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THE EXPECTED UTILITY OF WHOLE-EXOME SEQUENCING RESULTS AND THE PSYCHOSOCIAL IMPACTS OF RECEIVING A DIAGNOSIS

Samantha Susan Schnell

Student number: 1914985

Supervisor: Mr Barry Shingwenyana

Co-supervisor: Ms Zandisiwe Goliath

A **research report (in the format of a "submissible" paper)** submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of **Master of Science in Medicine in the field of Genetic Counselling**.

Johannesburg, 2025.

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Letter to the Examiner

27 November 2024

Dear Examiner,

RE: RESEARCH REPORT SUBMITTED TO THE FACULTY OF HEALTH SCIENCES BY SAMANTHA SCHNELL IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN MEDICINE IN GENETIC COUNSELLING

Thank you for agreeing to examine the following research report, titled "*The expected utility of whole-exome sequencing results and the psychosocial impacts of receiving a diagnosis*". This research report is being submitted by the candidate, Samantha Schnell, in partial fulfilment of the degree, Master of Science in Medicine in Genetic Counselling, at the University of the Witwatersrand. Furthermore, this research is being submitted in the form of a "submissible" paper and contributes 30% towards the degree.

The candidate, with approval from her supervisors, Mr Barry Shingwenyana and Ms Zandisiwe Goliath, has selected the scientific journal, *Orphanet Journal of Rare Diseases*, for submission to the Faculty of Health Sciences. This journal was selected as it encompasses all aspects of rare diseases and is open-access and peer-reviewed. Samantha deemed this journal as a good fit for her own research because it focused on the diagnostic odyssey experienced by families recruited into the DDD-Africa study as well as the impact whole-exome sequencing results have on caregivers of children with rare genetic conditions. Furthermore, *Orphanet Journal of Rare Diseases* has a notable impact factor of 3.4 (2024). This research report was written in accordance with submission guidelines, see Appendix H. However, for the ease of referencing and marking purposes some of these guidelines have been deviated from as the Harvard referencing style was used instead of Vancouver and 1.5 line spacing in place of double spacing.

In Appendix C, the approved research protocol has been attached to serve as an extended literature review and to provide further context for the submitted research. The research protocol is not being submitted for examination as it was previously assessed and approved by the Faculty of Health Sciences.

Yours sincerely,

Samantha Schnell
Candidate

Mr Barry Shingwenyana
Supervisor

Ms Zandisiwe Goliath
Co-supervisor

This report is intended solely to record the observations and/or opinion of the writer. It does not constitute a medico-legal report

Declaration

I, **Samantha Schnell**, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of **Master of Science in Medicine in Genetic Counselling** at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Signature of candidate

22 June 2025, in Johannesburg

Contribution of Candidate to the Paper

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, **Samantha Susan Schnell**, student number **1914985**, declare that this research report is my own work and that I contributed adequately towards research findings presented in the paper stated below, intended for publication.

Signature of Student: 

Date: **22/06/2025**

Name of Primary Supervisor: **Mr Barry Shingwenyana**

Signature of Primary Supervisor: 

Date: 22/06/2025

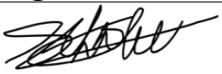
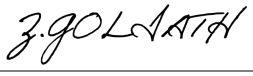
Name of Co-supervisor: **Ms Zandisiwe Goliath**

Signature of Co-supervisor: 

Date: 22/06/2025

Agreement of co-authors: By signing this declaration, the co-authors listed below agree to the use of this article by the student as part of her research report.

Article title: The expected utility of whole-exome sequencing results and the psychosocial impacts of receiving a diagnosis

Authors	Name	Signature	Date
1st author	Samantha Schnell		22/06/2025
2nd author	Zandisiwe Goliath		22/06/2025
3rd author	Barry Shingwenyana		22/06/2025

To my parents, Sharon and Bruce, and my sisters, Robyn and Maxine. Thank you for your unwavering support throughout this journey.

Presentations Arising from This Research

1. Faculty of Health Science Biennial Research Day & Postgraduate Expo, University of the Witwatersrand, 5th September 2024 (poster presentation)
2. Genetic Counsellors South Africa Research Showcase 2024, Virtual, 21st November 2024 (oral presentation)
3. Young Investigator Forum, Entebbe, Uganda, 3rd February 2025 (poster presentation)
4. 15th African Society of Human Genetics Conference and the 1st Ugandan Society of Human Genetics and Bioinformatics, Entebbe, Uganda, 3rd-7th February 2025 (poster and oral presentations)
5. World Congress on Genetic Counselling, Wellcome Genome Campus, United Kingdom and Virtual, 24th-26th February 2025 (virtual poster pitch presentation)

Abstract

From the Deciphering Developmental Disorders in Africa parent study, 58 families with probands affected with developmental disorders, who received whole-exome sequencing (WES) results, participated in this sub-study to explore caregivers' expected utility and the psychosocial impacts of WES results. This was achieved through the analysis of researcher-administered pre-result feedback questionnaires as well as post-feedback consultation notes, respectively. Prior to result feedback, 53/62 (85.5%) caregivers expected results to provide a label to the condition and 47/62 (75.8%) expected to gain knowledge of the condition's future trajectory. Immediately after WES result delivery, results elicited significant psychosocial and emotional responses from caregivers. This was illustrated by five codes commonly applied through quantitative content analysis: (1) providing a label, (2) relief and closure, (3) the parental burden, (4) overwhelmed and emotional and (5) loss of hope and grief. Overall, these findings accentuate the importance of confirming a diagnosis and emphasise the psychosocial impacts of ending the diagnostic odyssey in an African context.

Word count: 158 words

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Firstly, I would like to thank my supervisors, Mr Barry Shingwenyana and Ms Zandisiwe Goliath. Thank you for our check-in meetings and the support you have provided me with over this last year. I deeply appreciate the time and effort you have put into this research and supervising me. Your commitment to the DDD-Africa study and the families who were enrolled is admirable. Thank you for always going the extra mile.

Thank you to Dr Zané Lombard, Prof Amanda Krause and Mrs Nadja Louw for your encouragement and support in continuing this research as a genetic counselling student. Thank you to our collaborators, Ms Monica Araujo, Mrs Elzette Gilfillan and Mrs Bianca Rossouw, for your invaluable input.

To the research teams that fed back results in the Johannesburg (Ms Jamey Thom, Ms Ingrid Smit, Ms Kiara Haripersad, Dr Aliya Mukadam, Dr Njabulo Mabaso, Dr Daisy Mokwele, Dr Kgisane Mophiring, Dr Ashira Vania and Dr Michael Novelie), Pretoria (Dr Engela Honey) and Durban (Dr Thirona Naicker, Dr Prian Dookhoo, Sr Marlene Nadesan and Ms Lisa Mbhele), thank you for your commitment and for giving up your time to be involved.

Thank you to the University of the Witwatersrand for funding my studies through a Postgraduate Merit Award and a Wits Postgraduate Scholarship as well as the funding that I received for this project through a Faculty Research Committee Individual Research Grant.

Finally, a thank you to all the families and caregivers enrolled in the DDD-Africa study. This research would not have been possible without your contributions and commitment to the wellbeing of your children.

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List of Abbreviations

Array-CGH	Array comparative genomic hybridisation
DDD	Deciphering Developmental Disorders
DDD-Africa	Deciphering Developmental Disorders in Africa
DDs	Developmental disorders
DNA	Deoxyribose nucleic acid
DBN	Durban
FISH	Fluorescence *in situ* hybridization
FRAX	Fragile X syndrome
H3Africa	Human Heredity and Health in Africa
HPO	Human Phenotype Ontology
ID	Intellectual disability
IQR	Interquartile range
JHB	Johannesburg
MLPA	Multiplex ligation-dependent probe amplification
MS-MLPA	Methylation-specific multiplex ligation-dependent probe amplification
NGS	Next-generation sequencing
PTA	Pretoria
QF-PCR	Quantitative fluorescent-polymerase chain reaction
REDCap	Research Electronic Data Capture
SD	Standard deviation
SNVs	Single nucleotide variants
SOP	Standard operating procedure
UK	United Kingdom
WES	Whole-exome sequencing

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A research report in the format of a "submissible" paper.

This work has been written up as a paper for submission to *Orphanet Journal of Rare Diseases*. The author guidelines adhered to can be found in **Appendix H**, which have been included for ease of reference.

The expected utility of whole-exome sequencing results and the psychosocial impacts of receiving a diagnosis

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Abstract for Journal Submission

Background: Developmental disorders are a group of conditions that alter the trajectory of childhood development and exhibit great genetic and clinical heterogeneity. Therefore, identifying a diagnosis remains challenging, leaving approximately 60% of affected individuals without a known underlying cause. Consequently, probands and their families often experience a protracted and burdensome journey, termed the "*diagnostic odyssey*", which significantly impacts the mental, physical and financial wellbeing of families.

Results: From the Deciphering Developmental Disorders in Africa parent study, 58 families, who received returnable whole-exome sequencing (WES) results, participated in this sub-study which aimed to explore caregivers' expected utility and the psychosocial impacts of WES results. Prior to result feedback consultations, researcher-administered questionnaires were completed to determine caregivers' expectations of WES results and their motivations for wanting a confirmed diagnosis. 61/64 (95.3%) caregivers expected results to help them gain knowledge and understanding of their child's condition, while 61/63 (96.8%) anticipated receiving a better understanding of any additional health problems. Similarly, 19/62 (30.6%) caregivers ranked having a better understanding of their child's condition and any future health problems as their most important motivator for seeking a confirmed diagnosis. Analysis of short-text responses further emphasised the importance of confirming a diagnosis. Post-feedback consultation summary notes were assessed with a literature-informed codebook and quantitative content analysis to identify psychosocial aspects that arose immediately after receiving a result. Receiving a result was overwhelming and emotional for 22/58 (37.9%) families, of which 17/58 (29.3%) had caregivers who vocalised experiencing a parental burden. However, results also brought relief and closure to 26/58 (44.8%) families as it ended the diagnostic odyssey, which was vocalised by 15/58 (25.9%) families who felt that results provided a label for their child's condition. Additionally, 20/58 (34.5%) families felt grief and a loss of hope for a cure of improved medical treatments.

Conclusions: This study accentuates the importance of confirming a diagnosis in children with developmental disorders. Caregivers expected to better understand their child's condition, the cause and any potential future health problems. Receiving a WES result elicited significant psychosocial and emotional responses from caregivers. Thus, these findings emphasise the psychosocial impacts of ending the diagnostic odyssey and illustrate the importance of genetic counselling in preparing families for receiving a diagnosis.

Keywords: Rare diseases, Whole-exome sequencing results, Feedback of findings, Test utility, Caregiver perspectives

Background

Developmental disorders (DDs) are a heterogenous group of conditions that arise during embryonic and fetal development. These disorders manifest in early childhood and alter the trajectory of childhood development. This can involve delays in motor, cognitive, language and/or social and emotional developmental domains (Brown et al., 2020). While individually rare, DDs are collectively common with a global prevalence of 1-3% (Xiang *et al.*, 2021). The underlying aetiology of most DDs remains unknown; however, up to 40% are thought to possess a genetic aetiology including single nucleotide variants (SNVs), copy number variants, and chromosomal abnormalities (Vorstman and Ophoff, 2013; Blesson and Cohen, 2020). Consequently, DDs exhibit broad genetic and clinical heterogeneity, often involving multiple organ systems, presenting with congenital anomalies and dysmorphic features (Brown *et al*., 2020). Thus, reaching a diagnosis is challenging, with approximately 60% of children affected with DDs lacking a definitive cause (Langenfeld *et al*., 2021). As a result, affected individuals and their families often experience a protracted and burdensome journey to obtain a diagnosis, known as the "*diagnostic odyssey*" (Bauskis *et al.*, 2022).

The diagnostic odyssey is marked by delayed and incorrect diagnoses, multiple and potentially invasive investigations and inadequate access to appropriate healthcare services. Moreover, misdiagnoses may result in the use of treatments that are unsuitable to patients (Zurynski *et al.*, 2017). For many caregivers seeking a diagnosis for their child, this has been described as an "emotional rollercoaster" and has potential to significantly impact the mental, physical and financial wellbeing of families (Heath *et al.*, 2024; Pavisich, Jones and Baynam, 2024). Furthermore, this diagnostic odyssey is associated with poor patient, caregiver and family outcomes, including mental health challenges, reduced trust in healthcare providers and dissatisfaction with the healthcare system (Pavisich *et al.*, 2024). Contrastingly, achieving the correct diagnosis can alleviate the stress of not knowing the cause or expected trajectory of their child's condition. A diagnosis provides parents with a platform to better understand their child's condition and restore their reproductive confidence (Zurynski *et al.*, 2017).

Makela *et al*. (2009) concluded that caregivers value receiving a diagnosis for their child's developmental delay to provide validation, guide expectations and treatments, procure services in the school system, gain support, evoke curiosity and for reproductive choices. Validation emerged as the most important motivator in which caregivers experienced emotional relief as their child's intellectual disability (ID) was legitimised. Similarly, Krabbenborg *et al*. (2016) determined that other advantages of receiving a conclusive diagnosis include fostering greater

acceptance, helping caregivers attune the care needs of their child and enhanced coping with guilt. However, receiving a diagnosis is often emotionally challenging with some caregivers experiencing a loss of hope, especially if the diagnosis has a poor prognosis, a lack of available treatments or a cure (Krabbenborg *et al.*, 2016). Therefore, it is of vital importance that results are shared with families in a sensitive and supportive manner (Zurynski *et al.*, 2017).

In this context, genetic counsellors play a critical role in the diagnostic journey. Waxler *et al.* (2013) found a strong association between positive diagnostic experiences and the involvement of genetic counsellors among parents of children with Williams syndrome. This is likely a consequence of the extensive training that genetic counsellors receive in delivering difficult news and providing support to families affected by or at risk of genetic conditions. The role of genetic counsellors is crucial when returning whole-exome sequencing (WES) results, as they prepare parents prior to genetic testing and offer post-test support while establishing new care for their child (Krabbenborg *et al.*, 2016). Genetic counsellors help families understand genomic test results, educate them on inheritance and management strategies and connect them to resources (Resta *et al.*, 2006). Additionally, genetic counsellors can explore families' motivations for pursuing genetic testing and their expectations (Blesson and Cohen, 2020).

Given the large contribution of genetic factors to DDs, genomic testing is recommended for children with undiagnosed IDs and developmental delay. Previously, chromosomal microarray was the first-tier genetic test with a diagnostic yield of 15-20% (Blesson and Cohen, 2020). However, technological advances in next-generation sequencing (NGS) technology, including WES, have significantly improved the diagnostic yield in cases of DDs to 25-40% (Mollison *et al.*, 2020). Whole-exome sequencing is especially effective in accounting for the genetic heterogeneity of DDs as it detects SNVs and insertions/deletions in protein coding regions of the genome using massively parallel sequencing (Xiang *et al.*, 2021). However, WES is not yet routinely available in low-middle-income countries in Africa, such as South Africa, due to the scarcity of genetic services, limited infrastructure and restricted access to advanced sequencing technologies (Wiener *et al.*, 2023). In South Africa's state healthcare sector, WES is only available through research settings (Van Der Merwe *et al.*, 2022).

One such initiative is the Deciphering Developmental Disorders in Africa (DDD-Africa) study implemented through the Human Heredity and Health in Africa (H3Africa) consortium (Ethics Clearance Number: M230567; https://h3africa.org/index.php/ddd-africa/). The DDD-Africa study aims to elucidate the genetic aetiologies of DDs in African populations to improve

diagnostic and clinical genetics services across the continent (Baine-Savanhu *et al*., 2023). The DDD-Africa research team recruited a total of 521 African probands with undiagnosed DDs from various sites in South Africa and the Democratic Republic of Congo. Where possible, WES was performed on probands and both parents for trio-based analysis. Subsequently, a multidisciplinary team of research scientists, medical geneticists and genetic counsellors were involved in the communication of returnable WES research results back to families. Returnable results consist of the identification of a likely pathogenic or pathogenic variant or variants and the associated genetic diagnosis that is clinically actionable and communicated back to the family (Van Der Merwe *et al*., 2022).

Despite the diagnostic potential of WES in diagnosing DDs, a gap remains in understanding the experiences of families who undergo such genetic testing. Specifically, there is a scarcity of studies assessing the lived experiences of caregivers of children with DDs in an African context. Therefore, the present study, which is a sub-study of the DDD-Africa parent study, aimed to investigate the expected personal and clinical utility as well as the immediate psychosocial impacts of returnable WES research results received through the DDD-Africa parent study. Furthermore, this sub-study sought to determine if the diagnostic odyssey was a shared experience for these families.

Methods

Study participants

This sub-study cohort comprised of a subset of families (n = 63) that were enrolled in the DDD-Africa parent study in South Africa between June 2018 and June 2023. These families consisted of probands with undiagnosed DDs, who were known to clinical genetics services across the country, and their parents. Recruitment for the DDD-Africa parent study was both hospital- and community-based. Hospital-based recruitments occurred at academic hospitals in Johannesburg (JHB), Pretoria (PTA) and Durban (DBN). Additionally, community-based recruitments were only conducted in JHB at a school for individuals with IDs and special education needs. Subsequently, this sub-study cohort received returnable WES research results through the DDD-Africa parent study. While the parent study aimed for trio recruitment, an intake of duos and singletons were also observed and some families with multiple affected children were included. The unique identifying codes used in the parent study were maintained for anonymity.

Genetic counselling feedback consultations for WES results in the DDD-Africa parent study began in May 2021 and are ongoing to date. Result feedback consultations included in this sub-

study were held in-person or virtually via Zoom Workplace (https://www.zoom.com/). The standard operating procedure (SOP) for the feedback of returnable WES research results to families in the DDD-Africa parent study entails:

- Administration of pre-result feedback questionnaires by a researcher;
- Result feedback by a DDD-Africa-affiliated genetic counsellor;
- In-depth clinical examination undertaken by a medical geneticist, where further care and management are determined and outlined.

Families excluded from this sub-study included probands who received WES results directly with a lack of caregiver involvement (n = 1) and result feedback consultations occurring in-clinic, outside of the DDD-Africa parent study SOP for feedback of results (n = 4). This sub-study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Ethics Clearance Number: M240760) as a sub-study of both the DDD-Africa parent study (Ethics Clearance Number: M230567) as well as a DDD-Africa sub-study conducted by Shingwenyana *et al*. (Ethics Clearance Number: M220125), see Appendices D, E and F, respectively.

Instrumentation

Two primary instruments were used for data collection in this sub-study. The first instrument was an adapted version of the Australian Paediatric Surveillance Unit Impact on Family Survey developed and validated by Zurynski *et al.* (2017). The original survey focused on the demographics of their cohort and data that pertained to the diagnosis, amongst other sections of data such as health functioning and treatment. Furthermore, some survey questions aided in quantitatively analysing the diagnostic odyssey experienced by these families. In the adaptation used in this sub-study, survey questions pertained to the proband's age at their initial genetic service consultation, age at recruitment and age at WES result delivery, as well as previous genetic testing, see Appendix A.

The second instrument was a researcher-administered questionnaire that was developed by Shingwenyana *et al*. as another DDD-Africa sub-study (Ethics Clearance Number: M220125), titled '*Caregivers' expected and perceived utility of whole-exome sequencing results for children with developmental disorders*', see Appendix B. This questionnaire was first introduced to the DDD-Africa parent study's WES result feedback consultations in September 2022 and was updated in November 2022 with the addition of two open-ended questions. It comprised:

Part 1: Determining what parents think a diagnosis will be able to provide.

- Question 1 (1.1 and 1.2): Two open-ended questions assessing the expected personal and clinical utility of WES results, respectively.
- Question 2: A 16-item five-point Likert scale to determine whether each statement was aligned with what caregivers expected WES results would provide them.

Part 2: Determining why parents want a confirmed diagnosis for their child.

- Question 1: An ordinal ranking of six statements in order of importance for wanting a confirmed diagnosis.

Caregivers completed the questionnaire either independently or within their couple, and some responded with help from a research assistant who transcribed oral responses verbatim. The questionnaires were primarily administered in English, but research assistants also translated if possible, and when necessary.

Data collection

This study is primarily a retrospective quantitative analysis to evaluate the expected outcomes of returnable WES research results, from the perspectives of caregivers prior to receiving a diagnosis for their affected child as well as the immediate psychosocial impact of receiving that result. Broadly, three sets of data were obtained for this sub-study. Firstly, demographic data of the probands and their parents were collected retrospectively through the Research Electronic Data Capture (REDCap) database maintained by the DDD-Africa parent study (Harris *et al.*, 2009). This data was collected during initial recruitment of the DDD-Africa parent study (June 2018 to June 2023).

Secondly, researcher-administered questionnaire responses were collected prior to the return of returnable WES research results on the day of the result feedback. Participating caregivers provided written informed consent before completing the questionnaire. However, it is important to note that questionnaires were not completed for consultations conducted prior to September 2022 or for consultations held virtually via Zoom Workplace, specifically in cases where the proband had demised or the family had relocated. All questionnaire responses collected from September 2022 to March 2024 were included for analysis in this sub-study. Additionally, the administration of questionnaires are on-going as genetic counselling feedback consultations for WES results in the DDD-Africa parent study continue.

Lastly, electronic clinical records and consultation summary letters were obtained following feedback of returnable WES research results, where available, from September 2022 to March

2024. The attending genetic counsellor and medical geneticist summarised the contents discussed in the consult in consultation summary letters addressed to the caregiver/s who attended. The letters reinforced information that was discussed, including returnable WES research results, aetiology, familial implications, clinical manifestations and management of the conditions. Detailed psychosocial aspects were not included in the consultation letters as they were not pertinent to the medical management and care of the child. However, in-depth psychosocial aspects were recorded and analysed through electronic clinical records, accessible through the REDCap database (Harris *et al.*, 2009).

Data analysis

The demographic data (dataset 1 as illustrated in Fig. 1) was exported and transcribed into Microsoft 365 Excel for analysis. Subsequently, data was categorised as numerical, binary and nominal. Numerical data was analysed using descriptive statistics and Shapiro-Wilk tests were used to assess normality, while frequency distributions were used to describe the binary and nominal data. However, no further statistical testing was performed to investigate correlations or compare variables. Additionally, ordinal data was obtained from the Likert scale and ordinal ranking question responses (dataset 2). This data was classified as categorical survey items and transcribed for analysis with frequency distributions.

A quantitative content analysis was conducted on the short-text responses from the researcher-administered questionnaires (dataset 2), as well as the psychosocial notes documented in the consultation summary letters and electronic clinical records (dataset 3). As outlined by Coe and Scacco (2017), this methodology involves the systematic categorisation of textual data through observation and quantification, a process known as coding. To ensure standardisation, a codebook is developed comprising categories with clearly defined descriptions that guide the coding process.

The genetic counselling student (SS) conducted a targeted literature review using PubMed (https://pubmed.ncbi.nlm.nih.gov/) focusing on publications dated between 2015 and 2024 to screen for the most recent available and relevant literature. Search terms included combinations of: "*developmental disorders*", "*exome-sequencing*", "*genetic diagnosis*", "*diagnostic odyssey*", "*personal utility", "clinical utility*", "*caregivers*", "*perceptions*" and "*psychosocial*". In an additional round of screening, SS and the co-supervisor (ZG) identified the five most relevant articles independently. SS and ZG with input from the primary supervisor (BS) then identified potential categories based on insights from the literature. Categories, codes, and sub-

codes were refined and finalised through consensus with collaborators (MA, BR and EG), see Supplementary Table 1.

Once the codebook was finalised, it was applied to the textual dataset using MAXQDA Analysis Pro (Release 24.5.1), a software platform designed for mixed-methods and content analysis. This enabled the systematic quantification and comparison of categories across the textual data. The analysis was informed by the literature review, which helped shape the structure and application of the codebook. An overview of the study methodology is illustrated in Fig. 1.

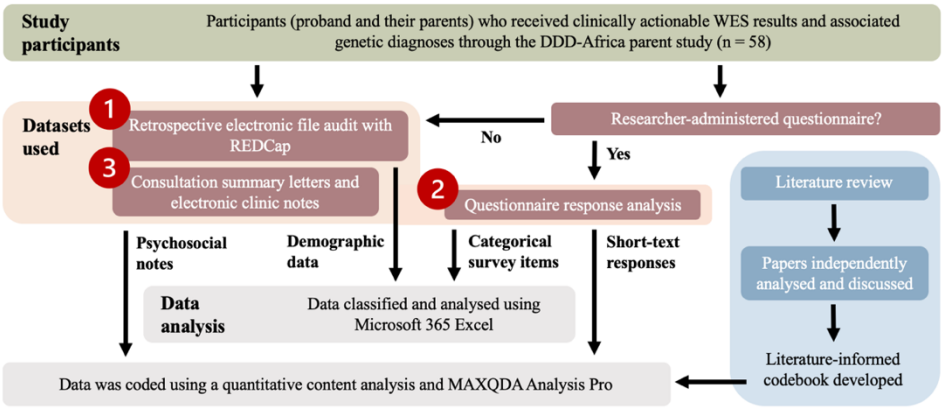


Fig. 1 Outline of the study methodology

The red numbering indicates the three data sets collected and analysed in this DDD-Africa sub-study; the first data set comprising of demographic data obtained through a retrospective electronic file audit through REDCap, the second including the short-text responses and categorical survey items obtained through questionnaire responses, and the third set being text obtained from consultation summary letters and electronic clinic notes.

Results

During the data collection period in this sub-study, a total of 63 families had received returnable WES research results through the DDD-Africa parent study. However, only 58 families met the inclusion criteria of this study. A total of 84 caregivers attended result feedback consultations and 64 questionnaires were completed in total, see Supplementary Table 2 for a summary of the result feedback consultations and attendance.

Demographic characteristics of families

Caregiver demographics

A total of 84 caregivers attended the WES result feedback consultations, primarily consisting of 56.84 (66.7%) mothers and 28/84 (33.3%) fathers, see Table 1. All mothers included in this sub-study were recruited into the DDD-Africa parent study, compared to 23/28 (82.1%) fathers. While most caregivers reported earning some form of income (either through employment and/or governmental grants), 14/84 (16.7%) reported no source of income at the time of initial

recruitment. 38/58 (65.5%) parental couples were still cohabiting or married at the time of initial recruitment; however, relationship dynamics were not consistently explored at result feedback. Additionally, 51/58 (87.9%) of families had a single affected child, though a minority reported multiple affected children.

Table 1 Demographic characteristics of caregivers who attended WES result feedback consultations

Caregivers (N = 84)		**Mothers (n = 56) Median (IQR) or n (%)**	**Fathers (n = 28) Median (IQR) or n (%)**
Age at proband's birth (years)		29 (25-33)	34 (30-37)
Age at DDD feedback (years)		40 (33.75-43)	44 (40.5-48.5)
Recruitment into DDD-Africa parent study			
Yes		56 (100)	23 (82.1)
No		0 (0)	5 (17.9)*
Highest level of education			
Primary		1 (1.8)	0 (0)
Secondary		40 (71.4)	18 (64.2)
Tertiary		15 (26.8)	5 (17.9)
Unknown		0 (0)	5 (17.9)
Income			
Employment only		12 (21.4)	16 (57.1)
Government grant only		23 (41.1)	1 (3.6)
Both		10 (17.9)	3 (10.7)
No income		11 (19.6)	3 (10.7)
Unknown		0 (0)	5 (17.9)
Families (N = 58)	**n (%)**	**Families (N = 58)**	**n (%)**
Marital status of parents		Affected children	
Married or living together	38 (65.5)	One	51 (87.9)
Never married or co-habited	16 (27.6)	Two	3 (5.2)
Divorced or separated	4 (6.9)	Three	4 (6.9)

DDD-Africa: Deciphering Developmental Disorders in Africa; IQR: Interquartile range
*Mother and proband recruited as a duo and father attended WES result feedback consultation despite not being recruited into the DDD-Africa parent study.

Proband demographics

Among the probands, there was an even distribution of 30/58 (51.7%) males and 28/58 (48.3%) females, see Table 2. More than half of the families consisted of trios, in accordance with the aim of the parent study.. *De novo* autosomal dominant was the most common inheritance pattern observed, in 27/58 (46.6%) families, succeeded by autosomal recessive and X-linked conditions. Notably, there was unknown inheritance in 10/58 (17.2%) families as the family was recruited as a duo. A significant proportion of probands had undergone prior genetic testing with 44/58 (75.9%) having previously undergone either one or two tests[1].

The average number of years between probands' initial recruitment into the DDD-Africa parent study and result feedback consultations were 3.4 (± 1.3) years with 4/58 (6.9%) probands demising during this period. For the families recruited in JHB, the average time from probands' earliest recorded genetic clinic consultation to the WES result feedback consultation was 6.5 (±

[1]Genetic tests included karyotyping, multiplex ligation-dependent probe amplification (MLPA), testing for fragile X syndrome (FRAX) and array comparative genomic hybridisation (array-CGH). Other genetic tests were performed such as quantitative fluorescent-polymerase chain reaction (QF-PCR), fluorescence *in situ* hybridization (FISH), methylation-specific MLPA (MS-MLPA), single gene testing and NGS panels.

2.8) years. However, this information was not available for families from other recruitment sites, including PTA and DBN.

Table 2 Demographic characteristics of probands whose families received WES results

Probands (N = 58) **Median (IQR) or n (%) or mean (± SD)**		**Probands (N = 58)** **Median (IQR) or n (%) or mean (± SD)**	
Males	30 (51.7)	**Mortality**	
Females	28 (48.3)	Alive	54 (93.1)
Family type recruited		Deceased	4 (6.9)
Trio	34 (58.6)	**Genetics clinic history**	
Duo	18 (31.1)	Age at first recorded consultation at genetics clinic (years)	3 (1-5.75)**
Extended	6 (10.3)	Age at DDD-Africa recruitment (years)	5.5 (3-8)
Inheritance pattern		Age of child at DDD-Africa feedback (years)	9 (7-12)
Autosomal dominant *de novo*	27 (46.6)	Years between recruitment and feedback	3.4 (± 1.3)
Autosomal recessive	13 (22.4)	Years between first recorded genetics clinic consultation and feedback	6.5 (± 2.8)**
X-linked	8 (13.8)	**Referrals and cascade testing offered post result feedback consultation**	
Unknown	10 (17.2)*	Referrals only	35 (60.4)
Proband resides with		Cascade testing only	6 (10.3)
Both parents	37 (63.8)	Both	9 (15.5)
Single parent	21 (36.2)	Neither	8 (13.8)
Previous genetic tests[1]			
Three or more	10 (17.2)		
Two	26 (44.8)		
One	18 (31.1)		
None	4 (6.9)		

DDD-Africa: Deciphering Developmental Disorders in Africa; IQR: Interquartile range; SD: Standard deviation
* Could not confirm *de novo* inheritance as the family was recruited as a duo.
** Data only available for the 42 families who attended feedback consultations in academic hospitals across JHB due to access to electronic clinical records on REDCap.

Categorical survey item analysis

Likert and ordinal scale responses

Regarding the Likert scale responses, some caregivers did not rate statements that they deemed irrelevant to their circumstances. As such, some statements only had responses from 62 or 63 caregivers for analysis, see Supplementary Table 3. As seen in Fig. 2, 61/64 (95.3%) caregivers agreed or strongly agreed that results would help them gain knowledge and an understanding of their child's condition. A further 61/63 (96.8%) of caregivers agreed or strongly agreed that results would aid in anticipating any additional health problems. Additionally, 59/64 (92.2%) caregivers believed results would benefit their family members. Conversely, responses to the statement that WES results would influence reproductive choices and decisions on having future children showed lower levels of agreement with 33/64 (51.6%) caregivers agreeing or strongly agreeing, see Fig. 2 and Supplementary Table 3.

For the ordinal scale, caregivers who ranked the six statements equally were excluded as their responses would skew findings, leaving 62 caregiver responses for analysis, see Fig. 3 and Supplementary Table 4. As seen in Fig. 3, these responses were similar to the Likert scale. 19/62 (30.6%) caregivers ranked having a better understanding of their child's condition and any future health problems and 18/62 (29.0%) ranked understanding the cause of their child's

condition (as their most important motivator for pursuing WES. Additionally, in keeping with Likert scale responses, 4/62 (6.5%) caregivers ranked having accurate information about whether this could happen again with another child as the most important motivator.

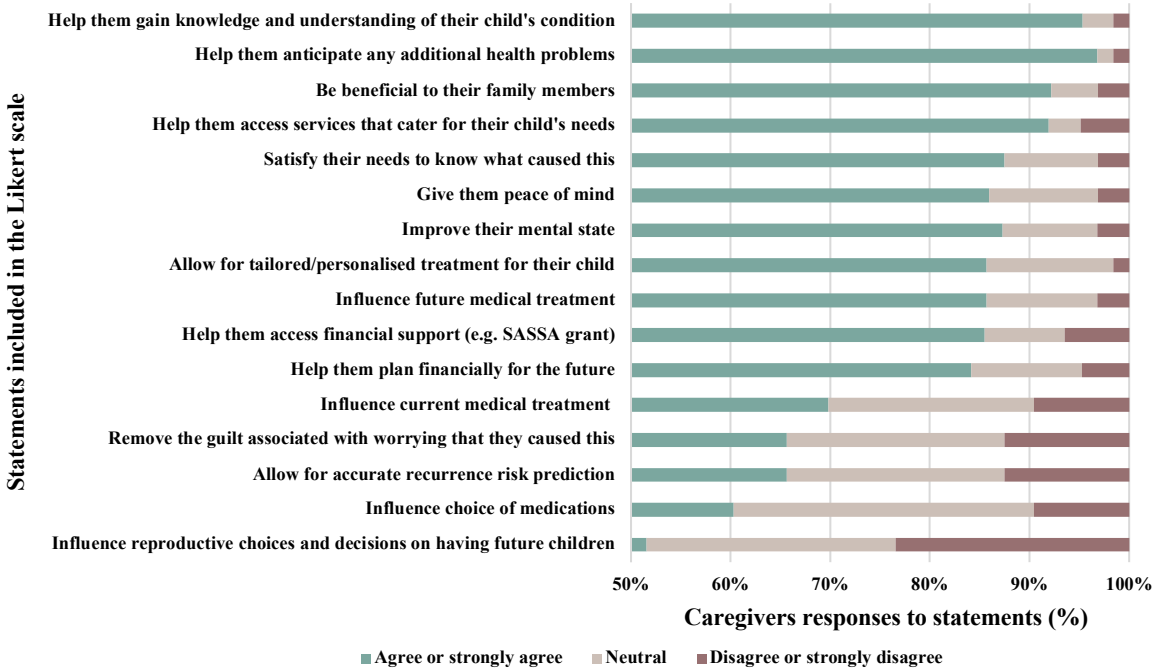


Fig. 2 100% stacked bar chart representing what caregivers expected from WES results

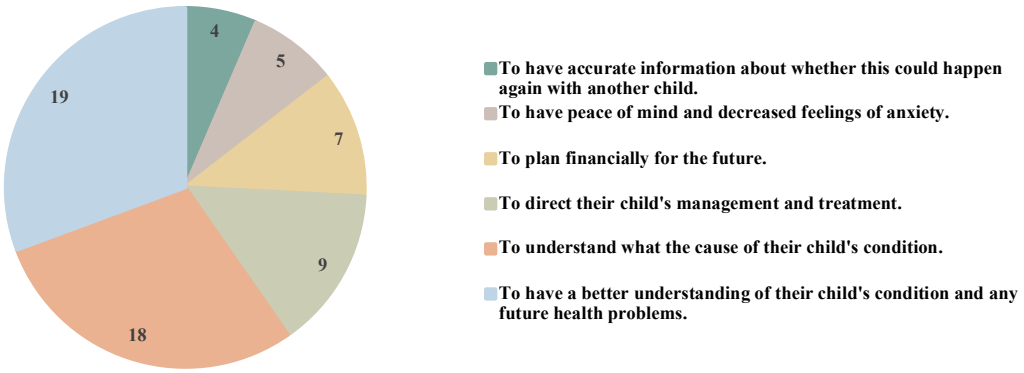


Fig. 3 Pie chart illustrating why caregivers most wanted a confirmed diagnosis for their child

Quantitative content analysis

Codebook application to the textual dataset

A total of 38 codes were applied across six categories, including the importance of confirming a diagnosis, emotional impacts of a diagnosis, need for support, the diagnostic odyssey, changes to familial relationships and impact on family planning. 182 individual codes were applied to short-text responses and 370 to consultation summary letters and electronic clinic notes. During the quantitative content analysis, an additional category, the genetic counsellor agenda, was added for topics typically covered in a genetic counselling consultation. These topics were discussed on an *ad hoc* basis by the attending genetic counsellor emerging in 23/58 (39.7%)

result feedback consultations. These topics included discussions around future pregnancies, prenatal testing options and/or advanced maternal age with its associated risks for common chromosomal aneuploidies.

Short-text questionnaire responses

Short-text responses from researcher-administered questionnaires were analysed to determine caregivers' expected personal and clinical utility prior to receiving WES results. As seen in Fig. 4 and Supplementary Table 5, 53/62 (85.5%) caregivers expected results to provide a label for their child's condition and 47/62 (75.8%) expected to gain knowledge of the future trajectory of their child's condition. This re-emphasises the results from the Likert and ordinal scale responses observed in the categorical survey items. 13/62 (21.0%) caregivers anticipated that receiving WES results would promote sharing the genetic diagnosis with others, which extended to healthcare professionals. This was further illustrated by the lack of practitioner knowledge that was expressed by 12/62 (19.4%) caregivers. Regarding anticipated emotional impacts of WES results, 10/62 (16.1%) caregivers felt that receiving a result would provide relief and closure. Additionally, 8/62 (12.9%) caregivers had mentioned accepting their child's condition prior to receiving a WES result. Others had an altruistic attitude as 7/62 (11.3%) caregivers felt that knowledge of such conditions would help other families with similarly presenting children.

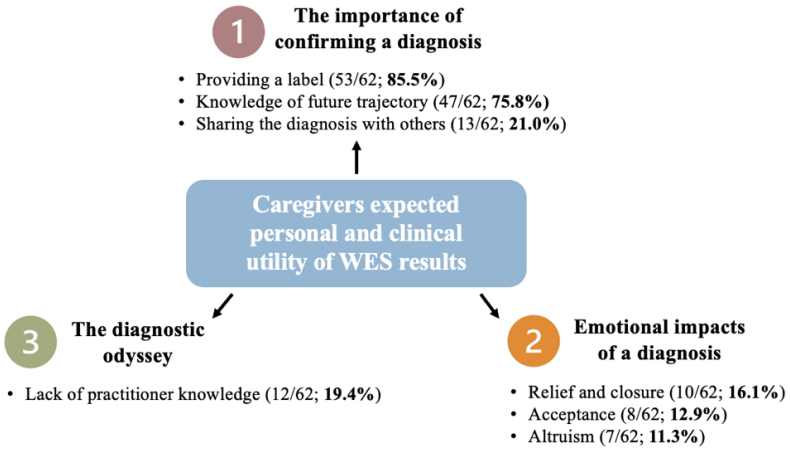


Fig. 4 Cluster diagram representing the main codes applied regarding caregivers expected personal and clinical utility of WES results prior to result feedback

Consultation summary letters and electronic clinic records

All codes included in the codebook were applied, along with two additional codes that emerged during the quantitative content analysis. These included instances where caregivers felt overwhelmed and emotional during the feedback of results as well as how they made sense of the condition or circumstances prior to receiving WES results. As seen in Supplementary Table

6, the most frequently applied codes related to the importance of confirming a diagnosis, particularly when results provided a label, which was noted in 29/58 (50.0%) result feedback consultations. Emotional impacts of a diagnosis were also prominent, with 26/58 (44.8%) caregivers expressing relief and closure, 22/58 (37.9%) feeling overwhelmed or emotional and 20/58 (34.5%) experiencing grief or a loss of hope. Additionally, the parental burden was identified in 22/58 (37.9%) result feedback consultations. The least commonly applied codes included psychological support, altruism, and preferences regarding termination of pregnancy or prenatal genetic testing, each of which emerged in only 2/58 (3.4%) consultation summary letters or electronic clinic records.

Upon further analysis of the five most frequently applied codes to the consultation summary leters and electronic records, a heat map was generated using MAXQDA to determine if these codes overlapped within families. This heat map utilises a colour gradient to indicate correlations between codes; red shades indicate higher values with correlations of greater significance and blue shades indicate lower values with less significance. As seen in Fig. 5, the caregivers in 17/58 (29.3%) families who reported feeling overwhelmed and emotional during the result feedback consultation were also those who vocalised their parental burden. Additionally, caregivers in 15/58 (25.9%) families who valued receiving a result as it provided a label, also felt that a result provided relief and closure.

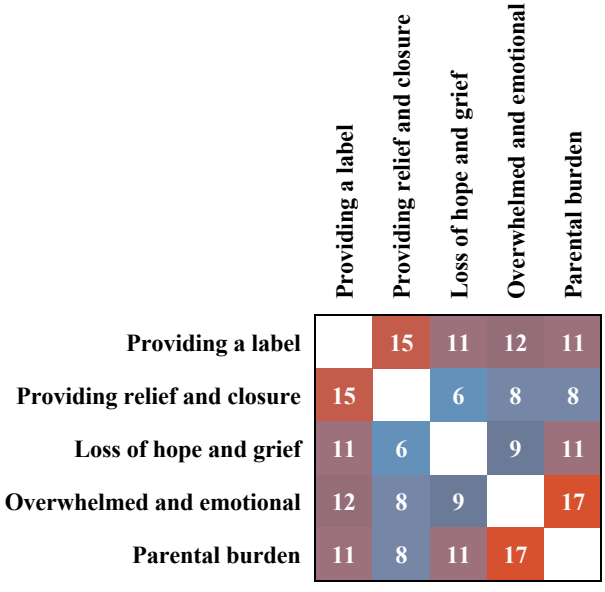


Fig. 5 Heat map illustrating the overlap between the top five applied codes to consultation summary notes
Red represents stronger correlations and blue illustrating weaker correlations (figure adapted from MAXQDA).

Discussion

There were notable differences in parental attendance at result feedback consultations, with the majority of the caregiver cohort comprising mothers. While some couples attended the

consultations together, more than half of the mothers attended alone. In a South African context, caregiving responsibility for children including those with disabilities typically rests exclusively on mothers, while fathers tend to adopt roles with a greater focus on financial stability (Mbanjwa and Harvey, 2023). Additionally, it has been noted that fathers are more likely to neglect their paternal roles if their child is disabled, contributing to an increasing prevalence of single motherhood (Mbanjwa & Harvey, 2023). Krabbenborg *et al*. (2016) further emphasised that parents of children with rare diseases are confronted with a great burden of care. This encompasses many duties such as administrative tasks, obtaining equipment and resources and nursing disabled children. Consequently, some parents, mostly mothers, resign from their jobs or decide to work fewer hours to care for their children.

In a study exploring the psychosocial impacts of mitochondrial disease among children in Austria, Heath *et al.* (2024) reported higher levels of marital strain as caregiving responsibilities took precedence over the parent's relationship. The parental burden experienced is multifaceted and influenced by several factors, including marital support and strain, the number of affected children and income. Financial distress is often exacerbated when one or both parents are unable to maintain fulltime employment due to the demands of caring for their child (Robertson *et al.*, 2024). In some cases, receiving a diagnosis can improve access to support, including , but not limited to, financial support from the government (Pavisich *et al*., 2024; Robertson et al., 2024). In South Africa, families may be eligible for various government issued-grants to alleviate some of this financial burden (https://www.gov.za/faq/government-services/how-do-i-apply-social-grant). However, when parents are unemployed, these grants are frequently insufficient to cover both medical and household needs (Magidigidi *et al*., 2023). Beyond financial challenges, having a child with a DD, can also affect caregivers physically and psychologically (Jeffrey *et al.*, 2021).

Receiving a returnable WES result marks the end of the diagnostic odyssey for many families. However, delays in receiving a genetic diagnosis may dilute its psychological impact (Jeffrey *et al.*, 2021). In this sub-study, several families experienced lengthy diagnostic journeys, with an average of 3.4 (± 1.3) years between initial recruitment and result feedback consultations. For those known to clinical genetics services in JHB, the average time between the proband's earliest recorded genetics clinic consultation and receiving WES research results was 6.5 (± 2.8) years. Delayed diagnoses are a well-described theme of the diagnostic odyssey, often attributed to limited access to testing, lack of practitioner knowledge and prolonged waiting times (Pavisich *et al.* 2024). For comparison, a Canadian study conducted in a hospital-based

paediatric genetics clinic reported an average diagnostic period of 2.5 years, involving an average of 5.4 visits or tests per child (Michaels-Igbokwe *et al.*, 2021). The findings of this sub-study are comparable to literature, as it has been previously suggested that the diagnostic odyssey spans from one to eight years (Michaels-Igbokwe *et al.*, 2021). In South Africa, a low-middle-income country, individuals affected by rare diseases often experience extended diagnostic odysseys lasting five years or more (Malherbe, 2023). This is exacerbated by limited access to treatments, management, multi-disciplinary care, as well as access to affordable healthcare services. For most of these families, genetics is not the only clinic that probands attend as they require on-going access to multiple medical specialists, making this process time- and cost-intensive (Zurynski *et al.*, 2017).

In South Africa, WES is not yet offered routinely as a diagnostic test and is currently available only through research studies (Van Der Merwe *et al*., 2022). Consequently, other genetic tests are often utilised in pursuit of elucidating a genetic cause, yielding negative results. This was evident in this sub-study cohort where almost all probands had previously undergone at least one genetic test and some had undergone three or more previous genetic tests. This consumes valuable time and resources while prolonging the diagnostic odyssey and leaving families without a diagnosis (Miller, 2021). This can adversely impact children affected by DDs and their families as valuable opportunities are missed such as possible therapy or prenatal testing for parents with multiple affected children. Notably, as years taken to receive a diagnosis increases, the personal utility lessens. Additionally, personal utility may be diminished through caregivers' previous experiences of guilt and trauma surrounding their child's health as well as coping with limited information (Jeffrey *et al.*, 2021). Lessened personal utility is further emphasised in cases where probands demised prior to WES results being returned to their families.

27/58 (46.6%) returnable results included *de novo* autosomal dominant variants. Caregivers commonly experience relief and comfort upon learning that the condition was not inherited (Jeffrey *et al.*, 2021). In such cases, results have potential to help parents accept their child's condition and alleviate guilt or self-blame (Diedericks *et al*., 2024). While this may offer reassurance to parents, some who may have already decided to not have more children might regret their decisions after receiving such results (Rosell *et al.*, 2016). This highlights the importance of a timely diagnosis to support informed reproductive decision-making. In contrast, when a child's condition results from inherited variants, autosomal recessive or X-linked, caregivers may find it upsetting but may be relieved to know that it was out of their

control (Jeffrey *et al.*, 2021). As such, inherited diagnoses have previously been associated with higher levels of parental guilt, although this was not investigated in this sub-study (Copeland *et al.*, 2021). Furthermore, inheritance not only impacts future reproductive planning of the parents of an affected child but might also be of benefit to other at-risk family members. In this sub-study cohort, some families were offered cascade testing comprising diagnostic testing for siblings of probands, if necessary, and carrier testing for at-risk family members. This aligns with the majority of caregivers believing that results would be beneficial to their family members.

A prominent theme that arose both before and after WES result disclosure was the importance of caregivers providing a label for their child's condition. Notably, in 29/58 (50%) of the result feedback consultations, caregivers emphasized the importance of finally being able to label their child's DD. These findings are similar to those from the original Deciphering Developmental Disorders (DDD) study conducted in the United Kingdom (UK). The DDD study determined that parents' main motivation for participating in the study was seeking answers for their child's health problems after many experienced complicated and lengthy searches for a diagnosis (Copeland *et al.*, 2021). Comparably, Krabbenborg et al. (2016) determined that families often engage in knowledge seeking behaviour pertaining to their child's condition and prognosis. In a South Africa context, research on parental perspectives regarding genomic research results for neurodevelopmental disorders showed that parents hoped the results would aid in their child's management and provide diagnostic closure (Diedericks *et al*., 2024). These efforts reflect the ongoing care duties of parents and concerns for their child's long-term health and any future support needs (Miller *et al.*, 2023). These challenges are further compounded in families with multiple affected children, a lived experience for some caregivers in this sub-study. In such cases, caregiving demands are intensified, often increasing exhaustion and isolation as well as reducing social and community participation (Thompson-Hodgetts *et al.* 2024).

Additionally, just over half of the participating caregivers indicated that WES results would influence their reproductive choices and decision-making choices. However, only a minority of caregivers ranked recurrence risk information as their most important motivator for pursuing WES through the parent DDD-Africa study. Similarly, only a few families had preferences for prenatal genetic testing and termination of pregnancy. Despite this, previous research conducted by Rosell *et al*. (2016) found that parents sought information regarding the cause of their child's DD to inform future reproductive planning. This also aligns with findings from South African

research, which highlights that parents valued genetic results for their potential to inform personal reproductive potential (Diedericks *et al*., 2024). The absence of a diagnosis in a child with a DD can complicate reproductive decision-making due to unknown recurrence risks and fears of having additional children with similar conditions (Pond and Dimond, 2018). These decisions are complex and are often affected by many factors including maternal age, physical capabilities and financial resources (Pond and Dimond, 2018). In this sub-study cohort, the median parental ages at the time of result feedback were 40 years for mothers, classified as advanced maternal age, and 44 years for fathers. These parental ages likely influenced parental perspectives on future reproductive choices. In contrast, Heath *et al*. (2024) found that half of the parents in their Austrian cohort experienced a shift in family planning desires following a diagnosis of mitochondrial disease. As such, two thirds of parents indicated that they would pursue prenatal genetic diagnosis in future pregnancies, and most reported that they would consider a termination of pregnancy if a pregnancy was confirmed to be affected (Heath *et al*., 2024).

The importance of receiving a result that provides a label, alongside feelings of relief and closure, was emphasised in several families in this sub-study cohort. Similarly, Jeffrey *et al*., (2021) found that caregivers often viewed a diagnosis as validating, providing knowledge of the condition's future trajectory, instilling hope and enabling parents to relate to others. Receiving a diagnosis is frequently an emotionally charged experience with many caregivers feeling relieved to end their search for a diagnosis (Mollison *et al.*, 2020; Alam *et al.*, 2022). Relief may be immediate as a diagnosis helps to clarify expectations for the future (Heath *et al.*, 2024). However, some families expressed mixed emotions, feeling relief and closure with grief and a loss of hope. This highlights that emotional responses to a diagnosis are not mutually exclusive and can elicit varied emotions.

For some caregivers, grief and a loss of hope may stem from the loss of hope for a cure or medical treatments to improve health outcomes (Alam *et al.*, 2022). Additionally, a study by Nevin *et al*. (2022) exploring the psychosocial impact of genetic testing in children with developmental and epileptic encephalopathies found that parents described experiencing a psychological toll. This stemmed from the dual stress of managing their child's medical needs while also making sense of complex genetic information and associated implications. Thus, the role of genetic counsellors in disseminating the results of genomic testing is vital as they are trained to deliver difficult news sensitively while offering psychosocial support to families

(Waxler *et al.*, 2013). Notably, the WES result feedback in the DDD-Africa parent study is provided by qualified genetic counsellors.

Some families expressed feeling emotional or overwhelmed when sharing experiences of their parental burden at result feedback consultations. This highlights the importance of ensuring that parents are emotionally prepared for the potential outcomes of genetic testing when obtaining informed consent (Rosell *et al.*, 2016). Thus, recognising the potential psychological trauma associated with parental experiences and providing tailored psychological support that includes psychoeducation on managing uncertainty may help parents process and emotionally prepare for the implications of a genetic diagnosis. (Nevin *et al*., 2022). Furthermore, the diagnostic odyssey has previously been described as an emotional rollercoaster for caregivers, and for many, the search for a diagnosis ends when a diagnosis is received (Heath *et al.*, 2024). This can be overwhelming for caregivers; however, the ongoing demands placed on caregivers also contribute to this emotional toll. Parents often navigate multiple roles and care duties, are an expert on their child's management and care, advocate for their child and communicate complex information to others, which has been reported as mentally and emotionally exhausting (Pavisich *et al*., 2024).

Limitations

The findings of this study are limited by some practical considerations. Firstly, this sub-study focused on positive WES research result deliveries from the DDD-Africa parent study and excluded a significant point of view from participants with negative results. Additionally, access to proband demographic data was limited due to paper-based records and some data was only available for families that were recruited and received feedback in JHB. Regarding pre-result questionnaire responses and result feedback consultation attendance, most of the attendees were mothers, which may have introduced bias into the findings of this study. All questionnaires and some result feedback consultations were conducted in English, which is not the home language of the majority of the participating families. Therefore, there is room for lack of understanding and a subsequent inability for caregivers to participate effectively or respond optimally. Finally, a qualitative study conducting in-person in-depth interviews with caregivers could have potentially been more effective in elucidating caregivers' expected utility of WES results. As this study was conducted retrospectively, the genetic counselling student and her supervisors were limited to the data that was available through the DDD-Africa parent study and the DDD-Africa sub-study conducted by Shingwenyana *et al*.

Future studies and considerations

This study is the first phase of a two-part DDD-Africa sub-study (Shingwenyana *et al*.). The second phase includes following up with these families after a minimum of six months post-result feedback. Through semi-structured interviews with the caregivers who received results in this study, the perceived personal and clinical utility of receiving results through the DDD-Africa parent study and caregivers' recollection and emotions regarding the results will be determined. This second phase also aims to determine to what extent WES results improve health outcomes of children with DDs and their caregiver's physical and psychological wellbeing as well as any additional benefits. Additional qualitative research could also explore caregivers' experiences of the diagnostic odyssey pre- and post-receiving a genetic diagnosis, specifically in the context of South Africa. The diagnostic odyssey does not necessarily end with a diagnosis (Rosell *et al.*, 2016). Even though the diagnostic odyssey and search for a diagnosis ended for some families in this study, there were additional referrals to other healthcare professionals and medical specialists for assessments and management made during the WES result feedback consultation. Therefore, in some instances, the ending of the diagnostic odyssey is the beginning of a new therapeutic journey (Mollison *et al.*, 2020).

Conclusion

This DDD-Africa sub-study highlights caregivers' expectations of receiving a confirmed diagnosis through returnable WES research results as well as the immediate psychosocial impact of receiving such results. Differences in caregiver attendance during result feedback consultations, where mothers attended more frequently than fathers, reflect broader societal caregiving norms in South Africa with children often remaining in care of their mothers. As a result, some parents, mainly mothers, are unable to work full-time or at all, often exacerbating financial strain and intensifying the parental burden of caring for a child with special needs. The diagnostic odyssey experienced by these families further contribute to this burden as caregivers are required to navigate multiple roles and care duties. This underscores the necessity of timely genetic testing, particularly in light of missed opportunities and the reported lack of practitioner knowledge. For many caregivers, the most important motivator for pursuing WES was to understand their child's condition, help them anticipate additional health issues and determine the underlying cause of the DD. The majority of caregivers also recognised the benefit of a diagnosis for their family, with some families being offered cascade testing post result feedback consultations. However, WES results were unlikely to influence reproductive decisions of many caregivers, potentially due to advanced parental age at the time of receiving a diagnosis or the length of the diagnostic odyssey. While a confirmed diagnosis brought a

sense of relief and closure to many caregivers, others reported feeling overwhelmed, emotional, or experienced grief and a loss of hope. These findings emphasise the psychosocial and emotional implications of ending the diagnostic odyssey as well as highlight the importance of genetic counselling in preparing families for receiving a confirmed diagnosis through WES.

List of abbreviations

Array-CGH: array comparative genomic hybridisation; DDD: Deciphering Developmental Disorders; DDD-Africa: Deciphering Developmental Disorders in Africa; DDs: developmental disorders; DNA: deoxyribose nucleic acid; DBN: Durban; FISH: fluorescence *in situ* hybridization; FRAX: fragile X syndrome; H3Africa: Human Heredity and Health in Africa; HPO: Human Phenotype Ontology; ID: intellectual disability; IQR: interquartile range; JHB: Johannesburg; MLPA: multiplex ligation-dependent probe amplification; MS-MLPA: methylation-specific multiplex ligation-dependent probe amplification; NGS: next-generation sequencing; PTA: Pretoria; QF-PCR: quantitative fluorescent-polymerase chain reaction; REDCap: Research Electronic Data Capture; SD: standard deviation; SNVs: single nucleotide variants; SOP: standard operating procedure; UK: United Kingdom; WES: whole-exome sequencing

Declarations

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand as a sub-study of DDD-Africa (Ethics Clearance Number: M240760) as a sub-study of both the DDD-Africa parent study (Ethics Clearance Number: M230567) and a DDD-Africa sub-study conducted by Shingwenyana *et al*. (M220125).

Consent for publication

Not applicable.

Availability of data and materials

All data analysed during this study is included in this published article and in its supplementary material.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors and collaborators contributed. The principal investigators of the DDD-Africa parent study (ZL, AK and NC) and DDD-Africa study co-ordinator (NL) approved the research that was conducted. BS, MA, EG and BR conceived and created the questionnaire used in the DDD-Africa sub-study, "*Caregivers' expected and perceived utility of whole-exome sequencing results for children with developmental disorders*' (Shingwenyana *et al*.; Ethics Certificate Number: M220125). As part of the larger DDD-Africa parent study, IS, SS, MA and EG facilitated the researcher-administered questionnaires and ZG, BS and JT conducted result feedback consultations as DDD-affiliated genetic counsellors. For this sub-study, SS performed the data collection and subsequent analysis with assistance from BS, ZG, MA, EG and BR for the codebook development and the identification and discussion of the literature-informed codebook (BS and ZG). SS wrote the manuscript, reviewed and approved by BS and ZG. The genetic counselling student (SS), her supervisor (BS) and co-supervisor (ZG) read and approved the final manuscript.

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References

Alam, A. *et al.* (2022) 'Targeted Whole Exome Sequencing in Children With Early-Onset Epilepsy: Parent Experiences', *Journal of Child Neurology*, 37(10–11), pp. 840–850. Available at: https://doi.org/10.1177/08830738221113901.

Bauskis, A. *et al.* (2022) 'The diagnostic odyssey: insights from parents of children living with an undiagnosed condition', *Orphanet Journal of Rare Diseases*, 17(1). Available at: https://doi.org/10.1186/s13023-022-02358-x.

Blesson, A. and Cohen, J.S. (2020) 'Genetic counseling in neurodevelopmental disorders', *Cold Spring Harbor Perspectives in Medicine*, 10(4). Available at: https://doi.org/10.1101/cshperspect.a036533.

Brown, K.A., Parikh, S. and Patel, D.R. (2020) 'Understanding basic concepts of developmental diagnosis in children', *Translational Pediatrics*, pp. S9–S22. Available at: https://doi.org/10.21037/TP.2019.11.04.

Coe, K. and Scacco, J.M. (2017) 'Content Analysis, Quantitative', in *The International Encyclopedia of Communication Research Methods*, pp. 1–11. Available at: https://doi.org/10.1002/9781118901731.iecrm0045.

Copeland, H. *et al.* (2021) 'Systematic assessment of outcomes following a genetic diagnosis identified through a large-scale research study into developmental disorders', *Genetics in Medicine*, 23(6), pp. 1058–1064. Available at: https://doi.org/10.1038/s41436-021-01110-3.

Diedericks, A., Bruwer, Z., Laing, N. *et al*. (2024) 'Parental perspectives regarding the return of genomic research results in neurodevelopmental disorders in South Africa: anticipated impact and preferences.' *Journal of Community Genetics*, 15, pp. 539–548. Available at: https://doi.org/10.1007/s12687-024-00723-w.

Harris, P.A. *et al.* (2009) 'Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support', *Journal of Biomedical Informatics*, 42(2), pp. 377–381. Available at: https://doi.org/10.1016/j.jbi.2008.08.010.

Heath, O. *et al.* (2024) 'Ending an Odyssey? The Psychosocial Experiences of Parents after the Genetic Diagnosis of a Mitochondrial Disease in Children', *Journal of Personalized Medicine*, 14(5). Available at: https://doi.org/10.3390/jpm14050523.

Jeffrey, J.S. *et al.* (2021) 'Developmental and epileptic encephalopathy: Personal utility of a genetic diagnosis for families', *Epilepsia Open*, 6(1), pp. 149–159. Available at: https://doi.org/10.1002/epi4.12458.

Krabbenborg, L. *et al.* (2016) 'Understanding the Psychosocial Effects of WES Test Results on Parents of Children with Rare Diseases', *Journal of Genetic Counseling*, 25(6), pp. 1207–1214. Available at: https://doi.org/10.1007/s10897-016-9958-5.

Langenfeld, A., Schema, L. and Eckerle, J.K. (2021) 'Genetic developmental disability diagnosed in adulthood: a case report', *Journal of Medical Case Reports*, 15(1). Available at: https://doi.org/10.1186/s13256-020-02590-8.

Magidigidi, L., Roman, N. V and Sonn, I.K. (2023) 'Human capabilities of South African parents who have children with developmental disabilities', *African Journal of Disability* [Preprint]. Available at: https://doi.org/10.4102/ajod.

Makela, N.L. *et al.* (2009) 'Parental perceived value of a diagnosis for Intellectual Disability (ID): A qualitative comparison of families with and without a diagnosis for their child's ID', *American Journal of Medical Genetics, Part A*, 149(11), pp. 2393–2402. Available at: https://doi.org/10.1002/ajmg.a.33050.

Malherbe, H. (2023) 'Introducing the South African Rare Diseases Access Initiative', *South African Medical Journal*, 113, pp. 1301. Available at: https://doi.org/10.1038/d41573-019-00180-y.

Mbanjwa, S. and Harvey, C. (2023) 'South African single mothers' experiences of raising a child with a disability', *African Journal of Disability* [Preprint]. Available at: https://doi.org/10.4102/ajod.

Michaels-Igbokwe, C. *et al.* (2021) '(Un)standardized testing: the diagnostic odyssey of children with rare genetic disorders in Alberta, Canada', *Genetics in Medicine*, 23. Available at: https://doi.org/10.1038/s41436.

Miller, D. (2021) 'The diagnostic odyssey: our family's story', *American journal of human genetics*, 108(2), pp. 217–218. Available at: https://doi.org/10.1016/j.ajhg.2021.01.003.

Miller, I.M. *et al.* (2023) 'Continuing a search for a diagnosis: the impact of adolescence and family dynamics', *Orphanet Journal of Rare Diseases*, 18(1). Available at: https://doi.org/10.1186/s13023-022-02598-x.

Mollison, L. *et al.* (2020) 'Parents' perceptions of personal utility of exome sequencing results', *Genetics in Medicine*, 22(4), pp. 752–757. Available at: https://doi.org/10.1038/s41436-019-0730-8.

Nevin, S.M., *et al*. (2022) 'Psychosocial impact of genetic testing on parents of children with developmental and epileptic encephalopathy.' *Developmental Medicine & Child Neurology*, 64, pp. 95-104. https://doi.org/10.1111/dmcn.14971

Pavisich, K., Jones, H. and Baynam, G. (2024) 'The diagnostic odyssey for children living with a rare disease – Caregiver and patient perspectives: A narrative review with recommendations', *Rare*, 2. Available at: https://doi.org/10.1016/j.rare.2024.100022.

Pond, E. and Dimond, R. (2018) 'Reproductive decision making: interviews with mothers of children with undiagnosed developmental delay', *Journal of Community Genetics*, 9(3), pp. 315–325. Available at: https://doi.org/10.1007/s12687-017-0354-0.

Robertson, E.G. *et al.* (2024) 'Psychological wellbeing among parents of a child living with a serious chronic illness: A cross-sectional survey study', *Journal of Child Health Care* [Preprint]. Available at: https://doi.org/10.1177/13674935241238485.

Rosell, A.M.C. *et al.* (2016) 'Not the End of the Odyssey: Parental Perceptions of Whole Exome Sequencing (WES) in Pediatric Undiagnosed Disorders', *Journal of Genetic Counseling*, 25(5), pp. 1019–1031. Available at: https://doi.org/10.1007/s10897-016-9933-1.

Thompson-Hodgetts, S. *et al.* (2024) "It makes me a better person": The unique experiences of parenting multiple children who experience neurodevelopmental disability', *Research in Developmental Disabilities*, 147. Available at: https://doi.org/10.1016/j.ridd.2024.104697.

Van Der Merwe, N., Ramesar, R. and De Vries, J. (2022) 'Whole Exome Sequencing in South Africa: Stakeholder Views on Return of Individual Research Results and Incidental Findings', *Frontiers in Genetics*, 13. Available at: https://doi.org/10.3389/fgene.2022.864822.

Vorstman, J.A.S. and Ophoff, R.A. (2013) 'Genetic causes of developmental disorders', *Current Opinion in Neurology*, pp. 128–136. Available at: https://doi.org/10.1097/WCO.0b013e32835f1a30.

Waxler, J.L. *et al.* (2013) 'Hearing from parents: The impact of receiving the diagnosis of Williams syndrome in their child', *American Journal of Medical Genetics, Part A*, 161(3), pp. 534–541. Available at: https://doi.org/10.1002/ajmg.a.35789.

Wiener, E.K., *et al*. (2023) Retrospective file review shows limited genetic services fail most patients – an argument for the implementation of exome sequencing as a first-tier test in resource-constrained settings, *Orphanet Journal or Rare Diseases*, 18. Available at: https://doi.org/10.1186/s13023-023-02642-4.

Xiang, J. *et al.* (2021) 'Genetic Analysis of Children With Unexplained Developmental Delay and/or Intellectual Disability by Whole-Exome Sequencing', *Frontiers in Genetics*, 12. Available at: https://doi.org/10.3389/fgene.2021.738561.

Zurynski, Y. *et al.* (2017) 'Australian children living with rare diseases: experiences of diagnosis and perceived consequences of diagnostic delays', *Orphanet Journal of Rare Diseases*, 12(1). Available at: https://doi.org/10.1186/s13023-017-0622-4.

Electronic References

H3Africa Research Project. 2023. Deciphering Developmental Disorders in Africa (DDD-Africa) – Evaluating Clinical Exome Sequencing in an African Setting. Available at: https://h3africa.org/index.php/ddd-africa/. Accessed: September 2024.

National Library of Medicine. 2024. PubMed. Available at: https://pubmed.ncbi.nlm.nih.gov/. Accessed: June 2024.

South African Government. 2024. Government Services: How do I apply for a social grant? https://www.gov.za/faq/government-services/how-do-i-apply-social-grant. Accessed: December 2024.

Zoom Communications, Inc. (n. d.). Zoom. Available at: https://www.zoom.com/

Supplementary Material

Supplementary Table 1 Codebook pertaining to the diagnostic odyssey and the psychosocial impact of receiving returnable WES results that was applied to short-text questionnaire response and consultation summary letter and electronic record analysis

The importance of confirming a diagnosis		
D1	Providing a label	Better understanding of the nature of the condition, inheritance pattern and recurrence risk
D2	Sharing the diagnosis with others	Providing a platform for parents to share, explain and discuss their child's condition with friends and family
D3	Knowledge of future trajectory	Guiding expectations and treatments Anticipating possible health outcomes Optimism for future treatments
D4	Validation	Confirming suspicions Legitimising the condition Result provides finality Legitimate medical diagnosis with no traditional influences/social/environment or injuries due to birth process
Emotional impacts of a diagnosis		
E1	Providing relief and closure	Receiving a diagnosis Confirming the condition was medical and not a fault of the parents Receiving a better prognosis than expected Learning the condition is *de novo* and not inherited
E2	Providing hope	For the future, research and more effective treatments
E3	Loss of hope and grief	For a "normal" child, their child's independence and autonomy
E4	Disappointment	That there is no better treatment available or cure
E5	Uncertainty, anxiety and worry	Concerned about the lack of knowledge of the condition Variable prognosis Fear of the unknown
E6	Guilt and self-blame	Surrounding their child's health Learning that the condition is inherited
E7	Acceptance	Becoming more accepting of the condition and the situation as it is (acceptance of a delayed child) Parents accepting the condition as is and have made their own meaningful sense of the cause
E8	Appreciation	A sense of gratitude for results despite no changes in treatment
E9	Public stigma	Being aware of public perceptions and judgments
E10	Altruism	Helping others who are on similar journeys through contributing to research and a better understanding of the condition
E11	Overwhelmed and emotional	Name and rarity of the condition Lack of understanding the complexity of medical and genetic information
E12	Making sense of the condition and/or circumstances	Communal and/or cultural beliefs of the origin of the condition Religious beliefs Other medical reasoning
Need for support		
S1	Parental burden	Roles as navigators, experts and advocates Mothers often expected to maintain roles as caregivers Difficulties maintaining employment or reduced employment hours Impact on overall mental health (stress, anxiety, depression, etc.)
S2	General need for support	Limited access to aids, medical equipment, in-home care and social services No respite for parents
S3	Financial support	Lack of access to financial support (financial implications of caring for a child with special needs, unable to afford out-of-pocket expenses)
S4	Psychological support	Parents seeking support for themselves
The diagnostic odyssey		
O1	Lack of management guidelines and adequate care	Parents not knowing how to effectively care for and manage their children
O2	Missed opportunities	Research studies taking too long to provide results (other affected children; family, medical treatment, prognosis)
O3	Lack of practitioner knowledge	Inability of doctors to identify the correct diagnosis Referrals to multiple specialists coupled with numerous investigations
O4	Adaptation	Creating an adaptive way forward through the diagnostic odyssey
Changes to familial relationships		
R1	Strain on marital relationship	Taking precedence of parenting role

		Investing less time and energy into the couple which results in separation/conflict
R2	Impact on unaffected siblings	Taking on a caregiver role to help parents Shifting attention towards the affected sibling
R3	The impact of extended families	Providing support and relief Creating further strain on the parents
Impact on family planning		
F1	Influences on deciding to have more children	Change in desire of having more children or not Fear and uncertainty of having another affected child Still open to having more children despite having an affected child
F2	Preference for prenatal genetic testing	Pursuing prenatal genetic diagnosis for the condition in future pregnancies
F3	Preference for termination of pregnancy	Opting for a termination of pregnancy if a future pregnancy is confirmed to be affected
F4	Concerns of passing on the condition to the next generation	For unaffected siblings/parents being carriers and passing on the condition For the affected child passing on the condition to their children
The genetic counsellor agenda		
G1	Circumstantial topics discussed by the genetic counsellor	Discussion of future pregnancies, prenatal testing and/or advanced maternal age

Supplementary Table 2 Summary of returnable WES result feedback consultations, attendance of caregivers and pre-result feedback questionnaire completion in Johannesburg, Pretoria and Durban

Location of feedback consultation	Number of feedbacks consultations (%)	Caregiver attendance (%)			Number of questionnaires completed (%)			
		Both parents	Mother only	Father only	Both parents	Mother only	Father only	One per couple
JHB	42 (72.4)	19*	21	2	10*	17	2	6
PTA	6 (10.4)	3*	3	0	3*	3	0	0
DBN	10 (17.2)	4*	6	0	0	6	0	4
Totals	**58**	**52 (61.9)**	**30 (35.7)**	**2 (2.4)**	**26 (40.6)**	**26 (40.6)**	**2 (3.2)**	**10 (15.6)**
			84			**64**		

*Multiplied by 2 as both caregivers attended the consultation and completed the pre-result feedback questionnaires.

Supplementary Table 3 Likert scale responses for 16 statements that determined what caregivers believe WES results will provide them with

Items	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree	Total
Results will influence my reproductive choices and decision on having future children	6	9	16	18	15	64
Results will influence choice of medications	0	6	19	25	13	63*
Results will allow for accurate recurrence risk prediction	2	6	14	22	20	64
Results will remove the guilt associated with worrying that I caused this	4	4	14	15	27	64
Results will influence current medical treatment	2	4	13	21	23	63*
Results will help me plan financially for the future	0	3	7	27	26	63*
Results will help me access financial support (e.g. SASSA grant)	1	3	5	25	28	62*
Results will influence future medical treatment	1	1	7	30	24	63*
Results will allow for tailored/personalised treatment for my child	1	0	8	31	23	63*
Results will improve my mental state	1	1	6	23	32	63*
Results will give me peace of mind	1	1	7	22	33	64
Results will satisfy my needs to know what caused this	1	1	6	24	32	64
Results will help me access services that cater for my child's needs	1	2	2	30	27	62*
Results will be beneficial to my family members	2	0	3	22	37	64
Results will help me anticipate any additional health problems	1	0	1	34	27	63*
Results will help me gain knowledge and understanding of my child's condition	1	0	2	18	43	64

*Caregiver/s did not respond to statement on questionnaire.

Supplementary Table 4 Ordinal scale responses ranking six from most to least important to determine why caregivers most want a confirmed diagnosis for their child

Items	1 (most important)	2	3	4	5	6 (least important)	Totals
I want a confirmed diagnosis because it will direct my child's management and treatment.	9	15	18	7	8	5	62
I want a confirmed diagnosis because it will provide me with accurate information about whether this could happen again with another child.	4	7	6	9	10	25	61*
I want a confirmed diagnosis so that I can understand what caused my child's condition.	18	19	6	6	9	3	61*
I want a confirmed diagnosis for peace of mind and decreased feelings of anxiety.	5	3	9	14	16	15	62
I want a confirmed diagnosis so that I have a better understanding of my child's condition and any future health problems.	19	15	15	7	4	2	62
I want a confirmed diagnosis so that I can plan financially for the future.	7	3	8	19	14	11	62
Totals	62	62	62	62	61*	61*	

*A caregiver was unable to determine which options were the two least important.

Supplementary Table 5 Distribution of codes applied to short-text questionnaire responses

	Total (n = 62) (%)
The importance of confirming diagnosis	
Providing a label	53 (85.4)
Sharing the diagnosis with others	13 (21.0)
Knowledge of future trajectory	47 (75.8)
Validation	1 (1.6)
Emotional impacts of a diagnosis	
Providing relief and closure	6 (9.7)
Providing hope	10 (16.1)
Uncertainty, anxiety and worry	1 (1.6)
Acceptance	8 (12.9)
Altruism	7 (11.3)
Need for support	
Parental burden	4 (6.5)
General need for support	5 (8.1)
The diagnostic odyssey	
Missed opportunities	1 (1.6)
Lack of practitioner knowledge	12 (19.4)
Adaptation	2 (3.2)
Changes to familial relationships	
Impact on unaffected siblings	3 (4.8)
The impact of extended families	3 (4.8)
Impact on family planning	
Influences on deciding to have more children	3 (4.8)
Preference for prenatal genetic testing	1 (1.6)
Concerns of passing on condition to the next generation	2 (3.2)

Supplementary Table 6 Distribution of all codes applied to consultation summary letter and electronic record analysis as a whole (frequency) and per location

	Frequency (n = 58) (%)	JHB (n = 42) (%)	PTA (n = 6) (%)	DBN (n = 10) (%)
Providing a label	29 (50.0)	22 (52.4)	3 (50.0)	4 (40.0)
Providing relief and closure	26 (44.8)	21 (50.0)	4 (66.7)	1 (10.0)
Parental burden	22 (37.9)	15 (35.7)	3 (50.0)	4 (40.0)
Overwhelmed and emotional	22 (37.9)	15 (35.7)	4 (66.7)	3 (30.0)
Loss of hope and grief	20 (34.4)	15 (35.7)	1 (16.7)	4 (40.0)
Impact of extended families	18 (31.0)	10 (23.8)	3 (50.0)	5 (50.0)
Knowledge of future trajectory	17 (29.3)	14 (33.3)	2 (33.3)	1 (10.0)
Appreciation and gratitude	17 (29.3)	14 (33.3)	2 (33.3)	1 (10.0)
Acceptance	15 (25.8)	13 (30.1)	1 (16.7)	1 (10.0)
Strain on marital relationship	15 (25.8)	9 (21.4)	2 (33.3)	4 (40.0)
Lack of practitioner knowledge	12 (20.7)	10 (23.8)	1 (16.7)	1 (10.0)
Concerns of passing the condition on to the next generation	11 (19.0)	10 (23.8)	1 (16.7)	0 (0)
Making sense of the condition and/or circumstances	11 (19.0)	8 (19.8)	1 (16.7)	2 (20.0)
Influence on deciding to have more children	11 (19.0)	7 (16.7)	2 (33.3)	2 (20.0)
General need for support	10 (17.2)	7 (16.7)	0 (0)	3 (30.0)
Guilt and self-blame	10 (17.2)	7 (16.7)	1 (16.7)	2 (20.0)
Disappointment	9 (15.5)	6 (14.3)	1 (16.7)	2 (20.0)
Adaptation	8 (13.8)	7 (16.7)	0 (0)	1 (10.0)
Financial support	8 (13.8)	5 (11.9)	2 (33.3)	1 (10.0)
Impact on unaffected siblings	7 (12.1)	5 (11.9)	2 (33.3)	0 (0)
Providing hope	6 (10.3)	4 (9.5)	1 (16.7)	1 (10.0)
Lack of management guidelines and adequate care	6 (10.3)	6 (14.3)	0 (0)	0 (0)
Missed opportunities	5 (8.6)	5 (11.9)	0 (0)	0 (0)
Validation	4 (6.9)	4 (9.5)	0 (0)	0 (0)
Sharing the diagnosis with others	4 (6.9)	2 (4.8)	1 (16.7)	1 (10.0)
Uncertainty, anxiety and worry	4 (6.9)	3 (7.1)	0 (0)	1 (10.0)
Feelings associated with public stigma	3 (5.2)	2 (4.8)	1 (16.7)	0 (0)
Psychological support	2 (3.4)	2 (4.8)	0 (0)	0 (0)
Preference for termination of pregnancy	2 (3.4)	1 (2.4)	1 (16.7)	0 (0)
Altruism	2 (3.4)	1 (2.4)	1 (16.7)	0 (0)
Preference for prenatal genetic testing	2 (3.4)	2 (4.8)	0 (0)	0 (0)

Appendices

Appendix A: Adapted Survey for Demographic Data

Section 1: Demographic data regarding the patient and family.

1. What is the gender of the patient?

2. What is the age of the patient?

3. What was the age of the mother at birth?

4. What was the age of the father at birth?

5. Country of birth of the patient?
   a. South Africa
   b. Other (specify)

6. Ethnicity?
   a. Afrikaans
   b. Asian
   c. Bapedi
   d. Coloured
   e. English
   f. Indian
   g. Kikongo
   h. Lingala
   i. Ndebele
   j. Shona
   k. Sotho
   l. Swahili
   m. Swati
   n. Tshiluba
   o. Tsonga
   p. Tswana
   q. Venda
   r. Xhosa
   s. Zulu
   t. Unknown
   u. Other (specify)

7. Marital status of parents?
   a. Married or living together
   b. Never married or co-inhabited
   c. Divorced or separated
   d. Partner deceased
   e. Other

8. Who does the patient reside with?
   a. One of their parents (single-headed household)
   b. Both of their parents
   c. Other relative
   d. Other

9. Age of the patient when first seen by genetics clinic?

10. Previous genetic testing?
    a. Karyotype
    b. Multiplex ligation probe amplification (MLPA)
    c. Fragile-X (FRAX) testing
    d. Array comparative genomic hybridisation (a-CGH)
    e. Other (specify)

11. Age of the child when recruited into DDD-Africa?

12. What family type was recruited?
    a. Singleton
    b. Duo
    c. Trio
    d. Extended family with more than one affected child

13. Age of the child at the DDD-Africa WES result feedback session?

14. How many years were there between recruitment and feedback session?

Section 2: Data regarding the feedback consultations, WES result and diagnosis.

1. Who attended the feedback session?
    a. Mother
    b. Father
    c. Mother and father
    d. Other (specify)

2. Is the patient still alive?
    a. Yes
    b. No

3. What was the diagnosis?

4. What is the associated life expectancy or prognosis?

5. How was the variant inherited?
    a. Maternally
    b. Paternally
    c. One maternal copy and one paternal copy
    d. *De novo* variant

6. Were referrals made at the feedback session?
    a. Yes (specify)
    b. No, discharged from genetics clinic.

7. Were any other recommendations made to enhance the patient's quality of life?
    a. Yes (specify)
    b. No

Appendix B: Pre-Result Feedback Questionnaire

Participant ID: _____

Question 1

1.1. In your own words, tell us, what do you expect from the genomic test results of your child from DDD? What are some of the benefits?

_____
_____
_____
_____

1.2. How do you think the result will help your child, your family and managing doctors?

_____
_____
_____
_____

Question 2

Rate whether you agree or disagree that whole-exome sequencing will be able to provide you with the following:

	Strongly disagree	**Disagree**	**Neutral**	**Agree**	**Strongly agree**
Results will influence current medical treatment.					
Results will influence future medical treatment.					
Results will influence choice of medications.					
Results will allow for accurate recurrence risk prediction.					
Results will influence my reproductive choices and decision on having future children (biological caregivers to answer only).					
Results will allow for tailored/ personalised treatment for my child.					
Results will help me gain knowledge and understanding of my child's condition.					
Results will be beneficial to my family members.					
Results will improve my mental state.					
Results will satisfy my need to know what caused this.					
Results will remove the guilt associated with worrying that I caused this.					
Results will give me peace of mind.					
Results will help me plan financially for the future.					
Results will help to anticipate any additional health problems.					

Results will help me assess services that cater for my child's needs.					
Results will help me access financial support (e.g. SASSA grant).					

Question 3

Rank the following in order of importance, 1 being the most important and 6 being the least important.

Rank	Item
	I want a confirmed diagnosis because it will direct my child's management and treatment.
	I want a confirmed diagnosis because it will provide me with accurate information about whether this could happen again with another child.
	I want a confirmed diagnosis so that I can understand what caused my child's condition.
	I want a confirmed diagnosis for peace of mind and decreased feelings of anxiety.
	I want a confirmed diagnosis so that I have a better understanding of my child's condition and any future health problems.
	I want a confirmed diagnosis so that I can plan financially for the future.

Appendix C: Approved Research Protocol

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

CANDIDATE'S SURNAME:	**SCHNELL**	FIRST NAME/S:	**SAMANTHA SUSAN**	STUDENT NUMBER:	**1914985**
CURRENT QUALIFICATIONS:	**Bachelor of Science (Human Physiology, Genetics and Psychology)** **Bachelor of Health Science Honours (Human Genetics)** **Master of Science in Medicine in Genomic Medicine**				
TEL: **082 331 1486**	CELL: **082 331 1486**	E-MAIL: **sammyschnell@gmail.com**		FAX: **N/A**	
DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: **MSc (Med) Genetic Counselling**					
PART-TIME OR FULL-TIME: **Full-time**					
FIRST REGISTERED FOR THIS DEGREE:		TERM: **1**		YEAR: **2024**	
DEPARTMENT: **Division of Human Genetics, School of Pathology**					
TITLE OF PROPOSED RESEARCH: **The expected utility of whole-exome sequencing results and the psychosocial impacts of receiving a diagnosis**					
CANDIDATE'S SIGNATURE:				DATE: **23/05/2023**	
SUPERVISOR 1 (NAME & SURNAME): **Mr Barry Shingwenyana**				% Supervision: **60**	
SUPERVISOR'S QUALIFICATIONS: **Master of Science in Medicine Genetic Counselling**					
SUPERVISOR'S DEPARTMENT: **Division of Human Genetics, School of Pathology**					
SUPERVISOR'S TEL/E-MAIL/ADDRESS: **[T]: 011 489 9335/9223 | [E]:** barry.shingwenyana@nhls.ac.za **Room 4, Jack Mets Building, National Health Laboratory Services, Braamfontein**					
SUPERVISOR 2 (NAME & SURNAME): **Ms Zandisiwe Goliath**				% Supervision: **40**	
SUPERVISOR'S QUALIFICATIONS: **MSc (Med) Genetic Counselling**					
SUPERVISOR'S DEPARTMENT: **Division of Human Genetics, School of Pathology**					
SUPERVISOR'S TEL/E-MAIL/ADDRESS: **[T]: 011 489 9225/9223 | [E]:** zandisiwe.goliath@wits.ac.za **Room 149, Watkins Pitchford Building, National Health Laboratory Services, Braamfontein**					
SYNOPSIS OF RESEARCH: **See next page.**					

WITS ETHICS NOT REQUIRED: Yes No WITS ETHICS PENDING: (Yes) No WITS ETHICS APPROVED: Yes No (Circle appropriate symbol) * ***Please note the final human ethics clearance certificate or animal ethics certificate must be available prior to starting research**	IF Y SUPPLY ETHICS CLEARANCE CERTIFICATE AS ATTACHMENT AND INCLUDE ETHICS NUMBER HERE:
As supervisors, we confirm that we have read the protocol which has been submitted for assessment.	
SIGNATURE OF SUPERVISOR/S: B. SHINGWENYANA	Z.Goliath

SYNOPSIS OF RESEARCH CONTINUED

Introduction:
Developmental disorders (DDs) are a heterogenous group of conditions that alter the trajectory of childhood development. These disorders are characterised by intellectual disability and/or delays in a variety of developmental domains. Due to the clinical and genetic heterogeneity of these disorders, identifying a diagnosis remains challenging. While genetic causes account for up to 40% of cases, many patients affected with DDs remain undiagnosed and their families experience a diagnostic odyssey as a result. Whole-exome sequencing (WES) greatly increases the diagnostic yield in comparison to the recommended first-tier genetic testing, chromosomal microarray. Subsequently, the Deciphering Developmental Disorders in Africa (DDD-Africa) study recruited participants with DDs of an unknown cause and their parents and employed WES to identify plausible genetic aetiologies.

Justification for Study:
The proposed study aims to assess the expected outcomes and psychosocial impacts of WES from the perspective of caregivers. This is to determine to what extent genetic testing improves mental health and well-being of caregivers and explore their expected utility of WES results received through DDD-Africa. Additionally, the proposed study will evaluate the diagnostic odyssey experienced by these families. The diagnostic odyssey is the years-long journey towards a diagnosis experienced by many people living with rare diseases. No studies have been conducted in South Africa to assess the lived experiences of caregivers of children with DDs. Therefore, this study will provide a greater insight into patient, caregiver, and family outcomes after receiving a genetic diagnosis.

Aim:
To investigate the expected outcomes and psychosocial impacts of returnable WES results from caregivers of children with rare DDs.

Proposed Methodology:
The demographic data will be analysed descriptively. Categorical survey items include demographic data, which will be separated into numerical, binary, and nominal data. Examples include numerical data (e.g., Age of participants, etc.), binary data (e.g., Is the patient still alive?, etc.) and nominal data (e.g., Diagnosis and prognosis, etc.). Other categorical survey items include diagnostic experiences obtained from electronic clinical records and medical histories, what caregivers believe WES will provide them with and what is most important to them about receiving a diagnosis. The data mentioned above will be analysed with frequency distribution and cross-tabulation (Zurynski et al. 2017). Furthermore, the responses obtained from the questionnaire will be separated into short text answers and other categorical survey items. Short text answers will be scanned for themes and categorical survey items will be quantified. Additionally, one of the survey questions includes a Likert scale and one accounts for ordinal data (e.g., Ranking in order of importance). Additionally, consultation summary letters will be scanned to identify emerging themes and psychosocial outcomes. This “scanning” method was used by Zurynski et al. (2017) to quantitatively identify emerging themes from short text responses. The scanning of emerging themes will be independently performed by the genetic counselling student (SS) and a genetic counsellor (ZG). A deductive approach will be used, and a thematic consensus will be reached with the assistance of an additional genetic counsellor (BS).

Expected Outcome/s:
Through the data obtained from the proposed study, knowledge of the lived experiences of caregivers with children with DDs will be better understood. There will also be greater insight into the diagnostic odyssey experienced by these families, as well as caregivers’ motivations for wanting a diagnosis for their children.

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I, **Samantha Schell** (Student Number: **1914985**), am a student registered for the degree of **MSc (Med) Genetic Counselling** in the academic year **2024**.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: 

Date: **22/04/2024**

Research Proposal

The expected utility of whole-exome sequencing results and the psychosocial impacts of receiving a diagnosis

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Abstract

Developmental disorders (DDs) are a heterogenous group of conditions that alter the trajectory of childhood development. These disorders are characterised by intellectual disability and/or delays in a variety of developmental domains. Due to the clinical and genetic heterogeneity of these disorders, identifying a diagnosis remains challenging. While genetic causes account for up to 40% of cases, a large proportion of individuals affected with DDs remain undiagnosed and their families experience a prolonged diagnostic journey as a result. Whole-exome sequencing (WES) greatly increases the diagnostic yield of DDs in comparison to the recommended first-tier genetic testing, chromosomal microarray. However, approximately 60% of individuals affected with DDs remain without an identified cause. The Deciphering Developmental Disorders in Africa (DDD-Africa) study recruited patient-parent trios to undergo WES to identify the possible genetic aetiologies of DDs in affected individuals. Currently, genetic counselling feedback sessions for returnable results are ongoing. Returnable results have been identified for 55/358 (15.4%) of families, of which 36 families have received a positive research result. This study aims to analyse participant demographic data, the pre-result feedback questionnaire responses exploring caregivers' expected utility of WES testing results and the caregiver's experience of diagnostic odyssey as well as genetic counselling consultation summary letters that encompass the psychosocial impact of receiving a diagnosis of a rare disease. The impact of receiving diagnoses of rare DDs following WES remains relatively understudied in the South African context. Ultimately, this study aims to explore caregivers' expected clinical and personal utility of WES results received through the DDD-Africa study.

1. Background Literature Analysis and Critique

1.1. Introduction

Developmental disorders (DDs) are a heterogenous group of conditions that manifest in early childhood with a prevalence of 1-3% worldwide (Xiang et al. 2021). These disorders arise during embryonic and fetal development, altering the trajectory of childhood development. Phenotypically, DDs are characterised by intellectual disability (ID) and/or delays in cognitive, physical, language and social development, often presenting with dysmorphic features. In addition, different organ systems may be affected such as the brain, cardiac, skeletal and renal systems. A wide range of aetiologies have been identified with up to 40% of DDs possessing an underlying genetic cause, namely single nucleotide variants (SNVs), copy number variants (CNVs) or chromosomal abnormalities (Langenfeld, Schema, and Eckerle 2021; Vissers, Gilissen, and Veltman 2016). Additionally, some genetic causes may be epigenetic, polygenic or multifactorial in nature. Therefore, delineating the underlying cause is challenging. Other non-genetic causes include, but are not limited to, teratogenic exposures, maternal illnesses, birth complications and *in utero* infections (Radford and Firth 2019; Vissers, Gilissen, and Veltman 2016). Due to the great clinical and genetic heterogeneity of DDs, diagnosing these disorders remains challenging. Consequently, around 60% of children affected with DDs are without an identified cause (Langenfeld, Schema, and Eckerle 2021).

1.2. Molecular testing for developmental disorders

In a retrospective file audit conducted by Wiener et al. (2023), it was concluded that patients with DDs are the largest group seen by genetics clinics in Johannesburg, South Africa, with 83% of patients in 2017 presenting with nonspecific features of DDs. The diagnosis of DDs involves extensive and costly investigations, encompassing conventional clinical examinations and various genetic evaluations which in many cases, does not provide the underlying cause of DDs. As a result, many patients and their caregivers experience a diagnostic odyssey, which refers to the years-long journey towards a diagnosis experienced by many people living with rare diseases (Bauskis et al. 2022). This is largely due to a paucity of knowledge surrounding genetic conditions (Langenfeld, Schema, and Eckerle 2021). However, as knowledge expands, additional testing and re-evaluations may be beneficial for diagnoses.

The recommended first-tier genetic testing for DDs are chromosomal microarrays with an expected diagnostic yield of ~15-20% (Xiang et al. 2021). However, through the advent of next-generation sequencing (NGS) technologies, such as whole-exome sequencing (WES), massively parallel sequencing became available where a large number of genes can be

sequenced and analysed simultaneously. Compared to chromosomal microarrays, WES has shown up to a 40% increase in diagnostic yield in cases of DDs (Mollison et al. 2020). Whole-exome sequencing is not yet offered routinely as a diagnostic test in the state health sector of South Africa. In low- and middle-income countries, like South Africa, there is a lack of resources and infrastructure as well as a selected number of genetic specialist services, consisting of medical geneticists and genetic counsellors (Wiener et al. 2023). However, WES may be accessible to patients and their families through research projects, such as the Deciphering Developmental Disorders in Africa (DDD-Africa) study.

1.2.1. Deciphering Developmental Disorders in Africa

The DDD-Africa study was developed with the aim of mapping genetic aetiologies of DDs in over 500 African probands across South Africa and the Democratic Republic of the Congo. Ultimately, DDD-Africa would serve to improve diagnostic and clinical genetic services in Africa (Baine-Savanhu et al. 2023). The recruitment of participants from both sites included the enrolment of community- and hospital-based participants. The study aimed to recruit 'trios' consisting of children with DDs and both parents, where possible. Several participants had previously undergone various genetic testing and remain undiagnosed. Consequently, WES was employed to identify plausible genetic aetiologies. Following the identification of pathogenic variants and patient diagnoses, a multidisciplinary team of researchers and genetic specialists arranged the return of findings to the families.

1.2.2. Multidisciplinary approaches for developmental disorders

Children with DDs often have complex healthcare needs involving input from many paediatric services and a multidisciplinary team of healthcare professionals (Radford and Firth 2019). If a diagnosis is confirmed, patient care can be enhanced by the initiation of condition-specific surveillance while discontinuing other investigations. Additionally, patients can be referred to other medical specialists for further evaluations. However, due to the complex heterogeneity of DDs, making a diagnosis based on clinical examinations and medical history alone is difficult, as reviewed by Srivastava et al. (2019). Therefore, for rare genetic diseases, including but not limited to DDs, there has been a rapid implementation of specialist clinics for diagnostic use (Taylor et al. 2019). Due to genetic factors having a stronger contribution to DDs, there is an increased demand for genetic evaluations and genetic specialists. This comprises medical geneticists and genetic counsellors. Medical geneticists specialise in the evaluation, diagnosis and management of rare genetic diseases. For conclusive diagnoses to be made, the clinical interpretation of WES incorporates the aligning of molecular test results with clinical features

(Akgun-Dogan et al. 2024). This is particularly challenging in cases of clinical and genetic heterogeneity, such as DDs. Therefore, there is a need for medical geneticists to perform deep phenotyping, which is the process of comprehensively assessing an individual's observable traits and assigning Human Phenotype Ontology (HPO) terms. Deep phenotyping can include the analysis of laboratory and radiological tests (Wang et al. 2022). Conversely, genetic counsellors educate families about the role of genetics and aid in their understanding of specific rare diseases. Genetic counsellors help families adapt to the medical, psychosocial and familial implications of genetic contributions to disease (Resta et al. 2006).

1.2.3. The role of genetics specialists

The caregivers of children with DDs pursue genetic evaluations for various reasons with differing expectations (Blesson and Cohen 2020). Therefore, genetic counselling is required to better understand these motivators and directly address them. In a study conducted by Ashtiani et al. (2014), it was found that 61.5% of parents who received a genetic diagnosis for their child from a medical geneticist alone had negative experiences. A further 23% felt positive, while 15.5% were indifferent. Positive experiences were influenced by offers of emotional support, follow-up plans being outlined and perspective and hope being provided to parents. Contrarily, negative experiences were associated with the use of medical jargon and parents being treated like passive receivers of information. Furthermore, Waxler et al. (2013) identified significant associations between positive diagnostic experiences and the presence of genetic counsellors. This is likely the result of the extensive and specialised training genetic counsellors receive to deliver difficult news and provide emotional support. Cornelis et al. (2024) determined that genetic counselling is beneficial for aligning pre- and post-disclosure attitudes of caregivers during WES result delivery. Additionally, not only will caregivers receive a long-awaited diagnosis, but the lengthy diagnostic odyssey will come to an end. Receiving results and anticipating their impact may be emotional for caregivers, resulting in a need for additional emotional support as a result (Blesson and Cohen 2020).

1.3. The diagnostic odyssey and receiving a diagnosis

During the diagnostic odyssey, caregivers fulfil multifaceted roles as navigators, advocates, communicators and experts (Pavisich, Jones, and Baynam, 2024). This journey involves facing misdiagnoses, delayed diagnoses and inconclusive results, often accompanied by costly and invasive medical investigations. Misdiagnoses are compounded by features shared across genetic and non-genetic conditions, which adds complexity to reaching a diagnosis. This may lead to inappropriate investigations, treatment and management (Blesson and Cohen 2020).

Furthermore, valuable time can be lost by pursuing cheaper and less comprehensive genetic evaluations, still leaving caregivers lacking a diagnosis and often feeling hopeless (Miller 2021). On the contrary, reaching a genetic diagnosis can be beneficial as it enhances knowledge of the child's condition, provides emotional closure to caregivers and may alleviate feelings of blame, stress and uncertainty for the future (Zurynski et al. 2017). Moreover, it often allows caregivers to place blame on external factors, alleviating the guilt that they caused their child's condition. Some may feel absolved or express a sense of relief. Importantly, it allows for the identification of condition-specific clinical management and prognostic insight. Subsequently, recurrence risks can be determined and genetic counselling can be offered for family planning and future pregnancies (Copeland et al. 2021). Reproductive and familial implications may weigh heavily on parents, who might fear having another similarly affected child. However, a diagnosis can restore reproductive confidence and enable the identification of at-risk family members and potential carriers, allowing for early intervention (Zurynski et al. 2017).

Providing a genetic diagnosis has both potential benefits, as well as limitations, see Table 1. Unfortunately, even once a diagnosis is received, the vast majority of genetic conditions have no curative therapy available. However, obtaining a diagnosis can alter clinical management by up to 70% (Radford and Firth 2019). Additionally, once a patient is diagnosed, caregivers may experience acute grief and may need to come to terms with the loss of hope for their child's future (Blesson and Cohen 2020).

Table 1. The potential benefits and risks of providing a genetic diagnosis, adapted from Blesson and Cohen (2020).

Potential benefits	Potential limitations
The diagnostic odyssey ends	Negative emotional responses to results
Caregivers provide a name to the condition	May not alter medical management
Targeted medical management and treatment	Limited or no prognostic information available
Caregivers adapt expectations based on prognostic information	No actionable treatment available
Access to services and condition-specific support groups	Blame and guilt of caregivers in cases of inherited conditions
Emotions such as blame or guilt may be alleviated	Discussion of incidental findings
Recurrence risk and future reproductive options	

1.3.1. The psychosocial impact of receiving a positive result

When receiving a positive result, caregivers are typically provided with a genetic test report. This discusses the disease-causing variant/s, the implicated gene, the name of the associated genetic condition, if available, and the mode of inheritance (Mollison et al. 2020). Research indicates that receiving a diagnosis is potentially psychologically and clinically beneficial as it

alleviates the psychological distress experienced by caregivers and improves health outcomes of their child. It has been reported that caregivers who have received genetic diagnoses for their children through WES studies, typically have positive experiences. Additionally a diagnosis can have significant personal, clinical, psychosocial and emotional outcomes for the patient, caregivers and family (Copeland et al. 2021). Previous studies have evaluated the parental experiences of receiving a positive result and identified emerging themes that highlighted the importance of emotional support, access to condition-specific information and resources, communicating hope and following up with families (Ashtiani et al. 2014; Waxler et al. 2013).

1.3.2. The clinical and personal utility of a positive result

Clinical utility encompasses many aspects of care but is rarely uniformly defined (Hayeems et al. 2020). Therefore, it is not limited to a specific health outcome. Clinical utility is complex and compounded by the clinical and genetic heterogeneity of DDs. Niguidula et al. (2018) separated clinical management outcomes into categories of changes in medication and medical management, discontinuation of diagnostic testing, reproductive planning and the availability of psychosocial services. Conversely, personal utility includes the perceived benefits of genomic test results as ascribed by patients, regardless of the potential to improve healthcare (Pollard et al. 2021). As reviewed by Kohler, Turbitt, and Biesecker (2017), personal utility is divided into affective, cognitive, behavioural and social outcomes, see Table 2.

Table 2. The division of personal utility into personal and social outcomes.

Personal outcomes			**Social outcomes**
Affective outcomes	**Cognitive outcomes**	**Behavioural outcomes**	
Enhanced coping	Information provided	Future planning	Research altruism
Mental preparation	Self-knowledge	Reproductive autonomy	Confidentiality
Feelings of responsibility	Curiosity	Communication with relatives	Concerns about stigma and discrimination
Improved spiritual well-being	Potential to improve knowledge		Change in social support

No studies have been conducted in South Africa to assess the lived experiences of caregivers of children with DDs. Therefore, this study will provide a greater insight into patient, caregiver, and family outcomes after receiving a genetic diagnosis. This is to determine to what extent genetic testing improves mental health and well-being of caregivers and explore their expected utility of WES results received through the DDD-Africa study. Additionally, the proposed study will evaluate the diagnostic odyssey experienced by these families.

2. Study Objectives

2.1. Aim

To investigate the expected outcomes and psychosocial impacts of returnable WES results from caregivers of children with rare DDs.

2.2. Objectives

1. To analyse the demographic data of families who have received positive research results through the DDD-Africa study.
2. To investigate caregivers' expected utility of a returnable WES result.
3. To evaluate the psychosocial aspects following the return of a positive research result.
4. To assess whether the diagnostic odyssey is a shared experience through the analysis of genetic counselling consultation notes.

3. Methods

3.1. Study Participants

This study cohort comprises a subset of participants and their caregivers recruited into the DDD-Africa study in South Africa between June 2018 to July 2023 and have subsequently received a positive research result. Participants were enrolled through hospital-based and community-based recruitments, mainly in academic institutions and specialised centres for individuals with special needs, respectively. Furthermore, unique identifying codes were used to maintain anonymity in the parent study, which have been maintained in the proposed sub-study. Recruitment has been finalised and currently, WES data analysis and the feedback of returnable results are simultaneously being undertaken by the DDD-Africa team. A returnable result, also referred to as a positive result, consists of the identification of a disease-causing variant/s and the associated genetic diagnosis that can be communicated back to the family. Genetic counselling feedback sessions for returnable results began in May 2021, with the addition of pre-result feedback questionnaires in September 2022. Currently, returnable results have been identified for 15.4% (55/358) of families, of which 36 families have received a positive research result. Genetic counselling sessions for the feedback of returnable results are ongoing as WES analysis continues. Therefore, the number of families included in this study will be determined once all returnable results have been fed back to caregivers. The anticipated study cohort is between 50 and 70 families.

3.2. Design of the Study

The study has a retrospective design to primarily evaluate the expected outcomes of caregivers prior to receiving a genetic diagnosis for their child. The demographic data of these families

will be evaluated through a participant electronic file audit using the Research Electronic Data Capture (REDCap) (Harris et al., 2009) database utilised by the DDD-Africa study for data storage. Data that will be analysed is based on an adapted survey by Zurynski et al. (2017), which includes demographic data and data regarding feedback sessions (Appendix A; Section 1 and 2). Zurynski et al. (2017) aimed to describe the experiences of families living with children affected by rare diseases, including seeking and receiving a diagnosis. This will aid in the quantitative assessment of the diagnostic odyssey experienced by these families.

Prior to the genetic counselling feedback sessions, caregivers were invited and consented to completing a research-administered questionnaire (Appendix B). This questionnaire was conceptualised for a DDD-Africa sub-study titled, *Caregivers' expected and perceived utility of whole-exome sequencing results for children with developmental disorders*. Furthermore, the questionnaire focuses on determining what parents think a diagnosis will be able to provide and why parents of children with DDs want a confirmed diagnosis for their child. The responses of this questionnaire will be analysed in this study.

Post completion of genetic counselling feedback sessions, consultation summary letters were concisely written for the caregivers by the attending genetic counsellor and medical geneticist to summarise and reinforce the contents discussed in the consultation. This includes the discussion of research results, aetiology and familial implications, clinical manifestations as well as the management of the condition. Additionally, the psychosocial aspects identified in the consultation were explored and documented. The psychosocial aspects and emotional information included in the letters was euphemised for communication back to caregivers and potentially other healthcare professionals. Therefore, these consultation summary letters will be assessed in conjunction with electronic clinical records on REDCap that documented the consultations in greater depth.

4. Data Analysis

The demographic data will be analysed descriptively. Other data includes categorical survey items, such as diagnostic experiences obtained from electronic clinical records and medical histories, what caregivers believe WES will provide them with and what is most important to them about receiving a diagnosis. See Appendix A; Section 1 and 2. The aforementioned data will be separated according to the type of data present. Examples can be found in Figure 1 (A). Subsequently, this data will be analysed with frequency distribution and cross-tabulation (Zurynski et al. 2017). This will be performed using Microsoft Excel 365. The responses obtained from the questionnaire in Appendix B will be separated into short text answers

(Questionnaire 1, Questions 1 and 2), and categorical survey items (Questionnaire 1, Question 3; and Questionnaire 2). Short text answers will be scanned for themes and categorical survey items will be quantified. To quantitatively analyse themes, themes and experiences will be pre-determined through a literature analysis of the diagnostic odyssey from the perspective of caregivers. Categorical survey items include demographic data, which will be separated into numerical, binary and nominal data. Additionally, Questionnaire 1, Question 3 includes a Likert scale (illustrated in Appendix C) and Questionnaire 2 accounts for ordinal data. Lastly, consultation summary letters will be scanned to identify emerging themes and psychosocial outcomes. This "scanning" method was used by Zurynski et al. (2017) to quantitatively identify emerging themes from short text responses. The scanning of emerging themes will be independently performed by the genetic counselling student (SS) and a genetic counsellor (ZG). A deductive approach will be used and a thematic consensus will be reached with the assistance of an additional genetic counsellor (BS), see Figure 1 (B).

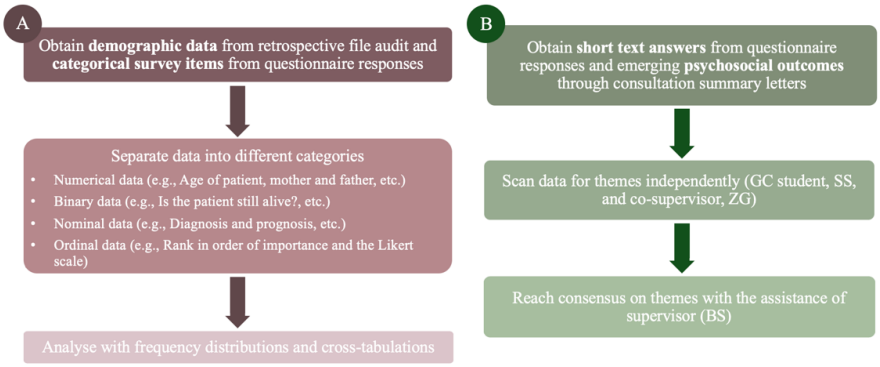


Figure 1. Data analysis of **(A)** demographic data and categorical survey items from questionnaire responses, and **(B)** short text answers from questionnaire responses and emerging psychosocial impacts identified from consultation summary letters.

5. Ethics

The DDD-Africa parent study is titled, '*Deciphering Developmental Disorders (DDD-Africa) – Evaluating Clinical Exome Sequencing in an African Setting*' (Ethics Certificate Number: M230567). The proposed study will be a sub-study of a DDD-Africa sub-study, '*Caregivers' expected and perceived utility of whole-exome sequencing results for children with developmental disorders*' (Shingwenyana et al.; Ethics Certificate Number: M220125). A sub-study ethics application was submitted to the Human Research Ethics Committee (Medical) of the University of the Witwaterstrand on the 18th April 2024.

6. Timing

This study will be undertaken over a 12-month period in 2024 and 2025 (see Figure 2).

	2024											2025	
	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb
Literature Review													
Protocol Write-up													
Ethics Application													
Protocol Assessment													
Data Analysis													
Research Write-up													
Research Assessment													

Figure 2. A Gantt chart representing time allocations for the proposed study.

7. Funding

This study will require no funding as it is a retrospective data analysis and retrospective file audit of caregivers and their families who have received diagnoses through the DDD-Africa result feedback sessions. The DDD-Africa study is supported by the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH) under award number U01MH115483 (H3Africa NIMH/NIH: U01MH115483). This funding was largely used for personnel costs, travel, participant and trainee support costs and costs relating to recruitment, DNA extraction and WES.

8. Anticipated Problems and Study Limitations

- Information gathered through the participant electronic file audit is limited to electronic file notes made using patient clinical files held at the Division of Human Genetics, University of the Witwatersrand/National Health Laboratory Service. Information from patient clinical files that are missing and information from investigations undertaken by other healthcare professions may not be included in this study.
- Regarding the questionnaire responses, a broad range of perspectives are accounted for, including ages, levels of genetic literacy and education. However, there may be biases in questionnaire responses as the majority of the participating caregivers are mothers.
- The research-administered questionnaire was conducted in English, which is not the first language of the majority of these families. As a result, caregivers may have felt inadequate and unable to participate effectively. This provides room for a lack of understanding and/or caregivers being unable to respond optimally (Shingwenyana et al. 2023).

9. Expected Outcomes

- Through the data obtained from the proposed study, knowledge of the lived experiences of caregivers with children with DDs will be better understood, especially in a South African context where this has not previously been explored. Furthermore, there will be greater insight into the diagnostic odyssey experienced by these families, as well as caregivers' motivations for wanting a diagnosis for their children.
- In South Africa, WES is not offered routinely to patients in the state health sector and is only available in a research setting through projects such as DDD-Africa. Obstacles hindering the clinical implementation of WES in South Africa include, but are not limited to, a lack of resources and skilled personnel, funding and buy-in, as well as standardised guidelines for the feedback of WES results (ref – Van Der Merwe).
- GCs lack experience with WES and need to know what to focus on when feeding results back to families.
- Ultimately, the findings of this study could provide a framework to develop guidelines for the feedback of WES research results to families affected by the diagnostic odyssey.
- Results and findings will be disseminated through departmental seminars, presentations and research days, conferences or congresses, such as the Wits Faculty of Health Sciences Research Day & Postgraduate Expo. Additionally, findings could potentially be published in accredited peer-reviewed human genetics journals, namely Genetics in Medicine, Orphanet Journal of Rare Diseases or Clinical genetics. Importantly, this data will be shared with other African genetics specialists, researchers and healthcare professionals.

10. References

Akgun-Dogan, Ozlem, Ecenur Tuc Bengur, Beril Ay, Gulsah Sebnem Ozkose, Emre Kar, Fuat Baris Bengur, Aybike S. Bulut, et al. 2024. "Impact of Deep Phenotyping: High Diagnostic Yield in a Diverse Pediatric Population of 172 Patients through Clinical Whole-Genome Sequencing at a Single Center." *Frontiers in Genetics* 15 (March). https://doi.org/10.3389/fgene.2024.1347474.

Ashtiani, Setareh, Nancy Makela, Prescilla Carrion, and Jehannine Austin. 2014. "Parents' Experiences of Receiving Their Child's Genetic Diagnosis: A Qualitative Study to Inform Clinical Genetics Practice." *American Journal of Medical Genetics, Part A* 164 (6): 1496–1502. https://doi.org/10.1002/ajmg.a.36525.

Baine-Savanhu, Fiona, Shelley Macaulay, Nadja Louw, Alanna Bollweg, Kaitlyn Flynn, Mhlekazi Molatoli, Patracia Nevondwe, et al. 2023. "Identifying the Genetic Causes of Developmental Disorders and Intellectual Disability in Africa: A Systematic Literature

Review." *Frontiers in Genetics*. Frontiers Media S.A. https://doi.org/10.3389/fgene.2023.1137922.
Bauskis, Alicia, Cecily Strange, Caron Molster, and Colleen Fisher. 2022. "The Diagnostic Odyssey: Insights from Parents of Children Living with an Undiagnosed Condition." *Orphanet Journal of Rare Diseases* 17 (1). https://doi.org/10.1186/s13023-022-02358-x.
Blesson, Alyssa, and Julie S. Cohen. 2020. "Genetic Counseling in Neurodevelopmental Disorders." *Cold Spring Harbor Perspectives in Medicine* 10 (4). https://doi.org/10.1101/cshperspect.a036533.
Copeland, H., E. Kivuva, H. V. Firth, and C. F. Wright. 2021. "Systematic Assessment of Outcomes Following a Genetic Diagnosis Identified through a Large-Scale Research Study into Developmental Disorders." *Genetics in Medicine* 23 (6): 1058–64. https://doi.org/10.1038/s41436-021-01110-3.
Cornelis, Candice, Aad Tibben, Eva Brilstra, Ineke Bolt, Marieke van Summeren, Nine Knoers, and Annelien L. Bredenoord. 2024. "Hope, but Never Expect? Comparing Parents' Pre- and Post-disclosure Attitudes toward Return of Results from Diagnostic Exome Sequencing for Their Child." *Molecular Genetics & Genomic Medicine*, February. https://doi.org/10.1002/mgg3.2341.
Harris, Paul A., Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, and Jose G. Conde. 2009. "Research Electronic Data Capture (REDCap)-A Metadata-Driven Methodology and Workflow Process for Providing Translational Research Informatics Support." *Journal of Biomedical Informatics* 42 (2): 377–81. https://doi.org/10.1016/j.jbi.2008.08.010.
Hayeems, Robin Z., David Dimmock, David Bick, John W. Belmont, Robert C. Green, Brendan Lanpher, Vaidehi Jobanputra, et al. 2020. "Clinical Utility of Genomic Sequencing: A Measurement Toolkit." *Npj Genomic Medicine*. Nature Research. https://doi.org/10.1038/s41525-020-00164-7.
Kohler, Jennefer N., Erin Turbitt, and Barbara B. Biesecker. 2017. "Personal Utility in Genomic Testing: A Systematic Literature Review." *European Journal of Human Genetics*. Nature Publishing Group. https://doi.org/10.1038/ejhg.2017.10.
Langenfeld, Adam, Lynn Schema, and Judith K. Eckerle. 2021. "Genetic Developmental Disability Diagnosed in Adulthood: A Case Report." *Journal of Medical Case Reports* 15 (1). https://doi.org/10.1186/s13256-020-02590-8.
Miller, Danny. 2021. "The Diagnostic Odyssey: Our Family's Story." *American Journal of Human Genetics* 108 (2): 217–18. https://doi.org/10.1016/j.ajhg.2021.01.003.
Mollison, Lonna, Julianne M. O'Daniel, Gail E. Henderson, Jonathan S. Berg, and Debra Skinner. 2020. "Parents' Perceptions of Personal Utility of Exome Sequencing Results." *Genetics in Medicine* 22 (4): 752–57. https://doi.org/10.1038/s41436-019-0730-8.
Niguidula, Nancy, Christina Alamillo, Layla Shahmirzadi Mowlavi, Zöe Powis, Julie S. Cohen, and Kelly D. Farwell Hagman. 2018. "Clinical Whole-Exome Sequencing Results Impact Medical Management." *Molecular Genetics and Genomic Medicine* 6 (6): 1068–78. https://doi.org/10.1002/mgg3.484.
Pavisich, Kascia, Hannah Jones, and Gareth Baynam. 2024. "The Diagnostic Odyssey for Children Living with a Rare Disease – Caregiver and Patient Perspectives: A Narrative Review with Recommendations." *Rare* 2:100022. https://doi.org/10.1016/j.rare.2024.100022.
Pollard, Samantha, Deirdre Weymann, Jessica Dunne, Fatemeh Mayanloo, John Buckell, James Buchanan, Sarah Wordsworth, et al. 2021. "Toward the Diagnosis of Rare Childhood Genetic Diseases: What Do Parents Value Most?" *European Journal of Human Genetics* 29 (10): 1491–1501. https://doi.org/10.1038/s41431-021-00882-1.
Radford, Elizabeth J, and Helen V Firth. 2019. *The Genetics of Developmental Disorders*.

Roggenbuck, J., R. Temme, D. Pond, J. Baker, K. Jarvis, M. Liu, S. Dugan, and N. J. Mendelsohn. 2015. “The Long and Short of Genetic Counseling Summary Letters: A Case–Control Study.” *Journal of Genetic Counseling* 24 (4): 645–53. https://doi.org/10.1007/s10897-014-9792-6.

Shingwenyana, Barry, Bianca Rossouw, Jamey Thom, Nadja Louw, Amanda Krause, and Zané Lombard. 2023. “Research Participants’ Perspectives Regarding the Feedback of Secondary Findings–A Cohort from the DDD-Africa Study, South Africa.” *Journal of Genetic Counseling*. https://doi.org/10.1002/jgc4.1830.

Srivastava, Siddharth, Jamie A Love-Nichols, Kira A Dies, David H Ledbetter, Christa L Martin, Wendy K Chung, Helen V Firth, et al. 2019. “Meta-Analysis and Multidisciplinary Consensus Statement: Exome Sequencing Is a First-Tier Clinical Diagnostic Test for Individuals with Neurodevelopmental Disorders and the NDD Exome Scoping Review Work Group.” *Genetics in Medicine*. https://doi.org/10.1038/s41436.

Taylor, John, Jude Craft, Edward Blair, Sarah Wordsworth, David Beeson, Saleel Chandratre, Judith Cossins, et al. 2019. “Implementation of a Genomic Medicine Multi-Disciplinary Team Approach for Rare Disease in the Clinical Setting: A Prospective Exome Sequencing Case Series.” *Genome Medicine* 11 (1). https://doi.org/10.1186/s13073-019-0651-9.

Vissers, Lisenka E.L.M., Christian Gilissen, and Joris A. Veltman. 2016. “Genetic Studies in Intellectual Disability and Related Disorders.” *Nature Reviews Genetics*. Nature Publishing Group. https://doi.org/10.1038/nrg3999.

Wang, Qingqing, Xia Tang, Ke Yang, Xiaodong Huo, Hui Zhang, Keyue Ding, and Shixiu Liao. 2022. “Deep Phenotyping and Whole-Exome Sequencing Improved the Diagnostic Yield for Nuclear Pedigrees with Neurodevelopmental Disorders.” *Molecular Genetics and Genomic Medicine* 10 (5). https://doi.org/10.1002/mgg3.1918.

Waxler, Jessica L., Elizabeth M. Cherniske, Kristen Dieter, Pamela Herd, and Barbara R. Pober. 2013. “Hearing from Parents: The Impact of Receiving the Diagnosis of Williams Syndrome in Their Child.” *American Journal of Medical Genetics, Part A* 161 (3): 534–41. https://doi.org/10.1002/ajmg.a.35789.

Wiener, Emma K., James Buchanan, Amanda Krause, and Zané Lombard. 2023. “Retrospective File Review Shows Limited Genetic Services Fails Most Patients - an Argument for the Implementation of Exome Sequencing as a First-Tier Test in Resource-Constraint Settings.” *Orphanet Journal of Rare Diseases* 18 (1): 81. https://doi.org/10.1186/s13023-023-02642-4.

Xiang, Jingjing, Yang Ding, Fei Yang, Ang Gao, Wei Zhang, Hui Tang, Jun Mao, Quanze He, Qin Zhang, and Ting Wang. 2021. “Genetic Analysis of Children With Unexplained Developmental Delay and/or Intellectual Disability by Whole-Exome Sequencing.” *Frontiers in Genetics* 12 (November). https://doi.org/10.3389/fgene.2021.738561.

Zurynski, Yvonne, Marie Deverell, Troy Dalkeith, Sandra Johnson, John Christodoulou, Helen Leonard, and Elizabeth J. Elliott. 2017. “Australian Children Living with Rare Diseases: Experiences of Diagnosis and Perceived Consequences of Diagnostic Delays.” *Orphanet Journal of Rare Diseases* 12 (1). https://doi.org/10.1186/s13023-017-0622-4.

Appendix A

Section 1: Demographic data regarding the patient and family.

1. What is the gender of the patient?

2. What is the age of the patient?

3. What was the age of the mother at birth?

4. What was the age of the father at birth?

5. Country of birth of the patient?
   a. South Africa
   b. Other (specify)

6. Ethnicity?
   a. Afrikaans
   b. Asian
   c. Bapedi
   d. Coloured
   e. English
   f. Indian
   g. Kikongo
   h. Lingala
   i. Ndebele
   j. Shona
   k. Sotho
   l. Swahili
   m. Swati
   n. Tshiluba
   o. Tsonga
   p. Tswana
   q. Venda
   r. Xhosa
   s. Zulu
   t. Unknown
   u. Other (specify)

7. Marital status of parents?
   a. Married or living together
   b. Never married or co-inhabited
   c. Divorced or separated
   d. Partner deceased
   e. Other

8. Who does the patient reside with?
   a. One of their parents (single-headed household)
   b. Both of their parents
   c. Other relative
   d. Other

9. Age of the patient when first seen by genetics clinic?

10. Previous genetic testing?
    a. Karyotype
    b. Multiplex ligation probe amplification (MLPA)
    c. Fragile-X (FRAX) testing
    d. Array comparative genomic hybridisation (a-CGH)
    e. Other (specify)

11. Age of the child when recruited into DDD-Africa?

12. What family type was recruited?
    a. Singleton
    b. Duo
    c. Trio
    d. Extended family with more than one affected child

13. Age of the child at the DDD-Africa WES result feedback session?

14. How many years were there between recruitment and feedback session?

Section 2: Data regarding the feedback sessions, WES result and diagnosis.

1. Who attended the feedback session?
    a. Mother
    b. Father
    c. Mother and father
    d. Other (specify)

2. Is the patient still alive?
    a. Yes
    b. No

3. What was the diagnosis?

4. What is the associated life expectancy or prognosis?

5. How was the variant inherited?
    a. Maternally
    b. Paternally
    c. One maternal copy and one paternal copy
    d. *De novo* variant

6. Were referrals made at the feedback session?
    a. Yes (specify)
    b. No, discharged from genetics clinic.

7. Were any other recommendations made to enhance the patient's quality of life?
    a. Yes (specify)
    b. No

B

Appendix B

Participant ID: _____

Questionnaire 1: Determining what parents think a diagnosis will be able to provide.

1. In your own words, tell us, what do you expect from the genomic test results of your child from DDD? What are some of the benefits?

_____
_____
_____
_____

2. How do you think the result will help your child, your family and managing doctors?

_____
_____
_____
_____

3. Rate whether you agree or disagree that whole-exome sequencing will be able to provide you with the following:

	Strong disagree	**Disagree**	**Neutral**	**Agree**	**Strongly agree**
Results will influence current medical treatment.					
Results will influence future medical treatment.					
Results will influence choice of medications.					
Results will allow for accurate recurrence risk prediction.					
Results will influence my reproductive choices and decision on having future children (biological caregivers to answer only).					
Results will allow for tailored/ personalised treatment for my child.					
Results will help me gain knowledge and understanding of my child's condition.					
Results will be beneficial to my family members.					
Results will improve my mental state.					
Results will satisfy my need to know what caused this.					
Results will remove the guilt associated with worrying that I caused this.					
Results will give me peace of mind.					
Results will help me plan financially for the future.					
Results will help to anticipate any additional health problems.					
Results will help me assess services that cater for my child's needs.					
Results will help me access financial support (e.g. SASSA grant).					

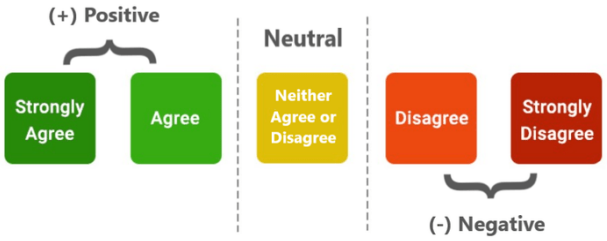
C

Questionnaire 2: Why do parents of children with developmental delay want a confirmed diagnosis for their child?

Rank the following in order of importance, 1 being the most important and 6 being the least important.

Rank	Item
	I want a confirmed diagnosis because it will direct my child's management and treatment.
	I want a confirmed diagnosis because it will provide me with accurate information about whether this could happen again with another child.
	I want a confirmed diagnosis so that I can understand what caused my child's condition.
	I want a confirmed diagnosis for peace of mind and decreased feelings of anxiety.
	I want a confirmed diagnosis so that I have a better understanding of my child's condition and any future health problems.
	I want a confirmed diagnosis so that I can plan financially for the future.

Appendix C



D

Appendix D: Ethics Certificate for Current Study (M240760)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Ms S Schnell

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M240760

NAME: (Principal Investigator)	Ms S Schnell	**DEGREE:** MSc
DEPARTMENT:	School of Pathology Division of Human Genetics Faculty of Health Sciences	
TITLE:	*The expected utility of whole-exome sequencing results and the psychosocial impacts of receiving a diagnosis*	
DATE CONSIDERED:	Ad hoc	
DECISION:	Approved unconditionally	
CONDITIONS:	Sub-study under M22/01/25 and M23/05/67	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office <Nicoleen.Potgieter@wits.ac.za>	
SUPERVISORS:	Mr MB Shingwenyana and Ms Z Goliath	
APPROVED BY:	Professor P Ruff, Chairperson, HREC (Medical)	

DATE OF APPROVAL: 22 August 2024 **EXPIRY DATE:** 21 August 2029

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report** in the format available at https://wits.ac.za/research/researcher-support/research-ethics/ethics-committees/. This report is due annually, for the duration of the Clearance Certificate, beginning on the first anniversary of Date of Approval above. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator — Date: 22/08/2024

Appendix E: Ethics Certificate for DDD-Africa Parent Study (M230567)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Professors A Krause & Z Lombard; Dr N Carstens; Ms N Louw

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M230567

NAME: (Principal Investigator)	Professors A Krause & Z Lombard; Dr N Carstens; Ms N Louw
DEPARTMENT:	School of Pathology Division of Human Genetics National Health Laboratory Service
PROJECT TITLE:	*Decyphering Development Disorders in Africa (DDD-Africa) - evaluating clinical exome sequencing in an African setting*
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Renewal of M18/06/78 - expired on 2023/07/05 NIH Study No. UO1MH115483
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Not applicable
APPROVED BY:	Dr M Vorster, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	2023/06/20 **EXPIRY DATE:** 2028/06/19

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **May** and therefore reports and re-certification will be due in the month of **May** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

Appendix F: Ethics Certificate for Shingwenyana *et al.* (M220125)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Mr B Shingwenyana, et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220125

NAME: (Principal Investigator)	Mr B Shingwenyana, et al
DEPARTMENT:	School of Pathology Division of Human Genetics National Health Laboratory Service
PROJECT TITLE:	*Caregivers' expected and perceived utility of whole-exome sequencing results for their children with developmental disorders*
DATE CONSIDERED:	2022/01/28
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Not applicable
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/04/12

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **January** and therefore reports and re-certification will be due in the month of **January** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

19 APRIL 2022
Date

Appendix G: Turnitin Originality Report

Samantha Schnell_Research Report without References.pdf

ORIGINALITY REPORT

4%	3%	3%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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3	Christine Michaels-Igbokwe, Brenda McInnes, Karen V. MacDonald, Gillian R. Currie et al. "(Un)standardized testing: the diagnostic odyssey of children with rare genetic disorders in Alberta, Canada", Genetics in Medicine, 2020 Publication	<1%
4	Siobhan L. Johnstone, Nicola A. Page, Michelle J. Groome, Nicolette M. du Plessis, Juno Thomas. "Diagnostic testing practices for diarrhoeal cases in South African public hospitals", BMC Infectious Diseases, 2022 Publication	<1%
5	Nancy L. Makela. "Parental perceived value of a diagnosis for intellectual disability (ID): A qualitative comparison of families with and without a diagnosis for their child's ID",	<1%

Appendix H: Orphanet Journal of Rare Diseases Submission Guidelines

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design
- list the full names and institutional addresses for all authors
    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below
    - Large Language Models (LLMs), such as ChatGPT, do not currently satisfy our authorship criteria. Notably an attribution of authorship carries with it accountability for the work, which cannot be effectively applied to LLMs. Use of an LLM should be properly documented in the Methods section (and if a Methods section is not available, in a suitable alternative part) of the manuscript
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Results:** the main findings
- **Conclusions:** a brief summary and potential implications

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

For research articles this section should discuss the implications of the findings in context of existing research and highlight limitations of the study. For study protocols and methodology manuscripts this section should include a discussion of any practical or operational issues involved in performing the study and any issues not covered in other sections.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study to the field.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval and for experimental studies involving client-owned animals, authors must also include a statement on informed consent from the client or owner.
See our editorial policies for more information.
If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.
You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).
See our editorial policies for more information on consent for publication.
If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.
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- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- All data generated or analysed during this study are included in this published article [and its supplementary information files].
- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
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Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]

If you wish to co-submit a data note describing your data to be published in *BMC Research Notes*, you can do so by visiting our submission portal. Data notes support open data and help authors to comply with funder policies on data sharing. Co-published data notes will be linked to the research article the data support (example).

Competing interests

All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

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