COMMERCIAL IN CONFIDENCE

FINAL REPORT

Preventable burden of mito

Reducing the cost and providing benefits to people with mitochondrial disease and their communities

Prepared for
Mito Foundation

5 April 2024

THE CENTRE FOR INTERNATIONAL ECONOMICS
www.TheCIE.com.au

The Centre for International Economics is a private economic research agency that provides professional, independent and timely analysis of international and domestic events and policies.

The CIE's professional staff arrange, undertake and publish commissioned economic research and analysis for industry, corporations, governments, international agencies and individuals.

Creative Commons license

ISBN 978-1-763522817

Cataloguing data

This publication (and any material sourced from it) should be attributed as: *Preventable burden of mito: Reducing the cost and providing benefits to people with mitochondrial disease and their communities – April 2024, The Centre for International Economics. CC BY-NC.*

Clearly identify any changes or adaptations you have made to the work and abide by the other licence terms.

CANBERRA
Centre for International Economics
Ground Floor, 11 Lancaster Place
Canberra Airport ACT 2609

Telephone +61 2 6245 7800
Facsimile +61 2 6245 7888
Email cie@TheCIE.com.au
Website www.TheCIE.com.au

SYDNEY
Centre for International Economics
Level 7, 8 Spring Street
Sydney NSW 2000

Telephone +61 2 9250 0800
Email ciesyd@TheCIE.com.au
Website www.TheCIE.com.au

DISCLAIMER

Contents

BOXES, CHARTS AND TABLES

Summary

Primary mitochondrial disease ('mito') is debilitating and potentially fatal, reducing the ability of the mitochondria to produce energy to sustain life.

Around 1 in every 200 Australians have mitochondrial genetic mutations. Some of those with symptoms are undiagnosed, and unaware of how to manage their care. Around 1 in every 4300 Australians develop clinically overt disease, which dramatically changes their lives, and those around them, forever.

The Mito Foundation has commissioned The Centre for International Economics (CIE) to provide economic evidence about the preventable burden of mito disease in Australia to help understand the greatest challenges faced by people with mito, and the opportunities to intervene to make peoples' lives better.

This analysis draws on evidence about the costs of mito that are preventable to help identify strategies to achieve better outcomes for patients, families, and the wider community. We are grateful to the contributions of mito health professionals we consulted with, mito community members including those who provided case studies, and the support of the Mito Foundation.

Australian population and costs of mito

Mito costs Australia over $1 billion each year.

The biggest cost of mito is the lost quality of life from premature death or living with pain and disability, accounting for 80 per cent of total costs.

- Mito is sometimes **fatal**, particularly for childhood onset, with an annual mortality rate of 3.0 per cent for children and 1.6 per cent for adults. In 2022, we estimate that 10 children and 70 adults died due to mito, with a cost to Australia of **$435 million**.
- Living with mito can have severe **negative quality-of-life** impacts due to limitations of physical problems and lack of vitality. We estimate that **lost quality-of-life for people living with mito** in Australia in 2022 was 1805 Years Lived with Disability (lost years of better health), with that lost quality-of-life **valued at $424 million**.

In 2022, 345 children and 4283 adults lived with clinically overt mito, for whom this rare disease has challenged every aspect of life, including work, study, and play, and the time, energy, and financial resources available to live the rest of their lives.

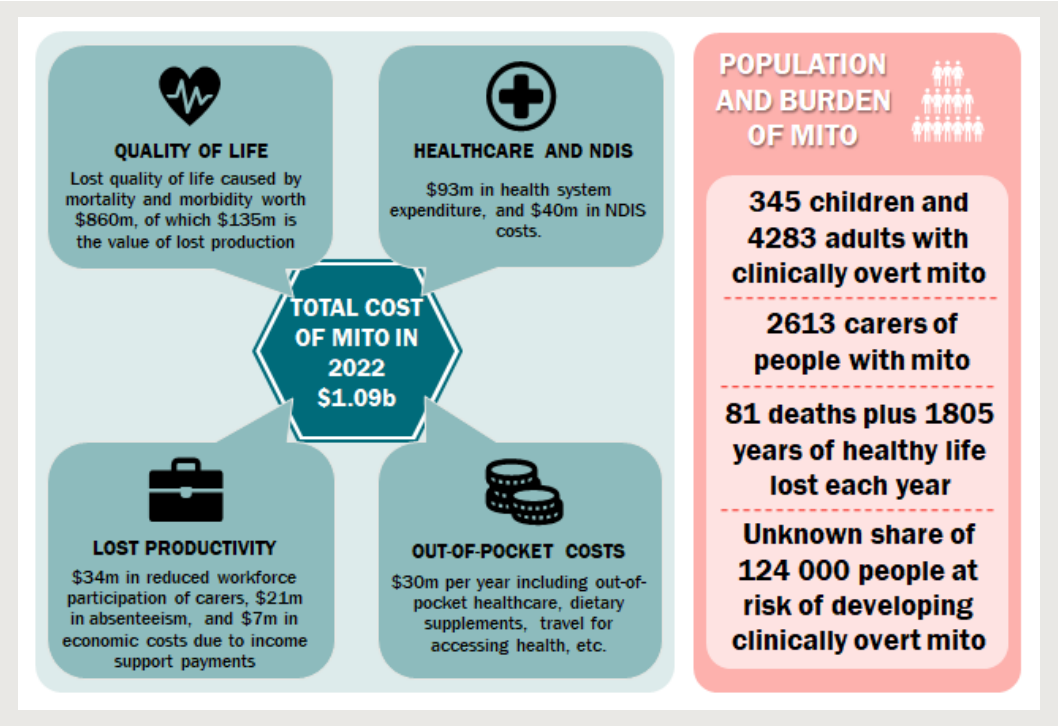
Another 124 000 Australians have a genetic risk factor for mito. An unknown proportion of these may have experienced symptoms of mito and are at risk of deteriorating health and wellbeing, particularly when they are not diagnosed. This can also mean they are missing out on preventative or early intervening care.

The second most substantial cost of mito relates to reduced workforce participation and productivity while at work, unplanned absences from work, and reduced educational attainment. People with mito and their carers often stop working or reduce their working hours, reducing total hours of work by people living with mito and their carers by 51 and 23 per cent, respectively. Deaths due to mito also result in lost productivity over a lifetime. Ill-health, deaths and absenteeism due to mito in 2022 caused a combined **productivity loss of $196 million**.[1]

Mito also burdens patients and their families with **out-of-pocket costs of $30 million** per year, and costs to the National Disability Insurance Scheme **(NDIS) of $40 million** per year.

The total cost of mito in 2022 is estimated to be $109 million for children and $976 million for adults (table 2).[2]

1 Overview of the population, burden, and costs of mito in Australia



Data source: CIE.

1 Note that $135 million of this is also counted within lost quality-of-life.

2 This is the cost of costs borne in 2022 due to people having mito, plus the value of lost quality-of-life due to deaths from mito in 2022. This is a standard approach to estimating the cost of disease each year, being the sum of costs due to morbidity and mortality in a single year.

2 Total cost of mito in Australia

Cost category	Child	Adult	Total
	$m/year	$m/year	$m/year
Quality of life and productivity lost: mortality			
Value of lost production	2	22	24
Remaining value of lost quality of life	53	358	411
Subtotal	**55**	**380**	**435**
Quality of life and productivity lost: morbidity			
Value of lost production	0	110	110
Remaining value of lost quality of life	32	283	314
Subtotal	**32**	**393**	**424**
Total healthcare cost	12	81	93
Reduced workforce participation among carers	5	29	34
Absenteeism	0	21	21
Out-of-pocket cost	2	28	30
Economic loss associated with reduced welfare payments	0	7	7
Total NDIS packages	4	37	40
Total	**109**	**976**	**1 085**

Note: All values are in 2023 dollars. Totals may not sum due to rounding.

Source: CIE.

Opportunities to reduce the burden of mito

Australia has recently made two significant changes that will combat some of the costs of mito:

- legislation for and funding of the pilot study of mitochondrial donation to prevent future cases, and
- the commitment to a genomics first approach to diagnosis through funding of whole-genome sequencing through Medicare, which means patients with mito can get earlier, preventative care and avoid years of diagnostic uncertainty and symptom burden.

However, more needs to be done for people with mito to reduce the burden and costs of the disease.

Offering reproductive choices can prevent future cases of mito and avoid the symptom burden.

Improved access to reproductive options will provide people who are at risk of having a child with mito increased choice. Reproductive carrier screening, earlier diagnosis of mito and cascade testing can all play a role in increasing the number of families who know they are at risk. They may then choose to use options such as mitochondrial donation, pre-implantation genetic testing, pre-natal testing, or egg donation to reduce their risk.

We estimate that for each case of mito avoided there would be an avoided cost of $3.0 million over the person's lifetime.

The number of parents who would choose to use reproductive options, thereby preventing cases of mito, is uncertain. If, with these choices, 20 cases of mito were avoided, this would reduce the burden of mito by $60.9 million per year.

More timely diagnosis could reduce costs by $20 million per year.

The extensive and delayed process of diagnosis (the 'diagnostic odyssey') spans an average of 6.4 years for adults and 1.8 years for children, resulting in poorer physical and mental health for people with mito. It also generates inefficient and often unnecessary health costs, estimated at $17 million for 2022, and imposes productivity costs of $3 million. Genomic testing of children is demonstrated to result in cost savings relative to conventional care, with greater diagnostic yield and better clinical management. It also ends diagnostic uncertainty, which is harmful to the mental health of people with mito and their families and carers. There is a 'value of knowing' provided by testing, with parents of children with suspected mito willing to pay $2918 for genomic testing.

Providing better health and other care for people with mito can improve quality of life, improve work participation, and reduce loneliness.

The majority of people with a genetic risk factor for mito are currently asymptomatic and are not getting mito-specific care. For some, this care may be valuable by preventing serious symptoms from developing in the future. Valuable preventative interventions set out in the Patient Care Standards[3] include:

- avoiding environmental and other noise exposure which exacerbates hearing loss
- use valproic acid to minimise seizures that precipitate liver failure, especially in patients with *POLG*-related disease, and
- engage in regular physical activity to increase energy production to improve symptoms of exercise intolerance and fatigability.

Clinical research offers potential for future treatment. Ensuring timely access to new treatments could substantially reduce or avoid the burden of mito, which currently costs $3 million per person over a lifetime.

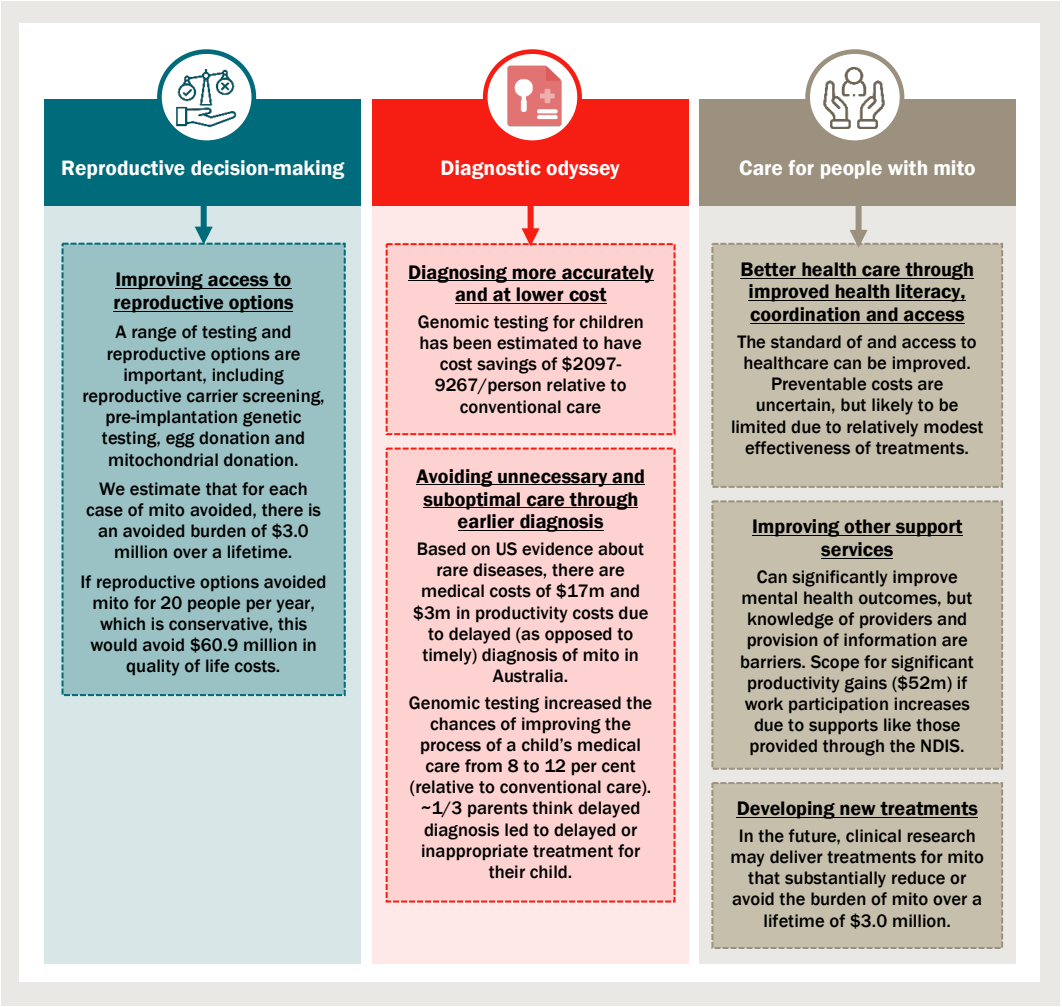
Many people with mito have unmet needs for other support services. For example, 24 per cent of people with mito, and 13 per cent of carers, have a need for disability support but have not applied. If people with mito and their carers who quit work due to mito instead reduced their work hours by 50 per cent, this would boost productivity by $52 million.

---

3 Sue, C.M., Balasubramaniam, S., Bratkovic, D., Bonifant, C., Christodoulou, J., Coman, D., Crawley, K., Edema-Hildebrand, F., Ellaway, C., Ghaoui, R., Kava, M., Kearns, L.S., Lee, J., Liang, C., Mackey, D.A., Murray, S., Needham, M., Rius, R., Russell, J., Smith, N.J.C., Thyagarajan, D. and Wools, C., 2022, 'Patient care standards for primary mitochondrial disease in Australia: an Australian adaptation of the Mitochondrial Medicine Society recommendations', *Internal Medicine Journal*, 52(1): 110-120, doi: 10.1111/imj.15505

Without a cure for mito, greater focus on preventable costs is needed to improve the life of those living with, or at risk of, the poor and debilitating health effects that mito can mean.

3 The preventable costs of mito



Data source: CIE.

Research qualifications and limitations

The existing evidence base is not comprehensive in terms of measuring the population with mito or its costs, with notable limitations relating to:

- the productivity impacts of mito
- impacts of treatment on the burden of mito, including quality-of-life impacts, and
- quantitative evidence about how community understanding and support affects mental health.

As a result, the estimated costs of mito presented in this report are high level estimates, with their purpose being to facilitate prioritisation of strategies to mitigate the preventable burden.

This study is focussed on measuring the burden of mito, and the size of potentially avoidable costs. This report has used a series of case studies to illustrate some of the key impacts of mito and share some of the real-life stories that lie behind the numbers in this report. This study also relies on calculating averages across the diverse mito community, but readers should keep in mind that experiences of mito differ very widely.

1 About this study

About mito

Mitochondrial disease ('mito') is a debilitating and potentially fatal disease reducing the ability of the mitochondria to produce energy to sustain life. It has many different manifestations and a wide range of symptoms, posing challenges for diagnosis and treatment.

In this report, mito refers specifically to primary mitochondrial disease (PMD) and not secondary mitochondrial disease (SMD). This is consistent with the definition of mito used by Mito Foundation. Classification of primary and secondary mitochondrial disease is based on whether mutations in genes related to oxidative phosphorylation (PMD) or not (SMD) elicit the disorder.[4]

Impact on health status

The symptoms of mito vary between individuals and affect multiple systems in the body. Fatigue and muscle weakness are common symptoms, typically managed with exercise therapy. Groups of mito symptoms include:

- Audiology — hearing loss is experienced by around half of patients and requires regular monitoring, and often hearing aids and cochlear implants
- Cardiology — 50 per cent of adults and 40 per cent of children have cardiac involvement, requiring annual electrocardiograms
- Critical care — people with mito are vulnerable to acute cerebral events and cardiopulmonary failure
- Endocrinology — common presentations include diabetes, thyroid, parathyroid and short stature, requiring screening and assessment for diabetes or insulin resistance
- Gastroenterology — mito causes gastrointestinal tract dysmotility, swallowing and bulbar muscle weakness and liver failure
- Haematology — in more rare cases, mito causes conditions such as sideroblastic anaemia, requiring haematology management
- Immunology — patients with mito take longer to recover from infections and are at greater risk of sepsis. Approximately one third of patients have a documented immunodeficiency
- Nephrology — mito is associated with asymptomatic kidney disease and reduced glomerular filtration rate, proteinuria and/or haematuria, metabolic acidosis, renal

4 Valenti, D. and Vacca, R.A., 2022, 'Primary and secondary mitochondrial diseases: Etiologies and therapeutic strategies', *Journal of Clinical Medicine*, 11(14): 4209, doi: 10.3390/jcm11144209

tubular acidosis, focus segmental glomerulosclerosis, progressive renal and rapid progression to renal failure

- Neurology — including seizures, stroke-like episodes, encephalopathy, headaches, movement disorders, muscle weakness and neuropathy. Some are life-threatening, and developmental delay is often observed in children
- Ophthalmology — progression vision loss is the most common presentation of mito
- Pregnancy —pregnancies are high-risk, and patients are referred to a specialised mito clinic or clinician. Prenatal and pre-implantation genetic diagnosis is available in Australia to inform family planning decisions.
- Psychiatry — depression and anxiety are very common in adult patients with mito
- Respiratory — respiratory function can be impaired by various other symptoms, and can be exacerbated by diaphragmatic weakness, obstructive sleep apnoea, infection, cardiac failure and so on, and
- Surgery — various surgical procedures are often needed, such as muscle biopsy and gastrostomy placement, and managing musculoskeletal complications.

Patients normally require management by a multidisciplinary team, mainly in tertiary hospitals, and all patients are encouraged to eat a healthy nutritious diet, often with supplements[5].

Scope of this review

The Centre for International Economics (CIE) has been commissioned to provide economic evidence about the preventable burden of mito. The aim of the project is to support the Mito Foundation in demonstrating the value of timely and appropriate diagnosis and improving quality of care provided to people with mito.

Method overview

Our approach involved:

- review of the evidence relating to prevalence, health system costs, the value of knowing, reproductive decision-making, quality of life impacts for adults and children, productivity impacts, and caring responsibilities related to mito
- development of an outcomes framework that is comprehensive and relevant to understanding the varied experience of mito, the burden, and preventative burden of the disease, and the way a person's experience impacts on the wider community and economy
- consultation with experts including the Mito Foundation and mito community members,

[5] Ibid.

- development of a high-level estimate of the costs of mito relating to the current mito population and their variable care needs,[6] and
- estimation of the preventable burden of mito, when diagnosis, treatment, and care can be delivered in a way that improves the lives of those living with disease.[7]

Limitations and qualifications

Our analysis relies on collating and interpreting existing evidence about the impacts of mito through an economic modelling framework, supplemented by consultation with experts. Further, the existing evidence base is not comprehensive in terms of measuring the population with mito or its costs, with limitations relating to:

- population with mito, as distinct from the broader population with mtDNA mutations, particularly in terms of the age distribution and phenotypes
- productivity impacts of mito
- impacts of treatment on the burden of mito including quality-of-life impacts
- depth of Australia-specific evidence
- differences in the population and impacts depending on age, sex, and other demographic characteristics, and
- quantitative evidence about how mental health is affected by community understanding and support.

Despite these limitations, summarising and integrating the current evidence in this economic analysis provides an opportunity to ensure that strategies to mitigate the preventable burden are appropriately prioritised.

Framework for understanding impacts

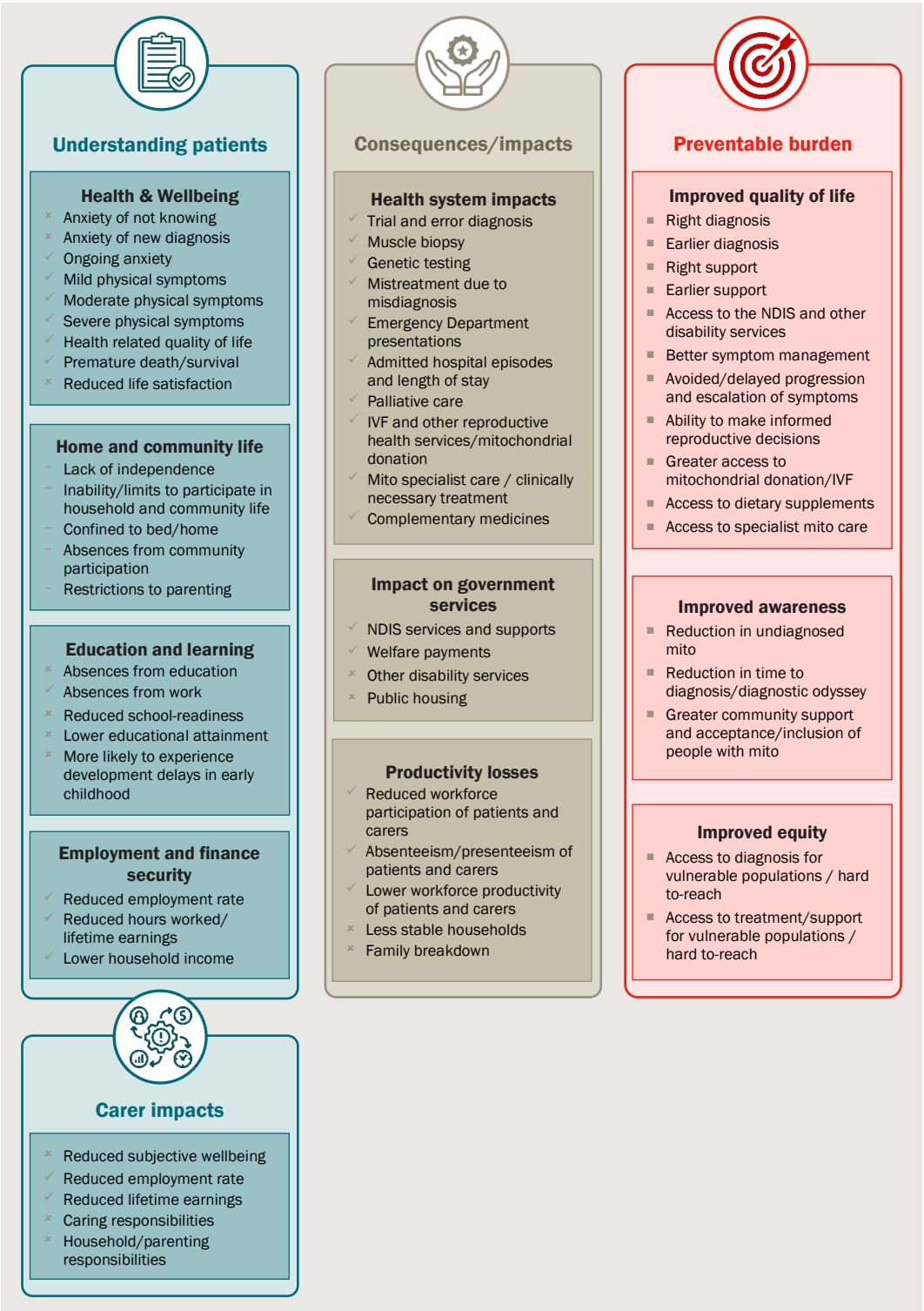
We, in conjunction with members of the Australian mito community and Australian professionals, developed a framework for understanding the experience of people with mito. This involves categorising aspects of the experience of mito into domains, identifying the system and economic impacts of the experience, and then identifying aspects of the burden which are preventable (chart 1.1). This framework is more comprehensive than the impacts we measure, which is limited by the available data.

---

6 This does not represent a comprehensive 'Cost of illness' study, which is under development through the MitoMOD project, see Schofield, D., Lim, K., Tan, O., Shrestha, R, Haque, S., Crawley, K., West, S., Percival, A., Parmar, J., Kraindler, J., Li, J., Tanton, R., Sue, C., 2022, 'The Development of a microsimulation model (MitoMOD) to estimate the economic impact of mitochondrial disease in adults', *International Journal of Microsimulation*, 15(2): 103-111, doi: 10.34196/ijm.00265

7 This project calculates the cost of mito using a prevalence-based approach that calculates the economic impact of all disease cases in 2022, together with any deaths attributable to mito occurring in that year. This aligns to the definition of a prevalence-based approach in: WHO, 2009, *WHO Guide to Identifying the Economic Consequences of Disease and Injury*, available at: https://iris.who.int/bitstream/handle/10665/137037/9789241598293_eng.pdf?sequence=1

1.1 A framework for understanding the burden of mito



Note: Ticks indicate an aspect of the patient/carer experience or consequences of mito has been costed, crosses indicate it has not been costed, while the '~' symbol indicates that it isn't explicitly costed but may be implicitly included in quality of life impacts. Note that health system costs are costed collectively, rather than individual cost categories being separately estimated.

Source: The CIE.

2 *Australian population with mito and burden of disease*

We estimate that 345 children and 4283 adults lived with mito in 2022, who were cared for by 2613 carers, including parents and spouses.

For these people, this rare disease has changed almost every aspect of life, including work, study, and play, and the time, energy, and financial resources to live the rest of their lives.

Mito is sometimes fatal, particularly for childhood onset. In 2022 we estimate that 10 children and 70 adults died due to mito, with a financial cost to Australia of $435 million.

The non-fatal burden of mito disease is also significant with often severe negative quality-of-life impacts. Reduced quality-of-life is mainly due the role limitations of physical problems and lack of vitality. We estimate that lost quality-of-life for people living with mito in 2022 was 1805 Years Lived with Disability (lost years of better health), with that loss valued at $424 million.

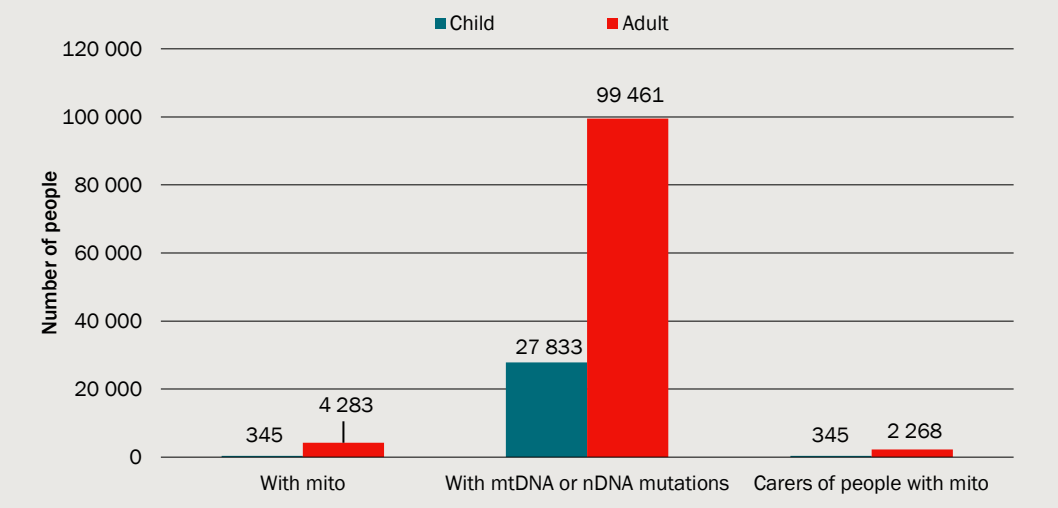
Population with mito and their carers

We estimate that in 2022[8] around 27 833 children and 99 461 adults carried a genetic mutation that could potentially lead to mito (chart 2.1). Of those, 345 children and 4283 adults have clinically overt mito, while the remainder are asymptomatic (having no symptoms) or oligosymptomatic (having few symptoms).

Many people with mito have carers, often parents, spouses, or formal carers. We estimate that there are 345 carers of children with mito and 2268 carers of adults with mito.

8 Most recent year for which data about the size of the general population is available by single-year age and sex from the Australian Bureau of Statistics (available at: https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/mar-2023).

2.1 Number of adults and children affected by mito in Australia



Data source: CIE.

The average time from onset of symptoms to clinical or genetic diagnosis is 1.7 years for children and 6.2 years for adults. We estimate that 13 per cent of children and 16 per cent of adults with mito are currently undiagnosed, based on the ratio of time from onset to diagnosis to number of years spent living with mito (see table 2.3). This means that around 85 per cent of people with mito in 2022 have a diagnosis, leaving 708 people with clinically overt mito but no diagnosis, most of whom are adults (table 2.2).[9]

2.2 Diagnostic status of people with mito in Australia

Measure	Child	Adult	Total
	Number of people	Number of people	Number of people
Diagnosed with mito	301	3 620	3 920
Currently undiagnosed with mito	44	664	708
With mtDNA mutations but without disease	27 488	95 178	122 666
Carers of people with mito	345	2 268	2 613
Total with mito	**345**	**4 283**	**4 629**
Total with mtDNA mutations	**27 833**	**99 461**	**127 294**
Total number with mito or who is a carer/spouse of someone with mito	**690**	**6 551**	**7 241**

Source: CIE.

These estimates rely on available data, estimates from the literature, and key assumptions as set out in table 2.3. These estimates are conservative. Further detail about the literature relating to prevalence is provided in Appendix A.

9 There are three 'states' of diagnosis. These are: people with clinical mito who have a diagnosis; people with clinical mito who are in the diagnostic odyssey (i.e. currently without a diagnosis, but will be diagnosed eventually), and; people with mtDNA/nDNA mutations causing some symptoms, but not at the level of clinical mito, who are undiagnosed. Our estimate of the undiagnosed population in conservative in that it doesn't include this third group.

2.3 Data and assumptions underpinning estimated population with mito

Measure	Children	Adults
Prevalence rate of mtDNA mutations	1/200 people, which is consistent with the prevalence assumption used in a recently published study (Schofield et al, 2022)[a], and we make the simplifying assumption that this rate is identical for children and adults [b]	
Prevalence rate of mito	6.2/100 000 people, based on Skladal et al (2003)[c], which implies that 1.24 per cent of children with a mutation have clinically overt disease.	1/4300 people, based on Gorman et al (2015)[d], which implies that 4.31 per cent of adults with a mutation have clinical disease
Share of those with mito who have been diagnosed	Based on an average of 13.3 years from onset of symptoms to end of childhood or death (whichever comes first) based on Eom et al (2017)[e] and Debray et al (2007)[f], and lead time to diagnosis of 1.7 years (Eom et al, 2017), we estimate 13 per cent of childhood years are spent undiagnosed, and thus 87 per cent of prevalent cases of disease have been diagnosed.	Based on an adult lifespan of 40 years[g] and average diagnostic period of 6.2 years (Rudaks et al, 2021)[h], estimate 16 per cent of those with mito are undiagnosed and 84 per cent of prevalent cases of disease are diagnosed.
Number of carers/spouses per person with mito	1 carer per child with disease[i]	0.53 carers per person with disease, based on the PEEK Study

[a] Schofield, D., Lim, K., Tan, O., Shrestha, R., Haque, S., Crawley, K., West, S., Percival, A., Parmar, J., Kraindler, J., Li, J., Tanton, R., and Sue, C., 2022, 'The development of a microsimulation model (MitoMOD) to estimate the economic impact of mitochondrial disease in adults', *International Journal of Microsimulation*, 15(2): 102-111, doi: 10.34196/IJM.00265

[b] Assuming the same rate of prevalence of mtDNA mutations ignores the higher mortality rate of children with mtDNA mutations (due to disease) compared to the general population, which would mean that mtDNA mutation prevalence decreases with age.

[c] Skladal, D., Halliday, J. and Thorburn, D.R., 2003, 'Minimum birth prevalence of mitochondrial respiratory chain disorders in children', *Brain*, 126(8): 1905-1912, doi: 10.1093/brain/awg170

[d] Gorman, G.S., Schaefer, A.M., Gomez, N., Blakely, E.L., Alston, C.L., Feeney, C., Horvath, R., Yu-Wai-Man, P., Chinnery, P.F., Taylor, R.W., Turnbull, D.M., McFarland, R., 2015, 'Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease', *Annals of Neurology*, 77(5): 753-759, doi: 0.1002/ana.24362

[e] Eom, S., Lee, H.N., Lee, S., Kang, H., Lee, J.S., Kim, H.D. and Lee, Y., 2017, *Pediatric Neurology*, 66: 82-88, doi: 10.1016/j.pediatrneurol.2016.10.006

[f] Debray, F., Lambert, M., Chevalier, I., Robitaille, Y, Decarie, J., Shoubridge, E.A., Robinson, B.H. and Mitchell, G.A., 2007, 'Long-term outcome and clinical spectrum of 73 pediatric patients with mitochondrial diseases', *Pediatrics*, 119(4): 722-733, doi: 10.1542/peds.2006-1866

[g] This is the approximate midpoint of the two life expectancy assumptions for adult-onset mito in Table 11 of the UK *Impact Assessment* (50 and 90, implying ~32 and 52 years since becoming an adult, respectively). We have rounded the midpoint of 42 to 40 for simplicity. See UK Department of Health, 2014, *Impact Assessment of Mitochondrial donation regulations*, available at: https://www.legislation.gov.uk/ukia/2015/9/pdfs/ukia_20150009_en.pdf

[h] Rudaks, L.I., Watson, E., Lubomski, M., Edema-Hildebrand, F., Ahmad, K., Liang, C., David, R., and Sue, C., 2021, 'The diagnostic journey of mitochondrial disease patients', BMJ Neurology Open 2021;3;doi: 10.1136/bmjno-2021-ANZAN.80

[i] There is upside risk to this number since for some children multiple people (e.g. two parents) may act as carers, but downside risk due to some families having one carer for multiple children with mito.

Source: As noted, CIE.

Mito covers a diverse range of conditions arising from different mutations of the mtDNA or nDNA. There is a distinction between the genetic mutation and the mitochondrial disease clinical syndrome, however, there is a correlation between mutations and clinical syndromes. For example, 80 per cent of individuals with MELAS have the m.3243A>G variant in the mitochondrial gene MT-TL1.[10]

10 El-Hattab, A.W., Almannai, M. and Scaglia, F., 2001, 'MELAS', *GeneReviews*, Feb 27 [Updated 2018 Nov 29], GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. available from: https://www.ncbi.nlm.nih.gov/books/NBK1233/

The most common types of mito in terms of disease prevalence (table 2.4) are:

- Leber Hereditary Optical Neuropathy (LHON) – usually non-fatal disorder associated with progressive visual loss,
- Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like episodes (MELAS) – fatal disorder that affects most systems in the body including the brain and nervous system and muscles,
- Myoclonic Epilepsy with Ragged-Red Fibres (MERFF) – fatal, childhood-onset disorder with symptoms including myoclonus (muscle twitching), seizures, impaired ability to coordinate movements, muscle weakness and exercise intolerance.

Many types of mito are rare to the point that we do not have a precise estimate of prevalence. For example, the m.8344A>G mutation, manifesting as MERRF, has prevalence of 0.2, which corresponds to only 5 people in the sample from Gorman et al (2015). Due to the sample size, the prevalence of rarer types of mito such as MERRF cannot be precisely estimated based on the data available.

The estimated prevalence of LHON from Gorman et al (2015) is more than twice as high as estimated by a recent study of prevalence in Australia (Sanchez, et al, 2021), which estimated prevalence of 1.5 people per 100 000 experiencing vision loss due to LHON.[11] We have relied on Gorman et al (2015) because it covers all types of mito within a single study.

2.4 Prevalence of mito by mutation among adults

Disorder	Prevalence rate
	Number/100 000
mtDNA mutations	
Primary LHON mutations	3.7
m.3243A>G mutation (most common mutation for MELAS)	3.5
Single large-scale mtDNA deletions	1.5
m.8344A>G mutation, manifesting as MERRF	0.2
Other mtDNA mutations	0.9
Total mtDNA mutations	**9.6**
nDNA mutations	
SPG7, ar	0.8
PEO1, ad	0.7
Other nDNA mutations	1.4
All nDNA mutations	**2.9**

11 This is a conversion of the minimum prevalence estimate reported by Sanchez et al (2021) of one in 68 403 to a rate per 100 000 people. Sanchez, M.I.G.L., Kearns, L.S., Staffieri, S.E., Clarke, L., McGuinness, M.B., Meteoukki, W., Samuel, S., Ruddle, J.B., Chen, C., Fraser, C.L., Harrison, J., Hewitt, A.W., Howell, N. and Mackey, D.A., 2021, 'Establishing risk of vision loss in Leber hereditary optic neuropathy', *American Journal of Human Genetics*, 108(11): 2159-2170, doi: 10.1016/j.ajhg.2021.09.015

Disorder	Prevalence rate
	Number/100 000
All mutations associated with mito	
Grand total	**12.5**

Source: Gorman et al (2015) table 2, CIE.

Burden of mortality and morbidity due to mito

Living with mito is a burden for people and their families, shortening life, and reducing the quality of life. The 'burden of disease' framework measures the compromised quality of life experienced by people with mito or those who die prematurely due to mito.

Burden of disease analysis quantifies the impact of health problems and premature deaths on a society. In a single year, the burden of disease is the extent to which disease has caused the nation's 'health capital' to be below 'healthy'. This burden can be split into:

- mortality, measured by the number of deaths or the number of Years of Life Lost (YLL), and
- morbidity, measured by the number of Years Lived with Disability (YLD), which is calculated by multiplying the number of people with disease by a 'disability weight', which captures the extent to which a disease reduces health-related quality-of-life. A disability weight takes a value between 0 (representing perfect health) and 1 (a state that a person considers equivalent to death).

There is an established literature measuring lost quality of life due to illness for hundreds of diseases[12], but there is no specific estimate for mito.[13]

Mortality due to mito

Mito can be fatal, and the mortality rate varies very significantly across conditions (chart 2.5). Keshavan and Rahman (2018)[14] conduct a systematic review of natural histories[15] of mitochondrial diseases. Some conditions are non-fatal (e.g. LHON), others have relatively low mortality rates (e.g. MERRF), and yet others have mortality rates of 50 per cent or more (e.g. MELAS).

---

12 Global Burden of Disease Collaboration Network. Global Burden of Disease Study 2019, (GBD 2019), Seatle, United States: Institute for Health Metrics and Evaluation (IHMA), 2020.

13 We expect that mitochondrial disease will fall under a range of disease categories used by GBD, such as 'other neurological disorders' and 'other vision loss'. It is noted that the value of mortality and morbidity using this approach includes the value of lost future productivity. Hence, these estimates should not be added to estimates of productivity losses, which are a subset of these values.

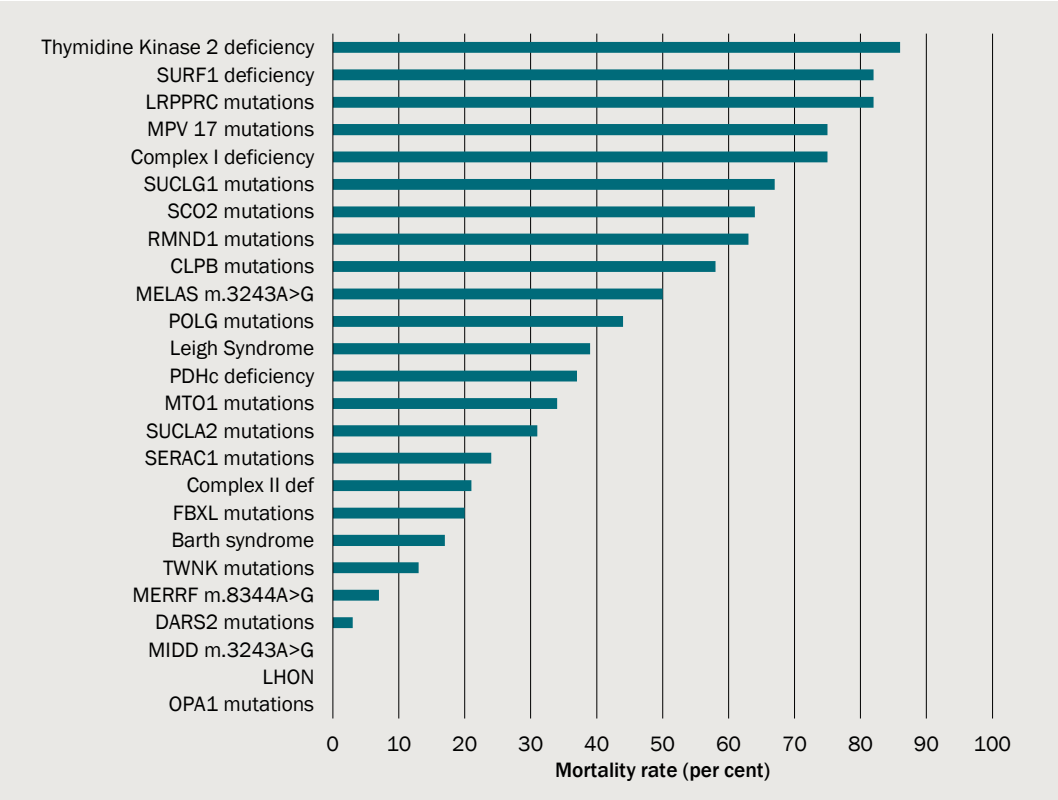
14 Keshavan, N. and Rahman, S., 2018, 'Natural history of mitochondrial disorders: a systematic review', *Essays in Biochemistry*, 62(3), doi: 10.1042/EBC20170108

15 As stated by Keshavan and Rahman (2018), "the natural history of a disease defines the age of onset, presenting features, clinical phenotype, morbidity and mortality outcomes of disease that is unmodified by treatments" (p.1).

Published data relating to mortality is relatively limited and may not be reliable for certain conditions.[16] There are instances of suicide and addiction-related mortality due to vision loss caused by LHON. For example, one respondent surveyed by Gale et al (2017) attempted suicide three times after vision loss.[17]

Due to limitations of the prevalence data available, we are unable to derive an average mortality rate based on these disorder-specific estimates of mortality rates.

2.5 Overall mortality rate (per cent), by disorder



Note: Keshavan and Rahman (2018) state that "mortality rates are expressed as a percentage of deaths over the duration of follow-up as a proportion of the total number of cases included in the study" (p.13).

Data source: Keshavan and Rahman (2018), figure 4, p.13.

Instead, we estimate the average mortality rate for adults (1.6 per cent) and children (3.0 per cent) across all types of mito:

- **Adults**: Mortality is estimated as the average across two studies of adults:

16 For example, Vestergaard et al (2017) notes that "few studies on mortality have been published" and "little is known of life expectancy and cause of death in LHON patients": Vestergaard, N., Rosenberg, T., Torp-Pedersen, C., Vorum, H., Andersen, C.U. and Aasbjerg, K., 2017, 'Increased mortality and comorbidity associated with Leber's Hereditary Optic Neuropathy: A nationwide cohort study', *Investigative Ophthalmology & Visual Science*, 58: 4586-4592, doi: 10.1167/iovs.17-21990

17 Gale, J., Khoshnevis, M., Frousiakis, S.E., Karanjia, R., Poincenot, L., Sadun, A.A. and Baron, D.A., 2017, 'An international study of emotional response to bilateral vision loss using a novel graphical online assessment tool', *Psychosomatics* 58(1): 38-45, doi: 10.1016/j.psym.2016.07.002

  - Papadopoulos et al (2019)[18] estimate an annual average mortality rate of 2.5 per cent based on a survey of 267 patients with genetically confirmed mito, and
  - Barends et al (2016)[19] study 380 adults over 10 years, during which 30 died, implying an annual average mortality rate of 0.8 per cent.
- **Children**: Mortality is estimated as the average across two studies of children from different age cohorts:
  - Eom et al (2017)[20] study 221 children and estimate a global mortality rate of 14 per cent over 10 years (1.4 per cent annual average mortality), and
  - Debray et al (2007)[21] study 73 children diagnosed with mito between 1985 and 2005, with 46 per cent of patients having died at a median age of 13 months.

Additional detail about the literature relating to child mortality is provided in Appendix B.

Based on these assumptions, we estimate there were 10 deaths of children and 70 deaths of adults due to mito in 2022 (table 2.6).

The monetary value of mortality can be quantified by multiplying the number of deaths in a year by the value of a statistical life, which the Office of Impact Analysis (OIA) prescribes to be $5.4 million (2023 dollars).[22] This captures the overall value of reductions in the risk of unforeseen fatality by chance. We estimate there is a total cost due to mortality of $435 million in 2022.

2.6 Lost value due to mortality

Cohort	Mortality	Lost value due to mortality
	Number of deaths	$m/year
Child	10	55
Adult	70	380
Total	**81**	**435**

Source: CIE.

18 Papadopoulos, C., Wahbi, K., Behin, A., Bougouin, W., Stojkovic, T., Leonard-Louis, S., Berber, N., Lombès, A., Duboc, D., Jardel, C., Eymard, B. and Laforêt, P., 2019, 'Incidence and predictors of total mortality in 267 adults presenting with mitochondrial diseases', *Journal of Inherited Metabolic Diseases*, 43: 459-466, doi: 10.1002/jimd.12185

19 Barends, M., Verschuren, L., Morava, E., Nesbitt, V., Turnbull, D. and McFarland, R., 2016, 'Causes of death in adults with mitochondrial disease', *JIMD Reports*, 26: 103-113, doi: 10.1007/8904_2015_449

20 Eom, S., Lee, H.N., Lee, S., Kang, H., Lee, J.S., Kim, H.D. and Lee, Y., 2017, *Pediatric Neurology*, 66: 82-88, doi: 10.1016/j.pediatrneurol.2016.10.006

21 Debray, F., Lambert, M., Chevalier, I., Robitaille, Y, Decarie, J., Shoubridge, E.A., Robinson, B.H. and Mitchell, G.A., 2007, 'Long-term outcome and clinical spectrum of 73 pediatric patients with mitochondrial diseases', *Pediatrics*, 119(4): 722-733, doi: 10.1542/peds.2006-1866

22 Department of Prime Minister and Cabinet, 2023, *Value of statistical life*, Office of Impact Analysis, available at: https://oia.pmc.gov.au/sites/default/files/2023-10/value-of-statistical-life.pdf

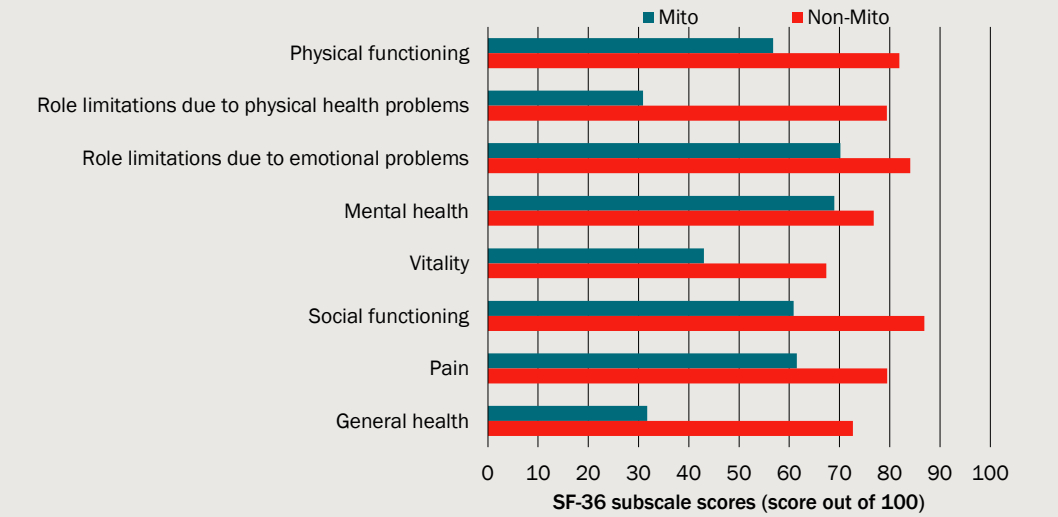
Morbidity due to mito

A range of studies have estimated the quality-of-life differences between people with and without mito. The most recent and authoritative source is Van de Loo et al (2022)[23], which included a survey of 95 people with mito. Van de Loo et al (2022) develop a conceptual and measurement framework for understand quality-of-life for people with mito. They also use statistical modelling to understand the relationship between biological and physiological aspects of disease and symptom status or overall quality-of-life.

The survey data collected and analysed by Van de Loo et al (2022) includes the SF-36 survey tool, which provides evidence about the difference between people with mito in the sample and normed levels of quality-of-life in the general population (chart 2.7). They find that:

- all aspects of health-related quality-of-life are worse for people with mito compared to the general population
- the average rating of general health for people with mito is less than half the level of the general population, and
- role limitations due to physical health problems are the most severely affected domain for people with mito. Role limitations due to physical health problems include, for example, where a person cuts down the amount of time they spent on work or other activities.[24]

2.7 Quality-of-life impacts due to mito



Note: 'Non-mito' refers to the normed levels for each domain for the general population.

Data source: Van de Loo et al (2022), CIE.

23 Van de Loo, K.F.E., van Zeijl, N.T., Custers, J.A.E, Janssen, M.C.H. and Verhaak, C.M., 2022, 'A conceptual disease model for quality of life in mitochondrial disease', *Orphanet Journal of Rare Diseases*, 17: 263, doi: 10.1186/s13023-022-02411-9

24 It also includes where they accomplished less than they would like, were limited in the kind of work or other activities they perform, or had difficulty performing the work or other activities (for example, it took extra effort).

A statistical modelling approach is available from Burstein et al (2015)[25] to convert SF-36 scores into disability weights, and therefore support estimating YLD and thus DALYs. This is one approach used to estimate the global burden of diseases in the literature (see, for example, Chandran et al, 2021).[26] This approach requires individual-level SF-36, rather than the aggregate results presented in Van de Loo et al (2022) or other studies.[27]

With the general health subscale result being less than half the amount of the general population norm, this suggests that a reasonable estimate of the disability weight for mito is 0.5, which is comparable to the following conditions:[28]

- severe anxiety disorders – 0.523
- severe motor impairment with blindness due to malaria – 0.512
- severe motor impairment and incontinence due to spina bifida – 0.483, and
- profound intellectual disability and moderate dementia due to Down syndrome – 0.499

In the UK Government Impact Assessment for creating regulations to enable mitochondrial donation,[29] a quality-of-life weight[30] of 0.61 (i.e. a disability weight of 0.39) was estimated for people with mito. This estimate was based on quality-of life data from the SF-12 survey for a small group of people with serious mito.

Based on a disability weight of 0.39, we have produced estimates of the burden of morbidity, which amounts to 1805 YLD in 2022 (table 2.8). The majority of YLD are associated with adults, which is due to a higher number of prevalent cases among adults compared to children.

The monetary value of morbidity can be quantified by multiplying the number of YLD by the Value of a Statistical Life Year, which is prescribed by the OIA to be $235 000.[31] We estimate a total cost of $424 million per year associated with morbidity.

---

25 Burstein, R., Fleming, T., Haagsma, J., Salomon, J.A., Vos, T. and Murray, C.J.L., 2015, 'Estimating distributions of health state severity for the global burden of disease study', *Population Health Metrics*, 13(31), doi: 10.1186/s12963-015-0064-y

26 Chandran, S.L.N., Lustosa, A.A., Demir, B., Bowers, B., Albuquerque, R.G.R., Prado, R.B.R., Lambert, S., Watanabe, H., Haagsma, J., and Richardus, J.H., 2021, 'Revised estimates of leprosy disability weights for assessing the global burden of disease: A systematic review and individual patient data meta-analysis', *PLoS Neglected Tropical Diseases*, 15(3): doi: 10.1371/journal.pntd.0009209

27 For this reason we do not convert the results of Van de Loo et al (2022) into an estimated disability weight.

28 GBD 2019 Disability Weights are available from the Institute for Health Metrics and Evaluation at: https://ghdx.healthdata.org/record/ihme-data/gbd-2019-disability-weights

29 UK Department of Health, 2014, *Impact Assessment of Mitochondrial donation regulations*, available at: https://www.legislation.gov.uk/ukia/2015/9/pdfs/ukia_20150009_en.pdf

30 A quality-of-life weight takes a value from 0 (corresponding to a state which the patient considers equivalent to death) to 1 (representing perfect health).

31 In the *Value of statistical life* publication, OIA explain that the VSLY can be used, together with a disability weight, to measure the benefit of reducing the risk of disease.

2.8 Lost value due to morbidity

Cohort	Years Lived with Disability	Lost value due to morbidity
	Years	$m/year
Child	135	32
Adult	1 671	393
Total	**1 805**	**424**

Source: CIE.

3 Costs of mito in the community

The total cost of mito in Australia in 2022 was $1085 million, of which $109 million relates to children and $976 million to adults with mito (table 3.1).

Annual healthcare costs associated with mito appear to vary significantly between Australia and overseas. Taking a conservative view of the overseas evidence, costs are $33 611/year for children and $18 988 for adults with mito. Converted into Australian estimates, this implies a total healthcare cost in Australia of $93 million per year.

Mito impacts on productivity of people with disease and their carers through reducing workforce participation, productivity while at work, unplanned absences from work, and reducing education attainment. We estimate that people with mito and their carers reduce their work hours by 51 and 23 per cent, respectively. We estimate that people with mito have 25 days of absence from work each year. After including the economic cost of welfare payments associated with reduced workforce participation, these productivity losses amount to $196 million.

Mito results in out-of-pocket costs of $30 million per year, costs to the NDIS of $40 million per year.

Overview of the costs of mito

Chart 3.1 provides a summary of the costs of mito, including the costs of mortality and morbidity. The most significant components of costs are quality of life losses, which are evenly split between the cost of mortality and morbidity (i.e. ill-health).

Note that productivity losses cannot be added to the cost of lost quality-of-life estimated in chapter 2, since quality of life losses implicitly include the value placed by individuals on future productivity. Hence, we report the split of the value of lost quality of life between the value of lost production, and the remaining value of lost quality of life.

3.1 Total cost of mito in Australia

Cost category	Child	Adult	Total
	$m/year	$m/year	$m/year
Quality of life and productivity lost: mortality			
Value of lost production	2	22	24
Remaining value of lost quality of life	53	358	411
Subtotal	**55**	**380**	**435**
Quality of life and productivity lost: morbidity			

Cost category	Child	Adult	Total
	$m/year	$m/year	$m/year
Value of lost production	0	110	110
Remaining value of lost quality of life	32	283	314
Subtotal	**32**	**393**	**424**
Total healthcare cost	12	81	93
Reduced workforce participation among carers	5	29	34
Absenteeism	0	21	21
Out-of-pocket cost	2	28	30
Economic loss associated with reduced welfare payments	0	7	7
Total NDIS packages	4	37	40
Total	**109**	**976**	**1 085**

Note: All values are in 2023 dollars. Totals may not sum due to rounding.

Source: CIE.

Considering the subset of these costs that are associated with living with mito, as opposed to the costs of mortality, this amounts to $140 000 per person (table 3.2). The largest cost of living with mito is lost quality of life (including lost productivity), followed by the cost of healthcare.

3.2 Cost of living with mito per person

Cost category	Child	Adult	Total
	$/year	$/year	$/year
Quality of life and productivity lost: morbidity			
Value of lost production	153	25 672	23 769
Remaining value of lost quality of life	91 497	65 978	67 881
Subtotal	**91 650**	**91 650**	**91 650**
Total healthcare cost	33 611	18 988	20 079
Reduced workforce participation among carers	14 499	6 800	7 374
Absenteeism	29	4 789	4 434
Out-of-pocket costs	6 493	6 493	6 493
Economic loss associated with reduced welfare payments	0	1 663	1 539
Total NDIS packages	10 969	8 558	8 738
Total	**157 252**	**138 942**	**140 307**

Note: All values are in 2023 dollars. Totals may not sum due to rounding.

Source: CIE.

Health system impacts

There are significant healthcare costs associated with mito. Healthcare spending can be categorised into the following areas:[32]

- hospital services for inpatients, outpatients, and the emergency room
- primary healthcare services including general practitioners, allied health, and pharmaceuticals, and
- referred medical services including specialist services, medical imaging, and pathology.

Experiences with the health system vary significantly across the mito community. Families with multiple people with mito can face a significant financial and non-financial burden associated with receiving care (box 3.3).

3.3 Case study of health service use by a family affected by mito

Gillian has a diagnosis of mito and also has two children, Sophie and Henry, with mito. Mito affects Sophie the most and this means she uses more health services than Gillian and Henry. Gillian says:

> "Sophie is a massive black hole for all the resources that it takes a family to keep a child with mito alive, in a mainstream school and accessing therapies. Those three things take the entirety of our family's resources: time and money. The reason that Henry and I have so little expenditure and resources for us is that it is all invested in Sophie."

Sophie uses a large range of health and other services:

- A metabolic medical service twice each year which usually includes pathology through the public hospital
- Cardiologist and ophthalmology every two years through the public hospital
- Hearing supports through the Commonwealth Hearing Services Program, appointments with an ENT specialist with $300 out of pocket each time, and an audiologist NDIS
- Special glasses, which cost around $700 due to special lenses.
- Educational supports through school that involve multiple additional teaching and support staff
- Private allied health services funded through a combination of private health insurance, NDIS and out of pocket costs. This cannot be accessed through the public system because Sophie is an NDIS participant.
- Emergency hospital admissions in the public system. For example, when Sophie had a gastrointestinal virus this resulted in a hospital stay. Gillian estimates that this is less than once per year in recent years.

---

32 This is the categorisation used by the *Disease Expenditure in Australia* publication by the Australian Institute of Health and Welfare: https://www.aihw.gov.au/reports/health-welfare-expenditure/disease-expenditure-in-australia-2019-20/contents/health-expenditure

Gillian uses many different health services:

- A GP that she sees 2 or 3 times per year
- A neurometabolic specialist who she is currently seeing through being a participant in a clinical trial. Being part of the trial also allows Gillian to access other specialists as things comes up, such as a cardiologist.
- A gastroenterologist seen privately once per year, with a gap cost of $300.
- Radiological studies once every second year, costing around $800 each time.
- Physiotherapist seen privately, partly covered by private health insurance, with an out of pocket cost of around $500 per year.

Henry sees the metabolic service annually. Beyond that, his mito is managed by his family including specific exercise activities and diet, both of which involve extra costs to the family's budget.

In addition to all of this, the family all has non-mito health needs, such as Gillian's need to see a dermatologist and Sophie's orthodontic treatment.

Hospital stays often lead to what Gillian describes as a 'mito crash' for her and/or her children.

> "A mito crash involves a sharp increase in pain, not being able to get out of bed due to a lack of energy, our digestive system not working, not being able to regulate our body temperature. This means time off school, time off work. This might last two weeks at its most severe and then need many months of recovery."

Source: Supplied by Mito Foundation.

Existing evidence about total healthcare cost relates to international cases of mito, which can be adapted to the Australian context with some qualifications (box 3.8).

Cohen et al (2018) measured the cost of mito in the United States of America based on administrative claims data (chart 3.4). They estimated that adults with mito have healthcare costs that are $54 422 more costly than adults in the general population, with this difference being $96 331 for children (75 per cent higher).[33]

Most of the cost difference is accounted for by just three cost categories, namely inpatient, surgery and pharmaceuticals (chart 3.5). Home health and durable medical equipment costs are 97 and 49 times higher for people with mito compared to the general population, respectively.

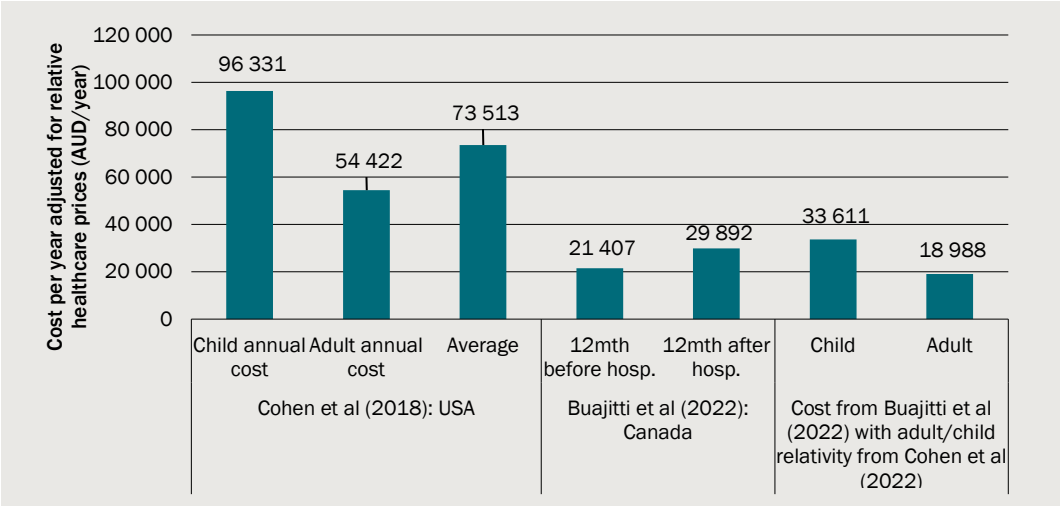
Buajitti et al (2022) measured the costs of mito in Canada in the year before and year after the first hospitalisation due to mito (not including the costs of that index hospitalisation). They found an average cost of $21 407 in the year before and $29 892 in the year after first hospitalisation. These costs encompass health care encounters including hospitalisations, emergency department visits, physician billings, drug payments, home care and long-term care and other categories.

33 This is the difference in average claims by people with mito ($8 378/month and $5 378 in 2023 AUD for adults and children, respectively) compared to average claims by the total member population ($350 and $843 in AUD for adults and children, respectively).

While Buajitti et al (2022) remarked that the findings of their study and Cohen et al (2018) are similar, their cost estimates differ significantly, with the average for the 24 months around the first hospitalisation from Buajitti et al (2022) being 35 per cent as high as the estimate by Cohen et al (2018). Buajitti et al (2022) relates specifically to the year before and after the first hospitalisation due to mito, while we interpret that Cohen et al (2018) is an average across all months between 2008 to 2015 that a person was a member of an insurance fund while having mito.[34]

Taking the more conservative estimate of annual costs (from Buajitti et al, 2022) but the adult/child price relativity from Cohen et al (2022) implies a cost of $33 611 for children and $18 988 for children. Applying this cost to all people with mito implies a cost of $107 million per year.

3.4 Comparison of international estimates of total health costs per year

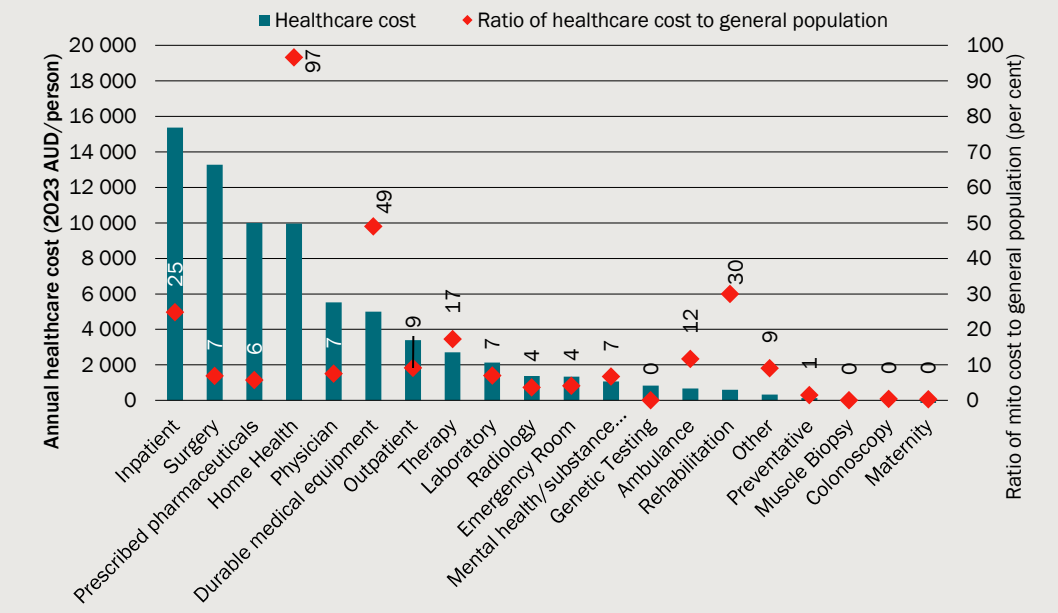


Note: All values are in 2023 AUD and have been adjusted to account for relative healthcare prices between Australia and USA/Canada.

Data source: The CIE, based on Cohen et al 2018 and Buajitti et al 2022.

34 We interpret that Cohen et al (2018) calculate expenditure (including patient cost sharing) per member per month by dividing total expenditure for people with mito by the number of member months by people during which they have mito, however, this is not explicitly stated.

3.5 Categories of health costs from Cohen et al (2018)



Note: The Colonoscopy and maternity costs are marginally lower for people with mito than the general population (<$300 difference), but for ease of reading the y-axis is cut off at zero on this chart so these values are not visible.

Data source: Cohen et al (2018), CIE.

3.6 Total healthcare cost associated with mito

Cohort	Average total healthcare cost
	$m/year
Child	12
Adult	44
Total	**55**

Source: CIE.

3.7 Comparing the cost of healthcare between Australia and overseas

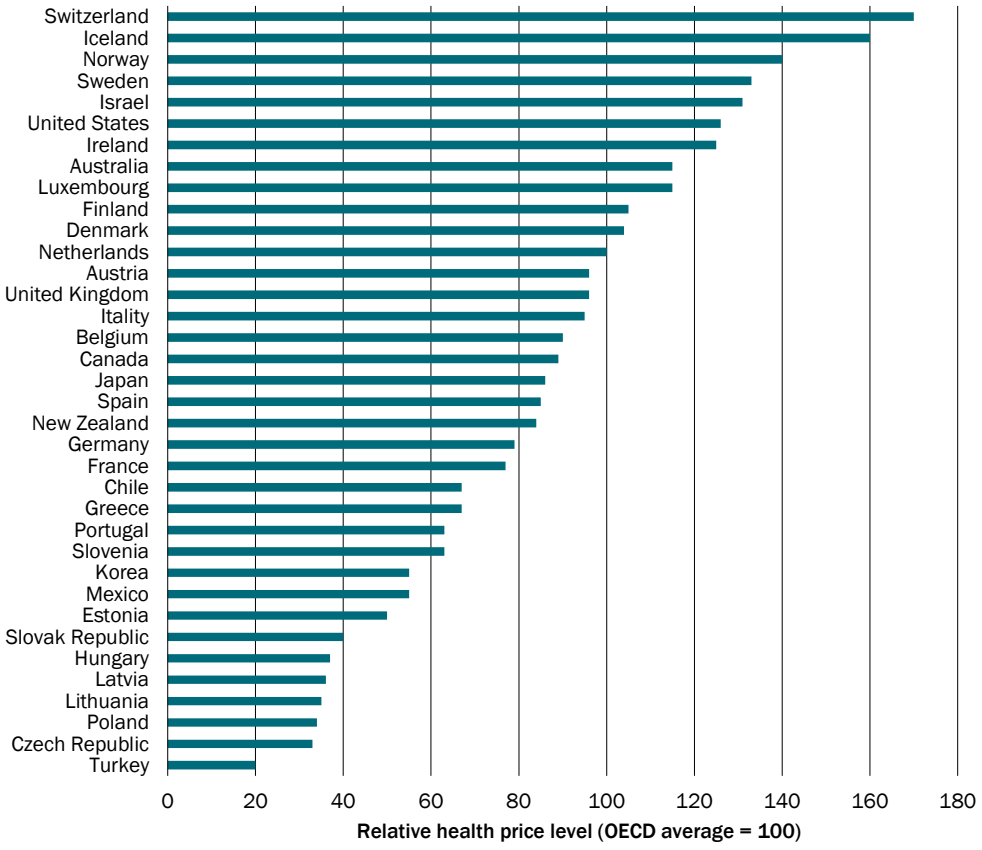
Comparisons of healthcare spending per person across countries can be misleading because the price of healthcare varies significantly across countries. Healthcare prices in Australia are 15 per cent higher than the OECD average, although, are not as high as prices in the United States (26 per cent higher than the OECD average) (chart 3.8). Differences in healthcare prices can be explained by relative productivity and local wages, organisation and governance of the healthcare system and the approach used to set or negotiate prices.

When adapting cost estimates from overseas studies such as Buajitti et al (2022), which measures healthcare costs of mito in Canada, we adjust these estimates for the relative price of healthcare between that country and Australia. Based on the relative healthcare price levels presented in OECD (2020) (chart 3.8), healthcare prices in the United States are 110 per cent as high as Australia, and prices in Canada are 77 per cent as high as Australia.

Note that this adjustment relies on the relative prices of healthcare, rather than just hospital prices. Hospital prices are relatively more similar across Australia, the United States and Canada than overall healthcare prices (OECD, 2020, p.4).

Note that we do not adjust for differences in the volume of healthcare provided in each country. In addition to having relatively high healthcare prices, the United States also has high healthcare volumes, leading to it having the highest healthcare expenditure globally. We have not adjusted for differences in the volume of healthcare by country. Hence, the estimates of healthcare spending adapted from overseas studies presented in this chapter can be interpreted as the cost in Australia of providing the volume of healthcare for mito that is provided in the country of the study.

3.8 Relative health price levels in the health care sector, 2017



Note: The OECD average corresponds to a value of 100 for this index.

Data source: OECD (2020) *Focus on Health Prices*, p.1, available at: https://www.oecd.org/health/health-systems/Health-Care-Prices-Brief-May-2020.pdf

Evidence is available about the magnitude of outpatient costs in Australia, which suggests that healthcare costs are likely to be at the lower end of the range from overseas

evidence. Haque et al (2023)[35] estimate the outpatient costs for people with mito from a mitochondrial disease clinic in Sydney. They stratify 91 adults with mito into three groups:

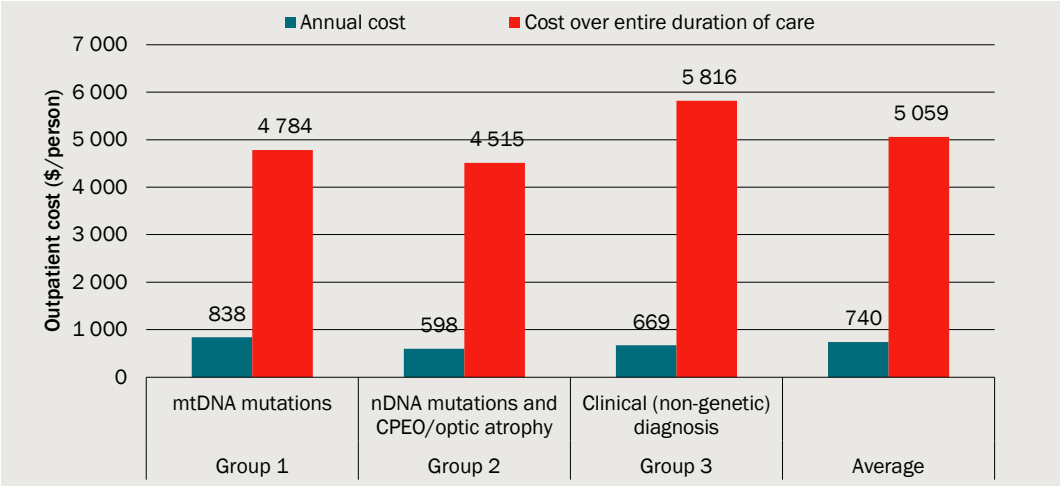
1 those with mtDNA mutations
2 those with nDNA mutations and predominant phenotype of Chronic Progressive External Ophthalmoplegia (CPEO) or optic atrophy, and
3 those without a confirmed genetic diagnosis but with clinical criteria and muscle biopsy findings supportive of a diagnosis of mito (i.e. a clinical but non-genetic diagnosis).

They estimate that there are outpatient costs between $669 – $838 per year across these cohorts. Those with a clinical but non-genetic diagnosis had higher costs over the entire duration of care compared to those with a genetic diagnosis, which the authors attribute to a lack of molecular diagnosis leading to a less customised management approach. However, costs were lower for this group on an annual basis.

Outpatient costs may be affected by long wait times. Mito Foundation state that anecdotal evidence suggests wait times of 6-12 months or as high as 24 months, which reflects pressure to see patients less frequently due to clinic capacity and workforce constraints.

Comparing these cost estimates to the estimated outpatient costs per year from Cohen et al (2018) suggests that outpatient costs in Australia ($740/year) are significantly lower than costs in the United States of America ($3 394/year, chart 3.5). This suggests that it is appropriate to take a conservative view of the overseas evidence about healthcare costs.

3.9 Outpatient hospital costs for mito patients in Australia (Haque et al, 2023)



Data source: Haque et al (2023), CIE.

35 Haque S, Crawley K, Shrestha R, Schofield D, Sue CM., 2023, 'Healthcare resource utilization of patients with mitochondrial disease in an outpatient hospital setting', *Orphanet J Rare Dis.* 2023 May 29;18(1):129. doi: 10.1186/s13023-023-02746-x

Productivity and employment impacts

Mito impacts on the productivity of people with disease and their carers in a range of ways:

- **reduced employment**: stopping working entirely or reducing the number of hours worked
- **presenteeism**: reduced productivity while working due to the burden of their disease or the impact of their caree's disease on their wellbeing/productivity
- **absenteeism**: time taken off work due to disease, including absences to receive healthcare, and
- **reduced human capital formation**: people may attain less formal and/or informal education, reducing future productivity.

Work participation and productivity are important because of the value of what people with mito can contribute to the economy, and loss of employment is a significant contributor to the financial burden of mito. Work also plays a key role in wellbeing and social connection.

3.10 Case study about the impact of mito on work

Francesca[a] originally trained in a writing profession in the United Kingdom. After doing this for three years, she developed symptom of repetitive strain injury that stopped her from working as it meant she could no longer write. This "RSI" was much later recognised as one of Francesca's first symptoms of mito.

After immigrating to Australia and starting her family, Francesca re-trained as a teacher for children with special needs. She shared:

> "That was my passion… I think I really found what I wanted to do."

This was her career for the next 12 years, all spent working at one school within her local community. Francesca had to reduce to part-time work due to mito symptoms: fatigue, hearing impairment and muscle pains. For a time, Francesca combined part time work and a partial disability support pension. This worked well for several years, although Francesca did take a large amount of sick leave due to symptoms or mito.

Francesca describes the importance of support she received from colleagues during this time. This included others taking on physical aspects of her role, such as moving furniture between classrooms.

When the pain in Francesca's legs increased, one day of sick leave turned into weeks and then months. Eventually Francesca had to start using her income protection insurance. Francesca says:

> "It was becoming clear that this was not going to go away. It was time to seek a diagnosis of mito that I had assumed I had since my [female relative] died due to mito. A diagnosis would help to draw all of my symptoms, including pain, fatigue, hearing loss and diabetes together."

Francesca shared her feelings about stopping work earlier than planned.

> "Your job defines who you are. I can still remember the actual day it was finalised that I no longer worked for [employer]. It was really devastating. I had a lot of counselling through that period. I am still learning a new me."
>
> It was multiple symptoms of mito that led to Francesca not being able to work, but particularly her limited mobility. She also withdrew from her community, particularly the school that she had been teaching at:
>
> "I did not want anyone to see me as I had become, having to use the walking frame. I have little kids come up to me and say 'But you're not an old lady!'. It's deeper than vanity; the way people perceive me and treat me is so very different now. I still don't go to my local shopping centre."

[a] Name has been changed to protect privacy.

Source: Case study supplied by Mito Foundation.

We have focussed on estimating the cost of reduced employment, which is typically the largest component of productivity losses in cost of illness studies. Other types of productivity losses cannot be estimated due to data limitations.

Impact of mito on workforce participation

There is little evidence overall about productivity outcomes among adults with rare genetic disease. For example, Velvin et al (2023) undertake a systematic review of studies about work participation of people with rare genetic diseases published in peer reviewed journals, finding that while studies suggest work disability is highly prevalent in many people with rare diseases, research is scarce and fragmented. They did not identify any studies for inclusion that related to mito, with included studies relating to 33 diseases such as cystic fibrosis, haemophilia, and Marfan syndrome.[36]

The PEEK Study[37] is the only source of quantitative evidence we have identified about how mito affected the work status of people with mito and their carers.[38] The majority of people with a diagnosis of mito report that they reduced the number of hours worked or stopped working entirely. Carers experience relatively less impact, with 22 per cent reducing the number of hours worked and 13 per cent stopping work entirely. Around 22 per cent of carers took leave, which would be associated with a financial burden if it is without pay.

To yield an estimate of the overall impact of mito on productivity, we assume that those who reduced the number of hours worked due to mito reduced their hours by 50 per cent

---

36 Velvin, G., Dammann, B., Haagensen, T., Johansen, H., Strømme, H., Geirdal, A.O. and Bathen, T., 2023, 'Work participation in adults with rare genetic diseases – a scoping review', *BMC Public Health*, 23: 910, doi: 10.1186/s12889-023-15654-3

37 International Centre for Community-Driven Research, 2018, Mitochondrial Disease Australian Study, *PEEK*, 1(6), July 2018.

38 For example, a search of Google Scholar for "mitochondrial AND (employment OR employed OR workforce OR productivity) resulted in 17 results, none of which were related to workforce productivity (instead, most related to protein productivity).

on average. This implies a 51.0 per cent reduction in productivity by people with mito, and a 23.4 per cent reduction in productivity by carers.[39]

3.11 Changes to work status of people with mito and their carers

Changes to work status	Share of people with a diagnosis	Share of carers of people with a diagnosis
	Per cent	Per cent
Reduced number of hours worked	26	22
Stopped working	38	13
Took leave with pay	N/A	6
Took leave without pay	N/A	16
Unaffected	36	44

Source: PEEK Study.

Measuring the cost of reduced workforce participation

'Productivity losses' measure the change in the productive capacity of the economy because individuals (and their carers) are living with disease. In some cases, individuals are unable to participate in the labour market at all because of premature death or an inability to participate, and in other cases, individuals (and their carers) might continue to work, but with lower productivity.

Productivity losses associated with mito arise with respect to both paid work and unpaid work. Productivity in paid work is measured by reduced wages and other forms of income (excluding government payments). We have not measured productivity losses associated with unpaid work due to a lack of quantitative data about the reduction in unpaid work due to mito.

The methodology to estimate productivity losses associated with mito is summarised in box 3.13 and detailed further in Appendix C.

We estimate a financial cost of lost productivity due to mito of $169 million. This consists of lost productivity due to:

- mortality, which is the loss of future earnings (taking a present value at the time of death),
- morbidity, assuming that people with mito reduce work hours by 51.0 per cent,
- carers, which is the cost of a 23.4 per cent reduction in work hours for each carer, and
- the economic cost of income support payments, which depends on the extent of economic distortions caused by raising tax revenue.

39 For example, 26 per cent multiplied by 50 per cent gives a 13 percentage point reduction in hours worked due to reducing hours, and 38 per cent of people stopping work implies a further 38 percentage point reduction in work hours. The total effect of both reducing work hours and stopping work is, therefore, 51 per cent for people with mito.

3.12 Total productivity losses due to mito

Category	Reduction in productivity	Children with mito	Adults with mito	Total
	Per cent	$m, PV	$m, PV	$m, PV
Mortality	100.0	2	22	24
Morbidity	51.0	0	110	110
Carers	23.4	5	29	34
Economic cost of income support	N/A	0	7	7
Total		**7**	**161**	**169**

Note: All values shown are present values (PV).

The cost of lost production due to mortality and morbidity of people with mito is $135 million. This cost is also implicitly a component of the value of lost quality of life due to mito (see chapter 2). Hence, when reporting the total cost of mito (e.g. in table 3.1), we do not double-count the cost of lost productivity due to mortality and morbidity. Instead, we report the split of the value of lost quality of life between productivity losses and the remaining cost of lost quality of life.

3.13 Methodology for measuring productivity impacts

Measuring the impacts associated with premature death

Productivity impacts associated with premature death can be quantified based on a friction, or human-capital approach.

A friction approach considers the impact of intermittent and time limited displacements in labour, recognising that over time, workforce absences are overcome by substituted employment.

A human capital approach measures the loss of productivity over current and future years associated with newly diagnosed cases of the disease each year. However, it is limited in accuracy when unemployment and underemployment exist.[40]

Given that one approach overestimates, and one underestimates productivity impacts, this study uses a mid-point of the two to estimate the economic burden of disease.

Measuring the impacts associated with disability

Measuring the productivity losses associated with reduced capacity to work is more straightforward. We assume the productivity loss from paid work associated with each year lived with disability is equal to the lost income from that year. The personal income and the amount of time spent on paid work is derived from the 2021 Census

40 Lal, A., Moodie, M., Ashton, T., Siahpush, M. and Swinburn, B., 2012, 'Health care and lost productivity costs of overweight and obesity in New Zealand', *Aust N Z J Public Health*, 36(6): p.550-556, available at: https://www.ncbi.nlm.nih.gov/pubmed/23216496

and was adjusted to 2023 dollars.

Measuring the economic cost of income support payments

People with mito and their carers who no longer work are likely to receive income support payments, which is a transfer of money from government to recipients and not an economic cost.[41] We estimate that people with mito quitting work leads to $24 million in welfare payments per year, which doesn't include any welfare paid to carers.[42] This is based on 38 per cent of people with mito quit their jobs after being diagnosed (PEEK Study, 2018)[43] and an average welfare payment to this group of $18 700 (Vincent et al, 2023),[44]

Government uses taxation to fund income support payments, which leads to an economic cost because taxes distort economic activity and have administrative and compliance costs. This efficiency loss is collectively referred to as the deadweight loss of taxation. Assuming a deadweight loss of 30 cents per dollar of income support payments (Vincent et al, 2023),[45] this suggests there is an economic cost of income support due to mito of $7 million in 2022.

Source: CIE.

Impact of mito on absenteeism

We estimate that people with mito are absent from work 24.7 days each year. This is the average number of days of work missed for people with rare diseases (after receiving a diagnosis) in the Everylife Foundation (2023) study of rare diseases, shown in table 3.15.[46]

This implies a total cost of workplace absences for people with mito of $20.5 million, based on average Australian earnings per day.[47]

41 This is a standard approach to considering transfers in cost-benefit analysis or costing studies, where transfers from money represent an loss for one entity and an equal gain to another. Hence, there is no net economic cost. For further discussion, see: Abelson, P., 2012, *Public Economics: Principles and Practice*, p.141.

42 We do not have data about average welfare payments to carers.

43 International Centre for Community-Driven Research, 2018, Mitochondrial Disease Australian Study, *PEEK*, 1(6), July 2018, p.11.

44 Vincent, J., McCarthy, D., Miller, H., Armstrong, K., Lacey, S., Lian, G., Richards, D., and Berry, T., 2022, *Research Report – The economic cost of violence, abuse, neglect and exploitation of people with* disability, Taylor Fry, p.340.

45 Ibid.

46 EveryLife Foundation for Rare Diseases, 2023, *The cost of delayed diagnosis in rare disease: A health economic study*, available at: https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf

47 This is calculated by dividing average annual earnings by 260 work days per year.

3.14 Days of missed work for rare diseases with delayed diagnosis

Condition	Days missed of work (after delayed diagnosis)
	Days/year
Adrenoleukodystrophy	36.3
Pompe	16.8
SCID	38.7
Fragile X	21.4
Duchenne Muscular Dystrophy	13.9
Wilson Disease	26.9
Myasthenia Gravis (average for men and women)	19.2
Average	**24.7**

Source: Everylife Foundation (2023), CIE.

Out-of-pocket costs and the financial burden of mito

Mito poses a significant financial burden on people and their families. Key categories of financial costs borne by people with mito and their families include:[48]

- costs of dietary supplements and over-the-counter medications for pain or constipation relief,
- out-of-pocket payments for healthcare including allied health (physiotherapists or speech therapists) specialists, private hospital costs, and outpatient consultations, medication, and alternative medicine and care,
- travel costs, meals and accommodation related to accessing healthcare,
- accommodation, including residential care and respite care, and
- assistive technologies, home, and car modifications.

The case study about Gillian's family (box 3.3) showed the range of out-of-pocket health costs due to mito. Box 3.15 provides detail about other aspects of the financial burden.

48 This list is derived from the set of costs borne by patients used in MitoMod: Schofield et al (2022), table 3.

3.15 Case study of the financial burden of mito

Gillian has a diagnosis of mito and also has two children, Sophie and Henry, with mito. In addition to out-of-pocket costs for accessing health care:

- Gillian, Sophie and Henry all take multiple dietary supplements. For Gillian and Henry, these cost around $250 per year each. For Sophie, dietary supplements cost $600 per year. Gillian is interested to try to add another supplement for Sophie but there are just no funds available in the family's budget.
- The family's food budget is increased because of mito. Gillian estimates these costs as $200 a week extra for Sophie alone.
- Additional transport expenses as Sophie needs to be driven everywhere and the family must pay to park close to everywhere they go, including health services, because Sophie cannot walk long distances.
- A cleaning service.

Beyond expenses, mito has also impacted on Gillian's career and earning potential. This is particularly due to the need to work flexibly to navigate and negotiate the multiple different systems and services to arrange care for herself and her children.

Source: Supplied by Mito Foundation.

Estimates of out-of-pocket costs from the literature are highly variable:

- The PEEK Study[49] asked respondents about the total amount they spend on mito (chart 3.16). Around 30 per cent suggested they spent less than $100 per month,[50] while 24 per cent indicated they spent more than $1000 per month, with a mean value of $6493 per year.[51] Their survey also asked about out-of-pocket expenses for diagnostic tests and medical consultations, with an average one-off cost of $583, although 31 per cent had costs in the top spending band (over $1000).[52]
- Deverell et al (2022)[53] surveyed families with children diagnosed with mito or tuberous sclerosis. Only three families responded that had children with mito, with the out-of-pocket costs varying significantly. While one family indicated they had less than $5000 in out-of-pocket costs due to mito for their two children, another indicated

49 International Centre for Community-Driven Research, 2018, Mitochondrial Disease Australian Study, *PEEK*, 1(6), July 2018.

50 This question was asked monthly, and we have expanded this to an annual cost estimate by multiplying by 12.

51 We have calculated this average based on the count of people by spending band provided in the PEEK Study, using the midpoint of each spending band to calculate the average (e.g. $501–1000 corresponds to $750).

52 These proportions exclude those who don't know or can't recall their out-of-pocket costs associated with diagnosis.

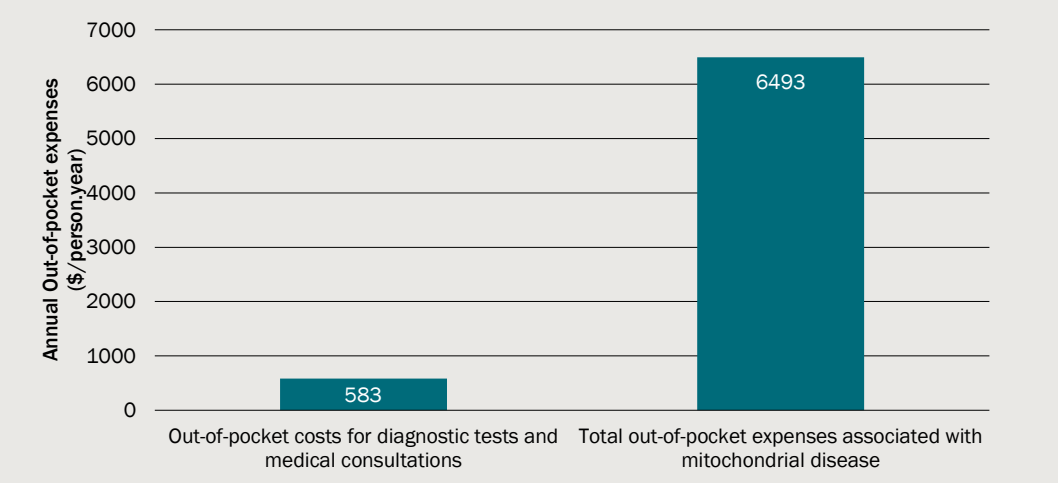
53 Deverell, M., Phu, A., Elliott, E. J., Teutsch, S. M., Eslick, G. D., Stuart, C., Murray, S., Davis, R., Dalkeith, T., Christodoulou, J., and Zurynski, Y. A., (2022), 'Health-related out-of-pocket expenses for children living with rare diseases - tuberous sclerosis and mitochondrial disorders: A prospective pilot study in Australian families', *Journal of Paediatrics and Child Health*, 58(4), 611–617, doi: 10.1111/jpc.15784

costs of $20 001–25 000 over the lifetimes of their two children (an annual cost of around $1670–2080 per child).

Out-of-pocket costs are highly variable across individuals, and most of the evidence derives from relatively small survey samples. Hence, they are difficult to estimate precisely. Applying a cost of $6493 per person to all people with mito in 2022 implies a total cost of $30 million per year (table 3.17).

Families with multiple members with mito may experience a particularly significant impact on household budgets, as is the case for Gillian's family (box 3.15).

3.16 Out-of-pocket costs based on the PEEK Study



Data source: PEEK Study data about the count of respondents with cost in various spending bands, averages calculated by CIE.

3.17 Total out-of-pocket cost

Cost category	Child	Adult	Total
	$m/year	$m/year	$m/year
Out-of-pocket cost	2	28	30

Source: CIE.

Impact on government services

The largest costs to government associated with mito are:

- healthcare costs borne by government, such as public hospital costs, medications listed on the Pharmaceutical Benefits Scheme (PBS)
- reduced tax revenue and additional income support payments due to reduced workforce participation
- costs of support services, including the NDIS, education support, and others, and
- other costs such as transport subsidies and public housing.

Change in income support payments due to reduced workforce participation

Mito reduces participation in the workforce for people with mito and their carers. Beyond the importance for an individual of not being able to work, this also creates a cost to government of providing income support.

The average payment per welfare recipient is $18 700 for those receiving either the Disability Support Pension or Jobseeker with a partial capacity to work (Taylor Fry and The CIE, 2023).[54] Consistent with our estimation of productivity costs, 38 per cent of working age people with mito quit their jobs after being diagnosed. Hence, 1270 people receive welfare payments of $18 700, amounting to total welfare payments of $23.7 million. The economic cost of tax to fund these welfare payments, assuming there is a 30 cent economic cost per dollar of tax revenue, is $7.1 million.

Costs to the NDIS

We assume that 28 per cent of people with mito participate in the NDIS. This is based on the PEEK Study, which found that among 50 respondents, 28 per cent were receiving domestic and home care support from government services and the NDIS.[55] The Mito Community Survey found a higher proportion of people receiving NDIS supports than the PEEK Study, with (out of 111 responses) 32 per cent of people with mito having received NDIS supports and 67 per cent of carers indicating the person they care for has received NDIS supports.[56]

We estimate that the total cost of NDIS payments to people with mito is $70 million per year (table 3.18), based on an average payment of $39 175 per person. Data by primary disability about average payments per participant and the number of active participants is available from the NDIS website most recently for the March 2023 quarter. While no single disability type relates to mito exclusively, we estimate the average payment across the range of disability types that we expect could include people with mito.[57] By comparison, participants with multiple sclerosis have average committed support of $59 863.

---

54 This is the mean welfare payment per person across ages 18 to 64, from Table C.47 in: Vincent, J., McCarthy, D., Miller, H., Armstrong, K., Lacey, S., Lian, G., Qi, D., Richards, N., Berry, T. (2022). *Research Report - The economic cost of violence, abuse, neglect and exploitation of people with disability*, Taylor Fry, available at: https://disability.royalcommission.gov.au/system/files/2023-09/Research%20Report%20-%20Economic%20cost%20of%20violence%2C%20abuse%2C%20neglect%20and%20exploitation%20of%20people%20with%20disability.pdf

55 International Centre for Community-Driven Research, 2018, Mitochondrial Disease Australian Study, *PEEK*, 1(6), July 2018.

56 Mito Foundation, 2022, *Mito Community Survey Insights Report 2*, p.17, available at: https://www.mito.org.au/wp-content/uploads/2022/11/Insights-Report-2-Final-151122.pdf

57 We have estimated the average payment across the multiple disability types that we expect include people with mito, namely 'hearing impairment', 'other', 'other physical', 'other sensory speech', and 'visual impairment'. We estimate a weighted average, using the number of active participants in each of these categories as the weight. This estimate

The division between responsibility for allied health services between the health system and NDIS may be leading to double-counting of allied health costs. The NDIS website states that "allied health services, such as physiotherapy and optometry, to improve the health of all Australians" are the responsibility of the health system.[58] However, allied health providers are one of the largest groups of registered NDIS providers,[59] and do provide therapeutic supports to participants. One specific area that may be double-counted is allied health therapy costs, which are included in Cohen, et al (2018) (see table 3.5) We have not identified detailed spending data with which to estimate the share of NDIS costs that would be potentially double-counted (such as therapy costs). Given the lack of such data, we have not made any adjustment to NDIS or healthcare costs to mitigate the risk of double-counting these costs.

3.18 Costs associated with the NDIS for people with mito

Cohort	Average NDIS payment	Share receiving NDIS	Number of people	Annual NDIS payments
	$/year	Per cent	Number	$m
Children	39 175	28	4 582	50
Adults (under 65)	39 175	28	1 796	20
Total			**6 378**	**70**

Source: NDIS payment and participant data, Mito Community Outcomes survey, CIE.

Wellbeing and mental health

Beyond impacts on health-related quality of life, people with mito and their caregivers experience a range of other wellbeing and mental health issues:

- anxiety due to a delayed or uncertain diagnosis or prognosis
- poor mental wellbeing, which may manifest as diagnosable mental health conditions such as anxiety or depression
- despair and a sense of grief and loss due to worsening symptoms[60]
- loneliness and social isolation
- trauma of difficult negotiations with the health system, and
- not being believed.

We have not costed these aspects of the mito experience, but the impact of mito on wellbeing and mental health is a key aspect of the experience for members of the mito community (box 3.19).

---

58 See https://ourguidelines.ndis.gov.au/how-ndis-supports-work-menu/mainstream-and-community-supports/who-responsible-supports-you-need/health

59 See https://www.ndis.gov.au/providers/working-provider/allied-health-providers

60 Moore, M., Yeske, P. and Parikh, S., 2023, 'Navigating life with primary mitochondrial myopathies: The importance of the patient voice and implications for clinical practice', *Journal of Primary Care and Community Health*, 14, doi:10.1177/21501319231193875

3.19 Case study of the impact of mito on quality of life and wellbeing

Andrew is in his 30s and lives with diabetes, hearing and vision problems, memory loss, fatigue and muscle weakness due to mito. These health issues make his daily life more challenging, and impact Andrew's sense of self.

> "I would spend time and energy comparing myself to others. It is upsetting to think 'but I am not old, there is no reason that I shouldn't be able to achieve much much more'. That feeling can be upsetting and difficult."

Andrew thinks that mito is somewhat isolating, even though he wishes it wasn't. Andrew's relationships with family and friends have been affected as not everyone is aware of the challenges he faces with mito. Due to health issues, he often cancels plans at the last minute, which can be frustrating to those close to him. The lack of understanding, and frequently changing plans have created difficulties in maintaining strong connections with his loved ones.

> "My low energy levels have led to me having to back out or not turn out for no explainable reason. I know this has let other people down when they expected something I just couldn't give due to my health. That hurts a bit."

Mito has impacted his memory and recall in particular. This led to Andrew seeing a neuropsychologist, which has recently increased due to declining mental health. This is funded by Andrew's NDIS plan and he values it as 'absolutely essential' even though it requires him to travel to the other side of the city he lives in. These symptoms of mito also contributed to Andrew needing to stop working recently.

> "If you put me back into where I worked previously in a people facing role, it would be a pretty frightening experience. But it shouldn't be for me."

Andrew has a history of mental health diagnoses, including anxiety and depression.

> "Definitely anxiety is there, depression some of the time. No matter what your next challenge is, your body doesn't give what you want it to. I have learnt to be in the moment. Where I am at [in my head] now is aligned with where my body is at right now."

Travel has always been important to Andrew and his love of trains has taken him on holidays around the world. However, during his most recent trip his physical symptoms of mito caused him to need to cancel part of his trip to rest. Realising that his declining physical health is slowly taking away the things he loves has had a significant impact on his mental health.

Source: Supplied by Mito Foundation.

Anxiety due to delayed or uncertain diagnosis or prognosis

Adults and children with mito, along with their carers, family, and other close members of their community, often feel anxiety associated with diagnosis. It is common for people with mito to report feelings of frustration, loneliness, and desperation during the diagnostic odyssey.[61]

61 Moore et al, 2023.

In some cases, particularly for infants, children may not be aware of their diagnosis/prognosis, but nonetheless there are likely to be parents/family who experience anxiety associated with diagnosis of their child. Further, anxiety due to diagnosis is likely to extend to family members more generally, such as spouses or siblings of people with mito.

There is little mito-specific evidence about the cost of such anxiety or magnitude of the impact on metrics such as psychological distress. However, there is a range of non-mito-specific analysis assessing the extent to which diagnostic uncertainty affects quality-of-life. The evidence suggests that there are significant differences across diseases:

- The GBD 2019 disability weights include a weight of 0.012 for generic uncomplicated disease with anxiety about a diagnosis, and a weight of 0.049 for generic uncomplicated disease with worry and daily medication. This weight is similar to the weight for mild motor impairment due to Motor Neurone Disease (MND) (0.01), but far lower than the disability weight from other symptoms of MND itself, ranging from speech problems due to MND (0.051) to severe motor impairment and severe respiratory problems due to MND (0.641).
- Violato and Gray (2019) compared health-related quality-of-life of people with coeliac disease before and after diagnosis. Coeliac disease, like mito, has a long pre-diagnosis period of symptoms (12.8 years on average), and undiagnosed coeliac is associated with substantially lower quality-of-life. However, symptoms were found to be less severe post-diagnosis.
- A systematic review about quality-of-life impacts from informing patients with cancer about their diagnosis and disease status found no evidence that informing patients of their diagnosis worsened quality of life (Wan et al, 2020).[62]

Despite the differences across diseases, the impact of diagnostic anxiety for MND is a reasonably comparator for mito given that it has profound impacts on quality-of-life, although it has a significantly greater mortality risk at least for adults.[63] A disability weight of 0.012, applied to the number of adults and children with mito, would imply a cost of $7.5 million per year due to diagnostic uncertainty from mito. Of this, $1.0 million is associated with children with mito. This quality-of-life loss would not be additive to the quality-of-life loss due to morbidity, since the disability weight for mito would include the impact of having a mito diagnosis on quality of life. Rather, this estimate is intended to show the proportion of the quality-of life impact that is associated with diagnostic uncertainty.

---

62 Wan, M., Luo, X., Wang, J., Mvogo Ndzana, L.B., Chang, C., Li, Z. and Zhang, J., 2020, 'The impact on quality of life from informing diagnosis in patients with cancer: a systematic review and meta-analysis', *BMC Cancer*, 20, 618, doi: 10.1186/s12885-020-07096-6

63 Brennan et al (2022) states that the mean period between diagnosis and death for MND is 3 years, with only 10 per cent surviving beyond eight years. This is a significantly higher mortality rate than adult mito, although perhaps comparable to mortality for mito among children or for more severe forms of disorder. Brennan, F.P., Gardiner, M.D. and Narasimhan, M., 2022, 'Motor neuron disease: The last 12 months', *Australian Journal of General Practice*, 51(5), doi: 10.31128/AJGP-07-21-6097

These estimates are not included in the total cost of mito to avoid double-counting with the lost quality of life from morbidity.

Poor mental wellbeing and social engagement

In a systematic scoping review of the literature about cognitive functioning and mental health for people with mito, Klein et al (2022) identified a range of impacts of mito on mental health. There were dramatic differences in prevalence of mental disorders across the range of studies considered, illustrating the variability in the experience of mito. Across seven studies which measured mental health outcomes:

- between 30-100 per cent of people with mito had any mental disorder,
- between 14-67 per cent had a mood disorder,
- between 0-60 per cent had an anxiety disorder,
- between 0-60 per cent had psychotic features, and
- between 0-42 per cent had personality disorders.

We have not estimated healthcare quality of life impacts of mental health disorders among people with mito, because this would double-count these costs measured elsewhere in our analysis. The disability weight for mito of 0.39 for mito based on the UK Government Impact Assessment for creating regulations to enable mitochondrial donation[64] is assumed to account for the average quality of life impact of mito, including any mental health impacts.

The *2022 Mito Community Survey* made a number of findings relating to mental wellbeing and social engagement among Australians diagnosed or caring for someone with mito:

- have been a very anxious person a good bit, most or all the time: 34 per cent[65]
- felt downhearted or blue a good bit, most or all the time: 28 per cent
- often feel lonely because of mito (agree or strongly agree): 41 per cent
- often feel socially isolated because of mito or caring responsibilities (agree or strongly agree): 56 per cent

Childhood mito negatively impacts the psychological health and quality of life of parents. Kim et al (2010)[66] found that 42 per cent of mothers of children with mito met a cutoff score for depression and 39 per cent met a similar cutoff score for anxiety.[67] Mothers of children with mito had scores on the SF-36 of 48 for mental health and 39 for overall health perceptions, which indicates significantly lower health-related quality of life.[68]

---

64 UK Department of Health, 2014, *Impact Assessment of Mitochondrial donation regulations*, available at: https://www.legislation.gov.uk/ukia/2015/9/pdfs/ukia_20150009_en.pdf

65 Mito Foundation, 2022, *Mito Community Survey Insights Report 4*, pp.6,14, available at: https://www.mito.org.au/wp-content/uploads/2023/04/MITO_REPORT4.CommunitySurvey23.R1.270423.pdf

66 Kim, K.R., Lee, E., Mankoong, K., Lee, Y.M., Lee, J.S., Kim, H.D., 2010, 'Caregiver's burden and quality of life in mitochondrial disease', *Pediatric Neurology*, 42(4): 271-276, doi:

67 This was based on Beck Depression Inventory and Beck Anxiety Inventory scores, respectively.

68 The general population benchmark for these scores from Van de Loo et al (2022) is between 70-80 for both mental health and general health perceptions.

4 Opportunities to reduce the burden of mito

Australia has recently made two significant changes that have the potential to decrease the economic impact of mito:

- **Legislation for and funding of the pilot study of mitochondrial donation, and**
- **The commitment to a genomics first approach to diagnosis through funding of whole-genome sequencing through Medicare.**

There are a range of further opportunities to reduce the burden of mito. While Australia is well-placed to realise some of these opportunities, others will require changes such as to health and other care for people with mito.

Improved access to reproductive options will provide people who are at risk of having a child with mito increased choice. Reproductive carrier screening, prenatal testing and pre-implantation genetic testing can support informed decision-making about mitochondrial donation, in-vitro fertilisation or termination.

We estimate that for each case of mito avoided there would be an avoided cost of $3.0 million over the person's lifetime. While reproductive options are currently the only way to fully avoid this burden, clinical research may in the future provide treatments that substantially or fully prevent this burden.

The number of parents who would choose to use reproductive options, thereby preventing cases of mito, is uncertain. UK Government analysis of the potential demand for mitochondrial donation, which is only relevant for a subset of inherited mtDNA mutations, suggested that take-up would be 20 people per year in the UK. We expect this would be similar in Australia, given the number of children born with mtDNA mutations. In addition, testing and reproductive options that are relevant for nDNA mutations further increase the potential for avoiding cases of mito. If, with these choices, 20 cases of mito were avoided each year, this would reduce the burden of mito by $60.9 million per year.

Genomic testing for children in Australia is estimated to yield cost savings of between $2097 and $9267 relative to conventional care. Parents of children with suspected mito are willing to pay $2918 for genomic testing. Evidence about testing for inherited retinal diseases suggests people place a higher value on testing that goes beyond diagnosis by providing prognostic information or that identifies new treatment to stabilise their condition.

The results of the Delayed Diagnosis Study in the United States suggest there are medical cost savings of $270 000 per person and productivity savings of $44 000 per person due to achieving timely rather than delayed diagnosis across 8 rare diseases.

Earlier diagnosis for people with mito affects clinical decision-making, particularly where the diagnosis is more certain. The chance of improving the process of a child's medical care is estimated to increased from 8 per cent under conventional care to 12 per cent under genomic testing. This has the potential to increase as more treatments for mito are developed.

Quality of life can be improved by delivery of appropriate health and other services, particularly in terms of mental health outcomes. However, there are a range of barriers to access, including knowledge of professionals and information being provided at appropriate times (e.g. diagnosis) to people with mito and their families.

Improving access to reproductive options

Mito can be caused by inherited variations in mtDNA and nDNA, as well as sporadic mutations where there is no family history.[69]

Screening for people with mito can provide information to support reproductive decision-making. Options for testing and screening available include the following, all of which provide information about mtDNA and nDNA mutations:

- **Prenatal diagnosis**: to identify genetic variations in a pregnancy,
- **Reproductive carrier screening**: a test of the parents to see if they carry genetic mutations that can cause mito.
- **More timely diagnosis for people with symptoms of mito**.

A range of reproductive options are available that can reduce the risk of mito in children:

- **Pre-implantation genetic testing (PGT)**: can be used to test embryos that have been created through in vitro fertilisation to select those with lower disease risk for transfer,[70]
- **Egg cell or embryo donation**, which involves a donor undergoing treatment through an IVF cycle, and
- **Mitochondrial donation**, an IVF technique that allows the creation of an embryo with the nDNA from propsective parents and the mtDNA from a donor egg..

While pre-implantation genetic diagnosis and egg cell or embryo donation can be used for preventing mito due to either mtDNA or nDNA mutations, mitochondrial donation is only relevant for mito caused by mtDNA mutations.

Preventing people from having mito offers very significant benefits because even with appropriate diagnosis and care, people will still experience significant negative quality-of-life impacts, many will be unable to work and have worse career prospects, and there are significant costs for the health system.

---

69 Mito Foundation, 2021, *Preventing mitochondrial disease: Reproductive choices for families*, available at: https://www.mito.org.au/wp-content/uploads/2021/05/Preventing-Mito-Disease.pdf

70 For those impacted by mtDNA mutations, PGT can help to select embryos with low-levels of mtDNA mutations. For parents that carry recessive nDNA changes, PGT can help to select embryos who do not carry both copies of these gene changes.

Recent developments have improved access to mitochondrial donation. In March 2022, the *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021* was passed in the senate, which legalised mitochondrial donation. One year later, the Commonwealth Government announced a Monash University led team will receive $15 million to conduct a pilot program for mitochondrial donation. Further, as of November 1st 2023, genetic testing for mito has been added to the Medicare Benefits Schedule, which can help more families identify when mitochondrial donation may be appropriate.

However, the availability of reproductive options and provision of genetic counselling could still be improved. Survey evidence from 2017[71] of parents with children living with rare diseases suggests that 75 per cent of parents believed that the diagnosis could have an impact on future family planning, although only 45 per cent received genetic counselling.[72] There remains a lack of government funding for the reproductive carrier screening that includes the nDNA changes relevant for mito.

Reproductive options are currently the only way to prevent mito, and box 4.1 illustrates how impactful reproductive carrier screening and pre-implantation genetic diagnosis can be for a family affected by mito.

4.1 Case study of reproductive options: Tracey, Mum to Dion

"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 mito, for which there is no cure. At just three years old, Dion succumbed to Leigh's Disease, 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-rending 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

71 This survey was conducted in 2017, prior to the passing of legislation and commitment of funding of the pilot study for mitochondrial donation, and funding of whole-genome sequencing through Medicare.

72 Zurynski, Y., Deverell, M., Dalkeith, T., Johnson, S., Christodolou, J., Leonard, H., Elliot, E.J. and APSU Rare Diseases Impacts on Families Study group, 'Australian children living with rare diseases: experiences of diagnosis and perceived consequences of diagnostic delays', *Orphanet Journal of Rare Diseases*, 12(68), doi: 10.1186/s13023-017-0622-4

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."

Source: Mito Foundation Submission Re: MSAC application 1637 – Expanded Reproductive Carrier Screening of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions, p.3, available at: https://www.mito.org.au/wp-content/uploads/2022/06/Mito-Foundation-Submission-re-MSAC-1637-8-June-2022.pdf

Burden that can be prevented by reproductive options

Preventing mito through reproductive options reduces the cost of mito across all domains, including avoiding the impacts of mito on quality of life, productivity, wellbeing of the person and their family, and healthcare costs. Ultimately, the burden that is preventable due to reproductive options depends on the number of cases of mito that are prevented, which depends on:

- how many births occur of children at risk of developing mito,
- how much that risk is reduced by each option, and
- Take-up of reproductive options.

Lifetime burden of mito

We have estimated the lifetime burden of mito for an individual under two approaches. The first is to combine the estimated costs of mito in Australia from the previous chapter with the disability weight from the *Impact Assessment*. This approach is as follows:

- Quality-of-life benefit: we convert the estimates from the *Impact Assessment* to Australian dollars , which assume a disability weight of 0.39, account for the decreased life expectancy due to mito, and apply a value of £60 000 per Quality-Adjusted-Life Year gained ($138 407 in 2023 Australian dollars),[73]
- Avoided productivity loss: we multiply the lifetime earnings of a person in the general population ($219 275)[74] by the proportional reduction in productivity due to mito (51 per cent), and

73 See Tables 12 and 13: UK Department of Health, 2014, *Impact Assessment of Mitochondrial donation regulations*, available at: https://www.legislation.gov.uk/ukia/2015/9/pdfs/ukia_20150009_en.pdf

74 This is a simple average of lifetime earnings across men and women.

- Healthcare cost saving: we multiply average annual cost per adult estimated by Cohen et al (2018) (converted to 2023 Australian dollars) by the ratio of outpatient costs over the entire duration of care to annual costs based on estimates by Haque et al (2023).[75]

We present the estimated lifetime costs of mito based on this approach in table 4.2, together with the estimates from the *Impact Assessment* of benefits per person converted to 2023 Australian dollars. The dominant benefit category is from avoided quality-of-life losses ($2.9 million). There is a large difference in the avoided productivity loss, which we understand is because of a different approach to estimating the discounted present value of future lost income.[76]

4.2 Benefit per avoided case of mito

Benefit per person	Approach 1 - Applying CIE estimates of the lifetime burden of mito
	$/person
Quality-of-life benefit	
Avoided production loss	107 445
Remaining quality of life loss	2 826 790
Subtotal	**2 934 234**
Healthcare cost saving	110 017
Total	**3 044 251**

Note: Healthcare costs estimated under Approach 2 have also been adjusted to account for the lower price of healthcare (83 per cent relative to Australia) based on OECD data.

Source: UK Department of Health (2014) *Impact Assessment of Mitochondrial donation regulations*, available at: https://www.legislation.gov.uk/ukia/2015/9/pdfs/ukia_20150009_en.pdf , CIE.

Likely take-up and avoided burden from improving reproductive options

The set of reproductive options available will vary from person-to-person, and it is difficult to estimate how many people would have each option available and likely rates of take-up.

The UK Government conducted a full economic assessment of creating regulations to enable mitochondrial donation treatment to take place. Prior to the creation of the regulations, it was illegal to provide treatment based on mitochondrial donation techniques. The *Impact Assessment* identified that the key benefit of the change to regulations would be Quality-Adjusted Life Year (QALY) gains to 20 individuals a year who will not have serious mtDNA disease.

---

75 Haque et al (2023) estimates the average annual cost and cost over the entire duration of care for three groups (depending on type of mito and clinical vs genomic diagnostic status). The average annual cost across these three groups is $740, while the cost over the entire duration of care is $5 059, implying a ratio of total to annual costs of 6.8. This would be equal to the number of years receiving care, if costs were constant over those 6.8 years.

76 In our calculations, we estimated the present value of future earnings from the perspective of a newly born infant at year 0. Hence, productivity losses, which all occur during working age years, are relatively heavily discounted.

The number of births per year among women at risk for transmitting mtDNA disease,[77] which is the number of women with inherited pathogenic mtDNA mutations, was estimated by Gorman et al (2015b).[78] We have extrapolated these estimates from England in 2011[79] to Australia based on the relative size of the female population in 2022 and the relative total fertility rate in 2021 (the most recent year of data available).[80] We estimate that there are 141 births per year in Australia among women with inherited pathogenic mtDNA mutations at risk for transmitting mito.

UK guidelines for mitochondrial donation state that it should only be permitted in cases of women for whom pre-implantation genetic diagnosis is inappropriate or likely to be unsuccessful.[81] Australian legislation also requires that approval for mitochondrial donation must not be granted unless other available techniques would be inappropriate or unlikely to succeed.[82] Pickett et al (2019) state that "preimplantation genetic diagnosis is suitable only for women who are expected to produce some eggs with low levels of mutated mtDNA and are therefore at lower risk for having a child with serious mtDNA disease".[83] They develop estimates of the share of women at risk of having a clinically affected child, which depend on the level of maternal m.3243A→G heteroplasmy.

This highlights that the reproductive options available for parents where there is a risk of transmitting mito depends on individual characteristics. As a result, it is difficult to establish a population-wide estimate of potential take-up of reproductive options.

4.3 Births among women with inherited pathogenic mtDNA mutations

Country	Units	England	Australia
Year		2011	2022
Population of women	Number	12 391 000	12 877 635
Total fertility rate	Children/woman	1.91 [a]	1.70
Average number of births per year among women at risk for transmitting mtDNA disease	Number of births per year	152	141

[a] This total fertility rate estimate is obtained from the OECD, and is an estimate for Great Britain rather than only England.

Source: Gorman et al (2015), ABS, CIE.

77 Note that this definition excludes nDNA mutations associated with mito.

78 Gorman, G.S., Grady, J.P., and Turnbull, D.M., 2015, 'Mitochondrial donation – How many women could benefit', *New England Journal of Medicine*, 372(9): 885-887, doi: 10.1056/NEJMc1500960

79 Gorman et al (2015) reports the size of the female population England in 2011, which we compare to the ABS's estimate of the Australian female population from the 2021 Census (see ABS, 2021, *Population: Census*, available at: https://www.abs.gov.au/statistics/people/population/population-census/latest-release)

80 The Organisation for Economic Cooperation and Development publishes estimates of the total fertility rate for Australia and Great Britain for each year.

81 Pickett, S.J., Blain, A., Shiau Ng, Y., Wilson, I.J., McFarland, R., Turnbull, D.M., Gorman, G.S., 'Mitochondrial donation – Which women could benefit', *New England Journal of Medicine*, 380: 1971-1972, doi: 10.1056/NEJMc1808565

82 *Mitochondrial Donation Law Reform (Maeve's Law) Act 2022*, section 28P, subsection 4c.

83 Ibid.

Providing mitochondrial donation to 20 people per year in Australia appears to be realistic given that the number of births per year among women at risk for transmitting mito is similar between England and the UK. In addition to this, using PGT to select embryos with low levels of mutated mtDNA along with increasing use of reproductive carrier screening is likely to lead to a much larger number of children who are born with a significantly reduced risk of mito.

Applying the more conservative estimate of preventing mito for 20 people for a single year would lead to a quality of life improvement of $60.9 million in present value terms, or $457.6 million in present value terms if maintained over 10 years.

This same magnitude of benefit would apply for any reproductive options that achieved a reduction of 20 cases. This could be mitochondrial donation or other options such as PGT.

Earlier diagnosis and earlier intervention

Timely diagnosis is essential to improving outcomes for people with mito.

However, current diagnostic processes involve significant delays. This is particularly the case for adults with mito, who wait on average 6.2 years of trial-and-error testing before receiving their diagnosis (Rudaks et al, 2022).[84] While the diagnostic process for children is shorter (1.7 years on average based on Eom et al, 2016)[85].

Late diagnosis results in a lack of opportunity to intervene with lifestyle factors, as well as avoid or mitigate more progressed symptoms. For many, it is an avoidable ordeal of multiple incorrect diagnoses, and unnecessary/inappropriate treatments for the wrong diagnosis. It can also limit the window of time where intervention is most likely to succeed. Further, there is the burden of a traumatic diagnosis when early diagnosis opportunities were missed, and severe symptoms present.

There is significant healthcare resource use associated with the diagnostic odyssey. Rudaks et al (2022)[86] found that a third of people with diagnosed mito had consulted five or more doctors prior to diagnosis. Similarly, in the United States, Grier et al (2018)[87] found that almost half of people saw 6 or more of doctors before diagnosis, with around a quarter seeing more than 10.

---

84 Rudaks, L.I., Watson, E., Lubomski, M., Edema-Hildebrand, F., Ahmad, K., Liang, C., David, R., and Sue, C., 2021, 'The diagnostic journey of mitochondrial disease patients', *BMJ Neurology Open* 2021;3;doi: 10.1136/bmjno-2021-ANZAN.80

85 Eom, S., Lee, H.N., Lee, S., Kang, H., Lee, J.S., Kim, H.D. and Lee, Y., 2017, *Pediatric Neurology*, 66: 82-88, doi: 10.1016/j.pediatrneurol.2016.10.006

86 Rudaks, L.I., Watson, E., Lubomski, M., Edema-Hildebrand, F., Ahmad, K., Liang, C., David, R., and Sue, C., 2021, 'The diagnostic journey of mitochondrial disease patients', *BMJ Neurology Open* 2021;3;doi: 10.1136/bmjno-2021-ANZAN.80

87 Grier, J., Hirano, M., Karaa, A., Shepard, E., and Thompson, J.L.P., 2018, 'Diagnostic odyssey of patients with mitochondrial disease', *Neurology Genetics,* 2018;4 e230: doi: 10.1212/NXG.0000000000000230

Further, 38 per cent of people with mito in Australia[88] and 54.6 per cent in the United States[89] received an alternative non-mito diagnosis before eventual diagnosis with mito. The most common non-mito diagnoses included psychiatric disorders such as depression, fibromyalgia and chronic fatigue syndrome (Grier et al, 2018).[90]

4.4 Health outcomes due to the diagnostic odyssey among the mito community

Improved testing pathways can reduce complex and risky clinical tests such as invasive muscle biopsies:

> "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

The diagnostic odyssey involves a long period of emotional strain, burden, and costs:

> "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

Timely diagnosis supports pro-active management, early intervention, targeted treatments and uncovering alternative causes for mitochondrial dysfunction:

> "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

88 Rudaks et al (2021).

89 Grier et al (2018).

90 Ibid.

husband is working, maybe some of those supports could be reduced or avoided." — Adult with mito

A confirmed diagnosis can spur testing of other members of the same family:

"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"

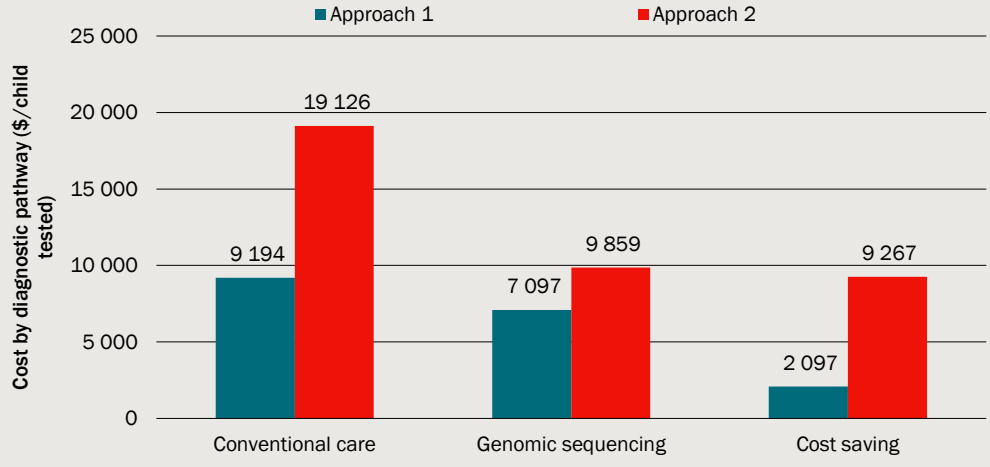
Source: Collated from Mito Foundation submission RE: MSAC application 1675 – Whole Genome Sequencing for the diagnosis of mitochondrial disease, available at: https://www.mito.org.au/wp-content/uploads/2022/10/Mito-Foundation-Submission-re-MSAC-1675-7-October.pdf

Medical cost savings and avoided productivity losses from earlier diagnosis

The economic evaluation of genomic sequencing for children (Wu et al, 2022)[91] estimated the healthcare costs associated with genomic sequencing compared to a 'conventional care' pathway. Using two approaches to estimating costs, they found a cost saving of between $2097 and $9267.

Most of the difference in costs is due to the difference in testing costs between the two pathways, with costs building up throughout the diagnostic odyssey under the conventional care pathway.

4.5 Costs of delayed diagnosis for Australian children



Note: All values are in 2023 dollars.

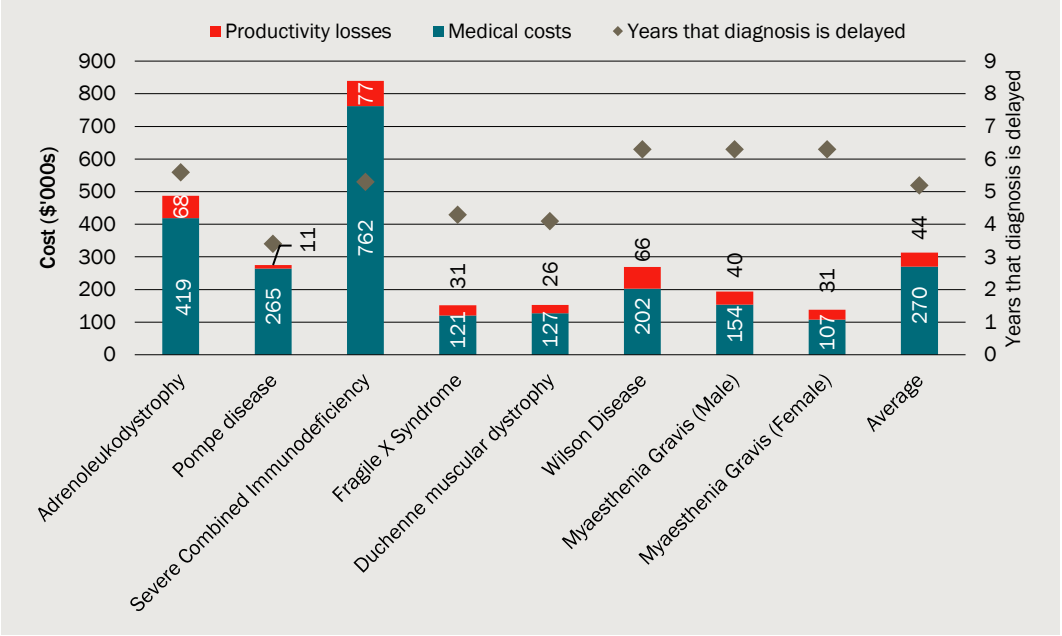
Data source: Wu et al (2022), CIE.

91 Wu, Y., Balasubramaniam, S., Rius, R., Thorburn, D.R., Christodoulou, J., and Goranitis, I., 2022, 'Genomic sequencing for the diagnosis of childhood mitochondrial disorders: a health economic evaluation', *European Journal of Human Genetics*, 30: 577-586, doi: 10.1038/s41431-021-00916-8.

The cost of delayed diagnosis in rare disease (EveryLife Foundation, 2023)[92] estimated the costs of delayed diagnosis for 8 rare diseases (listed in chart 4.6). The average medical cost saving across the 8 conditions (with Myasthenia Gravis [MG] split into men and women) is $270 000 per person, while the average productivity cost saving was $44 000 per person. If this average cost is multiplied by the number of people newly diagnosed in each year, this would amount to $20 million in cost savings (table 4.7).

This study defined timely diagnosis differently for each condition. For example, for MG, timely diagnosis was defined as being before age 40 in females and before age 50 in males. It is difficult to assess how the avoided costs for mito would compare to the costs estimated for the rare diseases analysed in the Delayed Diagnosis study. For example, MG is a chronic neuromuscular autoimmune disease affecting the use of muscles. Symptoms include double vision, slurred speech, breathing difficulties, fatigue, and an inability to use limbs. People with MG are frequent and intensive users of the health system, with most receiving ongoing medication and treatment including hospital admission for tests and emergency care.

4.6 Productivity and medical costs due to delayed diagnosis for rare diseases



Note: All values are in Australian dollars with a price year of 2023. Productivity losses have been converted to be applicable to Australia based on the average exchange rate from USD to AUD in 2021, and the ratio of US average hourly wages in 2021 (derived from EveryLife Foundation for Rare Diseases [2020], converted to AUD) to Australian median hourly earnings (ABS, 2022, *Employee earnings*, available at: https://www.abs.gov.au/statistics/labour/earnings-and-working-conditions/employee-earnings/latest-release). Medical costs have been converted to 2023 Australian dollars based on the average exchange rate from USD to AUD in 2021, the change in the Australian CPI from 2021 to 2023, and relative healthcare prices based on OECD (2020).

Data source: EveryLife Foundation for Rare Diseases (2023) *The cost of delayed diagnosis in rare disease: A health economic study*, derived from Exhibit 33, CIE.

92 EveryLife Foundation for Rare Diseases, 2023, *The cost of delayed diagnosis in rare disease: A health economic study*, available at: https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf

4.7 Total medical and productivity cost savings from timely diagnosis

Cost category	Child	Adult	Total
	$m/year	$m/year	$m/year
Medical cost savings from timely diagnosis	2	16	17
Avoided productivity losses from timely diagnosis	0	3	3
Total	**2**	**18**	**20**

Source: CIE.

Changes in clinical management due to diagnosis

Wu et al (2022) costed the changes in clinical management (e.g. treatment and surveillance) following testing of children for mito. Costing was achieved using a survey of clinicians to understand treatment changes and changes in screening tests and subspecialist referrals following genomic sequencing results.

Clinical management is affected by diagnosis. Wu et al (2022) find that clinical management is initiated or cancelled following a diagnosis for around 10-20 per cent of children. There was a cost of changes to clinical management from genomic testing of $372 per person and from conventional care of $403 per person. This suggests that there are savings from the genomic testing based on the changes in clinical management it leads to, rather than only the savings is diagnostic costs from more rapid/definitive diagnosis.

Since genomic testing has a higher diagnostic yield[93] and clinical management can be improved by diagnosis, there would be improvements to clinical management if all children were genomically tested. Based on the survey of clinicians, Wu et al (2022) found the chance of improving the process of the child's medical care was increased from 8 per cent under conventional care to 12 per cent under genomic sequencing.[94]

Similarly, Zurynski et al (2017) found that, among children with rare diseases, delayed diagnosis led to delays in treatment and inappropriate treatment in 25 per cent and 10 per cent of 462 respondents.[95]

---

93 Wu et al (2022) estimate that diagnostic yield for genomic sequencing is 38 per cent, compared to 27 per cent for conventional care, see table 1: Wu, Y., Balasubramaniam, S., Rius, R., Thorburn, D.R., Christodoulou, J., and Goranitis, I., 2022, 'Genomic sequencing for the diagnosis of childhood mitochondrial disorders: a health economic evaluation', *European Journal of Human Genetics*, 30: 577-586, doi: 10.1038/s41431-021-00916-8.

94 The study authors provide this data point in Table S.4 of the online supplementary material for the study. It is unclear what question in the survey this result is derived from, but may be a response to when clinicians were asked if a 'patient has been redirected towards palliation as a result of testing' or a 'previous decision to palliation has been reversed'. The set of questions included in the survey is also available as supplementary information at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9090793/

95 Zurynski, Y., Deverell, M., Dalkeith, T., Johnson, S., Christodolou, J., Leonard, H., Elliot, E.J. and APSU Rare Diseases Impacts on Families Study group, 'Australian children living with rare diseases: experiences of diagnosis and perceived consequences of diagnostic delays', *Orphanet Journal of Rare Diseases*, 12(68), doi: 10.1186/s13023-017-0622-4

Further, diagnosing more children means that genomic testing facilitates greater access to clinical trials (which use diagnostic status as a filter when recruiting) and to support services.

We have not identified quantitative evidence of how clinical management of adults diagnosed with mito changes with diagnosis. The CIE consulted with Australian clinicians, who suggested that care such as lifestyle, exercise and diet modifications can be effective. For some types of mito there are specific treatments that have been shown to be effective, such as Idebenone to treat visual impairment in adults with LHON.[96] Further, one consultation highlighted that the cohort who can benefit from greater treatment is larger than just those with clinical overt mito, since there is an opportunity to intervene and prevent symptoms.

Value of knowing

People with mito and their communities value knowing their diagnosis because this knowledge can reduce uncertainty and enable planning. This brings a range of psychological benefits and peace of mind, along with having a practical impact on management of mito and supports that can be accessed (box 4.8).

Medical diagnostics Garrison et al (2016)[97] and similarly Wurcel et al (2019)[98] establish frameworks for valuing medical diagnostics, which includes but is not limited to:

- Reduction in health years of life (i.e. QALYs) lost
- Health system cost savings
- Avoided productivity losses
- Non-medical cost savings (e.g. transport costs and caregiving)
- Reduction from uncertainty
- Value of hope, which is more relevant for curable conditions, and
- Real option value associated with future technologies to extend life.

Garrison et al (2016) was preceded by a literature review (Phase 1 of the project), which captured value across the medical, planning and well-being dimensions. Of relevance for mito, it identified evidence supporting psychological benefits from knowing. Diagnostics have been found to have beneficial effects on mental health and wellbeing, personal control, and reproductive decision making.

---

96 See Lyseng-Williamson, K.A., 2016, 'Idebenone: A review in Leber's Hereditary Optic Neuropathy', *Drugs*, 76(7): 805-813, doi: 10.1007/s40265-016-0574-3.

97 Garrison, L., Mestre-Ferrandiz, J., and Zamora, B., 2016, The value of knowing and knowing the value: Improving the health technology assessment of complementary diagnostics, White Paper, Office of Health Economics and EPEMED, available at: https://www.ohe.org/wp-content/uploads/2016/07/WP_EpemedOHE_final.pdf

98 Wurcel, V., Cicchetti, A., Garrison, L., Kip, M.M.A., Koffijberg, H., Kolbe, A., Leeflang, M., Merlin, T., Mestre-Ferrandiz, J., Oortwin, W., Oosterwijk, C., Tunis, S. and Zamora, B., 2019, 'The value of diagnostic information in Personalised Healthcare: A comprehensive concept to facilitate bringing this technology into healthcare systems', *Public Health Genomics*, 22: 8-15, available at: https://www.karger.com/Article/Pdf/501832

4.8 The 'value of knowing' expressed by the mito community

There are psychological benefits to knowing your diagnosis, with many people living with a provisional diagnosis when clinical tests are inconclusive:

> "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

Certainty of diagnosis is important for peace of mind:

> "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

Once someone is diagnosed, this improves their access to non-health 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

Understanding your diagnosis is also important to make 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

Source: Collated from Mito Foundation submission RE: MSAC application 1675 – Whole Genome Sequencing for the diagnosis of mitochondrial disease, available at: https://www.mito.org.au/wp-content/uploads/2022/10/Mito-Foundation-Submission-re-MSAC-1675-7-October.pdf

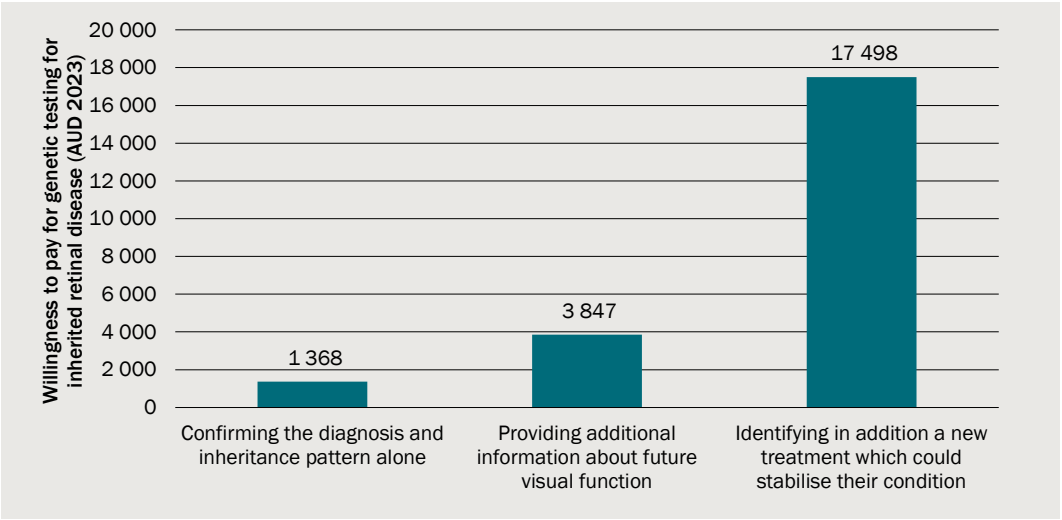
The best available evidence about the value of knowing are estimate of willingness to pay for testing. The amount that a person with mito or their carer/parent is willing to pay for a testing will captures the psychological, clinical, and other values of knowing that you do or don't have a diagnosis. Many studies have estimated willingness to pay using contingent valuation techniques, with 66 studies identified in a literature review by Lin et al (2013) across many diseases.[99]

99 Lin, P., Cangelosi, M.J., Lee, D.W., and Neumann, P.J., 2013, 'Willingness to pay for diagnostic technologies: a review of the contingent valuation literature', *Value in Health*, 16(5): 797-805, doi: 10.1016/j.jval.2013.04.005

Meng et al (2022) estimate average willingness to pay for genomic testing of $2918 (2023 AUD) for mito.[100]

A similar study about willingness to pay for genetic testing for inherited retinal diseases (Tubeuf et al, 2015) found that willingness to pay was far higher where the test provided prognostic information, and far higher again if it enabled treatment that could stabilise the condition (chart 4.9). While this is not yet the case for most types of mito, advances in clinical research, including natural history and biomarker research, may enable this for mito in the future.

4.9 Willingness to pay for genetic testing for inherited retinal disease



Data source: Tubuef et al (2015), CIE.

Improving health care

Once a diagnosis of mito disease has been established, there remains a challenge of providing people with appropriate health care and other support.

While this is a challenge with all rare diseases, it is particularly the case for mito because it can affect any organ, has highly variable clinical presentations, and usually involves multiple systems[101]. The initial health issues that patients face are variable, can present differently in paediatric and adult-onset forms, and clinical features evolve over time.

These features add considerable complexity to approaches to management, and contribute to the variability from one clinical centre to another.

In many cases, patients receive sub-optimal care due to lack of specialist knowledge and inadequate tailoring of care plans to individual needs.

---

100 Meng, Y., Clarke, P.M., and Goranitis, I., 2021, 'The Value of Genomic Testing: A Contingent Valuation Across Six Child- and Adult-Onset Genetic Conditions', *PharmacoEconomics*, 40: 215-223, doi: 10.1007/s40273-021-01103-9

101 Pfeffer, G. and Chinnery, P.F., 2013, 'Diagnosis and treatment of mitochondrial myopathies', *Annals of Medicine*, 45(1): 4-16, doi: 10.3109/07853890.2011.605389

An example of inappropriate treatment due to poor health knowledge among medical practitioners and lack of consensus on management approaches is inappropriate provision of medication. Appropriate clinical management should consider avoidance of medications that are toxic to mitochondrial function.[102] However, the diversity of manifestations of mito means these considerations will differ across individuals. De Vries et al (2020) develop consensus guidelines for safe medication use for people with mito.[103] Some medications are clearly contraindicated (e.g. valproic acid for people with mito due to POLG mutations), while for others they make recommendations about assessing whether the benefits of usage against the risks (e.g. aminoglycosides). Lack of knowledge of contraindications, unnecessary withholding of a drug in a situation of clinical need, or a lack of a tailored plan for each patient can all lead to suboptimal care.

As set out in chart 4.10, key elements of best practice for clinical management involve:

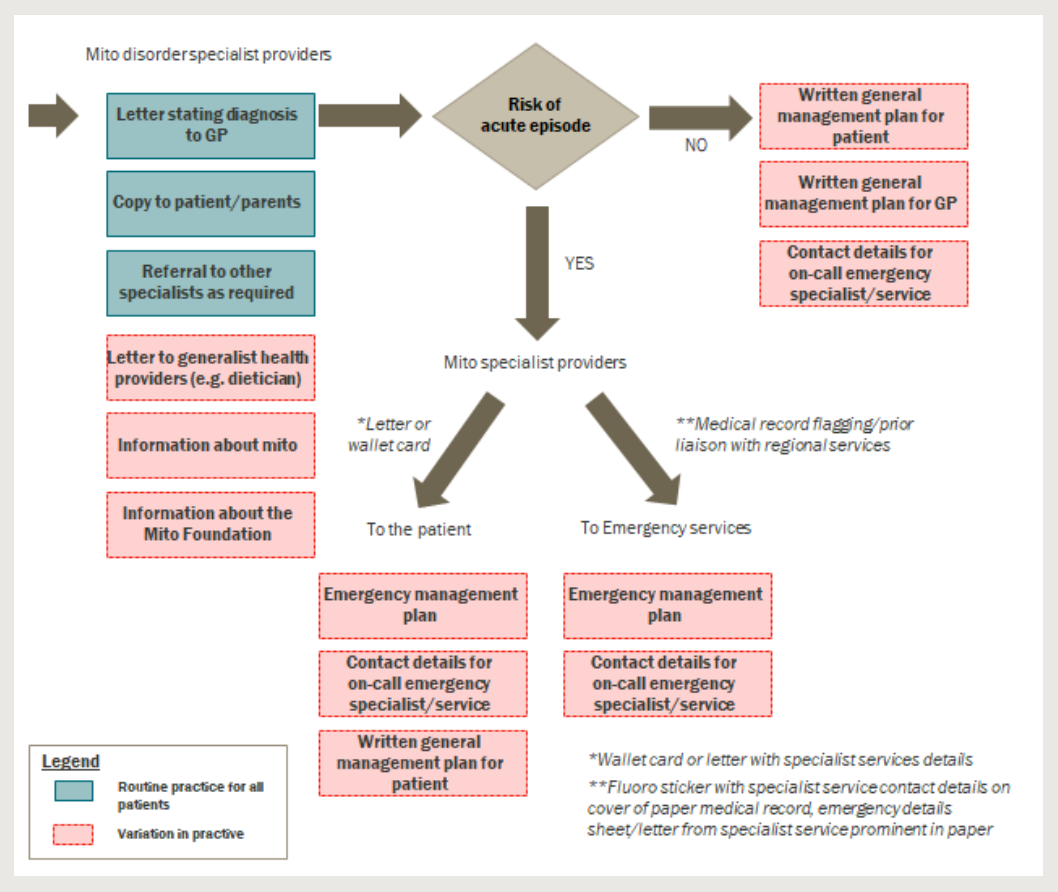
- provision of a diagnosis letter from a mito disorder specialist stating a diagnosis of mito to a patients' General Practitioner (GP), and to patients and parents to use as needed
- referral to other health care professionals as required
- assessment of the risk of an acute episode
- for those not at risk, provision of resources to assist day-to-day management
- for those at risk, provision of an emergency management plan for patients, and another for Emergency services, including contact details for on-call emergency specialists and services that and other relevant information.

Better treatment can also include better scheduling of the myriad of health care appointments required, with greater consideration of minimising wait times between appointments.

102 De Vries, M.C., Brown, D.A., Allen, M.E., Bindoff, L., Gorman, G.S., Karaa, A., Keshavan, N., Lamperti, C., McFarland, R., Ng, Y.S., O'Callaghan, M., Pitceathly, R.D.S., Rahman, S., Russel, F.G.M., Varhaug, K.N., Schirris, T.J.J. and Mancuso, M., 2020, 'Safety of drug use in patients with a primary mitochondrial disease: An international Delphi-based consensus', *Journal of Inherited Metabolic Disease*, 43: 800-818, doi: 10.1002/jimd.12196

103 Ibid.

4.10 Best practice and resources for mito patients on diagnosis



Data source: Long, J.C., Best. S., Hatem, S., Braithwaite, J. and Christodolou, J., 2022, . *Improving post-diagnosis management and communication for people with mitochondrial disorders: Insights from Mitochondrial Disorder Specialist Services in Australia and people living with mito*, Sydney, Australia, p.9, available at: https://www.mq.edu.au/__data/assets/pdf_file/0004/1210396/Improving-post-diagnosis-management-1March2022-Mito-LONG.pdf

Most mito community members experience uncoordinated care for mito, characterised by difficulty accessing mito-knowledgeable specialists, a lack of a management plan, and health professionals without sufficient mito-specific expertise (box 4.11).

4.11 Case study of fragmented care

Most community members find accessing health care for mito difficult:

> ""I have a mito specialist but their role is largely limited to telling me to see certain specialists. They don't offer help with medication, supplements, and don't ever recommend specialists who know about mito…I have a dietitian but they [know] nothing about mito so they rely on the limited information I can supply. I have an excellent exercise physiologist … he understands my condition better than anyone and has been an enormous support."

Most community members have a GP that helps them manage their mito, but mito-specific knowledge is variable and care can be uncoordinated:

> "[My care is] managed by my GP who is incredibly supportive but admits to knowing virtually nothing about mito and looks to me to give him info about what I need"
>
> "The GP that I had originally was very conversant with mito but he retired and I have struggled to find another who knows mito well"
>
> "Significant difficulty. GP has retired. [I have] multiple specialists but no coordination of care"

Most have access to a mito specialist, many would like more access:

> "Impossible so far to find a specialist [who is] interested. Got "you have mito. There is no treatment. See you in a year" from my 2nd neurologist"
>
> "Doctors have not been very helpful mostly just get a merry go round of referrals"

Most community members do not have a management plan for their mito:

> "Having access to a multi-disciplinary clinic, I've engaged with a dietician once, and all seemed OK. I've discussed exercise with my specialist doctor and again, all seems OK there. This may, therefore, be my "management plan", but I am unaware of anything formal in place"
>
> "I haven't seen the mito specialist, [I] don't have any relevant information for daily management. Also I have never seen a dietician. I don't have guidelines for management plan. I am managing my condition on my own".

Source: Quotes selected by CIE from Mito Community Survey 2022, Insights Report 3.

Access to care in Australia may be lacking

People with mito experience a lack of access to healthcare:

- The Mito Community Survey found that many in the mito community in Australia want more personalised information, particularly about prognosis.[104] Many Australian community members also report that they do not have a management plan for their mito (75 per cent), nor have they received professional advice about the best

104 Mito Foundation, 2022, *Mito Community Survey Insights Report 2*, p.12, available at: https://www.mito.org.au/wp-content/uploads/2022/11/Insights-Report-2-Final-151122.pdf

diet for mito (64 per cent) (chart 4.12). All of these things are acknowledged as best practice in the Australian Patient Care Standards.[105]

- Long et al (2021) report that people with or caring for a child with mito need to devote significant effort to self-advocacy.[106] This includes the need for ongoing negotiation to access advice and services to manage their condition, negotiating related to joint decision-making, and advocating for their care with non-specialist services (e.g. dieticians). Few participants in this study reported having their mental health formally addressed or assessed at any time.
- Teutsch et al (2023)[107] found that, among children with rare diseases, those living in regional and remote areas experienced significantly more barriers to accessing healthcare than those in major cities, including travel distance, out-of-pocket costs, and lack of specialist and other health care services.
- There is anecdotal evidence of long wait times to see a mito specialist in Australia, which delays treatment and management and adversely affects quality of life and speed of progression (Equity Economics and Development Partners and Rare Voices Australia, 2022).[108]

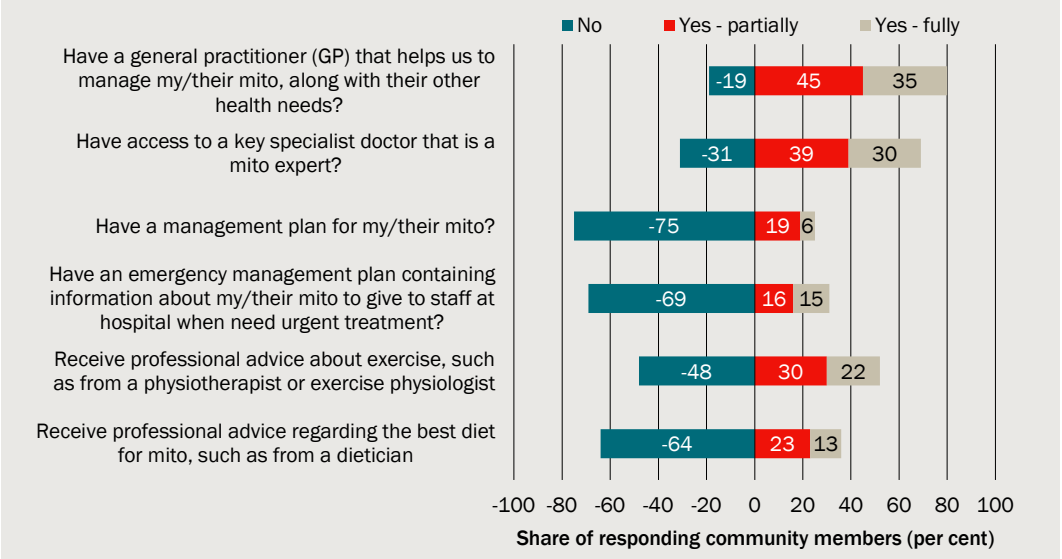
105 Sue, C.M., Balasubramaniam, S., Bratkovic, D., Bonifant, C., Christodoulou, J., Coman, D., Crawley, K., Edema-Hildebrand, F., Ellaway, C., Ghaoui, R., Kava, M., Kearns, L.S., Lee, J., Liang, C., Mackey, D.A., Murray, S., Needham, M., Rius, R., Russell, J., Smith, N.J.C., Thyagarajan, D. and Wools, C., 2022, 'Patient care standards for primary mitochondrial disease in Australia: an Australian adaptation of the Mitochondrial Medicine Society recommendations', *Internal Medicine Journal*, 52(1): 110-120, doi: 10.1111/imj.15505

106 Long, J.C., Best, S., Hatem, S., Theodorou, T., Catton, T., Murray, S., Braithwaite, J. and Christodolou, J., 2021, ' The long and winding road: perspectives of people and parents of children with mitochondrial conditions negotiating management after diagnosis', *Orphanet Journal of Rare Diseases*, 16(1): 310, doi: 10.1186/s13023-021-01939-6

107 Teutsch, S., Zurynski, Y., Eslick, G.D., Deverell, M., Christodolou, J., Leonard, H., Dalkeith, T., Johnson, S.L.J. and Elliot, E.J., 2023, 'Australian children living with rare diseases: health service use and barriers to accessing care', *World Journal of Pediatrics*, 19: 701-709, doi: 10.1007/s12519-022-00675-6

108 Equity Economics and Development Partners and Rare Voices Australia, 2022, *Towards a strengthened rare disease workforce for Australia*, p.16, available at: https://rarevoices.org.au/wp-content/uploads/2022/02/RareMetabolicDiseaseWorkforce_WhitePaper.pdf

4.12 Mito community's access to healthcare



Data source: Mito Foundation, 2022, *Mito Community Survey Insights Report 3*, Figure 2, available at: https://www.mito.org.au/wp-content/uploads/2023/02/MITO_REPORT.CommunitySurvey23.R3.150223.pdf

Better management of pre-symptomatic people to prevent onset

The majority of people with with a genetic risk factor for mito are currently asymptomatic (having no symptoms) or oligosymptomatic (having few symptoms). This means they are unlikely to receive any mito-specific care, unless they are aware of their risk of developing mito (e.g. through a cascade diagnosis).

There is an opportunity to prevent people developing serious symptoms of mito. The Australian Patient Care Standards state that early diagnosis and referral to specialists enables "intervention and treatment that may prevent severe clinical sequelae".[109] Examples of recommendations from the Patient Care Standards that can prevent severe sequelae include:

- "Counsel patients to avoid environmental and other noise exposure as this can exacerbate hearing loss and lead to a stepwise deterioration in hearing … [which] may or may not be reversible"
- "Use valproic acid, especially in patients with *POLG*-related disease as it exacerbates seizures and may precipitate liver failure", and
- "Recommend graded, regular physical activity to improve symptoms of exercise intolerance and fatigability, given the evidence that aerobic exercise in patients with MD increases energy production".

109 Sue, C.M., Balasubramaniam, S., Bratkovic, D., Bonifant, C., Christodoulou, J., Coman, D., Crawley, K., Edema-Hildebrand, F., Ellaway, C., Ghaoui, R., Kava, M., Kearns, L.S., Lee, J., Liang, C., Mackey, D.A., Murray, S., Needham, M., Rius, R., Russell, J., Smith, N.J.C., Thyagarajan, D. and Wools, C., 2022, 'Patient care standards for primary mitochondrial disease in Australia: an Australian adaptation of the Mitochondrial Medicine Society recommendations', *Internal Medicine Journal*, 52(1): 110-120, doi: 10.1111/imj.15505

Such recommendations cover a mix of lifestyle modifications, monitoring and pharmaceutical or other treatments. It is unclear whether following the Care Guidelines for an oligosymptomatic person with relevant mutations is sufficient to result in that person remaining oligosymptomatic. Even if development of symptomatic mito is not prevented, symptom burden is likely able to be decreased.

Quantifying the cost savings from improved treatment

We are not able to estimate the preventable costs of mito associated with improvements to treatment because evidence about how treatment impacts other costs of care, workforce participation or out-of-pocket costs is not available.

There is some evidence to support that current interventions have a positive impact on quality-of-life for adults with mito. Klein et al (2021)[110] undertook a systematic scoping review of evidence related to cognitive functioning and mental health in mito. They identified ten studies that included quality of life as an outcome measure when studying interventions such as exercise training, pharmaceuticals, supplements, and dietary interventions.[111] Of the ten studies, half found some impact on quality of life for at least some subscales or time points. While studies of exercise interventions found mixed evidence of quality of life improvements, all found impacts on physical parameters (e.g. muscle mass). Pharmacological treatment of mental disorders and symptoms among people with mito has been more often described in case studies (Klein et al, 2021), with most case studies finding improvements in mental health.

Dietary supplementation is a key aspect of care for people with mito. Malnutrition has been found to be frequent in people with mito, with half of adults and 47.4 per cent of children consuming less than 75 per cent of daily caloric needs, and that 26.7 per cent of study participants had malnutrition (DiVito et al, 2023).[112] DiVito et al (2023)[113] observed that increased nutritional intake was correlated with to improved muscle strength, decreased muscle fatigue, and improved quality of life. They concluded that these results emphasise the critical importance of nutritional assessment and interventions for people with mito. Klein et al (2021) identified two studies investigating dietary supplements, neither of which were found to improve quality of life, but one study for a dietary intervention found improvements in vitality and fatigue.

---

110 Klein, I., van de Loo, K.F.E., Smeitink, J.A.M., Janssen, M.C.H, Kessels, R.P.C., van Karnebeek, C.D., van der Veer, E., Custers, J.A.E. and Verhaak, C.M., 2021, 'Cognitive functioning and mental health in mitochondrial disease: A systematic scoping review', *Neuroscience and Biobehavioral Reviews*, 125: 57-77, doi: 10.1016/j.neubiorev.2021.02.004

111 Note that Klein et al (2021) state that they identified nine studies, but ten studies are listed in their table summarising the findings across the range of studies.

112 DiVito, D., Wellik, A., Burfield, J., Peterson, J., Flickinger, J., Tindall, A., Albanowski, K., Vishnubhatt, S., MacMullen, L., Martin, I., Muraresku, C., McCormick, E., George-Sankoh, I., McCormack, S., Goldstein, A., Ganetzky, R., Yudkoff, M., Xiao, R., Falk, M.J., Mascarenhas, M.R., Zolkipli-Cunningham, Z., 2023, 'Optimized nutrition in mitochondrial disease correlates to improved muscle fatigue, strength and quality of life', *Neurotherapeutics*, doi: 10.1007/s13311-023-01418-9

113 Ibid.

People with mito perceive treatments to be effective at improving their health. Karaa et al (2017) found that most people with mito report that supplements improved their health.[114] In the PEEK Study,[115] people with mito rated the effectiveness of treatments they received from a score of 1 (ineffective) to 5 (very effective), with 3 corresponding to moderately effective. The average score fell between 2.4-3.5 for all treatments, with the lower score for vitamins and the highest for respiratory therapy. The set of treatments available were relatively limited, with coenzyme Q10, diet, physical therapy and speech therapy being the other treatment options.

Psychotherapeutic interventions may also offer an effective way to improve quality of life. For example, in the context of cancer patients, short psychotherapeutic interventions were found to be effective at reducing fear of progression (Herschbach et al, 2009).[116]

Across a set of 21[117] rare diseases, Andreu et al (2022) find that the value of treatment in reducing mortality and other health care costs outweighs the cost of treatment to the health system (chart 4.13).[118] However, the size of this reduction varies very significantly across diseases, even where the annual cost per person is similar. For example, congenital diseases and haematological diseases have similar costs with treatment, but not having treatment is associated with 2 per cent and 16 per cent higher costs, respectively. Hence, while these estimates suggest it is likely that treatment leads to a net reduction in total societal cost of mito, the large variation across diseases suggests they are unreliable for use in deriving the impact of mito treatment on total social cost.

---

114 Karaa, A., Kriger, J., Grier, J., Holbert, A., Thompson, J.L.P., Parikh, S. and Hirano, M., 2016, 'Mitochondrial disease patients' perception of dietary supplements' use', *Molecular Genetics and Metabolism*, 119(1-2): 100-108, doi: 10.1016/j.ymgme.2016.07.005

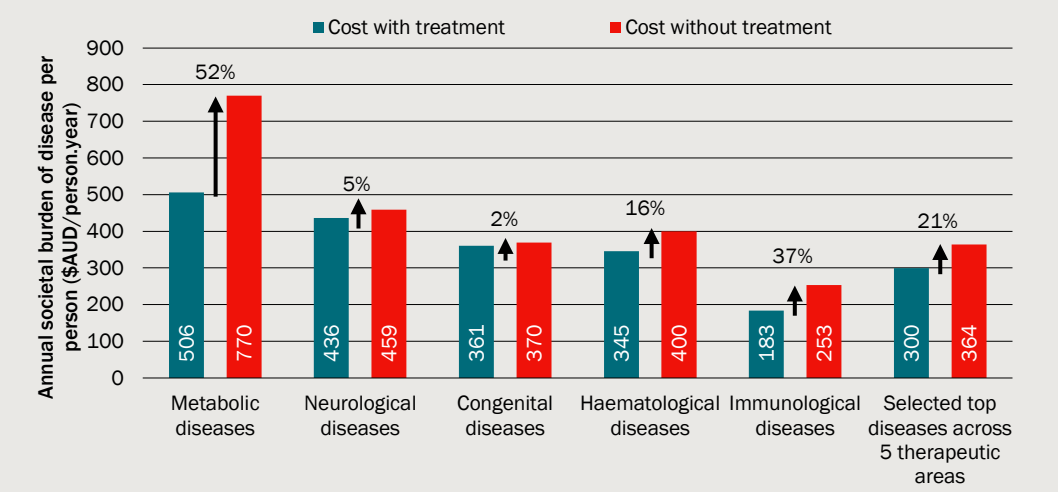
115 International Centre for Community-Driven Research, 2018, Mitochondrial Disease Australian Study, *PEEK*, 1(6), July 2018, p.99.

116 Herschbach, P., Book, K., Dinkel, A., Berg, P., Waadt, S., Duran, G., Engst-Hastreiter, U., Henrich, G., 2009, 'Evaluation of two group therapies to reduce fear of progression in cancer patients', *Support Care Cancer*, 18(4): 471-479, doi: 10.1007/s00520-009-0696-1

117 Andreu et al (2022) exclude spinal muscular atrophy from neurological disorders for this comparison because it was an outlier, and exclude Christianson syndrome and Deletion 5p from congenital disorders because no treatment exists for these diseases (and hence, there is no difference in costs). Hence, this comparison includes 21 out of the total 24 diseases in-scope for their study.

118 Andreu, P., Karam, J., Child, C., Chiesi, G. and Cioffi, G., 2022, *The burden of rare diseases: An economic evaluation*, whitepaper published by Chiesi Global Rare Diseases, available at: https://chiesirarediseases.com/assets/pdf/chiesiglobalrarediseases.whitepaper-feb.-2022_production-proof.pdf

4.13 Burden of rare diseases with and without treatment



Note: All values are in Australian dollars with a price year of 2023. The total social cost (which includes the value of lost mortality, healthcare costs, productivity losses and other indirect costs) have been converted to be applicable to Australia based on the average exchange rate from USD to AUD in 2022 and the change in the Australian CPI from 2022 to 2023. For simplicity, we have not applied different conversion factors for each component of costs (e.g. a different conversion of productivity losses based on relative earnings between Australia and the USA).

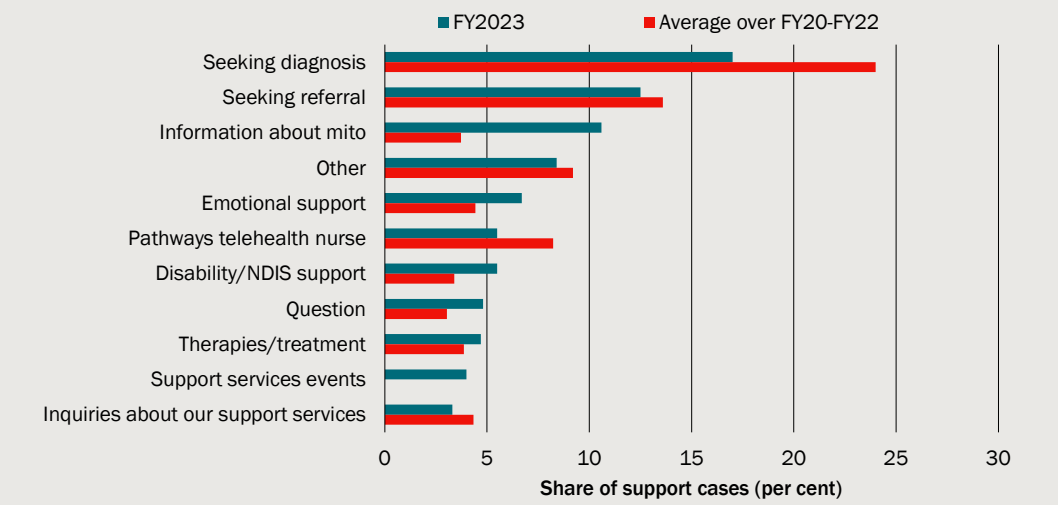
Data source: Andreu et al (2022), p.5.

Improving other supports and community awareness

Support services are important to improving quality of life and wellbeing for people with mito. The Mito Community Survey found that feelings of hope about the future are influenced by the support received.[119]

Key reasons that people seek support from organisations such as the Mito Foundation including trying to get a diagnosis, seeking information, emotional support and support relating to the NDIS (chart 4.14).

4.14 Reasons for seeking support from the Mito Foundation helpline



Data source: Mito Foundation Support Cases – FY2023 Annual Report, p12, CIE calculation of average over FY20-FY22.

119 Mito Foundation, 2022, *Mito Community Survey Insights Report 4*, p.6.

However, there is scope for support services to further improve quality of life through reducing barriers to access, providing more information about support services where needed, and fundamentally by delivering more support services to those who need them. More people with mito feel they did not receive helpful mental health support (31 per cent) than the share who feel they received helpful support (25 per cent), and around half of community members feel they lacked support in one or more areas.[120] A key barrier that prevents people from obtaining the support they need include a lack of professionals who are knowledgeable about mito. Many people with mito also feel that they want more information about support services, since while 87 per cent of families living with rare disease wanted information about support groups at diagnosis, only half of those (i.e. 43 per cent) received such information.[121]

Potential impact of support services on wellbeing

Delivering appropriate support services to people with mito can improve mental health outcomes. Evidence from the UK about people with rare diseases suggests that poor mental health can have knock on impacts on physical health (87 per cent), on work/education (81 per cent) and on personal relationships (69-76 per cent across relatives, friends, and partners).[122] Spencer-Tansley et al (2022)[123] found that:

- around half of people (49 per cent) who had accessed psychological support found it helpful, but fewer felt it was tailored to their needs (37 per cent),
- most people (59 per cent) accessed emotional support (e.g. peer support online), with the majority of them having found it themselves.

The NDIS provides a range of important supports for people with disability, such as support with activities of daily living, transport, and employment. While many people with mito access the NDIS, the Mito Community Survey suggests that 24 per cent of people with mito and 13 per cent of carers have a need for disability support but haven't applied.[124] This is a significantly higher share than the proportion who applied but were found to be ineligible (7 per cent).

The NDIS provides a range of benefits to participants and their carers. An evaluation of the NDIS by Mavromaras et al (2018)[125] found that the NDIS led to modest

120 Ibid.

121 Anderson, M., Elliot, E.J., and Zurynski, Y.A., 2013, 'Australian families living with rare disease: experiences of diagnosis, health service use and needs for psychological support', 8: 22, doi:10.1186/1750-1172-8-22

122 Spencer-Tansley, R., Meade, N., Ali, F., Simpson, A. and Hunter, A., 2022, 'Mental health care for rare disease in the UK – recommendations from a quantitative survey and multi-stakeholder workshop', *BMC Health Services Research*, 22(648), doi: 10.1186/s12913-022-08060-9

123 Ibid.

124 Mito Foundation, 2022, *Mito Community Survey Insights Report 2*, p.18.

125 Mavromaras, K., Moskos, M., Mahuteau, S., Isherwood, L., Goode, A., Walton, H., Smith, L., Wei, Z. and Flavel, J., 2018, *Evaluation of the NDIS*, available at:

improvements in the wellbeing of people with disability, but this is further improving with time in the NDIS. Better wellbeing was found to be associated with increased levels of support and independence for people with disability. Opportunities for greater social participation, improved skills and developmental progress also contributed to enhanced wellbeing under the NDIS.

Potential impact of reducing barriers to work

People with mito may receive insufficient supports to enable workplace participation and productivity. Box 4.15 provides a case study of how participation in work is impacted by mito and highlights that work flexibility and support services can play an important role in enhancing work outcomes.

4.15 Case study of support services and workforce participation

When she was diagnosed with mito, Sarah was almost finished with her apprenticeship as a hairdresser. Sarah says

> "Becoming a hairdresser had always been my dream and I was training under an award-winning hairdresser and each day falling more in love with this as my career."

Sarah took time off work with what she thought was the flu. She ended up in the hospital and never went back to her dream career. Primarily this was due to her lung function declining rapidly combined with the physical nature of the job.

> "When I received the diagnosis of mito I didn't really understand what it meant, but being told by a doctor I couldn't go back to hairdressing was what absolutely rocked me. That was the hardest thing to deal with."

Sarah now receives the disability support pension at varying rates depending on her fluctuating ability to work. She also helps with her family's small business for a few hours each day. Having flexibility in being able to work for a few hours each day and spend time with her husband during the day has improved Sarah's day to day life. Sarah also has time to spend on her online hobby business, which makes very little money, but helps to raise awareness of hidden disabilities.

When thinking about what advice to offer others with mito, Sarah says

> "If you are told you cannot do one thing, find something else you are passionate about, something you can do, and pursue that. Break up what you need to get done into small parts and focus on just one at a time. Understand that you are giving 100% of what you can and that is ok, even if it is different to what you could give before your diagnosis."

Sarah thinks that mental health support and coaching is the most important thing that can help people with mito improve their lives.

> "The combination of my friends and family pushing me to be more proactive and the message of empowerment from the Mito Foundation has shaped how I can live positively with mito."

Source: Supplied by Mito Foundation.

https://www.dss.gov.au/sites/default/files/documents/04_2018/ndis_evaluation_consolidated_report_april_2018.pdf

In analysis for the Royal Commission into Violence, Abuse, Neglect and Exploitation of People with Disability, Taylor Fry and The CIE estimated that 30.5 per cent of non-participation in the labour force of people with disability was due to neglect. This was the proportion of non-participation in the workforce by people who said it was due to health reasons, but stated that their disability was not work-limiting. It is likely that there are people with mito who would not characterise their disability as work-limiting but who nonetheless would stop work because of mito. For example, those who require significant amounts of sick leave for doctors appointments are not limited in their ability to undertake work, but nonetheless may leave the workforce as a result of this.

To illustrate the significance of achieving improvements in workplace participation, we model the avoided productivity losses if people with mito and their carers no longer quit their jobs due to mito, but instead work reduced hours. If those who quit their job due to mito instead reduce hours worked by 50 per cent, we estimate this would have avoid productivity losses of $40m for people with mito and $12m for carers of people with mito (table 4.16). Note that this assumes that people with mito and their carers have the same productivity as a member of the general population (of the same age and sex) during their reduced hours of work.

There is significant scope for improvement to employment-related support. The *Mito Community Survey 2022* found that 26 per cent disagree or strongly disagree that they or the person they care for has helpful support relating to employment.[126]

4.16 Potential impact of avoiding reduction in work hours

Cost category	Child	Adult	Total
	$m/year	$m/year	$m/year
People with mito	0	40	40
Carers of people with mito	2	10	12
Total	**2**	**50**	**52**

Source: CIE.

Value of improved community awareness

Many in the mito community highlight the importance and interdependence of empathy and understanding about mito. Out of 14 interviews conducted by Valverde et al (2022) with adults with mito, 11 subjects identified a lack of empathy and compassion from others as a theme, and all 14 identified the theme of a lack of mito disease awareness (box 4.17).

126 Mito Foundation, 2022, *Mito Community Survey Insights Report 4*, p.15, available at: https://www.mito.org.au/wp-content/uploads/2022/11/Insights-Report-2-Final-151122.pdf

4.17 Community empathy and understanding about mito

Others may have less empathy or compassion for people affected by mito because of a lack of understanding, but it depends on individual circumstances:

> "I think an interesting experiment would be to have mito patients say that they have mitochondrial cancer; what would the reaction be? What would that mean for people, and… what you are going through."

> "For the most part people are pretty understanding now that I walk with a cane, it's a visual cue to people. It makes it obvious that I've got difficulties. Early on people cannot look at you and know that you have trouble with your vision or whatever. They were not quite as sympathetic. So as things progressed… as things got worse, people were more understanding."

People in the mito community experience a lack of general knowledge and understanding of mito:

> "I go to the dentist and they are intrigued by my mitochondrial disease, everyone is. I mean, it's 2020, and I was diagnosed in the 1990s and it still has not changed in terms of knowledge."

> "Yes, the literature is growing, and there's a lot more (information) than there was in the 80s. It's (PMD) still rare compared to say diabetes. We're all still trying to understand."

Source: Quotes from Valverde et al (2022).

A lack of community understanding and connection may contribute to higher rates of loneliness among people with mito. Noorda et al (2012) interviewed 16 adults with mito and found a loss of vitality, fatigue, and a reduced ability to function independently leads to restricted social participation and possible loneliness and isolation.[127]

People with disability have higher rates of loneliness than people without disability, which leads to reduced wellbeing. Vincent et al (2023) identified higher rates of loneliness among people with disability, stating that people with disability aged between 15-64 report feelings of loneliness that are 0.7 points out of 10 higher than people without disability, which is associated with an annual cost of $1750 per person in reduced wellbeing.[128]

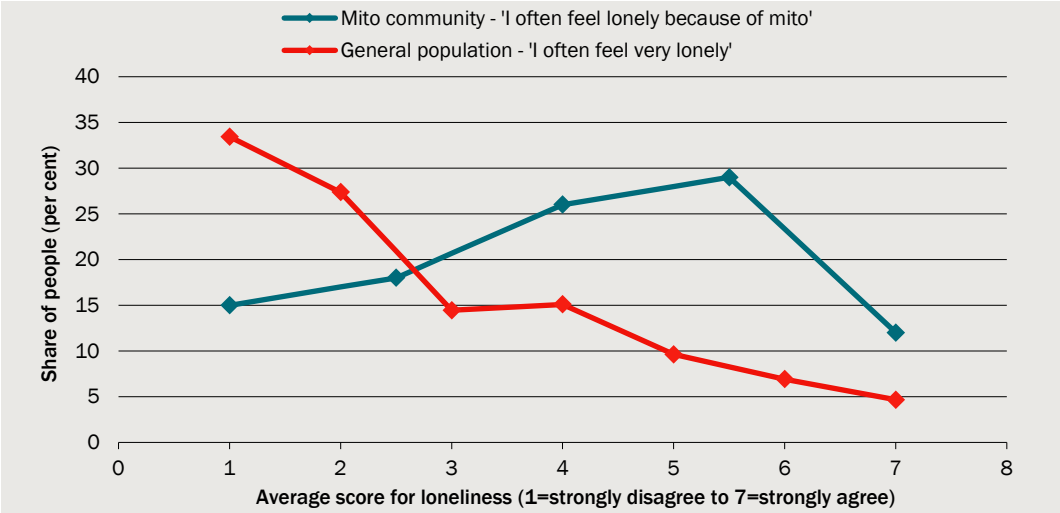
We have not identified data for the mito community that can be reliably compared with the measures of feelings of loneliness from the Household Income and Labour Dynamics in Australia (HILDA) survey. The Mito Community Survey found that a higher share of community members agree or strongly agree that they feel lonely because of mito (41 per

127 Noorda, G., van Achterberg, T., van der Hooft, T., Smeitink, J., Schoonhoven, L., van Engelen, B., 2012, 'Problems of adults with a mitochondrial disease – The patients' perspective: focus on loss', *JIMD Reports*, 6: 85-94, doi: 10.1007/8904_2011_121

128 Vincent, J., McCarthy, D., Miller, H., Armstrong, K., Lacey, S., Lian, G., Richards, D., and Berry, T., 2022, *Research Report – The economic cost of violence, abuse, neglect and exploitation of people with* disability, Taylor Fry, pp.7, 116.

cent) compared to the share who disagree or strongly disagree (31 per cent).[129,130] Chart 4.18 shows this alongside data from the HILDA survey about the share of the general population who report that they 'often feel very lonely', which is significantly lower. However, much of this difference may be due to the difference in the specific question, with the share of those who 'often feel very lonely' expected to be significantly lower than the share who 'feel lonely'.

4.18 Comparison of loneliness between the mito community and general population



Note: The response scale from the Mito Community Survey has been converted from 1-5 to a 1-7 scale to align to the scale used in the HILDA survey (see https://hildaodd.app.unimelb.edu.au/VariableDetails.aspx?varn=lssupvl&varw=22) Both surveys use 'strongly disagree' and 'strongly agree' as the boundaries of the scale.

Data source: Data from the HILDA survey for wave 22 (available at: https://hildaodd.app.unimelb.edu.au/VariableDetails.aspx?varn=lssupvl&varw=22), Mito Foundation, 2022, *Mito Community Survey Insights Report 4*, Figure 6, p.14, available at: https://www.mito.org.au/wp-content/uploads/2023/04/MITO_REPORT4.CommunitySurvey23.R1.270423.pdf.

If people with mito aged 15-64 experienced the same elevated rates of loneliness as people with disability, this would imply a total cost of $5.9 million per year. We do not include this result in our main cost estimates because it is not mito-specific.

Community understanding is often tied in with whether a person has a confirmed diagnosis of mito. For example, people with subjective or non-specific symptoms often feel that people meet their medical needs and clinical diagnosis with scepticism and disbelief (Krieg et al, 2016), which can lead to a cycle of rejection and isolation.[131]

129 The remaining 26 per cent of mito community respondents neither agreed nor disagreed with this statement.

130 Mito Foundation, 2022, *Mito Community Survey Insights Report 4*, Figure 6, p.14, available at: https://www.mito.org.au/wp-content/uploads/2023/04/MITO_REPORT4.CommunitySurvey23.R1.270423.pdf

131 Krieg, E., Calderwood, L., Campion, M and Krepkovich, K.E., 2016, 'Confirmed versus suspected: The social significance of a genetic or non-genetic diagnosis of mitochondrial disease', *Mitochondrion*, 28: 60-66, doi: 10.1016/j.mito.2016.03.008

A Literature review about prevalence

A range of studies have been conducted measuring the prevalence of mito. There are two key types of measures of the population with mito:

- The number of people with mtDNA or nDNA mutations that are potentially associated with mito, e.g. Manwaring et al, Elliot et al (2008), and
- The number of people with clinically overt mito, e.g. Schaefer et al (2008)

Studies measuring prevalence of mtDNA and nDNA mutations

An overview of these studies is shown in table A.1. Prevalence is difficult to measure because many people remain undiagnosed, but approaches such as testing sequential live births (as in Elliot et al, 2008) or population sampling are used to estimate the share born with relevant genetic mutations.

A.1 Comparison of mito prevalence estimates from the literature

Citation	Country	Cohort	Measure	Point estimate (bounds of 95 per cent confidence interval)
				Per cent
Manwaring, et al (2006) [a]	Australia	Adults aged 49 and older in the Blue Mountains Eye and Hearing Studies (BMES and BMHS)	Prevalence of MELAS 3243A>G mtDNA mutation	0.24 (0.10-0.49)
Vandebona, et al (2009) [b]	Australia	Adults aged 49 and older in the BMHS	Prevalence of M.1555A→G mutation	0.21 (0.08-0.46)
Elliot, et al (2008) [c]	England	Sequential live births	Prevalence of 10 mtDNA mutations (including m.155A→G and m.3243A→G.	0.54 (0.40-0.89)
Schaefer, et al (2008) [d]	England	Working age adults	Clinically affected mtDNA disease (most commonly m.3243A>G)	0.0092 (0.0078-0.0108)
		Children and adults below retirement age	Currently asymptomatic first-degree relatives of people with mtDNA point mutations, at considerably increased risk for development of disease	0.0165 (0.0148-0.0183)
Bitner-Glindzicz, et al (2009) [e]	England	7-9 year-old children in England	Prevalence of M.1555A→G mutation	0.19 (0.10-0.28)

Citation	Country	Cohort	Measure	Point estimate (bounds of 95 per cent confidence interval)
Watson, et al (2023) [f]	Australia	Medical Genome Reference Bank, elderly adults	Prevalence of homoplasmic primary LHON mutation	0.125 (0.040-0.291)

[a] Manwaring, N., Jones, M.M., Wang, J.J., Rochtchina, E., Howard, C., Mitchell, P., and Sue, C., 2007, 'Population prevalence of the MELAS A3243G mutation', *Mitochondrion* 7 (2007): 230-233. DOI: 10.1016/j.mito.2006.12.004.

[b] Vandebona, H, Mitchell, P., Manwaring, N., Griffiths, K, Gopinath, B., Wang, J.J., and Sue, C, 2009, 'Prevalence of mitochondrial 1555A→G mutation in adults of European descent', *The New England Journal of Medicine*, 2009 Feb 5; 360(6): 642-644. DOI: 10.1056/NEJMc0806397.

[c] Elliot, H.R., Samuels, D.C., Eden, J.A., Relton, C.L., and Chinnery, P.F., 2008, 'Pathogenic mitochondrial DNA mutations are common in the general population', *American Journal of Human Genetics*, 8392): 254-260. DOI: 10.1016/j.ajhg.2008.07.004

[d] Schaefer, A.M., McFarland, R., Blakely, E.L., He., L., and Whittaker, R.G., 2008, 'Prevalence of mitochondrial DNA disease in adults', *Annals of Neurology*, 63(1): 35-39. DOI: 10.1002/ana.21217.

[e] Bitner-Glindzicz, M., Pembrey, M., Duncan, A., Heron, J., Ring, S.M., and Hall, A., 2009, 'Prevalence of mitochondrial 1555A→G mutation in European children, *The New England Journal of Medicine*, 2009 Feb 5, 360;6: 640-642. DOI: 10.1056/NEJMc0806396

[f] Watson, E.C., Davis, R.L., Ravishankar, S., Copty, J., Kummerfeld, S. and Sue, C.M., 2023, 'Low disease risk and penetrance in Leber hereditary optic neuropathy', *American Journal of Human Genetics*, 110(1): 166-169, doi: 10.1016/j.ajhg.2022.11.013.

Source: Studies as noted, CIE.

In Manwaring et al (2007), among participants identified with the 3243A>G mtDNA mutation, the mean age was 70.1 years with a range of 59-83 years. Participants in Manwaring et al (2007) underwent comprehensive clinical evaluation. The seven people identified with the mtDNA mutation were oligosymptomatic (i.e. having few or minor symptoms). Note, however, that the prevalence of hearing loss in the general population is very high between the age of 60-80, which likely makes it unrepresentative of the Australian population. For example, 40 per cent of women and 80 per cent of men aged 70-74 have hearing loss in their better ear.[132] Hair follicle samples were used for DNA sampling rather than blood samples, and hair follicle samples appear to detect mtDNA mutations more often. Among the seven identified as having mtDNA mutations based on their hair follicle samples, the mutation was not found to be present in blood samples.

Prevalence of disease among adults

Gorman et al (2015)[133] and Schaefer et al (2007) are both studies of prevalence of mito in the North East of England. The key difference between these studies is that Schaefer et al (2007) measure only prevalence of pathogenic mtDNA mutations, while Gorman et al (2015) also includes pathogenic mutations in nDNA. Gorman et al (2015) find somewhat higher prevalence rates (0.0125 per cent compared to 0.0092 per cent), at least in part due to the inclusion of those with nuclear genome mutations.

132 Deloitte Access Economics, 2020, *Hearing for Life: The value of hearing services for vulnerable Australians*, available at: https://www.hcia.com.au/hcia-wp/wp-content/uploads/2020/02/Hearing_for_Life.pdf

133 Gorman, G.S., Schaefer, A.M., Gomez, N., Blakely, E.L., Alston, C.L., Feeney, C., Horvath, R., Yu-Wai-Man, P., Chinnery, P.F., Taylor, R.W., Turnbull, D.M., McFarland, R., 2015, 'Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease', *Annals of Neurology*, 77(5): 753-759, doi: 0.1002/ana.24362

These estimates are significantly higher than a more recent estimate for New Zealand (Missen et al, 2023),[134] which estimated minimum prevalence for mito of 4.7 per 100 000. However, the authors compare this to the estimates from Gorman et al (2015), concluding that the difference is due to underdiagnosis in New Zealand rather than a truly lower rate of disease in New Zealand compared to England.

A recent study of prevalence of LHON in Australia (Sanchez, et al, 2021)[135] estimated minimum prevalence of vision loss due to LHON in Australia of one in 68 403 people, across both adults and children.

Prevalence of disease among children

Evidence about prevalence of mito among children is somewhat more limited than for adults. Schaefer et al (2004)[136] provides a somewhat dated summary of two studies estimating the prevalence of mito among children:

- Skladal et al (2003)[137] estimated minimum birth prevalence of 5.0/100 000 for mitochondrial respiratory chain disorders in Australia, based on referrals to the Melbourne children's hospital over a 10-year period (including children from Victoria, New South Wales and South Australia).
- Darin et al (2001)[138] estimated minimum point prevalence of 4.7/100 000

In more recent analysis, incidence of mito that fits the definition of childhood dementia is estimated to be 7 per 100 000 births (Elvidge et al, 2023).[139] This includes at least 12 clinical categories (including Leigh syndrome, Alpers-Huttenlocher syndrome, MCHS, MEMSA, MEGDEL, Pearson syndrome, congenital lactic acidosis, Kearns-Sayre

---

134 Missen, S., Wilson, C., Potter, H., Vincent, A.L., Murphy, R., Roxburgh, R., Rodrigues, M., Poke, G., Robertson, S.P., Thorburn, D.R. and Glamuzina, E., 2023, 'Mitochondrial disease in New Zealand: a nationwide prevalence study', *Internal Medicine Journal*, 2023: 1-10, doi:10.1111/imj.16211

135 Sanchez, M.I.G.L., Kearns, L.S., Staffieri, S.E., Clarke, L., McGuinness, M.B., Meteoukki, W., Samuel, S., Ruddle, J.B., Chen, C., Fraser, C.L., Harrison, J., Hewitt, A.W., Howell, N. and Mackey, D.A., 2021, 'Establishing risk of vision loss in Leber Hereditary Optic Neuropathy', *American Journal of Human Genetics*, 108(11): 2159-2170, doi: 10.1016/j.ajhg.2021.09.015

136 Schaefer, A.M., Taylor, R.W., Turnbull, D.M. and Chinnery, P.F., 2004, 'The epidemiology of mitochondrial disorders – past, present and future', *BBA Bioenergetics*, 1659(2-3): 115-120, doi: 10.1016/j.bbabio.2004.09.005

137 Skladal, D., Halliday, J. and Thorburn, D.R., 2003, 'Minimum birth prevalence of mitochondrial respiratory chain disorders in children', *Brain*, 126(8): 1905-1912, doi: 10.1093/brain/awg170

138 Darin, N., Oldfors, A., Moslemi, A.R., Holme, E., Tulinius, M., 2001, 'The incidence of mitochondrial encephalopathies in childhood: clinical features and morphological, biochemical, and DNA abnormalities', *Annals of Neurology*, 49: 377-383, doi: 10.1002/ana.75

139 Elvidge, K.L., Christodoulou, J., Farrar, M.A., Tilden, D., Maach, M., Valeri, M., Ellis, M., Smith, N.J.C. and the Childhood Dementia Working Group, 2023, 'The collective burden of childhood dementia: a scoping review', *Brain*, 2023: 00; 1-10, doi: 10.1093/brain/awad242

syndrome, MELAS, MERRF) of mito, and 200 genes (both nuclear and mitochondrial). This is published in the supplementary materials for Elvidge et al (2023)[140]

People 'at-risk' of mito

Some studies (such as Schaefer et al, 2008) identify a further cohort Among this remainder without clinically overt disease, a proportion is 'at-risk', on the basis that they are first-degree relatives of an affected female with an mtDNA point mutation or a wider group of relatives if a sibling of the affected female individual has the same mtDNA point mutation.[141] For example, the findings of Schaefer et al (2008) suggest that there are 18 children and adults younger than retirement age at risk for development of mito for each 10 people with clinically manifest (i.e. overt) mito.[142]

140 Ibid.

141 See Figure 1 in Schaefer et al (2008): Schaefer, A.M., McFarland, R., Blakely, E.L., He., L., and Whittaker, R.G., 2008, 'Prevalence of mitochondrial DNA disease in adults', *Annals of Neurology*, 63(1): 35-39. DOI: 10.1002/ana.21217.

142 Schaefer et al (2008): "9.2 in 100 000 people have clinically manifest mtDNA disease … in addition, a further 16.5 in 100 000 children and adults younger than retirement age are at risk for development of mtDNA disease". Ibid.

B Additional detail about paediatric mortality

There are two studies of mortality of children with mito that we have identified, but they yield striking different estimates of mortality rates:

- Eom et al (2017)[143] study a cohort of 221 children between 2006 and 2015, and estimate a global mortality rate of 14 per cent over 10 years, with average age at death of six years. Leigh syndrome and MELAS were estimated to have higher mortality rates of 17 and 50 per cent respectively. Age at symptom onset, lead time to diagnosis, duration of illness and duration of life were estimated to be 1.8, 1.7, 4.3, and 6.1 years respectively.
- Debray et al (2007)[144] study a cohort of 73 children diagnosed with mito between 1985 and 2005, with 46 per cent having died at a median age of 13 months (80 per cent of whom were <3 years of age). Despite the high mortality rate, among children aged >5 years, 62 per cent have only mild impairment or a normal functional outcome.

Debray et al (2007) find age at first symptoms is a key predictor of mortality. Since Debray et al (2007) has a cohort with an earlier age of onset (median of 7 months) than Eom et al (2017) (mean of 1.8 years), this may explain the higher mortality rate estimated in Eom et al (2017).

The implied annual average mortality rate is 3.0 per cent across the two studies (table B.1)

B.1 Calculation of average mortality rate for children with mito

Measure	Eom et al (2016)	Debray et al (2007)	Average
Average age at death (years)	6.1	1.1	
Mortality rate (i.e. share who died, with average age of those who died = 6.1)	14%	46%	
Mean/median age at symptom onset [a]	1.8	0.6	
Average years with mito within child cohort	16.3	10.2	
Number of child-years at risk per child	10	10.2	
Annual mortality rate	1.4%	4.5%	3.0%

[a] Eom et al (2016) report the average age at symptom onset, while Debray et al (2007) report the median age. We assume, for simplicity, that the median age is equal to the mean age for the Debray et al (2007) cohort.

Source: Eom et al (2016), Debray et al (2007), CIE.

143 Eom, S., Lee, H.N., Lee, S., Kang, H., Lee, J.S., Kim, H.D. and Lee, Y., 2017, *Pediatric Neurology*, 66: 82-88, doi: 10.1016/j.pediatrneurol.2016.10.006

144 Debray, F., Lambert, M., Chevalier, I., Robitaille, Y, Decarie, J., Shoubridge, E.A., Robinson, B.H. and Mitchell, G.A., 2007, 'Long-term outcome and clinical spectrum of 73 pediatric patients with mitochondrial diseases', *Pediatrics*, 119(4): 722-733, doi: 10.1542/peds.2006-1866

Finsterer and Zarrouk-Mahjoub (2017)[145] identify a range of concerns with Eom et al (2017), with key issues being that:

- diagnosis was not based upon genetic investigations,
- the drugs and diet of people who died was not identified, and this is relevant to survival, outcome, and prognosis of mito, and
- that information about echocardiography, epilepsy and pulmonary involvement in the metabolic defect is lacking.

This highlights that mortality of people with mito is a complex issue, and that conclusions drawn from the relatively few studies relating to mortality will be highly uncertain, particularly due to the extent of heterogeneity across disorders and age groups.

145 Finsterer, J., and Zarrouk-Mahjoub, S., 2017, 'Death in pediatric mitochondrial disorders', *Pediatric Neurology*, doi: 10.1016/j.pediatrneurol.2017.03.003

C Literature review about healthcare utilisation

We have not identified any studies estimating the total societal cost of mito in Australia or overseas, with the only studies estimating costs of mito being focussed on cost categories such as health system costs, outpatient costs, or out-of-pocket costs.

Health system utilisation

We conducted a search of Pubmed to identify studies estimating healthcare utilisation for mito.

The search returned 39 studies that met the criteria, of which we determined that eight were studies estimating the cost of healthcare utilisation by people with mito. The remaining studies variously relate to research about specific therapeutics or vaccinations, mechanisms of disease in different types of mito, or studies relating to mitochondria but not to mitochondrial diseases (e.g. relating to mitophagy).

To this list, we have also added one study that is not available through Pubmed, which is the PEEK study.

Table C.1 summarises the studies identified about healthcare utilisation of people with mito.

C.1 Summary of literature on healthcare utilisation by people with mito

Citation	Country	Approach	Cohort	Costs estimated
Haque S, Crawley K, Shrestha R, Schofield D, Sue CM., 2023, 'Healthcare resource utilization of patients with mitochondrial disease in an outpatient hospital setting', *Orphanet J Rare Dis*. 2023 May 29;18(1):129. Doi: 10.1186/s13023-023-02746-x.	Australia	Retrospective chart review and alignment to Medicare Benefits Schedule	91 adults with mito, split into those with mtDNA mutations (Group 1), those with nDNA mutations and predominant phenotype of CPEO or optic atrophy (Group 2), and those with a clinical but not genetic diagnosis (Group 3)	▪ Outpatient costs per person per annum of $838 for Group 1, $591 for Group 2 and $669 for Group 3 ▪ Largest driver of costs was neurological investigations ▪ Also assessed costs over the entire duration of the patients' medical care in the mitochondrial outpatient clinic: $4784 for Group 1, $4515 for Group 2 and $5816 for Group 3.
Buajitti E, Rosella LC, Zabzuni E, Young LT, Andreazza AC., 2022, 'Prevalence and health care costs of mitochondrial disease in Ontario, Canada: A population-based cohort study', *PloS One*. 2022 Apr 8;17(4):e0265744. Doi: 10.1371/journal.pone.0265744. eCollection 2022.	Canada	Linked health administrative data	3069 people hospitalised with mitochondrial disease between 1988 and 2019, both adults and children, identified by International Classification of Disease (ICD) codes corresponding to mitochondrial disease	▪ Period prevalence of 25.1 per 100 000 in Ontario ▪ Mean healthcare cost of $24 023 CAD ($21 407 in 2023 Australian dollars and after adjusting for relative healthcare prices) in the 12 months before hospitalisation, and $33 545 CAD ($29 892) in the 12 months after hospitalisation
Deverell M, Phu A, Elliott EJ, Teutsch SM, Eslick GD, Stuart C, Murray S, Davis R, Dalkeith T, Christodoulou J, Zurynski YA., 2022, 'Health-related out-of-pocket expenses for children living with rare diseases – tuberous sclerosis and mitochondrial disorders: A prospective pilot study in Australian families', *Journal of Paediatric Child Health*. 2022 Apr;58(4):611-617. doi: 10.1111/jpc.15784. Epub 2021 Oct 27.	Australia	Surveys of families	13 families in Australia with 15 children, of which 5 had mitochondrial disease and 10 had tuberous sclerosis	▪ Estimated out-of-pocket expenses over the life of children with mito to-date, but sample size was only 5 children. These were converted to costs per year of a child's life. One family with one child had an annual cost of >$909, a family with one child had an annual cost of $556 – 1 111, and another family with two children had an annual cost of $3 334 – 4 167. ▪ Most (62 per cent) of mothers reduced or stopped work due to caring responsibilities, although this wasn't reported separately for mito and tuberal sclerosis. ▪ Out-of-pocket expenses were also tracked over 6 months for 8 families (including both children with mito and tuberal sclerosis), with projected annual costs of $10 578 per family. The largest cost categories were health service visits ($2 774), prescription medications ($2 084), health-related consumables ($2 378) and special programmes ($2 238), with non-prescription medications ($1 324) and travel-related costs ($392) being smaller.

Citation	Country	Approach	Cohort	Costs estimated
Wu Y, Balasubramaniam S, Rius R, Thorburn DR, Christodoulou J, Goranitis I., 2022, 'Genomic sequencing for the diagnosis of childhood mitochondrial disorders: a health economic evaluation', *European Journal of Human Genetics*. 2022 May;30(5):577-586. doi: 10.1038/s41431-021-00916-8. Epub 2021 Jun 8.	Australia	Modelling using primary clinical and economic data	Total of 159 paediatric patients suspected of having mito	▪ Modelled the costs under two approaches. Approach 1 used a decision-tree to model costs and outcomes associated with genomic sequencing and conventional care. Approach 2 used a discrete event simulation to incorporate heterogeneity in the condition and clinical practice. ▪ Genomic sequencing was less costly and more effective than conventional care, saving $1997 (approach 1) to $8823 (approach 2) and leading to 11 – 14 more diagnoses per 100 children tested.
Cohen B, Balcells C, Hotchkiss B, Aggarwal K, Karaa A., 2018, 'A retrospective analysis of health care utilization for patients with mitochondrial disease in the United States: 2008-2015', *Orphanet J Rare Dis*. 2018 Nov 22;13(1):210. doi: 10.1186/s13023-018-0949-5.	United States of America	Administrative claims data over an 8-year period	3 790 children (<16) and 4 390 adults, identified by International Classification of Disease (ICD) codes corresponding to mitochondrial disease	▪ Estimated total claims (i.e. spending) for children with mito of $8 378 per month (2023 AUD), and adults of $5 378 per month. These were much higher than average claims for the general population ($350 and $843 for children and adults respectively).
McCormack SE, Xiao R, Kilbaugh TJ, Karlsson M, Ganetzky RD, Cunningham ZZ, Goldstein A, Falk MJ, Damrauer SM., 2017, 'Hospitalizations for mitochondrial disease across the lifespan in the U.S', *Mol Genet Metab*. 2017 Jun;121(2):119-126. doi: 10.1016/j.ymgme.2017.04.007. Epub 2017 Apr 19.	United States of America	Cross-sectional and longitudinal observational study using hospital activity/cost data	Individuals admitted to hospital with a specific diagnosis of mitochondrial disease based on ICD9-CM code 277.87 (disorder of mitochondrial metabolism)	▪ Rates of inpatient hospitalisations per 100 000 people for children (1.9) and adults (0.8) ▪ In-hospital mortality rates for children (2.4 per cent) and adults (3.0 per cent) ▪ Median cost per hospitalisation (in 2023 AUD) for children ($15 481) and adults ($14 896) with mito, compared to children ($7 264) and adults ($11 197) without mito.
International Centre for Community-Driven Research, 2018, Mitochondrial Disease Australian Study, *PEEK*, 1(6), July 2018.	Australia	Structured interview and questionnaire	44 Adults and 6 carers of adults with mito	▪ Costs at diagnosis:42 per cent of participants reported zero costs of diagnosis, with 4, 12 and 26 per cent reporting $0-500, $501-1000, and over $1000, respectively. The remainder (16 per cent) couldn't not recall or didn't know. The cohort was equally split between those who found these costs not at all significant and those who found them to be between slightly and extremely significant. ▪ Out-of-pocket expenses: the median monthly expense was between $101-500, although 24 per cent reported monthly expenses of over $1000

Citation	Country	Approach	Cohort	Costs estimated
Karaa, A., Kriger, J., Grier, J., Holbert, A., Thompson, J.L.P., Parikh, S., and Hirano, M., 2016, 'Mitochondrial disease patients' perception of dietary supplements' use', *Mol Genet Metab* 119(1-2): 100-108.	United States of America	Survey of adults with mito and caretakers of children with mito	162 adults and parents of children with a diagnosis confirmed by electron transport chain abnormalities or molecular genetic testing	▪ A third of participants spend more than AUD268 per month (as reported in the PEEK study)
Franik, S., Huidekoper, H.H., Visser, G., et al, 2015, 'High prevalence of complementary and alternative medicine use in patients with genetically proven mitochondrial disorders', *J Inherit Metab Dis*, 38(3): 477-482.	Netherlands	Survey of adults with mito and caretakers of children with mito	33 adults and 24 children with genomically confirmed mito	▪ Mean monthly spending of AUD568 for adults and AUD774 for children. ▪ High use of complementary and alternative medicine with 88 per cent of children and 91 per cent of adults using some form in the past 2 years.

Note: The search strategy applied in Pubmed was: "(mitochondria[Title/Abstract] OR mitochondrial[Title/Abstract] OR mito[Title/Abstract]) AND (healthcare[Title/Abstract] OR "health care"[Title/Abstract]) AND (utilisation[Title/Abstract] OR utilization[Title/Abstract] OR expenditure[Title/Abstract] OR cost[Title/Abstract])", with only studies published from 2013 onwards included. All values referred to are 2023 Australian dollars. Overseas estimates have been adjusted for relative healthcare prices to Australia unless stated otherwise.

Source: Pubmed, CIE.

Some studies have estimated the health care costs associated with similar diseases. For example, Schofield et al (2023)[146] estimated an overall lifetime healthcare cost of $690 725 per person with an Inherited Retinal Disease (IRD) in Australia. Some IRDs may be associated with mitochondrial myopathies, such as neuropathy, ataxia, and retinitis pigmentosa (NARP) and mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS).[147]

146 Schofield, D., Kraindler, J., Tan, O., Shrestha, R.N., West, S., Hart, N., Tan, L., Ma, A., Grigg, J.R., and Jamieson, R.V., 2023, 'The health care and societal costs of inherited retinal diseases in Australia: a microsimulation modelling study', *Medical Journal of Australia*, 219(2): 70-76, doi: 10.5694/mja2.51997

147 Yu-Wai-Man, P., and Newman, N.J., 2017, 'Inherited eye-related disorders due to mitochondrial disfunction', *Human Molecular Genetics*, 26(R1): 12-20, doi: 10.1093/hmg/ddx182

D Measuring productivity impacts

Productivity losses associated with mito arise with respect to both paid work and unpaid work. Productivity in paid work is measured by reduced wages and other forms of income (excluding government payments). In this analysis, due to data limitations, we have not quantified losses of unpaid work.

To determine average income including people who are not working, we divide the total income from employed persons by the total number of people (including people in and out of the labour force). That is, the assumed income for each age cohort and sex combination is given by the following equation.

$$\overline{Income_{as}} = \frac{\sum_e (\overline{Income_{ase}} \times N_e)}{\sum_e N_e + N_{unemployed} + N_{not\ in\ labour\ force}}$$

Where:

- e denotes the categories of employed people (full-time, part-time, away from work),
- $\overline{Income_{ase}}$ refers to the average annual income of an employment category (e),
- N_e, which is the number of people in that employment category (e),
- $N_{unemployed}$ and $N_{not\ in\ labour\ force}$ is the number of people unemployed or not in the labour force.

Measuring the impacts associated with premature death

Friction approach

The friction approach measures the loss of production[148] associated with the period during which a worker who leaves the labour force due to disease has not yet been replaced. This approach assumes that the economy is not at full employment, and that there is no long run impact to the number of employed people in the economy. That is, a worker who leaves the labour force due to death or disablement associated with mito is replaced, and the total number of workers does not change. Estimates based on this approach will be a lower bound to the total productivity impact each year.

148 Formally, productivity measures the amount of production per unit of input, where production is the amount of output (e.g. goods and services). We use the terms 'productivity losses' and 'productivity impacts' to refer to changes in production as a result of changes in productivity.

The productivity losses for a particular age cohort and sex combination are calculated by multiplying the number of people in that cohort who died in the current year by the amount of income they would have earned over the period they take to be replaced.

This period is referred to as the 'friction period'. We have assumed that the friction period is six months in duration, which is consistent with the duration assumed in Van den Hout (2010).[149] The friction approach to estimating productivity losses can be represented by the following equation:

$$Productivity\ loss = \sum_{s}\left(\sum_{a=0}^{100}[deaths_{as} \times \overline{Income_{as}} \times f]\right)$$

where

- *deaths* is the number of deaths in the current year,
- *a* refers to an age cohort (e.g. seventy-year-olds),
- *s* refers to sex,
- $\overline{Income_{as}}$ refers to average yearly income, and
- *f* refers to the duration of the friction period (in years) during which the person goes unreplaced. We assume $f = 0.5$.

Taken on its own, a friction approach underestimates productivity impacts because there may be multiple friction periods, and for certain industries, the economy may be at full employment and so a vacancy cannot be filled. This analysis assumes that workers who are removed from work because of mito are replaced after 6 months.

Human capital approach

The human capital approach estimates the value of production losses due to illness, disability, or premature death over the remaining working life of a person had they not been ill. This approach assumes that the economy is at full employment, and that the loss of a worker results in permanently lower economic output.

It is noted that this approach does not account for the effects of shifting labour supply and overstates the productivity impacts, as in practice, an unemployed person may take the job of the ill or diseased person, mitigating the net impact on productivity.[150]

However, this approach also does not account for other benefits of improved health status, such as increased capital formation. This source of inaccuracy is likely to be smaller than the effect of assuming full employment. Therefore, we consider the human capital approach an upper bound on the likely productivity impacts.

The human capital approach allows for a forward-looking estimate of the loss of productivity capacity to be estimated. This does not neatly align with the prevalence

149 Van den Hout, W.B., 2010, 'The value of productivity: human-capital versus friction-cost method', *Annals of Rheumatic Disease* 69 (Suppl I), p.i89–i91, available at: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.959.5340&rep=rep1&type=pdf

150 See http://www.who.int/choice/publications/d_economic_impact_guide.pdf

approach to estimating economic burden of disease, which would only measure the loss of productivity each year from people with the disease in that year.

Approach adopted in this study

To acknowledge some long run impacts of reduced productive capacity of the economy associated with workers who are unable to be replaced, consideration can be given to:

- a forward-looking approach, by estimating the present value of lost productivity in current and future years associated with people who are removed from the labour force in the current year, or
- a backward-looking approach by estimating the value of lost productivity in the current year associated with people who were removed from the labour force in current and past years.

The forward-looking approach has been followed for this study. While this is not strictly consistent with a prevalence approach, it avoids obtaining results that persistently understate productivity losses that are felt in the long-term.

The productivity losses for a particular age cohort and sex combination are calculated by multiplying the number of people in that cohort who died in the current year by the present value of their future income stream until their expected death. This income stream is determined by their current age and their life expectancy (to the nearest year).

This human capital approach to estimating productivity losses can be represented by the following equation:

$$Productivity\ loss = \sum_{s}\left(\sum_{a=0}^{100}\left[deaths_{as} \times \sum_{y=a}^{e_{as}} \frac{\overline{Income_{asy}}}{1+r}\right]\right)$$

where

- *deaths* is the number of deaths in the current year,
- *a* refers to an age cohort (e.g. seventy-year-olds),
- *s* refers to sex,
- $\overline{Income_{asy}}$ refers to average yearly income,
- e_{as} refers to the expected age at death for an individual of age *a* and sex *s*, and
- *r* is the real discount rate.

The real discount rate used in this analysis is 7 per cent and we present the results using discount rates of 3 and 10 per cent, consistent with the Department of Prime Minister and Cabinet Cost-benefit analysis guide[151] and Harrison (2010).[152]

151 Available at: https://www.dpmc.gov.au/sites/default/files/publications/cosst-benefit-analysis.docx

152 Harrison, M., 2010, *Valuing the future: the social discount rate in cost-benefit analysis*, available at: http://www.pc.gov.au/research/supporting/cost-benefit-discount/cost-benefit-discount.pdf

Measuring the impacts associated with disability

We assume the productivity loss from paid work associated with each year lived with disability is equal to the lost income from that year. Productivity losses associated with years lived with disability (prior to death) can be represented by the following equation:

$$Productivity\ loss = \sum_{s}\left(\sum_{a=0}^{100}[people\ with\ mito_{as} \times \%\ reduction\ in\ work \times \overline{Income_{as}}]\right)$$

where

- YLD is the number of years lived with disability,
- a refers to an age cohort (e.g. seventy-year-olds), and
- s refers to sex, $\overline{Income_{asy}}$ refers to average yearly income, and
- the $\%\ reduction\ in\ work$ is a parameter based on evidence from the PEEK Study,[153] equal to 51 per cent.

153 International Centre for Community-Driven Research, 2018, Mitochondrial Disease Australian Study, *PEEK*, 1(6), July 2018.

E Future research directions

In general, our modelling of the costs of mito is undertaken for all types of mito, without any disaggregation for specific types.

For some types of mito, data is available about measures such as their typical mutation prevalence, disease prevalence, and lead time to diagnosis. For example, Zilber et al (2023) reports results from a survey of 114 people caring for someone with Leigh Syndrome and 2 people diagnosed with Leigh Syndrome. Survey recruitment was based on a global patient registry, and information collected includes healthcare utilisation, quality-of-life, and caregiver burden. Their findings include:

- time to diagnosis was under 1 year for 65 per cent of respondents,
- the share of participants who never walked or lost the ability to walk was 78 per cent, and
- slightly less than half of people had at least one visit to the emergency room in the past 12 months, and a similar share had at least one inpatient night in the past 12 months.

Such data is not available consistently across the range of different types of mito. However, undertaking type-specific modelling poses a fruitful opportunity to better capture the diversity of experience across the mito community.

Further, because our modelling is not type-specific, we have derived assumptions that are implicitly averages across the entire mito cohort. For example, we estimate an average annual mortality rate of 2.5 per cent for adults with mito, derived from Papadopoulos et al (2019).[154]

Whether this is a representative average will depend on whether it is derived from a representative sample of mito patients in terms of the share with each disorder. If, for example, the sample of 267 patients in Papadopoulos et al (2019) had a lower share of people with a usually non-fatal disorder such as LHON than the true population share, this would upwardly bias the estimated average mortality rate.

Disaggregating the cost model by type of mito, or at least by group of disorder (e.g. child-onset and adult-onset, fatal vs non-fatal) would enhance the accuracy of outputs.

---

154 Papadopoulos, C., Wahbi, K., Behin, A., Bougouin, W., Stojkovic, T., Leonard-Louis, S., Berber, N., Lombès, A., Duboc, D., Jardel, C., Eymard, B. and Laforêt, P., 2019, 'Incidence and predictors of total mortality in 267 adults presenting with mitochondrial diseases', *Journal of Inherited Metabolic Diseases*, 43: 459-466, doi: 10.1002/jimd.12185

THE CENTRE FOR INTERNATIONAL ECONOMICS
www.TheCIE.com.au

ISBN 978-1-7635228-1-7