The Lived Experience of Parents with Children with Genetically Solved Developmental and Epileptic Encephalopathies

A thesis presented in partial fulfilment of the requirements for the degree of

Doctor of Clinical Psychology

at Massey University, Wellington

New Zealand

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2021

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ABSTRACT

Parents of children with developmental and epileptic encephalopathy (DEE) are at high risk of developing mental health difficulties due to caregiver burden and the unpredictability of seizures. Identifying genetic pathogenic variants improves clinical outcomes for children with DEE by directing therapy and enabling accurate reproductive and prognostic counselling for families; however, the additional personal value of a genetic diagnosis is currently under appreciated. The present research aimed to explore parental experiences of having a child with DEE and the personal utility of a genetic diagnosis for families.

Using the qualitative methodology of Interpretative Phenomenological Analysis (IPA), in-depth semi-structured interviews were conducted with fifteen families (seventeen parents) of children with a genetically solved DEE. The interviews stimulated discussion about the lived experience of caring for a child with a DEE when parents did not have a genetic answer, as well as what their experience was after they had received a genetic diagnosis.

Families discussed the detrimental impact of living with constant uncertainty regarding the aetiology of their child's DEE prior to the genetic diagnosis, which (in combination) with the uncertainty of seizures resulted in common trauma coping responses, such as hyperarousal, reactivity, vigilant monitoring, and avoidance behaviours. The diagnostic uncertainty prompted families to search for answers and attribute blame to themselves or others when they were unsuccessful. With regard to the genetic diagnosis, families reported that receiving a genetic label improved their knowledge about the likely trajectory of the DEE, increased their hope for the future and helped them communicate with others. The relief of finally having an answer for the cause of their child's DEE alleviated parental guilt and self-blame as well as helped families to process their grief and move forward. Delay in receipt of a genetic diagnosis diluted its psychological impact.

To date, the factors associated with the development of posttraumatic stress symptomology in parents of children with epilepsy have focused on caregiver burden

and seizure frequency. The present study demonstrates that uncertainty regarding the aetiology of their child's DEE may also contribute to the development of trauma responses in parents. In addition, the current research also demonstrates that identifying a genetic diagnosis for a child's DEE may be a psychological turning point for families. Consequently, early access to genetic testing is therefore important as it not only increases clinical utility, but also increases personal utility with early mitigation of family stress, trauma, and negative experiences.

ACKNOWLEDGEMENTS

Firstly, I would like to express my deep gratitude to the families who readily participated in this research. Each family showed courage and vulnerability when sharing their stories with me and I was humbled and inspired by their positivity and resilience. I hope that taking part in this research was a positive experience and will serve to give voice to the lived experience of families and children with developmental and epileptic encephalopathies.

To my primary supervisor, Professor Janet Leathem, thank you for your guidance, wisdom and support over the past four years. I appreciated you believing in me, even when I worried and did not believe in myself. I came to rely on your warmth and kindness. Your prompt and pragmatic responses helped to ground me when I was becoming overwhelmed.

Professor Lynette Sadleir, without you this research simply would not exist. Thank you for seeing something in me when I worked at UOW and taking a gamble on a student from an entirely different discipline at a different university. Your guidance was instrumental in shaping my writing style and I learnt a lot from your frank and timely feedback. Knowing you were always on my side helped me to persevere throughout numerous challenges.

To Doctor Kirsty Ross, thank you for your guidance and expertise in qualitative research and for your endless enthusiasm and encouragement. In particular, your confidence in the data, interpretation and more generally, my ability and clinical skill, provided me with the crucial reassurance I needed.

Lastly, to my friends and family. I know it has been a long journey (pushing 10 years!) to achieve my goal of becoming a clinical psychologist and not once have you wavered in your support or dissuaded me. Javier and Jax, my biggest cheerleaders, thank you for never allowing me to give up and always surrounding me with love and acceptance.

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LIST OF ABBREVIATIONS

ADHD – Attention-Deficit/Hyperactivity Disorder

ASD – Autism Spectrum Disorder

ASM – Anti-seizure medication

ASO - Antisense Oligonucleotide

CE - *PCDH19* Clustering Epilepsy

DEE – Developmental and Epileptic Encephalopathy

DSM – Diagnostic Statistical Manual of Mental Disorders

EE - Epileptic Encephalopathy

EEG – Electroencephalogram

HDEC – Human and Disability Ethics Committee

ID – Intellectual Disability

ILAE – International League Against Epilepsy

LGS – Lennox-Gastaut Syndrome

MCD – Malformations of Cortical Development

MDD – Major Depressive Disorder

PTSD – Posttraumatic Stress Disorder

PTSS – Posttraumatic Stress Symptoms

QoL – Quality of Life

SE – Status Epilepticus

SUDEP – Sudden Unexpected Death in Epilepsy

TBI – Traumatic Brain Injury

WES – Whole Exome Sequencing

WHO – World Health Organisation

Chapter 1: Introduction

1.1 Background

Prior to entering the Doctor of Clinical Psychology training programme, I had spent time on a research project in England working with parents of children who had behavioural difficulties. This was preceded by my Master's research which used a qualitative approach to explore adolescents' definitions of bullying in New Zealand. From these experiences, I developed a passion for working with children, young people, and families and was eager to continue my doctoral research broadly within the family population.

While completing the pre-clinical honours papers, I was also working part time as Departmental Manager of the Paediatrics and Child Health Department of the University of Otago, Wellington. Here, I met my external supervisor, Professor Lynette Sadleir, a paediatric neurologist and epileptologist whose research focuses on identifying the genes that cause epilepsy and characterising the epilepsy phenotypes associated with these epilepsy genes. At the time I was struggling to find a thesis supervisor at Massey who was interested in research with children and families, and when I mentioned this to Lynette in passing, she suggested I do my thesis with her focusing on paediatric epilepsy. I was intrigued but apprehensive, as I knew very little about epilepsy, and neuropsychology was not my forte. Fortuitously, two weeks later Lynette met Professor Janet Leathem at a conference and the initial discussions of my supervisory team began.

1.2 Context

We explored several possible topics, including the impact of sudden unexpected death in epilepsy, but eventually settled on applying a psychological lens to Lynette's main area of research, genetic childhood epilepsy. From years of clinical work, Lynette observed that families were relieved when they received a genetic

diagnosis for their child's severe epilepsy. Yet, to the best of our knowledge, the only focus of research for this population was the clinical utility of a genetic diagnosis. The personal psychological experience of families who received a genetic diagnosis had been largely ignored, aside from anecdotal accounts from clinicians. In order to truly understand the systemic utility of genetic diagnosis within childhood epilepsy, giving light to the psychological perspective and centring the voices of these families seemed like an important next step. This then became the central topic of my research; focusing on families with children (including adult children) with developmental and epileptic encephalopathies due to their severity and high likelihood of having a genetic aetiology (Scheffer et al., 2017).

The overarching research questions are:

1. What were families' experience of personal utility for their child's developmental and epileptic encephalopathy genetic diagnosis?
2. How did the genetic diagnosis change families' lived experience, if at all?

1.3 Significance and Scope

Our study was the first collaboration between the Department of Paediatrics and Child Health at University of Otago, Wellington (UOW) and Massey University. It bridged the gap between the disciplines of paediatric neurology, genetics and clinical psychology, giving voice to the lived experience of these families and promoting awareness across disciplines. This research not only highlights whether more support is needed for families but also may aid in the expansion of funding and accessibility of genetic testing in epilepsy as a whole. Our findings will be used to help advocate for routine clinical genetic testing for this group of children with severe epilepsies, as at the present time clinical genetic testing is not standard care in New Zealand.

1.4 Thesis Overview

This thesis has been written in the format of thesis with publication, with the results presented as two individual manuscripts. The chapter that follows includes an introduction to the present research with discussion of the relevant background literature. This begins with an overview of the definition and classification of epilepsy and the developmental and epileptic encephalopathies (DEEs), as well as the common comorbidities and aetiologies. Next, the impact of DEEs and caregiver burden is discussed, followed by associated risk factors for caregiver burden. Lastly, the importance of genetic diagnosis is reviewed, which considers both clinical and personal utility alongside the current research gaps. Given the relative sparsity of New Zealand based published literature on epilepsy in general, and more specifically DEEs, most research presented in Chapter 2 is international (predominantly North American and European). New Zealand and Australian literature will be highlighted where possible.

Chapter three provides a more detailed overview of the methodology than what was possible to include in the two manuscripts, due to tightly constrained journal word limits. Chapters four and five present findings of the data analysis written as the individual manuscripts. The first manuscript (Chapter four) will be submitted for publication. The second manuscript (Chapter five) has already been published in the *Epilepsia Open* (2020). There is some unavoidable repetition between chapters, especially in methods and discussion sections, to ensure the manuscript chapters are complete when read in isolation. It is noted that the manuscript chapters also contain references at the end of each chapter. References cited in all chapters are listed in the overall reference list at the end of the thesis. Chapter six concludes this thesis with a general discussion of the research findings as a whole, including implications from the research, methodological considerations, limitations, avenues for future research as well as some personal reflections.

Chapter 2: Background Literature

2.1 Overview of Epilepsy

Epilepsy is the most common neurological disorder worldwide. The prevalence of active epilepsy is 6.38 per 1,000 persons equating to ~30,000 New Zealanders and 50-65 million individuals worldwide (Fiest et al., 2017). Epilepsy has a higher prevalence in resource-poor countries than developed countries (Ngugi et al., 2011). The incidence of epilepsy is age-dependent, with higher incidence in those under five years and above 65 years of age (World Health Organisation (WHO), 2019). Epilepsy is a group of disorders characterised by recurrent seizures with a wide range of age of seizure onset, seizure types, seizure severity, prognosis, comorbid conditions and long-term outcomes.

This section will provide an overview of epilepsy in general, defining epilepsy and describing the new international classification framework. The aetiologies of epilepsy and common comorbid conditions will then be discussed. The following section will then discuss a specific group of childhood epilepsies, the developmental and epileptic encephalopathies (DEE), which are the focus in this thesis.

2.1.1 Definition of Epilepsy

Epilepsy is a chronic serious disorder of the brain. The International League Against Epilepsy (ILAE), the world's preeminent epilepsy organisation, provides terminology and a classification framework of the epilepsies to ensure consistency for clinicians globally (Fisher et al., 2017a; 2017b; Scheffer et al., 2017). The ILAE defines epilepsy as a disease of the brain where an individual must display either: 1) two or more unprovoked (or reflex) epileptic seizures occurring more than 24 hours apart, or 2) experience one unprovoked seizure with a probability of 60% or higher for further seizures to occur, or 3) be diagnosed with an epilepsy syndrome (Fisher et

al., 2014). Epilepsy is described as 'resolved' after individuals have remained seizure free for the previous ten years and have not required antiseizure medication for five of those years (Fisher et al., 2014). In addition, if an individual has an age dependent epilepsy syndrome and is past the applicable age range, their epilepsy would also be considered resolved (Scheffer et al., 2017).

2.1.2 Classification of the Epilepsies

The ILAE classification framework describes epilepsy using three levels: seizure type, epilepsy type, and epilepsy syndrome. Seizure types are classified as either focal, generalised or unknown (Fisher et al., 2017b). Diagnosis is made based on clinical evidence as well as interictal electroencephalogram (EEG) findings (Scheffer et al., 2017). Individuals are classified as "unknown" when there is insufficient information available to be able to determine whether the seizure is focal or generalised (Fisher et al., 2017a; 2017b). There are four classifications for epilepsy type, which are based on the seizure types an individual has, with the addition of a 'combined generalised and focal' epilepsy type for individuals who experience both focal and generalised seizures. Epilepsy type may be the final level of possible diagnosis for those whose epilepsy cannot be classified into a known epilepsy syndrome (Scheffer et al., 2017).

The third level of classification is the diagnosis of an epilepsy syndrome. Epilepsy syndromes are defined by age of seizure onset, types of seizure, development, neurological examination and the findings on the EEG and neuroimaging. The epilepsy syndromes have a range of outcomes and can be self-limited (where individuals outgrow their seizures) or lifelong disorders. The severity of the syndromes is varied, with some syndromes only having a few seizures or being very drug-responsive and others where the seizures are typically drug-resistant. The more severe epilepsies are associated with a range of comorbidities and poorer prognosis (Falco-Walter et al., 2018; Scheffer et al., 2017). The developmental and epileptic encephalopathies are a group of severe epilepsy syndromes, which generally present in childhood (Camfield & Camfield, 2008; Scheffer et al., 2017); these are the epilepsy syndromes that are the focus of this research.

2.1.3 Childhood Epilepsy in New Zealand

Epilepsy is one of the most serious neurological conditions in childhood (Feigin et al., 2019). An international meta-analysis reported the period prevalence of active epilepsy in individuals aged below 18 years to be 4.8 per 1000 and incidence of epilepsy as 46.9 per 100,000 (Fiest et al., 2017). The first epidemiological study to report the period prevalence and incidence of treated epilepsy in children and adolescents below 18 years in New Zealand was recently published (Ali et al., 2021). Results showed the period prevalence of treated epilepsy was 3.4 per 1000, with children in the lowest socioeconomic areas experiencing 1.9 times the rate of treated epilepsy than children in the highest socioeconomic areas. The study also reported similar rates of treated epilepsy in children across most ethnic groups; 3.7 for European/other, 3.6 for Pasifika peoples, 3.4 for Māori. Asian children showed a lower period prevalence of 2.3 per 1000 (Ali et al., 2021).

In New Zealand, all children with epilepsy are diagnosed by either a paediatrician or paediatric neurologist. This is based on the ILAE criteria discussed in the previous section, after taking a comprehensive clinical history and completing an EEG. Where possible, children and families should also be referred to Epilepsy New Zealand (Epilepsy NZ) for ongoing education, guidance and support of the child and their family. Epilepsy NZ can also facilitate the provision of resources, education and liaison, where appropriate, with extended family, teachers, police, ambulance staff and other community networks involved with the family (Paediatric Neurology Clinical Network (PNCN), 2021). There is a free national epilepsy helpline, as well as 11 Epilepsy NZ branches based across the country who provide local support for individuals/families and host support groups and seminars (Epilepsy New Zealand, 2021).

2.1.4 Aetiologies of Epilepsy

The ILAE classification system recognises six broad epilepsy aetiological groups: genetic, structural, infectious, metabolic, immune, and unknown.

Importantly, an individual's epilepsy may be caused by more than one of these aetiologies (Scheffer et al., 2017).

Previously, the aetiology of epilepsy was unknown in approximately three-quarters of individuals (Thomas & Berkovic, 2014). Genetic research, analysing the family history of people with epilepsy, and the emergence of next generation genetic sequencing technologies have highlighted the importance of the genetics in the aetiology of epilepsy. It is now recognised that most epilepsies are likely to have a genetic contribution (Perucca et al., 2020). This is particularly true for the DEEs and will be discussed in greater detail below.

An epilepsy is classified as having a structural cause when a neuroanatomical abnormality (such as a malformation, tumour, or stroke), can be identified by neuroimaging technologies (Lapalme-Remis & Cascino, 2016). There is emerging evidence that many malformations of cortical development (MCD) are due to underlying germline (in all the body's cells) or somatic (only in cerebral neurons) genetic abnormalities (Ye et al., 2019). When an individual's seizures are due to cerebral infection, their epilepsy is classified as having an infectious aetiology (Scheffer et al., 2017). This is the most common and preventable aetiology of epilepsy worldwide, especially in resource-poor settings where the prevalence of cerebral infections is high (Vezzani et al., 2016).

The cause of an individual's epilepsy may be metabolic in nature. This occurs when seizures are a core symptom of a metabolic defect where biochemical changes occur from the production and/or breakdown of substances within cells in the brain (Scheffer et al., 2017). It is not uncommon for metabolic disorders to be caused by genetic variants. Epilepsy due to an immune aetiology are auto-immune disorders, where the individual's immune system produces antibodies which attack their own neurons (Correll, 2013; Quek et al., 2012). In some cases, it is not possible to identify the cause of an individual's epilepsy. This may be due to a lack of resources, investigations or the specialised epilepsy knowledge of the clinician (Brodie et al., 2018). In other cases, despite intensive investigations a cause cannot be found due to a lack of present-day knowledge of the underlying aetiology.

2.1.5 Comorbidities of Epilepsies

Comorbidities of epilepsy are defined as conditions that occur more often in individuals with epilepsy than the general population (Thurman et al., 2011). The severity of comorbid conditions is wide ranging and reflects the heterogeneous nature of epilepsy. It has been approximated that 50% of adults with active epilepsy have at least one comorbid disorder (Keezer et al., 2017).

A United States population-based study compared somatic, psychiatric and neurodevelopmental comorbidities between persons with epilepsy (PWE), persons with migraine (PWM), persons with lower extremity fracture (PWLF), and healthy controls (Selassie et al., 2014). Not only were PWE shown to have significantly higher proportions of both somatic and psychiatric/neurodevelopmental comorbid disorders when compared with PWM and PWLF, PWE also experienced polymorbidity (presence of six or more comorbid conditions) 1.86 and 2.69 times more often than PWM and PWLF, respectively. Overall, somatic comorbidities occurred in 84.6% of PWE, 62.1% experienced psychiatric/neurodevelopmental comorbidities and 56% experienced both somatic and psychiatric/neurodevelopmental comorbid conditions. Cardiovascular disease was shown to be the most prevalent somatic comorbidity, whereas depression and anxiety were found to be the most common psychiatric comorbidities. In comparison to PWM, the odds of developing neurodevelopmental disorders in PWE, showed a 27-fold increase in intellectual disability, a 16-fold increase in cognitive dysfunction, and 18-fold increase in autism spectrum disorders. Ultimately, all 31 comorbid disorders were shown to be positively associated with epilepsy (Selassie et al., 2014). This study exemplifies the high prevalence of concurrent comorbidities experienced with epilepsy in comparison to other disorders. It helps to contextualise the immense impact these comorbidities can have on individuals and their families.

It is important to consider the additional complicating role that comorbidities play beyond the impact of epilepsy itself for an individual's quality of life, this is especially so for milder epilepsies. When taking into account the factors related to epilepsy, it quickly becomes a complicated and multi-layered picture. As with the aetiology of epilepsy, it is crucial to also identify the presence of possible

comorbidities early in the diagnostic process, allowing for early identification and improved management (Scheffer et al., 2017).

2.1.6 Developmental and Epileptic Encephalopathies

The developmental and epileptic encephalopathies are a group of severe epilepsy syndromes, which can present at any age, though the majority begin in infancy or childhood (Scheffer et al., 2017). An epileptic encephalopathy (EE) is defined as occurring when seizures and/or interictal epileptiform discharges inhibit childhood development resulting in a plateau or deterioration of cognitive, psychological, and behavioural functioning (Nickels et al., 2017). That is, the epileptic activity itself contributes to the developmental impairment and the deterioration is greater than would be expected from the underlying pathology alone (Berg et al., 2010; Khan & Al Baradie, 2012; Specchio & Curatolo, 2021). Successful, prompt reduction of the epileptic activity may minimise the developmental deficits caused by the disorder (Scheffer & Liao, 2020). In some children, there can be a developmental component that is independent from the epileptic encephalopathy itself (Scheffer et al., 2017). For example, an individual's developmental delay may predate the onset of the seizures or they may continue to deteriorate despite achieving control of the epileptic encephalopathy. The acknowledgement of the complex interplay between the epileptiform activity and developmental component prompted the modification in terminology to "developmental and epileptic encephalopathy" in the new classification system (Scheffer et al., 2017). The descriptors can be used independently or together to provide clarity regarding the disorder.

The DEEs are the most severe group of epilepsies, with a childhood mortality rate of approximately 25% before the age of twenty (Camfield & Camfield, 2008). Individuals who do survive may have profound intellectual, psychiatric, behavioural, and motor disabilities over the course of their lives (Keezer et al., 2016). Research has reported that nearly half of children with severe epilepsies (47%) attend special schools for children with special needs and over a third (38%) attend school later than expected (Jakobsen et al., 2020). Individual DEE syndromes are considered rare;

however, when combined as a group of epilepsies they have an incidence of 1 in 2000 infants (Howell et al., 2021). This is more common than childhood cancer (Ballantine et al., 2017), neuromuscular disease (Theadom, 2019) or cystic fibrosis (National Screening Unit, 2017). Most DEEs are pharmacoresistant to standard antiseizure medications (ASM) (Cross & Guerrini, 2013).

2.1.7 Aetiologies of DEEs

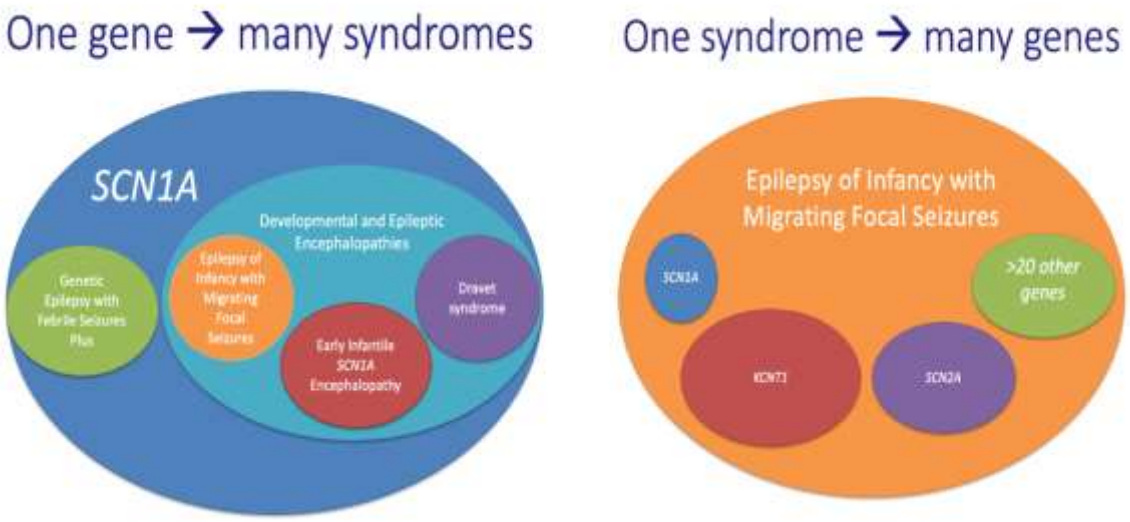
Prior to 2001 the aetiology of DEEs was largely unknown and were presumed to be acquired. Obvious acquired aetiologies included: hypoxia-ischaemia encephalopathy, cerebral infarcts, cerebral haemorrhages, and cerebral infections (Palmer et al., 2017). In the majority of cases the aetiology was not clear; however, as they presented sporadically, it was still felt likely to be acquired. With the discovery that 80% of Dravet syndrome, a type of DEE, was caused by pathogenic variants in *SCN1A*, an understanding of the importance of genetics in these disorders emerged (Claes et al., 2001; Scheffer & Nabbout, 2019). Subsequently, analysis of trio (child and both parents) whole exome sequencing in 264 children with either West syndrome or Lennox-Gastaut Syndrome, both DEE syndromes, revealed that *de novo* (only in the child and not their parents) pathogenic genetic variants were a significant cause of the DEEs (Allen et al., 2013).

There are now over 200 established DEE epilepsy genes (Palmer et al., 2017; McTague et al., 2016). Despite this, more than 50% of children with DEEs are presently unable to be genetically diagnosed (Scala et al., 2020; Sheidley et al., 2018; Symonds & McTague, 2020). This may be due to undiscovered epilepsy genes or variants in known genes that are not able to be detected with present genetic technology. There are regions of genes that are technically difficult to sequence and non-protein coding areas of the gene (intronic) that there is limited genetic understanding of. Identifying specific genetic variants as the cause of an individual's epilepsy can therefore be difficult, even when a genetic cause is suspected (Falco-Walter et al., 2018). In some individuals, their DEE can be caused by the presence of a single pathogenic variant (dominant disorder) in a gene, which has a major effect. This results in decreased production of the protein the gene encodes or a change to

the protein's structure so that it does not function normally. However, in other individuals the DEE requires two variants in the same gene (recessive disorder) or the complex interaction of several variants in multiple genes of minor effect (polygenic). To add to the complexity, the same genetic variant may cause different epilepsy syndromes in different individuals due to variability in their genetic background or environmental factors. Conversely, specific epilepsy syndromes can be caused by multiple different epilepsy genes (Scheffer et al., 2017). This variability in genetic aetiology is depicted in Figure 1.

Figure 1

Variability in genetic aetiology of the Developmental and Epileptic Encephalopathies



Note. The correlation between genotype and phenotype in the developmental and epileptic encephalopathies is complex; with some genes causing multiple epilepsy syndromes of varying severity (such as SCN1A) and some epilepsy syndromes being caused by many different genes (such as epilepsy of infancy with migrating focal seizure). Adapted from "The genetic landscape of epilepsy of infancy with migrating focal seizures", by R. Burgess and colleagues, 2019, *Annals of Neurology, 86*(6), p. 825.

Genetic epilepsy is not always inherited (Falco-Walter et al., 2018). In some individuals a random DNA mutation occurs soon after fertilisation, which results in their epilepsy. This is called a *de novo* genetic pathogenic variant as it is not inherited

from an individual's parents (McTague et al, 2016). Furthermore, it is also possible for a child to inherit a causative genetic variant from their parent(s), who does not have epilepsy. This may be due to the gene having incomplete penetrance or the variant being only present in the gonadal cells of the parent but not the parent's brain; this is known as mosaicism (Myers et al., 2018).

In addition to a pure genetic aetiology, DEEs can also be caused by structural or metabolic abnormalities, some of which have a genetic aetiology. In order for a structural abnormality to be the cause of an individual's epilepsy, a direct relationship needs to be established between the abnormality and seizures (Brodie et al., 2018). Acquired disorders such as hypoxic ischaemic encephalopathy or infection can result in structural changes in the brain that can be seen on neuroimaging. However, structural abnormalities can be due to underlying genetic abnormalities, such as in tuberous sclerosis (*TSC1* and *TSC2*) and the malformations of cortical development (*PAFAH1B1*, *DCX*, *ARX*, and *TUBA1A)* (Desikan & Barkovich, 2016). An example of a metabolic aetiology is GLUT1 Epileptic Encephalopathy, caused by a pathogenic variant in *SLC2A1.* This is an important aetiology as it responds to the ketogenic diet (De Giorgis & Veggiotti, 2013; Klepper et al., 2020; Ruiz Herrero et al., 2021). Rather than just targeting the seizures with antiepileptic drugs, correcting the underlying metabolic abnormality early in the course of the disorder improves the potential cognitive outcome (Scheffer et al., 2017).

2.1.8 Comorbidities of DEEs

Common comorbidities of DEEs include cognitive disorders (learning disorders and intellectual disability), motor disorders (cerebral palsy and movement disorders), psychiatric disorders (mood disorders, anxiety and schizophrenia), sleep disturbances, pain (headaches and neuropathic) and behavioural difficulties (attention-deficit/hyperactivity (ADHD) disorders) (Ottman et al. 2011; Verrotti et al., 2014). Psychiatric comorbidities are the most frequent epilepsy comorbidities and can impact the wellbeing and quality of life of the individual above and beyond the effect of the seizures (Verrotti et al., 2014). Unfortunately, they are known to be underdiagnosed and undertreated in individuals with epilepsy (De Boer et al., 2008),

indicating that the true comorbid prevalence may be even higher than estimates show. Other non-neurological medical disorders have also been consistently reported to be increased in individuals with epilepsy, including: diabetes mellitus, heart disease, hypertension, thyroid problems, asthma and arthritis (Chang et al., 2011; Elliot et al., 2009; Keezer et al., 2015; Lin et al., 2015; Ottman et al., 2011; Qin et al., 2005). It has been estimated that 50% of adults with active epilepsy have at least one comorbid disorder (Keezer et al., 2016).

One of the features which characterise specific DEE syndromes are their associated comorbidities (Specchio & Curatolo, 2021). Common comorbidities of DEE syndromes included in the current research are described below.

Dravet Syndrome

One of the most well understood DEE syndromes is Dravet syndrome. In this syndrome, seizures begin between four and 18 months of age in a normally developing infant (Dravet, 2011). At seizure onset, individuals may experience febrile focal seizures which are typically prolonged (longer than five minutes). Generalised tonic-clonic seizures, myoclonic and absence seizures can occur between the ages of one to four years. Developmental slowing or regression becomes increasingly apparent from the second year (Dravet, 2011). Moderate to severe intellectual disabilities and language impairment are commonly reported, as well as progressive gait abnormalities, sleep disturbances, ASD, and behavioural difficulties with inattention and hyperactivity (Knupp et al., 2017; Takayama et al., 2014). In fact, the prevalence of comorbid ASD in Dravet Syndrome has been reported to be 47.4% (Strasser et al., 2018).

A longitudinal study that followed 24 individuals with Dravet syndrome up to the age of 50, highlights the lifelong severe impact of Dravet syndrome (Genton et al., 2011). Findings showed that whilst the severity and frequency of seizures decreased after childhood, motor abnormalities were still common, with intention tremors, eye movement disorder, and walking is markedly impaired (Genton et al., 2011). Impaired intellectual functioning in adulthood was shown to be in the moderate to severe range, with the majority of individuals highly dependent on

constant care; only three individuals lived independently and 20% died prematurely at a mean age of 24.8 years (Genton et al., 2011). Darra and colleagues (2019) reported similar outcomes in adolescents and adults with Dravet syndrome, with seizures persisting in 73.6% of adolescents and 80% of adults. Concordantly, intellectual disability in the moderate to severe range was also shown to be high, 70.5% of adolescents and 80% of adults (Darra et al., 2019).

Pre-mature mortality is a known outcome of Dravet syndrome, with individuals most commonly dying before the age of 10 years and due to epilepsy related causes (Shmuely et al., 2016). The most common cause of death has been reported to be sudden unexplained death in epilepsy (SUDEP) for 49% of deceased individuals, followed by status epilepticus in 32%. The severity of epilepsy appears to be associated with an increased risk of pre-mature death (Shmuely et al., 2016). These findings highlight that the global outcome of Dravet syndrome is poor even after childhood. Despite the decrease in seizure activity, the profound developmental effects continue to have devastating impacts on individuals throughout their life.

West Syndrome

The most common DEE syndrome is West syndrome (Khan & Al Baradie, 2012; Wirrell, 2009). It affects both sexes, with a higher incidence in males at a 6:4 ratio (Pavone et al., 2014). It is characterised by the onset of epileptic spasms usually between three to 12 months old, with the median age of onset identified as five months (Gulati et al., 2015). This occurs alongside global developmental impairment and a severely abnormal EEG showing hypsarrhythmia (chaotic and disorganised electrical brain activity). The spasms are sudden, brief contractions of muscles in the neck, trunk and limbs, which typically present in clusters (there can be as many as 150 seizures in a cluster), with between several and up to hundreds of clusters experienced in a single day (D'Alonzo et al., 2017). The spasms may be preceded or followed by cry or screaming episodes, occurring more prevalently imminently prior to sleep or on waking (Pavone et al., 2020). Children's eyes may become fixed or deviated during these crises, with cardiac and respiratory involvement. Drowsiness or irritability may occur following the spasms. Common comorbidities include

cerebral palsy, intellectual disability (ID), visual impairment, hearing and feeding difficulties, ASD and microcephaly (Beriwal et al., 2021). A meta-analysis study reported that ASD was present in 19.9% of individuals with West syndrome in comparison to 4.7% for general epilepsy (Strasser et al., 2018). The likelihood of pre-mature mortality is high (Riikonen, 2020). Research has reported fatal outcomes in 13% of participants (Granström, 2003). A longitudinal study which followed individuals with West syndrome for 20 to 35 years, reported that 31% of the 214 participants died pre-maturely before the age of three years (Riikonen, 1996; 2001). Furthermore, only 24% the surviving individuals had normal or slightly impaired cognitive functioning, four individuals had professional occupations, eight were living with a romantic partner or spouse and five had healthy children (Riikonen, 1996; 2001). The aetiology is classified to be either genetic, structural, metabolic or unknown. Early recognition of West syndrome with prompt treatment, shorter duration of hypsarrhythmia, prompt treatment of relapses and any adverse effects of the most influential modifiable prognostic factors (Riikonen, 2020).

PCDH19 Clustering Epilepsy (CE)

PCDH19 clustering epilepsy is an example of a monogenic DEE. Since being first described in 2008 (Dibbens et al., 2008; Scheffer et al., 2008), diagnosis and understanding has increased rapidly (Trivisano et al., 2018). It arises from pathogenic variants on the *PCDH19* gene, which is on the X chromosome. It has an unusual pattern of expression where only females are affected and males are generally carriers (Dibbens et al., 2008). Seizure onset occurs at an average age of nine months, with predominantly focal seizures which occur in clusters. Some individuals also experience generalised seizures. Clusters of seizures are often induced by fever and may last from hours to days at a time. Development progresses normally until seizure onset, but girls can experience regression during the clusters. Although initially their development may improve between clusters, over time it becomes apparent that development is impacted. Cognitive outcomes vary; approximately a third have a normal intellect, while two thirds have intellectual disability (ID) and autism spectrum disorder (ASD) of varying degrees of severity. Earlier onset of epilepsy has been

shown to be a predictive factor for developing ID and ASD (Kolc et al., 2020; Trivisano et al., 2018). In their first decade, clusters of seizures are resistant to multiple ASMs however seizures begin to decrease in frequency around 10 years of age. During adolescence and young adulthood, individuals are at high risk of developing psychosis and other psychiatric disorders (Marini et al., 2012; Specchio et al., 2011). The neuropsychiatric comorbidities are heterogenous, with ID severity ranging from mild to profound and different combinations of autistic, obsessive compulsive, aggressive or attention-deficit/hyperactive symptoms arising (Kolc et al., 2020).

CDKL5-encephalopathy

Another well-known monogenic DEE is *CDKL5*-encephalopathy, which is characterised by the onset of pharmaco-resistant seizures before three months, alongside severe neurodevelopmental impairment and gross motor function (Specchio & Curatolo, 2021). Some of the development delay is independent from the epileptic seizures and appears before seizure onset.

The everyday functioning is significantly impaired for individuals with *CDKL5*-encephalopathy (Leonard et al., 2021). Gross motor function is often so severe that less than a quarter of affected females and even fewer males are able to walk independently. Only 25% of affected females are able to communicate by spoken language, signing or use of symbols (Fehr et al., 2016). Other common functional difficulties include gastrointestinal issues (constipation, reflux or air swallowing), feeding difficulties, respiratory infections, sleep disturbances, bruxism and abnormal muscle tone (MacKay et al., 2021). Compromised nutrition is commonly reported and has led to gastrotomy tubes being inserted for a quarter of affected females and approximately half of affected males by the age of seven and a half years old (Mangatt et al., 2016). Cortical visual impairment is also commonly reported and has been associated with worse developmental outcomes (Demarest et al., 2019). Frequent hospital admissions in the first five years of the child's life due to respiratory infections have been reported in over a third of affected families (Mangatt et al., 2016). Less common comorbidities may include breathing disturbances, laughing and

screaming spells as well as vasomotor disturbances (Fehr et al., 2013). Likelihood of developing such comorbidities has been found to increase with age, with males being more vulnerable than females (Mangatt et al., 2016).

A study of 160 families with children with *CDKL5*-encephalopathy demonstrated the significant impact that this DEE has on children (Leonard et al., 2021). Findings showed that 65.1% of children required maximal assistance/were unable to take 10 steps forward, 57.4% of children did not make eye contact, 52.7% experienced constipation, 38.7% experienced reflux, 25.6% had severe sleep difficulties, 27.9% experienced one to four seizures a day and 31% experienced more than five seizures daily (Leonard et al., 2021). Furthermore, the functional impact of the DEE was shown to have the biggest effect on the child's quality of life, with those of higher seizure frequency having lower quality of life.

In summary, the comorbidities and outcomes in the DEEs are wide ranging and heterogenous in severity. The significant impact that these comorbidities can have in addition to the epilepsy itself is clear. It is, therefore, crucial to identify the presence of possible comorbidities early in the diagnostic process, so that the child and family can have the best quality of life possible (Scheffer et al., 2017).

2.2 Impact of Caregiver Burden

The profound impact that DEEs and the multiple comorbidities have on children are well-established (Camfield & Camfield, 2008; Keezer et al., 2016; Scheffer et al., 2017; Verotti et al., 2014); however, the negative consequences are not limited to the child alone. Parents, siblings, extended family members and the wider community are significantly impacted by these epilepsies (Ostendorf & Gedela, 2017). Caregiver burden has been previously defined as "the extent to which caregivers perceived their emotional or physical health, social life, and financial status as suffering as a result of caring for their relative" (Zarit et al., 1986, p.261). This definition highlights the multifaceted nature of caregiving and how the burden of caring for a child with a chronic disease affects parents and families in numerous areas of life (Jones et al., 2019; Smith et al., 2014; Westphal-Guitti et al., 2007). A

more recent definition developed by an expert panel with regard to DEEs also emphasises the individualised context of caregiving, whilst giving more detail regarding the specific resources which may be affected: impact of caregiving is "the caregiver's perception of the physical, social, and emotional effects of caregiving on the caregiver's life. It also includes the caregiver's perception of the effects of caregiving on the financial resources, time resources and other resources available to the caregiver" (Jensen et al., 2017b, p.137). These definitions suggest that the threshold for 'burden' may differ due to the subjective experience of each caregiver. It is also important to acknowledge that whilst stressful, caregiving can also be emotionally rewarding and positively benefit the caregiver, through promoting family connection, building self-confidence and the reward of being an advocate (Jensen et al., 2017b; Magliano et al., 2014; Tarlow et al., 2004).

2.2.1 Physical Burden

Sleep

The physical health of a parent or caregiver of a child with epilepsy can be significantly impacted, with profound sleep deprivation being one of the most well recognised consequences (Jensen et al., 2017b; Wood et al., 2008). In comparison to parents of healthy children, parents of children with epilepsy report significantly lower sleep duration, efficiency, latency and overall decreased quality of sleep as well as higher daytime dysfunction (Yang et al., 2020). This was especially true for parents of infants with epilepsy, rather than older children. On average, parents of children with epilepsy have reported to sleep approximately four hours each night and wake at least three times, dependent on the frequency of seizures and their perceived severity (Cottrell & Khan, 2005). Thus, severity of epilepsy is positively correlated with increased parent and child sleep dysfunction, and parental fatigue (Larson et al., 2012). In a qualitative study of caregivers of children with DEEs, all described the burden of sleep deprivation and exhaustion as having a major impact on physical health (Jensen et al., 2017b). Such was the extent of their fatigue, their own self-care needs (such as staying physically fit and eating healthy) were unmet due to a lack of motivation and energy.

Given the unpredictable timing and frequency of seizures, as well as anxiety regarding the possibility of SUDEP, parents report an inability to "turn off" (Berg et al., 2019; Jensen et al., 2017b; Smith et al., 2014). As a result, parents commonly co-sleep with their children or share the same room in order to attend to night seizures (Larson et al., 2012). However, in comparison to healthy controls, children with epilepsy have consistently been shown to experience greater sleep disruptions, such as parasomnias, night waking, bedtime resistance and sleep onset delay (Larson et al., 2012; Tang et al., 2011). This is likely due to the bidirectional relationship between sleep patterns and seizure profiles (Dehghani et al., 2019; Grigg-Damberger & Foldvary-Schaefer, 2021). Therefore, the child's poor sleep quality is a significant predictor of poor parental sleep quality, whereby if the child is waking frequently, so is their parent (Meltzer & Mindell, 2007).

Sleep deprivation has been consistently linked to detrimental health outcomes with changes in neuroendocrine, immune, metabolic and inflammatory systems, resulting in increased risk of cardiovascular disease and diabetes mellitus as well as reduced emotional, cognitive and behavioural functioning (AlDabal & BaHammam, 2011; Faraut et al., 2012).

Seizure Related Injuries & Impact of Comorbid Conditions

A literature review on the quality of life of caregivers and children with Lennox-Gastaut Syndrome (LGS) described elevated physical demands for both child and caregiver (Gallop et al., 2009). This was due to the types of seizures experienced as well as the near universal (approximately 90%) presence of intellectual disability and severe behavioural problems that the children had (Gibson, 2014). The frequent drop seizures experienced with LGS put children at increased risk of injury. Therefore, caregivers must not only cope with the seizures themselves, but also attempt to prevent additional seizure related injuries, by catching, holding or walking with them (Gallop et al., 2009). Similarly, the high level of motor and other neurodevelopmental difficulties present in Dravet syndrome have a profound impact on caregiver health, with the majority of caregivers reporting significant amount of time spent managing difficulty behavioural problems and assisting with walking (Campbell et al., 2018).

Children with DEE often require a G-tube for ASM administration and feeding. The logistics of G-tube feeding are time consuming. Although it results in increased growth and better nutrition, the other side of this is that the children become heavier making them harder to lift and contributing to decreased physical health of their caregivers in comparison to orally fed children (Mori et al., 2017). However, mothers whose children were tube fed reported better mental health compared to those children with DEE who were orally fed. This suggests that reduced stress and burden of care at mealtimes as well as the knowledge that their child was adequately nourished and had received their medication, had positive effects on a mother's mental wellbeing (Brotherton et al., 2007; Wilken, 2012). This highlights the multidimensional nature of caregiver burden, where one area of a caregiver's health may be reduced, whilst another is elevated.

2.2.2 Impact of Reduced Financial and Temporal Resources

There are significant practical, organisational, temporal and financial requirements of caring for children with DEE (Jensen et al., 2017b). Parents have to make significant adjustments to family life to accommodate the management of their child's epilepsy (Duffy, 2011). There is an increased demand on their time due to constant surveillance of their child, watching for seizures (Berg et al., 2019), coping with various comorbidities such as behavioural problems (Gibson et al., 2014) as well as dispensing complex ASM and stringent diet management (Khan & Al Baradie, 2012; Roth et al., 2011). Parents must overcome scheduling difficulties and organise transportation for numerous outpatient visits, intensive medical procedures and prolonged hospitalization (Joshi et al., 2016; Scheffer et al., 2017). This is in addition to still completing daily household tasks, keeping up with personal care and maintaining logistical requirements for other family members who also have other commitments and responsibilities (Campbell et al., 2018; Jensen et al., 2017a; Villas et al., 2017).

These increased demands on a parent's time increases time constraints for other areas of their lives, such as their career, their parenting of their other children and their relationship with the other parent (Gibson, 2014). Given the extent of care

required to look after a child living with epilepsy, it is common that one parent is no longer able to work (Camfield et al., 2016). In one study, 26% of caregivers reported missing more than one day of work in the previous week, 46% indicated a substantial impact on work productivity, and 65% recorded switching, quitting or losing their job as a result of caregiving responsibilities (Campbell et al., 2018). Another study showed that 89% of fathers were in employment, in comparison to only 62% of mothers (Jakobsen et al., 2020). The severity and frequency of seizures and the complexity of managing DEEs reduces the likelihood of others, such as family members, agreeing to look after the child, which in turn, reduces parental opportunity for relief and respite (Camfield & Camfield, 2002). Major difficulties finding external caregivers as well as insufficient school assistance have also been reported (Nolan et al., 2006).

The ongoing care and high level of resources required from health, educational and welfare systems pose considerable burden (Camfield et al., 2016; Palmer et al., 2017). The financial burden of epilepsy does not just eventuate from parents' reduced ability to work, there is also additional pressure of the cost of treatment, which is not always publicly funded or covered by insurance (Jensen et al., 2017a). In fact, one study estimated the annual mean direct medical cost for caregivers in the USA ranged from $4344 for low seizure frequency to $10162 for high seizure frequency (Hussain et al., 2020). Mean indirect costs for caregivers ranged between an additional $20,000 to $40,000 annually. The amount of annual costs for caregivers of epilepsy was $48 billion in comparison to the general population in the USA, which highlights the economic burden faced by these families, especially for children with high frequency of seizures (Hussain et al., 2020). Whilst the financial costs may not be directly billed to families due to the public healthcare system in a New Zealand or Australian context, the same expenses do still apply and are, instead, absorbed by the hospitals and the tax payer (Howell et al., 2018).

However, technological advances can provide financial cost savings. A recent population-based study in Australia demonstrated the financial cost savings of earlier whole exome sequencing (WES), while also increasing the diagnostic yield of seven additional possible diagnoses for lower long term cost (Howell et al., 2018). Therefore, conducting WES earlier for severe childhood epilepsies could have

exponential flow on financial benefits, not only for the individual and family (by timely use of the gold standard medications), but also for the wider health system by freeing up resources, such as ambulance and emergency staff. It is imperative that technological advances are included into standard care when evidenced to be safe and cost-effective (Howell et al., 2018). Thus, the financial burden can be experienced at a societal, rather than familial level, or both. In New Zealand, cost of some medications, transport, specialist caregivers and respite are not necessarily publicly funded and still require families to pay, thus representing additional burden to these families.

Furthermore, rural communities in New Zealand are known to experience poor healthcare access (Adams & Carryer, 2019). There is no current research exploring the impacts of this for families with children with DEEs, however the implications are clear; either families partake in extensive travel to attend specialist appointments or they move to metropolitan areas for greater access to their child's care needs. Yet, cities (such as Auckland) are also the most unaffordable in terms of housing (Murphy, 2016; Terruhn, 2020). Therefore, for families who are forced to re-locate due to the health needs of their children, there is certainly an indirect financial burden on the cost of living. This is also likely to have flow on impacts to other areas of caregiver burden and their quality of life.

2.2.3 Psychological and Emotional Impact

The psychological and emotional component of caregiver burden is well recognised in caregivers of children with epilepsy (Ferro et al., 2011; Ferro & Speechley, 2009; Lv et al., 2009; Wood et al., 2008). Parents report experiencing high levels of stress (Cushner-Weinstein et al., 2008), feelings of anger, guilt and helplessness (Jensen et al., 2017b), as well as worry and perception of vulnerability (Ramaglia et al., 2007). For parents with children of Dravet syndrome, seizures were found to be the greatest source of caregiver stress, followed by the loss of original hopes for their child's future as the actuality of developmental delay and behavioural problems becomes realised (Camfield et al., 2016; Nolan et al., 2008). In addition, 74% of caregivers reported concerns about the emotional impact on siblings (Villas

et al., 2017). The associated anxiety and non-finite grief due to the high risk of death caused by SUDEP (up to 60% in some types of DEEs) or status epilepticus (SE) is another additional stressor for families of children with DEEs (Khan & Al Baradie, 2012).

Depression and Anxiety

Parents of children with epilepsy experience significantly higher levels of depression and anxiety than parents of healthy children (Akay et al., 2011; Lv et al., 2009) and mothers of children with other neuro-disabilities (Reilly et al., 2018). One longitudinal study examining the prevalence of depressive symptoms in 356 mothers of children with epilepsy found that 57% were in the at-risk range for clinical depression over the first 10 years after their child's epilepsy diagnosis (Puka et al., 2019). Over time, four unique trajectories of symptoms were identified: 'low stable' (29% of mothers), 'intermediate stable' (46%), 'high-stable' (20%), 'high decreasing' (5%). This indicates that the risk of clinical depression is significant and stable for mothers throughout their child's epilepsy journey. Caregivers of children with Dravet syndrome report higher prevalence rates, with 70% indicating slight problems with anxiety and depression and 34% reporting moderate problems (Campbell et al., 2018).

Families of children with *CDKL5* encephalopathy have also reported significantly impaired emotional wellbeing in comparison to US population norms, as well as greater impairment than caregivers of children with Rett syndrome and Down syndrome (Mori et al., 2017). Mental health scores were consistently impaired across all age groups, indicating that parental psychological wellbeing does not markedly improve throughout their child's life. Increased severity of sleep problems in the children with *CDKL5* and financial difficulties have been linked to impaired parental mental health of parents (Mori et al., 2017). This aligns with the research discussed above, again highlighting the association between reduced maternal sleep quality and child sleep disturbances as predictors for maternal depression.

Sex differences in the psychological aspect of caregiver burden have been noted. Up to 50% of mothers are reported to be at risk of clinical depression (Ferro

& Speechley, 2009), and approximately 30 – 35% actually develop it in the first 24 months after their child's epilepsy diagnosis (Ferro et al., 2011). In contrast, the prevalence of clinical depression in fathers ranged from 10 to 30% in the first 24 months (Ferro & Speechley, 2009). It is unclear whether these differences are due to sex differences or because mothers are most often the primary caregiver (Mu, 2005; Ferro & Speechley, 2009). Another study reported mothers of children with epilepsy experience greater burden of care and higher levels of strain than fathers (Mu, 2005; Ramaglia et al., 2007). In particular, mothers are more likely to score in the at-risk range than fathers on three subscales: depression (55% vs 33%), anxiety (47% vs 26%) and stress (55% vs 31%) (Reilly et al., 2018). As previously discussed, fathers are more likely to be in employment than mothers (Jakobsen et al., 2020). This is consistent with the assertion that as mothers more commonly take on the primary responsibility of caring for a severely impaired child, the increased exposure may contribute to higher levels of psychological distress and subsequent caregiver burden. It is clear that whilst the psychological impacts of caregiver burden are reported to be experienced at higher levels by mothers, the emotional strain is still experienced by fathers and can result in psychopathology in both parents. However, despite the high rates of depression experienced, only 26% report receiving any form of family therapy (Villas et al., 2017).

Posttraumatic Stress Disorder

Depression and anxiety are not the only psychological disorders experienced by parents and caregivers of children with epilepsy (Iseri et al., 2006; Jensen et al., 2017b). A high prevalence of posttraumatic stress disorder (PTSD) has also been reported among caregivers (Carmassi et al., 2018), with prevalence rates ranging from 9.1% to 31.5% (Carmassi et al., 2017; Iseri et al., 2006). Similar to depression and anxiety, mothers experience higher risk of PTSD, with three times higher prevalence rates than fathers (Carmassi et al., 2017; 2018). Approximately 40% of caregivers report experiencing some trauma symptoms, meeting criteria for partial PTSD; most commonly identified were intrusion symptoms and distressing memories. Divorced parents or those living alone have also been shown to have significantly

higher prevalence of PTSD than those biological caregivers living together (Jakobsen et al., 2020). The presence of comorbid PTSD and major depressive disorder (MDD) in parents of children with epilepsy have also been reported (Carmassi et al., 2019), with 57% of parents meeting criteria for PTSD also developing MDD (Iseri et al., 2006).

Overall Quality of Life

It is important to acknowledge that the different areas of potential burden likely interact, influencing and compounding each other. For example, fatigue and exhaustion is a substantial contributor to parental stress levels, increased irritability, feelings of being overwhelmed and reduced perceived ability to cope with their child's needs (McCann et al., 2015). Research indicates that up to 90% of individuals with depression and up to 70% of individuals with anxiety also experience dysfunctional sleep (Staner, 2003; Tsuno et al, 2005). There is increasing evidence of the bidirectional relationship between sleep quality and psychological health difficulties, whereby sleep disturbances may precede mood difficulties, develop as a result of them or the relationship may be bidirectional and cyclical (Alvaro et al., 2013). Maternal sleep quality has been shown to be a significant predictor of maternal mood, stress and fatigue (Meltzer & Mindell, 2007). This highlights the complex interplay between different domains of life, where difficulties in one area have spill on effects in others.

Quality of life has been defined by the WHO as "individuals' perception of their position in life in the context of the culture and value system in which they live, and in relation to their goals, expectations, standards, and concerns" (Kuyken et al., 1995, p.1405). Similar to caregiver burden, it is recognised that quality of life is subjective. Therefore, the acknowledgement that when taken together the different areas contributing to caregiver burden accumulate, it is unsurprising that caregivers report significantly lower quality of life than parents of healthy children (Lv et al., 2009; Puka et al., 2018) or parents of children with other conditions, such as diabetes, asthma and cerebral palsy (Hoare et al., 2000; Moreira et al., 2013). Thus, families of children with DEE face the challenges discussed above to a greater extent and with more intensity (Gallop et al., 2009), which is further evidenced by their significantly

lower scores on quality of life measures than parents of children with well-controlled epilepsy (Bompori et al., 2014; Hoare et al., 2000).

However, the quality of life of parents is not only important for their own wellbeing, but also for their children (Puka et al., 2018). Higher levels of parental quality of life has been found to result in higher levels of child quality of life due increased perceptions of family cohesion (Mendes et al., 2017; Moreira et al., 2013). The quality of life of siblings of affected children have also been shown to be significantly impacted. In recent study, siblings of children with DEEs described feeling worried or scared during their sibling's seizures, as well as feelings of being overly responsible and experiencing higher levels of low mood and anxiety than perceived by their parents (Bailey et al., 2020). Whilst parents are known to show significant concern for the impact that the DEE is having on their unaffected children (Villas et al., 2017), it has also been reported that unaffected siblings receive less attention, experience a sense of isolation and may experience difficult transitions from childhood to adulthood (Berg et al., 2019; Gibson, 2014; Nolan et al., 2008).

In summary, the research discussed above paints a clear picture of the immense psychological, physical, financial, temporal and organisational burdens on caregivers of children with DEEs (Camfield et al., 2016; Gibson et al., 2014; Jensen et al., 2017b; Mori et al., 2017). Understanding the key risk factors that may impact on the extent of caregiver burden and negative outcomes is of particular importance and may help inform future interventions to improve outcomes for these families.

2.3 Risk Factors Associated with Caregiver Burden in DEEs

Several key risk factors have been identified to be predictive of caregiver burden, yet there is wide variation across studies (Jones & Reilly, 2016). For ease of understanding, the different types of influences have been organised into the following sub-sections and will be discussed in turn: clinical features, illness perceptions, uncertainty and the diagnostic journey.

2.3.1 Risk Factors Related to Clinical Features

Arguably the most apparent determinants of caregiver burden are the specific clinical features of the child's DEE. Severity and frequency of seizures are commonly cited predictors of caregiver burden (Puka et al., 2019; Williams et al., 2003). That is, increases in frequency and severity of seizures as well as pharmaco-resistance to ASMs are likely to lead to increases in caregiver burden and reductions in caregiver quality of life (Akay et al., 2011; Lv et al., 2009; Puka et al., 2019; Shatla et al., 2011; Vrščaj et al., 2020; Yong et al., 2006). Research has identified other clinically related predictors of caregiver burden, such as: comorbid child depression and cognitive impairment (Cushner-Weinstein et al., 2008; Puka et al., 2019); severe child sleep disturbances (Mori et al., 2017); the severity of behavioural difficulties (Reilly et al., 2018; Wirrell et al., 2008); presence of status epilepticus, greater number of ASM, ASM side effects and the cost of epilepsy (Lv et al., 2009; Yong et al., 2006).

In contrast, other studies have reported no association between caregiver burden with seizure type and level of seizure control (Williams et al., 2003), nor the age of seizure onset, duration of epilepsy or seizure frequency (Kerne & Chapieski, 2015; Mori et al., 2017). This is likely due to the varying characteristics of the epilepsies, children and family circumstances as well as the measures used and differing definitions of seizure frequency and severity across the studies (Jones & Reilly, 2016). It has been suggested that for DEEs, seizure frequency or type may not be significant predictors of caregiver burden due to the numerous other comorbidities present, which may dilute the sole influence of seizures on caregivers' health (Mori et al., 2017). Another explanation for these inconsistencies could be illness perceptions (Carmassi et al., 2018), as described in the following section. Thus, a clear consensus is yet to be reached regarding the extent to which clinically related factors influence caregiver burden.

2.3.2 Illness Perceptions as a Risk Factor

Illness perceptions are defined as "organised cognitive representations or beliefs that patients or caregivers have about their or their child's illness" (Petrie et al., 2007,

p. 163). These subjective beliefs are important predictors of behaviour and long-term outcomes for individuals with physical and/or psychological conditions (Petrie et al., 2008). Illness perceptions are structured in a consistent way, with individuals developing a perceived identity for their illness and its accompanying symptomology. Beliefs regarding the cause and longevity of the illness as well as views on the consequences, treatment outcomes, meaning and its ability to be controlled are also incorporated within illness perceptions (Petrie et al., 2007). That is, individuals who perceive their condition to be manageable, have a good understanding of its symptoms and causes and maintain a sense of personal control are likely to respond better than those who hold negative and defeatist views about their illness.

Studies of illness perceptions in epilepsy have demonstrated similar findings to other diseases (Rizou et al., 2015; Carlson & Miller, 2017; Harden et al., 2016). Individuals who hold negative beliefs about their epilepsy, such as believing they have less personal control over their illness or expecting the illness to have a high emotional impact, report higher levels of distress (Rizou et al., 2015). In contrast, those who hold more positive illness perceptions, such as believing their epilepsy would not affect them emotionally, scored higher on quality of life.

Illness perceptions do not only apply to the individuals with the condition, they are also influential for caregivers and parents, whereby subjective parental beliefs about their child's illness affect how they cope and manage it (Bassi et al., 2016). Carlson and Miller's (2017) recent study reported a significant relationship between mothers' perceptions of the severity of their child's epilepsy and decreased perceived social support. That is, mothers who held more severe illness perceptions regarding their child's epilepsy felt they also received less social support, which resulted in them reporting higher levels of depression and anxiety. Illness perceptions of increased burden on the family also played a role in increasing mothers' levels of depression, anxiety and stress (Carlson & Miller, 2017). Another study which found that clinically related factors (such as type of epilepsy, type and number of seizures) did not significantly predict the presence of PTSD symptoms in parents, suggests it is the subjective perception of seizures, rather than objective severity that is of importance (Carmassi et al., 2018). If a parent perceives their child's seizures to be severe, life

threatening and frightening, irrespective of how severe the seizure is by clinical standards, this may be more likely to trigger parental distress and increase caregiver burden.

2.3.3 Uncertainty and the Diagnostic Journey

The degree of uncertainty experienced by caregivers and families is another important factor that impacts on caregiver burden and subsequently results in reduced quality of life. Epilepsy is distinct from other chronic health conditions in that seizures are unpredictable and there are a lack cues signalling the onset of a seizure (Berg et al., 2019). This makes it difficult for caregivers/parents to plan and structure daily life and increases parental uncertainty (Mu, 2005; Smith et al., 2014), which in turn reduces parents' sense of control, perceived coping and increases the presence of parental depression and trauma (Bandstra et al., 2008; Carmassi et al., 2018; Hansen et al., 2018; Mu, 2005). For parents of children with DEE, the dual nature of the sudden and acute seizure events intertwined with the chronic but uncertain prognosis of their child's DEE is difficult to bear, resulting in feelings of helplessness, inadequacy, grief and guilt (Jensen et al., 2017b; Jones & Reilly, 2016).

Families of children with epilepsy experience several inherent forms of uncertainty (Webster, 2019); ranging from not knowing when a seizure will be triggered and when it will end, to possible uncertainty surrounding the type of epilepsy and whether it can be successfully treated (Berg et al., 2019; Smith et al., 2014). Families of children with DEEs often deal with an additional form of uncertainty regarding the diagnostic and/or causative label and trajectory of their child's condition (Joshi et al., 2016). In one study, 40% of children experienced a delay in epilepsy syndrome diagnosis of a month from their second seizure, 21% had a delay of one to four months, 7% recorded a delay of between four to 12 months and 13% were diagnosed more than a year past their second seizure (Berg et al., 2014). Delays in diagnosis and misdiagnosis of epilepsy and the epilepsy syndrome are common and may result in worse outcomes for the child (Auvin et al., 2012; Chowdhury et al., 2008). Identifying the cause of a child's DEE may be delayed even further, commonly

taking several months or years for families to receive an aetiological diagnosis (Joshi et al., 2016). This aetiological diagnostic uncertainty contributes to caregiver burden as they face the difficulty of coping with an uncertain future (Graungaard & Skov, 2006; Webster, 2019). There is limited research that directly explores how living without knowing the cause for their child's DEE impacts on caregiver burden and family quality of life.

In conclusion, there are several factors that contribute to caregiver burden of children with epilepsy in general but especially in the DEEs, which present significant challenges to families across several areas of life. Aside from the difficulty of managing the clinical features of paediatric epilepsy, other predictors of caregiver burden include illness perceptions as well as the diagnostic and/or causative uncertainty of their child's epilepsy.

2.4 Importance of a Genetic Diagnosis

Identifying the aetiology of DEEs as early as possible can have positive effects; not only for management and accurate prognosis trajectories but also for reducing the financial cost to both the affected family and the state (Howell et al., 2018; Palmer et al., 2017). Therefore, it is imperative that the focus on identifying the aetiology begins from seizure onset. As the aetiology of DEEs is most often genetic (McTague et al., 2015), genetic testing is critical.

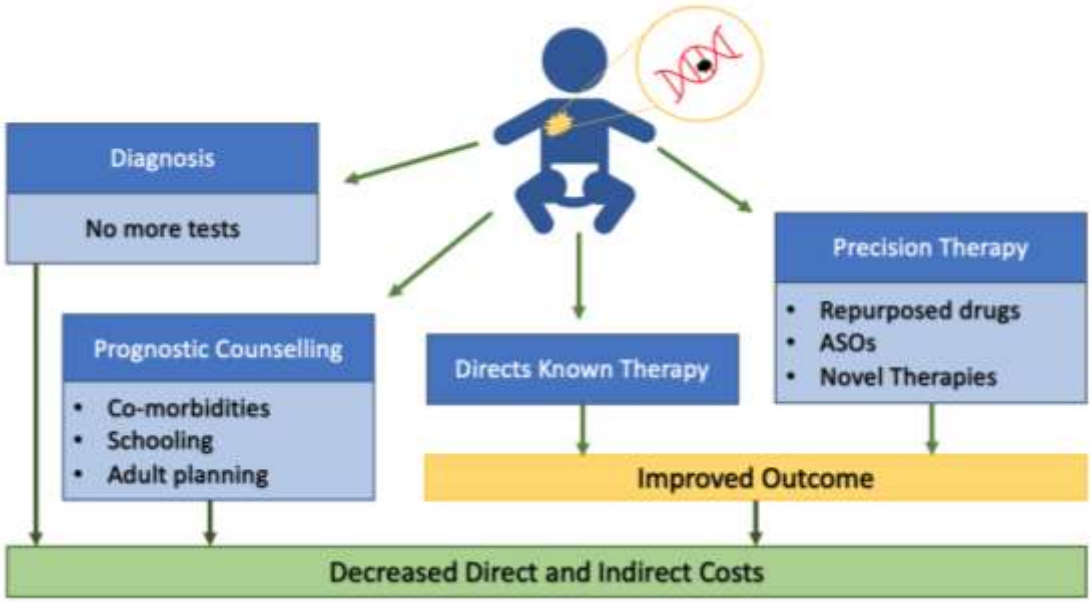
Genetic testing is becoming more prevalent in clinical practice for multiple neurological disorders, such as cancer, Alzheimer's disease, muscular dystrophy, spinal muscular atrophy and epilepsy (Finkel et al., 2016; Fox et al., 2015; Gooding et al., 2006). There are two main factors that contribute to the value of a genetic diagnosis (Poduri, et al., 2014). These are clinical utility (implications for a patient's clinical care) and personal utility (value of results for the patient, independent of any clinical implications).

2.4.1 Clinical Utility of a Genetic Diagnosis

The clinical utility of genetic testing is well established (Pitini et al., 2018), with a summary of the clinical implications depicted in Figure 2. Genetic diagnosis can end the expensive ($19,000 per child) and invasive investigations (lumbar puncture and organ biopsies) that children commonly undergo in the search for a cause (Howell et al., 2018; Joshi et al., 2016). As a result, early genetic testing has been shown to decrease DEE diagnostic costs, costs for hospital admissions and health appointments.

Figure 2

Possible clinical utility of a genetic diagnosis in a child with DEE.



Note. Figure developed as a pictorial summary for the different clinical uses of genetic diagnosis in developmental and epileptic encephalopathies.

Genetic diagnosis allows the initiation of appropriate therapy. For some genetic DEEs, identifying the gene can direct the choice of most effective antiseizure medication (Johannessen Landmark et al., 2021), with treatment implications for existing ASMs in up to 76% of children (Symonds et al., 2019). It can also play a vital role in identifying which therapies to avoid that could worsen the clinical outcome, such as carbamazepine in Dravet syndrome (Palmer et al., 2017). Another example,

is *PCDH19* Clustering Epilepsy, where seizures tend to improve in mid-childhood to early adolescence. Knowing a child has this genetic disorder makes weaning off ASMs after adolescence a reasonable decision compared to other types of DEE, where seizures are likely to stay refractory lifelong (Palmer et al., 2017).

Previously, a one-size-fits all approach was used for the treatment of epilepsy, with minimal improvement in gaining seizure control shown across 30 years of ASM development (Kearny et al., 2019). However, the revolution in epilepsy gene discovery is particularly important because understanding the underlying pathogenic process is the first step towards identifying targeted therapies. Precision medicine, defined as "treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics" (Jameson et al., 2015, p.2229) is already available for some genetic epilepsies, such as epilepsies caused by variants in *SLC2A1* which responds to the ketogenic diet (Perucca & Perucca, 2019). However, as many of these disorders are gain or loss of function of channel genes, the advent of antisense oligonucleotide (ASO) technology promises to further revolutionise this field (Petrou et al., 2018). This optimisation of treatment early in the DEEs course can improve long term outcome in seizure control and cognitive development (de Lange et al., 2018) as well as prevent premature death (Petrou et al., 2018; Richards et al., 2018).

Additional clinical utility of genetic diagnosis includes informing families with more accurate prognostic information (Johannessen Landmark et al., 2021). Appropriate information can be given to families regarding the likely long-term outcomes and comorbidities for which their child should be screened and monitored (Poduri et al., 2014). This allows for improved management and planning for support and resources required for the child's future. For example, the well-established risks for girls with *PCDH19* Clustering Epilepsy of psychosis and other mental health disorders in adolescence and young adulthood (Marini et al., 2012; Specchio et al., 2011). Being aware of this helps reduce uncertainty, allows earlier recognition and increases preparedness for mental health support for the girls and their families (Webster, 2019).

2.4.2 Personal Utility of a Genetic Diagnosis

In addition to clinical utility, individuals participating in genetic testing report interest in knowing their genetic diagnosis for reasons that extend beyond health parameters and medical management (Low et al., 2008; Wasson et al., 2013). This concept, termed 'personal utility', relates to an individual's subjective value or meaning taken from their genetic testing that is not health or medically related (Kohler et al., 2017). It is broader than psychological wellbeing and may include feelings of control with increased knowledge and understanding of their genetic condition (Poduri et al., 2014). Personal utility is not a novel idea and applies to any genetic condition, with early research recognising the importance of perceived personal control linked to genetic testing (Berkenstadt et al., 1999). However, until recently, personal utility has been largely overshadowed by the research investigating the clinical utility of genetic testing.

Personal utility has been previously critiqued for its lack of clear definition and has been used as an umbrella term with sometimes opposing agendas (Bunnik et al., 2015). Individuals' with genetic disorders caused by genes of major effect such as ovarian cancer (Fox et al., 2015) or multiple susceptibility genes such as Alzheimer's disease (Gooding et al., 2006), and healthy individuals who undertake direct-to-consumer genetic testing (Wasson et al., 2013), report an increased sense of control and ability to prepare for the future due to the knowledge and understanding they gained from their genetic result. This suggests personal utility is a multifaceted construct regardless of setting or type of disease.

Personal utility can be viewed from two key perspectives; the healthcare perspective and the consumer perspective (Bunnik et al., 2015). Within a healthcare setting, Bunnik and colleagues posit that personal utility can and has been used as a clinical reason to undergo genetic testing, even if the relative clinical utility is lacking. For example, testing for Huntingdon's disease does not change its clinical management, however the test has been offered clinically as it is known to reduce uncertainty and allow individuals at high risk to make psychosocial and practical decisions for their future (Grosse et al., 2010). Similarly, individuals report genetic testing for Alzheimer's disease to be a coping strategy and source of valuable

information (Gooding et al., 2006). It has been debated, therefore, that such outcomes should be taken into account and personal utility should be included in the ethical evaluation of genetic testing within the healthcare setting, given that many of the outcomes of personal utility are still '*health-related*' (Bunnik et al., 2015).

From the consumer perspective, autonomy and the desire to understand oneself is the key driver to undergo genetic testing; where personal utility evolves from self-determination, the access to and possession of genetic information (Bunnik et al., 2015). Even genetic findings that are not fully validated or bear little 'clinical significance' have been shown to still be of interest to consumers (Daack-Hirsh et al., 2013), with some participants willing to self-pay for genetic testing (Kopits et al., 2011), despite clinicians' and researchers' lack of perceived value in reporting results (Kohane & Taylor, 2010). Therefore, the consumer perspective asserts that it is the subjective experience of the individual that is of importance and the extent of personal utility should be dictated by oneself rather than the healthcare setting.

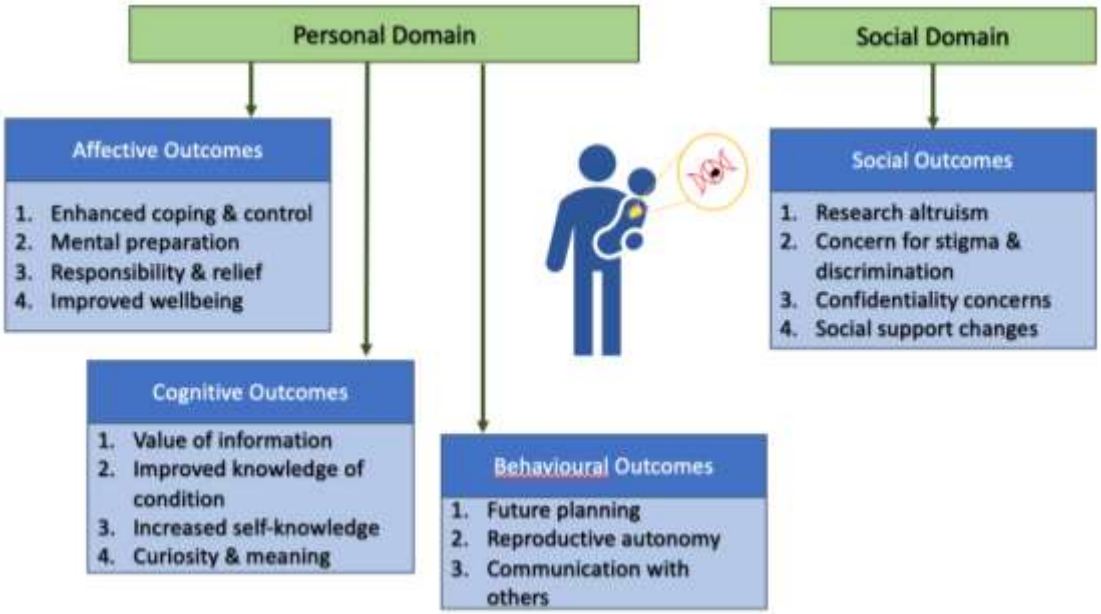
To broach the divide between the two perspectives, a revised definition of personal utility was proposed, "genomic information has personal utility if and only if it can reasonably be used for decisions, actions or self-understanding which are personal in nature… Personal utility can be (indirectly) related to health and disease, but is distinguished from clinical utility because it does not affect clinical management or lead to improved health outcomes" (Bunnik et al., 2015, p.324). Here, it is acknowledged that personal utility requires both useful information and a purpose for such information. The genetic information must maintain some merit or meaning, otherwise personal value placed on unvalidated information could lead to misunderstanding and ill informed choices. Thus, personal utility may not provide a sole overriding reason for direct access to genetic testing. However, it should be considered as a valuable alternative criterion for genetic testing, in addition to or in lieu of clinical utility, where necessary (Bunnik et al., 2015).

More recently, a systematic review identified 15 distinct elements of personal utility, clustered around three personal domains (affective, cognitive and behavioural) and one social domain (Kohler et al., 2017); a pictorial representation of this is depicted in Figure 3. Affective outcomes relate to one's emotional state, which

includes four components: 1) increase coping and perceived control, 2) mental preparation and visualising the future, 3) perceived responsibility and relief, and 4) improved wellbeing, such as increased sense of purpose and mindfulness. The components of the cognitive outcomes consist of 1) value of information, 2) improved knowledge of condition, 3) self-knowledge and 4) curiosity and meaning making. The behavioural outcomes describe practical uses of information, with three clusters: 1) ability for future planning, 2) reproductive autonomy, and 3) changes in communication. The social outcomes of personal utility referred to individual, familial and societal levels and included: 1) research altruism, 2) concern regarding stigma and discrimination, 3) concern for confidentiality of information and 4) change in social support from family, friends and social networks (Kohler et al., 2017).

Figure 3

Personal and Social Domains of Personal Utility of a Genetic Diagnosis



Note. Pictorial summary of the affective, cognitive, behavioural and social outcomes from the personal utility of genetic diagnosis. Adapted from "Personal Utility in Genomic Testing: a Systematic Literature Review" by J. N. Kohler and colleagues, 2017, *European Journal of Human Genetics, 25,* p.664.

In recent studies with parents of paediatric patients with various conditions (including ID, neurological disorders, neonatal alloimmune thrombocytopenia, congenital malformations or ophthalmo-logical disorders) have reflected similar experiences of personal utility for genetic diagnoses, which include: closure, control and hope, absolution from guilt, sense of relief, understanding of disease progression, drive to understand more about their child's disorder and undertaking information seeking processes (Mollison et al., 2020; Schofield et al., 2019; Wyn et al., 2018). However, an understanding of what a genetic diagnosis means to families of children with epilepsy, and specifically DEEs, remains largely unreported.

Given that the majority of individuals with DEEs have a *de novo* genetic aetiology (McTague et al., 2016), it has been suggested that identification of the cause may provide 'closure' for parents who may have guilt arising from a misunderstanding of the aetiology (Berkovic, 2015; Poduri et al., 2014). A small study of three families with mild inherited types of epilepsy suggested that receiving a genetic diagnosis may empower families, reduce feelings of isolation, remove guilt and responsibility, and improve quality of life (Vears et al., 2015). Participants explained the removal of responsibility was due to the genetic inheritance being out of the participants' control and was not something they had actively done and could be blamed for (for example, smoking during pregnancy).

As DEEs are severe epilepsies with typically no family history and due to *de novo* variants, it is possible that the personal utility is far greater for these families than for families where multiple individuals have epilepsy. A recent Australian study[1] explored the psychosocial impacts on parents of children with DEEs, describing the wide ranging emotions experienced by parents; from heartbreak to gratitude and solace from compassionate genetic counselling (Nevin et al., 2021). The diagnostic and prognostic uncertainty that remained even after genetic diagnosis had a large impact on parents, who experienced pervasive psychological distress regarding their child's uncertain future (Nevin et al., 2021). This study further highlights the importance of

[1] This study was not published at the time the doctoral thesis was originally submitted for examination.

the diagnostic journey and the profound effect of uncertainty has on increasing caregiver burden.

Genetic diagnosis can also aid in reproductive decision making and future family planning as it helps genetic counsellors give accurate information and effective support to families (Palmer et al., 2017). Research has shown that the presence of even milder epilepsies can affect reproductive decision making in affected individuals in comparison to their unaffected relatives (Nakamura et al., 2021). Results highlight that individuals with epilepsy have fewer children than their unaffected relatives. This is primarily due to their higher estimates of risk of genetic inheritance in offspring, rather than lack of desire for children. In fact, 25% of participants with epilepsy reported that they would have wanted more children, if it were not for their epilepsy (Nakamura et al., 2021). It is important to remember that children with a DEE are presenting at a time of family expansion and so knowledge regarding the chances of future children being affected is essential. A genetic diagnosis also allows families the opportunity to consider reproductive options, including prenatal testing, termination of affected pregnancies or IVF with selection of embryos without the genetic abnormality. Even if these are not options an individual family would consider, simply knowing a subsequent child is likely to be affected with a DEE can allow appropriate planning for this. In addition to providing information and reproductive options, genetic counselling itself has also been shown to have positive effects by increasing individuals' sense of empowerment (Vlaskamp et al., 2021). Empowerment is conceptualised as a set of beliefs that includes perceived decisional control (making informed decisions), cognitive control (sufficient information/knowledge), behavioural control (making effective use of health care systems), emotion regulation and a sense of hope for a fulfilling family life. Participants reported an increase in empowerment even after the pre-test counselling, which highlights the importance of knowledge and understanding prior to genetic testing as well as afterwards (Vlaskamp et al., 2021).

A genetic diagnosis may increase access for the family to financial and educational resources as well as allowing them to link up with disorder-specific support groups. Very shortly after an epilepsy gene is discovered, parents form

support groups to help support each other. With the accessibility of the internet, these start as small groups of parents from all over the world who interact by social platforms such as Facebook (Skluzacek et al., 2011; Nevin et al., 2021). As more individuals are diagnosed overtime, these groups can grow to become larger support networks who advocate for children with their disease, organise international meetings and fund research into the specific disorder. Examples of larger genetic disease support groups include: The International Dravet Syndrome Epilepsy Action League (IDEA League; Skluzacek et al., 2011), the Dravet Foundation, the *PCDH19* Alliance, the Cute Syndrome (SCN8A) and Wishes for Eliot (SCN8A).

To our knowledge, no research has been conducted that explores the personal utility for families with children with genetic DEEs. Exploration is needed to fully understand how receiving a genetic diagnosis impacts on families in NZ and globally. As discussed above, caring for children with DEEs can be highly distressing due to the unpredictable clinical features in combination with negative illness perceptions and diagnostic uncertainty. Therefore, understanding the personal utility may also provide further insight about whether genetic diagnosis can influence caregiver burden by reducing diagnostic uncertainty or by changing illness perceptions. In addition, further research may help to advocate for better access to genetic testing.

2.5 Summary: Gaps and Conclusions

In summary, childhood DEEs present many ongoing challenges for the entire family. The psychological stressors, time demands, and subsequent financial strain of caregiver burden in chronic disorders such as epilepsy have been thoroughly documented (Ferro & Speechley, 2009; Ostendorf & Gedela, 2017). DEEs are severe epilepsies that have the potential to put families under extreme pressure and stress, making it difficult for them to adapt and thrive (Mori et al., 2017; Nolan et al., 2006; Skluzacek et al., 2011). The clinical utility of a genetic diagnosis for a child with DEE is well established. However, to our knowledge, there have been no studies on the personal utility and importance of a genetic diagnosis for families with a child diagnosed with a DEE. This study addresses that gap.

To qualify and quantify the full personal benefits of a genetic diagnosis for a parents with a child with a DEE, the lived experience for the family prior to receiving a genetic diagnosis must first be understood. Thus, this research explores the lived experience for families of a child (including adult children) with a DEE both before and after receiving the child' genetic diagnosis. This will enable a thorough understanding of the personal utility of that genetic diagnosis for the individual family.

The overarching research questions are:

1. What were families' experience of personal utility for their child's developmental and epileptic encephalopathy genetic diagnosis?
2. How did the genetic diagnosis change families' lived experience, if at all?

Chapter 3: Methodology

3.1 Methodology

3.1.1 Using a Qualitative Approach

Qualitative methodology is a naturalistic approach to research (Golashani, 2003), whereby research findings are a result of phenomena occurring in real-life settings with no external manipulation (Patton, 2002). The experience of individuals in a particular situation or setting is of central importance (Yardley, 2000). Unlike other forms of research, qualitative research is not preoccupied with prediction, causality, or generalisation (Hoepfl, 1997); rather, the focus remains on understanding, exploration, depth and detail (Golashani, 2003). Qualitative research uses words as data, whereas quantitative research uses numbers (Braun & Clarke, 2013). Through words, qualitative methodology allows the researcher to gain an understanding of the underlying processes by which individuals make sense of what happens to them and how they attach meaning to it (Larkin, 2015). This provides in-depth insight, yielding rich descriptions of phenomena as well as highlighting the context within which the phenomena occurs (Sofaer, 1999).

Qualitative research incorporates both data collection and analysis techniques with a wider framework or theoretical lens underpinning the research (Braun & Clarke, 2013). It embraces and considers the role of the researcher as well as the interaction between researcher and participant (Golashani, 2003). Given the lack of previous research regarding the personal utility of a genetic diagnosis for families of children with DEEs, this exploratory and inductive approach of inquiry is appropriate for the aim of this research.

3.1.2 Interpretative Phenomenological Analysis

Interpretative Phenomenological Analysis (IPA), a qualitative approach, was selected for the current research. IPA uses a detailed exploration approach, which attempts to understand how individuals' make sense of their significant life experiences (Smith et al., 2009). Three philosophical perspectives, phenomenology, hermeneutics and idiography, are drawn on to form the theoretical underpinnings of IPA, which when taken together, yield the epistemological framework upon which IPA hinges (Shinebourne, 2011).

Rooted within philosophy, phenomenology is the study of experience; the experience of being human and the experiences humans have that matter and constitute their lived world (Smith et al., 2009). Phenomenology emphasises the subjective experience of a situation, event or context, rather than prioritising objectivity (Smith et al., 1999). According to Husserl, in order to systematically explore the everyday experience, one must first separate from the 'natural attitude' of unreflective immersion in the daily world (Shinebourne, 2011). Through the methodical process of 'phenomenological reduction', one can achieve a 'phenomenological attitude' of reflection and interpretation of the everyday experience. Thus, humans have the capacity to be reflective and self-interpretative beings, who reflect on the experiences they have had, and through their reflections are able to interpret and make sense of what the experience meant to them (Braun & Clarke, 2013). The term 'lived experience' is employed by researchers to demonstrate this intentional reflection and interpretation within an individual's specific social, cultural, and historical context (Eatough & Smith, 2008; Eatough & Smith, 2017).

The subject matter of psychological research is the experiences of other people; therefore, modifications are required to achieve the phenomenological attitude and to systemically reflect on the everyday lived experience of others (Shinebourne, 2011; Smith et al., 2009). It is the second philosophical movement informing IPA, known as hermeneutics, the theory of interpretation, which helps to make the modifications to phenomenology. This perspective acknowledges that researchers cannot directly access a participant's world. Rather, by using a dual interpretative

process known as a double hermeneutic, researchers must attempt to understand, interpret and make sense of the participant's world, whilst the participant is also attempting to reflect, interpret and make meaning of their world (Braun & Clarke, 2013; Shinebourne, 2011). That is, the researcher is attempting to make sense of the participant trying to make sense (Smith, 2004).

The interpretative role of IPA is critical, where the researcher tries to stay close to the meaning of the participant's words, staying true to the participants account and understanding (hermeneutics of empathy), whilst then using a critical lens to question and identify assumptions behind their accounts (hermeneutics of suspicion) (Shinebourne, 2011; Smith, 2007). However, researchers themselves hold their own preconceptions, assumptions, biases and beliefs resulting from their lived experiences (Eatough & Smith, 2017). Further, it is not always possible to know in advance what a researcher's assumptions might be; these may become apparent during the interpretive process (Smith, 2007). Therefore, it is important for researchers to reflect and maintain self-awareness throughout the interpretative process, creating multiple hermeneutics and levels of interpretation (Eatough & Smith, 2008; Smith et al., 2009).

The third theoretical perspective that informs IPA is idiography; an approach that highlights in-depth, detailed analysis of the specific, rather than the general (Smith et al., 2009; Shinebourne, 2011). Idiographic knowledge centres on the unique perspective of the individual, also contributing to the rationale for case studies (Smith, 2004). Thus, IPA is committed to the detailed exploration of small groups. It is a thematic approach also placing emphasis on the specifics of individual experiences (Braun & Clarke, 2013). The analytic process commences with in-depth analysis of specific cases or individuals before transitioning to examination of similarities and differences across cases (Shinebourne, 2011). This accumulates in rich accounts of meaning and reflection of shared experience (Smith et al., 2009). Finally, IPA has also been linked to symbolic interactionism, due to its concern for how meanings are constructed by individuals within both a social and personal world (Smith & Osborn, 2015).

3.1.3 Rationale for IPA

Initially, the researchers intended to use an inductive thematic analysis as the method for the study. Other qualitative methodologies, such as narrative analysis and grounded theory, were also considered. However, the aim of the research was not to explore *how* families *construct* narratives of around genetic testing and diagnosis (narrative analysis), nor was it intended to generate a theoretical account of the phenomenon, as demonstrated in grounded theory (Braun & Clarke, 2013). The research focus was on parents' lived experienced and the personal meaning they took from their child's genetic diagnosis. Upon further consideration, it became apparent that IPA's detailed focus on idiography and sense making better aligned with the research question than thematic analysis ,which focuses on the data as a whole (Braun & Clarke, 2006). Therefore, the study used IPA as it allowed the researchers to gain an in-depth understanding of the lived experience each family went through and the meaning they made from it as indicated by their narrative (Larkin, 2015).

IPA is a well-established method of analysis within the research area of clinical, health and counselling psychology. IPA is well suited to understanding under-researched areas or perspectives (Peat et al., 2018). The credibility of IPA research can be evaluated with four broad principles: transparency, coherence of the narrative produced, impact and importance (Finlay, 2002). These principles were used as a guide in the current research so as to adhere to standards of well executed qualitative research.

IPA provides specific guiding principles and analytic procedures, especially useful when concerned with complexity, process or novelty (Smith & Osborn, 2015). Furthermore, due to its level of attention and empathetic engagement, IPA is known to be particularly valuable when exploring emotionally laden topics, such as the current study (Smith & Osborn, 2015). It is an iterative, contextual approach that focuses on persons-in-context (Larkin et al., 2006). This enabled a detailed, in-depth examination into the lived experiences of parents who have a child or children with a genetic DEE.

3.2 Method

3.2.1 Participants

Inclusion Criteria. Eligible participants were parents of individuals (children or adult children) with a DEE who had received a genetic diagnosis and were participating in the 'Genetic Basis of Epilepsy' study at the University of Otago Wellington, New Zealand. Parents had to have had contact with the research team within the last 10 years (2010 – 2020), speak English fluently and be within the greater Wellington region for ease of recruitment and interview purposes. All individuals were already diagnosed with a DEE by Professor Sadleir (director of ERG) based on ILAE diagnostic criteria of DEE and after review of all the clinical notes, clinical interviews and EEG data. Clinical severity and information provided in Table 1 was already determined by previous neurocognitive assessments completed as part of the clinical work up and accessed as part of the research.

Participant Recruitment. The study was introduced to participants who met the inclusion criteria either by phone or in person during Professor Sadleir's epilepsy clinic. If interested in taking part, participants were then provided with an information sheet and consent form (Appendix A and Appendix B), either by letter or email, dependent on their preference. A total of 19 families met the inclusion criteria; three could not be contacted, and one withdrew prior to the interview due to scheduling difficulties, which left 15 participating families. Whilst the study invited either or both parents from each family to participate, for the majority only the mother was available to take part. Two of the 15 interviews interviewed both mother and father together, meaning that 17 parents (15 mothers and two fathers) were interviewed.

Participant Characteristics. 15 families who met the inclusion criteria consented to participate. Two families had two affected children. The clinical features of the children are reported in Table 1. Children presented with seizures at an average of 1.5 years (ranging from one day to 11 years). Developmental delay was noted by

three years seven months (range three months to three years seven months). Nine children had ongoing pharmaco-resistant seizures at the time of the interview. In 12 families the variant was *de novo*, in two it was maternally inherited, and for one child the inheritance was unknown (mother negative, father not tested). The average time between seizure onset and genetic diagnosis was nine years four months (range of six months to 23 years seven months). Demographic characteristics of the parents who participated are reported in Table 2.

Table 1

Summary of clinical features of participants' children

Case	Age at study (sex)	Epilepsy syndrome	Gene	Variant	Inheritance	Age of seizure onset [offset]	Onset of Dev. Delay	Cognitive outcome	Functioning (motor, language, behavioural, feeding)	Time between sz onset & genetic diagnosis (year)
1	5y (F)	West	*ALG13*	c.320A>G p.Asn107Ser	*de novo*	4m	4m	Severe ID	walked 3y, non-verbal, follows 1-step commands, self-feeds finger foods	4y8m (2017)
2	17y (F)	DEE	*GABRB2*	c.911C>T p.Ala304Val	*de novo*	4y	6m	Profound ID	walks with support, non-verbal, self-feeds with fork or spoon	11y (2017)
3	6y (F)	Dravet	*SCN1A*	c.384-2 A>G	*de novo*	6m	6m	Severe ID	walked 3y, <10 words, sensory seeking behaviour, self-feeds finger foods	6 m (2013)
4	8y (F)	DEE	*CDKL5*	Exon 4 Deletion	*de novo*	5w	3m	Profound ID	crawling only, non-verbal, PEG fed	1y8m (2013)
5	5y (F)	DEE	*EEF1A2*	c.1150G>C p.Gly384Arg	*de novo*	1d	5m	Profound ID	non-ambulatory, non-verbal, PEG fed	1y (2015)
6	17y (F)	CE	*PCDH19*	c.1919T>G p.Leu640Arg	*de novo*	16m [11y8m]	3y7m	Borderline ID	walked 15m, normal speech, behaviour and eating	7y8m (2011)
7a	12y (F)	CE	*PCDH19*	c.497_498insA p.Tyr166*	*de novo*	10m [5y2m]	3y3m	Severe ID	walked 15m, single words, autistic features, normal eating	4y2m (2011)
7b	12y (F)	CE	*PCDH19*	c.497_498insA p.Tyr166*	*de novo*	10m [5y2m]	3y4m	Mild ID	walked 15m, normal speech, behaviour and eating	4y2m (2011)
8	32y (M)	Dravet	*SCN1A*	c.512T>A p.Ile171Lys	*de novo*	7m	7m	Severe ID	walks independently, self-feeds, in assisted living environment	23y5m (2010)

9	32y (F)	Dravet	*SCN1A*	c.4062delT p.Asp1355Thrfs*8	*de novo*	5m	2y6m	Severe ID	walks independently, single words, obsessive behaviour, in assisted living environment	23y7m (2010)
10	7y (M)	Dravet	*SCN1A*	c.5347G>A p.Ala1783Thr	*de novo*	6m	2y	Moderate ID	walked 18m, normal speech and behaviour, PEG fed	1y6m (2013)
11	26y (F)	CE	*PCDH19*	c.2534C>T p.Ser845Asn	Mother negative, father not tested	8 m	11m	Moderate ID	walks independently, normal speech, in assisted living environment	23y4m (2017)
12	12y (F)	Epilepsy with Myoclonic atonic seizures	*SCN1A*	c.32C>A p.Pro11His	Maternally inherited	2y [3y]	2y	Normal	walked 12m, first words 12m, normal behaviour and eating	5y (2013)
13	7y (F)	Early onset epileptic encephalopathy	*KCNQ2*	c.1700T>A p.Val567Asp	*de novo*	4d [10m]	9m	Severe ID	walks with assistance, <10 words, self-feeds finger foods	3y (2015)
14a	31y (F)	CE	*PCDH19*	Exon 6 deletion	Maternally inherited	14m [22y]	1y1m	Mild ID	walks independently, first words 3y, autistic behaviours, normal eating	22y4m (2012)
14b	27y (F)	CE	*PCDH19*	Exon 6 deletion	Maternally inherited	19m [21y]	1y6m	Mild ID	walks independently, first words 6y, autistic behaviours, normal eating	18y3m (2012)
15	22y (F) (Died)	DEE	*PAFAH1B1*	Intronic deletion	*de novo*	11y [22y – died]	2y	Mild ID	walked independently, minimal speech, normal eating, in assisted living environment	2y (2005)

F: female; M: male; y: years; m: months; w: weeks; d: days; sz: seizure, DD: developmental delay, DEE: developmental and epileptic encephalopathy; CE: clustering epilepsy; ID: intellectual disability, PEG - percutaneous endoscopic gastrostomy

Table 2
Summary of participants' demographics

Age at interview	
Age range	29 – 58 years
Mean age	46 years
Sex	
Female	15
Male	2
Employment status	
Employed full time	7
Employed part time	6
Unemployed	4
Marital status	
Married/de facto	14
Separated	3

3.2.2 Interview Structure

In line with the preferred IPA approach (Smith et al., 2009), a semi-structured interview schedule with open-ended questions was developed by the research team. This format of interview allows researchers to gather elaborate and detailed information about particularly meaningful experiences for the participants, without being constrained by an overly rigid structured interview (Braun & Clarke, 2013).

The interview schedule consisted of three general sets of questions. First, families were asked generally about their experience of their child's DEE. For example, "Tell me about how you felt when you first found out or realised your child had a severe epilepsy." Tell me about how [child's name] epilepsy affects [her/him] and your family life". The second group of questions asked about the experience of receiving a genetic diagnosis, e.g., "What was it like to receive the result? How did you feel about it?". The final group of questions explored participants experience after receiving a genetic diagnosis, e.g., "What does the genetic result mean to you now? How, if at all, has your view of [child's name] epilepsy changed since receiving the genetic result? Has the result affected you or your family? After having this experience, what advice would you give to someone who has just received a

diagnosis?". The questions were designed to stimulate discussion and be driven by what was important to participants. The flexibility elicits discussion on what is most meaningful for each individual and gives the researcher opportunity to probe, follow up and explore the topic area as appropriate for each participant (Smith & Osborn, 2015). There was no pilot of the interview schedule prior to the commencement of the interviews. The interviews ranged in duration from 32 to 75 min, with an average length of 56 min. For the full interview schedule see Appendix C.

3.2.3 Procedure

In-depth semi-structured interviews were conducted with one or both parents of each participating family by the first author. Interviews were completed at a time and location that was convenient to the families. Eleven interviews were carried out in the families' own homes, two were completed at the parents' place of work, one in a hospital room while the participant waited for an appointment, one at a university and one was conducted via video conference using Zoom teleconferencing software as the parents could not attend in person but still wanted to participate. Seven interviews were completed in the presence of children with DEEs or other children. The children present during the interviews were either the affected child/children or young infant siblings. None of the children had the cognitive capacity to understand the content of the interviews and so did not appear to affect parental discussions. Occasionally the interviews had to be paused to address the caregiving needs of the child, however this did not appear to affect the content of interview discussions. No adult children were present during the interviews. Interviews were recorded and transcribed verbatim by the first author. Transcripts were then reviewed for accuracy. Families were invited to read and review their interview transcript and make any changes they felt necessary in order to accurately represent their experience. Only one family made a change to the phrasing of a single sentence, the rest were happy with their transcript.

3.2.4 Data Analysis

Data collection commenced in November 2018 and was completed in March 2019. Data analysis began after the completion of all interviews. IPA researchers assert that IPA is not prescriptive, with previously described methodological steps serving as guidelines that can be adapted, rather than steadfast rules (Smith & Osborn, 2008). That is, IPA uses a set of common processes to create an iterative and inductive cycle. By employing several different strategies, IPA progresses from the particular to the shared, and from descriptive to interpretative (Smith et al., 2009). It is important to note that a reflexivity journal was also used throughout the data collection and data analysis processes. After each interview, the primary researcher noted down their reflections from the interview, including any salient and emotional reactions or content. These reflections were used as a supplement throughout the analysis process to help inform theme development and maintain awareness of any personal or subjective biases present.

The current research followed the comprehensive guidelines outlined by Smith and colleagues (2009), which details six rigorous and systematic steps: 1) repeated reading, 2) initial noting, 3) development of emergent themes, 4) identification of connections across emergent themes, 5) identifying recurrent themes across transcripts, 6) identification of connections/patterns across recurrent themes (Smith et al., 2009). The first four steps of the analysis were carried out with each individual interview transcript before moving onto the next transcript. To become immersed with each transcript, it was read multiple times during which initial notes, ideas and observations on the semantic content of the data were made in the margin of the page. During these initial stages, it was also helpful to simultaneously re-listen to the audio-recording whilst reading, to allow the participant to become the focus of the analysis (Smith et al., 2009). Any highly emotive comments where participants laughed, became tearful or paused for extended periods of time were noted down as they often helped to identify and shape the salience of the content. Different types of notes were made throughout the transcripts, distinguishing between descriptive, linguistic and conceptual content. Drawing from these notes, line by line analysis transformed into initial emerging themes. These related to psychological concepts

and meaning making from the participants, which in turn developed into an interpretive account by clustering connected themes together.

Several techniques were employed to help establish emergent themes and the connections between themes. Abstraction was used to develop 'super-ordinate' themes, whereby similar themes are grouped together and a new name is developed for the super-ordinate theme which encompasses them all, for example 'Importance of the label'. Contextualisation was an another helpful analytic process that viewed emergent themes in particular narrative, temporal or cultural perspectives to frame understandings within the interview. For example, 'Factors that influence personal utility' was developed after detailed analysis of the temporal and cultural context for each parent and how this shaped their meaning making of genetic diagnosis. Examining particularly salient or meaningful transcript extracts purposely at different levels of interpretation (moving from descriptive to more interpretative) was also a helpful way to explore the meaning making in the extracts and develop themes. This was carried out by actively just 'describing' an extract using different words, then an interpretation of the meaning behind this description was made. Finally an interpretation of the interpretation was attempted in order to expand and push the depth of interpretation. This method was particularly advantageous to avoid merely superficial, descriptive themes; a common weakness of novice IPA researchers (Smith et al., 2009).

The next stage included steps five and six, where emergent themes from individual transcripts were then closely examined for shared experiences across all transcripts. Patterns of meaning or themes were identified through the processes of familiarisation, reflection, integration, interpretation and thematising, with the aim to capture the shared understandings of the personal utility of a genetic diagnosis for the DEE, whilst also giving light to each participant's individual variation of the experience (Eatough & Smith, 2017). NVivo software was used to help this phase of analysis, with salient clusters of themes grouped together in a systematic structure that illustrated the relationships between themes; transcript extracts were coded under each theme (Smith et al., 2009). NVivo allowed the primary researcher to easily see how many interviews spoke about each theme. Importance of themes was

evaluated based on multiple criteria, not just the prevalence across participants. Themes discussed by at least seven of the families that had the thematic significance and added overall insight to the interpretative account were included in the analysis write up (Vaismoradi et al., 2016). This promotes an idiographic perspective whilst also representing shared experiences (Dickson et al., 2008).

Importantly, the analysis is multi-directional and open to change; shifting between different analytic processes, moving from the 'part' to the 'whole' hermeneutic circle and back again. Therefore, analysis becomes fixed only at the point of write up. In line with the double hermeneutic, the final outcome is fundamentally an account of how the researcher thinks the participants are thinking, whilst adhering as close to their lived experience and meaning making as possible (Smith et al., 2009).

The first author coded and developed the interpretative thematic framework. Four transcripts were also analysed by another member of the research team (one of the thesis supervisors), in order to minimise researcher bias and increase transparency of analysis, along with trustworthiness of the data (Guba, 1981). Analysis between the two researchers was consistent and the themes aligned. Personal and identifying information has been edited from the selected extracts to ensure confidentiality.

3.3 Ethical Issues

A substantial amendment to conduct this research was submitted as part of the Epilepsy Research Group's 'Genetic Basis of Epilepsy' application and was approved by the Central Human and Disabilities Ethics Committee (HDEC), reference number: NTY/12/06/053/AM12. All participants were provided with a detailed information sheet outlining the purpose, benefits and risks of the study. By giving their written informed consent, participants acknowledged that their participation was entirely voluntary and should they wish, they were able to terminate the interview for any reason, at any point during the process. Withdrawal or refusal from the interview did not affect their participation in the Genetic Basis of Epilepsy study or their clinical

care. No participants withdrew or ceased their interviews or participation once they had consented.

The interviews were carried out in a sensitive manner and every effort was made to avoid the distress of participants. This was done by taking significant time at the beginning of the interview to build rapport and whakawhanaungatanga (connections), open with a karakia or pray (if the participant wished), answer any of the participants' questions or concerns and re-iterate that participants could cease the interview at any point as participation was entirely voluntary. Participants had previously had their child's genetic diagnosis explained to them by a paediatric neurologist and had access to genetic counselling if they desired. In the event that a participant became distressed during the interview, the interview would have been paused to address the needs of the participant. A senior member of the research team (the primary researcher's supervisor, a consultant clinical psychologist/neuropsychologist) would have been contacted to further ascertain the needs of the participant and provide the appropriate support or referral for ongoing psychological if required. It is noted that none of the participants became significantly distressed or wished to postpone the interview.

All data collected from participants was stored in locked filing cabinets within the ERG offices or on a password protected computer. Only members of the research team have access to these files. Confidentiality was ensured by removing or changing all identifying information in the transcripts. All files and published quotes were labelled using assigned participant case numbers. Upon completion of the study, the data will be transferred to the ERG's secure server and stored for 10 years after completion of the wider study before being destroyed.

All participants who wished to receive an annual newsletter with updates on how the research is progressing. The latest news letter was sent out earlier in 2021 and included a summary of the published paper included in this thesis. As part of the larger genetics study where gene mutations related to seizures are identified as a result of the study, participants are sent a letter explaining we have some results and inviting the participant to contact us if they would like further details. If further information is requested the investigators will explain the results to them or their

clinician where appropriate. In some instances, they may be offered genetic counselling to explain the results and possible implications.

3.4 Vision Mātauranga

As part of the wider 'Genetic Basis of Epilepsy' study, the ERG consulted with Ngati Tahu several times to ensure the research and the storage of study data (including medical samples) aligned with tikanga and Vision Mātauranga. Regarding the doctoral research specifically, all participants (including Māori families) were asked if they would like to begin the interview with a karakia/prayer. Cultural perspectives were considered throughout the interview and data analysis process. However, this was led by the participants about how much cultural discussion they included, as it was important for the researchers not to make any assumptions about participants involvement in Te Ao Māori or other cultural lenses.

3.5 Reflexivity

The researcher plays an integral role to the research process of IPA, which involves the close engagement and rich interpretation from both the participants and the researcher (Peat et al., 2018). Therefore, recognition of and reflection upon the researcher's prior conceptions is of great significance for IPA, as researcher biases can influence how the experiential data is interpreted (Smith et al., 2009). Reflexivity is the process of 'being aware' of how the research topic relates to the researcher on a personal and/or social level, and the subsequent pre-conceptions or beliefs held by the researcher, which inevitably shape the lens through which the researcher engages with the research and participants (Hamdan, 2009). This explicit self-appraisal and reflection on one's own beliefs, perceptions and experiences throughout the research process is thought to advantageous, as it strengthens the credibility and ethical quality of the research (Goldstein, 2017; Peat et al., 2018). Therefore, the following discussion is a summary of my reflexivity and positioning prior to and throughout the research process.

I am a female in my late twenties in a *de facto* relationship with no children. I do not have epilepsy, and my only family member with epilepsy is my partner's 5 year old niece who lives in America. Accordingly, my own lived experience of epilepsy is minimal, to say the least. Even with my background of working with children with developmental and behavioural difficulties and my studies as a clinical psychology student, I was worried throughout the research process about my lack of lived experience and ability to connect to the participating families from an 'insider' perspective. I was wholly aware of how families may react if they perceived me as a young Pakeha (New Zealand European) woman with no knowledge of parenting (let alone parenting children with high needs) arriving at their house to eagerly carry out her research and then be on her way. Another belief I experienced was concern that I was creating additional burden and inconvenience to the families' already busy and challenging schedules.

Returning to the IPA literature helped me to re-frame these doubts and "emphasise the importance of the positive process of engaging with the participant more than the process of bracketing prior concerns, in the sense that the skilful attention to the former inevitably facilitates the latter" (Smith et al., 2009, p.35). I was then able to be intentional about the time I spent at the beginning of each interview to build rapport and whakawhanaungatanga (connection/relating well to others), ensuring to my best ability that they felt comfortable with me before we began.

After several interviews, it became clear that my pre-conceptions about being an added inconvenience proved to be wrong. Multiple families expressed their enjoyment or gratitude of the opportunity to discuss their experiences and that many of them found it soothing and cathartic. In fact, one mother disclosed to me at a later date (when I contacted her to review her interview transcript), that our interview had prompted her to realise all she had to contribute as a parent. Consequently, she had decided to write a book about her experiences as a parent of a child with a DEE, in the hopes that it might help other families going through similar difficulties. Hearing this made me feel humbled and privileged to have been a part of the process and re-iterated to me the importance of this research; to increase the voices of parents with lived experience.

Another major reflection I had throughout the interview process was just how profoundly difficult these families' lives were. I had researched DEEs extensively and knew on an academic level how debilitating DEEs could be; however, seeing this in reality and hearing parents recount their experiences laden with emotion and grief was shocking to me. The first few interviews were particularly hard, I left feeling sad and upset by how unfair it seemed. Simultaneously, I was in awe at these families' ability to persevere and find joy in the smallest things, such as their child's rare smile or a successful outing to the dairy without a seizure or complication. My own worries and hardships were harshly put into perspective. Using my reflection journal after each interview as well as discussing the interviews with my supervisors was beneficial. This allowed me to acknowledge and process my emotional reactions before data analysis and interpretation, whilst still harnessing my empathy in a useful way.

Successful IPA research is both empathetic and questioning, taking a central ground between the two broad interpretative positions of hermeneutics of empathy and hermeneutics of suspicion (Smith et al., 2009). The empathetic component attempts to understand the participant's perspective and experience, essentially striving towards an 'insider's perspective'. Whereas, the questioning component draws from standing alongside the participant, using a different angle or perspective to question and interpret their account. The word 'understanding' summarises this stance effectively, both through understanding someone's experience and through making sense of their experience (Smith et al., 2009). I found this part of the explanation of IPA's philosophical theoretical framework extremely helpful. This was especially true during the interview and data analysis process. During my pre & post interview self-reflections as well as my reflections during the process of data analysis, I continued to deliberate the effect that my very much 'outsider' stance was having on the data collection and analysis process. I experienced self-doubt and questioned how adequately I could *understand* the families' experiences when my own lived experience of not being a parent or experiencing epilepsy was so starkly different. Referring back to these theoretical underpinnings, helped me to remember that no researcher could truly reach the 'insider' perspective. That the very premise of IPA acknowledges the limitations of the researcher to truly make sense of the

participant's experience. Even with increased shared experiences, the researcher's sense-making will always remain second order. The following quote was particularly instrumental in shaping my thinking around how I was going to adequately interpret the data.

> *"The researcher is like the participant, is a human being drawing on everyday human resources in order to make sense of the world. On the other hand, the researcher is not the participant, she/he only has access to the participant's experience through what the participant reports about it, and is also seeing this through the researcher's own, experientially-informed lens… the participant's meaning-making is first-order, while the researcher's sense-making is second-order"* (Smith et al., 2009, p.36).

Upon reflection, the IPA research process felt like it mirrored my clinical sessions, where rapport is essential and the clinician comes alongside the client to elucidate their make meaning of their experiences. This research also increased my understanding of the complex interplay between physical and mental health, the impact a diagnosis can have on a family, as well as the power of being heard and having a space to talk things through that cannot be 'fixed'. In this sense, I see how this research has also helped shape my clinical practice.

As described in the introductory chapter of this thesis, this research originated from a collaboration between different disciplines. None of my three supervisors expert knowledge base significantly overlapped, therefore I became the glue between paediatric neurology, specifically epilepsy and genetics, neuropsychology and qualitative research. I, therefore, learnt the importance of flexibility, open-mindedness and how to find appropriate compromises, whilst still maintaining integrity to the research and method. Navigating the different disciplines was challenging at times but ultimately helped me to build my confidence in myself as a researcher.

Achieving publication in a medical journal was significant for me, as it felt validating to have this field accept my qualitative research as important and worthwhile. However, with this success also came challenge and tension. A key reflection that came up frequently in my reflection journal, as well as in discussions

with my supervisors, was how to represent the level of detail and interpretation from my IPA analysis in the tightly constrained word limit of the journal articles. This was especially true for the published paper in *Epilepsia Open*, where the word limit was only 4000. It was important that this paper was published in an epilepsy journal, where the neurologists, pediatricians and epileptologist's who work with children with DEEs were most likely to read it. However, it was very difficult to translate that level of detail of analysis into the article, even after using a table for quotes to circumnavigate the word limit. It was a constant worry and reflection for me, which has forced me to improve my writing to portray both detail and brevity.

Outline of Results

The current research explored the lived experience of families with children who have a genetically solved developmental and epileptic encephalopathy and their experience of personal utility for the genetic diagnosis. The findings from the interpretative analysis are presented across the following two chapters. Each chapter is written up in the format of a manuscript for publication. The overall outline of the main themes and subthemes across both chapters is depicted in Table 3.

Table 3
Main themes and sub themes

Chapter	Main Themes	Sub Theme
4	Chronic traumatic stress response	• Living with uncertainty • Hyperarousal, reactivity & vigilant monitoring • Cognitive & behavioural avoidance
	Diagnostic odyssey – search for the cause	• Importance of understanding & problem solving • Parental attribution of blame
5	Importance of the label	• Knowledge of future trajectory • Hope for the future • Relating to others
	Relief to end the diagnosis journey	x
	Factors that influence personal utility	x

The first manuscript focuses on the retrospective accounts of families' lived experience of living without a genetic diagnosis for their child's DEE and their coping after the onset of these epilepsies. These findings are themes that emerged from parental discussions on what it was like to live with constant uncertainty on several

levels, from seizure uncertainty to aetiologic and/or diagnostic uncertainty. Although these experiences do not directly answer the research questions of this study, it was clear during both the interviews and the data analysis process that in order to explore the personal utility of a genetic diagnosis for their child's DEE, it was important to first discuss and understand the family experience of living with a DEE prior to the genetic diagnosis. Therefore, the first paper focused on these emergent themes, which give supplementary context to the findings in the second paper.

The second manuscript describes the personal utility of genetic diagnosis for these families; the outcomes from the genetic diagnosis as well as influential factors that contributed to the extent of personal utility that the families gained.

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STATEMENT OF CONTRIBUTION
DOCTORATE WITH PUBLICATIONS/MANUSCRIPTS

We, the candidate and the candidate's Primary Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of candidate:	Jennifer Jeffrey
Name/title of Primary Supervisor:	Professor Janet Leathem
Name of Research Output and full reference:	
Developmental and Epileptic Encephalopathy: the impact of uncertainty for families	
In which Chapter is the Manuscript /Published work:	4
Please indicate:	
• The percentage of the manuscript/Published Work that was contributed by the candidate:	90%
and	
• Describe the contribution that the candidate has made to the Manuscript/Published Work:	
Candidate lead the entire research progress and wrote 100% of the manuscript. Supervisors contributed to review and edits.	
For manuscripts intended for publication please indicate target journal:	
Health Psychology Journal	
Candidate's Signature:	Jennifer Jeffrey Digitally signed by Jennifer Jeffrey Date: 2021.05.20 13:30:44 +12'00'
Date:	
Primary Supervisor's Signature:	Digitally signed by Leathem, Janet Date: 2021.06.10 12:05:14 +12'00'
Date:	

(This form should appear at the end of each thesis chapter/section/appendix submitted as a manuscript/ publication or collected as an appendix at the end of the thesis)

Chapter 4: Developmental and Epileptic Encephalopathy: the impact of uncertainty on families

Jeffrey, J. S., Leathem, J., Ross, K., & Sadleir, L. G. (2021). *Developmental and Epileptic Encephalopathy: impact of uncertainty for families.* Manuscript in preparation.

4.1 Abstract

Parents of children with developmental and epileptic encephalopathy (DEE) are at high risk of developing mental health difficulties due to caregiver burden and the unpredictability of seizures. Our study retrospectively describes the psychological parental experience of having a child with DEE and its impact on mental wellbeing prior to receiving a genetic diagnosis. Semi-structured interviews were conducted with fifteen families of children with a genetically solved DEE. The interviews stimulated discussion about the impact of living and caring for a child with a DEE when parents did not have a genetic answer. They reflected on how this impacted on their family wellbeing. Interview transcripts were analysed using the six-step systematic process of Interpretative Phenomenological Analysis (IPA). Two key themes were identified: 'Chronic traumatic stress response' and 'Diagnostic Odyssey – Search for the cause'. Families discussed the detrimental impact of living with constant uncertainty regarding the aetiology of their child's DEE, which in combination with the uncertainty of seizures resulted in common trauma coping responses, such as hyperarousal, reactivity, vigilant monitoring, and avoidance behaviours. The diagnostic uncertainty prompted families to search for answers and attribute blame to themselves or others when they were unsuccessful. To date, the factors associated with the development of posttraumatic stress symptomology in parents of children with epilepsy have focused on caregiver burden and seizure frequency. This study demonstrates that uncertainty regarding the genetic diagnostic label and aetiology of DEEs may also contribute to the development of trauma responses in parents.

4.2 Introduction

Chronic childhood illnesses evoke significant stress, isolation, psychological distress and sorrow in parents and families (Cohen, 1999; Coughlin & Sethares, 2017; Kratz et al., 2009. This is especially so in severe childhood epilepsy (Camfield et al., 2016; Gibson et al., 2014), where parents are required to quickly learn complex medical information, manage the possibility of seizure related injuries and medication side effects as well as provide ongoing care, time and encouragement to the affected child and other children in the family (Gallop et al., 2009; Ostendorf & Gedela, 2017). The emotional impact of dealing with these issues can leave caregivers feeling angry, guilty and helpless, with little or no time to themselves (Jensen et al., 2017).

Parents of children with epilepsy are at greater risk of developing mental health psychopathology and experience a lower quality of life than parents of healthy children (Lv et al., 2009). Whilst studies have focused on the high prevalence of depression and anxiety (Ferro & Speechley, 2009; Mu, 2005; Reilly et al., 2018), evidence shows parents also experience posttraumatic stress symptomology (Berg et al., 2019). The prevalence of post-traumatic stress disorder (PTSD) and major depressive disorder (MDD) has been reported as 31% for parents of children with epilepsy, with most common symptoms being re-experiencing and arousal symptoms, followed by avoidance and numbing symptoms (Iseri et et al., 2005).

The psychological effects on families with children with developmental and epileptic encephalopathies (DEEs), the most severe group of epilepsies (Scheffer et al., 2017; Sillanpää & Shinnar, 2010), are likely to be even greater than those with milder forms of epilepsies (Bompori et al., 2014; Hoare et al., 2000). DEEs are characterised by frequent drug-resistant seizures and interictal epileptic activity which impact negatively on the developing brain (Scheffer et al., 2017). This results in intellectual, psychiatric, behavioural, and motor disabilities with a mortality rate of ~25% by 20 years (Camfield & Camfield, 2008; Keezer et al., 2016). Studies of families with children with Dravet syndrome, a type of developmental and epileptic encephalopathy, have shown that seizures were the greatest source of stress, followed by the loss of original hopes for their child's future as the actuality of cognitive and behavioural problems becomes realised (Camfield et al., 2016; Nolan et al., 2008). The

ongoing care and high level of resources required from health, educational and welfare systems for children with DEE pose a considerable burden (Camfield et al., 2016; Palmer et al. 2017). Caregivers experience higher rates of psychopathology, with 43% of parents meeting criteria for one or more mental health diagnoses, including PTSD (Jakobsen et al., 2020).

Epilepsy's sudden and erratic symptoms set it apart from other chronic health conditions (Reis, 2001). Not only does seizure frequency and severity have a detrimental impact on families' quality of life, but the unpredictability of seizures plays an important role in parental stress and mental health difficulties (Berg et al., 2019). Families of children with DEEs deal with an additional layer of uncertainty regarding the aetiology and trajectory of their child's condition (Joshi et al., 2016). The majority of individuals with DEEs are genetic and due to *de novo* pathogenic variants, although, recessive and X-linked variants are also found (Palmer et al., 2017). DEE genes are rapidly being reported with more than 200 genes associated with DEEs (Palmer et al., 2017; Scala et al., 2020; Sheidley et al., 2018; Symonds & McTague et al., 2020). Access to genetic testing is, therefore, increasingly important in clinical practice (Kohler et al., 2017; Pitini et al., 2018), yet it often takes several months or years for families to receive genetic testing (Joshi et al., 2016).

To date, research has not considered how the additional uncertainty surrounding the genetic diagnostic label and not knowing the cause of their child's DEE might influence parental coping and the development of mental health concerns. This study retrospectively describes the parental experience of having a child with DEE and its impact on parental wellbeing for 15 families (17 parents) prior to a genetic diagnosis. The findings presented in this paper are emergent themes, which were part of a larger study exploring the personal utility of a genetic diagnosis.

4.3 Method

Participants

All parents of children with a DEE who had received a genetic diagnosis, were participating in the 'Genetic Basis of Epilepsy' study at the University of Otago Wellington, New Zealand and fulfilled the inclusion criteria were invited to participate. Inclusion criteria

were contact with the research team within the last 10 years (2010 – 2020); fluent spoken English; and being available within the greater Wellington region for face to face recruitment and/or interviews. A total of 19 families met the inclusion criteria; three could not be contacted, and one withdrew prior to the interview due to scheduling difficulties, leaving 15 participating families. Due to availability reasons, only two families had both parents participate in the interview; for the other 13 families only the mother was interviewed. The education level of the interviewees ranged from high school graduate to postgraduate tertiary qualifications. The ethnicities of the interviewees included European, Māori, and Asian.

Two families had two affected children. The clinical features of the children are reported in Table 4. Children presented with seizures at an average of 1.5 years (ranging from one day to 11 years). Developmental delay was noted by three years seven months (range three months to three years seven months). Nine children had drug-resistant seizures at the time of the study. In 12 families the variant was *de novo*, in two it was maternally inherited, and for one child the inheritance was unknown (mother negative, father not tested). The average time between seizure onset and genetic diagnosis was nine years four months (range of six months to 23 years seven months).

Procedure

The first author conducted in-depth semi-structured interviews with one or both parents at a time and location convenient to the participants between November 2018 and March 2019. Eleven interviews were carried out in the parents' own homes, two were completed at the parents' place of work, one in a hospital room while the participant waited for an appointment, one at a university clinic and one was conducted via video conference using Zoom teleconferencing software. Seven interviews were completed in the presence of children with DEEs or other children. Interviews were digitally recorded and transcribed verbatim. Participants were invited to review their interview transcript and make any changes they felt necessary in order to accurately represent their experience. Ethical approval was granted by the New Zealand Health and Disability Ethics Committee.

Table 4

Summary of clinical features of participants' children

Case	Age at study (sex)	Epilepsy syndrome	Gene	Age of seizure onset [offset]	Onset of Dev. Delay	Cognitive outcome	Functioning (motor, language, behavioural, feeding)	Time between sz onset & genetic diagnosis (year)
1	5y (F)	West	*ALG13*	4m	4m	Severe ID	walked 3y, non-verbal, follows 1-step commands, self-feeds finger foods	4y8m (2017)
2	17y (F)	DEE	*GABRB2*	4y	6m	Profound ID	walks with support, non-verbal, self-feeds with fork or spoon	11y (2017)
3	6y (F)	Dravet	*SCN1A*	6m	6m	Severe ID	walked 3y, <10 words, sensory seeking behaviour, self-feeds finger foods	6 m (2013)
4	8y (F)	DEE	*CDKL5*	5w	3m	Profound ID	crawling only, non-verbal, PEG fed	1y8m (2013)
5	5y (F)	DEE	*EEF1A2*	1d	5m	Profound ID	non-ambulatory, non-verbal, PEG fed	1y (2015)
6	17y (F)	CE	*PCDH19*	16m [11y8m]	3y7m	Borderline ID	walked 15m, normal speech, behaviour and eating	7y8m (2011)
7a	12y (F)	CE	*PCDH19*	10m [5y2m]	3y3m	Severe ID	walked 15m, single words, autistic features, normal eating	4y2m (2011)
7b	12y (F)	CE	*PCDH19*	10m [5y2m]	3y4m	Mild ID	walked 15m, normal speech, behaviour and eating	4y2m (2011)
8	32y (M)	Dravet	*SCN1A*	7m	7m	Severe ID	walks independently, self-feeds, in assisted living environment	23y5m (2010)
9	32y (F)	Dravet	*SCN1A*	5m	2y6m	Severe ID	walks independently, single words, obsessive behaviour, in assisted living environment	23y7m (2010)
10	7y (M)	Dravet	*SCN1A*	6m	2y	Moderate ID	walked 18m, normal speech and behaviour, PEG fed	1y6m (2013)
11	26y (F)	CE	*PCDH19*	8 m	11m	Moderate ID	walks independently, normal speech, in assisted living environment	23y4m (2017)
12	12y (F)	Epilepsy with Myoclonic atonic seizures	*SCN1A*	2y [3y]	2y	Normal	walked 12m, first words 12m, normal behaviour and eating	5y (2013)
13	7y (F)	Early onset epileptic	*KCNQ2*	4d [10m]	9m	Severe ID	walks with assistance, <10 words, self-feeds finger foods	3y (2015)

		encephalopathy						
14a	31y (F)	CE	*PCDH19*	14m [22y]	1y1m	Mild ID	walks independently, first words 3y, autistic behaviours, normal eating	22y4m (2012)
14b	27y (F)	CE	*PCDH19*	19m [21y]	1y6m	Mild ID	walks independently, first words 6y, autistic behaviours, normal eating	18y3m (2012)
15	22y (F) (Died)	DEE	*PAFAH1B1*	11y [22y – died]	2y	Mild ID	walked independently, minimal speech, normal eating, in assisted living environment	2y (2005)

F: female; M: male; y: years; m: months; w: weeks; d: days; sz: seizure, DD: developmental delay, DEE: developmental and epileptic encephalopathy; CE: clustering epilepsy; ID: intellectual disability, PEG - percutaneous endoscopic gastrostomy

Measures

An interview schedule with open-ended questions was developed as a guide for the semi-structured format. The interview schedule consisted of groups of questions related to: 1) their experience of their child's DEE, e.g., "Tell me about how you felt when you first found out or realised your child had a severe epilepsy." 2) their experience around receiving a genetic diagnosis, e.g., "What was it like to receive the result? How did you feel about it?", 3) experience after receiving a genetic diagnosis, e.g., "What does the genetic result mean to you now? How, if at all, has your view of [child's name] epilepsy changed since receiving the genetic result? Has the result affected you or your family?". The questions were designed to stimulate discussion and be driven by what was important to participants. This allowed the interviewer to probe or ask to follow up questions to clarify the participant's responses. The interviews ranged in duration from 32 to 75 min, with an average length of 56 min. Findings related to the second and third set of questions has been published (Jeffrey et al., 2021). This report describes the findings relating to the first set of questions.

Data Analysis

The study used a qualitative methodology to allow the researcher to gain an understanding of the underlying processes by which individuals make sense of what happens

to them and how they attach meaning to it (Larkin, 2015). Interpretative phenomenological analysis (IPA) is a well-established method of analysis within clinical, health and counselling psychology. It provides specific guiding principles and analytic procedures, especially useful when concerned with complexity, process or novelty (Smith & Osborne, 2015). It is an iterative, contextual approach that focuses on persons-in-context (Larkin et al., 2006; Smith & Osborne, 2015), which enabled a detailed, in-depth examination into the lived experiences of parents who have a child or children with a genetic DEE.

Patterns of meaning or themes were identified through the processes of familiarisation, reflection, integration, interpretation and thematising, with the aim to capture the shared understandings of the experience of receiving a genetic diagnosis for the DEE, whilst also giving light to each participant's individual variation of the experience. Analysis followed the six key rigorous and systematic steps: 1) repeated reading, 2) initial noting, 3) development of emergent themes, 4) identification of connections across emergent themes, 5) identifying recurrent themes across transcripts, 6) identification of connections/patterns across recurrent themes (Smith et al., 2009). The first author coded and developed the thematic framework. Four transcripts were also analysed by another member of the research team: this minimised researcher bias and increased transparency of analysis, along with trustworthiness of the data (Guba, 1981). Personal and identifying information has been edited for the selected extracts to ensure confidentiality.

4.4 Results

Interpretative Analysis

Two key themes emerged which described parents' lived experience of managing their child's DEE prior to receiving a genetic diagnosis as the cause: 1) Chronic Traumatic Stress Response and 2) Diagnostic Odyssey - Search for the Cause. Both themes were discussed by all the families and include several subthemes (Table 5).

Table 5

Representative quotes related to each of the two themes: chronic traumatic stress response and diagnostic odyssey – search for the cause

Theme ***Subtheme***	**Families discussing each theme**	**Representative quotes**
Chronic Traumatic Stress Response		
Living with Uncertainty	15/15	"It's really hard. Because the physical hardship is the hard thing. No sleep, always in and out of hospital. You go to hospital and then you go home, and you don't expect another. Just stay home one day and then you're back to hospital again the next day. Not really more the emotional but more the physical. Really, really hard. Will drain you out, like no sleep… Like one time I was really, really tired and I was like '[child's name]' and I was just crying in front of her but she still doing what she was doing. And that made me more cry a lot cause 'uhh this is like hopeless'. Like even if you tell her 'ouch', she wouldn't care. And then after that you hug her and she's back again to normal. She will kiss you again and then- it's like a switch. Like you're sad and then you're happy again, sad, happy." - C3
		"There's nothing we were doing that would cause them or there's no signs that something was coming on. It was just all of a sudden and that's it, in the hospital. It was our life for 5 years. I guess the hardest bit is the not knowing. And for [child's name] as well, because she didn't know when she was going to start seizing and it would just happen out of the blue" – C7
		"We ended up in hospital with up to 20 seizures a day. So, it doesn't really give you a lot of time to, you know, you're just trying to keep your child alive, so you're really focusing on that. You're more looking at 'oh my god is she going to live through this one, can we make until tomorrow night?'" – C9
		"What was more frightening for me is, I mean she had a seizure, where was she? Was she riding on the bicycle? Was she in the middle of the road? How dangerous the result of a seizure could be; not the actual seizure but a fall because there were times when she hit her head at the back or when she fell down and cut her eye, you know. Where was she? Because there was no warning of the seizure, it could happen at any time." - C11
Hyperarousal Reactivity & Vigilant monitoring	13/15	"Just keeping a real eye on her…I get quite uptight and quite stressy about it. I'm scared she's going to hurt herself, because we've had the two fractured wrists. She's had black eyes, bleeding noses, fat lips, all the rest of it. I get really, really wound up, internally stressed." – C2
		"I felt that to keep her alive I had to focus my whole time on her because I didn't know when she was going to have

		her seizures… Every seizure is different, and you just don't know when they're going to happen. Patience. I've learnt to be a patient person… I think it's a 24-hour thing and I don't think people realise that it's 24 hours, seven days a week. And they think 'ah yeah 12 hours and then you sleep'. It's not. I got myself into a habit where I didn't sleep fully, because my ear was always open for that noise and you just automatically jump." - C9
		"So [child's name]'s incredibly well monitored and that he's got a kind of video monitor in his room as well as a sound monitor. When he was a wee baby in his cot, we had a sleep apnoea kind of monitor as well. Yeah, I guess in reaction to just, I don't know, being able to be aware if anything was going to happen as much as possible." - C10 "[Father] has high levels of anxiety and just as ongoing, his mind has re-trained his body to be in that permanent flight or fight mode. His adrenaline and anxiety are always on. Even within that, the peaks and troughs are after [child's name]'s had a seizure, so that's definitely had an impact, kind of like a type of post-traumatic stress disorder thing. So that's definitely had an impact. And I guess in terms of we manage [child name]'s seizure, it's not just through medication but through just his day to day activities… I think it's just something that we want [child's name] to experience as much as he can and try to always allow him those opportunities. And I think it's just, for us, almost not letting our own anxiety get in the way of doing stuff." - C10
		"There were a couple times when my husband and I looked at each other like 'oh my god was that? Is she having a seizure?' but she had just fallen asleep on the couch and her head nodded like that, that's exactly what it used to do. We're kind of like waiting, you know, and you just get this hot flash of sweat, like a cold sweat over you, like oh my god is it happening again." - C12
Cognitive & behavioural avoidance	7/10	"I just try not to spend too much time thinking about it. I actually don't process it really, because if I was to sit and think about it all day long and that's all I would get accomplished. It's not worth it, it's just not worth it… It is what it is. Taking it day by day, try not to think about what does next year look like? Because you just got to get through each day. Things change really quickly." - C1
		"Yeah it's hard and I can't watch people seizing. I'm obviously I'm a [job title] and last year a customer in one of the supermarkets did have a seizure and I just went into autopilot. But I was quite a mess afterwards, I made sure he was ok and stayed with him until the paramedics got there and everything, but it just brought it all back" - C7
		"I think we just did it as a way it was, I suppose. I think some people delve too quickly into the whys, and I'm like sometimes, this is what it is. You can go why, why, why, and not get an answer at the end. This is what's happened, this is who he is." - C8

		"How did I feel? Just living with it. I can't say that I was sad or- I didn't have any emotions, I just took one day at a time… I just went on with everything. Just got on with it, that's the kind of person I am. Just get on with it, this has to be done" - C11
Diagnostic Odyssey - Search for the Cause		
Importance of Understanding and Problem Solving	13/15	"You have hope and then you have your hopes dashed. And then you have more hope and then you have the hopes dashed- you know like, but actually as time goes on and you're on to your tenth medication then that looks quite different to when you're on your second medication" - C1
		"So, although it was very hard because it was solid, it was like if this is what it is, this is what you're going to be dealing with. But yeah, because if I knew what the beast looked like I guess, I could deal with it." – C4
		"We were just so dumbfounded; we had no idea what was going on. I mean it was just like what was happening here, you know, we were so confused… the problem being is that any parent wants it to happen immediately, an answer, and I'm like you got to know it [clicks fingers], within an hour. Well you got to realise that it doesn't happen like that, you know, it's like a lot of time and waiting, it's because these guys at the hospital are trying to figure it out as well." - C6
		"It was pretty hard because there was nothing we could do. It was just very hard watching her" - C7 [Father] "Yeah you feel very helpless, it is out of your control" - C7 [Mother] "I said I just want answers and not- not only answers for us, but answers for other people, so that they didn't have to go through three and a half or four years before you've got control. You know, because that was lost time we can't get back." – C7
		"I absolutely wanted to fix it and I didn't know it was epilepsy. I guess once I did know it was epilepsy I was like why?... Anyway, I connected it to one million things and I'm sure I asked [Doctor] a hundred times 'could it have been this? could it have been that? could it have been that?' and I don't know if that's just human nature wanting to solve a problem, you know, wanting to have something to point at to say this is why… For me and my personality, the fact that it was an unknown, unsolvable problem really, really weighed on me. Like I was constantly trying to balance that equation, you know, always, always, always in my mind I could not stop thinking about it." - C12 "So, it was chaotic, it was really emotional, and I just felt helpless I guess most of the time… Just because I wanted to figure it out, I think that was it, I wanted to figure out and fix it. But the time in the hospital was pretty dark…. It's just the sense of helplessness in not being able to fix it or change what was happening." - C12

		"Our concerns were would she grow out of it? What would happen? Would it cause her to be deaf? How is this going to affect her? Is there going to be any permanent damage from it? How do we help her? Just all of those kind of questions were just blowing through us" - C13
Parental Attribution of Blame	15/15	"That part where you resent, like where you took blame. I didn't really blame anybody, it was him who blamed… it's the same with grief, you tend to blame a lot. So, he was like that. He wanted to put that anger or blame to somebody just for him to make, maybe to release it? So, he thought of a lot of things that caused the seizure" - C3
		"You want to search for answers quite a bit you know, is it something that I've done? Is it something that I did previously? Is it something that I passed onto him? Is it - you know, because I smoked some marijuana in high school and so I've given him this? Is it a defect that I've given him personally?" - C5
		"I was thinking, you know, did I do something when I was pregnant with her? If I had done something would this have happened or if I haven't have done something would this have happened?... he [Father] felt like it was his fault as well, even though he didn't carry her, he was like 'well maybe there is something in my genes that has caused, how do I know I'm not the problem and it's not you', so he was very adamant that he wanted to find out why it was happening to her and how do we solve the situation." - C13
		"I think there was a lot of 'what have I done wrong', we got the water tested, we got the dirt tested. I think we got a Māori pastor to climb up the hill over the house and pray over the land. We tried everything" - C14

Chronic Traumatic Stress Response

All families described ways of coping with the day to day management of their child's DEE, that followed a pattern of trauma responses, which are detailed in three subthemes: 1) living with uncertainty, 2) hyperarousal, reactivity and vigilant monitoring and 3) cognitive and behavioural avoidance.

Living with Uncertainty

All the families discussed their experience of living with near constant unpredictability regarding their child's DEE. From the onset of the first seizure, this unpredictability dominated family life, forcing parents to be perpetually ready for the next unpredictable seizure. Families discussed the physical consequences on themselves, such as the sleep deprivation and not being able to attend to their own basic personal needs, and the physical consequences for their child if seizures were to occur in hazardous situations. Each family's world markedly reduced to identifying, managing, and trying to alleviate threat and harm from unpredictable seizures and other symptoms of their child's DEE. They discussed the detrimental impact of fighting for their children's lives and the uncertainty of whether their child would survive each day. Families developed common trauma responses as a way of coping with the profound uncertainty and fear; these are discussed in the following two subthemes.

Hyperarousal, Reactivity & Vigilant Monitoring

The impact of psychological distress of living with uncertainty and lack of control was apparent through parent's coping responses. Thirteen families discussed being on constant high alert, in fight or flight mode, waiting for the next seizure or complication to arise. Resulting from this hyper-vigilance, families described their behavioural response of constantly monitoring and checking on their child, even when they were sleeping. For some, this may have been a subconscious attempt to try to exert some control back into the situation. Being aware of the slightest change in behaviour and watching for any abnormality helped parents to feel that they could anticipate the next seizure and gave them a small sense of control in a largely uncontrollable situation. However, such careful surveillance and

management of their child and the environment, required high levels of organisation and planning, making even the smallest household tasks or activities difficult to achieve.

Hypervigilant behaviour also developed as a coping response to manage their anxiety and fear. By monitoring and controlling as much of the environment as they could, some families reported they coped better with their own psychological distress, although this was not always effective. For case 10 (Table 4), the parental psychological distress from the trauma of witnessing their child's DEE develop was such that, vigilant monitoring of the environment was as much for their child's wellbeing, as it was for their own. However, rigorous monitoring was often not enough to offset severe parental hyperarousal and anxiety. This eventually resulted in families leading carefully constrained and routine lives, resulting in internal conflict as they also wanted to provide their child with positive experiences and not overly restrict their life.

Cognitive & Behavioural Avoidance

Seven families discussed their avoidance behaviours due to fear of triggering seizures or re-experiencing the trauma of past situations. Parents experienced both physiological and psychological trauma responses to stimuli associated with their child's DEE, even years after seizure control had been achieved. The families not only avoided behavioural stimuli (people, places, or situations) associated with triggering their child's DEE, they also experienced cognitive avoidance (Table 4, C1).

Families discussed their need to remain focused on the present and avoid ruminating not only on past seizures and traumatic events but also on the uncertainty of the future. Remaining tied to the 'here and now' was a coping strategy likely serving multiple functions. First, constant arousal and hypervigilance against the next seizure requires full attention in order to respond to threat immediately. Second, it may have been another way to exert a degree of control back into family life by choosing where to maintain their focus and attention. Third, families discussed the need of present focused problem solving as their child's future was too uncertain for future-oriented planning. Some attributed their 'day by day' or 'it is what it is' approach to characteristics from their personality. For others, it developed out of necessity demanded by their situation. They focused on the practicalities of

getting through each day and avoided emotion or cycles of rumination as a functional method to cope and support their family.

Diagnostic Odyssey and Search for the Cause

The second theme 'Diagnostic Odyssey - Search for the Cause' describes the importance the families put on identifying a cause and diagnostic label so they could increase their understanding and sense of control. All families reported immense difficulty of living without a known cause for their child's condition. This was an additional layer of uncertainty to the already unpredictable and devastating nature of their child's condition. Two subthemes, 'Importance of Understanding and Problem Solving' and 'Parental Attribution of Blame', highlight the reasons why searching for a cause was critical to families.

Importance of Understanding and Problem Solving

The unexpected trauma of witnessing their child's first seizure sent families into what can be conceptualised as 'survival mode'. They entered a state of shock, unable to process and understand their situation. Thirteen families described a fundamental need to fully comprehend what was happening to their child in order to process and cope with it. In the first instance, they relied on standard illness perceptions, whereby they expected medical professionals to immediately know what was wrong and to begin treating their child. Parents were plagued with numerous questions and concerns that they expected health professionals to alleviate. Yet, their concerns regarding both the short and long-term outlook for their child and family were largely unanswered. Unsurprisingly, parents found it difficult to wait for answers.

As it became apparent that there was no simple answer, families described how their need to understand and find answers drove them to problem solve. They tried to fill the void of understanding by attempting to become the experts themselves. If parents could gain answers, this would give them more perceived control and ability to fix or cope with their child's condition. If unable to do this, they were left with a profound sense of helplessness when they began to fully comprehend the severity and longevity of their child's condition (Table 4, C12). Parents also discussed their sense of helplessness as they watched the pain

their children experienced, whilst imagining the physical damage being done and long-term consequences after every seizure.

As the diagnostic journey continued, families' hopes for a cure to their child's DEE slowly diminished. With every failed medication trial and no new diagnostic information, a downwards spiral developed, whereby their hope for the future continually reduced.

Parental Attribution of Blame

The lack of answers resulted in parents questioning themselves and looking for someone or something to blame. All families discussed their own pursuit of blame, which suggests it was an integral part of the parental experience of living with their child's DEE. Parents worried about whether it was something biological they had passed on, or if it was a result of their behaviour or a choice they made prior to, or during pregnancy. Parents questioned whether external factors, such as the environment, could account for their child's condition. For some families, the need for an explanation and accountability also resulted in blaming within the parental unit. Resentment towards and blaming of their partner may have been a way of processing their grief and lack of knowledge.

4.5 Discussion

This study retrospectively explored the lived experience of a group of families who had a child with DEE. As all of these families subsequently received a genetic diagnosis for their child's DEE, they were able to reflect on what it was like prior to receiving the genetic diagnosis and the impact that living with profound uncertainty had on their lives. These families developed ways of coping with the unpredictability that reflected a pattern of post-traumatic stress symptomatology. They discussed how living with uncertainty led them to experiencing marked hypervigilance, reactivity and monitoring behaviours as well as sleep disturbances, exaggerated startle response, and avoidance of stimuli associated with the chronic trauma. Even years after achieving seizure control and receiving a genetic diagnosis, families still experienced these stress responses.

Our findings support the presence of paediatric medical traumatic stress (PMTS) and posttraumatic stress symptoms (PTSS) experienced by families after a traumatic medical event(s) or chronic condition (Kazak et al., 2006). The Integrative Trajectory Model of PMTS describes family adjustment and psychological reactions to paediatric illness or injury across three phases: peri-trauma, acute medical care, and ongoing care. The framework asserts that families' subjective appraisals of medical events are a central predictor for the development of PMTS (Price et al., 2016). That is, parents who perceive a high risk of threat to life, reoccurrence of the medical events or additional complications are more likely to experience PMTS. The lived experience of our families aligns with these findings. Their subjective appraisals of high threat to life as well as the severity, frequency and unpredictability of seizures resulted in all families discussing the presence of PTSS.

The study supports previous research examining severe childhood epilepsies and the reported 'domains of seizure burden' that contribute to chronic traumatic stress disorder in parents (Berg et al., 2019). However, our families highlight a gap in previous conceptualisations of the development of PTSS. Our findings suggest that for families of children with DEEs, the uncertainty extends beyond just the domains of seizure burden (frequency, severity and unpredictability) (Berg et al., 2019) and includes uncertainty regarding aetiology, which may also play a role in the development of PTSS.

The phenomenon, known as the 'diagnostic odyssey', is well-established across chronic health conditions and defined as "the time between when a parent or provider first becomes concerned about a child's symptoms and when a diagnosis is eventually reached" (Carmichael et al., 2015, p.326). Not having a diagnostic label can significantly increase the burden of disease, as this additional uncertainty reduces parents' perceived control. This, in turn, can lead to less effective coping, poorer adaptive functioning and increased emotional distress (Madeo et al., 2012). For children with DEEs, the diagnostic odyssey and identifying the cause commonly lasts several years, as children may undergo several tiers of invasive tests and medical investigations before a causative gene is found (Joshi et al., 2016). This was the lived experience for several of our families, who viewed the diagnostic odyssey as well as the "fear of the unknown" (C10), as integral in informing the way they coped with the condition.

The aetiological uncertainty prompted families to search for answers and make causal attributions. This can be conceptualised as a method of meaning making, processing their

grief and attempting to exert some control back into their lives (Affleck et al., 1985; Park, 2010; Tennen et al., 1986). Unfortunately, this was not always successful, resulting in guilt, self-blame and diminished levels of hope consistent with what has previously been reported (Berg et al., 2019). Thus, their subjective appraisals continued to align with high threat and risk to life, which likely perpetuated the presence of PTSS. In summary, the aetiological uncertainty likely played an important role alongside seizure unpredictability in not only the development of their PTSS but also its maintenance.

Given the exploratory nature of this study, the sample size is small and not necessarily representative of all families with children with DEEs. A sample size of 15 families (17 parents) is, however, in line with IPA methodological expectations and guidelines (Reid et al., 2005; Smith et al., 2009). The goal of our study was to better understand the experiences of these families and highlight individual experience, which does not require large or representative samples (Smith et al., 2009). Future research can now explore our themes and build on our findings with larger sample sizes. The 15 families in our study were part of an epilepsy genetic research program and so the sample may be biased towards families for which finding answers is critical. They also all eventually received a genetic diagnosis for their child's epilepsy, which may mean there is additional bias towards the importance of finding a diagnosis. However, these families are in the unique situation of being able to reflect on what it was like prior to the genetic diagnosis and contrast and notice how their lives had changed as a result. Their accounts are thus retrospective. This is a possible limitation of the study as their memory of the experience may have differed from their actual experience.

In conclusion, the retrospective accounts of fifteen families highlight the profound uncertainty they experienced when living without a causal diagnostic label for their child's DEE. This uncertainty was above and beyond the standard unpredictable nature of seizures and had a significant influence on the development of PTSS used as coping strategies by these families. This study demonstrates the importance of understanding, problem solving and perceived control. The instrumental role of living with uncertainty has been previously identified in research (Berg et al., 2019), yet linking this to the additional uncertainty created by an unknown aetiology as a possible major contributing factor has until now been under appreciated in families and children with DEE.

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MASSEY UNIVERSITY
GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION
DOCTORATE WITH PUBLICATIONS/MANUSCRIPTS

We, the candidate and the candidate's Primary Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of candidate:	Jennifer Jeffrey
Name/title of Primary Supervisor:	Professor Janet Leathem
Name of Research Output and full reference:	
Developmental and Epileptic Encephalopathy: personal utility of a genetic diagnosis for families.	
In which Chapter is the Manuscript /Published work:	5
Please indicate:	
• The percentage of the manuscript/Published Work that was contributed by the candidate:	90
and	
• Describe the contribution that the candidate has made to the Manuscript/Published Work:	
Candidate lead the entire research process and wrote 100% of the manuscript. Supervisors contributed to review and edits.	
For manuscripts intended for publication please indicate target journal:	
Published in Epilepsia Open (2021)	
Candidate's Signature:	Jennifer Jeffrey Digitally signed by Jennifer Jeffrey Date: 2021.05.20 13:34:01 +12'00'
Date:	
Primary Supervisor's Signature:	Digitally signed by Leathem, Janet Date: 2021.06.10 12:06:55 +12'00'
Date:	

(This form should appear at the end of each thesis chapter/section/appendix submitted as a manuscript/ publication or collected as an appendix at the end of the thesis)

Chapter 5: Developmental and Epileptic Encephalopathy: personal utility of a genetic diagnosis for families

This chapter is published in the open access journal Epilepsia Open, at https://onlinelibrary.wiley.com/doi/10.1002/epi4.12458

The full citation for this article is:

Jeffrey, J. S., Leathem, J., King, C., Mefford, H. C., Ross, K., & Sadleir, L. G. (2021). Developmental and epileptic encephalopathy: Personal utility of a genetic diagnosis for families. *Epilepsia Open, 6*(1), 149-159.

5.1 Abstract

Identifying genetic pathogenic variants improves clinical outcomes for children with developmental and epileptic encephalopathy (DEE) by directing therapy and enabling accurate reproductive and prognostic information for families. We aimed to explore the additional personal utility of receiving a genetic diagnosis for families. Semi-structured interviews were conducted with fifteen families of children with a DEE who had received a genetic diagnosis. The interviews stimulated discussion focusing on the impact of receiving a genetic diagnosis for the family. Interview transcripts were analysed using the six-step systematic process of Interpretative Phenomenological Analysis (IPA). Three key themes were identified: 'Importance of the label', 'Relief to end the diagnostic journey' and 'Factors that influence personal utility'. Families reported that receiving a genetic label improved their knowledge about the likely trajectory of the DEE, increased their hope for the future and helped them communicate with others. The relief of finally having an answer for the cause of their child's DEE alleviated parental guilt and

self-blame as well as helped families to process their grief and move forward. Delay in receipt of a genetic diagnosis diluted its psychological impact. To date, the factors associated with the personal utility of a genetic diagnosis for DEEs have been under appreciated. This study demonstrates that identifying a genetic diagnosis for a child's DEE can be a psychological turning point for families. A genetic result has the potential to set these families on an adaptive path towards better quality of life through increased understanding, social connection, and support. Early access to genetic testing is important as it not only increases clinical utility, but also increases personal utility with early mitigation of family stress, trauma, and negative experiences.

Keywords: family impact, genetics, caregiver, psychological wellbeing

Key Point Box

- The genetic diagnosis of children with DEEs has important personal value for families, beyond that of their clinical management.
- The genetic label increased families' knowledge and understanding, promoted hope for the future and facilitated social connection.
- Families experienced relief to have diagnostic answers and a reduction in guilt and self-blame.
- Improved access to prompt genetic testing may help families gain maximal personal utility with improved psychological outcomes.

5.2 Introduction

The Developmental and Epileptic Encephalopathies (DEEs) are a group of severe epilepsies characterised by seizures and interictal epileptic activity which negatively impacts on neurological development. These catastrophic disorders have a mortality rate of ~25% by 20 years (Keezer et al., 2016) and survivors have varying degrees of intellectual, psychiatric, behavioural, and motor disabilities (Sillanpää & Shinnar, 2010). DEEs were thought to be acquired disorders until 2001 when *de novo* variants in *SCN1A* were found in individuals with Dravet syndrome (Claes et al., 2001). There are now over 200 genes reported to be associated with DEE and although the diagnostic yield of clinical genetic testing in DEE varies with the cohort studied, yields of up to ~50% are reported (Palmer et al., 2017; Scala et al., 2020; Sheidley et al., 2018; Symonds & McTague, 2020). The majority of individuals with DEE have *de novo* pathogenic variants; however, recessive and X-linked variants have also been found.

A DEE genetic diagnosis is becoming increasingly important in clinical practice. In addition to potentially guiding management and treatment decisions, it also informs accurate prognostic and reproductive counselling (Palmer et al., 2017). While the clinical utility of genetic testing is well established (Pitini et al., 2018), there has been less research on the personal utility. Personal utility refers to the personal psychological and social value of a result to the patient and family (Kohler et al., 2017). A systematic review identified 15 distinct aspects of personal utility, clustered around personal (affective, cognitive, and behavioural) and social outcomes (Kohler et al., 2017). Individuals' with genetic disorders, such as ovarian cancer, disorders with genetic contributions, such as Alzheimer's disease, and healthy individuals who undertake direct-to-consumer genetic testing, report an increased sense of control and ability to prepare for the future due to the knowledge and understanding they gained from their genetic result (Fox et al., 2015; Gooding et al., 2006; Wasson et al., 2013). This suggests personal utility is a multifaceted construct regardless of setting or type of disease. A study of three families with inherited relatively mild epilepsy syndromes reported that receiving a genetic diagnosis empowers families, reduces feelings of isolation, and improves quality of life (Vears et al., 2015). As DEEs are severe epilepsies with typically no family history due to de *novo* variants, it is possible that

the personal utility of receiving a genetic diagnosis is far greater for these families. Here, we explore the personal utility of a DEE genetic diagnosis for 15 families (17 parents) using the qualitative approach of Interpretative Phenomenological Analysis (IPA).

5.3 Methods

5.3.1 Participants

All parents of children with a DEE who had received a genetic diagnosis, were participating in the 'Genetic Basis of Epilepsy' study at the University of Otago Wellington, New Zealand and fulfilled the inclusion criteria were invited to participate. Inclusion criteria were: contact with the research team within the last 10 years (2010 – 2020); fluent spoken English; available within the greater Wellington region for face to face recruitment. A total of 19 families met the inclusion criteria; three could not be contacted, and one withdrew prior to the interview due to scheduling difficulties, this left 15 participating families. For 13 families, the mother only was interviewed; and for two families both parents participated in the interview (total of 17 parents). No siblings were interviewed. The education level of the interviewees ranged from high school graduate to postgraduate tertiary qualifications. The ethnicities of the interviewees included: European, Māori, and Asian.

5.3.2 Procedure

In-depth semi-structured interviews were completed at a time and location convenient to participants. Interviews were carried out face to face, or if this was not possible via video conference. Interviews were digitally recorded and transcribed verbatim by the first author, who was not involved in the clinical care of the children. Data collection ran between November 2018 and March 2019. Ethical approval was granted by the New Zealand Health and Disability Ethics Committee.

5.3.3 Measures

An interview schedule, consisting of three groups of open-ended questions, was used as a guide for the semi-structured format. Participants were asked about their general experience of their child's DEE; their experience of receiving a genetic diagnosis and their experiences surrounding having a genetic diagnosis. The questions were designed to stimulate discussion about what was important to participants, allowing the interviewer to probe or ask follow up questions for clarification. The interviews ranged in duration from 32 to 75 min, with an average of 56 min.

5.3.4 Data Analysis

The study used IPA which is a well-established qualitative method of analysis within clinical, health and counselling psychology (Smith & Osborn, 2014). It is an iterative, contextual approach that focuses on persons-in-context (Larkin et al., 2006). Using this approach enabled a detailed, in-depth examination into the lived experiences of parents who have a child or children with a genetic DEE (Smith & Osborn, 2014).

Patterns of meaning or themes were identified through the processes of familiarisation, reflection, integration, interpretation and thematising, with the aim of capturing the shared understandings of the experience of receiving a genetic diagnosis for the DEE, whilst also giving light to each participant's individual variation of the experience. Analysis followed the six rigorous and systematic steps: 1) repeated reading; 2) initial noting; 3) development of emergent themes; 4) identification of connections across emergent themes; 5) identifying recurrent themes across transcripts; and 6) identification of connections/patterns across recurrent themes (Smith et al., 2009).

5.4 Results

5.4.1 Cohort

15 families who met the inclusion criteria consented to participate. Two families had two affected children. The clinical features of the children are reported in Table 6. Children presented with seizures at an average of 1.5 years (ranging from one day to 11 years). Developmental delay was noted by three years seven months (range three months to three years seven months). Nine children had drug resistant seizures at the time of the study. In 12 families the variant was *de novo,* in two it was maternally inherited, and for one child the inheritance was unknown (mother negative, father not tested). The average time between seizure onset and genetic diagnosis was nine years four months (range of six months to 23 years seven months).

Table 6

Summary of clinical features of participants' children

Case [Case # in previous publication]	Age at study (sex)	Epilepsy syndrome	Gene	Variant	Inheritance	Sz onset age [offset]	Developmental delay diagnosis	Cognitive outcome	Time elapsed between seizure onset and genetic diagnosis (Year)
1	5y (F)	West	*ALG13*	c.320A>G p.Asn107Ser	*de novo*	4m	4m	Severe ID	4y8m (2017)
2[Hamdan et al., 2017) [T21213]]	17y (F)	DEE unspecified	*GABRB2*	c.911C>T p.Ala304Val	*de novo*	4y	6m	Profound ID	11y (2017)
3	6y (F)	Dravet	*SCN1A*	c.384-2 A>G	*de novo*	6m	6m	Severe ID	6 m (2013)
4	8y (F)	DEE unspecified	*CDKL5*	Exon 4 Deletion	*de novo*	5w	3m	Profound ID	1y8m (2013)
5 [Carvill et al., 2020) 13]	5y (F)	DEE unspecified	*EEF1A2*	c.1150G>C p.Gly384Arg	*de novo*	1d	5m	Profound ID	1y (2015)
6 [Sadleir et al., 2020) [B3]	17y (F)	GCE	*PCDH19*	c.1919T>G p.Leu640Arg	*de novo*	16m [11y8m]	3y7m	Borderline ID	7y8m (2011)
7a[Sadleir et al., 2020) [A1]	12y (F)	GCE	*PCDH19*	c.497_498insA p.Tyr166*	*de novo*	10m [5y2m]	3y3m	Severe ID	4y2m (2011)
7b[Sadleir et al., 2020) [A2]	12y (F)	GCE	*PCDH19*	c.497_498insA p.Tyr166*	*de novo*	10m [5y2m]	3y4m	Mild ID	4y2m (2011)
8[Harkin et al., 2007) [55]	32y (M)	Dravet	*SCN1A*	c.512T>A p.Ile171Lys	*de novo*	7m	7m	Severe ID	23y5m (2010)
9[Harkin et al., 2020) [68]	32y (F)	Dravet	*SCN1A*	c.4062delT p.Asp1355Thrfs*8	*de novo*	5m	2y6m	Severe ID	23y7m (2010)
10	7y (M)	Dravet	*SCN1A*	c.5347G>A p.Ala1783Thr	*de novo*	6m	2y	Moderate ID	1y6m (2013)
11[Sadleir et al., 2020) [E7]]	26y (F)	GCE	*PCDH19*	c.2534C>T p.Ser845Asn	Mother negative, father not tested	8 m	11m	Moderate ID	23y4m (2017)
12	12y (F)	Epilepsy with Myoclonic atonic seizures	*SCN1A*	c.32C>A p.Pro11His	Maternally inherited	2y [3y]	2y	Normal	5y (2013)
13	7y (F)	Early onset epileptic encephalopathy	*KCNQ2*	c.1700T>A p.Val567Asp	*de novo*	4d [10m]	9m	Severe ID	3y (2015)
14a[Sadleir et al., 2020) [C5]]	31y (F)	GCE	*PCDH19*	Exon 6 deletion	Maternally inherited	14m [22y]	1y1m	Mild ID	22y4m (2012)
14b[Sadleir et al., 2020) [C4]]	27y (F)	GCE	*PCDH19*	Exon 6 deletion	Maternally inherited	19m [21y]	1y6m	Mild ID	18y3m (2012)
15	22y (F) (Died)	DEE unspecified	*PAFAH1B1*	Intronic deletion	*de novo*	11y [22y – died]	2y	Mild ID	2y (2005)

In the case column, the superscript number denotes the reference number of the paper in which this individual has been previously published. The case # denotes the specific patient identification number in that publication. F: female; M: male; y: years; m: months; w: weeks; d: days; DEE: developmental and epileptic encephalopathy; GCE: girls clustering epilepsy; ID: intellectual disability

5.4.2 Interpretative Analysis

Three key themes emerged and describe parents' lived experience of receiving a genetic diagnosis as the cause of their child's DEE: 1) Importance of the label, 2) Relief to end the diagnostic journey and 3) Factors that influence personal utility. All families discussed more than one theme: all themes (eight families), two themes (seven families) (Figure 4 and Figure 5).

Figure 4

Pattern of responses across all themes and subthemes for each family

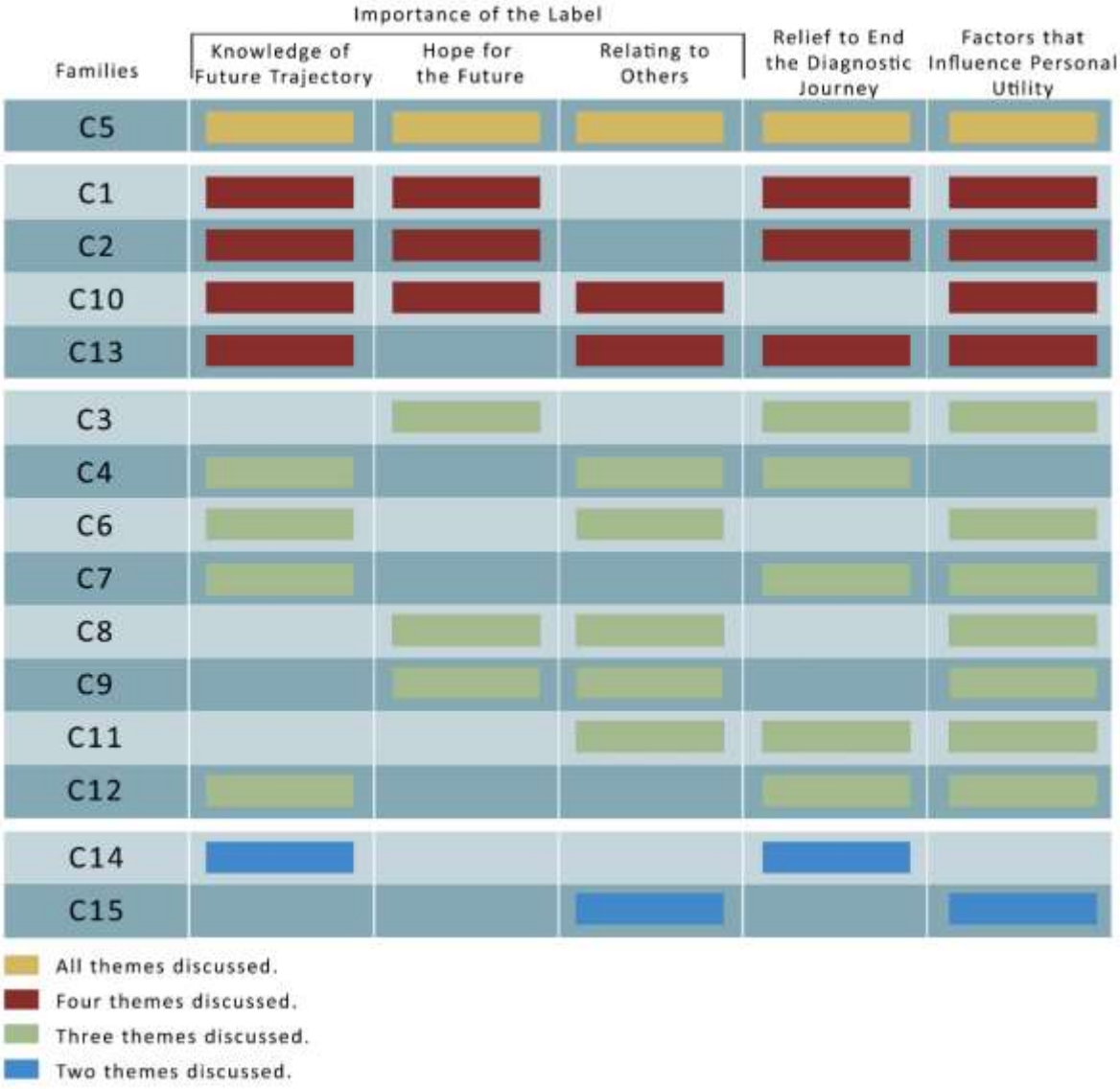
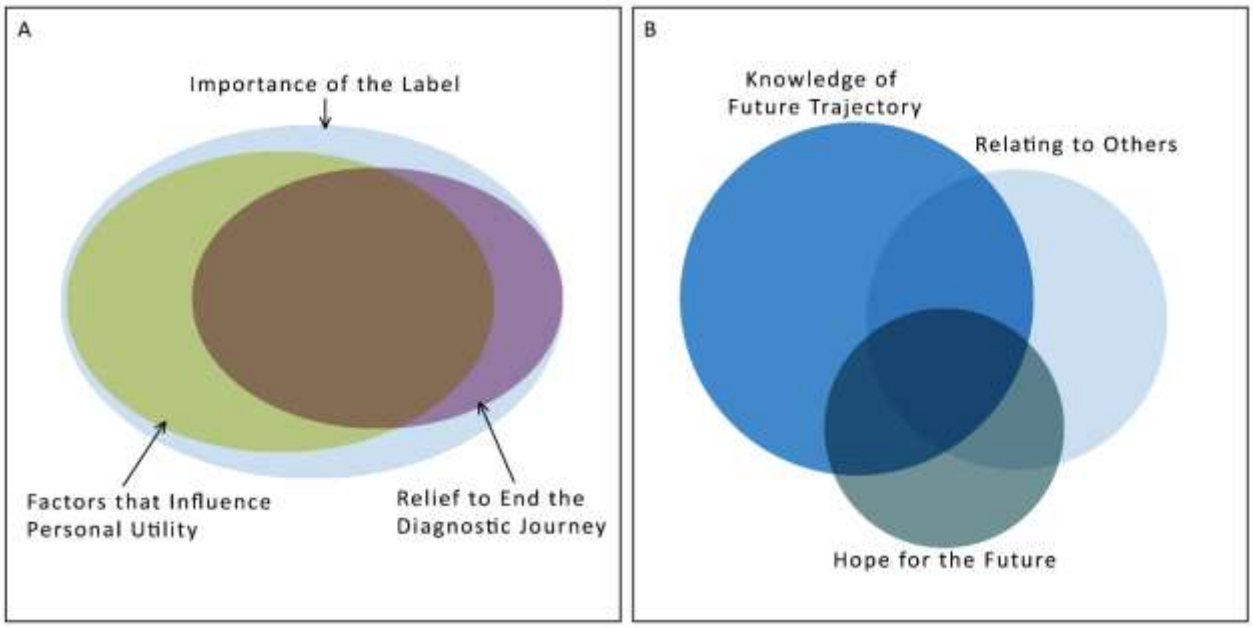


Figure 5

Conceptual Venn diagram showing the overlap of themes.



Note. Section A shows all themes. Section B shows the subthemes from the 'Importance of the Label' theme. This figure is a conceptualisation of the interaction of both the themes and subthemes. There was considerable overlap in the discussion of the three main themes with all families discussing the 'Importance of the Label'. Within the theme 'Importance of the Label', there was less overlap between the subthemes

Importance of the Label

Receiving a genetic label of a DEE was important for all 15 of the families as it validated that their child was not a medical anomaly and that their disorder, whilst rare, was known to medical professionals. Three subthemes emerged: 1) knowledge of future trajectory, 2) hope for the future and 3) relating to others. Two families discussed all three subthemes, seven families discussed two subthemes, and six families discussed one subtheme (Figure 4 and Figure 5).

Knowledge of Future Trajectory

For ten families, receiving the genetic result and label was a turning point to a new pathway with a set of expectations about how their child might develop and possible outcomes to anticipate. It brought control back into the family's life, as they could now research and learn

about their specific genetic DEE. This knowledge clarified their expectations for prognosis over the course of the child's life and minimised parental rumination on an array of possible negative outcomes. Thus, when the next seizure or comorbidity occurred, participants felt better informed and had made anticipated adjustments to their routine, home environment or behaviour as a way of preparing. This helped them to psychologically and practically cope more effectively.

Participants also used this ability to gather new information to help process their own feelings of loss, uncertainty, and anxiety. For example, receiving the label of *CDKL5* was the catalyst allowing case 4's (Table 7) family to move forward to a life without diagnostic uncertainty and fear. As receiving a genetic label increased scope for knowledge and understanding whilst decreasing fear of the unknown, families reported spending less time worrying about what they did not know and more time with their child, searching for a positive, adaptive way forward.

Hope for the Future

A genetic label led seven participants to have increased hope that medical professionals would have, or would develop through future research, better effective treatments for their own child and also other children with their genetic disorder. Participants were able to keep up to date on research developments for their child's gene, which gave them a sense of progress and accomplishment, and in turn fostered hope and a positive outlook for the future. However, for some participants their newfound hope was short lived when they realised that their child's gene was rare, novel or did not have a promising long-term prognosis. Seven of the 15 families discussed the initial difficulty of receiving such information. Despite this, participants tended to "hold onto hope" by drawing meaning that the lack of prognostic knowledge about rare or novel genes did not necessarily mean there was a bad prognosis in the future for their child.

Table 7 *Representative quotes related to each of the three themes: importance of the label, relief to end the diagnostic journey and factors to increase personal utility.*

Theme (*subtheme*)	# families who discussed each theme	Representative quotes
Importance of the Label	15/15	
Knowledge of Future Trajectory	10/15	"It was like a huge weight off our shoulders, it was like we have a name and now we can do research on it, now we can find out more about it." - C13
		"I guess it gives you a pathway, you know. You kind of know, yeah it's just that certainty. Kind of weird comfort in knowing that he's going to follow the same lines as what's expected. Just gives you some time to prepare or not be blindsided by what might come next" - C10
		"I felt like I was standing at a fork in the road and each fork in the road had a door and the CDKL5 one, was, you could see through it, it was like opaque glass but I could see what that looked like… I said 'you know I feel like you've just given me the key to that door and now we can actually move forward from the fork in the road'- C4
		"If we didn't get that diagnosis, we'd probably be feeling like there's something else lurking around every corner and it still can be a little bit like that with her, but we know why. But if we didn't know, we'd be living our lives on the edge of a sword just thinking what's going to happen next, what are we going to be dealing with in two months' time, six months' time, is she going to even be alive in a year?" – C4
Hope for the Future	7/15	"Maybe in the future they might find something that can be done for that specific gene to make things change, I don't know. But if they don't find these things then they can't work on, you know, what can be done about it. And possibly even if it's just preventing other children from having it then that's a good thing too" - C2
		"Reading articles like that makes you think 'maybe!', even if they say it's genetic, there's no cure; it just gives you hope that maybe one day. Like some cancers are cured now. Like leprosy before it was not cured, and it's cured now. So yeah, we hope" - C3
		"You hold onto hope and you go 'well ok if it's so rare, then who knows, you know?'. The future could be bright, it could be gloomy, but it could be bright, so yeah." - C5
Relating to Others	9/15	"Just knowing 'oh yes, it is a textbook thing', it's not just a random, she's not just a one off, there's other people out there like us." - C9
		"The label is, for me, for our family, it's been really important to move forward. You can then get onto like forums and connect with other people who've got the same sort of things going on. And that's huge in itself I think… it just makes you feel better, I can't really quantify that. It just does, it's helpful." - C4
		"Yeah it definitely has, just knowing what she has now, has definitely made it a lot easier to explain to people. Because so many people just stare and think ah what's happened? And now it's easier to just say this is what she has, and this is what happened, whereas before we couldn't really say that. We'd just be like 'I don't know; we don't know why she's like this'." - C13
Relief to End the Diagnostic Journey	10/15	

		"A huge weight lifted (tearful). Yeah, I guess it wasn't anything that I'd done. It was just- you know, she's a one off. It was quite a big impact to have had… I think it's just the weight has lifted off the guilt that I was carrying around. Now that I know that it wasn't anything, there was nothing that could've changed it basically." - C2
		"Lots of blaming, lots of thinking like "who, where'd she get it from"? Both sides, especially my husband's side, they're more like cultural beliefs it's caused by this, it's caused by that. But luckily, we did the genetic testing, so it was proven from the test that didn't come from both sides. It's a de novo mutation, yeah…it took out that part where you resent, like where you took blame. It's kind of reassuring that there was no cause, you were reassured that this was what happened to her. Unless because you can be thinking your whole life 'what caused it? what caused it?'" – C3
		"Yeah, it did make a difference though, because I wasn't constantly in the back of my mind worrying all the time. I was always wondering, was it this? was it that? did I do this? You know, she had a big fall when she was a baby and I often wondered oh god did she have brain trauma? So, I guess that would be for me the biggest result was that I just didn't question it anymore, wasn't looking for a magic cause you know." - C12
Factors that Influence Personal Utility	13/15	
		"It's really important from your researcher perspective to think about the context that came with this diagnosis, which wasn't a whole lot of other detrimental other things, it was just a piece of information… The fact that the gene mutation is there hasn't changed the presentation of what's happening with her physically, therefore there's nothing different yet. Like if all the children started to drop dead at 12 or 13 years old, then that will look completely different for us than it will look if those children are growing normally, not normally, but their normal."- C1
		"I guess from the information we got that it actually wouldn't make any difference in terms of the treatment. It would just kind of confirm the diagnosis one way or another" - C10
		"It would've been really nice to have had the genetic diagnosis earlier and it would've saved me 14 years of guilt. Yeah, that would've been really good actually to have had it at the time that she was diagnosed with that and when the epilepsy started and stuff like that, to actually know that it wasn't something that I'd done that it was just a random act of fate… I mean mental health is a big thing at the moment across all sectors. I mean it's not easy having a child with a disability and you see so many people and families just ripped apart by it. If you could know that there's nothing you could've done, then it probably does help." - C2
		"Yeah, just wish we could've controlled it maybe a lot earlier and maybe we wouldn't have had to go through so much. Because you only want your best for your children and when you reproduce that's all you want, you know, you want them to be healthy and you don't want anything wrong, you know." - C7
		"We always thought we'd have more, but after [affected child] and then after finding out, it's kind of made us think well what if our next kid is like [affected child] as well, like there's no way we could handle two kids like that. So yeah, we decided not to have anymore…I think we just decided that it's just too much to have anymore with all of her needs." – C13
		"The other thing is good to know is that it won't affect [sister]. If and when she has children because I guess that's something you always think of. I've always been grateful that [affected child] was my second child because if she'd been the first one, she probably would've been the only one. Because I would've been too scared to get pregnant again in case I ended up with two like her." - C2

Relating to Others

Receiving a genetic diagnostic label also helped reduce nine participants' sense of isolation and alienation. They were now part of a group of families with variants in the same gene and similar lived experiences. A third of the families described reaching out to other families through support groups, forums and social media. The support, shared understanding and advice they received significantly improved participants' coping and wellbeing. The genetic label was also important for families when relating to their external networks. Five families discussed the difficulty of being aware of public perceptions and judgements about their child, and their frustration of not being able to provide an adequate explanation for their child's condition. Receiving a genetic diagnosis meant they could now explain their child's genetic label to others, which was empowering and validating.

Relief to End the Diagnostic Journey

Most participants had spent many years coping with their child's DEE without knowing the cause. When their genetic cause was identified, nine participants experienced immense relief, as well as a reduction of guilt and self-blame. Relief was experienced primarily within the context of a *de novo* genetic variant, where participants were comforted by the information that their child had not inherited the DEE. Participants who learnt that they had passed on the pathogenic variant found it upsetting but also experienced relief that it was caused by something out of their control, not something they had actively done. Furthermore, reducing uncertainty and no longer having to search for answers had a large positive impact for participants.

Factors that Influence Personal Utility

Whilst receiving a genetic diagnosis alleviated psychological distress and improved participants' knowledge and hope for the future, 13 of the 15 families also discussed their experience of missed opportunities. Most participants expressed their views that the fact it took many years to receive a genetic diagnosis lessened the personal utility. These families had already

experienced the trauma and guilt surrounding their child's health and had to learn to adjust and cope with their child's DEE to the best of their ability with limited information. Participants hypothesised that the positive psychological effect of the genetic diagnosis would have significantly increased if they had received the information closer to the onset of their child's DEE. For one family (Table 6, C7), it took 13 years after seizure onset to receive a genetic diagnosis for their child. Although they acknowledged this was due to the limited knowledge and technology at the time, the family felt they had experienced years of uncertainty, anxiety, trauma and stress which could have been significantly alleviated with an earlier diagnosis.

Timing was important for families, not only to reduce negative psychological outcomes, but also in relation to their anxiety around family planning. For two thirds of families, finding out whether their child's DEE was inherited (or whether it was a *de novo* variant in the child alone) had a significant influence on families' decisions to have more children or not. Without a prompt genetic diagnosis, many families were uncertain whether their future children would also inherit the DEE, which sometimes resulted in the decision not to have more children, despite their desire to do so. Families also had ongoing concerns and anxiety about the possibility of their other children passing on the DEE gene to the next generation when they got older. Finding out that their child with DEE had a *de novo* variant meant they no longer had to worry about this.

Families discussed that the amount of personal utility they gained from a genetic diagnosis was influenced by family contextual factors. These factors varied depending on the child's specific genetic diagnosis and how the family had coped psychologically and practically during the period from their child's first seizure until the genetic diagnosis. For some, the genetic diagnosis was a confirmation of a suspected epilepsy syndrome such as an *SCN1A* variant in Dravet syndrome, which was already being managed appropriately. In these cases (C5, C8 and C11), the genetic diagnosis yielded no change in treatment or additional information regarding the child's prognosis. The genetic result therefore had minimal emotional impact for the family. However, for families with a causal variant in a gene which was well established but not suspected until the genetic result, identifying a gene in this context was more impactful. This change from living with uncertainty and limited understanding to finally having answers through their genetic diagnosis was considerable and provided significant personal utility. For families with a novel or rare

genetic diagnosis the initial emotional response was positive and hopeful. However, this was relatively quickly followed by despair with the realisation that not much was known about their specific gene and the diagnosis did not lead to new treatments or prognostic information. Over time they became more positive and hopeful as they realised that research was ongoing, and they followed these new developments.

5.5 Discussion

This is the first study to explore the lived experience of parents after receiving a genetic diagnosis for their child's DEE. We found that due to the impact of receiving a genetic label and relief that they had reached the end of the diagnostic journey, families reported positive and meaningful personal utility from receiving a genetic diagnosis. The genetic label gave these families better insight into possible outcomes, an increased hope for the future and improved ability to communicate about their child's disorder to others (reducing both public and self-stigma). The extent of positive utility depended on the timing of the diagnosis and contextual factors specific to each family.

Having a child with a DEE can place immense physical, financial, and psychological burden on families (Camfield et al., 2016; Gallop et al., 2009; Skluzacek et al., 2011). Our families reported that receiving a genetic diagnosis relieves guilt and corrects false causative beliefs. Subsequently they experienced a sense of closure allowing them psychological freedom to process their grief and move forward. This occurred not only for families with *de novo* variants but also for those with inherited variants, as parents recognised the genetic change was outside of their control. The positive outcomes reported by these families supports conjecture and findings from previous epilepsy research (Berkovic, 2015; Poduri et al., 2014; Shostak et al., 2011; Vears et al., 2015). It is also consistent with what has been found in other genetic disorders (Rosell et al., 2016) and direct to consumer genetic testing (Wasson et al., 2013).

Coming to the end of the diagnostic journey and finally receiving a genetic DEE diagnosis reduced our parents' emotional burden as they no longer dwelt on finding answers and were

able to receive support from other families with similar experiences. The discovery of DEE genes has led to the widespread development of patient support groups for specific genes. With the advent and popularity of social networking, these support groups can easily connect families from all over the world. This means that the rarity of their child's genetic condition is no longer a barrier to finding other similar families. These family gene support groups not only provide information for families but also enable access to other families who can provide support, friendship, and a shared sense of purpose. Having a genetic diagnosis allows families to be part of these communities, which our study shows increases personal utility of the diagnosis.

Receiving health diagnoses can have both positive and negative impacts (Gillman et al., 2000). How an individual perceives a diagnosis is influenced by how the individual perceives their illness (Plug et al., 2010). It is likely that a DEE families' positive experience of their child's genetic diagnosis was shaped by their experience of living with fear and uncertainty for periods of time prior to that diagnosis. Our results are similar to those from families with milder inherited epilepsies who also reported feelings of relief, validation and hope from receiving a genetic result (Vears et al., 2015). Some described a lifting of perceived responsibility as the gene transmission was out of their control, even if inherited. However, for others the finding of a gene consolidated their feeling of guilt at having passed the epilepsy on to their children. As these individuals already had knowledge that epilepsy ran in their families and in some the epilepsy was quite mild, knowing the exact gene did not appear to have had the same impact on anxiety as it did in our families with children with DEEs. Indeed, some individuals with milder epilepsies described that receiving a genetic diagnosis had such a minimal impact that they could not even remember receiving it (Vears et al., 2015). This contrasts starkly with the DEE families in our study, where most of the families reported positive psychological impact from receiving the genetic diagnosis. When discussing their experience of receiving a genetic diagnosis and its impact, DEE families touched on 13 out of the 15 components of personal utility (Kohler et al., 2017), such as: to enhance coping, mental preparation, feelings of responsibility, knowledge of condition, self-knowledge, ability for future planning and communication with relatives. This congruence between our families' disclosures with the conceptualisation of personal utility strongly supports

the importance of including personal utility when measuring the overall impact of genetic testing in children with DEE.

Consideration of individual family circumstances and differences is crucial when quantifying the impact of a genetic diagnosis. Our study highlights the importance of prompt diagnosis and understanding contextual factors for families. Families reported that the amount and intensity of stress due to not knowing why their child had a DEE was most profound in the first years following their child's DEE presentation. With time, they found ways to manage this stress as they became more accustomed to having a child with DEE. A genetic diagnosis late in the families' disease journey, therefore, had less impact as it came too late to alleviate the early psychological trauma and negative experiences. If clinical genetic testing for children with DEE becomes routine early in the diagnostic journey, then our study suggests families would likely experience improved psychological outcomes and a better quality of life.

Limitations of this study relate to sample size and cohort recruitment. This study was a focused in depth look at the personal utility of a genetic diagnosis for families with children with DEE. However, due to the nature of IPA methodology the cohort is small and may not be representative of the larger group of families. *SCN1A* and *PCDH19* were the causative genes for over half of our cases. This is not completely unexpected as *SCN1A* and *PCDH19* are common DEE genes (Symonds et al., 2019). Given the numbers of our families with these genes, the results may be more consistent with the lived experience of families with established genes, and not as representative of families with rarer or newer genetic DEEs. In addition, as all families had previously consented to participating in genetic research, it is possible they were more inclined to have a positive attitude to a genetic result. Nonetheless, the project has identified themes which could be used to develop an online survey that could be given to a larger number of families to ascertain if these themes are representative of the wider group of families with children who have a DEE. Larger cohorts would also allow a more thorough analysis of the impact of age at DEE presentation, the timing of diagnosis during the diagnostic journey and different genetic diagnoses on the personal utility of a genetic diagnosis for families.

In conclusion, the personal utility of a genetic diagnosis for people with epilepsy, and in particular DEEs, has been underappreciated and under researched. Using IPA, the present study

demonstrates that receiving a genetic diagnosis had high personal utility through increased knowledge and connection for families whilst simultaneously decreasing guilt and blame. The positive psychological benefits and increased understanding allows families to move forward and better cope with their child's DEE, ultimately improving their quality of life and wellbeing. This study shows that a clinical genetic DEE diagnosis has personal utility in addition to the already well-established clinical utility. Whilst there is benefit of genetic testing for families of all ages, our findings further reinforce the need and importance of early clinical genetic testing in children with DEE.

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Chapter 6: General Discussion

6.1 Summary of Findings

The findings of the research presented in the previous two chapters describe the overall parental experience of caring for a child or children with a DEE, as well as their lived experience after receiving a genetic diagnosis for their child's DEE. The first paper focused on the retrospective account of the families' first experiences after their child's DEE onset and how they adjusted and coped with the difficult and profound alteration in their child's developmental trajectory. As these families had subsequently received a genetic diagnosis for their child's DEE, they reflected on what it was like prior to receiving the genetic diagnosis and the impact that living with profound uncertainty had on their lives.

Specifically, the first paper discussed the families' ways of coping with the unpredictability, which reflected a pattern of PTSS. The families discussed how living with uncertainty led them to experience marked hypervigilance, reactivity and monitoring behaviours as well as sleep disturbances, exaggerated startle response, and avoidance of stimuli associated with the chronic trauma of witnessing and managing their child's DEE symptomology. Even years after achieving seizure control and receiving a genetic diagnosis, families still experienced these stress responses. As discussed in Chapter Four, these findings reflect a common parental experience of PTSS for chronic childhood illnesses and highlight the importance of subjective appraisal on influencing the presence of PTSS and development of PMTS (Kazak et al., 2006; Price et al., 2016). Given the severity of DEEs, and frequency and unpredictability of seizures, it is understandable that the subjective appraisals of the families in the current research tended to involve high threat and risk to their children's life; thus all the families discussed the presence of PTSS.

The first paper also supports previous research more specific to severe childhood epilepsies and the 'domains of seizure burden' (frequency, severity and unpredictability) that contribute to chronic traumatic stress disorder in parents (Berg et al., 2019). Importantly, the current findings extend previous conceptualisations, suggesting that for families of children with DEEs their uncertainty goes beyond merely the domains of seizure burden to also include uncertainty regarding the cause of their child's epilepsy. 'Fear of the unknown' for some of the families in the current study not only included the onset of the next seizure or set of symptoms, but also involved the longer-term illness trajectory of their child's DEE. Naturally, this extent of uncertainty on several different levels reduced families' perceived sense of control, which is known to be emotionally distressing (Madeo et al., 2012). Families developed ways of functioning, such as perpetual monitoring and hyper-vigilance, in an attempt to exert back control.

The aetiological uncertainty also prompted families to search for answers and make causal attributions of their own, in lieu of concrete medical information. This meaning making and processing of their grief also appeared to be an attempt to exert some control back into their lives, consistent with previous research (Affleck et al., 1985; Park, 2010; Tennen et al., 1986). Unfortunately, it was not always adaptive, and instead resulted in guilt, self-blame and diminished levels of hope, which is consistent with previous reports (Berg et al., 2019). Yet, for families of children with DEEs, the diagnostic odyssey and identifying the cause commonly lasts several years, as children may undergo several tiers of invasive tests and medical investigations before a causative gene is found (Joshi et al., 2016). Therefore, whilst strategies such as constant monitoring, increased startle response and avoidance behaviours may be functional in the sense that they help manage the DEEs and potentially aid in keeping their child alive, over time there is significant emotional, psychological and physical burden to the families as well as reduced quality of life. This was the lived experience for our families, which is consistent with the extensive previous research on caregiver burden in epilepsy (Carmassi et al., 2019; Cushner-Weinstein et al., 2008; Jensen et al., 2017b; Ostendorf & Gedela, 2017).

The second paper discussed the lived experience of parents after receiving a genetic diagnosis for their child's DEE. The impact of receiving a genetic label and

parents' relief to have reached the end of the diagnostic journey is illustrated. The genetic label gave these families better insight into possible outcomes for their child and gave back a sense of control to the families, who now had an improved understanding of what to expect and could continue their own learning and research with more specific baseline knowledge of the genetic cause of their child's DEE. Multiple families also experienced increased hope for the future and improved ability to communicate about their child's disorder to others (reducing both public and self-stigma).

The families reported that receiving a genetic diagnosis relieved guilt and corrected false causative beliefs. Subsequently they experienced a sense of closure allowing them psychological freedom to process their grief and move forward. This occurred not only for families with *de novo* variants but also for those with inherited variants, as parents recognised the genetic change was outside of their control. The positive outcomes reported by these families supports conjecture and findings from previous epilepsy research (Berkovic, 2015; Poduri et al., 2014; Shostak et al., 2011; Vears et al., 2015). It is also consistent with what has been found in other genetic disorders (Rosell et al., 2016) and direct to consumer genetic testing (Wasson et al., 2013). In addition, these outcomes, especially families' reduction in guilt, sense of closure and increased perceived control, likely improved the well-established psychological caregiver burden that was the lived experienced of our families and common among caregivers of children with epilepsy (Camfield & Camfield, 2016; Gallop et al., 2009; Skluzacek et al., 2011).

The findings in the second paper were consistent with those from families with milder inherited epilepsies who also reported feelings of relief, validation and hope from receiving a genetic result (Vears et al., 2015). Some described a lifting of perceived responsibility as the gene transmission was out of their control, even if inherited. However, for others the finding of the gene responsible consolidated their feeling of guilt at having passed the epilepsy on to their children. As these individuals already had knowledge that epilepsy ran in their families and the epilepsy was quite mild compared to our children with DEEs, knowing the exact gene did not appear to have had the same impact on anxiety as it did in our families. Indeed, some

individuals with milder epilepsies described that receiving a genetic diagnosis had such a minimal impact that they could not even remember receiving it (Vears et al., 2015). This contrasts starkly with the DEE families in our study, where most of the families reported positive psychological impact from receiving the genetic diagnosis. When discussing their experience of receiving a genetic diagnosis and its impact, DEE families touched on 13 out of the 15 components of personal utility (Kohler et al., 2017), such as: to enhance coping, mental preparation, feelings of responsibility, knowledge of condition, self-knowledge, ability for future planning and communication with relatives. This congruence between our families' disclosures with the conceptualisation of personal utility strongly supports the importance of including personal utility when measuring the overall impact of genetic testing in children with DEE.

The extent of the personal utility of the genetic diagnoses for the families depended on the timing of the diagnosis and contextual factors specific to each family. The prolonged delay between seizure onset and genetic diagnosis for several families in the current research meant that family planning decisions were not able to be made with knowledge of the genetic diagnosis. In addition, the delay led to extended diagnostic and prognostic uncertainty and subsequently more chronic psychological distress and trauma, which is consistent with previous research (Graungaard & Skov, 2006; Webster, 2019). Had the diagnosis been identified closer to seizure onset, families' personal utility of the genetic label may have increased due to its earlier alleviation of the uncertainty and the accompanying ramifications. Yet, overall families reported positive and meaningful personal utility from receiving a genetic diagnosis regardless of the timing of testing.

These findings also add further support to the influence that illness perceptions have on how parents manage and cope with their child's epilepsy (Bassi et al., 2016; Carlson & Miller, 2017). Although the current study did not directly measure this impact, it is apparent from their lived experience, that the level of uncertainty parents experienced prior to receiving the genetic diagnosis had an influence on parental distress and coping. Therefore, once this uncertainty had been reduced by the genetic diagnosis, parents discussed the shift in their outlook and

wellbeing. They were able to view their child's DEE symptomology from a more positive or strengths-based perspective, which in turn empowered them to keep moving forward.

Ending of the diagnostic odyssey through genetic diagnosis also plays an important role. When taken together, the findings from both papers highlight the complex interplay between the theoretical underpinnings of the diagnostic odyssey and illness perceptions; demonstrating how they come together to inform the personal utility of genetic testing. As previously discussed, the illness perceptions of parents of children with DEEs are that of high risk and threat to their child's life (Berg et al., 2019). The unpredictability and physical damage that DEE seizures can have on children's brains intensify parents' negative subjective appraisals of their child's illness. This is further exacerbated for DEEs by the profound uncertainty that accompanies the diagnostic odyssey of not only not knowing the type of DEE in some cases, but also the uncertainty around the aetiological diagnosis. For parents for whom the genetic diagnosis gave increased knowledge and understanding of their child's likely developmental trajectory (thereby shifting their illness perceptions) and in addition ended the diagnostic odyssey, the personal utility of the diagnosis appeared to be greater as it alleviated these factors that contribute to caregiver burden. For parents whose genetic diagnosis simply confirmed the suspected DEE or whose pathogenic variant offered only minimal information regarding trajectory or likely outcomes due to it being so novel, the personal utility of the diagnosis was not as impactful. Yet, simply gaining more knowledge and a diagnostic label does have some utility (Mollison et al., 2020). Consequently, parents' illness perceptions in combination with diagnostic uncertainty appear integral to the conceptualisation of personal utility for these parents. Thus, the findings from the current research add to the body of literature on parental caregiver experiences for severe childhood epilepsy, and further extends the currently limited literature of the personal utility of genetic diagnosis within epilepsy.

6.2 Implications of Findings for Clinical Practice

This project presents important findings and has significant clinical implications in light of the growing understanding of the genetic DEEs (Scala et al., 2020; Sheidley et al., 2018; Symonds & McTague et al., 2020). There are now more than 200 genes on clinical genetic epilepsy panels and multiple genetic testing companies that provide these tests. The turnaround time for these tests is improving and results can be now obtained within 2 to 6 weeks of sending DNA. Unfortunately, access to this testing is limited for most children with DEEs within New Zealand and globally. This is due to the cost of these investigations, the perception that these are "special" tests to be done when no other cause has been found, and a lack of knowledge of the impact of a genetic diagnosis. Although these tests are expensive, the yield is much higher (up to 50% of children being solved by clinical genetic testing) than many of the other expensive clinical investigations that are ordered routinely in these children (Howell et al., 2021; Symonds et al., 2019). Recent studies have proven the cost effectiveness of early genetic testing compared to other strategies used to determine aetiology (Howell et al., 2018).

The ideal situation for a child with a DEE would be that genetic testing is ordered at the same time as other routine diagnostic tests. However, shifting the perception to view genetic testing as a routine investigation, rather than a "special" test requires the clinicians and their health funders to appreciate not just the high yield of the test, but also its significant impact. Although the clinical utility of genetic testing is becoming increasingly recognised (de Lange et al., 2018; Johannessen Landmark et al., 2021; Kohler et al., 2017; Pitini et al., 2018), this study now shows the psychosocial importance of a genetic diagnosis for the families of children with a DEE. The valuable information reported in the current research, outlining the positive psychological impact of knowing the cause of a child's DEE, can be added to studies on the yield and clinical utility of genetic testing to advocate for, not only access but specifically, early access to genetic testing. Ideally, this will lead to national and international guidelines that recommend early genetic testing in this group of children.

For some families receiving a genetic diagnosis can be a distressing experience, where they are given devastating information about the likely trajectory of their child's life or their hopes are dashed when there is minimal information due to the novelty of their child's specific genetic variant (Nevin et al., 2021; Vears et al., 2015). The current research also points to this experience, especially when parents find out their child's DEE has been inherited. Our findings speak to the importance of parents finding a balance between acknowledging the disappointment or distress, whilst also maintaining hope for new technological or research developments in the future. The current research further demonstrates that a genetic diagnosis can be a lot to process for families, as they come to terms with the clinical and developmental implications for their child. This emphasises the importance of access to genetic counselling, which has been shown to be beneficial for families not only after they have received the diagnosis but also in their cognitive preparations prior to receiving the results (Palmer, 2017; Vlaskamp et al., 2021). Genetic counselling can increase individuals' sense of empowerment through higher levels of perceived cognitive control and improved ability to make informed decisions (Vlaskamp et al., 2021). Therefore, caregivers should be offered access to genetic counselling both prior and after receiving a genetic diagnosis for their child's DEE. Enabling caregivers to begin the therapeutic process prior to receiving the genetic results may allow them to then gain greater personal utility from the diagnosis due to their likely head start in cognitive control and sense of empowerment; essentially beginning the shift in negative illness perceptions earlier. Furthermore, irrespective of whether caregivers initially found the genetic diagnosis to be distressing or limited in its information, for these families the genetic diagnosis still represented the end of the diagnostic odyssey. This finding alone was helpful for parents, who no longer had to search for answers or live with uncertainty, and aligns with previous research detailing the attribution of personal utility even with clinically uninformative results (Mollison et al., 2020).

Our families emphasised the benefit of social connection with other families with children who had the same diagnosis. The shared experience and understanding helped to mitigate feelings of isolation and loneliness and fostered a sense of hope. Not only did our families appreciate the emotional online support from other

families, they also gained practical knowledge through shared resources, research, advice and coping strategies. This highlights the importance of family gene support groups. It is, therefore, important for clinicians to foster the development of these groups and to ensure that following a genetic diagnosis their families are made aware of the online family gene support groups for their child's gene.

The results of our study will help increase health professionals' understanding of the psychological trauma these families are suffering and the several ways parents cope with this. Consistent with previous epilepsy research (Berg et al., 2019; Webster, 2019) and with other illnesses (Mollison et al., 2020; Fox et al., 2015; Gooding et al., 2006; Schofield et al., 2019; Wasson et al., 2013), our study illustrated the importance of increased sense of control and illness perception. If clinicians are aware of these psychological issues, they will be better placed to be able to identify them in families and provide additional education, resources and support, if possible.

Furthermore, organisations, such as Epilepsy NZ, may be able to use the findings from the current resource to promote awareness not only in the health sector, but also in the education sector. Children with DEEs commonly require specialist education needs; they may be delayed in their entry to the educational system or may not be able to attend school at all (Jakobsen et al., 2020). It is important for teachers, teacher aids and special education educators to be aware of the different types of strain that parents of children with DEEs are under and how the unpredictability and diagnostic uncertainty may be affecting their ability to cope. Navigating both the health and educational systems may be significantly adding to their uncertainty and overall burden. With increased understanding and awareness, educators may be better placed to aid and support these children and their parents, for example by helping apply for caregiver support or identifying different possible avenues for funding of specialist education services. Consequently, the burden of finding appropriate education for their child will no longer be solely on the caregivers, allowing them more time and resources to attend the wellbeing of themselves, their child and the whole family.

6.3 Methodological Considerations

The current research used the qualitative approach of IPA to give voice to the experiences of caring for a child with a DEE after receiving a genetic diagnosis, adding new evidence to the minimal existing research regarding the importance of personal utility for genetic diagnoses within epilepsy. The idiographic nature of IPA allowed for a detailed examination of each of the 15 families' unique experience before a cross-case analysis was carried out (Smith, 2004). This yielded an in-depth exploration of parent experiences, stepping beyond simple descriptions and instead critically analysing the ways families made sense of their child's DEE and the genetic diagnosis. A particular strength of this approach is the focus on lived experience within social, cultural and theoretical contexts (Callary et al., 2015). The current study included the individual thematic patterns within family and recognised the importance of the unique social, cultural and clinical context relevant for each family, which in turn became a recurrent theme across all families. Exploring families' ways of functioning and coping provided an opportunity to drawn upon trauma, grief and illness perception theory and literature to interpret experiences of caregiving and making sense of their child's genetic diagnosis within a wider context (Kazak et al., 2006).

The methodology of the current study allowed for rich and meaningfully data, giving detailed insight into a previously underappreciated area. However, there are also limitations that need to be considered. Given the exploratory nature of this study, the sample size is small and not necessarily representative of all families with children with DEEs or of epilepsy more generally. *SCN1A* and *PCDH19* were the causative genes for over half of our cases. This is not completely unexpected as *SCN1A* and *PCDH19* are common DEE genes (Symonds et al., 2019). Given the numbers of our families with these genes, the results may be more consistent with the lived experience of families with these established genes, and not as representative of families with rarer or newer genetic DEEs. However, IPA is not concerned with representative samples or the generalisability of findings; it takes an idiographic stance highlighting nuanced analyses of *particular* instances or contexts (Larkin et al., 2008). The goal of our study was to better understand the experiences of these families and highlight individual experience, which does not require large or

representative samples (Smith et al., 2009). A sample size of 15 families (17 parents) is in line with IPA methodological expectations and guidelines, which also suggest homogeneity within the sample as a positive (Reid et al., 2005; Smith et al., 2009). Generalising the findings was never the intention; findings presented here can be explored with larger populations in future research.

In addition, as the 15 families in this study were part of an epilepsy genetic research programme the sample may be biased towards families for whom finding answers is critical. However, this epilepsy genetics research project has been recruiting children with DEE for over 20 years. It is the experience of Professor Sadleir who sees these children clinically as a paediatric epileptologist that almost all families consent to be part of this genetic research project when approached. This would suggest that most families with children who have a DEE are looking for answers. Further, the fact that our families all eventually received a genetic diagnosis may have further increased their positive attitude to a genetic result and possible bias towards the importance of finding a diagnosis. Nevertheless, these families were in the unique situation of being able to reflect on what it was like prior to the genetic diagnosis and contrast and notice how their lives had changed as a result. Given that only a single interview was carried out at a time point after the receipt of a genetic diagnosis their accounts of living with diagnostic and causative uncertainty were retrospective, which may be a possible limitation of the study as their memory of their experience may have differed from their actual experience. Yet, the hermeneutic perspective within phenomenology posits that it is the subjective experience and the participant's meaning-making taken from that experience, which is the focus of IPA, not the experience itself (Smith et al., 2009; Smith, 2018). Therefore, even though families' accounts were retrospective, this should not have hindered their discussion of the meaning they took from their experience, regardless of the timeframe.

Participants' mental health status is another consideration worth noting. Parental mental health and their emotional reactions to discussing difficult topics was considered as part of the ethical assessment of this study. Given the significant amount of time since their child's genetic diagnosis, parents had been living with the realities of their child's DEE for several years and had already developed coping strategies to manage their emotions. This, in combination with the fact that the study

was not directly exploring parental mental health, meant that no specific exclusion criteria regarding the mental health of participants was included. Although formal screening was not carried out, in actuality, all participants confirmed having no diagnosis of psychological disorder at the time of the interview.

The majority of participants in the current study were mothers. This is often the case when exploring parental or caregiving experiences (Harden et al., 2016; Moreira et al., 2013; Mu, 2005). Again, this adds to the homogeneity of the sample, which is not necessarily a flaw or limitation in the study (Smith et al., 2009). However, it may make it difficult to understand the family's social context and functioning, as the experience and meaning making of an integral family member is absent from the analysis for most of the cases (Kazak et al., 2006). Thus, it is important to acknowledge the current study's findings may not be representative of both parents' views or experiences of living with a DEE and receiving a genetic diagnosis.

6.4 Future Research

The themes identified in this study could be extrapolated and used to inform the development of an online survey. Collaborations with the international family gene support groups would allow a global reach to a very large number of families. This larger cohort could determine how generalisable the findings are to the wider group of families with children who have a DEE.

Larger numbers would also enable subgroup analysis and comparison between groups of children with DEE to determine if certain groups gain more personal utility from a genetic diagnosis than others. A survey of personal utility could be developed using the 15 dimensions identified in previous research (Kohler et al., 2017). Once developed and tested, this survey could then be used in larger quantitative studies to be able to make group comparisons between:

- specific DEE syndromes (e.g. common DEE syndromes such as West syndrome and rarer syndromes such as Epilepsy of Infancy with Migrating Focal Seizures)

- specific DEE genes (e.g. Dravet syndrome with *SCN1A* variants and *PCDH19* clustering epilepsy)
- children with specific comorbidities (e.g. movement disorders or feeding difficulties requiring G-tube feeding).
- degrees of severity of seizure control (e.g. frequency, severity and type).
- degrees of severity of comorbidities (e.g. degree of ID, motor impairment, ASD, ADHD)
- children and families from different areas of the world, which would allow for increased understanding of how culture may shape the extent or content of personal utility

In addition, subgroup analyses could assess the impact of age of DEE onset and the time from diagnosis of DEE to receipt of genetic diagnosis on the personal utility of the genetic diagnosis. Research exploring any differences in personal utility between mothers and fathers or primary and secondary caregivers could also elucidate insights into the mechanisms that drive personal utility for different groups.

Furthermore, a longitudinal study following families' experiences from initial onset of their child's DEE through the diagnostic journey to receiving a genetic diagnosis and their subsequent coping over time could be beneficial to identify fluctuations in parental distress and track the trajectory of symptoms (Puka et al., 2019). This could yield further insight into periods of time where additional support is most needed for families and could be most effective.

An important aspect of personal utility for our families was the impact on reproductive planning. Qualitative research aimed at more thoroughly examining the impact of a genetic diagnosis on family planning decisions would be beneficial. As previously mentioned, these families are in expansion mode and the possibility of subsequent children with a DEE is a major concern when parents are considering having more children.

6.5 Conclusion

In conclusion, this research examined the lived experiences of families caring for children with a DEE and the personal utility of a genetic diagnosis. The personal utility of a genetic diagnosis for people with epilepsy, and in particular DEEs, has been underappreciated and under researched. Using the in-depth, exploratory analysis of IPA, the current research identified the profound difficulty and distress that accompanies having a child with DEE. Families' lived experience centre around the unpredictable and uncertain nature of seizures and DEE symptomology more generally. Reduction in perceived control shaped families' coping response, which aligned with common trauma responses, such as hypervigilance, hyperarousal, sleep disruptions and avoidance. Not knowing the cause of their child's DEE resulted in self-doubt, blame and grief for families. In contrast, receiving a genetic diagnosis had high personal utility through increased knowledge and connection for families, whilst simultaneously decreasing guilt and blame. The positive psychological benefits and increased understanding of a genetic diagnosis allows families to move forward and better cope with their child's DEE, ultimately improving their quality of life and wellbeing. This study shows that a clinical genetic DEE diagnosis has personal utility in addition to the already well-established clinical utility. Whilst there is benefit of genetic testing for families of all ages, our findings emphasise the need and importance of early clinical genetic testing in children with DEE. Gaining greater understanding of the experiences of families with children with severe childhood epilepsy provides clues as to how best to enhance adaptive coping, wellbeing, and quality of life.

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Chapter 7: Appendices

Appendix A: Participant Information Sheet

GENETIC BASIS OF EPILEPSY

What does finding the gene that causes a child's severe epilepsy mean to the family?

PARTICIPANT INFORMATION SHEET

An invitation

You and your family are invited to participate in an additional interview as an extension to the Genetic Basis of Epilepsy study that you are already participating in. This extension of the study is being conducted by Jenny Jeffrey, a Doctor of Clinical Psychology student supervised by Associate Professor Lynette Sadleir at the University of Otago and Professor Janet Leathem at Massey University. Participation in this extra interview is entirely voluntary and you are free to withdraw from this part of the Genetic Basis of Epilepsy study or indeed the entire study at any time. You can take as much time as you need to decide whether or not to take part.

Aim of the study

The Genetic Basis of Epilepsy study has identified new epilepsy syndromes and discovered the genes that cause them. This knowledge has led to an improved understanding of the epilepsies and is providing the basis for better diagnostic tests and therapies.

However, there has been no research into how receiving a genetic result as the cause of a child's epilepsy has impacted their family. For example, this may have had indirect cognitive and psychological consequences. By interviewing parents of children with a severe epilepsy in whom a causative gene has been identified, we hope to gain a better understanding about the personal impact of finding out the genetic cause of epilepsy.

What participation involves

If you would like to participate in this research project, a consent form will be sent to you and an interview appointment will be made for a time and place that is convenient for you. The interview will take about an hour. You will be asked questions about how life has been since receiving the genetic result and whether there have been any changes for you and your family.

All information will be completely confidential, and you are free to decline from answering any question. If during, or after, the interview you are worried about any issues which were raised, you may contact the researcher to discuss these further. Contact phone numbers are listed at the end of this sheet. With your permission the interview will be audio-taped to allow the researchers to accurately write down what you say during the discussion. It is important that we correctly record all the ideas you have.

Your participation in this additional interview is completely voluntary and if you choose not to participate it will have no impact on your involvement in the rest of the Genetics Basis of Epilepsy study or your child's ongoing clinical care. You will not be paid to participate in the research project, and you do not stand to gain financially from participation even if useful scientific discoveries are made.

Confidentiality

All of the information you provide in the interview will be restricted to the research team. Once the recorded interview is transcribed into written form the audio tapes will be erased. Research records are confidential, and information in them may not be given to others without your consent. However, the ethics committee may audit them and we are obliged to store your records safely for at least 10 years. Results from the study will be published in scientific journals and presented at scientific conferences. There will be none of your personal identifying information included in these publications or presentations.

If you have any questions or concerns about your rights as a participant in this study you can contact the Health and Disability Advocate Telephone 0800 555 050, email advocacy@hdc.org.nz or the Wellington Ethics Committee, on 0800 4 38442, or email hdecs@moh.govt.nz.

Ethics

This study has received ethical approval from the Central Health and Disability Ethics Committee which reviews national and multi-regional studies. HDEC reference number: NTY/12/06/053/AM12.

Please feel free to contact the researchers if you have any questions about the study:

Wellington Epilepsy Research Group
Department of Paediatrics
University of Otago, Wellington
PO Box 7343, Wellington South 6242

Phone: Jenny Jeffrey (DClinPsych Student) 04 918 6292/[redacted]
Jenny.jeffrey.1@uni.massey.ac.nz

Associate Professor Lynette Sadleir 04 918 6138
(Paediatric Neurologist)

Appendix B: Participant Consent Form

MASSEY UNIVERSITY
TE KUNENGA KI PŪREHUROA
UNIVERSITY OF NEW ZEALAND

GENETIC BASIS OF EPILEPSY

What does finding the gene that causes a child's severe epilepsy mean to the family?

PARTICIPANT CONSENT FORM

REQUEST FOR INTERPRETER

English	I wish to have an interpreter.	Yes	No
Māori	E hiahia ana ahau ki tētahi kaiwhakamāori/kaiwhaka pākehā kōrero.	Āe	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai

1. I have read and I understand the information sheet about taking part in the study designed to explore the personal impacts on families after receiving a genetic diagnosis of developmental and epileptic encephalopathy. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

2. I have had time to consider whether I should take part. I know who to contact if I have any questions about the study.

3. I have had the opportunity to use whānau support or a friend to help me ask questions and understand the study.

4. I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care.

5. I understand that my information will be confidential, and my name will not be associated with my answers.

6. I have had this project explained to me by _____.

7. I consent to my interview being audio taped for the purposes of transcribing the data.

8. I consent to the publishing of results from this study provided my personal identifying information is not included.

9. I would like a copy of an annual newsletter detailing study progress.
YES/NO

   a. Email_____

   OR

   b. Post_____

10. I _____ hereby consent to participate in this study.
(full name)

Signed _____ **Date:** _____

Date of birth (DD/MM/YYYY) _____

This study has been given ethical approval by the Multi-region Ethics Committee. This means that the Committee may check at any time that the study is following appropriate ethical procedures.

For more information about ethical issues concerning this research you may contact

Health and Disability Ethics Committees, phone 0800 4 384 427

Appendix C: Semi-Structured Interview Schedule

The following list of general questions will be used as a guide. Suggested prompts have been included under each question to aid participants if they are struggling with the question. However, these prompts are not unique questions and will only be used if necessary. Likewise, the interview is participant led, and if participants address subsequent questions in their discussion of earlier questions, those subsequent questions will not be repeated.

Small talk/Rapport building

1. Introduction, explanation about the study and answering any questions.
2. Confirm demographic information: ages, ethnicity, education of family members

General

1. How long has [child's name] had epilepsy?
2. Tell me about how you felt when you first found out or realised your child had a severe epilepsy?

   Prompts:

   a. What were your major concerns and questions at that point?

   b. How important was it to you at that stage to know why this had happened?

   c. What did you think was the cause?
3. Tell me about how [child's name] epilepsy impacts on [her/him] and your family life?
4. What helps you manage the stress of [child's name] epilepsy?

Participation

1. What motivated you to take part in the Genetic Basis of Epilepsy study?
2. What has been your experience of taking part?

Genetic result

1. When did you receive the genetic result?
2. How long after the original diagnosis of epilepsy was this?
3. Was the result from a research test or a clinical test?
4. What was it like to receive the result?

5. How did you feel about it initially?
6. Did this change later on? If yes, how so?

Post genetic result

1. What does the genetic result mean to you now?
2. How do you feel knowing the change in the epilepsy gene was occurred only in your child and was not passed down from one of their parents? (when applicable)
3. How, if at all, has your view of [child's name] epilepsy changed since receiving the genetic result? Elaborate.
4. Did finding out the result change the way your child was managed by your doctor?
5. Has the result affected you or your family? Elaborate.

    Prompts:

    a. Has this changed how you and your family function on a day to day basis?

    b. What positive changes, if any, have occurred in you and your family's life since receiving the result?

    c. What negative changes, if any, have occurred in you and your family's life since receiving the result?
6. Have you received more support? Elaborate.

    a. *Prompts:* What/who has been the most helpful and why?
7. Have you been in contact with any other families with children with changes in this gene?
8. Do you know if there are any family groups with your gene that can provide support – either on the web or facebook?

    a. If there are have you contacted them?

    b. How have you found that experience?
9. Have you received genetic counselling? Was this useful or not – why? If they haven't, why not?
10. Has the result made any difference to you with regard to having more children?

    a. How might finding out the cause of your child's epilepsy within a month of their diagnosis have changed your child or families' lives do you think?

    b. Would it have changed your thoughts on more children?
11. After having this experience, what advice would you give someone who has just received a diagnosis?

12. Is there anything that you might not have thought about before that occurred to you during this interview?
13. Is there anything else you think I should know to understand the impacts of a genetic result?
14. Is there anything you would like to ask me?

Appendix D: Email Template to Participants re: Interview Transcripts

Kia ora [participant],

It was a pleasure to meet with you and interview you for the study on family experiences after receiving a genetic diagnosis of childhood developmental epileptic encephalopathy.

I have now transcribed your interview, so would like to ask whether you would like to review the transcript, make any changes or additions before I begin data analysis for the study? If you would like to, please respond to this email within a week and I will send the transcript through.

If I don't hear back from you within in a week, I will assume you are happy for me to proceed with the transcript as it stands. Please do not hesitate to contact me if you would like to discuss this or have any questions.

Once again, thank you for your support and being part of this research.

Best wishes,

Jenny

Jenny Jeffrey

Epilepsy Research Group

https://www.otago.ac.nz/epilepsy/index.html

Appendix E: Clinical Case Study

Research Case Study

How my doctoral thesis research has contributed to my clinical practice as an intern psychologist

A research case study in partial fulfilment of
The degree of Doctor of Clinical Psychology

Jennifer Sian Jeffrey
2020
Intern Psychologist at Massey Psychology Clinic, Wellington

This case study represents the work of Jennifer Sian Jeffrey during her thesis from 2018 to 2020 and reflections as an intern psychologist in 2020.

Candidate: Jennifer Jeffrey Date: 23/11/2020

Supervisor: Professor Janet Leathem Date: 23/11/2020

Abstract

This research case study gives an overview of my doctoral thesis and provides reflections on transitioning from researcher to clinical psychology intern. The case study is organised into two main sections. The first section provides a summary of my thesis, including: the rationale, aims, methodology and initial findings. The second section consists of my self-reflections on transitioning from a researcher into the role of intern psychologist at Massey Psychology Clinic in Wellington. These reflections include a discussion regarding the subjective experience of receiving a diagnosis as well as the influence of diagnosis on access to services.

Keywords: Research, self-reflection, intern, clinical psychology

Doctoral Thesis Overview

My doctoral thesis topic focused on the lived experience of families after receiving a genetic diagnosis for their child's developmental and epileptic encephalopathy (DEE). This overview of my thesis will firstly include a summary of the development of the thesis topic followed by an overview of the aims, methodology of the study.

Thesis Topic Development

In 2017 I worked as the Departmental Manager for the Department of Paediatrics and Child Health at the University of Otago Wellington. At this time, I was trying to decide the topic area for my thesis. I knew I wanted to focus on children and families, but I was struggling to find a supervisor who specialised in an area that interested me. One of the paediatric neurologists in my department, Professor Lynette Sadleir, suggested my thesis could focus on her area of research, genetic diagnosis in paediatric epilepsy. Coincidentally, Lynette met Professor Janet Leathem the following week at a conference and began the initial discussions regarding what would eventually become my research and supervisory team.

The discovery of new causative genetic pathogenic variants for the epilepsies has grown exponentially in recent years. To our knowledge, no research had applied a psychological lens in this area, especially regarding the developmental and epileptic encephalopathies (DEE's) prevalent in childhood. There was limited knowledge and understanding regarding how families experienced not having a known cause for their child's DEE until a genetic pathogenic variant was identified. Our research team decided my thesis could fill this gap. This initial literature review supported the research in this area is summarised below, followed by a discussion of the aims and methodology.

Summary of Literature

A developmental and epileptic encephalopathy is defined as a disorder in which seizures and interictal epileptiform discharges inhibit development resulting in a plateau or deterioration of cognitive, psychological and behavioural functioning,

which is lower than would be expected from the underlying pathology alone (Berg et al., 2010; Khan & Al Baradie, 2012). The DEEs are the most severe group of epilepsies, with a childhood mortality rate of approximately 25% before the age of twenty (Sillanpää & Shinnar, 2010). Most of the DEEs present in early childhood, are pharmaco-resistant to standard antiepileptic drugs (AEDs) and have a poor developmental prognosis (Cross & Guerrini, 2013). Prior to 2001 the cause of DEEs was largely unknown but presumed to be acquired. Researchers have now discovered the aetiology to be heterogeneous, with the majority of cases due to *de novo* genetic pathogenic variants, i.e., a random mutation in the child's DNA sequence which is not inherited from their parents (McTague et al, 2015).

A childhood epilepsy diagnosis affects the family unit as a whole, extending beyond just the clinical management of the disorder. Parents are required to quickly learn and understand the complex medical information relevant to their child's epilepsy, as well as provide ongoing care, time and encouragement to the affected child and other children in the family (Ostendorf & Gedela, 2017). They must cope with new anxieties and stress from unpredictable seizures, the possibility of seizure related injuries, and medication side effects (Gallop et al., 2009); whilst simultaneously dealing with the uncertainty of their child's long-term prognosis. The emotional impact has been reported to leave caregivers feeling angry, guilty and helpless with little or no time to themselves (Jensen et al., 2017). The severity of the DEEs is such that the indirect effects are increasingly difficult for families to manage. The ongoing care and high level of resources required from health, educational and welfare systems pose a considerable burden (Camfield et al., 2016; Palmer et al. 2017). Studies of families with a child who has Dravet syndrome (a type of DEE) have shown that seizures were the greatest source of stress, followed by the loss of original hopes for their child's future as the actuality of developmental delay and behavioural problems becomes realised (Camfield et al., 2016; Nolan et al., 2008).

Genetic testing is becoming more prevalent in both research and clinical practice for multiple disorders, such as hereditary cancers, Alzheimer's disease, muscular dystrophy and epilepsy. Genetic testing can result in a genetic diagnosis, which usually enables more accurate prognostic information to be given to the family. Identifying a genetic cause can also guide treatment decisions such as, AED

choice and may even be helpful in avoiding therapies that could worsen the clinical outcome (Palmer et al., 2017). Even if the genetic diagnosis does not have clear implications for treatment or prognosis, it may provide information regarding associated abnormalities that should be screened for and monitored (Poduri et al., 2014).

Whilst a genetic diagnosis yields important insight into the aetiology of an individual's disorder and may have implications for clinical utility, research has shown that individuals often express additional benefits for receiving genetic results beyond that of their medical management (Wasson et al., 2013). This is referred to as 'personal utility' and relates to an individual's feelings of control when they increase their knowledge and understanding of their child's epilepsy. However, minimal research has been conducted into the underlying mechanisms that drive personal utility. The rationale for wanting to know their genetic result and any personal benefits for individuals and families after finding out the genetic cause of the epilepsy remain largely unknown. Given that the majority of individuals have a *de novo* genetic etiology (McTague et al., 2016), it has been suggested that identification of the cause may provide 'closure' for parents who may have guilt arising from a misunderstanding of the aetiology (Berkovic, 2015; Poduri et al., 2014). A small study of three families with mild inherited types of epilepsy suggested that receiving a genetic diagnosis may empower families, reduce feelings of isolation and improve quality of life (Vears, Dunn, Wake & Scheffer, 2015). It also aids in reproductive decision making and future family planning as it help genetic counsellors give accurate information and effective support (Palmer et al., 2017). To our knowledge, no research had been conducted to examine these outcomes in families with children with genetic DEEs.

In summary, childhood DEEs presents many ongoing hurdles for the entire family. The psychological stressors, the time demands, and subsequent financial strain has been well established and thoroughly documented (Ferro & Speechley, 2009; Ostendorf & Gedela, 2017). DEEs are devastating epilepsies that have the potential to put families under extreme pressure and stress, making it difficult for them to adapt and thrive (Mori et al., 2017; Nolan et al., 2006; Skluzacek et al., 2011). Identifying the genetic cause of a child's epilepsy may be instrumental in determining

the long-term prognosis and treatment management as well as the likely comorbidities (Palmer et al, 2017). In addition to these clinical outcomes, the knowledge of the genetic result may have wider reaching effects for the individual and their family. The personal impacts of reducing isolation, removing guilt, increasing support and quality of life has been reported in a small study (Vears et al., 2015; Wasson et al., 2013). It is important to give light to the personal effects on families, as a way to maximise the benefits and help identify positive ways to reduce the challenges they face. To date, there have been no studies which have examined the impact of receiving a genetic diagnosis on families with a child diagnosed with a DEE; my doctoral thesis addresses this gap.

Research Study Aims

The research was undertaken in collaboration with the Department of Paediatrics and Child Health at University of Otago, Wellington (UOW). The study was an additional arm of the research being conducted by the Epilepsy Research Group (ERG) at the UOW, which explores the genetic basis of epilepsy. The study examined how receiving a genetic diagnosis for children with developmental and epileptic encephalopathy impacts on the family. In order to quantify the full benefits and applications of genomic diagnosis in epilepsy syndromes, the effect of receiving a genetic diagnosis of DEE on individuals and families must first be understood. Empiric evaluations may not only highlight whether more support is needed for families but also aid in the expansion of funding and accessibility to genomic testing in epilepsy as a whole. Consequently, the research findings may be used to help advocate for routine clinical genetic testing for this group of children with severe epilepsies, as at the present time routine clinical genetic testing is not standard care in New Zealand.

The overarching research questions are:

1. What were families' experience of personal utility for their child's developmental and epileptic encephalopathy genetic diagnosis?
2. How did the genetic diagnosis change families' lived experience, if at all?

Methodology

Ethics

A substantial amendment to include my research as part of the Epilepsy Research Group's 'Genetic Basis of Epilepsy' application was approved by the Central Human and Disabilities Ethics Committee (HDEC), reference number: NTY/12/06/053/AM12.

Participants

All parents of children with a DEE who had received a genetic diagnosis, were participating in the 'Genetic Basis of Epilepsy' study at the University of Otago Wellington, New Zealand and fulfilled the inclusion criteria were invited to participate. Inclusion criteria were contact with the research team within the last 10 years (2010 – 2020); fluent spoken English; available within the greater Wellington region for face to face recruitment. A total of 19 families met the inclusion criteria; three could not be contacted, and one withdrew prior to the interview due to scheduling difficulties, leaving 15 participating families (17 parents). For 13 families, the mother only was interviewed; and for two families both parents participated in the interview. No siblings were interviewed. The education level of the interviewees ranged from high school graduate to postgraduate tertiary qualifications. The ethnicities of the interviewees included: European, Māori, and Asian.

Procedure

In-depth semi-structured interviews were conducted with one or both parents of each participating family by the first author. Interviews were completed at a time and location that was convenient to the participants. Eleven interviews were carried out in the parents' own homes, two were completed at the parents' place of work, one in a hospital room while the participant waited for an appointment, one at a university and one was conducted via video conference using Zoom teleconferencing software. Seven interviews were completed in the presence of children with DEEs or other children. Interviews were digitally recorded and

transcribed verbatim by the first author. Transcripts were then reviewed for accuracy. Participants were invited to check their interview transcript and make any changes they felt necessary in order to accurately represent their experience. Data collection commenced in November 2018 and was completed in March 2019.

Measures

An interview schedule with open-ended questions was developed by the research team as a guide for the semi-structured format. The interview schedule consisted of three general grouping of questions. First participants were asked generally about their experience of their child's DEE. For example, "Tell me about how you felt when you first found out or realised your child had a severe epilepsy." Tell me about how [child's name] epilepsy affects [her/him] and your family life". The second group of questions asked about the experience of receiving a genetic diagnosis, e.g., "What was it like to receive the result? How did you feel about it?". The final group of questions explored participants experience after receiving a genetic diagnosis, e.g., "What does the genetic result mean to you now? How, if at all, has your view of [child's name] epilepsy changed since receiving the genetic result? Has the result affected you or your family? After having this experience, what advice would you give to someone who has just received a diagnosis?". The questions were designed to stimulate discussion and be driven by what was important to participants. This allowed the interviewer to probe or ask to follow up questions to clarify the participant's responses. The interviews ranged in duration from 32 min to 75 min, with an average length of 56 min.

Data Analysis

Given the lack of previous research, the study used a qualitative methodology as it allows the researcher to gain an understanding of the underlying processes by which individuals make sense of what happens to them and how they attach meaning to it (Larkin, 2015). Interpretative phenomenological analysis (IPA) is a well-established method of analysis within clinical, health and counselling psychology. It provides specific guiding principles and analytic procedures, especially useful when concerned with complexity, process or novelty (Smith & Osborne, 2015). It is an

iterative, contextual approach that focuses on persons-in-context (Larkin et al., 2006), which enabled a detailed, in-depth examination into the lived experiences of parents who have a child or children with a genetic DEE (Smith & Osborne, 2015).

Patterns of meaning or themes were identified through the processes of familiarisation, reflection, integration, interpretation and thematising, with the aim to capture the shared understandings of the experience of receiving a genetic diagnosis for the DEE, whilst also giving light to each participant's individual variation of the experience. Analysis followed the six key rigorous and systematic steps: 1) repeated reading, 2) initial noting, 3) development of emergent themes, 4) identification of connections across emergent themes, 5) identifying recurrent themes across transcripts, 6) identification of connections/patterns across recurrent themes (Smith et al., 2009). The first author coded and developed the thematic framework. Four transcripts were also analysed by another member of the research team, in order to minimise researcher bias and increase transparency of analysis. Personal and identifying information has been edited for the selected extracts to ensure confidentiality.

Clinical Psychology Internship

In January 2020, I began my year-long internship in the Massey Psychology Clinic. The service is a private clinic that accepts referrals of mild to moderate severity of mental distress across all age ranges and types of disorders. The following section provides a discussion and self-reflection on my transition from a researcher to intern psychologist working at this service. My reflections include: the subjective experience of receiving a diagnosis, diagnosis and access to services, as well as IPA semi-structured interviews reflecting clinical interviews.

The subjective experience of receiving a diagnosis

Receiving a diagnosis of any kind can be an extremely profound experience for the individual and their family. Depending on the context, the type of diagnosis, as well as the subjective perception of the individual, for some it may be a devastating experience and for others it may result in immense relief and understanding. Often it may be a combination of both. This was what my research aimed to explore; the

lived experience of receiving a genetic diagnosis for DEEs. Listening to my participants tell their stories and explain the complexity that surrounds such a diagnosis gave me a deeper understanding of nuances behind giving and receiving a diagnosis and its impacts, both obvious and subtle. The participants discussed their experience of living for years without answers, information or knowledge of their child's illness and their hope for the genetic diagnosis to provide everything they had been living without. In this case, most individuals held a positive perception of diagnosis and viewed it as beneficial and insightful. The same may be true for many individuals with regards to mental health diagnoses; parents wanting to better understand their child's difficulties and pinpoint the specific cause and best way to help them. For others, receiving a diagnosis may be a painful, discriminatory experience, that they were given without choice or consultation and which they view as a negative label that removes their power and voice.

My doctoral research caused me to reflect deeply throughout my internship on the power of a diagnosis and the importance of, not only accurate diagnosis, but also the reasons behind it, the way it is delivered, and the support offered afterward. Some of my clients during my internship had a similar experience to my research participants, receiving a diagnosis (such as posttraumatic stress disorder) gave them validation and knowledge that their experience was not an anomaly but a common experience felt by others in similar situations. It helped to alleviate some of the blame, guilt and negative cognitions they had about themselves and their experience, and alongside psychological therapy, were able to find hope in their recovery. Yet for other clients, their diagnosis had become their identity; something they relied on to explain their unhelpful thinking or behaviour. To an extent, their diagnosis had become a hindrance to their progress. It was perceived as a justification and a barrier preventing recovery. Both my research and experience during my internship allowed me to witness both the positive and unhelpful sides to diagnosis and helped me to understanding that its impact is truly subjective and unique to each individual's situation and context.

Diagnosis and access to services

After acknowledging the importance of careful consideration with regards to diagnosis and understanding the complex nuances of each individual's unique experience, the juxtaposition of then being required to make a diagnosis, in some cases, to gain better access to services was difficult for me. On one hand, if a diagnosis is made in order for an individual to have better access to funded services, then it is, by definition, beneficial for the individual. However, if the diagnosis is given solely for that purpose, I then questioned how truly helpful it was; especially if the individual did not view the diagnosis as helpful or necessary for themselves. Of course, the diagnosis should always be an accurate representation of the individual's presenting difficulties and they must adequately met all diagnostic criteria, yet at times I was concerned that the diagnosis a psychological disorder officially recorded in order for service access would then become a potentially lifelong stigmatising label for the individual, that may inhibit their access in other areas; such as getting insurance cover or particular occupations. Through reflection, I learnt that it is a careful balance of the pros and cons for each pathway, which should be carried out in collaboration with the client; their lived experience and voice should always be heard. If getting access to funded services allows the individual an increased chance of recovery and flourishing, then perhaps it is worth the possible less helpful consequences later on. Hopefully, in the meantime, the unfortunate discriminatory lens on mental distress will continue to lift.

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