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Cases from the Undiagnosed Diseases Network: The Continued Value of Counseling Skills in a New Genomic Era

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Abstract

The “diagnostic odyssey” is well known and described in genetic counseling literature. Studies addressing the psychological, emotional, and financial costs of not having a diagnosis have shown how it permeates the lives of patients and families. The Undiagnosed Diseases Network aims to end this odyssey by providing diagnoses to individuals with undiagnosed conditions through multidisciplinary evaluations, whole exome and genome sequencing, and basic science research. It also provides an opportunity to learn from patients and families and to better understand their journeys and the impact of receiving a diagnosis.

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EFM designed, planned, and drafted the manuscript.

KS and EGK contributed to the conceptualization, writing, and revising of the manuscript.

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All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest Statements

The authors declare that they have no conflict of interest.

Human Studies and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Animal Studies

No animal studies were carried out by the authors for this analysis and paper.

Seven cases are presented that outline challenges that come from working with chronically undiagnosed and newly diagnosed patients in a time when sequencing for clinical diagnosis is rapidly increasing. They illuminate the emotional journey of patients and families searching for a diagnosis and the mental health problems, financial distress, and chaos that can accompany not having answers. They also illustrate the surprising reactions patients and families can have to receiving a diagnosis, including anger, grief, and disappointment. While the lessons learned from these families are not novel, new strategies are presented for handling these challenges in undiagnosed and ultra-rare populations, groups that will increase with the rise of clinical sequencing.

Keywords

WES/WGS; rare disease; case vignettes; grief; psychosocial

Introduction

In recent years, the cost of comprehensive genetic testing such as whole exome and genome sequencing (WES/WGS) has decreased enough to make it a cost-effective tool in the diagnosis of individuals with suspected genetic conditions (Nolan and Carlson, 2016; Stark, et al., 2017). Through use of this technology, patients and families who have been searching for answers for years are finally given an explanation (de Ligt, et al., 2012; Lee, et al., 2014; Sawyer, et al., 2016; Shashi, et al., 2014; Yang, et al., 2013). However, despite evaluation and sequencing, many patients remain undiagnosed (Lee, et al., 2014; Need, et al., 2012; Yang, et al., 2013). The journey these individuals and families undertake to find a diagnosis has been termed the “diagnostic odyssey” (Rosenthal, et al., 2001) and may involve years of clinical evaluations, numerous imaging studies, and extensive genetic and laboratory testing.

Previous studies have demonstrated high rates of emotional distress in parents of children with undiagnosed conditions (Carmichael, et al., 2015; Madeo, et al., 2012; Rosenthal, et al., 2001; Spillmann, et al., 2017; Yanes, et al., 2017; Zurynski, et al., 2017) as well as differences in experiences between adults and parents of children with undiagnosed conditions (Palmer, et al., 2018; Spillmann, et al., 2017). During the diagnostic odyssey, adult patients and parents often experience frustration with medical providers. For parents, this frustration appears to stem from concerns that crucial diagnostic evidence is being overlooked while for adults this frustration seems to come from the need to validate symptoms in light of previously uninformative diagnostic testing (Spillmann, et al., 2017).

Prior research indicates that the uncertainty associated with the experience of having an undiagnosed condition poses a substantial challenge for family coping. Parents of children with undiagnosed genetic conditions have significantly lower hope, perceived social support, and coping self-efficacy compared to parents of children with diagnosed conditions (Peay, et al., 2016; Yanes, et al., 2017). Similar results were found comparing quality of life scores between mothers of children with an unconfirmed versus confirmed chromosome abnormality (Lingen, et al., 2016). Research suggests that the sense of empowerment is also affected, particularly for adult patients compared to parents of children with undiagnosed

conditions (Palmer, et al., 2018). The experience of receiving a diagnosis can affect individuals and families differently. For parents, receiving a diagnosis for their child's condition may reduce uncertainty about what the future holds and provide information to improve management and quality of life for their children (Lewis, et al., 2010; Zurynski, et al., 2017). In contrast, data suggest that adult patients seek a diagnosis in hopes that they will be able to resume the lives they led prior to onset of illness (Spillmann, et al., 2017).

There is extensive research that discusses the impact of receiving an unexpected diagnosis and the grief that accompanies this diagnosis, particularly the psychological aftermath of receiving an unexpected diagnosis during pregnancy. Women explain that the diagnosis is a period of shock and disbelief, that it is the lowest point in their lives, and that grief and depressive symptoms are long lasting (Dallaire, et al., 1995; Korenromp, et al., 2005; Korenromp, et al., 2007; VanPutte, 1988). A recent study of young athletes who screened positive for lethal cardiac disease demonstrated the stages of psychological adjustment and the grief these athletes face when forced to refrain from competition (Asif, et al., 2015). Although there is much research on the diagnostic odyssey experience, there is a lack of data regarding the aftermath of a diagnosis and how families react to receiving an answer.

In 2013, the Undiagnosed Diseases Network (UDN) was launched with the mission to find answers for patients and families with rare and undiagnosed conditions. Supported by the National Institutes of Health Common Fund, its goal is to "help patients who ha(ve) long sought a precise diagnosis and to discover new pathways and mechanisms of disease" (Gahl, et al., 2016; Gahl and Tifft, 2011). To this end, seven clinical sites across the nation, a coordinating center, two DNA sequencing cores, a model organisms screening center, a metabolomics core, and a central biorepository work together to solve rare and undiagnosed cases. The UDN has provided a unique opportunity to balance the clinical needs and research goals for patients and families with undiagnosed medical conditions. The participants in the UDN often have exhausted clinically available testing with many having already undergone WES, resulting in no diagnosis.

UDN clinical sites typically operate as multidisciplinary clinics bringing various types of specialists into the evaluation, which allows for concise phenotyping. Since the UDN started accepting applications in September 2015, 2710 applications have been received, 877 patients have been accepted and evaluated, and 225 diagnoses have been made. Eleven of these diagnoses were previously undescribed conditions. Each patient comes with a unique presentation and experience.

Currently there are 22 genetic counselors, with one to four counselors per site, working in various roles across the UDN. Genetic counselors perform pre-test counseling for WES and WGS, participate in the development and coordination of in-person evaluation schedules, manage genetic testing strategies and interpretation of results, disclose results to patients and provide genetic counseling, and serve as the point of contact for many patients during and after their visits.

Here, seven case vignettes from the UDN are presented. These cases were specifically chosen as they are illustrative of the diagnostic process experienced by patients in the UDN

and outcomes when the diagnosis is resolved. As the use of WES and WGS expands in the future, genetic counselors will increasingly care for patients and families who receive an ultra-rare diagnosis after years of searching. For this reason, we are sharing challenges we have faced working with this population as well as some new counseling strategies that can be employed to manage these situations.

All patients were evaluated under the protocol 15-HG-0130, “Clinical and Genetic Evaluation of Patients with Undiagnosed Disorders Through the Undiagnosed Diseases Network,” approved by the National Human Genome Research Institute Institutional Review Board. Some details have been altered or excluded to protect the anonymity of our patients and their families.

1. The Emotional Odyssey

Parents of undiagnosed children who participated in the UDN were recently surveyed and found to have high rates (~40%) of anxiety and depression (McConkie-Rosell, et al., 2018). Similar struggles have been described by adults applying to participate in the UDN (Spillmann, et al., 2017). “Illness narratives” written by patients and parents of pediatric patients also show that their descriptions of the medical journey are frequently disorganized and chaotic, and the authors suggest that disorganization likely stems from fear and uncertainty about the unknown, resulting in difficulty communicating relevant symptoms, and concern about leaving out an important piece of information for medical providers (Spillmann, et al., 2017). These concerns and emotions often come to light during patient evaluations and conversations with their families.

Case 1.1 Emotional and Financial Desperation—A 2-year-old male was referred to the UDN on the basis of a severe neurological disorder including intractable epilepsy. His parents appeared to be coping well and did not express concerns during the consenting process or during previous discussions with the genetic counselor. However, while completing a survey assessing psychological well-being, the father indicated that he had considered suicide in the recent past. The genetic counselor and primary UDN physician met with the father to assess both the immediate risks and to identify if medical intervention was needed. After assessment, he was not thought to be at immediate risk to himself or others. The father explained that their financial reserves had been exhausted by medical bills, which led to significant family distress. He explained that he had considered the benefit of his family receiving life insurance money, but he knew that suicide was not a decision he would actually make. The mother was unaware that the father had these feelings. The physician and genetic counselor facilitated open discussion between the parents, reflected on the difficulties of parenting a child with a chronic undiagnosed disorder, and provided positive reinforcement for the steps they had taken together. The medical team encouraged him to seek local mental health services to manage these feelings and provided referrals.

Case 1.2 Staying Silent about Personal Distress—A 21-year-old female with a chronic medical condition of unknown etiology that developed three years prior to her evaluation was seen by the UDN. Despite adherence to medical recommendations, she continued to experience unusual symptoms that prompted the UDN referral. While she did

not endorse depressive or anxious feelings during the medical intake, she acknowledged having these feelings while completing a survey assessing psychological well-being. The genetic counselor asked her about these feelings and she shared that she had had severe depression for the past 10 years, which worsened with her symptom onset three years prior and included thoughts of self-harm. The genetic counselor also spoke with her parents, who were aware of their daughter's depression, but unaware that it had worsened. The genetic counselor and physician triaged the situation and referred her for an urgent psychiatric evaluation where she was determined to not be in immediate danger. A clinical social worker met with the family, provided information about coping strategies, and discussed warning signals, including how to recognize behavioral triggers. She also helped the patient identify people and places where she would be safe and distracted from her distress and encouraged her to think about how she could limit access to things that could harm her. Local follow-up was strongly recommended, and she was provided with contact information for local mental health services for future crisis situations. The involvement of the psychiatrist and the social worker allowed for the patient to safely complete her UDN evaluation and allowed for new strategies to be put into place.

1.3 Chaos of Remaining Undiagnosed—A 7-year-old female was seen by the UDN on the basis of a suspected immunological disorder. Her mother provided detailed information to each of the medical providers during the UDN evaluation, which was perceived by several physicians as disorganized and overwhelming with the amount of details, many of which were not pertinent to the undiagnosed condition. Similar to the description of parents of patients with undiagnosed conditions in Spillmann et al. (2017), this mother aimed to include every detail of the illness possibly due to concern she was “leaving something out” that may be the key to identifying a diagnosis. The genetic counselor acknowledged that the worry of leaving something out was very common and rephrased and summarized the concerns to ensure that the mother felt that her daughter's symptoms were documented. Her psychological well-being was not formally assessed through a standardized measure, but her affect appeared anxious and fearful. Based on her affect the UDN primary physician and genetic counselor affirmed that the family had done an outstanding job seeking medical expertise for their child, commended their recognition of important details about the medical journey, and encouraged self-care for the parents as well as attention to their child's progress. The family has stayed in touch with the UDN team and provides updated information regularly as they continue to search for a diagnosis.

2. Unanticipated Feelings That Accompany a Diagnosis

Often a diagnosis is assumed to be associated with a feeling of relief from finding answers. At the start of the UDN evaluation process, patients and families express feelings of hopefulness. In particular, they convey that a diagnosis may be able to lead to treatment options, reduce uncertainty, change management, and improve quality of life (Spillmann, et al., 2017). However, finding an answer can also unearth complex emotions, especially for patients and families who have been on the diagnostic odyssey for many years.

Case 2.1 The Pain of the Past—A 30-year-old male with a history of severe medical problems including intellectual disability and musculoskeletal abnormalities was referred to

the UDN. Exome sequencing for the patient and unaffected parents and siblings identified a *de novo* pathogenic variant in a gene associated with a well-described neurodevelopmental disorder that fit well with the phenotype.

The diagnosis was disclosed to the parents and patient during an in-person wrap-up session. Based on previous interactions with the family, the expectation was that they would be relieved to have a definitive diagnosis after so many years without answers. However, the parents became upset and expressed anger that their son was found to have a diagnosis that no one had been able to identify previously. The genetic counselor explained that this genetic condition had only been recently described and it would not have been possible for the patient to receive this diagnosis more than a few years ago since the condition had not yet been described; nevertheless, the family was frustrated that they were not able to get these answers before now. The parents reiterated that their child had been seen by numerous specialists over the last 30 years, his story had been presented at medical conferences worldwide, and yet no one had ever been able to give the family a diagnosis until now.

The diagnosis for this family seemed to be ‘too little, too late’. The genetic counselor explored with the parents their feelings and it became clear that there was a time in their lives when they would have given anything to have a diagnosis. But at this point, they had already gone through the devastation and pain of not having that answer, and they had accepted the reality of their son’s condition and of not having an answer for the cause of his severe problems. Receiving a diagnosis through the UDN was an unexpected outcome that seemed to open old wounds.

While the hope is that time will help the parents process and adjust to life with a diagnosis for their son, for this family having a diagnosis did not erase the pain of the past. The timing and age when a diagnosis is made can change the experience of the family, and should potentially change expectations and plans for a disclosure session.

Case 2.2 Losing the Child you Knew—A 4-year-old female who presented with global developmental delays, absent speech, and autistic-like features was evaluated in the UDN. The clinical evaluation was suggestive of a specific developmental disorder and, in discussing this possibility with the family, the nuances of what comes with a diagnosis became evident.

While the genetic counselor was discussing the behavioral characteristics of the suspected condition, the mother became visibly upset. The behaviors described were traits the mother identified with as her daughter’s unique personality. Her daughter was not very communicative given her expressive language delay and, though she had a significant history of self-injurious and aggressive behaviors, her parents labeled some of these behaviors as stubbornness. This stubbornness and the frustration that resulted when people did not understand her was something her mother had grown to identify with and see as a representation of her daughter. Labeling these behaviors as symptoms of a condition was taking away the parts of her daughter that she understood best.

Although the family wanted a diagnosis, giving them this possible diagnosis made them feel like they would lose the daughter they thought they knew. After years spent trying to adapt to life without a diagnosis, they were back where they started—feeling like they did not know their daughter. The genetic counselor and nurse practitioner further explored these feelings of grief, asked the parents in what other ways they identified with their daughter, and reminded them, with examples they had witnessed, of how well the parents knew and understood her.

There can be a period of grief that comes with receiving a diagnosis, indicating a diagnosis does not always provide relief. Identifying the source of the grief is not always straightforward, and further dialogue with the family may reveal the source along with unexpected emotions. This mother's grief demonstrated the importance of reminding patients and parents throughout their diagnostic odyssey that a diagnosis does not necessarily change an identity.

Case 2.3 Closing the Door on Hope—A 15-year-old male with a history of progressive external ophthalmoplegia, and severe myopathy was referred to the UDN for evaluation. His presentation and evaluation strongly suggested a mitochondrial disorder and targeted testing confirmed this diagnosis.

His family had already lost three of their five children to possibly related conditions. They participated in the UDN in the hopes of finding a diagnosis, but more importantly, of finding a way to help their son. Mitochondrial disorders had already been discussed in the diagnostic differential and they were hopeful that the UDN would make a diagnosis that specified a treatment plan.

When the family was brought in to disclose the diagnosis, it felt like the diagnosis erased all their hope; the father leaned away from the table and put his head in his hands. He tried to bargain, saying they already knew about mitochondrial disorders and something new must have been learned that would be helpful, the UDN must know people who are doing research and can help him, there must be a better answer than this. The genetic counselor reassured the family that they had taken excellent care of their son and made use of every opportunity available to them. However, hearing that no matter what they did for their son, he was likely to die of his condition completely deflated the father and he remained silent for the duration of the conversation.

Many parents in situations like this know how severe their child's condition is even without a diagnosis. They witness the progression as their children lose skills they once had. Some parents make comments about fear of early mortality, but many live in the moment and hold on to hope that a diagnosis will provide an alternative. Unfortunately, many of the diagnoses made in individuals with ultra-rare conditions are not yet amenable to treatments or cures, and families are faced with finding new hope in the face of devastating news.

Case 2.4 A Diagnosis Without a Home—Through the UDN a 6-year-old female with significant global developmental delay, epileptic encephalopathy, and intractable epilepsy was given a diagnosis of an extremely rare condition, one with limited information online

and without a support network. The participant's mother desperately wanted to know, "Now what?" After feeling so lost while going through their diagnostic odyssey, the patient's mother was placing all her hope in knowing what genetic condition her child had. While receiving the genetic diagnosis was a relief for the family, due to its rarity, the diagnosis did not easily lead to the support the mother was seeking. Without disease-specific resources, she lacked a sense of direction and connection. The genetic counselor encouraged her to create a Facebook group for the diagnosis to start networking with other families with the same condition.

A few months later, a second family was diagnosed by the UDN with the same condition. The family had two affected adult siblings, a 16-year-old female and an 18-year-old male who both had a history of global developmental delay, intellectual disability, and severe intractable epilepsy. After caring for her children for more than 18 years, the mother desperately wanted to connect with other families and had a lot of wisdom to share. This time, the genetic counselor was able to tell the mother that there was a private Facebook group that she could join. The Facebook group has now grown to over 30 members from all over the world. The two families, among many others, are able to connect with each other, share their stories, and receive helpful information about their child's condition. Not readily having support resources for patients after a rare diagnosis can be difficult. Eliciting the patient's desire for connection with other affected individuals or their parents and giving them direction on how to create opportunities for connection is one way genetic counselors can advocate for their patients and families.

Discussion and Practice Implications

Genetic counselors have been helping patients manage uncertainty and new information since the birth of the profession. Although the definition of genetic counseling has evolved, in 2006 it was updated to reflect changes in genetic counseling practices due to advances in genomic medicine (National Society of Genetic Counselors' Definition Task, et al., 2006). Practice-based competencies for genetic counselors were revised in 2015 (Doyle, et al., 2016), and the interpersonal, psychosocial, and counseling skills described in Domain II are frequently utilized by genetic counselors working with undiagnosed or recently diagnosed patients. These UDN cases highlight that, although families often have a shared or similar experience navigating the diagnostic odyssey, there are nuanced differences in each family's experience resulting in adjustments needed for the genetic counseling process. For many, the diagnosis is not the end of the journey, as it is often described, but rather one chapter of a longer story. Below we discuss the strategies UDN genetic counselors employ for helping these families.

Remain aware of the prevalence of mental health concerns in undiagnosed and recently diagnosed populations, and be prepared to address them.

The emotional toll of being undiagnosed is well described (Madeo, et al., 2012; Rosenthal, et al., 2001; Spillmann, et al., 2017; Yanes, et al., 2017; Zurynski, et al., 2017); however, the severity and prevalence of anxiety and depression among undiagnosed patients and family members is not always recognized and addressed. Cases 1.1, 1.2, and 1.3 illustrate the

importance of medical professionals being aware of this risk, establishing a trusting relationship with families, exploring their feelings as well as strategies for coping, and empowering them to continue to advocate for themselves or their child. The depression described in case 1.2 and the anxiety described in case 1.3 hindered the families' abilities to fully engage with the medical teams caring for them. Although busy genetics clinic schedules often do not permit more systematic screening for mental health concerns in patients and families affected by undiagnosed conditions, genetic counselors are well positioned to recognize and address these concerns, and triage more serious concerns that may require immediate treatment or intervention. Connecting patients with additional resources within the institution such as a social worker, providing referrals to mental health care providers closer to their home, or suggesting online sources of support or connection with similar others may be helpful.

Despite pre-test counseling, managing expectations and anticipating family responses is difficult.

Our experience has shown us that it is not uncommon to be disappointed when a long-sought diagnosis is identified. Several cases in this series demonstrate that families may have other strong emotions that are less anticipated, such as anger in case 2.1 and intense grief associated with loss of a child's perceived identity in case 2.2. Despite the poor outcome for other affected family members and grim prognosis of the affected child in case 2.3, the family expressed disbelief and removal of hope following a diagnosis. The genetic counselor helps manage patient expectations by listening to the family's goals, reflecting upon how realistic these goals are, discussing different types of outcomes and how the family would react to them. Due to the nature of the UDN research study, genetic counselors are closely involved with families during planning for their visit, the week-long evaluation at the clinical site, and communication and follow-up after the visit. Despite this closely established relationship and ongoing dialogue with families, the counselors were surprised by the families' reactions and adjusted their counseling accordingly. These examples also highlight the need to manage personal expectations as well as those of the rest of the medical team.

Families with recently diagnosed or undiagnosed conditions need clear "next steps".

Research has shown that finding other parents with similar experiences and being able to offer and receive support from these parents is particularly important in the undiagnosed community (Macnamara, et al., 2018). Even for those receiving a rare diagnosis, it does not end "the odyssey" as there is a remaining sense of frustration, loneliness, and isolation (McConkie-Rosell, et al., 2018). The framing of a diagnosis as the end of the journey is therefore limited. While receiving a diagnosis may mark the end of one period, it often signals the beginning of another, the search to find similar others and understand and treat the condition. Patients and families frequently want to know the next steps they can take when the diagnosis is newly described, rare, or lacking community or support, or when WES or WGS has failed to provide a diagnosis.

Next steps for patients and families with a diagnosis

One strategy that has been adopted by UDN patients and families is the creation of Facebook support groups or basic web pages to foster a sense of community. These groups

also serve as a way to find additional people with the same condition. As many of the diagnoses made by the UDN are extraordinarily rare or newly described conditions, there are seldom existing support groups for families to join. The work of raising awareness and being involved helps these families make meaning, which can be an important part of adapting to a new diagnosis (Helm, 2015).

For patients and families who are eager to find additional support, starting a non-profit foundation, partnering with a research team to pursue next steps, writing blogs, and sharing medical and genetic information on public websites like MyGene2 (<https://mygene2.org/MyGene2/>) have been productive ways to build community. The Global Genes organization has created RARE Toolkits to help families navigate this process and advocate for rare disease, including information about how to fundraise for rare disease research and support, how to network with government representatives to advocate for a rare disease, and how to navigate health insurance (<https://globalgenes.org/toolkits/>). Genetic counselors can help patients and families navigate these endeavors and identify best next steps. Caution should be exercised to provide this information at an appropriate time so as not to burden a patient or family who is already overwhelmed. When informed at the right time, knowing about these avenues can be beneficial for the patient's and family's emotional well-being.

Next steps for patients and families without a diagnosis

For those who remain undiagnosed after extensive evaluation, there is often a profound desire to connect with others who have undergone a similar experience. Support groups such as Syndromes Without a Name (SWAN) and U. R. Our Hope offer space for undiagnosed patients and families to connect and discuss their shared experiences and frustrations. Global Genes created a resource for people with undiagnosed conditions called "Becoming An Empowered Patient: A Toolkit For The Undiagnosed" which provides guidance on how to partner with physicians for medical care and how to become a research advocate. A referral to the Undiagnosed Diseases Network or other clinical program may be an option for some undiagnosed patients.

We previously demonstrated that only a small percentage of UDN participants belong to a support group (Palmer, et al., 2018), and our experience in the UDN has been that many participants report difficulties relating to support groups for the undiagnosed, as the experience of simply being undiagnosed is not enough to feel connected. To address this, the UDN participant advisory group, Participant Engagement and Empowerment Resource (PEER), developed a Facebook group for all UDN families. This group has served to create a sense of belonging for members since all have been through the UDN evaluation process, reduce feelings of isolation that are frequently associated with the diagnostic odyssey, and provide a place to discuss research involvement. Here, patients and families feel involved and included in the research project, encounter others in similar situations, and feel they are doing their part to push research further.

Research Recommendations

Numerous studies have examined the diagnostic odyssey. Studies have looked at the psychosocial impact and long-term effects of not having a diagnosis, why having a diagnosis

matters, and the role of genetic counseling for these individuals (Carmichael, et al., 2015; Madeo, et al., 2012; McConkie-Rosell, et al., 2018; Palmer, et al., 2018; Rosenthal, et al., 2001; Spillmann, et al., 2017; Zurynski, et al., 2017). However, few studies have explored the effect of receiving a diagnosis for these families who have spent so long searching. Further research could focus on the diagnostic odyssey longitudinally with attention to the emotional aspects of receiving, and not receiving, a diagnosis.

Conclusions

The cases from the UDN presented here demonstrate the importance of remembering the basic strategies of genetic counseling. It is critical that genetic counselors continue to grow and learn from patients and their families in order to adapt to their specific needs while incorporating the new diagnostic approaches. These cases also highlight that the diagnostic odyssey is not a straight line but rather an emotional, financial, and physical roller coaster that does not end with a diagnosis. The diagnosis is only a stop in their journey.

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