *Nat Genet.* 51(11):1566-1571. DOI:10.1038/s41588-019-0520-x.

NVivo qualitative data analysis software; QSR International Pty Ltd. Version 12, 2018

Olusanya, B.O., Davis, A.C., Wertlieb, D., Boo, N.-Y., Nair, M., Halpern, R., Kuper, H., Breinbauer, C. et al. 2018. Developmental disabilities among children younger than 5 years in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Global Health.* 6(10):e1100-e1121.

Ortiz-Osorno, A.B., Ehler, L.A. & Brooks, J. 2015. Considering Actionability at the Participant's Research Setting Level for Anticipatable Incidental Findings from Clinical Research. *The Journal of Law, Medicine & Ethics : a Journal of the American Society of Law, Medicine & Ethics.* 43(3):619-632. DOI:10.1111/jlme.12304.

Oti-Boadi, M., Dankyi, E. & Kwakye-Nuako, C.O. 2020. Stigma and Forgiveness in Ghanaian Mothers of Children with Autism Spectrum Disorders (ASD). *Journal of Autism and Developmental Disorders.* 10.1007/s10803-020-04366-x. DOI:10.1007/s10803-020-04366-x.

Presidential Commission for the Study of Bioethical Issues; 2013. *Anticipate And Communicate: Ethical Management Of Incidental And Secondary Findings In Clinical, Research, And Direct-To-Consumer Contexts.* Washington (DC). Available: http://bioethics.gov/node/3183 (accessed 2020 Feb. 8).

Pullman, D. & Hodgkinson, K. 2006. Genetic knowledge and moral responsibility: ambiguity at the interface of genetic research and clinical practice. *Clin Genet.* 69(3):199-203. DOI:10.1111/j.1399-0004.2006.00581.x.

Rawal, L.B., Saurabh; Mishra, S; Malhotra, R; Sumit. 2019. Chromosomal Microarray Analysis Uncovers Pathogenic Copy Number Variations in Unexplained Neurodevelopmental Disorders and Congenital Anomalies. *J Biomedical Sci Vol.8 No.1:3.* 10.4172/2254-609X.100099. DOI:10.4172/2254-609X.100099.

Rotimi, C., Abayomi, A., Abimiku, A.l., Adabayeri, V.M., Adebamowo, C., Adebiyi, E., Ademola, A.D., Adeyemo, A. et al. 2014. Research capacity. Enabling the genomic revolution in Africa. *Science (New York, NY).* 344(6190):1346-1348.

Rutakumwa, R., de Vries, J., Parker, M., Tindana, P., Mweemba, O. & Seeley, J. 2019. What constitutes good ethical practice in genomic research in Africa? Perspectives of participants in a genomic research study in Uganda. *Global Bioethics.* 10.1080/11287462.2019.1592867:1-15. DOI:10.1080/11287462.2019.1592867.

Sanderson, S.C., Diefenbach, M.A., Zinberg, R., Horowitz, C.R., Smirnoff, M., Zweig, M., Streicher, S., Jabs, E.W. et al. 2013. Willingness to participate in genomics research and desire for personal results among underrepresented minority patients: a structured interview study. *Journal of Community Genetics.* 4(4):469-482. DOI:10.1007/s12687-013-0154-0.

Sanderson, S.C., Linderman, M.D., Suckiel, S.A., Diaz, G.A., Zinberg, R.E., Ferryman, K., Wasserstein, M., Kasarskis, A. et al. 2016. Motivations, concerns and preferences of personal genome sequencing research participants: Baseline findings from the HealthSeq project. *European Journal of Human Genetics : EJHG.* 24(1):153-153. DOI:10.1038/ejhg.2015.179.

Sapp, J.C., Dong, D., Stark, C., Ivey, L.E., Hooker, G., Biesecker, L.G. & Biesecker, B.B. 2014. Parental attitudes, values, and beliefs toward the return of results from exome sequencing in children. *Clinical Genetics.* 85(2):120-126. DOI:10.1111/cge.12254.

Savin-Baden, M. & Major, C.H. 2013. Qualitative research : the essential guide to theory and practice. Available: https://www.taylorfrancis.com/books/e/9780203084403.

Schaefer, G.B. & Lutz, R.E. 2006. Diagnostic yield in the clinical genetic evaluation of autism spectrum disorders. *Genetics in Medicine.* 8(9):549.

Scherr, C.L., Aufox, S., Ross, A.A., Ramesh, S., Wicklund, C.A. & Smith, M. 2018. What People Want to Know About Their Genes: A Critical Review of the Literature on Large-Scale Genome Sequencing Studies. *Healthcare (Basel).* 6(3). DOI:10.3390/healthcare6030096.

Shalowitz, D.I. & Miller, F.G. 2008. Communicating the results of clinical research to participants: attitudes, practices, and future directions. *PLoS Medicine.* 5(5):e91-e91. DOI:10.1371/journal.pmed.0050091.

Shalowitz, D.I. & Miller, F.G. 2008. The search for clarity in communicating research results to study participants. *Journal of Medical Ethics.* 34(9):e17-e17.

Tabor HK, Brazg T, Crouch J, et al. 2011. Parent perspectives on pediatric genetic research and implications for genotype-driven research recruitment. *J Empir Res Hum Res Ethics*. 6(4):41-52. doi:10.1525/jer.2011.6.4.41

Tekola, F., Bull, S., Farsides, B., Newport, M.J., Adeyemo, A., Rotimi, C.N. & Davey, G. 2009a. Impact of social stigma on the process of obtaining informed consent for genetic research on podoconiosis: a qualitative study. *BMC Medical Ethics.* 10(1):13. DOI:10.1186/1472-6939-10-13.

Tekola, F., Bull, S.J., Farsides, B., Newport, M.J., Adeyemo, A., Rotimi, C.N. & Davey, G. 2009b. Tailoring consent to context: designing an appropriate consent process for a biomedical study in a low income setting. *PLoS Neglected Tropical Diseases.* 3(7).

Terry, S.F. 2012. The tension between policy and practice in returning research results and incidental findings in genomic biobank research. *Minn. JL Sci. & Tech.* 13:691.

Tindana, P. & de Vries, J. 2016. Broad Consent for Genomic Research and Biobanking: Perspectives from Low- and Middle-Income Countries. *Annual Review of Genomics and Human Genetics.* 17(1):375-393. DOI:10.1146/annurev-genom-083115-022456.

Traore, K., Bull, S., Niare, A., Konate, S., Thera, M.A., Kwiatkowski, D., Parker, M. & Doumbo, O.K. 2015. Understandings of genomic research in developing countries: a qualitative study of

the views of MalariaGEN participants in Mali. *BMC Medical Ethics.* 16(1):42. DOI:10.1186/s12910-015-0035-7.

Urban, M.F. 2015. Genomics in medicine: From promise to practice. *SAMJ: South African Medical Journal.* 105:545-547. Available: http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S0256957420150007000 19&nrm=iso.

Wolf, S.M. 2012. The past, present, and future of the debate over return of research results and incidental findings. *Genetics in Medicine : Official Journal of the American College of Medical Genetics.* 14(4):355-357. DOI:10.1038/gim.2012.26.

Wolf, S.M., Branum, R., Koenig, B.A., Petersen, G.M., Berry, S.A., Beskow, L.M., Daly, M.B., Fernandez, C.V. et al. 2015. Returning a Research Participant's Genomic Results to Relatives: Analysis and Recommendations. *The Journal of Law, Medicine & Ethics : A Journal of the American Society of Law, Medicine & Ethics.* 43(3):440-463. DOI:10.1111/jlme.12288.

Wolf, S.M., Crock, B.N., Van Ness, B., Lawrenz, F., Kahn, J.P., Beskow, L.M., Cho, M.K., Christman, M.F. et al. 2012. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genetics in Medicine : Official Journal of the American College of Medical Genetics.* 14(4):361-384. DOI:10.1038/gim.2012.23.

Wonkam, A. & de Vries, J. 2020. Returning incidental findings in African genomics research. *Nature Genetics.* 52(1):17-20. DOI:10.1038/s41588-019-0542-4.

World Medical Association Declaration of Helsinki – Ethical principles for medical research involving human subjects. WMA General Assembly, Fortaleza, Brazil; October 2013. *World Medical Journal.* 2013 Oct;59(5):199-202

Wu, Y.P., Thompson, D., Aroian, K.J., McQuaid, E.L. & Deatrick, J.A. 2016. Commentary: Writing and Evaluating Qualitative Research Reports. *Journal of Pediatric Psychology.* 41(5):493-505. DOI:10.1093/jpepsy/jsw032.

Xu, M., Ji, Y., Zhang, T., Jiang, X., Fan, Y., Geng, J. & Li, F. 2018. Clinical Application of Chromosome Microarray Analysis in Han Chinese Children with Neurodevelopmental Disorders. *Neurosci Bull.* 34(6):981-991. DOI:10.1007/s12264-018-0238-2.

Ziniel, S.I., Savage, S.K., Huntington, N., Amatruda, J., Green, R.C., Weitzman, E.R., Taylor, P. & Holm, I.A. 2014. Parents' Preferences for Return of Results in Pediatric Genomic Research. *Public Health Genomics.* 17(2):105-114. DOI:10.1159/000358539.

APPENDIX A – PRELIMINARY OPEN-ENDED INTERVIEW GUIDE FOR "PARENTAL PERSPECTIVES ON THE RETURN OF PERTINENT GENOMIC FINDINGS" STUDY AT UNIVERSITY OF CAPE TOWN

1) What do you remember about enrolling in the NeuroDev study?
    - What happened on that day? (PROMPT: mention names of recruiters (Emma, Kirsty, others))
    - Do you remember signing a form? Do you recall what the form was about? o Did you give blood? What was that for?
    - Do you remember what was explained in the consent form?

2) Could you tell me about the study you are participating in?
    - What is NeuroDev about? (PROMPT: genomics? why NDDs?)

3) What do you believe to be the reason for your child's condition?
    - What is it like living with a child with an undiagnosed condition?

4) Why did you choose to participate in this study?
    - What do you think your chances are of receiving a result?
    - Do you remember what kind of results they said you can receive? (PROMPT: Only NDD-related/only if they know what the result means for their child/even if they don't know what the result means)
    - What kind of results would you like to receive? o What kind of result are you expecting?
    - What would it mean for you and your family to receive a result? (PROMPT: diagnostic closure, gendered blame, stigma, others?)

5) Do you remember when they said they will give you a result?
    - PROMPT: after 2nd sample is taken and verified o When would you want to hear about possible results – before the 2nd sample is taken or only after validation?
        - What are your reasons for wanting/not wanting the results before verification?
    - If we contact you, how should we do this? (PROMPT: phone call, hospital) o What would you like to know when we take the second sample?
    - Would you want to be contacted with a negative result?

6) If we have a verified result, where should we give this result to you and how? (PROMPT: At RXH, at home, phone or Skype) o Who do you feel should be involved?
    - Who would be your support/who would you talk to regarding the result?

7) Is there anything else you would want to share with me that I haven't asked about?

APPENDIX B – PARTICIPANT INFORMATION SHEET

Dear Parent,

My name is Angelique Diedericks and I am a student at the University of Cape Town, doing a Master's degree in Genetic Counselling.

As previously explained, this study aims to examine the perspectives and understanding of parents whose children are participating in the NeuroDev study, regarding the feedback process and anticipated contributions of individual genetic findings of significant neurodevelopmental-related variants.

This study has been initiated through the Division of Human Genetics at the University of Cape Town and is for a minor dissertation for the completion of a Master's degree in Genetic Counselling.

You have been invited for involvement in this research because:

- **You are part of the NeuroDev South Africa Study and have given your permission for me to contact you for participation in my study, whereafter a time and date for this interview was arranged**

As you have agreed to participate, I would like to talk to you about your perceptions and understanding of the NeuroDev study, your reasons for wanting to participate, and your preferences for receiving results, if any. The discussion will take about an hour, expectedly at Red Cross War Memorial Hospital, and R100 per individual parent or R250 voucher per family present for interviewing will be offered for transport. The interview will be audio- recorded and any identifying information, such as your name, will be kept confidential and only be known by the researcher and, only if necessary, her supervisors. Some parts of the audio-recorded interview may be used in reporting of this study but identifying information will be kept confidential.

Your participation is entirely voluntary and you can withdraw from the study at any point, with no consequences for either you or your child. This being a research study, there will be no medical benefits to you or your child. Some of the questions that will be asked may be of a sensitive

manner. If you need further assistance in this regard, referral to appropriate health care professionals will be arranged.

The Human Research Ethics Committee at the Faculty of Health Sciences, University of Cape Town, has approved this study. If you have any questions about your rights as a participant, please contact **Prof Marc Blockman,** Chair of the Human Research Ethics Committee on 021 406 6496.

Should you have any questions about the research project, please contact me at DDRANG001@myuct.ac.za or by phone at 021 404 6235 or the project supervisor **Dr. J. De Vries** at jantina.devries@uct.ac.za or by phone at 021 650 5716**.**

Please read the Consent Form attached.

APPENDIX C – CONSENT FORM

MSc (Med) Genetic Counselling Research Project

Qualitative exploration of the preferences of results disclosure of the parents of children undergoing genome sequencing in the NeuroDev study in the Western Cape, South Africa

STATEMENT BY PARTICIPANT

I, _____ confirm that:

1. I have been invited to be involved in the above-mentioned research project which has been initiated through the division of Human Genetics at the University of Cape Town. I understand that ~30 - 40 other adult participants will be involved in the study and that my name and other personal information will not be discussed with the other participants or with anyone else not involved in the study.

2. I understand that the objective of the study is to understand how individuals, in the Western Cape Province of South Africa, perceive genomic testing and what their preferences are regarding the return of research results involving their children.

3. I understand that the interview will take place in a private setting at Groote Schuur Hospital (GSH), Red Cross War Memorial Children's Hospital (RXH) or in a private setting on a pre-scheduled date and time that is agreeable for me, the participant, and the researcher.

4. I understand the interviews will take approximately 60 minutes. Should it be required that the interview run for longer than this allocated time, I, the participant, would be invited to return at my earliest convenience to continue the interview and such transport costs shall be covered by the researcher.

5. I understand that I voluntarily choose to participate in this study and if I choose to no longer continue that my decision will not in any way affect the health care services my child currently receive at RXH or any other health care institution.

6. I understand that the questions may cause emotional reactions and that I may choose not to answer any questions if I do not wish to do so. I understand that I may decide to stop with the interview process at any point if I feel uncomfortable or too emotional and that this will not impact on my preexisting and future healthcare in any way. A genetic counselling session can be arranged if I would like to discuss anything further.

7. I understand that all information collected will remain confidential and will be used for research purposes only.

8. I understand that the interview will be recorded for research purposes. All audio recordings will be safely stored away in locked cupboards and information stored on a password-protected computer. I understand that only the researcher, her supervisors and examiners will have access to the data. All recordings will be destroyed upon completion and publication of this study and all identities will remain anonymous.

9. I understand that the interview will take place in English and that the researcher will be administering the interviews herself and if I do not feel comfortable communicating in English and require a translator, a suitably trained individual will be used to translate the interview and supplementary documentation.

10. I understand that this study has been approved by the registered Human Research Ethics Committee at the Faculty of Health Sciences at the University of Cape Town. I have been given contact details should I wish to contact the committee about how I was treated as a research participant.

11. I have the researcher's contact details in the event that I would like to contact her regarding further questions about this study.

12. _____ has explained the information of this study in English or in _____ through the use of a suitable translator and I understand this information.

I_____(participant name) hereby declare that I have voluntarily agreed to participate in the above-mentioned research study and that the interview can be audio-recorded.

Signed at:
(Address of venue) _____ on _____ 2019.

Participant Name **Witness Name**

Participant Signature **Witness Signature**

THANK YOU FOR YOUR PARTICIPATION!

APPENDIX D – INTERPRETER CONFIDENTIALITY & NONDISCLOSURE AGREEMENT

INTERPRETER CONFIDENTIALITY &
NONDISCLOSURE AGREEMENT

I, _____ understand that when employed as an Interpreter, my responsibility is to facilitate communication between two or more parties that do not speak or understand the same language. All information discussed between the parties is considered to be “confidential”.

I agree to hold confidential or proprietary information in trust and confidence and agree that information discussed at a meeting/activity shall be used only for the purposes of conducting such meeting/activity and shall not be used for any other purpose or disclosed to a third party.

Furthermore, at the conclusion of the meeting/activity, I agree to return all written information (i.e., forms, notes, etc.) provided to me for the purposes of conducting such meeting/activity.

AGREED AND ACCEPTED BY:

_____ _____

Interpreter Applicant Date

_____ _____

Witness Title

APPENDIX E – DESCRIPTION OF CODES OUTLINED AS PER RESULTS THEME AND SUB-THEME

4 Chapter 4 RESULTS – PARTICIPANT UNDERSTANDING, EXPECTATIONS & REASONS FOR PARTAKING IN GENOMIC RESEARCH

4.1 Sociodemographic data

4.2 Theme 1 | People want to know

Findings that have preventable implications

4.3 Theme 2 | Reasons to participate in/support genomic research

4.3.1 **Altruism**

Helping others
- To accept condition
- Increased support

Increase access to resources – for prevention
Meeting other parents and self-advocacy
Results won't change anything

4.3.2 **Participating for personal or family benefit**

Decrease the risk of developing the condition/prevent it from happening
To prepare or plan for the future
To increase intervention
Cure or treatment

4.4 Theme 3 | Expectations about the impact of the NeuroDev research study & general study results

4.4.1 **Best chance in life**

Education
Cure or improved outcome
Understanding prognosis and how to support their child
Information and support through NeuroDev

4.4.2 **Establishing certainty**

Obtain direction about future treatment and management
Establishing a diagnosis

4.4.3 **Fulfilling the need for information**

Understanding the nature of Autism
Understanding what causes Autism ('why') – maternal health vs. environmental triggers (e.g. vaccinations)
How to support and manage child
Self-empowerment
Acceptance through diagnostic closure
Reduce risk of recurrence
Feeling let down by healthcare system in general

4.5 Theme 4 | Understanding the study

Only receiving positive results
Issues of terminology (positive vs. negative meaning)
Understanding of genetics and DNA
- 'runs in families'
- 'occurring for first time in the child'

Beliefs over cause of child's condition
- Environmental
- Genetic
- 'Many things that come together at one point'

4.5.1 **Expectations of Nature of results**

Causative
Confirming an inherited genetic cause
Environmental cause such as exposure

4.5.1.1 *Uncertainty over nature of study results and its implications*

Meaning of results depends on kinds of results
Uncertain
Not expecting results
- Reasons:
  - NeuroDev study is for data collection only
  - Long time since researcher contact

4.5.1.2 *Perceived utility of receiving non-Pertinent results*

Participants want:

All results, good or bad

- Reasons:
  - To plan for future
  - Provide quality of life
  - Inform personal health risk
  - Promote future research
  - Information discovery

Results of significance to their child's health

All results including IF

- Reasons:
  - Warn of child's potential health risk
  - Inform of personal health
  - Inform of future intervention
  - Better quality of life by being prepared and planning for their family's future

All results including VUS'

- Reasons:
  - Future research

Don't want VUS'

- Reasons:
  - Unsure of usefulness and concern over new information discovery
  - Potential to create anxiety

Negative results

- Reasons:
  - Could reassure researchers did all they can
  - Confirmation of acknowledgement from the healthcare system
  - Personally having done all they can

5 5 Chapter 5 PERTINENT RESULTS

5.1 Theme 5 | Expectations About the Impact of Pertinent Study Results

Personal value of results

- Closure
- Improved management for their child's condition
- Information regarding recurrence risks

5.1.1 **[Diagnostic] closure**

5.1.1.1 Acceptance

Awareness and acceptance – form of peace

Relief regardless of the meaning of the result or cause of condition

A name for child's condition

Knowing the cause

5.1.1.2 Guilt and (self-)blame

Understanding why this happened and where it stems from
Put unknown to rest and move on, knowing they are not the cause
Grief and guilt relieved by knowledge gained by participating in the study or comfort of knowing help is available
Internal guilt over carrying this genetic flaw and passing it on
- Relieved by knowing it is a spontaneous, new occurrence in child
- Won't take guilt away

Confirmation that they are not personally to blame
Reproductive decision-making and blame

5.1.1.3 Self-empowerment – what's in a name?

A name for their child's condition
- Defined management and treatment
- Conducting their own research

5.1.2 **Improving the management of child's condition**

Becoming as educated as possible and have greater understanding of their child's condition
Would make things easier, raising hopes for treatment, medicine and an improved life for their child
A genetic diagnosis would not change the fact that the child has the condition

5.1.3 **Recurrence risks**

Inform participants of personal or their children's reproductive potential
- Reasons:
  - To have more children
  - To help next generation of their family

Inform recurrence risk of affected child's future offspring

5.1.4 **Results won't change anything**

Won't change how they relate to their child and the condition
Won't add further value other than knowing the cause

6 Chapter 6 PREFERENCE TO FEEDBACK

6.1 Theme 6 | The value of a negative result – acknowledging personal utility

Want to know if there are no results

- Reason:
  - to guide future planning

Want to be contacted with a negative result

- Reasons:
  - Getting closure
  - Peace of mind
  - Keeping calm
  - Stay informed of research progress
  - Reassurance they did the best they could
  - Sense of entitlement over their blood

Participants appreciation of feedback

Meaning of a negative result:

- An answer in itself
  - Religious factors influencing meaning

Negative results could bring:

- Closure
- Peace and acceptance

6.2 Theme 7 | Preferences for explanation of preliminary results

6.2.1How much is too much?

Preference to second sample contact:

- Broad explanation

  Includes:
  - Reasons for second sample
  - What it would be for – was first sample tainted or do researchers need more information
  - Generic information – likely results which need to be verified

  Reasons:
  - Eliminate worry and anxiety

- Detailed explanation

  Includes:
  - All information including what the preliminary result is that requires verification
  - Result explained in comprehensible manner
  - Researcher transparency regarding any uncertainty over meaning of results

  Reasons:
  - To be aware of findings and the process
  - To see which tests were done and what treatment is available
  - To be a part of the process

- To be kept informed regarding progression of the study

- Don't want to know what was found at this stage

- Would know pertinent variant was found if contacted for second sample
  - Impact on participant

6.3 Theme 8 | Timing Of Feedback

When should they be told of their results

- After verification
  - Reasons:
    - Avoid unnecessary stress and worry over inconclusive results
    - Need for certainty
    - Maintaining peace of mind – even willing to wait longer for results

- Before verification
  - Reasons:
    - Need for study involvement
    - To prepare for possible outcome
    - To know if they need to be concerned
    - Desire to assist in the research being conducted
    - The right to know and be informed
    - To cure or treat their child – early intervention

6.3.1 **Who should explain results - Familiarity**

No preference - anyone
Original study researchers
Someone capable of explaining everything in an understandable manner
Someone the participant is familiar with and who listens
Someone who is familiar with their child, knows child's background and who participants are comfortable with asking questions
Their doctor or GP
A doctor involved in child's management – RCWMCH doctors

- Want to be told:
  - Thorough explanations
  - Reassurance

NeuroDev researchers

- Would foster ease
- Could answer all their questions
- Have knowledge and insight of child's medical background and journey
- Can explain necessary information

6.3.2 **Where & how – Respect & Confidentiality**

Where they would like to receive feedback after verification:

- Phone call to come in
- Face-to-face
- RCWMCH
- WhatsApp
- Text message
- Over the phone for negative results
- Not over the phone
    - Reasons:
        - Distrust of technology and fear of breach of security
- In person
    - Reasons:
        - Would alleviate anxiety and worry
- Letter or email explaining (child undiagnosed)
    - Reasons:
        - Wouldn't change management or treatment

Sharing of their information:

- Value confidentiality
- Anxiety about sharing private information on public databases or telephonically

ETHICS APPROVAL LETTER

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

26 February 2019

HREC REF: 784/2018

A/Prof Jantina De Vries
Clinical Research Centre
J51, OMB

Dear A/Prof De Vries

PROJECT TITLE: PARENTAL PERSPECTIVES REGARDING THE RETURN OF GENOMIC FINDINGS IN NEURODEVELOPMENTAL DISORDERS - LISTENING TO THE VOICE OF THE FAMILIES - A SOUTH AFRICAN STUDY (SUB-STUDY LINKED TO 810/2016) MSc Candidate - Ms A Diedericks

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 28 February 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Angelique Diedericks will also be involved in this study.

Yours sincerely Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 784/2018

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.