The Factors Affecting Result Delivery in the Inherited Retinal Disease Project in South Africa-Including Insights from Genetic Counsellors.

By

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Declaration

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

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Abstract

The Inherited Retinal Disease (IRD) Biorepository based in the Division of Human Genetics at the University of Cape Town, has conducted research into the molecular basis of IRD since 1990. Historically, and as part of this programme, patients with IRD are recruited and research into the genetic cause of the patient's disease is initiated, with the ultimate objective of identifying the genetic basis of the disease. An important aspect of the project was to feedback results, especially if it had clinical relevance. The aim of the present research project is to identify factors affecting the result delivery process, with a focus on the non-delivery of results.

Method

A mixed methodology was used to explore the possible factors which affected non-delivery of results. Quantitative data was collected from the IRD biorepository, and the demographics and other characteristics of patients were explored to gain insight into whether any of these features/characteristics had an impact on result delivery. In addition, a qualitative approach was taken to gain insight into the opinions and experiences of genetic counsellors regarding the delivery of results. The data from this combined mixed methods project provided a reasonably comprehensive view of the result delivery process.

Results

In the quantitative aspect of the project, analysis of the database reveals that the IRD project had recruited 3413 individuals from 1553 families in the study period analysed (1985-2019). Of these, disease-causing mutations have been identified in 1171 individuals (inferring that they were eligible to receive this information as a 'result').

Of these individuals, there was evidence that 416 had received their results. Deductively, 755 individuals from 191 families had not received their results. Upon closer inspection of the dataset (including the electronic database and physical subject files/records), there was evidence that an additional 76 subjects had received their results, 46 were deceased and 5 entries were duplicated. This reduced those eligible for results to 628 individuals (referred as the primary cohort). This primary cohort of interest could be divided into 131 subjects where there was a categoric statement on the database indicating that the result was not yet delivered, referred to as a high confidence cohort, and 497 subjects where there was no definitive indication on the database that results were given or not, but for whom one presumed result were not delivered. This group is referred to as the low confidence cohort.

In this study, an analysis of the primary cohort (n=628), high confidence cohort (n=131) and low confidence cohort (n=497) was carried out. This was done to ascertain whether

any trends and characteristics might emerge from the primary cohort which were a logical extrapolation of the respective cohorts.

It was found that patients from large families, mostly recruited during the earlier part of the research drive of 1995 to 2004, were more likely not to have received results.

Minors were of particular importance in the database as they represented 20.4% (n=128) of the primary cohort and their results ought to have been expedited. More effort was also made to deliver results to affected individuals as the high confidence cohort had more interaction with affected individuals than unaffected, but other characteristics like sex and age did not affect result delivery.

From the qualitative data, it was found that the current process of notifying patients/subjects (directly that a result was available), as opposed to through health professionals, had an impact on the result delivery. This is perceived to be the case since the result delivery hinged on personal initiative and the perceived value of the result by the patient. Genetic counsellors also thought that lower socioeconomic background may have contributed to a reduced delivery of results.

Conclusion

Result delivery in the IRD project was found to be affected by a number of factors, some of which researchers have control over and some that are beyond their control. The qualitative data corroborated some of the findings from the quantitative results. The results from the genetic counsellors' opinions provided additional insights which may play a role in non-delivery of results, some of which are patient related factors. The study therefore provided insights and proposed strategies that can be used to improve the result delivery process.

Acknowledgements

All thanks and praise to the Almighty for making this dream a reality!

I would like to dedicate this mini dissertation to my beloved husband, Enver, without whom this journey would never have started.

Thank you for being in my corner, no matter what!

To my late parents who by example taught me to push all boundaries.

To Aaliya, Ridhaa and Tasneem - Thank you for your encouragement and support.

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Table of contents

List of tables and figures

List of terms and abbreviations

AAV	Adeno Associated Virus
ARMD	Age related Macular Degeneration
COD	Confirmation of Diagnosis
CRISPR	Clustered regularly interspaced short palindromic repeats
GC	Genetic Counsellors
DNA	Deoxyribonucleic acid
GSH	Groote Schuur Hospital
HCC	High Confidence Cohort
HG	Division of Human Genetics
HP	Health Professionals
HPCSA	Health Professional Council of South Africa
HREC	Human Research Ethics Committee
IRD	Inherited Retinal Diseases
IRDPT	Inherited Retinal Disease project team
LCA	Leber Congenital Amaurosis
LCC	Low Confidence Cohort
MD	Macular Degeneration
MCGM	Manchester Centre for Genomic Medicine
NGS	Next Generation Sequencing
NHLS	National Health Laboratory Service
OECD	Organisation for Economic Co-operation and Development
HREC	Human Research Ethics Committee
RetinaSA	Retina South Africa
RP	Retinitis Pigmentosa
SA	South Africa
SASHG	Southern African Society for Human Genetics
STGD	Stargardt Disease

UCT	University of Cape Town
VUS	Variant of Unknown Significance
WES	Whole Exome Sequencing
WHO	World Health Organization

Chapter 1: Literature Review

1.1 Introduction

Globally, 36 million people are defined as legally blind, 217 million are moderately or severely vision impaired and 188 million people have mild vision impairment (Bourne et al., 2017). The term 'blindness' is defined by a corrected visual acuity of less than 3/60 in both eyes or a corresponding field loss of less than 10 degrees in the healthier eye with the best possible correction (WHO, 2013). Vision loss can be described as being on a continuum, from reduced vision to the total absence of perception of light. Vision loss occurs in virtually all populations over each individual's lifetime (Klein & Klein, 2013). It is estimated that the number of blind and visually impaired individuals are increasing, which is attributed to population growth, as well as ageing (Flaxman et al., 2017). Visually-impaired individuals are unequally distributed across age groups, as 82% are above 50 years or older; these individuals are also impacted by their lack of access to health-care resources in the developing world (WHO, 2017).

The World Health Organization (WHO) emphasizes the overwhelming human and socioeconomic impact of blindness in society, which includes the loss of productivity, rehabilitation requirements and education costs. Visual impairment affects individuals in a physical, psychological, intellectual, and sensory manner and leads to the inability of that individual to optimally interact, as well as perform essential activities of daily living. This has a devastating effect on the individual, family, and society (WHO, 2017). Smoking, Vitamin A deficiency, exposure to ultraviolet light, obesity and metabolic disorders are all risk factors that exacerbate the problem. The eye, however, presents as a perfect model for innovative therapies due to its relative ease of access, easy observation, compartmentalization, immune-privileged significance, and optical clarity (Sengillo et al., 2016).

The retina is an essential component of the eye, detecting and processing visual stimuli, needed for the interpretation of vision. The retina lines the posterior part of the inner eye and consists of multiple cell layers, as seen in Figure 1.1. The innermost layer consists of the photosensitive rod and cone photoreceptor cells, which detect light and trigger the phototransduction signalling pathway. In bright light, the centrally-situated cone photoreceptor cells are used whereas in dim light, the peripherally-situated rod photoreceptor cells are used (Dyer & Cepko, 2001). The photoreceptors synapse with the interneurons in the second layer of the retina, which in turn transmit the photochemical signal to the third layer, the retinal ganglion cells (Dyer & Cepko, 2001). The ganglion cells form a nerve layer which becomes the optic nerve. The signal is then transmitted to the brain for visual interpretation (Sanjurjo-Soriano & Kalatzis, 2018).

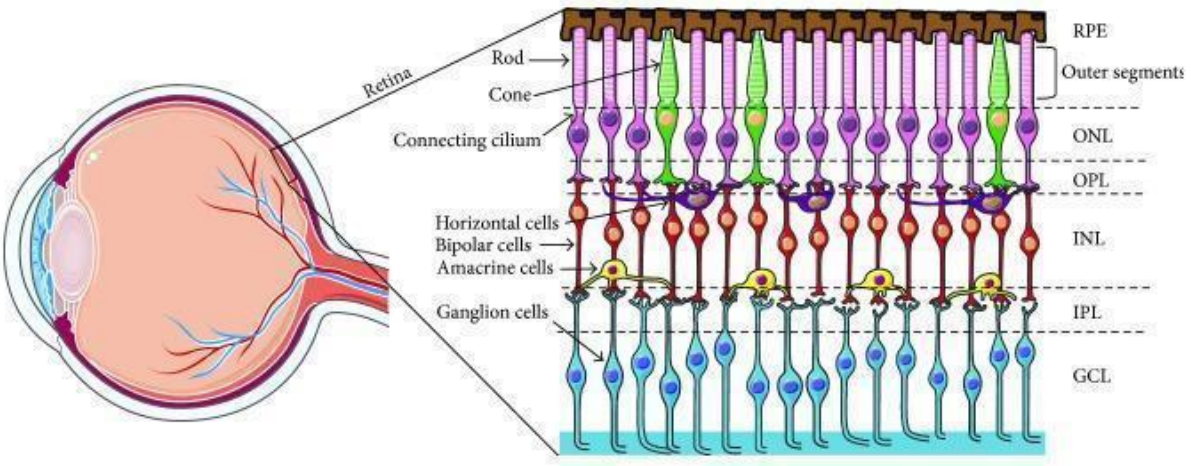

Figure 1.1: Schematic representation of the retina and the retinal cell layers. Abbreviations: RPE- Retinal pigment epithelium; ONL-Outer nuclear layer; OPL-Outer plexiform layer; INL-Inner nuclear layer; IPL-Inner Plexiform layer; GCL-Ganglion cell l layer. Reproduced from (Sanjurjo-Soriano & Kalatzis, 2018).

If the photochemical signal is not transmitted to the brain, it results in visual loss. Diseases like glaucoma, diabetic retinopathy, cataracts as well as trauma to the eye adds to the global burden of blindness and are prevalent in all human populations (WHO, 2013). However, a large subcategory of vision loss can also be attributed to retinal degeneration, which has a genetic origin (Berger, Kloeckener-Gruissem & Neidhardt, 2010).

1.1.1 Inherited Retinal Disease

Genetics play a significant role in retinal degeneration and can lead to severe vision loss in children and young adults. Inherited Retinal Diseases (IRD) have an estimated incidence of 1:2000 internationally and are the leading cause of blindness in people between the ages of 15-45 years (Cremers et al., 2018). IRD are defined as a group of conditions with dissimilar clinical symptoms as well as diverse underlying genetic mutations, but which all result in progressive photoreceptor death, leading to irreversible loss of vision (Sengillo et al., 2016). Most IRD currently have no proven cure, although many gene-based therapies have been initiated and clinical trials are underway. Management is currently centred around genetic counselling, enhancing the use of residual vision, and treating any complications that may develop (Smith et al., 2015). Up until two decades ago, the lack of research into IRD had resulted in a dearth of knowledge of the prevalence of this group of conditions in South Africa (SA) and many countries worldwide. Grouping regions together such as ‘Southern Africa’ or ‘Sub-Saharan Africa’, obscures significant differences between regions (Courtright & Lewallen, 2011). More research is needed to counteract this deficit of information on the African continent, as this could lead to enhanced quality of life for the individuals with visual loss. Phenotypical differences between patients with IRD are also an important aspect to consider.

i. Classification of phenotypes

This wide overlap in IRD phenotypes adds to the challenge in identifying the correct disease affecting the patient. It can be divided into three broad groups. If peripheral vision is primarily affected and night blindness occurs, the IRD is classified as Retinitis Pigmentosa (RP) or Choroideremia. If the IRD primarily affects the central vision, it is known as a macular or central dystrophy (MD), and if both the centre and the periphery are affected, the IRD is termed cone-rod or rod-cone dystrophy (Broadgate et al., 2017). Identifying congenital, late onset and progressive IRD, from relatively non-progressive (i.e., stationary) IRD, is a formidable challenge, especially in paediatric patients (Taylor et al., 2017). This is because IRD occur in non-syndromic forms of diseases, such as Stargardt disease (STGD) or syndromic forms, e.g., Bardet Biedl syndrome. Another confounding factor is that the inheritance pattern also impacts the risk for the patient's progeny, as it increases or decreases the risk of transmission from parent to child. In IRD, (genetic) mutations can be transmitted within families, in either an autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance pattern (Sengillo, 2016).

ii. Genetics and Heterogeneity

A large number of genes implicated in IRD, have also added to the challenge, as has the progression of the retinal degeneration in the patient, which may lead to their condition being reclassified over time. These 'IRD genes', directly or indirectly, affect the rod and cone photoreceptors of the retina, resulting in retinal degeneration and loss of vision. According to RetNet (an international resource for IRD genetics), 271 genes are currently listed as being associated with IRD (Daiger., 1996-2020). This large degree of clinical and genetic heterogeneity contributes to the challenge in finding causal mutations in specific individuals (Roberts et al., 2016b). In STGD, for example, a range of clinical presentations, may be evident in childhood to late adulthood, with over 900 causal variants identified in the *ABCA4* gene (Tanna et al., 2017). Figure 1.2 illustrates the extensive phenotypic and genotypic overlap for IRD; as an example, mutations in the *ABCA4* gene are causative not only of STGD, but also RP, MD as well as forms of cone-rod and cone dystrophies. Genetic testing can therefore assist in the classification of the IRD, as the phenotype alone is often

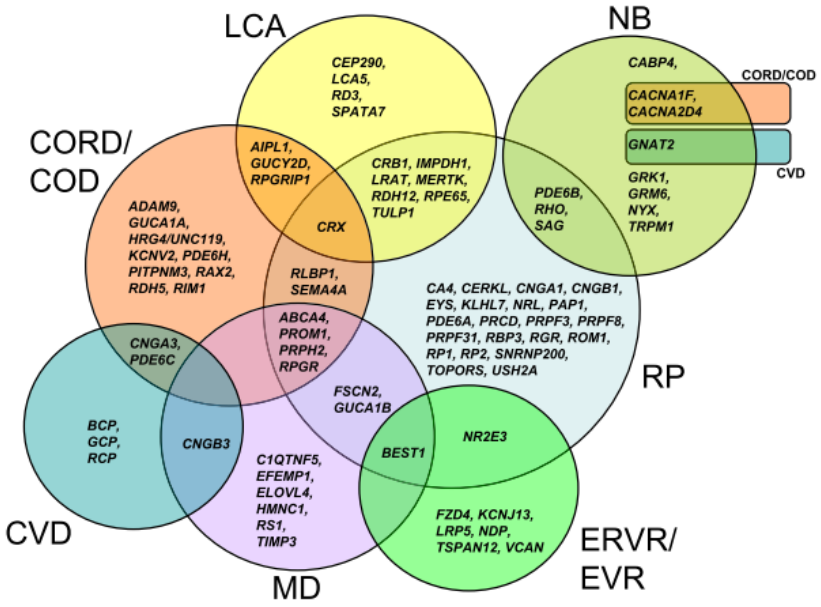

Figure 1.2: Clinical symptoms of non-syndromic monogenic and vitreoretinal diseases and their causative genes. Clinical diagnosis is indicated by coloured circles. Gene symbols in the overlapping areas show that mutations in the same gene can lead to different phenotypes. Abbreviations: RP: retinitis pigmentosa; NB: night blindness; LCA: Leber congenital amaurosis; CORD/COD: cone rod and cone dystrophies; CVD: colour vision defects; MD: macular degeneration; ERVR/EVR: erosive and exudative vitreoretinopathy. Reproduced from Berger, Kloeckener-Gruissem & Neidhardt (2010).

insufficient to fully diagnose the patient. The multitude of causative mutations/genes, however, adds to the complexity of delineating a patient's disease.

iii. Genes and Testing

The human genome consists of 3.5 billion base pairs and the protein coding-genes make up just over 1% of the genome, with the remaining 99% comprising intergenic or intronic regions (Broadgate et al., 2017). It had previously been proposed that 85% of disease-causing mutations in Mendelian diseases, would be found in the exome or the splice sites flanking the exomes, and that whole-exome sequencing (WES) would be relatively efficient in finding even rare mutations (Ng et al., 2009). Historically, genetic testing for IRD did not yield satisfactory results. In the 1990s, the global molecular diagnosis of individuals affected with IRD, was measured as less than 5%, with the main limitations being the lack of knowledge of the human genome, as well as the crude and relatively laborious methods used for investigating it (Stone et al., 2017). In the last 25 years, the development of Next Generation Sequencing (NGS) improved the effectiveness, decreased costs and turnaround times, leading to IRD genetic testing being successfully applied in over 75% of cases (Stone et al., 2017).

Apart from WES, gene panels used for IRD, as for various other inherited conditions, consist of many genes which are tested simultaneously in order to increase the chances of finding the causative mutations; as with WES, however, this process can also yield variants of unknown significance (VUS) which cannot be classified as either benign or pathogenic

(Murray., 2011). This represents new challenges for Health Professionals (HP) as support or lack of evidence dictates the categorization of VUS (Murray, 2011; Pollard, Sun & Regier, 2019). Gene variants are therefore at risk of misinterpretation, due to the lack of clear guidance to HP on how to manage the risk which in turn can lead to mismanagement of the patient (Wright et al., 2018). Despite extensive international efforts at standardizing classification of mutations ranging from benign to pathogenic e.g., American College of Medical Genetics (ACMG) guidelines, (Richards et al., 2015); novel variants found in indigenous African populations may be different to those found in the more-extensively studied European populations within which these panels have been tested and validated. Novel variants, not previously reported, may indeed be pathogenic in indigenous populations, but there is insufficient information on such rare variants, especially where they may not be obviously identified as functionally pathogenic (e.g., introducing a stop codon, or leading to loss of function) but as VUS. This speaks to the desperate need to undertake genomic research in diverse populations across the globe.

iv. Gene Therapy

Gene therapy is an exciting approach, which involves viral vectors and 'genome surgery'. It is currently being used to deliver genes to specific retinal cells, with the aim of replacing defective genes (Wang et al., 2019). Gene therapy trials started in 2001, when visual function was restored in animal models, with a recombinant adeno-associated virus (AAV) which was introduced intraocularly in three dogs who had Leber Congenital Amaurosis (LCA) (Acland et al., 2001). Several human clinical trials have since demonstrated improved results in LCA research, although the gene therapy effect did not remain beyond three years in the gene-therapy-trial participants (Bainbridge et al.,2015). Notably a French study in 2018, treated nine LCA patients with AAV4-gene therapy and showed that the unilateral subretinal injection of the viral vector had proven safety, while also improving vision (Le Meur et al., 2018).

Another promising treatment option is 'genome surgery'. This involves the "Clustered Regularly Interspaced Short Palindromic Repeats" (CRISPR) Cas editing technology. It has sparked great enthusiasm in the scientific community due to its precision, affordability, and relative ease of use in gene editing (Chan, Mahajan & Tsang., 2017). There are many clinical trials currently exploring CRISPR for IRD such as RP, LCA and Age-related Macular Degeneration (ARMD) (*Clinical Trials.Gov*, 2021).

The support group RetinaSA has always strived to ensure that SA participants benefit by being part of a clinical trial in order to empower their members (*Clinical Trials.gov.za*). In August 2019, the Acucela International clinical trial commenced in SA and many of the IRD project's STGD participants (in whom mutations on both alleles had been identified) were recruited onto the trial. This is a multicentred double blind, randomized, placebo-controlled trial evaluating the safety and efficacy of a drug called Emixustat in patients with macular atrophy secondary to STGD (Gregory, Birch & Kubota, 2020). RetinaSA also partners with

other HP, like Genetic Counsellors (GC), to ensure that affected participants on the IRD project are empowered with access to genetic information.

1.1.2 IRD Project

The IRD project at the University of Cape Town (UCT) was inspired by the patient-support group, Retina South Africa (RetinaSA), whose mission is to 'cure blindness'. Over the last three decades, the Division of Human Genetics (HG) at UCT has engaged in identifying the molecular genetic basis of IRD amongst South African patients. To date, the UCT IRD biorepository and electronic registry has archived biological material and clinical information from affected individuals and their families across South Africa as well as other African countries (Rebello, Greenberg & Ramesar., 2002). The registry is comprised of data and biological material from 3413 individuals in 1553 families affected with IRD (Roberts et al., 2019). The distribution of the archived IRD research-cohort throughout South Africa, is illustrated in Figure 1.3.

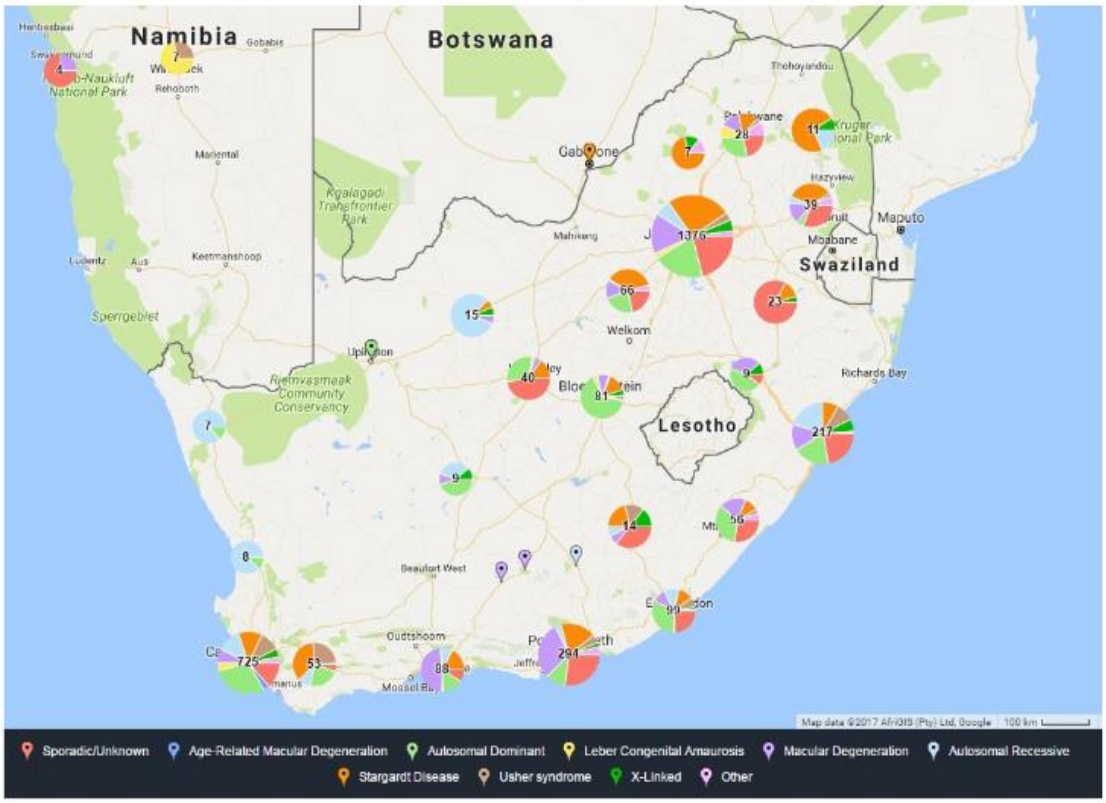

Figure 1.3: Geographical distribution of the IRD patient/family collection represented in the UCT Human Genetics repository. Source: (Batchgeo, 2012)-IRD Project map compiled by researcher. Key: The different colours of the pie chart represent distinct clinical phenotypes (as defined in the black strip at the bottom of the figure).

The timeline of IRD research in HG is indicated in Figure1.4. Initially, single candidate gene/locus screening was performed by HG researchers, who needed large families for

linkage studies, but as technology evolved, individual (patient) samples were also sent to a commercial laboratory, Asper Biogene in Estonia, for microarray chip testing. This microarray technology allowed the genotyping of specific, known mutations in multiple IRD genes. A SA diagnostic test, called the Quick7, which tests for seven common founder mutations in the *ABCA4* gene, underlying STGD, was also developed (Roberts et al., 2013). Founder mutations occur due to genetic drift in small populations, which could be followed by a geographic expansion of the population. Understandably, a higher incidence of monogenic disorders like STGD, amongst others, are therefore seen in Caucasian patients of Afrikaner ancestry (Krause, Seymour & Ramsay, 2018). The carrier frequency of the common *ABCA4* mutations in the Afrikaner population is 4.46 per 100 individuals (Roberts, 2012). This assay is offered for diagnostic screening via the SA National Health Laboratory Service (NHLS) and resolves about 52% of Afrikaner STGD cases (Midgley et al., 2020).

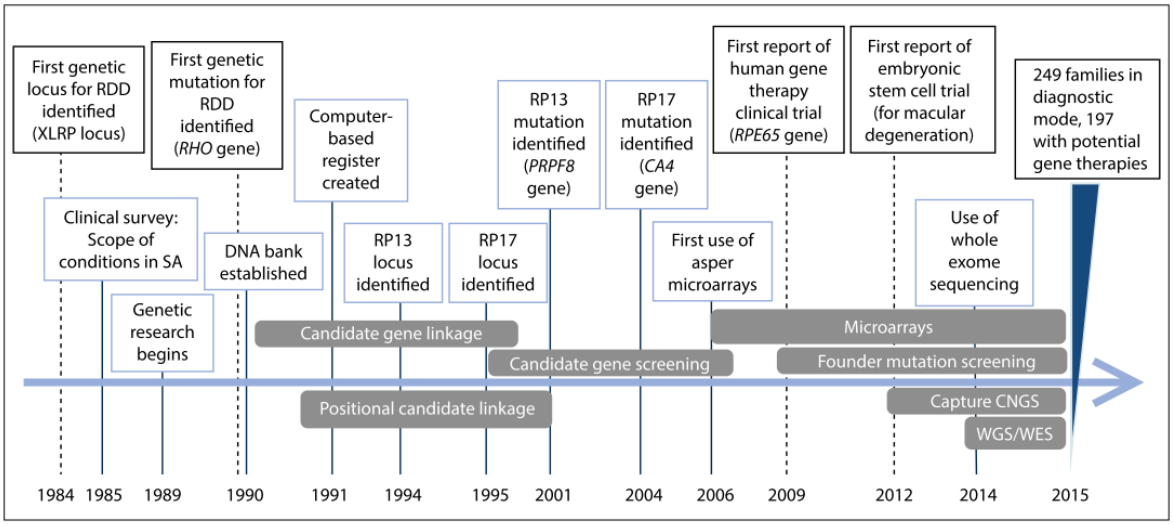

Figure 1.4: Timeline of milestones reached during the 25 years of retinal research in SA. The black boxes represent international milestones, while the blue boxes represent local SA milestones. The molecular approaches used during different time periods are indicated in grey bars. (CNGS = capture next-generation sequencing; WGS = whole genome sequencing; WES = whole exome sequencing.) Reproduced from Roberts et al., (2016b).

The Manchester centre for Genomic Medicine (MCGM) was used for NGS, due to their ability to fully sequence a large panel of genes. The detection rate for the samples that were sent from the IRD project to the MCGM, was 63% (Roberts, personal communication 2018). NGS technology has led to novel genes being identified in different countries, notably our indigenous African population in South Africa, in which a novel gene (*IDH3A)* was identified, as well as six novel mutations, in six known genes (*RHO, PRPF3, PRPF31, ABCA4, CERKL* and *PDE6B)*, in six different families (Roberts et al., 2016a).

In 2019, the UCT NGS panel was developed by the IRD research group. This panel includes sequencing the coding regions of 124 of the known 271 IRD genes (Daiger, 1996-2020). The UCT panel is designed to test specific IRD genes of interest which are relevant to our

SA population, and new genes are added to the panel as they become available from the manufacturers. For eligibility into many clinical trials, a molecular diagnosis is a prerequisite. The IRD project in 2016, had 197 families with affected members, who were eligible for entry into clinical trials for the following genes*: RPE65, AIPL1, MYO7A, ABCA4*, and *CHM (*Roberts et al., 2016b). The IRD project has identified mutations in 43 different genes (Roberts, 2018).

i. Genetic counselling

Genetic results are given by a health professional registered with the Health Professional Council of South Africa (HPCSA), and preferably registered GC, who can interpret and deliver the molecular report to the patient. The large amount of data produced, and the likelihood of uncertainty of interpretation, are characteristics of the current era of genomic testing (Patch & Middleton, 2018). Genetic counselling can be described as patient centred, with the emphasis on the use of genetic information to assess risk in affected individuals, while providing psychotherapeutic support in order to assist the understanding and independent decision-making by the individual, as well as their adaptation to their new reality (Bamshad, Magoulas & Dent., 2018). Referral options, as well as risk information regarding future offspring or risk to other family members, are explored during this process of result delivery (Veach, LeRoy & Bartels, 2003).

ii. IRD Genetic result process

In 2012 the outstanding records (n=395) were mapped by the researcher, Figure 1.5. These results were concentrated in the urban areas, as well as scattered throughout SA, which added logistical challenges. This map also corresponds to Figure 1.3 which shows the geographical distribution of all the participants on the IRD project. By 2019, with the start of the present study, the 'results outstanding' records had increased to 755. The current outstanding results of the primary cohort is n=628 and represent individuals from families in which the disease-causing mutation has been identified.

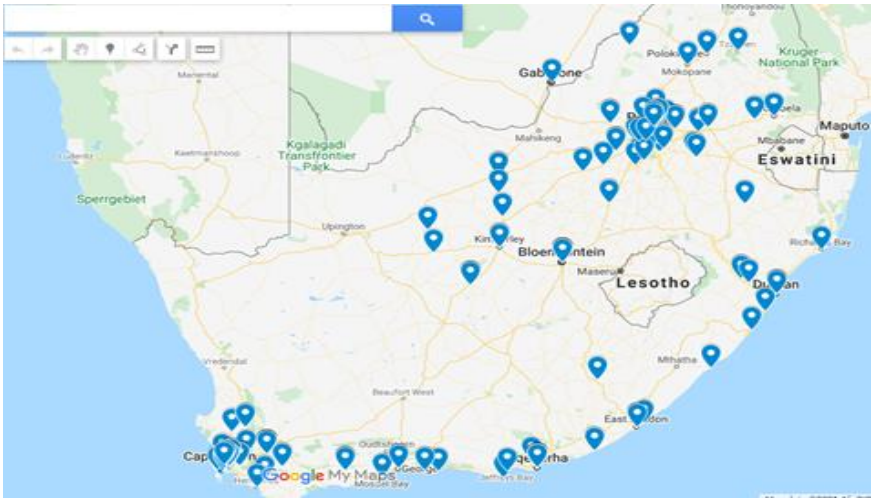

Figure 1.5: Distribution of outstanding results in 2012. Source: Google maps (Rasmussen, 2015). IRD project map compiled by researcher. It is important to note that a large amount of clustering occurs in urban areas and pins are superimposed.

iii. IRD Project Recruitment Process

a. Pre-1995

- Research participants donated their biological material to the research project (Figure 1.6).
- A compulsory confirmation of diagnosis (COD) form was needed from ophthalmologists, as well as a signed consent form from the participant.
- Participants were informed that if and when meaningful results became available, it would be delivered by the referring HP/GC.

b. Post-1995

- Individuals who wanted diagnostic testing were required to join RetinaSA, as financing of the testing is arranged through the support group. This became necessary as the IRD project is based at an academic institution without billing or financing capacity. RetinaSA's role is to provide additional capacity for patient contact due to the IRDPT's limited staff, as well as maintenance of the patient's current contact information.
- A COD and consent form was still compulsory.
- A pre-test counselling session with HP/GC are essential to clarify and explore the individual's reasons for testing.
- An appropriate test is selected in consultation with referring HP/GC.
- A biological specimen is collected, and after payment to RetinaSA, sent to the IRD biorepository for testing.

Individuals who are unable to afford genetic testing, are informed that their biological material will be added to the IRD project for research purposes and that any results will be conveyed to them if and when available via their referring HP/GC. This may lead to samples being stored in the repository for many years.

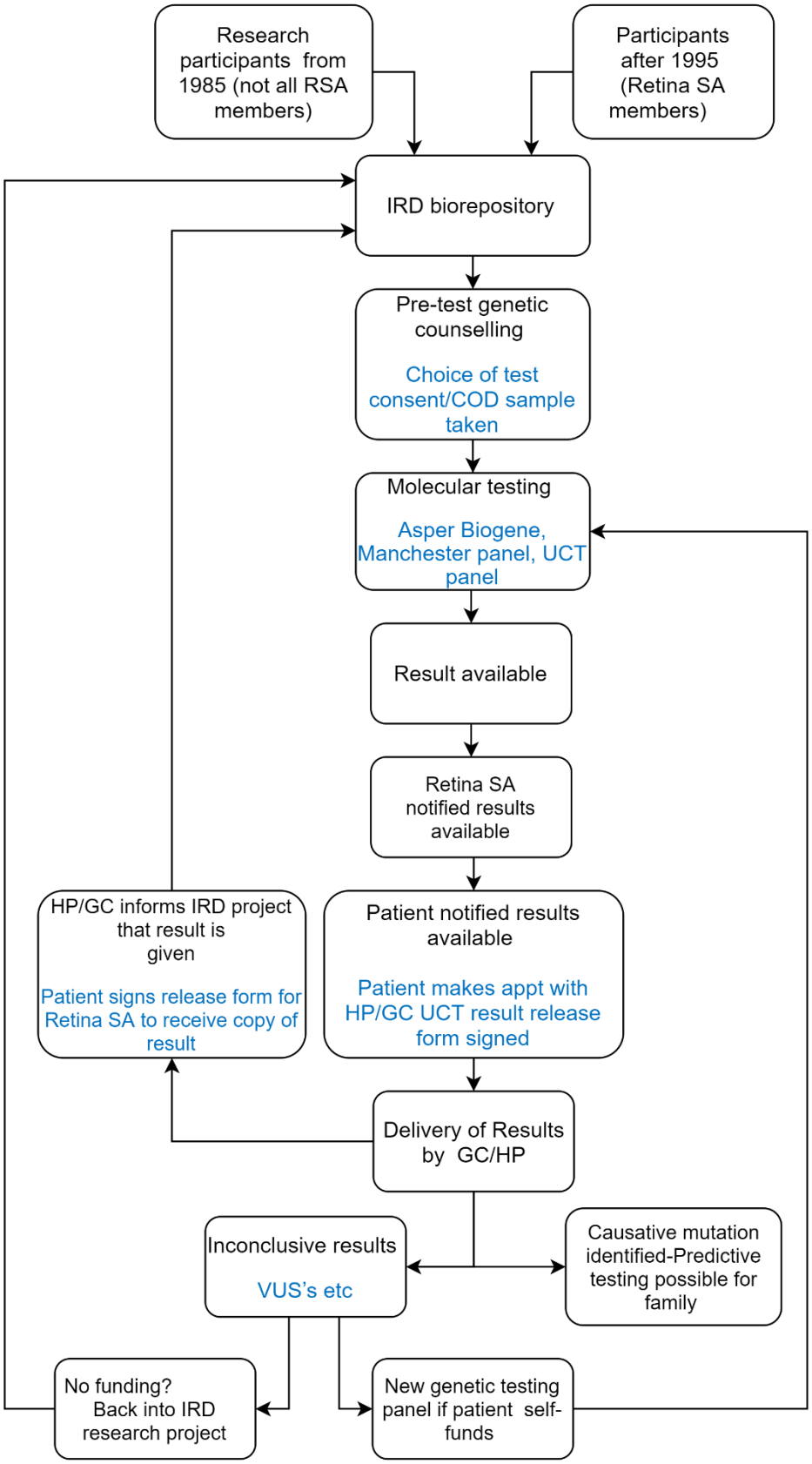

Figure 1.6: Result delivery process.

iv. Result process

Delivery of results are carried out according to a strict protocol to ensure patient confidentiality.

- When the results are available, RetinaSA is notified by the IRDPT.
- RetinaSA contacts the patient who requested the test, informing them that the result is available.
- RetinaSA organises for the patient to sign the UCT-and RetinaSA-release forms (permitting the results to be released to specific GC/HP) and submits them to the IRDPT.
- RetinaSA also informs the GC/HP that results are available.
- Designated GC/HP informs the IRDPT when the patient has made an appointment and requests the report.
- The IRDPT emails the (result) report to the authorised GC/HP.
- The GC/HP informs the IRDPT when results have been delivered.
- A copy of the result is sent to RetinaSA if the patient has signed RetinaSA's biometric release form. This release form is filed with all the patient documentation.

If the results are inconclusive, the patient can request further testing, in consultation with the HP/GC, and the process will restart. If self-funding is not an option, the sample will remain in the IRD biorepository for possible future research/request for testing. This is an advantage for the research participant because as new technologies and genetic findings become available, the sample can be retested in order to find the causative mutation. If the results are conclusive, carrier testing can be offered to at risk family members. The responsibility of informing other at-risk family members, lies with the participant.

v. Psychosocial issues

a. Family communication

There are many factors affecting the dissemination of genetic information amongst family members. Some factors mentioned are anxiety and guilt felt by the proband, their understanding of the inheritance pattern of their disorder, as well as their family relationships (Hodgson et al., 2016). There are different family dynamics, and the communication style in each family will be specific to that particular family. This is also dependent on whether family members have a close or distant relationship. The participant, however, should be urged to share information with at-risk family members and be informed that it is their responsibility to do so. Cancer-research studies recommend that probands who are mutation positive share their information with parents and siblings, but not with their minor children (Vadaparampil et al., 2012). The GC/HP are not ethically responsible for ensuring that results filter to families (Genetics, 2017), but it is their role to facilitate family communication. This communication of sensitive information to family members needs to be with their consent, as some people decline to receive genetic results.

b. Refusal of Genetic results

Patients declining to receive their genetic results is a phenomenon that has been observed. Researchers found that a cohort of anxious colorectal cancer patients declined to receive genetic results because they anticipated becoming depressed (Esplen et al., 2003). There were also positive associations between income, quality of life, concern for family members and a negative association in the belief that they could not cope with the results (Vernon et al., 1999). A breast cancer study found that even when genetic testing was offered at no cost, there was reluctance, hesitancy and inexplicable inconsistency in individuals wanting to know their mutation status (Keogh, 2004). Perhaps, a little more understandable is the situation as it pertains to late onset neurological diseases where studies refer to the incurable nature of the disease, implying that individuals felt genetic testing would be of little or no value (Paneque et al., 2019).

c. Ethics

Some would argue that the availability of these genetic results implies a moral responsibility by the IRD project to ensure that such results are returned. As society has had a global shift regarding genetic results, there are claims that this could influence medical decision making, especially in children. The participants of many research projects with large biorepositories, have increasingly expressed the need to receive their individual results (Wallace & Kent, 2011). The Organisation for Economic Cooperation and Development (OECD; of which South Africa is a member) provides guidelines for Human Biobanks and Genetic Research Databases, further suggest that biorepositories should have policies in place guiding the feedback process (OECD, 2009). Research project teams also have a responsibility to be open and transparent with participants about whether results will be returned when the consent is taken for research (Bollinger et al., 2012). It has been reported that research participants were interested in their genetic results for treatment purposes, making good health choices and sharing results with other at-risk family members (Jewell, 2012).

d. Type of results

Other participants also expressed that the type of result was important, in that they wanted to receive medically actionable results, non-actionable results and their carrier status, although they were less interested in VUS (Wright et al., 2014). Participants therefore want results that will make a difference to their lives or their understanding of their disease which will enable them to adapt/manage their disease. Although various delivery models have been used in order to increase the uptake of genetic counselling, it has been reported that some GC were reluctant to use virtual delivery models (Otten et al., 2016). However, since 2020, many areas of healthcare have changed due to the Covid-19 pandemic and virtual communication has become widely used among the GC/HP community (Claypool, 2020).

e. Telemedicine

Geographical limitations have also been explored with large health-care systems and telemedicine has been identified as a means to overcome the issues of uptake and delivery of effective genetic services (Brown et al., 2018). The shortage of genetic counsellors and clinical geneticists also impacts service delivery, and strategies to obviate this has led to innovative ideas like web-based tools and genetic counselling chatbots (Flannery, 2018). Cost and time are also listed as challenges in the return of results by biorepositories but employing a research GC has made the result-delivery process more efficient; in this instance the presence of a dedicated member of the team in a Canadian biobank increased the proportion of results returned and was found to reduce the burden of pre and post-test counselling (Papaz et al., 2019).

1.1.3 Rationale

The IRD Biorepository based in the Division of Human Genetics at the University of Cape Town, has conducted research into the molecular basis of IRD for the last 35 years. Many genes have been identified in this period and by 2019, 3413 patients and their families had been recruited onto the project. In this time, many papers have been published reflecting research aimed at identifying the genetic basis of disease in patients/families, and as technologies evolved the molecular diagnosis of patients increased, with results of more and more patients becoming available.

Novel therapies like those involving gene replacement generally require the molecular diagnosis of patients before enrolment. The vision of RetinaSA underlies the importance of genetic results for patients participating in gene therapy trials.

By 2019, of 3 413 individuals recruited onto the project, 1171 individuals had disease-causing variants identified; 416 results were delivered thus far, and another 755 results were evidently outstanding. This study aims to understand the reasons why so many results remain outstanding, as well as to explore the factors that have contributed to this. Any information uncovered would help to improve result delivery.

The research aimed to engage with GC who have delivered results to gain insight from a HP perspective. They would be interviewed to gather further insights into the result delivery process to ascertain whether they were aware of any barriers that may be affecting the result delivery process. A mixed methods approach was therefore taken as quantitative and qualitative data are combined. This translational research study has the prospect of benefitting individuals presently enrolled in the IRD project as well as improve processes currently in place.

1.2 Research question

What are the factors affecting the result delivery process to patients/subjects who had consented getting results from the IRD project (if and when these became available), and what are the experiences of GC involved in this process?

The aim of this project is to determine factors influencing the result delivery process.

The objectives of this study are:

1. To have a clear understanding of the IRD database in the Division of Human Genetics at UCT, and the result delivery process.
2. To interrogate the database to ascertain the reasons recorded therein for the non-delivery of results.
3. To explore the views of GC about their experience with the result-giving process.

Chapter 2: Methodology

2.1 Research context and Study Design

Quantitative, qualitative, and mixed methods research are three methodological study designs which are typically used in the social and behavioural sciences (Tashakkori & Teddlie, 2003). Quantitative research focuses on data in the form of numbers. After the data has been obtained, they are usually transferred to a computer-readable format and correlations between variables and outcomes are established (Choy, 2014). Data are recorded and verified so that other researchers can validate and replicate the findings (Dudwick et al., 2006).

Qualitative research is aimed at gaining an in-depth understanding of people's experiences, perceptions, behaviour, and processes, as well as the meanings they attach thereto, and is usually collected by semi structured, open-ended, and in-depth interviews (Moser & Korstjens, 2017). Qualitative descriptive methods involve human experience and perception (Sandelowski, 2000). Qualitative content analysis is an active form of analysis of verbal and visual data with the aim of summarising the information extracted (Sandelowski, 2000). The collected information is in the form of impressions, words, sentences, photos etc. and therefore different research strategies and data collection are used (compared to quantitative studies) (Choy, 2014). Purposive sampling is typically utilised, since a small, well-defined participant group is required to provide the depth and richness required. Transcripts of the audio recordings and the field notes are very important, as they enrich the other data sources. In Figure 2.1 below, the 'codes to theory model' proposed by Saldaña (2016) is illustrated to explain the process of qualitative research.

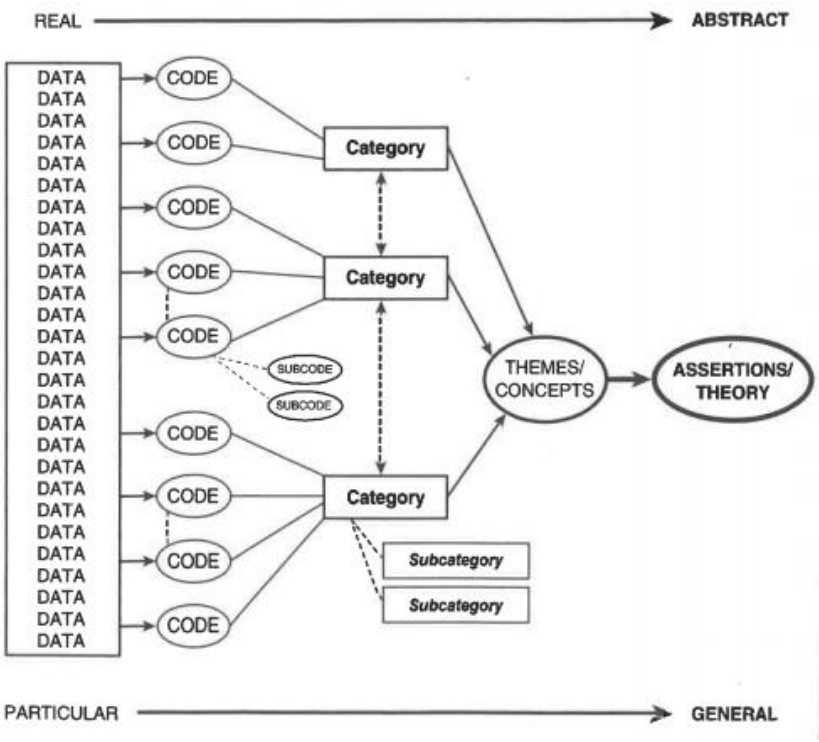

Figure 2.1: A streamlined codes-to-theory model for qualitative enquiry, reproduced from (Saldaña, 2016)

Mixed methods research is a methodology which is distinct from qualitative research (Creswell, 2007). Through the use of this approach, a more complete picture emerges, as insights are gained from both a quantitative and qualitative perspective, (Cresswell, 2013). The advantages and disadvantages of mixed methods methodology as discussed by Creswell (2007) is outlined in Table 2.1.

Table 2.1: Advantages and disadvantages of Mixed methods methodology (Creswell, 2007)

Advantages	Disadvantages
All tools of data collection (both quantitative and qualitative) can be used	It takes more time and resources
Researchers can collaborate across quantitative and qualitative methods	Complicates the procedure of research
Multiple paradigms can be considered	Knowledge of both forms of data needed by researcher
It is a practical method - solving problems using numbers and words providing a complete picture	

The mixed methods sequential explanatory design consists of two different stages-quantitative analysis which is followed by qualitative analysis (Cresswell,2007). Four different outcomes are possible in a mixed method design. The quantitative and qualitative approaches will either corroborate each other's findings, elaborate on the findings of one approach, be complementary in that they collectively generate new insights, or contradict each other, if their findings conflict (Brannen, 2005).

In the current study, a mixed method approach was thought to be the best method to obtain a richer and deeper understanding of the result delivery process. The resultant data from both methods could then be combined which could uncover possible reasons why results were not delivered to the individuals in the IRD project. It was anticipated that the results of the quantitative database analysis would also assist in formulating the open-ended questions directed at the GC. Consequently, the quantitative data analysis was completed first. This combination of qualitative and quantitative data produced valuable insights which impacted this project. In subsequent sections, the quantitative data will be discussed first, followed by the qualitative data.

2.1 Quantitative Data

2.1.1 Data Source

As depicted in Figure 2.2, the IRD database is a sub-database in the HG Biorepository. There are 3413 samples stored from 1553 families in the IRD database. The amount of data in the IRD project changes daily due to the interaction between HP, researchers, and arrival of new samples in HG.

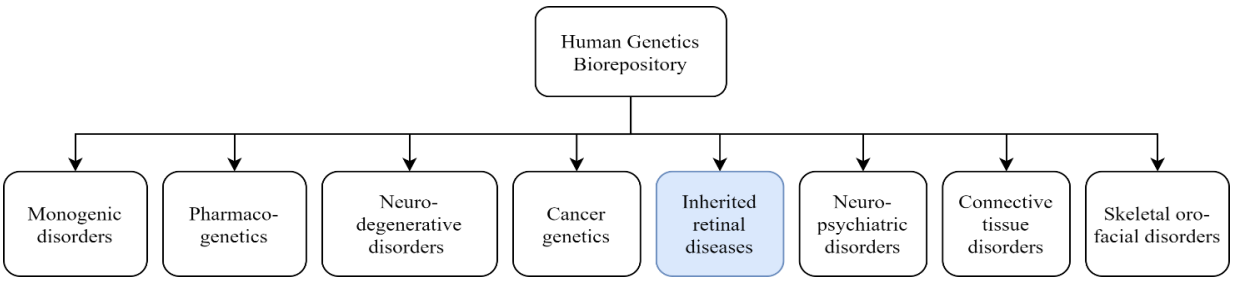

Figure 2.2: Human Genetics Biorepository

The data utilised for the quantitative analysis consisted of 755 records representing research participants who had not received their genetic results. These individuals had been recruited since 1985 and consisted of a heterogeneous sample of individuals who were either affected, at-risk, unaffected, parents, spouses, or carriers, who had consented to genetic research aimed at identifying the underlying genetic cause of IRD (either in themselves or their affected relative) and if the mutation was confirmed, to receive the ensuant genetic test result via the IRD project. Inconclusive results are returned to the

database for future analysis as it is hoped that, as technology changes over time, causative variants may still be identified.

2.1.2 Data extraction

As data is entered into various interrelated fields in the form structure, a query can be run on the database and the information exported as an Excel spreadsheet. Figure 2.3 shows a screenshot of the Graphical User Interface (GUI) in the background and the actual Microsoft Access database where the IRD data is stored in the foreground.

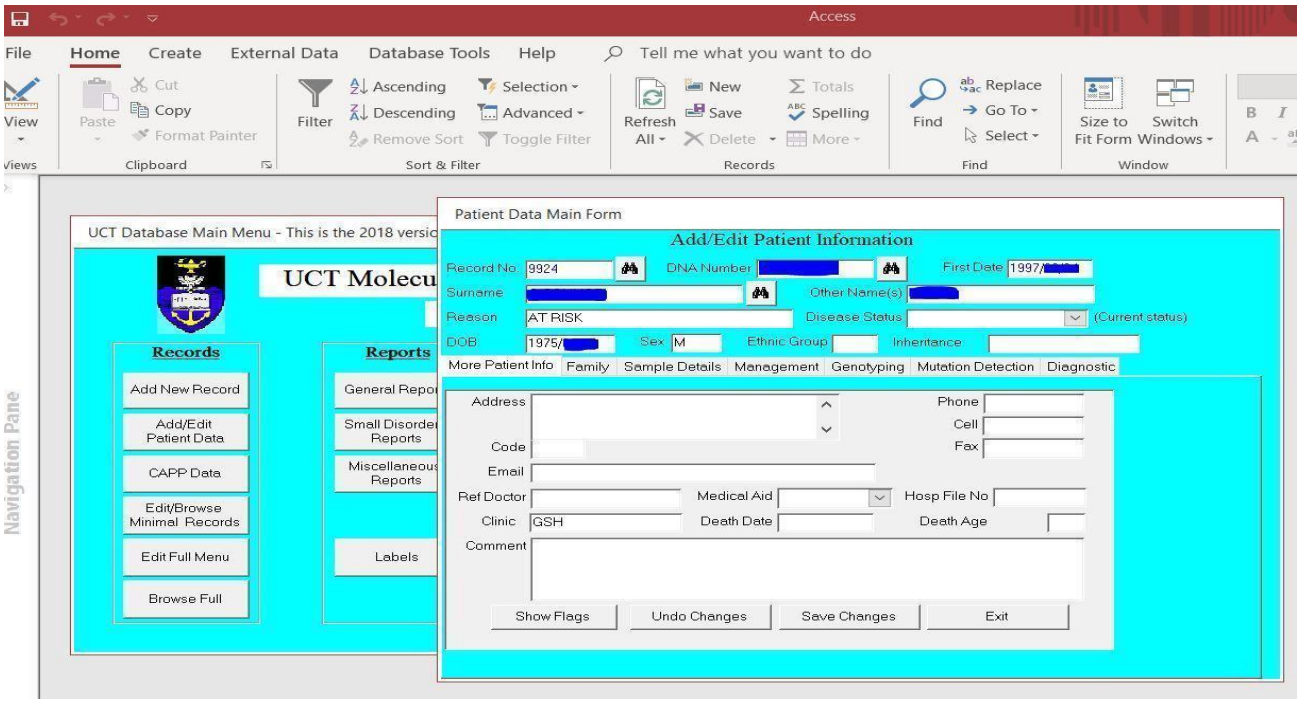

Figure 2.3: Form structure of the Microsoft Access Database which accompanies the HG biorepository.

A query was run on the IRD database (accessed 17 July 2019) to identify all individuals who were in diagnostic mode. **"Diagnostic mode"** refers to individuals for whom a causal mutation was found. This included records of affected individuals as well as family members who were in 'diagnostic mode'.

The total sample set consisted of 1171 records. Of the 1171 records, 416 were of individuals who had already received their results, leaving 755 records of individuals who had apparently not received their results.

The original 'study query' run on the data (17 July 2019) targeted various fields. These are listed and described in Table 2.2.

Table 2.2: Specific fields extracted from database.

Fields	Explanation
DNA number	Participant's unique ID number on IRD database and sample tubes
Record number	HG Biorepository record no
Birthdate	Date of birth
Sex	Male/Female
First date	Date first entered IRD project (i.e., when sample arrived in laboratory)
Diagnosis code	Code given to participant to represent their disease status (e.g., affected, unaffected, spouse, etc.)
Test date	Date the test was performed
Family tab	General information regarding the family
Patient information	Personal data captured about participant
Number of counsellor comments	How many patient contacts made by a counsellor
Counselling comments	Comments written after GC/HP contacted participants
Person last contact	Person who last contacted patient
Results given	Whether results have been given (Yes/No)

2.1.3 Data Exploration

The 755 electronic records were explored. The open text fields "Patient information" and "Counselling comments" were mined for more detailed information to clarify why results were not delivered. The 17 features obtained through this exploration are shown in Table 2.3.

Table 2.3: The 17 features extracted from the "Patient information" and "Counselling comments"

Features	Explanation
Incomplete data entries	No data recorded as to why results were not given
Results were given	Database recorded results were not given
Patient did not make contact	Participant did not contact GC after being informed that results were available
Deceased	Died
Loop closed	The GC was sent the result, but IRD project unsure if result was delivered as GC did not confirm this
In Process of result delivery	In Result delivery process but not contacted yet
Patient closed off	After numerous attempts to contact participant and appointments made, patient did not attend. No further attempts will be made.
Duplicate	Participant has two DNA numbers on database
Uncontactable	Outdated contact details
Sample failed	Results not available as sample failed, but incorrectly recorded in database as result available
Did not arrive for appointment	Appointment made but participant did not arrive, thus no results given
No Release form received	Result not delivered due to patient not authorising release of results to HP/GC
Report deleted	Mutation subsequently downgraded to a VUS (prior to result delivery)
Family emergency	Patient family emergency prevented them keeping appointment for result delivery
Counsellor not available	Reason not listed
Minor	Under 18 years of age
Family result	Member of a family

The 17 features from the preliminary dataset were inspected and the frequency of these were recorded. The Microsoft Power BI visualization tool was used to summarize the data into interactive charts and tables (Microsoft Power BI, 2019).

The records were grouped into "age" bins (1-7) as seen in Table 2.4. Grouping the data into ages bins correlate the age the person was at the time of enrolment into the study to the age the person would have been when the query was run. The ages ranged from 3-120 years old. Some individuals were enrolled in the 1980s; they have therefore been in the database for many years. If a few individuals were 70 years of age or older when they were recruited, they would now be 100 years or older. It is assumed that those individuals who fall in the >100 years of age category are deceased and were coded 6 and 7.

Table 2.4: Categorised age ranges (in years) of participants

Age bin	Code
0 to 17	1
18 to 39	2
40 to 59	3
60 to 79	4
80 to 99	5
100 to 109	6
110 onwards	7

The diagnostic codes ranged from 'unaffected', 'affected', 'spouse', 'at risk', 'carriers', 'parents', and 'unconfirmed carriers' and are illustrated in (Table 2.5). It is not clear what the difference between unaffected and at risk refers to as this is clearly defined in the database. An at-risk person could also be unaffected, an unaffected person could be a spouse or a carrier or unconfirmed carrier.

Table 2.5: Categories of diagnostic codes

Diagnostic codes
Affected
Unaffected
At Risk
Carrier
Unconfirmed Carrier
Parent
Spouse

2.2 Qualitative Data

2.2.1 Participants

The five participants interviewed were GC registered with the Health Professional Council of South Africa (HPCSA), who have worked on the IRD project. The GC varied in age and experience. Their ages ranged from 34 to 68 years, and their experience with result delivery ranged from four to 35 years. Some GC worked in private practice and some in the public or government sector, or in both.

2.2.2 Recruitment

In qualitative research, purposive sampling is done and therefore specific GC were personally approached to recruit them onto the study. The GC were selected as they have first-hand experience in result delivery on the IRD project and are well known to IRD project and RetinaSA. The researcher was aware of recurring names of GC who had previously done pre-test counselling, as well as delivery of results on the IRD project. Two GC were recruited at the Southern African Society for Human Genetics (SASHG) conference in August 2019 and three GC were recruited from HG at UCT. A total of seven GC were eligible to participate in the study, of which five were successfully recruited. One GC was not recruited as she is the supervisor of this project and the other had emigrated. As the selection of GC were based on their experience with result delivery in the IRD project, as well as their background of private practice or state employment, the number recruited includes almost all eligible (GC) participants.

2.2.3 Data Collection

i. Interview question guide

An interview question guide was developed to ensure that a set of topics were explored relating to result delivery in the IRD project. Open-ended questions were used to elicit individuals' thoughts, feelings, and experiences (Moser & Korstjens, 2018). Close-ended questions were also used in the consent form to collect demographic data. One mock interview was done with a genetic counsellor to assess whether the questions were suitable, and the question guide was adjusted accordingly. The researcher and supervisor discussed the interview guide, and some questions were subsequently amended after the exploration of the quantitative research. The information sheet, consent form and interview question guide can be found in Appendix 1, Appendix 2, and Appendix 3.

a. Interviews

The interview question guide was emailed to the GC participants ahead of the interview, for familiarisation and to facilitate thoughtful responses. Questions were used as prompts to make the interview as unstructured as possible. Before the interview commenced, informed consent was obtained. The recorded interviews were conducted in English and

were between 25-50 minutes long. The venue was decided by mutual consultation. Three interviews face to face and two were virtual. The virtual interviews were due to one genetic counsellor's geographical location and the other was due to lockdown in South Africa during the Covid-19 pandemic. The researcher strove not to influence the participants during the interviews by ill-chosen comments or behaviour. Field notes were also taken by the researcher to record any non-verbal behaviour and other observations during the interviews.

b. Data filing

The raw data, in the form of audio recordings, were filed and coded with a unique code. The GC data was coded as GC1-GC5, and all the field notes generated were labelled with the same code. All personal details of the GC were removed during the filing process. Access to the data was protected and stored on the researcher's password protected personal laptop.

c. Transcribing

The audio recordings were played twice over by the researcher so that familiarisation of the data could take place. Field notes were reflected upon, before the data was transcribed. The non-verbal actions were also described in detail (Moser & Korsten's, 2018). Data was transcribed verbatim by the researcher and was therefore an accurate reflection of the interview. All referrals to names in the text were removed to ensure confidentiality of the GC. Other possible identifying information was removed from the description of the participants and quotes to ensure anonymity. As it is a small community, readers may be able to recognise participants. The transcribing was done as soon as the interview was completed in order that the subtle nuances of the interview would not be lost to the researcher.

2.2.4 Data analysis

The transcribed interviews were printed and read twice by the researcher in order to get a sense of the data. Data analysis started from the first interview, as the iterative approach and emerging design is an important aspect of qualitative research (Moser & Korstjens, 2018). By moving back and forth between data collection and analysis, rich data was accumulated.

a. Coding

In qualitative research, a code is a "word or short phrase" (Saldaña, 2016) that represents an assigned attribute in a certain text, such as a transcribed interview. The codes were assigned in the third read-through of the transcribed interview and checked again with more cycles of coding in order to extract the data's primary content and essence (Saldaña, 2016). The codes were also used continually, all the way through the five transcripts. These codes were later grouped together into categories. This coding was done manually by the researcher due to the small sample size. The coding of the interviews was done from the

perspective of the researcher, (Saldaña, 2016) and therefore can be affected by the researcher's ethnicity, gender, race as well as level of personal involvement in the research. At best, coding of the data is a subjective process, but when discussed with peers and supervisors, this can be mitigated to increase reliability of the coding data. Discussion in research method meetings were also done where feedback and suggestions from peers were explored. The codes generated from the data were discussed with the supervisor, to assist with the reliability of the codes as well as the grouping of the codes into categories, before deciding on the final themes.

b. Themes

After the codes were defined, these codes were grouped into various categories and subcategories and then into potential themes. Themes are patterns, trends, or concepts, which recur in the various GC transcripts and are "active creations of the researcher" (Clarke & Braun, 2018). These themes were also analysed in the context of the research question. To illustrate the process, "moral responsibility" was a code grouped into the theme "Ethical Research". The emerging themes from the qualitative research were further analysed, in conjunction with the quantitative data to ascertain whether there was any overlap.

c. Researcher Bias

One aspect of the project is that it may be considered "insider research" (Fleming, 2018), as the researcher is currently working on the IRD project as a research nurse and interacting with GC, as well as the IRD project participants. This could be a potential source of bias, however, it may also enable a "deeper understanding and interpretation of the data" (Fleming, 2018), leading to valuable insight into the various issues under investigation. By working on the project, the researcher has an innate understanding of how the various processes work, as well as the issues described by the GC interacting with the project. Aspects of this research could be influenced by the researcher's subjectivity and engagement with the IRD project, but this can be mitigated if the researcher is self-aware and consciously striving for objectivity. Discussing research issues with the main supervisor also assisted in reducing bias.

2.2.5 Ethical Considerations

The Declaration of Helsinki was developed by the World Medical Association, as a guide for physicians and other medical personnel, to abide by ethical principles when involving human subjects in research as well as human material and related data (Association, 2013). Principles addressed by this Declaration were used throughout the study. The larger study (Umbrella Project - "Genetics of Inherited Retinal Diseases") of which the current study is a sub-study, has been approved by the UCT Human Research Ethics committee (HREC), 226/2010. Before data collection, this specific study obtained ethical approval from the UCT HREC, 422/2019 (Appendix 4).

The information sheet and consent form were read and signed by the participants before the interviews commenced. The GC who were interviewed virtually, emailed the

signed consent form to the researcher. GC are experienced in administering consent sheets to patients and it was therefore anticipated that they had a good understanding of the study's requirements. All consent forms were filed during data collection and scanned electronically for future referral if necessary. The IRD database was available for data analysis, and authorised by the Head of HG, who is the second supervisor on this project. Access to the data was uncomplicated as a confidentiality agreement was signed by the researcher when employed by HG.

2.2.6 Privacy and Confidentiality

In terms of quantitative analysis, the participants of the IRD project who have not received their results, had consented that future research, not yet identified and subject to HREC approval, could take place, provided that their anonymity was not compromised. Full confidentiality was maintained in terms of the data analysis, and no names were selected in the initial query.

The GC participants were informed that the researcher would be transcribing the audio recordings and would ensure confidentiality. Only the researcher and supervisors would be able to link their audio responses to their identity. Any referrals to names were removed as well as other identifying information to ensure confidentiality. All participants were also assured that they would not be identified directly in the research outcomes of the project, as well as any presentation, whether at conferences or seminars. After the research concludes and findings are published, the audio recordings would be deleted, and all data destroyed. All information generated by the project will remain confidential and will only be used for this research project.

2.2.7 Benefits and Risks

The possible impact and results of this study was considered to outweigh the possible risks. The data generated could provide insights into aspects influencing result delivery. The perception of the GC could also show insight into the quantitative data and result delivery process. Any recommendations could ultimately improve the result delivery process for all stakeholders.

Chapter 3: Results and Discussion

The purpose of this study was to investigate (i) the extent to which results emerging from the IRD project had not been communicated back to patients/families, (ii) the factors affecting the project's result delivery process from the IRD project to patients/families who had requested molecular testing, and (iii) to ascertain what the experiences of GC involved in this process were. As this mixed methods research study consists of quantitative and qualitative data, the findings of each method will be presented, followed by a discussion on the collective findings in order to provide a comprehensive picture.

3.1 Quantitative Results

Following the identification of the initial cohort (n=755); further exploration of the database and the physical subject files, showed that 76 of these individuals had received results, but were not entered as such onto the database. Of the remaining 679 individuals, 46 were deceased and 5 records were duplicated, reducing the initial cohort to a primary cohort of n=628. In this primary cohort (n=628), there was categoric evidence i.e., stated on the database, that results were not delivered to 131 individuals. This group is referred to as the high confidence cohort (HCC), and the remaining group of n=497 records with blank text fields, are referred to as the low confidence cohort (LCC). Both cohorts were analysed for comparison as illustrated in Figure 3.1.

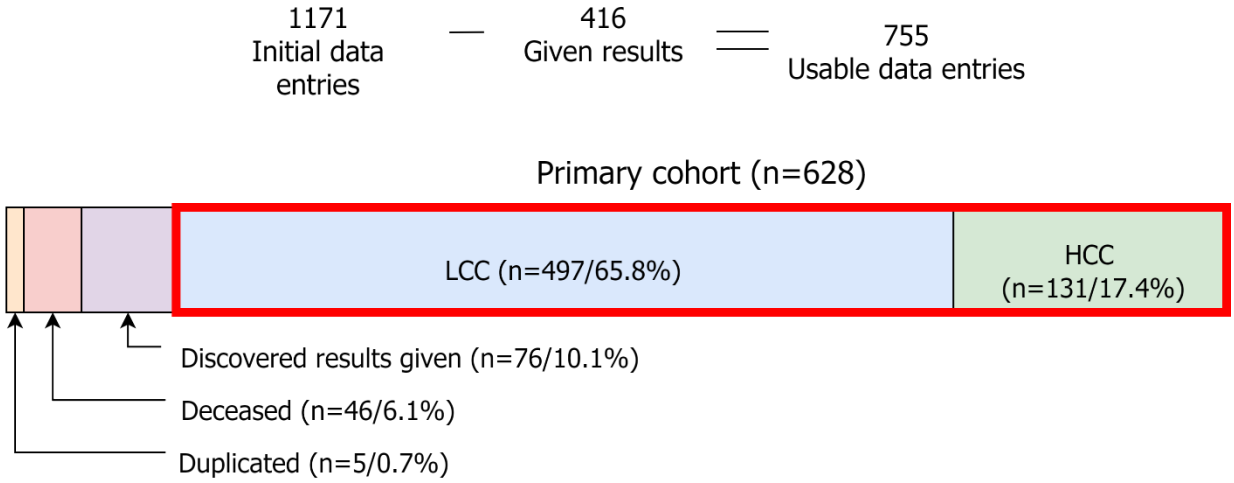

Figure 3.1: Breakdown of dataset.

3.1.1 Data Exploration

i. Primary cohort

The Primary cohort (n=628) was analysed and fields containing low amounts of data was identified. It can be deduced that the features would have a negligible impact on the dataset as can be seen in Table 3.1. If they registered less than 5%, they were filtered out as outliers or 'noise'.

Table 3.1: Features with low amounts of data

Features with small amounts of Data	Number in Primary cohort n=755	Percentage in Primary cohort
Counsellor not available	1	0.1%
Family emergency	1	0.1%
Report deleted	1	0.1%
No release form received	3	0.4%
Patient did not arrive for appointment	5	0.7 %
Sample failed	4	0.5%
Uncontactable	17	2.3%

The 628 individuals were part of 160 families. The demographic information revealed that the mean age was 55.7 years. Females represented 52% (n=326) of the cohort and males 47.8% (n=300), showing a closely distributed sample set. In two individuals, the sex was unknown. Minors constituted 20.4% (n=128) of the primary cohort. A minor in the IRD research project, and according to South African Law, is defined as an individual who is under the age of 18 years and unable to give legal consent for participating in non-therapeutic research (Van Wyk, 2003). From a clinical perspective, minor participants have a parent or guardian who signs consent for their genetic testing.

The largest proportion are affected individuals 29.6% (n=186) as illustrated in Figure 3.2. 'Affected status' may simply reflect the effort put into identifying mutations and recording this on the database.

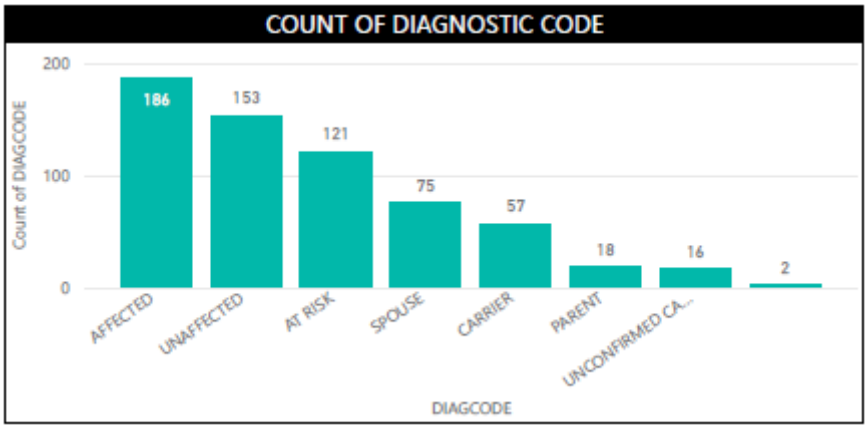

Figure 3.2: Count of diagnostic codes.

The data was subsequently evaluated to look at variables that could influence whether results were delivered or not. It was found that the largest number of outstanding results were in the years 1990-2004. The outstanding results from 1990-2004 equates to 89.4% (n=564) individuals out of the Primary Cohort of (n=628). These years coincide with the recruitment drive in the 1990's when the candidate gene approach was used, and large numbers of affected individuals and families were recruited for genetic research as illustrated in Figure 3.3. This can be seen e.g., from 2000-2004 when 1012 individuals were recruited onto the IRD project.

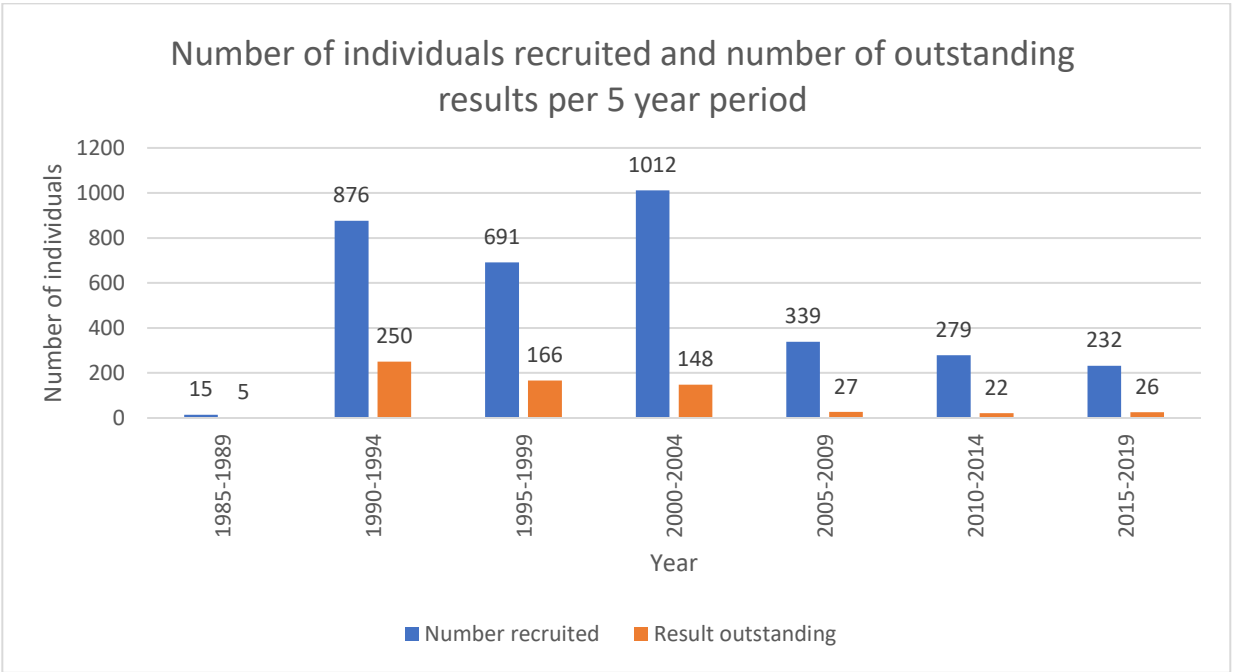

Figure 3.3: Number of individuals recruited and number of outstanding results per five-year period.

Figure 3.4 shows the percentage of results not given per 5-year period. For example, in 1990-1994, 876 individuals were recruited, 291 had outstanding results from that period which equates to 33% of the results that were not given in that time period. Over the 35

years it can be seen that the result delivery has steadily improved from 1985 to 2014 with a decrease in result delivery noted from 2014 to 2019.

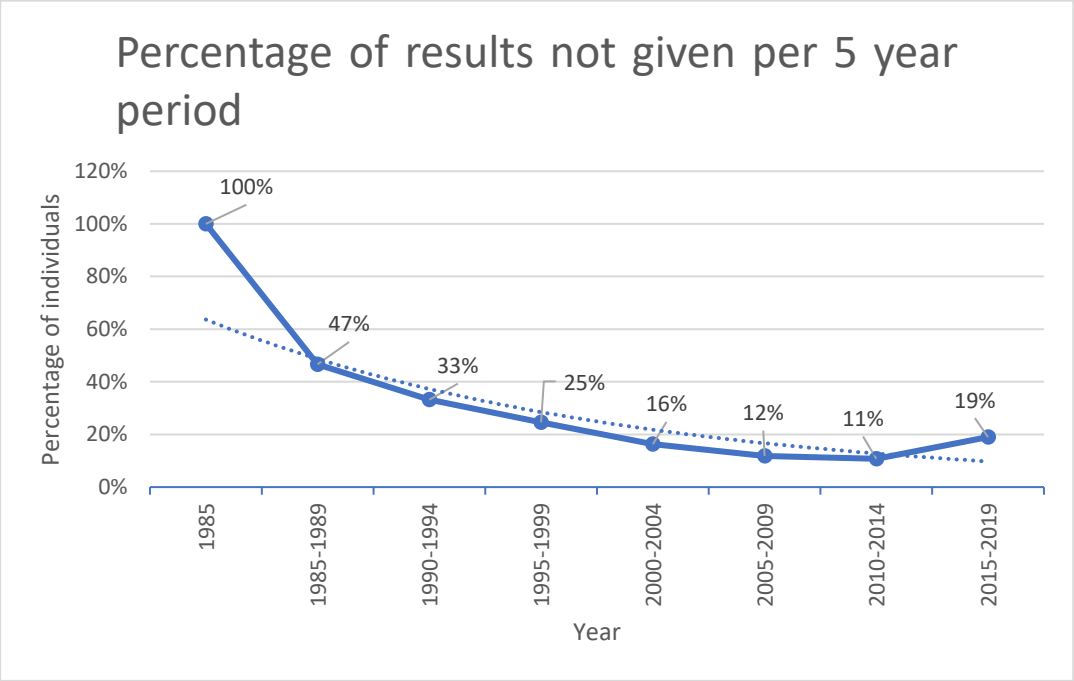

Figure 3.4: Percentage of results not given in five-year periods. The solid blue line indicates the percentage of results available for result delivery in each five-year period and the dotted line shows the overall trend of the data.

ii. High Confidence Cohort (HCC)

Just under a quarter, 20.9% (n=131) of the primary cohort of 628 was found to contain data that referred to result delivery. These 131 individuals were from 77 families. Females represented 54.2% (n=71) and males, 45.8% (n=60). The age range of the individuals were between 5-120 years old (Figure 3.5). More than half of the individuals in this HCC, 58.8% (n=77) were affected.

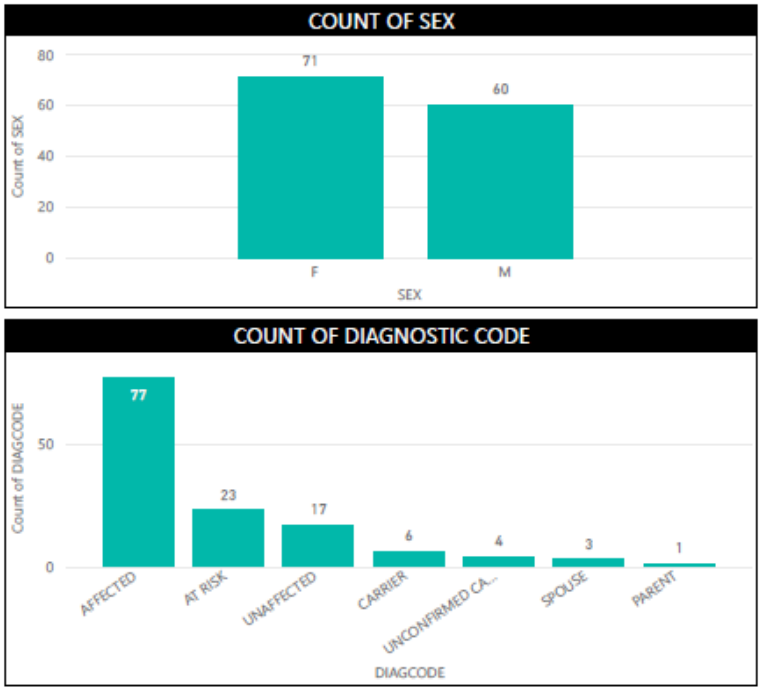

Figure 3.5: Count of Age, Sex and Diagnostic code

What was noteworthy is that a quarter of the individuals 25.2% (n=33) in the HCC were minors as illustrated in Figure 3.6.

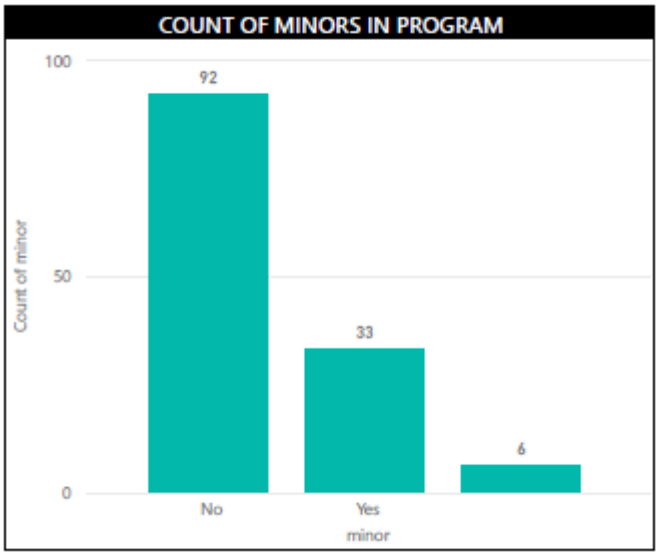

Figure 3.6: Count of Minors

In the HCC, 77.1% (n=101) of individuals were recruited from 1990-2005, as illustrated in Figure 3.7.

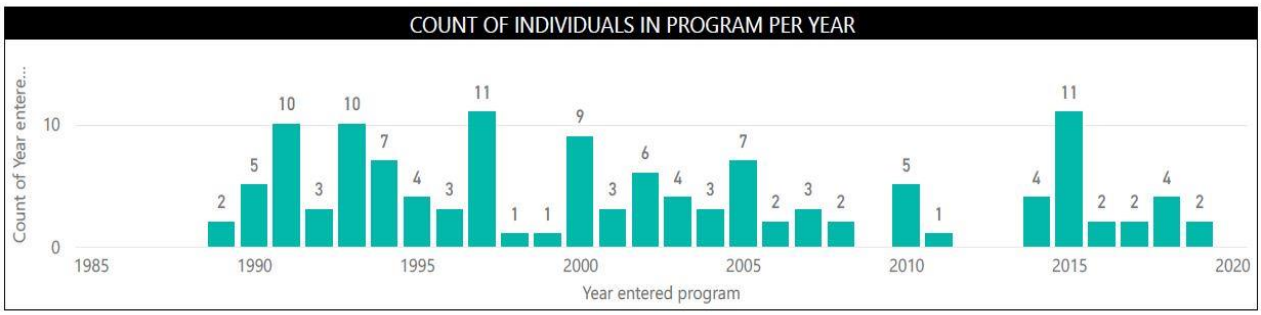

Figure 3.7: Count of individuals recruited per year

In Table 3.2 a further breakdown of HCC was done. Data that registered above 5% were explored to ascertain whether they were important factors that could explain the lack of result delivery.

Table 3.2: Breakdown of High Confidence Cohort

Features	Explanation	HCC cohort	Percentage
Patient did not make contact	Participant did not contact GC after being informed results were available	56	42.7%
Loop not closed	The GC was sent the result but did not confirm result delivered	24	19.8%
Result delivery in process	In process of results being given but patient not informed yet	21	16%
Patient closed off	After numerous appointments patients did not attend any result delivery sessions and no further attempts will be made.	19	14.5%
Uncontactable	Outdated contact details	17	13%

In the "patient did not make contact" category, these patients were aware that the results were available, but did not engage with the IRDPT. In the 'loop not closed' category, the GC has confirmed to the IRDPT that they have appointments with the patients and the

result was sent to the GC. The GC, however, had not confirmed to the IRDPT that the result had, in fact, been delivered.

"Result delivery in process" refers to results that are almost ready for delivery, but the patient is not aware of it. The "Patient closed off" refers to numerous attempts being made to deliver the results, but the patient does not arrive for unknown reasons and therefore the result delivery is closed off and no attempts to contact that patient will be made in the future. "Uncontactable" refers to outdated contact details and if we consider that the database is 35 years old, then this number is likely to be much higher in the primary cohort.

ii. Low Confidence Cohort (LCC)

A substantial percentage, i.e., 79% (n=497) of the primary cohort was found to contain no data that referred to result delivery. Although demographic information was recorded, there was no record of any contact between the IRDPT and the individual, post recruitment. These 497 individuals were from 118 families.

The demographic information of the LCC can be found in Figure 3.7. The females comprised 51.5 % (n=255) and the males 48.5% (n=240), including two individuals whose sex was unspecified. The age range was between15-120 years. A quarter of individuals, 27.4% (n=136) were classified as unaffected.

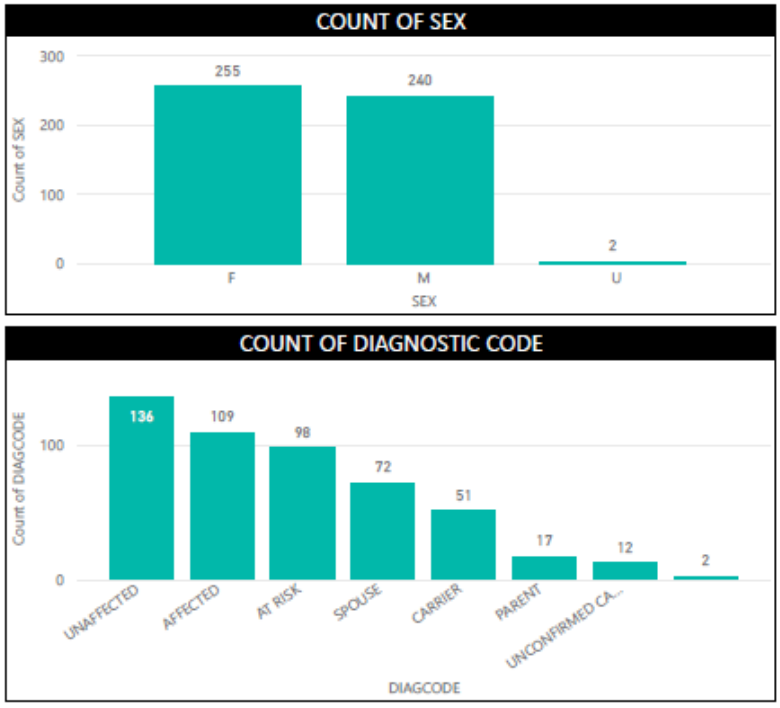

Figure 3.8: Age, Sex and Diagnosis in the Low Confidence Cohort

Minors represented 19.1% (n=95) of the LCC. Figure 3.9. illustrates 95.2% (n=473) of individuals who were recruited from 1990-2005.

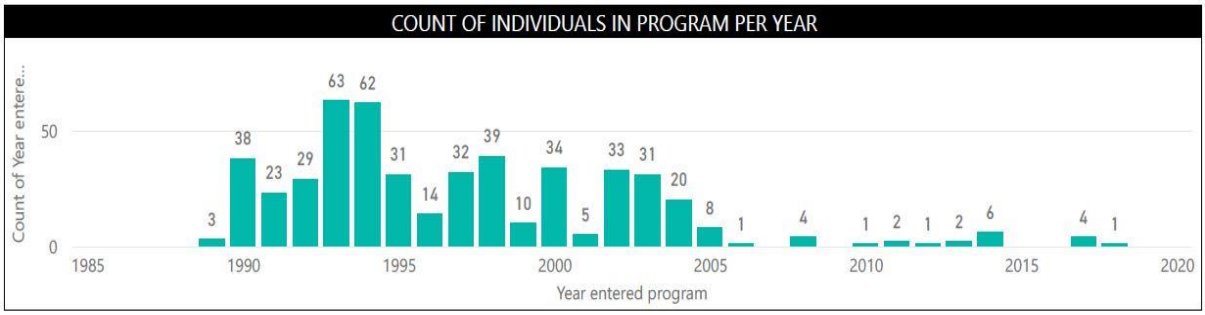

Figure 3.9: Count of individuals in program per year in Low Confidence Cohort.

3.2 Cohort comparison

The HCC and the LCC were compared to see if there are any similarities or significant differences between the cohorts. A comparison of the cohorts is illustrated in Table 3.3.

Table 3.3: Comparison of Cohorts

	Low Confidence Cohort (n=497)		High Confidence Cohort (n=131)		P-Value*
	Number	Percentage	Number	Percentage	
Males	240/495	48.5%	60/131	45.8%	
Females	255/495	51.5%	71/131	54.2%	
Age range (in years)	15-120		5-120		
Minors	95/497	19.1%	33/131	25.2%	
Individual families	118		77		
Recruited between 1990 -2005	473/497	95.2%	89/131	67.9%	<0.1
Affected	136/497	27.4%	77/131	58.8%	<0.1
Unaffected	109/497	21.9%	17/131	13%	
At risk	98/497	19.7%	23/131	17.6%	
Carrier	51/497	10.3%	6/131	4.6%	
Unconfirmed carrier	12/497	2.4%	4/131	3.1%	
Parent	17/497	3.4%	4/131	3.1%	
Spouse	72/497	14.5%	3/131	2.3%	<0.1
Unknown diagnosis code	2/497	0.4%	0	0	

**Chi-Square test only performed on variables that looked as if they were significant*

The age ranges and sex of the individuals across the two cohorts showed an even spread and the number of minors were not significantly different between the two cohorts. More

individuals in the LCC 95.2% (n=473) were recruited between 1990 and 2005. More than half of the individuals 58.8% (n=77) in the HCC were affected, which is also more than the LCC, where only 27.4% (n=136) of the individuals were affected. There were also more parents and spouses present in the LCC compared to the HCC.

3.3 Qualitative results

The participants in the study, as discussed in Chapter 2, were five female GC who practiced in state, private or both. During the interviews, the GC discussed a range of topics which affected their interaction with the IRD project, as well as result delivery. On analysis of the raw data, four broad themes, as well as several related sub-themes, were observed, as illustrated in Figure 3.10.

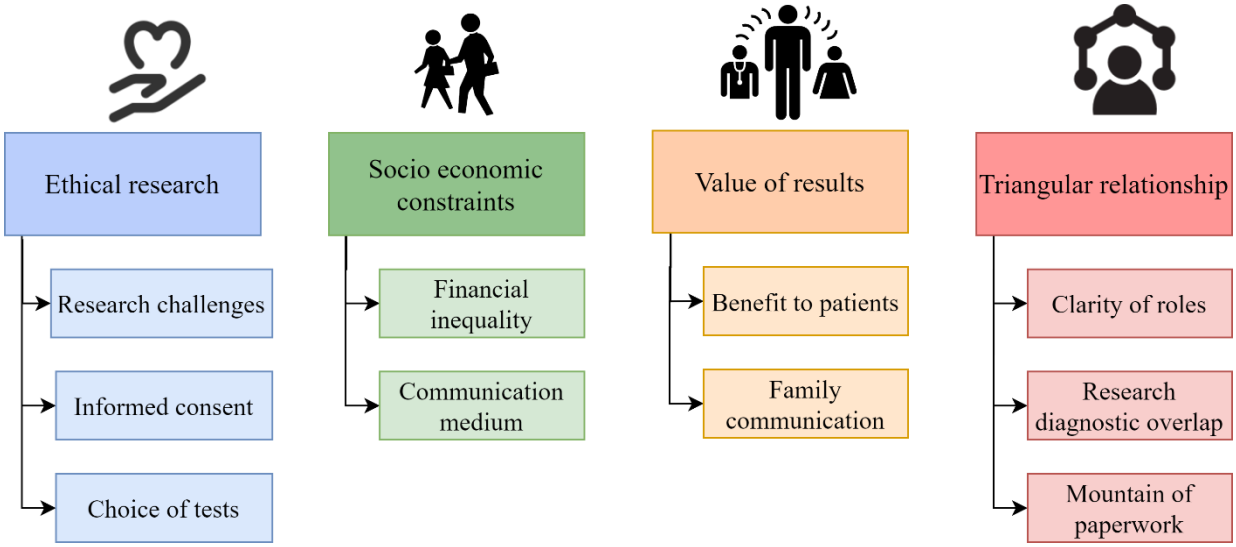

Figure 3.10: Summary of the themes and sub themes.

3.3.1 Theme 1: Ethical Research

The ethical responsibility to provide results and feedback on the research done on the IRD participants' biological material arose in most of the interviews. GC felt that the IRD project team (IRDPT) had gained from scientific research and had benefited from research outputs. The sub themes relate to "research challenges", the "informed consent" process as well as the "choice of tests" illustrated in Figure 3.11.

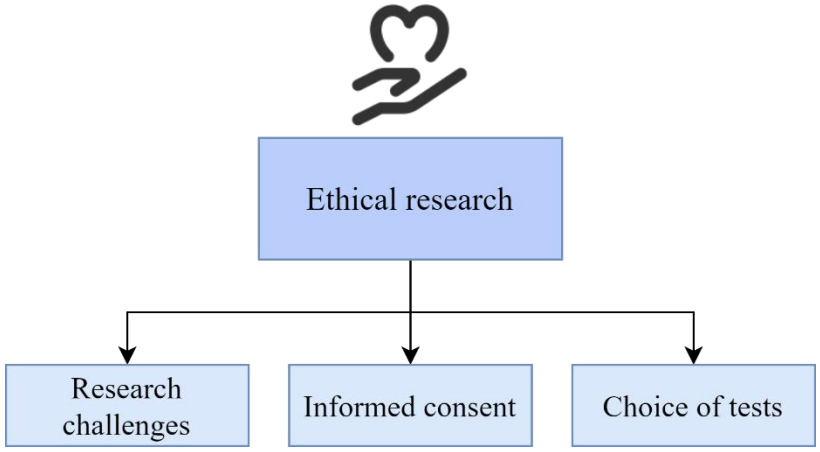

Figure 3.11: Illustration of Theme1 and sub themes.

i. Sub theme 1.1: Research challenges

GC were of the opinion that the IRD project had collected these samples and therefore had a moral obligation to return the results. This ethical responsibility of the IRDPT to ensure that these results were returned was important in order to be of benefit to the patients. The accumulation of these results, the GC thought, were due to the recruitment drive in the 1990's.

"I think at the moment, we are still dealing with a lot of backlog from years and years and years of people not getting results" (GC1)

"I think a lot of those that you have on your database are because they were involved in research and it could not be translated to service."(GC2)

The GC thought that the IRD project should have a designated budget to deal with the return of results.

"But I do think that part of that funding, part of the budgeting, part of the ethical responsibility of a research project, is saying this is part of the process, yes." (GC5)

The consensus amongst the GC were that the results needed to be returned and that a budget needed to be allocated for the return of the results. Some GC commented that research participants may not be aware that results were available, as they may have been minors when they were recruited. The result may have been delivered to parents or other family members and they may not follow up to hear if their results are available.

"In a research setting, then you know, I forget about it, they took my blood, I can't remember what it is really for, maybe I participated out of interest, but I did not really expect anything to come out of it." (GC3)

GC felt that the HREC should be involved and consulted about the return of results as the health professionals involved in the recruitment of patients for the last 35 years may have

retired. Guidance would then be needed by the HREC in terms of the method used to contact research participants.

"But are those practitioners still seeing those patients, are those practitioners still around? I would ask the ethics committee to forward an opinion on that." (GC3)

Other GC were also concerned about possible repercussions that the IRD project can encounter if results were not given. The issue of only some participants receiving results, may lead to distrust in research projects.

"As long term, one might, create reputational harm, because patients will talk and say okay, here we are again, asking and recruiting, but the family standing next to them at a Retina SA meeting says, well, I did give my blood samples, two, five, ten years ago, but I never heard anything." (GC5)

Another aspect that emerged was the method of result delivery in the future. GC felt that the patient needed to drive the result delivery. They needed to be informed that a result was available and that they needed to contact the HP/GC in order to receive their results. The result delivery would then be patient driven and not research driven in order to give patients a choice.

"The patient must drive the research result, in my opinion." (GC3)

The researcher's commitment is to prevent or reduce harm and this protection of human subjects is deeply embedded at the core of research in many countries (Beauchamp, 2019). The moral responsibility to return results is evident. Historically, researchers have acquired samples from individuals and many communities were exploited worldwide, notably vulnerable people in Third world countries. There is open recognition of the fact that research is often associated with exploitation (Benetar, 2000). The GC felt that there was an ethical obligation to return results to IRD research participants. This non-delivery of results may be seen as the IRD project withholding important information that could make a difference to an individual's family planning or treatment choices.

ii. Sub theme 1.2: Informed consent

The GC all felt that some patients did not understand the consent process. As informed consent has evolved over the years, the old consent forms were not sufficient to protect patients' rights.

"I know they do consent, but I've been thinking, in a space where they consent it's not necessarily completely understood, and I don't know if we will ever get that right." (GC4)

"To be informed, you need to understand what you are doing." (GC1)

GC felt that the IRD research participants were not adequately pre-test counselled. When this is not done, it makes the counselling more complex.

"Some of the patients had had really good upfront counselling and some of them haven't had such good upfront counselling, so you often sit and redo a whole session with a patient, before you give them a result." (GC1)

"I don't think, all of them are being adequately counselled, because going through Asper or a different pathway, they need to have a practitioner pre-test counsel them and whether it's a genetic counsellor or a different practitioner, it doesn't matter, but a doctor or someone needs to take responsibility of that and then people will think, oh, this test...I can expect an answer from in some way or another." (GC3)

They also commented on the participants' motives for testing and the meaning attached to it.

"I think it's important to be very honest with families in terms of what they want from testing and what it is going to mean. So, I feel pre-test counselling is extremely important in terms of helping the patient." (GC5).

The risk is higher for affected or at-risk minors, as these results could influence treatment options for them. This lack of pre-test counselling can also be seen in the context of the initial recruitment phase when large numbers of participants were important and capacity for pre-test counselling was low.

A recent H3Africa study reported that individuals expect feedback when they participate in research studies and the consent process is seen as an interactive process for the duration of the project (Tindana et al., 2020). If feedback is not given, people are also reluctant to participate in the future. It is evident that because consent is not fully understood, patient expectation is elevated, and result feedback becomes important and necessary. The GC also mentioned the importance of pre-test counselling and its role in genetic testing. This viewpoint is supported by research that claim consent forms are normally long and overly complicated documents which are normally above the reading ability of the average research participant (Leopeng, 2019). Level of education and home language all affect the consent process and in the SA context, this is problematic, especially when genetic results are given to participants who do not understand research. SA's eleven official languages, cultural diversity as well as unequal education system has led to barriers in understanding research (Williams, 2019). In the past, the consent forms were also not translated into Afrikaans, isiXhosa, or other African languages.

iii. Sub theme 1.3: Choice of tests

Pre-test counselling also leads to the choice of tests and whether these tests are of benefit to the patient. GC felt that testing cannot solely be limited to the IRD project at UCT, as there was a range of testing options available for their patients and they were ethically bound to offer all the alternatives to their patients. They also felt that not all genes were covered by the UCT panel and that a larger panel with more gene coverage, was available overseas, at a cheaper cost.

"I don't limit the testing options just to the research project, because at the end of the day the patient will be funding, so that they have a choice really, just from an ethical and appropriate professional manner." (GC4)

"For just a little more money we can get patients tested overseas and do double the number of genes, so that is a problem-in terms of a private counsellor I can't within good conscience say to someone here, you can have a panel done here for 250 genes for R9000 or we can send it overseas for R10 000 and get 500 genes looked at. It's not really ethical for me to say to them to go for the smaller panel." (GC1)

IRD testing is difficult to manage due to its heterogeneity and genetic counsellors explained the dilemma very clearly.

"It feels like this is a maze of dead ends and it is quite difficult to try and positively manage expectations for families. I also try to be very careful about not creating the expectation that as soon as you understand the cause, that you are going to be able to jump to different treatments or different management."(GC5)

The lack of treatment and appropriate management are aspects of these IRD conditions, and this impacts decision-making regarding appropriate tests. The implications of testing and what it signifies will need to be discussed with the individuals to allow them to make an informed decision. Genetic testing is an important aspect of genetic counselling, as the patient needs to understand the importance of testing, as well as choosing the best test according to their resources. All the GC in the study felt that there was an ethical obligation to return results to IRD research participants and the importance of pre-test counselling was emphasized in order for the patient to be aware of the implications of their decision.

3.3.2 Theme 2: Socio-economic constructs

South Africa's health system has a bearing on this project. In South Africa, medical care can be accessed through a state-funded health care system or through a privately funded system. People who cannot afford private health care, use state funded medical care. The state system, however, is severely encumbered by the volume of people as well as the budget restraints within which the system must function (Mathews et al., 2019). All GC noted that there was a marked difference between private and state patients, which had a direct bearing on genetic testing and result delivery. The sub themes relating to socio-economic constructs are "financial inequality" and "communication challenges" faced in the IRD project, illustrated in Figure 3.12.

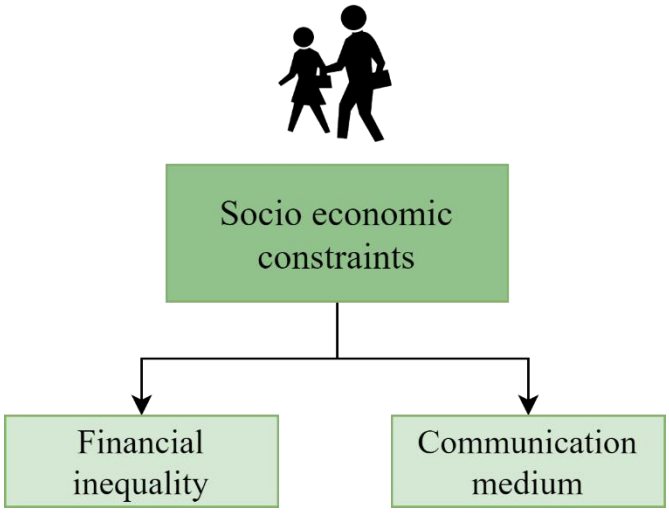

Figure 3.12: Illustration of Theme 2 and sub themes.

i. Sub theme 2.1: Financial inequalities

Financial inequities are commonplace in SA society and permeates the lives of the people, from housing, employment, access to healthcare and education (London, 2008). SA is still struggling with the aftermath of the apartheid legacy, and 27 years of democracy has not changed the financial imbalance in society. GC admitted that it was challenging to work in this environment as it impacts the access and care of patients.

"It's actually, a very tricky healthcare system to work in, in South Africa." (GC5)

"Not yet delivered? in my experience, it depends on how the patient was recruited, it also depends where the patient is, in an economic or socio-economic status." (GC4)

GC discussed that when the IRD patients are state patients, this impacts the result delivery as the patients' focus are on their basic needs due to poverty. As they have a clinical diagnosis, receiving genetic testing results was not a priority for them.

"Actually, up till the point of the genetic result, genetics really didn't play a big role in the care and the diagnosis of the child in all honesty." (GC4)

"Because, especially in the rural kind of areas where the Eastern Cape delivery was happening. They don't have access to anything" (GC1)

GC mentioned that some patients in the low socio-economic areas in the Eastern Cape, may not be aware of their recruitment into a research study. This is also exacerbated by their visual impairment and interaction in an unfamiliar environment, as their low vision makes them more vulnerable in society (Simcock, 2017).

This vulnerability also plays a role in the delivery of results as they may be reluctant to travel to the main centres due to long hours in public transport. For state patients, some GC also undertake to deliver results as their social responsibility due to patients being unable to afford their services. This is done in conjunction with RetinaSA who arranges transport and facilitators to aid the result delivery process.

"Most of those we do as a pro bono service, knowing that patients don't have the money." (GC4)

Private patients are contracted into one of many medical aid schemes which offer various options that allow access to better health care using private doctors and private hospitals. These options depend on level of income and choice (Gordon, Booysen & Mbonigaba, 2020). The GC explained that the focus in private patients is divergent from state patients, as the private patients, generally, are more concerned about their risk of having another affected child, as well as management of the medical needs of an affected child. As the level of education is higher in some strata of society in SA, the private patients' needs are distinctly different from the state patients.

"And I think one almost expects it in private practice setting or context, because I think one can maybe make an assumption that people with a higher educational level, may well put more value on risk, understanding their risks." (GC5)

"I think private practice, very often, we dealing with a more educated population group." (GC5)

The GC also mentioned that the emotional needs of private patients are different, as their concern over the results are elevated, especially in X-linked and autosomal dominant IRDs.

"That's a very very different story, in fact the anxiety level then become quite high." (GC4)

There is limited coverage by medical aids for genetic testing in SA and supplementation is needed from private patients (Smith et al., 2020). Due to the higher level of education and consequently better understanding of the testing implications, the private patients are more inclined to request genetic testing. Private patients often use an overseas provider who test their family members for free if a causal mutation is found.

ii. Sub theme 2.2: Communication

South Africa has 11 official languages, and language barriers will understandably remain an issue in result delivery (Claassen et al., 2017). This was discussed as a concern by most GC. When delivering results in the Eastern Cape, they mentioned that social workers were used. These social workers worked with patients from rural areas and were familiar with them. Initially, the GC felt that they were unsure of the content explained, as well as what was understood by the recipients. This was due to the social workers not being familiar with genetic terms and concepts which was also confounded by the fact that genetic terms do not exist in African languages (Shingwenyana, 2020).

"So, if I found some people really understand what's going on, but quite often, there is a language barrier. So with the Eastern Cape, people from the Eastern Cape, always got a translator with me." (GC1)

"When you translating, depends on what the translator or interpreter, how well they can interpret or understand what I am actually saying." (GC4)

Some GC discussed that they were part of result drives that travelled to different parts of South Africa in order to deliver results. Due to the geographical location of patients in the Eastern Cape, RetinaSA transported patients and GC to main centres in order to receive their results.

"And you would travel around from main centre to main centre for about a week and you would deliver the results and they would bring the patients, plus their families to the centre where you were counselling" (GC2)

Telemedicine has been used sporadically on the IRD Project, due to geographical limitations in the rural areas of SA. All of the GC interviewed were regular users of telemedicine in their private practices, as well as sporadically on the IRD project.

"I find it very good, very effective, but I do it for a lot of my patients, access is still an issue, regardless of private practice or not, so we've been using Skype for quite a while." GC4).

Some GC were, however, concerned that a counselling session cannot be replaced by a virtual delivery model, as they felt the patient's nonverbal cues and level can be missed with Skype.

"And you might miss the patient's level. But I think that is the case with any sort of electronic media for any condition. But because of the nature of our country and where our patient's live, sometimes there is no choice." (GC3)

The way people sit tells you a lot and you have to learn that and if it's on the end of a telephone you can't assess that and so I think it's vitally important that the right kind of adaptations are made." (GC2)

All GC were not opposed to virtual communication, and most agreed that it was a solution to ensure result delivery. Some GC mentioned that Skype was more convenient for private patients who had time constraints. Travel distance has been directly related to decisions to provide genetic counselling using a telemedicine communication model, (Cohen et al., 2016). Due to the low socio-economic status of the majority of South Africans, access to personal virtual technology is still a challenge as only one third of the South African population has access to a smartphone (Statista, 2021). All GC mentioned that there was a marked difference between private and state patients, as their challenges and needs were different. South Africa's health disparities and financial inequities therefore can influence result delivery in the IRD project.

3.3.3 Theme 3: Value of results

The value of receiving genetic results may seem self-evident, but in this regard, the GC had mixed feelings. On the one hand, the GC were satisfied that they played an important part in delivering and counselling patients about the results and condition, but they also expressed difficulty with the value of genetic testing for the IRD patients. These results were reflected upon, and the meaning of results were questioned. As explained previously,

genetic testing could produce VUS's, partial results, incidental findings, or no definitive mutation.

The sub themes linking to this theme were "benefit to patients" and "family communication" illustrated in Figure 3.13.

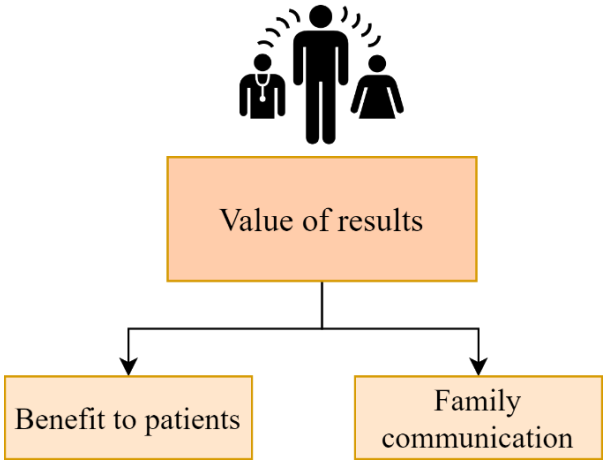

Figure 3.13: Illustration of Theme 3 and sub themes.

i. Sub theme 3.1: Benefit to patients

GC explained that they experienced satisfaction that their role was meaningful during result delivery. The patients often expressed that they benefited from receiving the results, understood the implications of their condition and the precautions needed to prolong sight.

"That AHA moment as we call it. Definitely there was a point of recognising the role of genetics, and maybe not necessarily, the deep science of genetics, but actually how this thing has come about. One mother actually held, held a very wrong belief (witchcraft), so it was really amazing. Her daughter was about twelve already. That really did, count." (GC4)

As IRD are so heterogeneous, GC expressed the challenging nature of working with IRD, because if the causative mutation is found, it does not lead to surgery options or major treatment for the patient. Symptoms within one family may differ as well as prognosis and age of onset.

"In general, working with retinal degenerative conditions, there remains a certain amount of frustration with working with this group of conditions, because it is so variable and so heterogeneous." (GC5)

"And because it's so difficult to counsel patients and manage expectations, that you can spend a fortune on testing and not get an answer that is useful or meaningful." (GC5)

They felt that the patient incurred costs and transportation difficulties to get to an appointment, only to learn that the findings yielded no clear results. The GC therefore were of the opinion that if these results were not actionable for the patients, they were not worth delivering. Although there was a degree of understanding that this was the nature of the

genetic testing, the GC found it difficult to manage the expectations of the patients, as they felt that the patient is left with more uncertainty than before they had testing or participated in the research.

"In terms of it being a research project, I am not sure we should be returning those results at this point. It feels to me that we are not giving them anything. We giving them more anxiety rather than anything and we know that those variants of unknown significance often end up being, 80% of them end up benign". (GC1)

"Particularly if there is only a single variant identified compared to an answer, and so for them coming through and learning actually, there is a partial result, for them is actually just, I think is worse than not having a result at all. "(GC4)

On the other hand, the GC also discussed that some results are also life changing, especially in dominant and X Linked conditions, in that if the genetic results were given, the patient will live with the implications of that result for the rest of their lives. The consequences of that information may also impact the family in the future.

"*They've come for pre-symptomatic testing, which they've been wondering about for many years. Kept on going in and out of wanting to know. Didn't want to and once they have it done, the information given you can't take away" (GC2)*

"I think dominant and X-linked recessive are the two that one must be aware of." (GC2)

GC were also wary of the IRDPT contacting patients with these results as they felt that many patients may attach more value to the result than it warrants. GC felt that some patients may have accepted their condition and by presenting them with a genetic result, it may create expectations which the results cannot fulfil.

"I think many times people to some extent have made peace with their diagnosis and kind of being contacted out of the blue, there's sometimes,. A lot of expectations as to what that is going to mean and you almost under-deliver, because it's nothing, life changing." (GC5)

Another reason for patient expectations to be elevated are the gene therapy trials. The improved vision in these trial participants were encouraging, although retention of the visual changes has not been sustained for more than three years (Bainbridge, 2015). GCs felt that this has not led patients to lose hope that a cure will be found.

"I have always experienced patients finding it helpful for them to understand their condition more. But they do have a bit of a sense of false hope that then gets attached to the results, because now I have something and now there may be a trial. (GC3)

"I think the other side of things is that if the research picks up meaningful results, for something that is immediately treatable, uhm, you know for example, if there was now an ABCA4 trial coming out and you have ABCA4." (GC3)

Some GC also felt that genetic mutations will not be important in the future as technology to assist the blind was developing faster than gene therapy. This assertion is supported by research into bionic eyes, with two devices already approved for clinical use (Nowik et al., 2020).

"And the hype around the possibilities of cures have been there for a long time now and it is not really bearing fruit at this point, so some of the options for people who are blind nowadays are tending to be the cameras and stuff. It doesn't really matter if you have genetic mutations or not, you can just fix it with technology" (GC1)

GC acknowledged that knowing the family mutation will benefit their families. Medical records, therefore, need to be carefully stored for possible reference in the future.

"But it's actually important. The point is they need to have access to that information and that's probably where the biggest challenge is to simplify the reports and say this is your information to keep." (GC2)

GC felt that if the results were meaningful and led to treatment, then this would be more beneficial for the patient and the delivery of results would then be worthwhile. This would enable patients to participate in clinical trials or be of benefit to future progeny. Meaningful results are not always attained in genetic testing and the patient needs to be adequately prepared to manage expectations. This highlights the importance of pre-test counselling, as it prepares the patient for the results in the context of genetics (Edwards et al., 2015).

ii. Sub theme 3.2: Family communication

Family communication varies in families and are affected by relationships and degree of closeness within families. Family relationship breakdown, estrangement, and difficult relationships were discussed as the most common cause of lack of communication within families (Young et al., 2019). Genetic information can cause family dysfunction or exacerbate existing poor relationships. The task to inform estranged family members can also be seen by patients as a burden.

The GC in this study were unsurprised that there was a large number of undelivered family results in the database. They explained that in autosomal recessive conditions, lack of family communication was a common occurrence.

"Totally family dependent. It's going to be again like any genetic condition. I think any recessive condition often does not get filtered down, so I think about the recessive kinds of diagnosis we sometimes see in retina, cystic fibrosis, sickle cell. They hardly ever inform the family members that they could be carriers." (GC3)

The GC mentioned that family members may also be aware of the result, and that may have led to disinterest in collecting their personal results as the knowledge is recognised and accepted within the family.

"There are people who have had results indirectly, in so much as they are part of a big family." (GC2)

GC also referred to shame and guilt as one of the reasons that communication in families was variable. Some individuals who have passed on genetic conditions to their family, often feel guilt or shame and perceive themselves to be socially unacceptable and unworthy (Veach, LeRoy & Bartels, 2003). Denial and avoidance of the topic or condition may prevail in these families and the topic becomes unmentionable.

"*But then again, genetics, we know, not everyone wants to know how genetics sits because it becomes that shame, guilt thing."(GC4)*

"The problem comes when they don't want to share, they don't want people to know and I think when people are affected, it's perhaps less of an issue, but that's age related, the older they are, the more they are sort of protective because they are scared that they passed it onto the children. They don't want to have the blame." (GC2)

Shame and guilt vary in many cultures and people do not readily discuss family conditions. The stigma attached to a genetic condition can inhibit families from discussing it. In indigenous African communities in SA, causes of disability are sometimes believed to be due to witchcraft, poisoning or bad spirits (Mkabile, 2020).

Recent research suggests that patients are not always aware of the importance of communicating genetic information to other family members (Young et al., 2019). Although genetic results impact families due to its inheritance pattern, especially in dominant and X-linked IRD, the HP are not ethically bound to ensure that these results are conveyed to the rest of the family (Genetics, 2017). In contrast, other current research describes this as a moral failure on behalf of the HP, as they have a "duty to inform" (Grill & Rosen, 2020). They suggest that the HP only has a duty to make information available and not necessarily to ensure that the information reaches at-risk family members. In genetic counselling, informing family members is important as the condition can affect other family members' choices. The GC participants were in agreement that the genetic results needed to be passed on to other family members.

3.3.4 Theme 4: Triangular relationship

This theme discusses the GC view on the different role players and how the interaction between these different role players influences result delivery. Sub themes observed were "clarity of roles", "research diagnostic overlap" and "mountain of paperwork" illustrated in Figure 3.14.

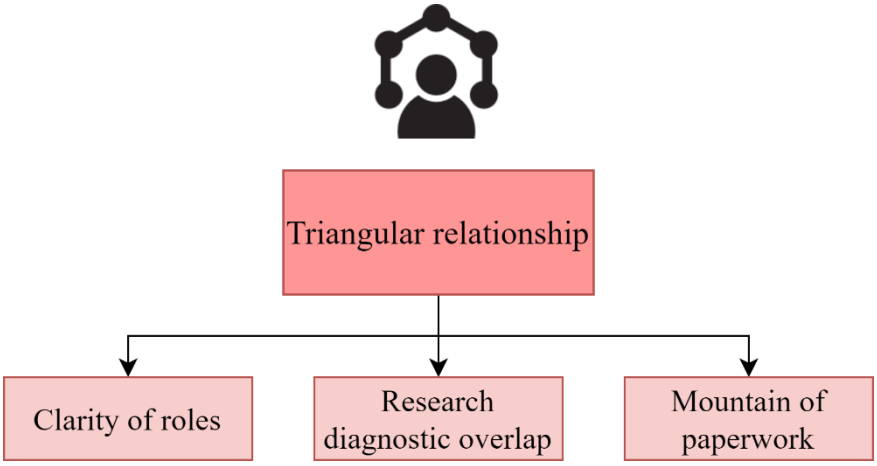

Figure 3.14: Illustration of Theme 4 and sub themes.

i. Sub theme 4.1: Clarity of roles

The GC were ambivalent when discussing the role of RetinaSA. Some discussed the positive role RetinaSA played in the support and organization of result delivery for patients and others were concerned that the roles were muddled.

"I think they do provide a good service to patients in terms of their newsletters, support, I think their financial aid that they offer to some patients are wonderful, but I think they shouldn't take so much ownership when it comes to the process." (GC3)

"The role of all is so different and sometimes it just becomes quite muddled." (GC4)

RetinaSA's involvement with the selection of tests was seen as problematic, as this is normally decided by the GC/HP and the patient. By their involvement in testing decisions, there is some confusion as to what their role should be.

"I have had a number of patients who came back and said that RetinaSA has said this. We made the decision (to go for this test and then RetinaSA comes back and says other things which are not helpful)."(GC3)

The method used to relay the results to the participants was discussed as they felt that the IRDPT should inform the HP/GC that the results were ready and not RetinaSA and then the patient. When the patient receives notification that the result is ready from RetinaSA, RetinaSA assumes the role of the GC.

"And then I think the practitioner should receive the result and not the patient being notified that there is a result available. I think it blurs lines, I think it makes it very difficult for the practitioners actually. They receive this random form that says you are going to do, someone wants you to do their result delivery." (GC3)

The GC also mentioned that they received notification of result delivery to patients who were unknown to them. As a link with the patient is important, the GC does not have a sense of continuity with the patient and the result is delivered without context. With the current system, the GC role is therefore marginalised.

"It hasn't been working that well and that is half my problem because sometimes I get a written release form and I don't know the patient and that shouldn't be the case and it is not always old research patients, which worries me." (GC3)

GC suggested that a new strategy could be implemented. When a state patient cannot afford a genetic test, then the GC/HP could apply for funding from RetinaSA, and if it is granted, they can then relay that to the patient, instead of the current process.

"*If someone wants genetic testing, they should be referred to their closest public sector. And that is something that RetinaSA could foster and then if the patient doesn't have money and it is a public patient, then the provider and the patient together applies for that funding and then the provider takes it further to say you have been granted funding via Retina, we can go ahead with the test-you know. That is not really, I think Retina's role."* (GC3)

The GC also suggested that instead of the current system, the IRD project could be managed like a research business model, which is currently being used by other research projects at UCT and abroad. This business model as well as external funding could be explored, so that the IRD project could be independent.

"I think that if research, if RetinaSA wants to offer a research test, through UCT, that's great, but that it should be managed by a research project management group, like every other big research genetic testing facility in the rest of the hospital and involved with other research groups as well. There can be a translational research diagnostic arm." (GC3)

ii. Sub theme 4.2: Research diagnostic overlap

GC were appreciative of the assistance the IRDPT provides in terms of support and scientific knowledge. GC acknowledged that the scientific advice was particularly useful as they can consult and discuss complex cases with the IRDPT.

"I think there is a lot of trust that there is expertise, and I think that has a lot going for the research project, and the ophthalmology community and the support group community." (GC5)

"It's been very positive actually and very helpful." (GC4)

GC were, however, concerned about the research diagnostic overlap and mentioned that the distinction between research testing and diagnostic testing was unclear. The IRD research project is subject to the UCT's HREC, yet also involved in commercial diagnostic testing facilitated by RetinaSA. The GC are involved in the selection of tests and have to ensure that the appropriate tests are selected in consultation with the patient.

"That there is an overlap in the research project of the diagnostic research testing, and I think for example, the new UCT panel has been marketed as a diagnostic panel, and it's not and I have a big problem with that." (GC3)

The GC found that it was difficult to promote the IRD project as a diagnostic service when it did not operate as such. The genetic testing offered was more research than diagnostic and that testing should be left to the diagnostic service providers instead of the research project.

"I think it starts with the acknowledgement of what you are. If you are a research project, you are not a diagnostic service because you are not going to meet the expectation that a diagnostic service has." (GC5)

"And there I think it's important to understand my needs as a genetic counsellor in private practice because, you know, it's always difficult to, uhm, make sense and really know where research fits in and where diagnostics fit in." (GC5)

GC noted that not all the genes available in overseas IRD diagnostic tests were present in the UCT panel, complicating matters.

"*So, some are being left out of the panel here that are really quite necessary - some of them are common genes." (GC1)*

"I cannot in good conscience say to somebody here, you can have a panel done here for R9000 or we can send it overseas for R10 000 and get 500 genes looked at." (GC1)

GC explained that ophthalmologists also have the expectation that the turnaround times for results were equivalent to diagnostic laboratories and did not understand that the research project may not currently be doing research on that patient's specific gene and a result may take many years. GC were concerned that private patients also expected turnaround times for results to be much faster for diagnostic tests and did not understand research timelines. These private patients also expected that the diagnostic test would have an answer for their vision loss.

"Whereas in private practice, I think people have less patience for the workings of research and the expectations thereof." (GC5)

"You also create expectations for families, that this is in some way a diagnostic service." (GC5)

It was observed by the GC that IRD research on samples that diagnostic testing laboratories were unable to diagnose, would be beneficial. In this regard, patient's samples that require more extensive genetic testing, could be referred to the IRD research project.

"But there's always great value in being able to offer more time and focussed energy on a difficult question that can't be answered easily through a diagnostic process, uhm, so it can definitely complement a diagnostic service." (GC5)

"I think there is always going to be a need for a research project, to take things further for some families where we don't have a complete answer." (GC5)

That would then lead to the IRD research project fulfilling an important function in IRD research.

iii. Sub theme 4.3: Mountain of paperwork

The triangular relationship between the different role-players is affected by factors like the administration forms that are part of the testing process. GC mentioned that the paperwork required to be part of the project was too cumbersome and too difficult to access and this led to fewer referrals to the IRD project.

"It's just too long for people and I have had similar conversations with ophthalmologists in private practice where I have made the suggestion that they send for research and they just say you know, it's, it's just too much of a hassle." (GC5)

Suggestions to improve the paperwork were made by the GC to facilitate the process.

"Should have a retinal research project that is very easy to find, with a fillable PDF form, so that you can literally download the PDF, complete it online, not online, but literally download it, have it electronically fillable and on the website and that form can be definitely shorter than what it currently is. I can understand that there is a lot of information that is really necessary, but you have to kind of relook and ask the question, has people just added and added, an added" (GC5)

All this paperwork leads to frustration and has led to patients not being referred by HP. All of the GC understood the ethical aspects of the IRD research project, as all of them have dealt with the required forms used for enrolment of patients, as well as result delivery. Ease of use has been emphasized by the GC in order to make enrolment onto the project uncomplicated for all users. This suggestion to reduce paperwork in IRD research is supported by the electronic advances seen in transforming healthcare (Barbour, 2020). We are increasingly using online forms and the reduction of paperwork is important as it can also minimise incomplete or partially filled in documentation and reduce the manpower needed to follow up. This perception of large amounts of forms being necessary before enrolment onto the database can affect current and future recruitment and needs to be addressed by the IRDPT.

3.4 Discussion

This study explored the reasons why the IRD project at UCT has n=628 (initial number was n=755) outstanding results. The views of GC were obtained in relation to the IRD project, and the result delivery challenges encountered by them. The mixed method approach allowed perspectives from both the quantitative data, obtained through interrogating the database, and the qualitative data, which explored the experiences and views of the GC as it pertains to the overall result delivery process.

Results showed that the bulk of the outstanding results are from the IRD project's recruitment drive from 1990-2004, when the project was initiated. It was found that

90.4% (n=568) of individuals in the primary cohort (n=628) were recruited during 1990-2005. Result delivery also improved from 1985 to 2014, although a decrease in result delivery was noted from 2014 to 2019. These qualitative findings where the GCs also shared that they thought the outstanding results were probably from the research drive supported the quantitative analysis. The GC did not comment on the decrease in result delivery from 2014 to 2019, but this could possibly be linked to a key researcher that retired during this period.

Literature searches have not revealed other studies with the same challenges regarding large amounts of outstanding result data. Jewell (2012) asserts that biorepositories should be held accountable to the same standards that are in place for clinical testing. The validation of the research results needs to be seen alongside the meaningfulness of the results to the research participant's health or treatment and that guidelines have to be established for this (Jewell, 2012).

Database issues have also been observed in the primary cohort. The number of results that were in fact given (n=76) but not recorded as such in the database is an example of this. Deceased individuals were also not recorded in the appropriate field on the database. There were five duplicated records where results had already been given, but the duplicated recorded was listed as having an outstanding result. There were also incomplete data entries which had no record of any contact between the IRDPT and the individual. This may be due to poor record keeping or no patient contact. The diagnostic codes were also difficult to interpret as the differences between the two groups relating to unaffected and at-risk status could not be explored due to inappropriate classification. The structure of the text fields was also not conducive to easy data extraction, as the selected text field had multiple data entries that have to be mined individually to extract data. A more efficient database like REDCap is needed to be able to store and extract data that is in keeping with contemporary research (Harris et al.,2009). In the qualitative component, this was not mentioned mainly because the GC do not work directly on the database.

Individuals in the primary cohort were members of 191 families. Family communication was discussed by the GC in that a reason for non-delivery may be because some individuals might not be expecting results as they are aware of the pathogenic mutation that is present in their families. This also suggests lack of motivation in receiving results. These samples would have been included in the research in the 1990's when large numbers of affected and unaffected family members were recruited. The GC were of the opinion that information in families may or may not be disseminated. The retinal condition, mode of inheritance, including family relationships, affect the transmission of information. Blame, guilt, or shame with the resultant stigma associated with a genetic condition, are mentioned by the GC as factors which can affect the transmission of genetic information in families (Hodgson et al., 2016). Research also shows that probands who were mutation positive for cancer, all (100%) shared their information with parents and siblings (Vadaparampil et al., 2012). It was emphasized by one GC that information "given cannot

be taken away" (GC2) and the importance of the family or individual's consent has to be obtained as information may also affect health insurance premiums or cause anxiety.

As seen in the database extract, 19.1% (n=144) of individuals were minors. GCs mentioned that minors posed delivery challenges because results needed to be delivered to parents timeously so that treatment decisions could be made. Participation in gene therapy trials hinges on a molecular diagnosis, which emphasizes the importance of these results. Results of minors in the database therefore need to be prioritised.

One aspect that was interesting was that 7.4% (n=56) of research participants did not contact GC after being informed that results were available. The GC also mentioned that participants did not necessarily value genetic testing. This is supported by other research studies where little value is attached to genetic testing especially when the condition is regarded as unchangeable (Paneque et al., 2019). Patients who paid for their tests were also more likely to attend and set appointments for result delivery. When comparing the two cohorts, it was noted that in the HCC, 55.8% (n=86) were affected individuals. However, when exploring the LCC, it was found that 26.5% (n=38) were unaffected individuals. From this, we can infer that as the HCC had a substantially higher percentage (55.8%) of affected individuals compared to unaffected (13%), more effort was expended to deliver results to affected individuals.

Ethical research discussed the moral responsibility to return the research participants' results in order that it could be of benefit to participants in the future. The GC believed that it was the moral obligation to return these results and that a budget had to be allocated for this by the IRDPT. Other studies have also supported the supposition that research participants should receive their results (Wallace & Kent, 2011). The GC suggested that UCT's HREC guide this process in order to ensure that the patient rights are not infringed. Issues with consent were also identified which were affected by language barriers, interpreters, as well as the level of the language used in consent forms. Translation of consent forms were raised as well as lack of pre-test counselling to adequately prepare individuals for their results. This links to previous research findings which found that the level of consent forms were not appropriate for the patient's educational level (Leopeng, 2019). In the South African context, due to the disparity in education levels and the language barriers within our population groups, special care needs to be taken to ensure that all research individuals understand the consent process and possible benefits of genetic testing (Kale, 1997). The OECD has also published guidelines about feedback to research participants which is intended to guide repositories (OECD, 2009).

Growing awareness of research participants' rights are presently protected by HRECs who have strict guidelines for researchers to ensure that archaic practices of the past are changed into transparent and open interactions (Bollinger et al., 2012). Wide choices of tests were an issue that GC felt strongly about as they felt obligated to offer their private patients all options available and felt ethically bound by that. GCs felt keenly that pre-test counselling should be offered because patients need to know why they are testing and

what the benefits are for themselves and their families. If this is not understood, then the patient attaches minimal value to the result and implications. Although building capacity for genetic testing in SA remain a concern, they felt that all options had to be presented to their patients in order that they could decide what is best for the patient according to their financial means.

Although patient characteristics have been researched, aspects like lower education and socio-economic aspects of participants had relevance as to whether the patients were referred to healthcare (Navaneethan, Aloudat & Singh, 2008). No patient characteristics like sex, age, family results or deceased participants, showed significance. Patient characteristics like low socio-economic status and low level of education were mentioned by some GC as concerning as it impacts the importance that the patient attached to the results. Even though free transport to result delivery sessions are provided (from RetinaSA), individuals still did not arrive. GC were of the opinion that participants may not be aware of participating in a research project, especially if their samples were taken in rural hospitals with no pre-test counselling. According to GC, individuals who come from low socio-economic backgrounds, were more likely to be concerned with their basic needs and genetic results did not feature as important.

Participants who were deceased represented 7.3% (n=46) of the primary cohort. Families of deceased individuals who have donated blood or organs for research have also expressed interest in receiving genetic results that could be relevant to their health (Siminoff et al., 2016). This supports the opinion that the deceased patients' results cannot be excluded from the results delivery data. If the results are relevant to other family members, attempts should be made to contact the family of the deceased.

Socio economic differences played a role in the result delivery process as the needs of different socio-economic groups differ. Concerns of state patients also differ to those of private patients. State patients are focused on their basic needs, and genetic testing results are not deemed important to most (Williams, 2019). This disparity in patients' needs and wants influences their motivation to receive their results. This is also connected to whether RetinaSA has sponsored the genetic testing. A breast cancer study in Australia found that there was a slow uptake by individuals of free *BRCA1/2* testing as they were not self-motivated to do genetic testing (Keogh, 2004). This correlates with RetinaSA sponsoring the genetic testing of indigenous individuals with IRD, but the patient may not be as invested in the testing and its implications.

Research studies also highlight that geographic location, poor diet as well as financial constraints lead to lower levels of participation in research trials as well as proper treatment for their ophthalmic condition (Williams, 2019). Socio-economic inequalities also affected telecommunication with patients due to their lack of access to virtual communication. GC had various levels of experience with telecommunication, but most agreed that it was preferable to patients not receiving their results. Studies have shown comparable levels of satisfaction between virtual and face to face communication (Platten et al., 2012).

GC were aware of the heterogeneity of IRD which complicates finding a genetic diagnosis, but they were also cautious in not giving patients false expectations as to the meaning of the results. The type of results delivered, such as VUSs, partial results and no mutation identified, were also a concern. These results they felt were not worth delivering and just caused anxiety for the patient as it had no benefit. This is supported by researchers who questioned the value of returning results that were of no clinical utility, stating that it leads to disappointment and frustration and unnecessary treatment and follow up (Pollard, Sun & Regier, 2019).

When consent is taken, participants are told that genetics testing may not return "meaningful results", but the reality of actually returning these results are disheartening for the patients. Some results may be partial or inconclusive and the patient samples are usually returned to the biorepository for further research. This adds to the length of time they are present in the research project in the hope that new technologies could provide the individual with a definitive diagnosis. These samples were also consented for research, and this also affects the value of the result as patients may not necessarily expect a result as discussed by the GC.

The IRDPT requests that GC inform them whether results are given. In this dataset, the IRDPT had little feedback from GC as to whether individual results were delivered. The interactive relationship between the IRDPT, RetinaSA and the GC was discussed. The clarity of roles, research diagnostic overlap, as well as the mountain of paperwork were identified as obstacles. GC noted that the functions of the respective role players were not always clearly defined. This led to disagreements between GC and RetinaSA with regards to test selections. Furthermore, GC noted that patients were notified of their results, as opposed to the GC/HP. They felt that this marginalised their role and that the HP should receive notification of the patient's result and not the patient. A new business model was proposed which could be utilised by the IRD project. Research groups in UCT are successfully utilising various business models in research projects and this could be utilised by the IRD project as well, as seen in the Impi project at UCT (Mayosi et al., 2006).

The role of the IRD research project overlapping with a diagnostic service was deemed problematic, as it did not have the freedom of a diagnostic service because its actions are regulated by UCT's HREC. Patient and HP expectations could therefore not be met successfully due to long turn-around-times as well as HP and patient expectations. The large amount of paperwork required due to two bodies administering paper-based forms were also deemed cumbersome. The paperwork directly contributed to the HP reluctance to refer patients to the IRD project.

The qualitative and quantitative data were shown to support the fact that most of these results were from the research that was undertaken from 1990-2005. The GC were also not aware of database issues and so could not comment on the database issues found in the quantitative results. The study data was supplemented by the insights revealed by

the GC, especially patients concerns, which enhanced the study. No areas of contradiction was found.

The findings show that the qualitative and quantitative data corroborated and complemented each other. The recruitment drive that was implemented by the IRD project in 1990-2004, was supported by the GC recollections and experiences. Participants whose results were outstanding, were part of large families that were recruited on the IRD database. The GC were aware that these results do not always reach all members of a family due to the psychosocial issues like blame, guilt and stigma. The data converged where the qualitative data complemented the quantitative data. Complementary data was found which enriched this study in that a triangular relationship between RetinaSA, the IRD project and GCs was observed, notably where the roles of the respective organisations were not distinctly defined. There was no contradictory or unique elaborative links which were mentioned in either the corroborated or complementary sections.

Chapter 4: Conclusions and Recommendations

This research provides a view into the IRD biorepository's result delivery process using a mixed methods approach. By supplementing quantitative data with qualitative data, valuable insight was gained into the database management as well as the experiences and perceptions of the GC working with the IRD project. The IRD project was initiated in 1985 and in the last 35 years, there have been many families and individuals recruited onto this database. The study has revealed that outstanding results were due to issues related to data management as well as patient related issues.

As the project evolved over time there were many staff working on the project, as well as student researchers. Research participants recruited in the period of 1990-2004 constituted the bulk of the outstanding results. This coincides with the recruitment drive in the 1990's when large numbers of individuals were recruited for genetic testing using the technology available at that time. The recruitment drive generated a large number of results not all of which has clinical management implications.

The data that was available for analysis was about 21% of the primary cohort. The errors uncovered in the database included incorrect data capturing and that n=76 results were actually given to subjects, 5 duplicate records and 46 individuals were deceased and not recorded as such. A substantial number (79%) contained incomplete entries and as a result no information was available to interrogate reasons for non-delivery of results. The need for accurate management of the database has been highlighted by this study.

Individuals recruited into the project were from 160 families. The implications of this is that 10 outstanding results could be family members of one individual who may already have received results. This information could not be verified as this data is not available. Family communication and individuals' motivation to receive their results, as the GC reported could therefore be a contributing factor.

The moral obligation for the IRDPT to return the results to the research participants were evident in the GC responses and that a budget should be allocated to ensure this (OECD, 2009). These results could be important for carrier testing or predictive family planning in relatives. The pre-test counselling was a pre-requisite for genetic testing as patient expectations could be contained. GC felt that low socio-economic issues affect the value that the individual attaches to the results and affect result delivery. The South African context were alluded to by the GC as difficult to navigate as each patient had different needs. It is clear that the GC feel that their role is marginalised by the current result delivery process. The overlap between the IRD project as research as well as a diagnostic service is problematic as it cannot compete with the laboratories who have faster turn-around times and lower costs. The excess paperwork that is required to enrol patients onto the IRD project is also seen as a barrier by HP.

The GC recommended that a more streamlined research data storage system could be implemented to eliminate storage of patient paper files. The delivery of results to minors

need to be prioritised as it is important for entry into clinical trials where molecular results are a prerequisite. A dedicated GC could be employed to manage the result delivery process as seen in other biorepositories.

The aim of this project was to ascertain factors affecting the result delivery process as well as explore the views of the GC involved and this was accomplished. Other findings have resulted in recommendations which can be implemented by the IRD project in order to improve the result delivery process as well as the management of the project.

4.1 Strengths and limitations of the study

4.1.1 Strengths

- The mixed method design of this project provided both quantitative and qualitative data which resulted in a more comprehensive understanding of the IRD result delivery process
- The interviews were conducted in the GC language of choice and due to their ability to choose the location, as well as the assurance of confidentiality, allowed the GC to express themselves freely via the open-ended questions. Their insights supported by their experience has enriched this research study.
- The participants for the qualitative component were almost all the GC that have worked with the IRD project. The qualitative results are therefore a good representation of the issues involved with result delivery irrespective of the small number of participants.
- The researcher's position as a research nurse on the IRD project may be construed as insider research, but it has also led to a deeper understanding of the result delivery and the issues affecting it.

4.1.2 Limitations

- The raw data was obtained from the IRD biorepository and analysed as a snapshot of undelivered results. This abstraction of the data was chosen and focussed on, and this could be a source of bias as only the variables chosen were explored.
- Incomplete data recorded in the IRD, limited the analysis and subsequent information that could be obtained.
- The data that was delivered to individuals could have been explored to ascertain the characteristics that led to successful result delivery, but that was beyond the scope of this project and could be addressed by the IRD project in future.
- All opinions expressed were those of the GC and the data collected could be a source of bias.

- The researcher attempted to reduce bias, but this may be unavoidable as the researcher is known to all the GC and is part of the IRDPT.
- This explanatory sequential design of this study could be a source of bias, in that some questions were influenced by data that emerged during the analysis. The questions were emailed to the GC before the interview and that may have influenced their responses. The rationale for this action was that responses would be deliberated and reflected upon.

4.2 Recommendations

- The database should be examined for clinical utility and individuals identified whose results should be delivered, including family members. Other records, such as deceased individuals, can be archived and removed from available results. Reports that have no clinical utility to the patient can be removed from database.
- Online fillable consent and COD forms could be utilised for requesting genetic testing in order to streamline the process. Documents could be condensed and need for separate release forms could be incorporated into the existing consent form.
- Provision for a text field describing the reason why delivery was unsuccessful could be implemented in the database.
- There are data quality issues that are due to legacy processes. These can be assessed and rectified.
- A new database like Redcap could be utilised to manage the data in a more comprehensive way. This would enable all documents to be stored electronically and will simplify data retrieval.
- The molecular results of minors need to be prioritised in order to improve their likely medical management and their possible participation in gene therapy trials.
- Consent forms need to be translated in the patient's home language and these forms need to be aimed at an appropriate school level for most individuals.
- Supervised student GC could be used as a resource to deliver results. This training would be of mutual benefit to both the IRD project and HG clinical department.
- Telephone counselling was suggested as an alternative method because not all patients have access to video platforms such as Skype or Zoom. Use of an alternative communication platform such as "What's App" could be implemented.
- If IRD research subjects are informed that results are available, they need to drive the result giving process by contacting the IRDPT or their GC/HP.
- A GC could be employed to manage the IRD project to ensure improved result delivery.
- The IRD project could use a new business model in order to be fully autonomous. The initial testing should preferably follow a conventional diagnostic approach.

- The role of the GC should be more clearly defined, in terms of how they relate to both diagnostic and research testing.
- The relationship between RetinaSA and the IRD project needs to be reviewed.

4.3 Future Research

- The IRD conditions were not specified in this study and whether that had aand be comparable toother n influence on result delivery could be explored in future studies.

- Geographic location could be explored to ascertain whether urban or rural locations were an important factor that affected result delivery.

- The results that were delivered could be explored and compared to the undelivered results in order to ascertain whether there were characteristics that enhanced their result delivery.

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Appendix 1: Information sheet

INFORMATION SHEET

Brief overview of Study

Title: The Factors affecting result delivery in the IRD project in South Africa-including insights from genetic counsellors

This study will include database analysis as well as explore the experiences of genetic counsellors in the delivery of results to IRD patients that requested genetic testing. The non-delivery of available results is of concern and this study aims to improve result delivery in the future.

PARTICIPANT INFORMATION

1. Thank you for agreeing to participate in this project.

2. I would like to assure you that your participation will remain anonymous and that your name will not appear anywhere on the documentation.

3. Any information discussed will not be given to other participants as well as anyone else not involved in the study.

4. The interview will take place in a location and time of your choosing and should not take longer than one hour.

5. By your involvement, the results of this study could lead to improved service delivery of results.

6. The interview will be recorded for research purposes and all information will be transcribed. This information will then be stored in a locked office and saved on a password protected computer. Only the researcher and her supervisors will have access to these recordings. The recordings will be destroyed after the dissertation has been written up and published.

7. This participation is completely voluntary and withdrawal from this study will not affect you in any way.

8. This research project has been approved by the Human Research Ethics Committee at the Faculty of Health Sciences, University of Cape Town (HREC 422/2019).

9. Participation in this research project will not be compensated and will not cost you anything.

10.The results of this study may be published in a scientific journal, but no names of participants will be published.

Appendix 2: Consent form

REQUEST FOR M.Sc. RESEARCH PARTICIPATION

Genetic counselling

Division of Human Genetics

UCT Medical School

Observatory

7925

Tel: (021)406 6467

Please fill in all the information requested

Surname: _____ First Name (s): _____

Sex: M • F • Date of Birth: Year: _____Month: _____Day: _____

Email Address: _____

Tel/Cell no: _____

For Research Use Only

Participant Number:_____

Date Received: Year:_____Month:_____Day:_____

CONSENT FOR STUDY PARTICIPATION

I, the undersigned _____consent to participating in this research project: ***The Factors affecting result delivery in the IRD project in South Africa- including insights from genetic counsellors.***

I understand that by participating, I will be interviewed.

I understand the objectives of this study.

I understand that it is voluntary.

I understand that the interview will be recorded.

I understand that it is anonymous and completely confidential.

I have the right to stop the interview at any time.

I understand that the de-identified information may be analysed for publication.

ALL OF THE ABOVE HAS BEEN EXPLAINED IN A LANGUAGE I UNDERSTAND, AND ALL MY QUESTIONS HAVE BEEN ANSWERED
BY:_____Date_____

Participant Signature_____

Interviewer Signature_____

IMPORTANT INFORMATION

Thank you for agreeing to participate in the study. If you have any questions or would like to withdraw from the study, please contact the researcher or supervisors below:

Sr Gameda Benefeld (Researcher) Cell:0848188394 - Email: gameda.benefeld@uct.ac.za

Dr Tina-Marié Wessels (Main Supervisor) - Email: Tina.Wessels@uct.ac.za

Prof Raj Ramesar (Co-supervisor) - Email: Raj.Ramesar@uct.ac.za

If you have any questions regarding the Ethical aspects of this research, please contact the Human Research Ethics Committee (HREC) at the Faculty of Health Sciences, University of Cape Town.

Prof Marc Blockman (Chairperson of the HREC): (021) 406-6496

Appendix 3: Question guide

Open ended question guide- (Preliminary)-Genetic counsellors

1. What has been your experience with result delivery to the patients via Retina South Africa and the IRD project?
2. In your opinion what factors affect this process?
3. Can you describe what has worked really well in this system?
4. Can you describe what has not worked well in this system?
5. Why do you think patients are not coming for their results?
6. Do you feel that communication of results within families are effective? And if not, how do you think this may be improved?
7. What has to change, in your opinion, to improve the result delivery service?
8. Would you like feedback regarding the results of the study?

Appendix 4: Ethics approval

Formal Ethics Approval From UCT

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

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

16 July 2019

HREC REF: 422/2019

Dr Tina-Marie Wessels
Human Genetics
Level 4
Falmouth Building

Dear Dr Wessels

PROJECT TITLE: THE FACTORS AFFECTING RESULT DELIVERY IN THE IRD PROJECT IN SOUTH AFRICA-INCLUDING INSIGHTS FROM GENETIC COUNSELLORS (SUB-STUDY LINKED TO 226/2010) MSc Candidate - Sr G Benefeld

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

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

Approval is granted for one year until 30 July 2020.

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

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

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

The HREC acknowledge that the student, Gameda Benefeld will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE