MSAC Secretariat
Australian Government Department of Health
MDP 960
GPO Box 9848
Canberra ACT 2601

7 October 2022

Dear Committee members,

Re: MSAC application 1675 – Whole Genome Sequencing for the diagnosis of mitochondrial disease

Thank you for inviting Mito Foundation to provide additional input on this application. Genomic testing can be a life changing experience for people with symptoms of mitochondrial disease (mito), and Mito Foundation supports improved access to testing through Medicare listing of Whole Genome Sequencing (WGS) for the diagnosis of mito.

The aim of this submission is to provide input from the mito community into this process. We have sought advice from the Consumer Evidence and Engagement Unit to better understand the issues where the mito community's experience would be most valuable. This submission includes many of the issues raised in our submission prior to the PICO Advisory Subcommittee as we are unsure which issues were included in the economic evaluation. We trust that providing these insights will assist the committee in its decision making.

The key issues covered in this submission are:

- Current access to genomic testing is not equitable throughout Australia
- It is important that the new items support extensive analysis to maximise the benefits of genomic diagnosis
- There are benefits of avoiding complex and risky clinical tests
- Health outcomes are positively impacted by a genomic diagnosis of mito
- There is significant 'value of knowing' in a genomic diagnosis
- Genomic diagnosis supports mito research progress
- The mito community experiences minimal harms from diagnostic genomic testing

Background

Mito Foundation supports patients with mito and their families, funds essential research into the prevention, diagnosis, treatment and cures of mito, and increases awareness and education about this devastating disease. Mito Foundation was founded in 2009 by several families personally impacted by mito along with professionals with a special interest in mito.

Our work is informed by our Mito Community Advisory Panel, regular engagement with the wider mito community through support services and through research projects. To prepare this submission, Mito Foundation staff interviewed nine mito community members about their experiences with genomic testing and their hopes for the role of genomic testing in the future. This group included people with mito, parents of children with mito and other family members of people with mito. Our aim was to get a variety of perspectives. We have used their stories to illustrate the key points in this submission.

Current access to genomic testing is not equitable throughout Australia

People with suspected mito access genomic testing through several options:

State and territory health funding: Hospital based clinical genetics services have funded genomic testing for their patients. We hear from the mito community that there is significant variation in the ease of access to genetic services and to funded genomic testing for mito.

Out of pocket: Individual patients can pay directly/privately for genomic testing, often ordered through a private specialist such as a neurologist.

Research: Some research projects will fund (or have funded) genomic testing for people with mito. The projects run for fixed recruitment periods and have restrictive criteria based on multiple factors. Major projects include the Australian Genomics Health Alliance (NHMRC funded project), a project funded under the NSW Genomics Collaborative Grant, and more recently a new project funded by the MRFF.

Medicare: Some, but not all, children with mito can access genomic testing through MBS items 73358–73363 *Genomic testing for childhood syndromes.*

Given the variation in access to these options, particularly for those in regional, rural and remote areas, Mito Foundation supports this application to improve equity of access to genomic testing.

It is important that the new items support extensive analysis to maximise the benefits of genomic diagnosis

The proposed item numbers in the PICO provide for access to whole genome sequencing (WGS) and whole exome sequencing (WES). Mito Foundation supports improved access to WGS as it has the highest diagnostic yield for mito and also the highest chance of identifying other diseases that may be masquerading as mito. We understand there are challenges accessing WGS and support the flexibility offered by the proposed item numbers to also support patient preferences.

There are benefits of avoiding complex and risky clinical tests

The application proposes genomic testing replaces tissue analysis for some people. While there is a potential cost saving to this change, there is also the opportunity to avoid the risks and pain of these tests on the patient and their family.

We understand the proposed clinical management pathway would mean that the need for invasive muscle biopsies in particular would be reduced.

> The muscle biopsy and MRIs were complicated because of risks of anaesthetics and the use of contrasts that were mito toxins. It took a lot of self-advocacy to organise these tests to minimise the damage they did to me– but I just didn't want to get any worse.
>
> Adult living with mito

> The physical recovery from the muscle biopsy wasn't so bad. It was hard to walk afterwards so I rested for a few days. The main challenge was the cost. It was $700 out of pocket for me with private health cover. And if I didn't have that cover, then I don't know how long I would have waited in the public system.
>
> Older adult living with mito

> My daughter had a profound hearing loss and then a massive seizure. The doctor suspected mito, but she told us that sadly, we had to go through the whole process of multiple tests to eliminate everything else first.
>
> For our little girl this meant four lumbar punctures, which triggered her to have more seizures. Lumbar punctures also were a source of potential infection and were really distressing for all of us. Our daughter had two muscle biopsies as the first one failed. That meant a second anaesthetic which impacted her physically. This was in addition to other tests - the moment we took her into the pathology room I knew she knew: 'I am going to get poked!' I remember every part of her body having band-aids on it because she was prodded so many times.
>
> Earlier access to whole genome sequencing would have meant less hospital stays, less infections, less anaesthetics. Every admission shortened her lifespan.
>
> Parent of a child who had mito

Health outcomes are positively impacted by a genomic diagnosis of mito

The PICO for this application identifies some of the key health outcome improvements enabled by genomic diagnosis. We know that there is limited research on these, so we offer insights from the mito community to supplement published evidence.

1. Reducing the duration, burden, cost and emotional strain of the diagnostic odyssey (*Time to diagnosis*)
2. Supporting existing pro-active management, early intervention and targeted treatments (*Impact on clinical management*)
3. Uncovering an alternate cause of mitochondrial dysfunction (*Impact on clinical management*)
4. Allowing cascade diagnosis for family members (*Earlier and more effective management of the condition*)
5. Restoring reproductive confidence and supporting access to prevention options (*Providing information for informed reproductive decisions*)

1. Health outcomes: Reducing the duration, emotional strain, burden and cost of the diagnostic odyssey

A diagnosis of mito in Australia can take more than 20 years. One study reported that for more than half of patients with mito, the time from first symptoms to a diagnosis was more than three years(1). This is consistent with international studies(2). Improving access to WGS is very likely to reduce this duration for many people with mito. For those people, the positive impact on their lives will be significant.

> I know many people who have spent more than ten years getting a diagnosis. This destroys their lives. I think particularly of one man - the testing they have put him through has risked his health. He completed an exercise stress test that caused him to collapse. This search for a diagnosis through clinical tests has caused people huge emotional and physical stress, wasted a huge amount of health resources and personal finances. If genome testing was available earlier and more easily, this could have been avoided.
>
> Mito Foundation peer support leader who is also an adult living with mito and a parent of children with mito

Mito community members tell us about the emotional impact of this process. Some describe this as negatively impacting their mental health and others describe their specific feelings.

> There is a huge mental health impact of all the testing. It affects not just the person with mito but their family and friends too. I've lived through that – feeling like you're on the edge. Dreading the next test result in the never-ending process of elimination.
>
> Parent of a child who had mito

> It was just hard. I found supportive colleagues and friends really reassuring, particularly those that also worked in healthcare. I often thought about all the possible outcomes and how I might cope with each of them. I had one specialist informally provide a diagnosis and I got really excited by that, but then this was also ruled out, which was another challenge. This was all on top of being in huge amounts of nerve pain and I had severe cramps, so I wasn't sleeping. We were just trying to manage symptoms and get through each day and night.
>
> Adult living with mito

As the above quote highlights, people navigating this odyssey are also managing often debilitating symptoms, particularly fatigue.

> It all took so much time and energy. Because of the time taken to organise and attend all of the tests and appointments I had to stop my part time study – I just couldn't fit it all in. If I had been working full time I expect I would have had to change to part time.
>
> Adult living with mito

Genomic testing may also reduce the out of pocket costs households face through the diagnostic odyssey.

> The tests and appointments were mostly done through the private health system, with only some Medicare funding. It was expensive, but we were fortunate that we could afford it. Let's just say that we hit the safety net quite quickly!
>
> Adult living with mito

2. Health outcomes: Supporting existing pro-active management, early intervention and targeted treatments

While there are no cures and very limited pharmacological interventions for mitochondrial diseases, non-pharmacological interventions and management approaches can play critical roles in helping to reduce symptoms or slow disease progression and decline in health. Because of this, the earlier an accurate diagnosis can be made the better the prognosis and health outcomes for patients.

> For the whole time that we were investigating the cause of my symptoms I was advised to rest as much as possible. This was to keep my lactate levels from going any higher, so I understand why this was important. By the time I was diagnosed and could start rehab, my husband had to carry me upstairs and help me get ready for bed – I just couldn't manage stairs anymore.
>
> I do sometimes wonder what it would be like if that rest was for just one month. So only one month of lost muscle tone. I don't think the rehab would have been as complex as it has been. I now receive supports under the NDIS to help get the kids to school when my husband is working, maybe some of those supports could be reduced or avoided.
>
> Adult with mito

Some examples of these management approaches are:

- exercise and endurance training
- heightened attention to nutrition
- mitigation of symptoms in times of physiological stress
- oral arginine supplementation for patients with MELAS (Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes)
- avoidance of particular toxins, such as smoking in LHON (Leber's Hereditary Optic Neuropathy)
- co-factor treatment in some other forms of mito.
- protocols for administration of general anaesthetics and fasting

Noah and Kat's story (see *Appendix 1*) provides more examples of these and the impact they can have.

Management can be better informed by knowing the risk of acute symptoms of mito, such as stroke-like episodes.

> My diagnosis did mean that my other specialists find it easier to know their role in my care and acknowledge that I know more about my condition than they do. The diagnosis has meant that I can see a specialist clinic that sees multiple patients with the same form of mito. The management approaches still involve some trial and error but I know I am seeing the doctors with the most experience possible.

Adult with mito

> If I could get an accurate genetic diagnosis of mito it would really clear things up in my head. I could move forward with my life. I also know that it would help me get appropriate treatments and avoid things that could make my symptoms worse

Adult with undiagnosed mito

> If we had a diagnosis sooner, we could have been proactive with supplements and other active management. I think this could have given my daughter more years of life with better quality and less suffering. I would have done anything for another two years with my daughter.

Parent of a child who had mito

An accurate diagnosis can also ensure that known mito toxins are avoided. For example:

- a common anti-epilepsy medication, sodium valproate, which is toxic to patients with some forms of mito.
- streptomycin and certain related antibiotics that can cause deafness in patients with one of the most common mitochondrial DNA mutations.

> My wife was prescribed an antibiotic to treat a gastrointestinal problem. Unfortunately, this brought on a metabolic crisis. This caused worsening physical symptoms – every step she took was like walking through concrete. The silver lining was that this is what led to her eventual diagnosis, but it would have been so much better to avoid this toxic medication.

Spouse of an adult with mito

3. **Health outcomes: Uncovering an alternate cause of mitochondrial dysfunction**

Mito Foundation understands that genomic testing is a useful tool for identifying patients who may have been given a clinical diagnosis of mito, but actually have another underlying condition causing their mitochondrial dysfunction. During the Australian Genomics Mitochondrial Flagship project several children were provided with a diagnosis of a different genetic condition that had targeted treatment available(11). Some of these conditions have treatments and/or management approaches that can drastically improve health and quality of life.

The new item numbers need to allow for analysis of not only genes known to cause mito, but also other known disease causing genes.

4. **Health outcomes: Allowing cascade diagnosis for family members**

The discovery of the gene change causing mitochondrial disease allows other members of the same family to be more easily tested, even if they are not showing noticeable clinical symptoms. This then supports proactive monitoring and management to preserve their health and detect emerging mito symptoms early.

> Genetic testing for myself and my two children was very straightforward. But this was only because members of my family went through a tortuous process to confirm the diagnosis and find the gene change in our family. Particularly one of my aunts, who spent ten weeks in hospital seeking a diagnosis. This included a muscle biopsy under general anaesthetic which was a life-threatening procedure for her.
>
> Adult with mito who is also a parent of children with mito

> Trying to get my clinical symptoms of mito understood has been incredibly difficult. My sister was diagnosed in 2004, and following discussions with her she suggested that my symptoms were also indicative of mito. Genetic testing could be a way for me to get a faster diagnosis and stop me having to push each doctor to take me seriously.
>
> Adult with possible mito

5. Health outcomes: Restoring reproductive confidence and supporting access to prevention options

A genomic diagnosis of a child with mito can allow their parents to plan further pregnancies. Depending on the nature of the gene change causing their child's disease, parents can use assisted reproductive technologies or prenatal testing to ensure future children will not be born with mito. A genomic diagnosis can restore reproductive confidence. Dion's story (see *Appendix 2*) illustrates the role of genomic testing when mito is caused by recessive gene changes.

The *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021* was passed in the Senate in March 2022 and it is expected that the MRFF funded pilot stage will commence in 2023. Having a confirmed mtDNA genetic cause of mito is a key eligibility criterion for mitochondrial donation. It will be critical that testing is available to seek a genomic diagnosis of mito to help families understand whether mitochondrial donation is an option they may be able to pursue.

> Without a formal diagnosis, how on earth are you supposed to make reproductive choices for your future children? The genetic diagnosis was key for us.
>
> Adult with mito who is also a parent of children with mito

> Our daughter was diagnosed with mito when she was 18 months old. It took a lot of fighting to have her various symptoms recognised but eventually an MRI revealed changes in her brain typical of Leigh syndrome. This was great to help us understand her health condition, but it didn't give us answers for the rest of our family.
>
> As we learnt more about mito we understood that it can be passed through a family in many different ways. We were really concerned for our two other children as we knew they could also have mito and just not be showing any signs or symptoms yet. Or maybe they were carriers and their children, our future grandchildren, would have mito. One of our siblings put her plans to start a family on hold because she was unsure if she should be having a child. It was haunting to hear the stories of other families where mito is inherited. We were frequently overwhelmed by concern for our other children.
>
> We were really fortunate to have our daughter's gene change found as part of a research project. We got the results only recently, which was 4 years after she was diagnosed with mito. They found that our daughter was a de novo mutation, which meant there was minimal risk of any of our other family members having mito.
>
> This gave us clarity and has helped us get on with living our best lives with all of our children. We are fortunate and grateful.
>
> Parents of a child with mito

There is significant 'value of knowing' in a genomic diagnosis

In this submission we are sharing insights from the mito community on the value of knowing they have mito through a genomic diagnosis.

1. Psychological benefits
2. Improving access to non-health supports
3. Making decisions based on improved understanding of prognosis

1. The value of knowing: Psychological benefits

It is common for many people in the mito community to live with a provisional diagnosis of mito when clinical tests are inconclusive. Improved access to genomic testing will reduce this number by providing a definitive diagnosis for more people with mito.

> Not knowing was the hardest thing. My mind was always wandering: Is it MS? Is it some other weird disease? Is my wife going to be here in three years' time?

Spouse of an adult with mito

> It was an amazing relief to get the diagnosis. Even though this was followed by confusion and lots of questions for my doctors.

Adult with clinical diagnosis of mito

> I always believed that my symptoms were personal character failings: I thought I was lazy, depressed and just not very good at things. Finding out I had a genetic disease helped me understand a whole set of symptoms under that diagnosis. Getting a formal diagnosis also allowed me to educate myself on how to manage my mito symptoms, which has improved my health and enabled me to keep working. Overall, this improved my quality of life, my access to support and understanding from my employer. It led to a huge improvement in my mental health.

Adult with mito

Mito community members without a genomic diagnosis tell us they have to convince health professionals of their clinical diagnosis and that this not only prevents them from accessing the health care they need, but takes an emotional toll.

> Not having a confirmed diagnosis of mito is extremely frustrating and debilitating. I live with a constant doubt about the underlying cause of my symptoms. When I see doctors I always have to say "I think…" or "I believe…" about my mito. Often they don't believe me, they think I have been on Dr Google and am making it up. On top of my mental fatigue, this is just exhausting.
>
> Adult with undiagnosed mito

Kat and Noah's story (see *Appendix 1*) provides another example of the mental strain of an uncertain diagnosis. Before her son's genomic diagnosis, it was suggested that Kat had Munchausen syndrome by proxy.

> From a very selfish point of view, (after the genomic diagnosis), I stopped feeling bonkers and like that somehow I had made something up and somehow I've missed that part of my own psyche and questioning that constantly.
>
> Parent of a child with mito

For mito community members with a definite clinical diagnosis, the promise of genomic testing is valued to remove the remaining uncertainty:

> There are some symptoms that don't quite match the (clinical) diagnosis. A genetic diagnosis will give us more certainty and peace of mind, to really know that the diagnosis is correct.
>
> Spouse of an adult with mito

One family shared with us that the emotional challenges extended to their children:

> Our children have been through trauma linked to my wife's symptoms and mito. During that period of time when my wife was not able to move it really impacted them and we weren't able to offer much re-assurance as we didn't know what was going to happen. Now that we know it is mito we can answer their questions and get help from Mito Foundation. One example of this was when they each took the Mito Foundation picture book to school to explain why their Mum wasn't able to come to birthday parties or other events.
>
> Spouse of an adult with mito

2. The value of knowing: Improving access to non-health supports

Mito community members who have received a genomic diagnosis of mito tell us that the definitive nature of the diagnosis is helpful in accessing health, disability, workplace and education supports.

> Once my kids had a formal diagnosis of mito, we were able to access a whole range of supports that we couldn't get previously. During the time that their records said 'suspected mitochondrial disease' we couldn't get allied health services at the hospital, we couldn't get disability supports and we couldn't get help at school for them. That piece of paper with the gene test result was the deciding factor to get support and get support for them at school.
>
> Without a diagnosis we are just two annoying parents with a child with a range of non-specific issues. With a diagnosis we can ask them to provide the supports they need and to follow the best medical advice.

Parent of children with mito

Recent Australian research reports on the significant burden mito community members face in negotiating for access to health and social care(3). A genomic diagnosis of mito can make this a little easier.

3. The value of knowing: Making decisions based on improved understanding of prognosis

Although natural history data for mito is limited, what is known can support care decisions.

> Once I had a confirmed diagnosis of mito I had answers as to why I couldn't do things, why I was like that. My doctor explained that with mito I was unlikely to be able to do those things again and that while things can go slowly with mito, they can also suddenly get worse.
>
> Because of that information, I made the decision to go into a nursing home. It was a really good decision for me.

Older adult living with mito

> If we hadn't had his mito diagnosis confirmed, we wouldn't have put him in a wheelchair in the same way, we'd have still being trying to push him to move and walk and all of that stuff, which we know now causes huge consequences.

Parent of a child with mito

Genomic diagnosis supports mito research progress

Increasing numbers of Australians with a genomic diagnosis of mito can support both natural history and treatment research, leading to two key patient benefits:

1. Enabling access to emerging therapies, including through clinical trials
2. Growing knowledge on prognosis

1. Research: Enabling access to emerging therapies, including through clinical trials

There has been an exponential expansion in the development of new pharmacological and non-pharmacological treatments for mito, including an unprecedented period of gene therapy development(4,5). More than 130 clinical trials involving pharmacological intervention in the treatment of mito have been registered publicly on Clinicaltrials.gov.

In many cases, to be eligible for a clinical trial, patients need to have a confirmed genomic diagnosis of mito and present early in their disease progression. Early genomic diagnosis is key to ensuring Australian patients have equitable opportunities to access emerging therapies through clinical trial participation. Increased numbers of genomically diagnosed patients make Australia more attractive for site selection in international clinical trials.

The Australian Government invests significantly in clinical trials through the Medical Research Future Fund (MRFF) and through National Health and Medical Research Council (NHMRC) funding. This includes $614.2 million MRFF funding over 10 years to increase clinical trial activity in Australia, with a focus on rare cancers, rare diseases and unmet needs(6). The NHMRC provided $74.2 million in funding towards clinical trials in the 2020-21 financial year(7). The economic benefits of clinical trials have been widely reported(8,9).

There have been over 182 interventional clinical trials for mito(4). Less than 10 of these trials have Australian sites. Only one industry sponsored trial has established sites in Australia. This means Australian patients are effectively unable to access these medicines and there is no Australian data for any future regulatory approvals or reimbursement.

Being able to participate in clinical trials is important to the mito community:

> We have found one study that we're not eligible for. We might be eligible if we had a genetic diagnosis. That's pretty disappointing and frustrating.

Adult with mito

> If I am properly diagnosed, I know I will be on the books. If there are research trials in the future, I might be able to be part of that research or be able to access those treatments.

Adult with possible mito

2. Research: Growing knowledge on prognosis

Mito community members tell us that one of the hardest parts of living with mito is the uncertain future. More research is needed to build the natural history data for different types of mitochondrial disease. More people with mito having a genomic diagnosis will play a key role in building this knowledge.

One family told us how important prognosis was for them:

> After we understood the type of mito my daughter had I was desperate for information about other children with the same condition. I managed to find five other children around the world with a mutation on the same gene as my daughter. That was informative.
>
> One of the worst parts was that doctors had to give us their best guess on what the future would hold. They told us she had probably ten years, but we only got two. I feel robbed. I wish they could have been more precise.
>
> I would love to be able to have my daughter's story inform a future child's experience with mito. If research could help us understand her particular type of mito that would be a meaningful legacy for her to leave behind.
>
> Parent of a child who had mito

The mito community experiences minimal harms from diagnostic genomic testing

Receiving a diagnosis of mito is not always positive. The mito community shares with us that finding out they have a rare condition can be very isolating. There is grief involved in discovering that mito have been passed unknowingly through a family.

> I think of mito as a very lonely condition. Although I was relieved to know what it was, I am still processing that there is no cure and no one knows about it

Adult with mito

Harms from knowing has not been a theme of our discussion with the mito community. Mito community members who have a genomic diagnosis describe how valuable this was:

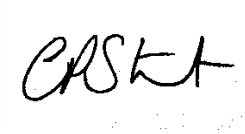
> Having a definite diagnosis, even if it's not what you want to hear, is way more beneficial to the person with mito, because the uncertainty is far worse.

Parent of a child who had mito

Further information

Please do not hesitate to contact me for further discussion regarding this application: clare.stuart@mito.org.au or 0410 685 181.

Yours sincerely,



Clare Stuart
Policy and Advocacy Manager

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Appendix 1: Noah and Kat's Story:

This story illustrates the impact of having an uncertain diagnosis and provides several examples of how care can change after a confirmed diagnosis of mito.

Noah started having symptoms of mito when he was a baby. Noah was seven before a genetic test finally showed he had mito. In the intervening time, his Mum, Kat, was accused of poisoning her baby and Noah's health deteriorated due to inappropriate care.

> We fought and fought for an MRI when Noah was two. That showed bilateral symmetrical brainstem damage, indicative of a mito condition, but no one really knew what. And then it took another two years of fighting to get a muscle biopsy. And that muscle biopsy showed no results for Noah. The change in Noah's care was catastrophic to the point where Noah nearly lost his life. Because some of the treating physicians said it was now only my opinion that things were happening.
>
> And so they just diminished care, stopped listening, stopped paying attention. Noah's condition continued to deteriorate at quite a rapid rate. Noah was living most of his time at the hospital because he was so unwell, he was on total parenteral nutrition and he couldn't eat any food.
>
> Every time Noah went into hospital, they were convinced it was me. We were put in video rooms, they would watch us and I would say "I hope it is something I'm doing because then it's fixable!" I'm an intelligent person - how am I getting this so wrong? Am I not cleaning something I should be? I asked them to send a social worker to the house. I said "Come and see, am I washing bottles wrong?".
>
> They didn't find anything. They made him so unwell that they put him in high dependency because obviously it was mito and not anything I was doing. And so it was only at that point once they'd made him so catastrophically unwell they were like, "oh, it isn't you."

Kat, Mum to Noah, who has mito

A new health care professional advocated for a genetic test and put in place management plans that assumed Noah had mito. The difference was incredible.

> They stopped using certain medications that were exacerbating issues. Noah was having a lot of general anesthetics (GA), and they started to use the mitochondrial protocol, they started to not fast him. As a result, instead of Noah being very desperately unwell after each GA, and all sorts of horrendous consequences, he started to fare better in those circumstances, because they followed mito protocols.
>
> From the day we got the genetic diagnosis, the change in the physicians was off the charts. Everybody was now willing to help. Everybody understood that this was an actual thing. Everybody started to pay attention. Noah is alive because we have that genetic diagnosis. Because otherwise everybody would have kept pretending it wasn't happening. He would have diminished and declined.

Kat, Mum to Noah, who has mito

Kat shared other examples of how, even thought there was no targeted therapy for Noah's mito, having a genomic diagnosis improved his life.

> One thing they've tried with Noah with his stroke like episodes is to give him this type of amino acid formula into his IV when it starts happening. This has meant that he's gone from 22 weeks in hospital on average, when he has a stroke like episode to now six weeks, like one is half your life one is a little blip. This difference is absolutely life changing.
>
> We have met with a lot of people that say "Well, you can't fix it." Yeah, but we can change his quality of life. We can pay attention to what we are doing that is making a huge difference. Blended diet for Noah, food for Noah, all of the research around that specifically for mitochondria and feeding real food as opposed to formula. There's so many layers to what is possible, not fixable or treatable, but to be able to have longevity and have a peaceful, calm version of your life, rather than this hectic, horrible hospitalization and it being chaotic and painful.
>
> Noah had a metabolic stroke. And overnight, he lost vision in his eye. Now, two weeks before the genetic diagnosis, the doctors said "that can't have happened. You must have missed it." I would say "Well, he did and that did happen." And then as a result of having a genetic diagnosis, the doctors will now say "yeah, that's a mito thing that can happen as a result of this, this and this." And so instead we got treatment plans, if there was any for that particular version of whatever was happening for Noah, or - And whilst this sounds awful, even when there was no treatment and no cure for that, particularly, at least we knew. And at least it wasn't something that was we were trying to fight to find another reason for.

There were also other benefits of knowing that Kat explained:

> From a very selfish point of view, (after the genetic diagnosis), I stopped feeling bonkers and like that somehow I had made something up and somehow I've missed that part of my own psyche and questioning that constantly.
>
> Because (the genomic diagnosis) totally changed how all physicians treated us, I now know that Noah is safer when I take him to a hospital. If I walk into any hospital all around the world, I can say "This is what he has. And this is what he needs." And it's believed and it's noted and it's understood.
>
> Even in among our friends, they have a focus, like the Bloody Long Walk (a Mito Foundation fundraising event) now they can help, nobody wants to feel helpless, no one on earth. And so giving people a reason and a way forward, whatever that looks like in many different forms is helpful for everyone.
>
> Also, now we can talk to Noah about his battery, so it also helps him take autonomy for his condition and make the choices he wants to make. He is 12, he does get to choose. So if that's going hard, and then falling over, you get to choose, but at least he knows what that is and why that is instead of just not understanding why that would happen.
>
> I'll say to his friends when Noah has another symptom, or another thing happening, I'll just say "Noah is like this today, it's a mito thing," and they go, "okay."

Kat, Mum to Noah, who has mito

Appendix 2: Dion's story

We were just like any other couple expecting their second child: excited and perhaps a little more confident than the first time round when we welcomed our little girl Erin into the world a couple of years previously. We dreamt about his first day at school, about teaching him to ride a bike and what he'd want to be when he grew up.

Dion was a perfect little package when he arrived. He was born into a doting family and had the world at his tiny feet. When Dion reached 8 months, we realised that something was wrong and after many exasperating visits to various doctors and specialists, Dion was diagnosed with Leigh syndrome, a fatal type of mitochondrial disease, for which there is no cure. At just three years old, Dion succumbed to Leigh syndrome, after a brave and inspiring fight.

We talk about Dion all the time. We'll always have that person missing at the Christmas table. We'll save a spot for him and put his star on the Christmas tree.

The loss of a child is perhaps the hardest thing anyone can experience, but we picked up the pieces of our lives and tried to move forward. I fell pregnant again but this unborn baby was also diagnosed with Leigh syndrome. We made the heart-wrenching decision to terminate the pregnancy. We wanted to try again for another child, but did not to risk him or her having to suffer the pain and debilitation of Leigh syndrome. So we decided try in vitro-fertilisation and pre-implantation genetic diagnosis. We identified the gene change that my husband and I carried that caused Dion's Leigh syndrome. We were able to test the embryos for a defective copy of the gene.

On the 18th November 2011, I gave birth to a beautiful, bouncing – and most importantly disease-free – little boy. Thanks to advances in science and to the big brother he'll never meet, Levi is growing into a happy, healthy little boy with his whole life ahead of him.

More recently, my eldest daughter went through genetic counselling to understand her own risk of having a child with mito. It was a relief to have this testing available to her. I look forward to having this testing available to all Australians.

Tracey, Mum to Dion, who lived with Leigh syndrome

Appendix 3: Kathy's Story

Kathy asked us to share her story to explain what life with mito is like and what genomic testing means to her.

I have suspected Mitochondrial Disease and first developed symptoms as a young child and am now 55. My journey has been long, frustrating and at times cruel, and impacted every area of my life.

On living with mito

Every day I live with significant fatigue, muscle weakness, stiffness and pain. I find it difficult to accomplish even small tasks.

My weeks are filled with numerous appointments such as physio, exercise programmes, speech therapy and visits to specialists.

I have a severe breakdown of my core muscles making it difficult to stay upright for long. My diaphragm muscle is very stiff and tight making breathing difficult. My back is extremely stiff and tight making sitting uncomfortable, and even when lying down, my back is unable to relax into a mattress.

I'm often nauseous and vomiting is very unpleasant due to the tightness of my diaphragm muscle, and usually involves fainting and choking.

My mobility and balance are also affected and I have a fluctuating cognitive decline. As well as this I live with visual disturbances and some hearing loss. Also episodes where the right side of my body becomes weak and occasionally I find myself drifting in and out of consciousness.

The psychological impact of living with this is huge and not having a confirmed genetic diagnosis and therefore a specific treatment plan adds to this load. I have felt alone on this journey and as the years go by it is harder to keep going.

The consequences of uncertainty

Living with such significant symptoms without a clear genetic diagnosis has been very challenging for me and my medical treatment has often been compromised as a result. I have often been placed in the too hard basket, had my emotional stability questioned, had to live with a trial and error approach to treatment, and had to pay a high cost for inappropriate physio programmes over many years.

One example of this is when I was given a diagnosis of chronic fatigue. I was prescribed anti-depressants to treat this condition that I didn't have. My throat swelled due to these medications. An earlier diagnosis could have avoided this.

Recently I was at the emergency department as I was unsure if I was having a stroke like episode related to my mito. My neurologist and my GP had both told me the call an ambulance when I had these symptoms. The doctor that was on call repeatedly finished his discussions with me by adding "… and that's if you do have mito". This happened around six times. It made me feel hopeless. It told me that there was no point being there, that no one was going to listen to me. I wasn't going to be given appropriate consideration, let alone appropriate treatment. It also brought up traumatic experiences from before I even had the provisional diagnosis of mito- when people would not take me seriously and questioned my mental health.

As a result of an abnormal brain scan I was given IV steroid treatment, as my neurologist at the time believed I may have systemic lupus erythematosus. My body struggled to deal with this treatment, and is a good example of the trial and error approach often used.

The highest cost to me over the longest period of time has been inappropriate physio treatment and exercise programmes. Although my limbs have been significantly affected by this condition, it is my trunk that has been impacted to a greater degree. It was common for health professionals to tell me that they knew of no condition that could affect me in this way, and would consequently brush me aside. I have a diagnosed severe breakdown of my core muscles which is a lot like being a house with a crumbling foundation. I struggle to stay upright for long, my diaphragm muscle is very tight and I experience painful diaphragmatic muscle spasms and difficulty breathing. I need my diaphragm muscle, intercostal muscles and thoracic spine released weekly by my physio to assist with breathing and to make me more comfortable. This has been a positive physio experience for me.

A lot of what I live with daily could have been avoided by a genetic diagnosis, which would have led to more timely and appropriate treatment and understanding. Instead, physio treatment exacerbated the symptoms. The physios had no idea. They pushed me beyond the exercise limitations that a person with mito should stay within– I just crashed and got worse.

Having a genetic diagnosis wakes people up to the fact that there is an underlying cause and they will take you seriously. I believe I would have found physiotherapists that either knew about mito or were willing to learn. I could have learnt more myself and passed that information onto physios. I could have gotten the treatment I needed at least 20 years earlier.

What a genetic diagnosis would mean to me

Peace of mind after years of uncertainty and a huge weight off my shoulders. Even though I have numerous medical reports and test results to confirm my symptoms, I feel it would validate what I have suffered. Having knowledge of the specific genes affected would lead to clarity and direction in my care and would assist my neurologist, endocrinologist and others in the team that care for me to form an appropriate treatment plan. It would be useful in planning treatment for the future. At present if I end up in an emergency situation it is unlikely I will receive appropriate help, but with a genetic diagnosis, it will be easier to pinpoint and treat problems.