Out of the shadow

Transforming care for people living with hypophosphatasia

evohealth

June 2025

Evohealth acknowledges that we work on the traditional lands of many Aboriginal clans, tribes, and nations.

We commit to working in collaboration with Aboriginal and Torres Strait Islander communities and peoples to improve health, emotional and social well-being outcomes in the spirit of partnership.

About **Evohealth**

The delivery of healthcare is complex.
Our focus is not.

Better health for all.

OUT OF THE SHADOW

TRANSFORMING CARE FOR PEOPLE LIVING WITH HYPOPHOSPHATASIA

CONTENT.

ABOUT **THIS REPORT**

Background

Out of the Shadow: Transforming Care for People Living with Hypophosphatasia is an evidence-based report describing the challenges Australians living with hypophosphatasia (HPP) face, including delayed diagnosis, restricted access to treatment, and insufficient multidisciplinary care. The report outlines four key recommendations to improve early recognition, expand treatment access, and strengthen pathways to multidisciplinary and specialist support. Combined with enhanced patient advocacy, these recommendations aim to improve health outcomes and quality of life for Australians living with HPP and other rare diseases.

Approach

The report was independently prepared by Evohealth, a specialist health advisory firm, in collaboration with an expert Advisory Committee. It was informed by a comprehensive review of published academic and grey literature, interviews with Australian clinicians, researchers, a patient advocacy group, and people living with HPP.

Alexion Australia provided funding for this report, but did not participate in its development to ensure Evohealth's independence.

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We also thank the Advisory Committee for their invaluable insights, which were critical to the development of this report. The committee comprised the following members:

Trudy Morrison
Living with HPP

Professor Peter Ebeling, AO FAHMS
Endocrinologist and Head, School of Clinical Sciences, Monash University

Professor Craig Munns
Paediatric Endocrinologist Queensland Children's Hospital, and Director of Child Health Research Centre, Mayne Professor of Paediatrics and Convenor UQ First 10,000 Days Network, Faculty of Health, Medicine and Behavioural Sciences at The University of Queensland

Associate Professor David Scott
Exercise Scientist and National Health and Medical Research Council (NHMRC) Emerging Leadership Fellow, Institute for Physical Activity and Nutrition (IPAN), Deakin University

Professor Ravi Savarirayan
Clinical Geneticist and Group Leader, Molecular Therapies at Murdoch Children's Research Institute

Professor Verity Pacey
Associate Dean Graduate Health Education, Professor of Physiotherapy, Macquarie University

EXECUTIVE **SUMMARY**

Babies born with missing ribs. Children reliant on wheelchairs before primary school. Adults breaking bones from the most ordinary of actions.

> *One day, I was simply holding a cup of tea, and that action broke my wrist.*
>
> **– Anita, living with HPP**

This is not a medical anomaly — it is the reality for Australians living with hypophosphatasia (HPP), a rare and often misunderstood genetic condition that weakens bones. [1-3] While the clinical challenges of HPP are severe, they are compounded by something even more damaging: a health system that consistently fails to see, diagnose, treat or support those affected.

This report presents a clear case for reform. Through the lens of HPP, it illustrates how Australia's healthcare system remains unfit for people with rare diseases — and how small-scale, targeted reforms can drive broader improvements for the more than 2 million Australians living with rare conditions. [4]

Rare diseases in Australia

A disease is considered rare if it affects fewer than **1 in 2,000 people.** [4]

More than 7,000 rare diseases that are life-threatening or chronically debilitating. [4]

Around **8 per cent of Australians** (2 million people) live with a rare disease. [4]

HPP is not just a rare disease — it is a case study in system failure. It offers policymakers a unique opportunity: a ready-made test case to deliver long-promised changes outlined in key reviews, including the *New Frontier – Delivering Better Health for All Australians (2021), Accelerating Access to the Best Medicines for Australians (2024)*, and the *National Strategic Action Plan for Rare Diseases (2020)*. [5-7] Implementing reforms for HPP is a politically attractive, practical next step that shows momentum on rare disease reform — and delivers life-changing outcomes for a high-need community.

A rare condition

HPP is a genetic, multisystem condition that impairs the body's ability to properly mineralise bones and teeth, leading to weakened bones, fractures, deformities, and early tooth loss. [1-3] It is caused by variations in the alkaline phosphatase liver/bone/kidney (ALPL) gene, which disrupts the production of the enzyme essential for maintaining strong bones and teeth. [1-3, 8]

Despite being categorised as a rare disorder, the true prevalence of HPP is not well understood. International estimates suggest severe forms occur in 1 in 100,000 to 300,000 live births, while milder forms may be more common, though less easily identified. [9-11]

HPP is a rare disease and its true **prevalence** across all ages is **unknown**. [9, 10]

International estimates suggest severe forms of perinatal and infantile HPP occur in **1 in 100,000 to 300,000** live births. [11]

HPP can affect individuals at any stage, from neonates to adults, with a broad spectrum of severity, ranging from life-threatening manifestations to more subtle signs that are often overlooked. [9, 12] Given the broad range of symptom presentation, many individuals face delays in diagnosis, limited access to treatment, and fragmented care.

HPP is usually most severe and potentially life-threatening when it is identified before birth (perinatal onset) or during infancy (infantile onset). [13] In contrast, juvenile and adult-onset forms, are typically not life-threatening, but can still cause significant disability.

> *It is incredibly variable. I'm seeing adults who we know have HPP and yet have only ever shown relatively minor dental issues… It ranges from babies born with almost no bones to someone fracturing a metatarsal in their 80s. The spectrum is enormous.*
>
> **– Professor Ravi Savarirayan, Clinical Geneticist**

Infants with severe HPP may be born with soft, underdeveloped bones, malformed skulls, or missing ribs. They can experience seizures, skeletal deformities, respiratory failure, and failure to thrive, often requiring urgent intensive care. [13-16]

HPP can result in **stillbirth** or **infant mortality.** [13]

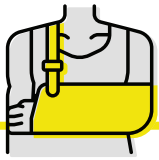
Median survival for untreated infants with HPP is **8.9 months** with **42 per cent 1 year survival** and **27 per cent 5 year survival**. [13]

In contrast, milder forms of HPP can emerge slowly and disrupt daily life over a longer period of time. [12, 15] People with these forms may experience frequent, painful fractures from minor activities like walking or lifting objects, along with chronic bone pain, joint stiffness, muscle weakness and pain, and early tooth loss. [3, 9, 16-26] Additional complications can include fatigue, mobility issues, respiratory difficulties, kidney problems, and neurological symptoms, all of which impact independence. [3, 9, 16-26] Even those with "mild" HPP often rely on mobility aids and face persistent physical discomfort. [3, 9, 16-26]

A global registry study on HPP revealed that:

Among paediatric patients, **36 per cent** use wheelchairs, **32 per cent** require crutches, and **27 per cent** use canes. [27]

For adults, **27 per cent** use crutches, while **21 per cent** require walkers and/or canes. [27]



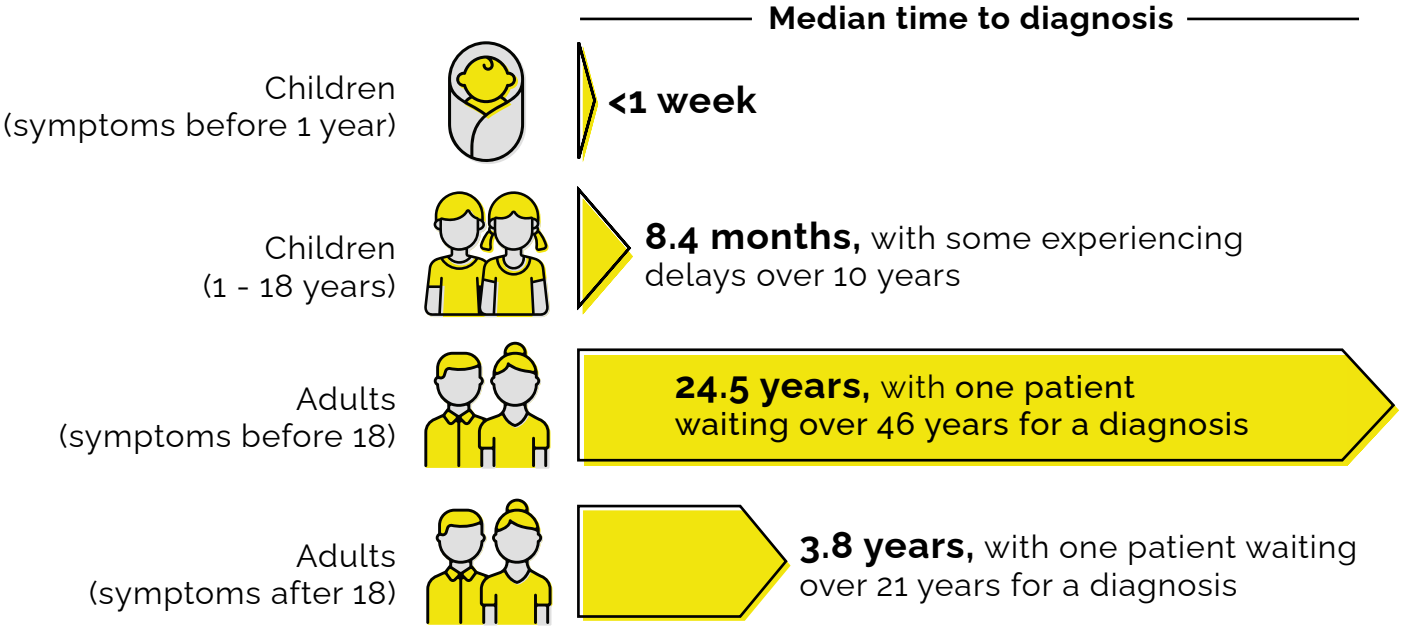
86 per cent of adults have experienced at least one fracture, with an average of nearly **13 fractures** per person. [27]

People living with HPP have nearly double the level of disability compared to the general population. [28] It is a challenge for them to navigate the health system, as well as engage in education and employment. Ultimately, this affects how they participate in society, as well as their economic security. They desperately need a health system that recognises and supports them to decrease this burden.

Missing the signs and diagnostic delays

For many Australians living with HPP, the first and most challenging hurdle is simply getting a diagnosis. Early signs are often subtle and misattributed to more common conditions like osteoporosis or arthritis. [29, 30] Lack of familiarity with the condition means diagnosis is frequently delayed or missed. [15, 31]

One study illustrates just how widely diagnostic timelines can vary:



Diagnostic delay has serious consequences. Patients can undergo unnecessary tests, receive ineffective or harmful treatments, and endure preventable pain. [31] HPP is often mistaken for osteoporosis, leading to inappropriate treatment with bisphosphonates, which can further impair bone mineralisation and increases the risk of atypical femur fractures. [31, 32]

A persistently low alkaline phosphatase (ALP) level is a key diagnostic clue, often missed. This is despite being included in Australian standard blood tests. Many clinicians typically look for high ALP levels as an indicator of liver conditions, but are unaware that low ALP levels can also be significant and may require further investigation, potentially pointing to a rare condition like HPP. [31] Sadly, this means the opportunity for early intervention can be missed, leaving people with HPP in prolonged distress and uncertainty.

Care without consistency or coordination

HPP is a lifelong, incurable condition. Care is focused entirely on managing symptoms, including pain relief, allied health support, dental care, assistive equipment, and surgery for fractures. [14]

But living with HPP involves far more than managing fragile bones. It is a complex, multisystem disorder that requires coordinated input from a wide range of clinicians including primary care providers, specialists, dental and allied health practitioners.

> *Hypophosphatasia is not just about bones; it requires a dedicated multidisciplinary care team to achieve the best health outcomes for our patients.*
>
> **– Professor Peter Ebeling, Endocrinologist**

In paediatric settings, care is well coordinated between different providers. However, this support often disappears during the transition to adult care and is typically unavailable for those diagnosed in adulthood. As a result, adults are left with the responsibility of finding and coordinating the services they need, which further adds to the burden of living with the condition.

To make matters worse, due to the rare nature of the disease, many healthcare professionals have limited knowledge of HPP. People living with HPP and their carers often need to educate providers while advocating for their own care.

> *I've had to explain to [clinicians], in my limited language around what HPP is, because a lot of the time they've not heard of it or they've heard of it, but they don't necessarily understand it.*
>
> **– Trudy, living with HPP**

There is no national model of care for HPP, no dedicated clinics, and no care coordinators to guide individuals through finding and managing their complex care needs. People living with HPP manage their condition within a health system that isn't designed to support them.

Unlocking access to innovation

Advances in diagnosis and treatment for HPP offer new hope for earlier detection and better long-term outcomes. These include AI-based diagnostic tools and emerging therapies such as enzyme replacement, gene, and small molecule therapies. [33-40] However, without reform to Australia's funding assessment processes, these innovations risk remaining out of reach for those who need them most.

Australia's approach to approving and funding new therapies, was not designed with rare conditions in mind. [41] Known as Health Technology Assessment (HTA), the system relies on data from clinical trials that included a large number of people and strict cost-effectiveness criteria. Ultimately this creates barriers that delay or deny access to life-changing therapies for small patient populations with rare conditions like HPP. [41]

Recent reviews of the HTA system, including *The New Frontier – Delivering Better Health for All Australians (2021)* and *Accelerating Access to the Best Medicines for Australians Now and into the Future (2024)*, highlight these shortcomings. [5, 6] Both reports call for more flexible assessment frameworks that consider a broader range of evidence and value factors beyond just cost. Without implementing these reforms, Australians with HPP will continue to be left behind. With new therapies on the horizon, urgent changes are needed to prevent history from repeating itself.

The chance to turn failure into reform

The challenges faced by Australians with HPP are not isolated — they are symptoms of a broader failure in how the health system responds to rare diseases. Delays in diagnosis, inequitable access to treatment, fragmented care, and a lack of clinical awareness are issues repeated across the more than 7,000 rare conditions affecting 2 million Australians. [4]

These problems are not new. What's missing is not insight — but action.

HPP is a clear example of where the system breaks down. But it's also a unique opportunity to show how it can be rebuilt. Targeted, achievable reforms to improve diagnosis, treatment access and care coordination for people with HPP would not only transform lives for this small, high-need group — they would road-test solutions for the broader rare disease community.

From diagnostic triggers to updated HTA processes and national models of care, the answers already exist. They've been outlined in major national strategies and reviews — including:

- *The National Strategic Action Plan for Rare Diseases (2020)*, [7]
- The Inquiry into approval processes for new drugs and novel medical technologies in Australia Final report, *New Frontier – Delivering Better Health for All Australians (2021)*, [5] and
- The HTA Policy and Methods Review – *Final report, Accelerating Access to the Best Medicines for Australians (2024)*. [6]

These frameworks set out the case for reform. HPP is the chance to implement them.

Elevating the patient voice: a critical enabler for change

Before meaningful reform can be achieved, one thing is clear: the patient voice must be embedded at the heart of these changes. Australians living with HPP currently have no formal advocacy group. Without a strong, organised patient voice, they remain excluded from the decisions that shape their care and future.

Patient advocacy is critical not only to raise awareness, but to ensure reforms are grounded in lived experience. It will be essential to the success of the solutions proposed in this report.

Out of the shadows

HPP may be rare, but Australians living with it cannot remain in the shadows in policy and care planning. The following recommendations outline practical, scalable reforms that respond directly to system gaps exposed by HPP — and create a model for change across the rare disease landscape:

RECOMMENDATION 1

Standardise pathology reporting to include alerts when ALP falls below normal range, to enable early recognition and referral of suspected HPP.

RECOMMENDATION 2

Develop Australian specific clinical guidelines and patient education materials for HPP and make them publicly available on the Rare Awareness Rare Education (RARE) Portal.

RECOMMENDATION 3

Progress HTA Review recommendations relevant to accessing therapies for rare and ultra-rare diseases, like HPP.

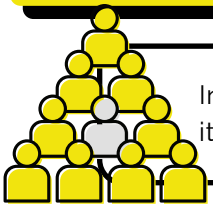
RECOMMENDATION 4

Fund the development of a national model for rare disease centres of expertise, including access to bone disease specialist care, care coordination and virtual service delivery for HPP patients.

By acting now, government can deliver meaningful reform for Australians with HPP — and set a blueprint for tackling rare disease care nationwide. This is a rare opportunity Australia cannot afford to miss.

What is Hypophosphatasia?

Hypophosphatasia (HPP) is a **rare genetic metabolic condition** caused by **variants** in the alkaline phosphatase liver/bone/kidney **(ALPL) gene**, leading to reduced activity of tissue-nonspecific alkaline phosphatase (TNSALP), an enzyme crucial for **bone and teeth mineralisation.** [1-3]



In Australia a condition is considered rare if it affects fewer than **1 in 2,000** people. [4]

8% of Australians (**2 million people**) live with a rare condition. [4]

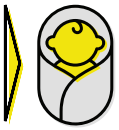
HPP is a rare condition and its true **prevalence** across all ages is **unknown**. [9, 10]

Over 400 different ALPL genetic variants identified to date. [8]

International estimates suggest forms of perinatal and infantile HPP occur in **1 in 100,000 to 1 in 300,000** live births. [11]

Median survival for untreated infants with HPP is **8.9 months** with **42% 1 year survival** and **27% 5 year survival**. [13]

Diagnostic delays are extremely variable as shown in one study where,



Children with symptoms before the age of one were diagnosed within **1 week**,

Children aged 1–18 had a median wait of **8.4 months**,

Adults with symptoms before age 18, waited a median of **24.5 years for diagnosis,** and

Adults with symptoms after age 18 waited a median **3.8 years for diagnosis**. [15]

HPP can result in **stillbirth** or **infant mortality**. [13]

2x A study of **212 HPP patients** found that disability scores were **double** those in the general population. [28]

More than half of patients in one study report their health negatively affects their physical and mental functioning. [28]

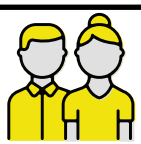
One patient case series study found

Among paediatric patients,

36% use wheelchairs,

32% require crutches, and

27% use canes.



For adults,

27% use crutches,

while **21%** require walkers and/or canes. [27]

A RARE CONDITION **LOST IN THE SYSTEM**

Babies born without fully formed ribs. Children with bowed legs. Adults unable to hold a cup of tea for fear of breaking a bone. People losing teeth without explanation.

This is the reality for Australians living with hypophosphatasia (HPP), a rare genetic condition that can affect people of any age with symptoms ranging from life-threatening to subtle and overlooked. Yet despite its devastating consequences, HPP remains largely invisible within Australia's health system.

HPP is more than an individual tragedy — it is a sharp illustration of systemic failure in rare disease care. From missed diagnoses to fragmented care and restrictive treatment access, the journey of Australians with HPP reflects the experiences of many across the rare disease community.

But this failure also presents an opportunity. HPP offers a clear, actionable test case for long-overdue reforms to diagnosis pathways, treatment access, and coordinated care — reforms that will benefit not only people with HPP, but millions of Australians living with rare conditions.

This report explores the barriers faced by people with HPP and outlines practical solutions to transform their care. It is both a call to action and a roadmap for government to deliver meaningful change, starting with HPP and scaling across the rare disease landscape.

UNDERSTANDING **HYPOPHOSPHATASIA**

What is hypophosphatasia?

Hypophosphatasia is a rare, inherited metabolic condition caused by variants in the alkaline phosphatase liver/bone/kidney (ALPL) gene. [1-3] To date, over 400 different ALPL variants have been identified, contributing to the extreme variability in disease manifestation, time to diagnosis, and patient outcomes. [8]

These genetic variants lead to reduced activity of tissue-nonspecific alkaline phosphatase (TNSALP), an enzyme essential for bone and tooth mineralisation. [1-3]

Over **400** different ALPL genetic variants have been identified to date. [8]

What is bone and tooth mineralisation?

Bone mineralisation is a biological process where minerals, primarily calcium and phosphate, are deposited in the bone matrix, strengthening bones and teeth. This process, regulated by TNSALP, is essential for maintaining skeletal integrity. [42] In HPP, the reduced enzyme activity disrupts mineralisation, leading to weak, fragile bones and teeth, increasing the risk of fractures, deformities, and functional impairments. [1-3]

This enzyme deficiency also causes the accumulation of substrates that impair calcium and phosphate uptake, affecting not only bone and teeth hardness but also multiple organ systems, including muscular, rheumatologic, respiratory, renal, and neurological systems. [1-3]

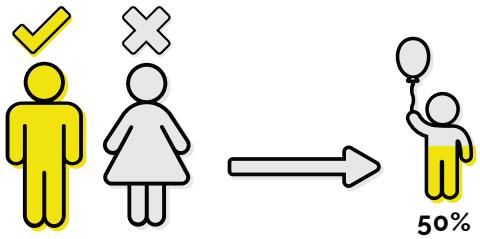
How is it inherited?

Genetic ALPL variants can be inherited in either an autosomal dominant or recessive pattern (Figure 1).

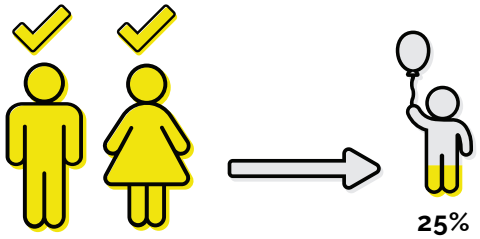
Figure 1 – Autosomal dominant and recessive inheritance

What is autosomal dominant and recessive inheritance?

Autosomal dominant and autosomal recessive describe different ways genetic conditions are inherited.



Autosomal dominant means a person only needs to inherit one faulty gene from either parent to have the condition. If a parent has the condition, there is a 50 per cent chance they will pass it on to their child. [43, 44]



Autosomal recessive means a person must inherit two faulty genes, one from each parent to develop the condition. If both parents are carriers (they have one faulty gene but no symptoms), there is a 25 per cent chance their child will inherit both faulty genes and have the condition. [43, 44]

Source: Evohealth from multiple sources [43, 44]

Autosomal recessive forms of HPP are typically associated with more severe and earlier-onset disease. [45, 46] However, even within the same inheritance pattern (e.g. family members), symptom severity and disease progression can vary greatly due to the complex interaction of genetic and environmental factors. [47, 48]

How rare is it?

In Australia, a disease is classified as rare if it affects fewer than 1 in 2,000 people. [4] Collectively, over 7,000 rare diseases affect around 8 per cent of Australians (approximately 2 million people), many of whom face life-threatening or chronically debilitating conditions with limited or no treatment options, placing a significant and lifelong burden on individuals and their families. [4]

Rare diseases in Australia

A disease is considered rare if it affects fewer than **1 in 2,000 people.** [4]

More than 7,000 rare diseases that are life-threatening or chronically debilitating. [4]

Around **8 per cent of Australians** (2 million people) live with a rare disease. [4]

Although Australian-specific data is unavailable, [9, 10] international estimates suggest severe forms of HPP, such as perinatal and infantile onset occur in approximately 1 in 100,000 to 300,000 births, while milder forms may be as common as 1 in 6,370 births. [11] However, these figures vary due to differences in genetic screening practices and diagnostic awareness between countries and the true number of affected individuals is likely higher. [11, 49-52]

Severe forms of **perinatal and infantile** HPP estimated to occur in **1 in 100,000 to 300,000** live births. [11]

Milder forms HPP may be as common as **1 in 6,370 births**. [7]

For those living with HPP, the rarity of the disease does not lessen its impact. Instead, it often amplifies the burden, as people may navigate a healthcare system that is largely unprepared to diagnose, treat, or support them - a reality shared by many Australians with rare diseases.

A COMPLEX DISEASE **WITH WIDESPREAD IMPACTS**

HPP is a highly variable disease, and understanding the challenges faced by individuals living with HPP requires recognition of its complexity.

> *It is incredibly variable. I'm seeing adults who we know have HPP and yet have only ever shown relatively minor dental issues… It ranges from babies born with almost no bones to someone fracturing a metatarsal in their 80s. The spectrum is enormous.*

– Professor Ravi Savarirayan, Clinical Geneticist

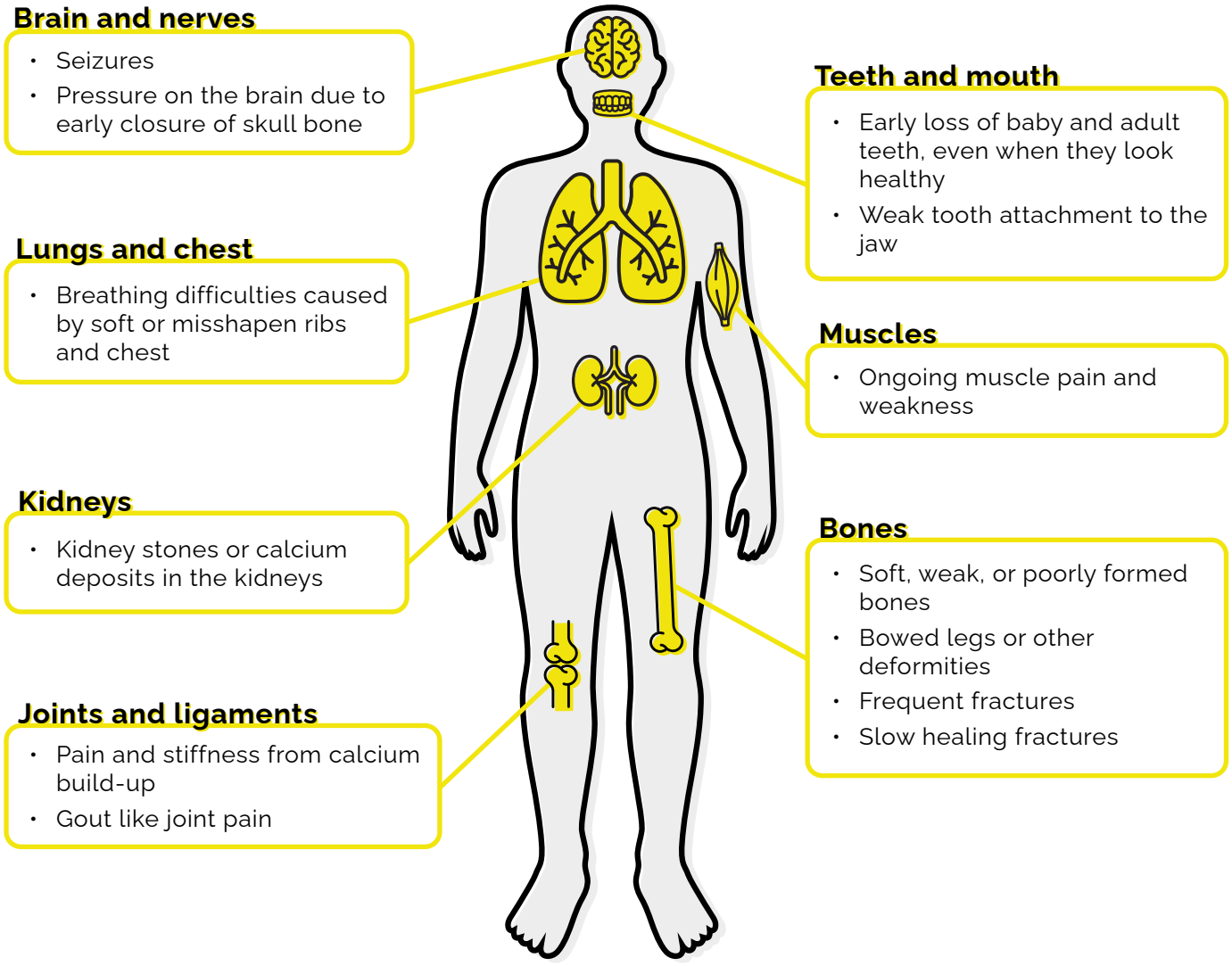
Some individuals experience severe skeletal abnormalities from birth, including bone weakness and life-threatening respiratory issues, while others live with chronic pain, fractures, and dental problems that may only be recognised later in life, or never diagnosed at all. [9, 12] Even within the same family, individuals carrying the same genetic variant can experience vastly different symptoms. [12, 15]

A systemic disease affecting the whole body

HPP is a lifelong condition affecting multiple organ systems and can present at any age. [9, 12] Symptoms range from mild signs, such as early tooth loss or low bone density to more severe complications, including frequent fractures, chronic pain, muscle weakness and mobility challenges. [15]

Beyond the skeleton, HPP can cause fatigue, joint pain, and complications in the muscular, renal, and nervous systems. [15, 17] These symptoms often progress unpredictably over time, accumulating and leading to increased disability. [12, 17] Figure 2 depicts the body systems that can be impacted by HPP and some of the common symptoms.

Figure 2 – Body systems affected by HPP and common symptoms



Source: Developed by Evohealth from multiple sources [3, 9, 16-26]

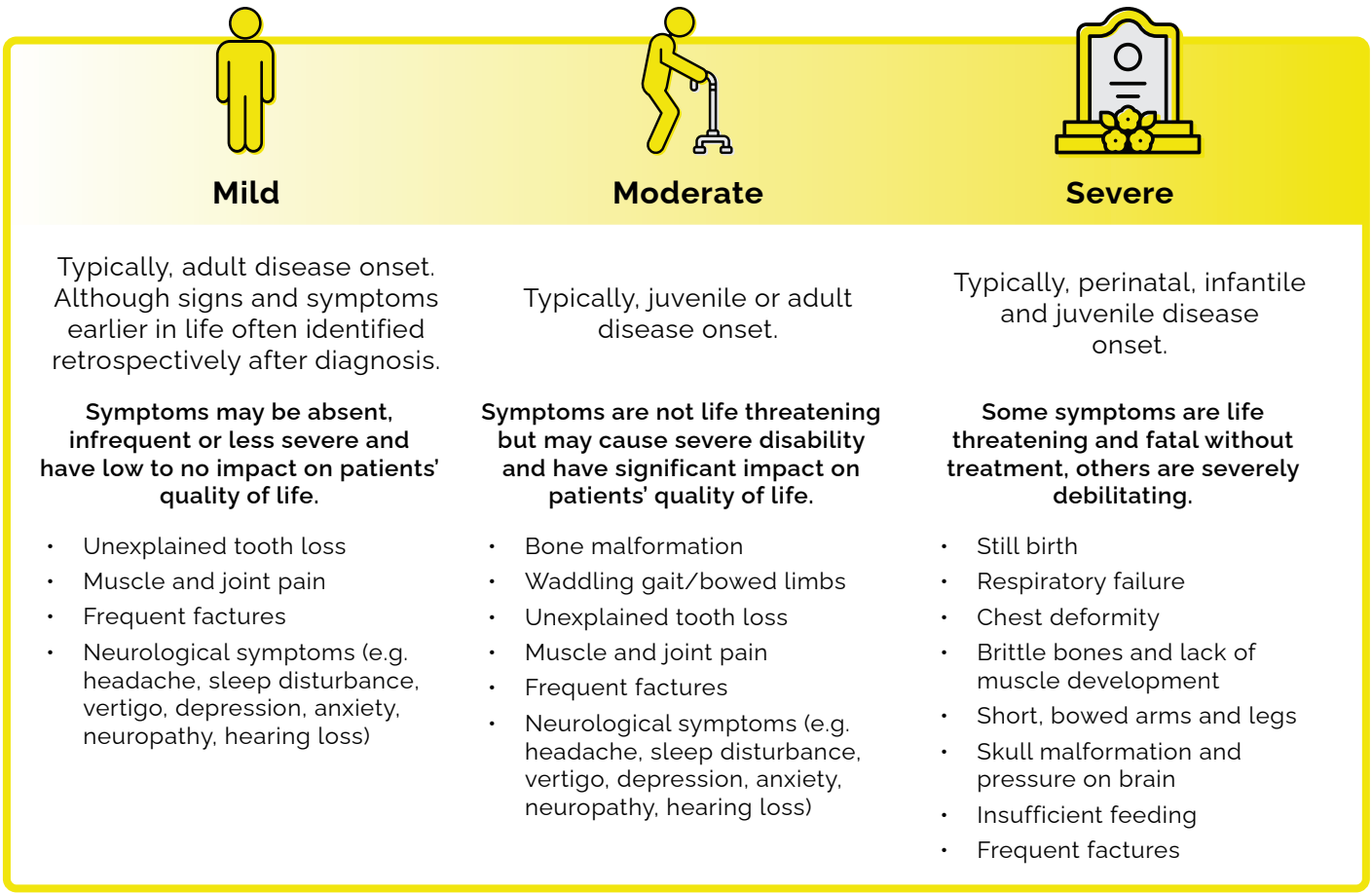
A spectrum of severity

The severity of HPP can vary significantly, with cases ranging from life-threatening forms in infancy to milder presentations that may go undiagnosed until adulthood. Typically, earlier symptom onset is associated with more severe disease and a higher risk of death or disability. Historically, HPP has been classified into distinct clinical forms based on age at diagnosis and symptom severity [14]:

- **Perinatal (or congenital) HPP**: The most severe form, often diagnosed in utero or at birth, characterised by profound skeletal hypomineralisation, chest deformities leading to respiratory failure, and high mortality. [14]
- **Infantile HPP:** Diagnosed within the first six months of life, presenting with failure to thrive, rickets-like skeletal abnormalities, early tooth loss, and respiratory complications. [14]
- **Childhood HPP:** Typically identified in early childhood due to delayed walking, muscle weakness, bone pain, fractures, and premature loss of primary teeth. [14]
- **Adult HPP:** Often diagnosed later in life, commonly in response to stress fractures, chronic pain, or osteomalacia-like symptoms. [14]
- **Odonto HPP:** The mildest form, primarily affecting dental health with early tooth loss but minimal skeletal symptoms. [14]

Although these classifications provide some insight into disease patterns, they do not fully capture HPP's progressive and variable nature, nor the significant overlap between these forms. As a result, emerging research recognises HPP as a disease continuum, with symptoms that can evolve, progress, and worsen over time. [17, 27] This disease continuum is depicted in figure 3.

Figure 3 – Disease continuum for HPP and common symptoms



Source: Developed by Evohealth from multiple sources [3, 9, 16-26]

Life-threatening forms of HPP

Perinatal and infantile forms of HPP are typically the most severe, with high risk of death without treatment. Infants may be born with under-mineralised bones, missing ribs, and/or skull defects, making normal breathing and development impossible. Respiratory failure and seizures are common complications. [13] Median survival for untreated infants with HPP is just 8.9 months, with only 42 per cent surviving to one year and 27 per cent reaching five years old. [13] Early symptom onset, respiratory complications requiring ventilator support, and seizures all increase the risk of premature death. [13, 15, 16]

Case study

Tom's story - Living with severe and complex HPP from childhood[1]

Tom was diagnosed at 11 months presented with poor growth, muscle weakness, a short neck, curved spine, and wide tooth spacing. He was frequently hospitalised with pneumonia, likely due to skeletal and muscular complications. [53]

By age 9, Tom developed persistent headaches. Imaging revealed craniosynostosis (a condition where the bones in the skull fuse too early), along with a Chiari malformation (a brain abnormality) and cerebellar tonsil herniation, requiring major brain surgery. [53]

Fractures became more frequent with age. At 17, he broke both femurs and underwent surgery to insert rods. At 18, he fractured his tibia while jumping; healing was prolonged. At 20, he again fractured both femurs - this time from a seizure-induced fall - requiring eight months of rehabilitation. [53]

By age 20, the estimated healthcare costs for Tom in Australia, excluding out-of-pocket expenses, were $179,435.[2]

Milder but still debilitating forms of HPP

Milder forms of HPP can still lead to significant, progressive disability if left untreated, with symptoms sometimes not appearing until childhood or adulthood. [12, 15] Some individuals remain asymptomatic or unaware of their condition, while others may experience symptoms that progress over time, including fatigue, fractures, mobility issues, and chronic pain. Even individuals with mild disease can eventually face severe disability, especially without timely diagnosis and intervention. [12, 15]

> *"It's a very unpredictable disease. Just because someone has a quiet period in childhood doesn't mean they won't face severe complications later in adulthood."*
>
> **– Professor Ravi Savarirayan, Clinical Geneticist**

[1]The following case study was taken from a published chart review of assessed healthcare resource utilisation by patients with HPP in the UK. A pseudonym has been used for illustrative purposes.

[2]Costs associated with each patient were estimated using a mixed-methods approach reflecting the Australian healthcare context (see Appendix)

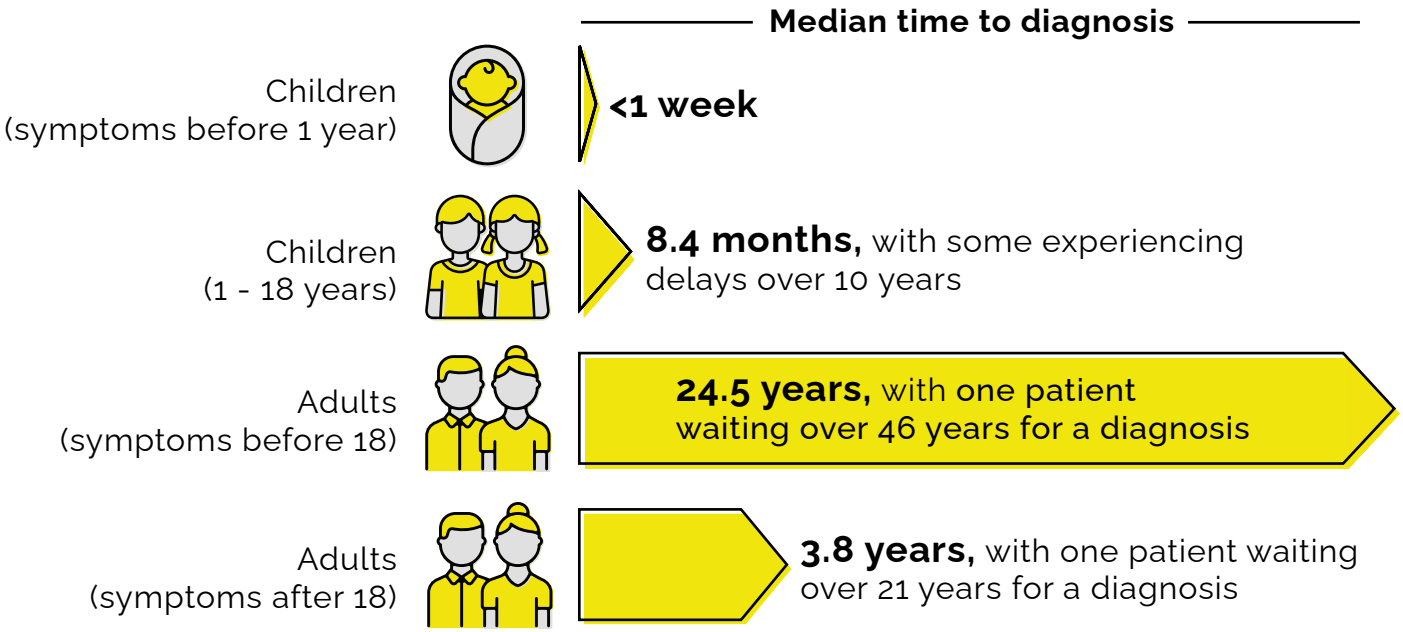
One of the greatest challenges of HPP is its variability. It spans a continuum from life-threatening complications in infancy to milder forms that often go undiagnosed or misdiagnosed for years, with no predictable symptoms or disease course.

MISSING **THE SIGNS**

For people living with HPP, the diagnostic journey is often fraught with delays and challenges. Symptoms can be vague and overlap with more common conditions, while the condition's biochemical hallmark, persistently low alkaline phosphatase (ALP), is frequently overlooked. This leads to significant delays in diagnosis, leaving many individuals without answers for years.

Delays in diagnosis are common in HPP and vary widely based on the age at symptom onset. [15]

One study illustrates just how widely diagnostic timelines can vary:



This variability in diagnosis time highlights the challenges people with HPP face. [31] Most patients begin their diagnostic journey with a visit to their General Practitioner (GP), often prompted by nonspecific symptoms such as muscle pain, fatigue, or fractures. [15, 31] However, due to HPP's rarity, it is rarely considered in primary care, and the biochemical hallmark of low ALP is often overlooked. [31]

While ALP is routinely tested in biochemical blood panels, most clinicians are trained to interpret elevated ALP levels, which are associated with liver damage or bone turnover. Low ALP, however, is not typically flagged as clinically relevant and may be dismissed. Without awareness of its significance, this critical clue is often missed. [54]

> *"GPs routinely test for ALP and are well trained to identify and act on high levels. But many haven't been taught to recognise the significance of low ALP. There needs to be more awareness that persistently low ALP can signal a serious rare condition—and that it warrants referral to a specialist."*
>
> **– Professor Peter Ebeling, Endocrinologist**

Symptoms of HPP are often misattributed to more common conditions, such as osteoporosis, vitamin deficiencies, or stress. As a result, many people with HPP are never properly investigated. [29, 30] Even when red flags are raised, people with HPP often enter a confusing referral loop. HPP is typically diagnosed by endocrinologists, however, individuals are often misdirected to rheumatologists or orthopaedic specialists, prolonging the search for answers. [55]

Annie's story – The long road to diagnosis

Annie, 50, is a wife, mother of two teenagers, and part-time manager. Once a passionate group fitness instructor with a thriving marketing career, her life changed dramatically after developing chronic pain, mobility issues and enduring a long, complex search for answers.

Her symptoms began in 2010, with frequent bilateral tendinopathies that didn't heal normally. Despite being fit and active, scans revealed unusually poor bone density. Gradually, she had to scale back her fitness regime while searching for answers from a range of perplexed healthcare specialists.

Doctors initially suspected kidney issues, then autoimmune disease. Years of extensive specialist appointments and tests, ineffective treatments and inconclusive results followed.

As her pain worsened and mobility declined, a referral to a rheumatologist ruled out arthritis. In 2019, an endocrinologist returning from a global congress on rare diseases recognised a pattern in her blood results.

A genetic test at Westmead Children's Hospital confirmed the diagnosis as HPP.

Diagnostic approach for HPP

When HPP is suspected, a definitive diagnosis relies on a combination of clinical, biochemical, and genetic investigations: [29, 30]

Clinical evaluation
Medical history and physical examination to assess symptoms and rule out other conditions that can present with similar symptoms. [3, 29]

Measurement of ALP levels
Blood tests to identify persistently low ALP levels compared to age and sex adjusted normal range. [3, 29, 54]

Genetic testing
Identifying variations in the ALPL gene can help confirm HPP, especially when clinical signs or family history raise suspicion. [3, 29]

Testing for elevated TNSALP substrates
Higher levels of biochemical markers such as inorganic pyrophosphate (PPi), pyridoxal 5'-phosphate (PLP), and phosphoethanolamine (PEA) can support an HPP diagnosis. However, tests for these markers are not widely available, and their levels can vary between individuals [3, 29]

Despite the availability of these diagnostic tools, they are not routinely used or readily accessible and are often misinterpreted outside of specialist care settings. International guidelines, such as those from the HPP Working Group, may be referenced by specialists but remain underutilised in the absence of national consensus or specific Australian clinical guidance. [3, 56]

These challenges reflect broader barriers in rare condition diagnosis. Most clinicians are unfamiliar with rare conditions and lack targeted education to support early recognition. [7] Detection is further hindered by reliance on biochemical markers, like low ALP, that are neither routinely flagged nor well understood. [29, 56] Without clear guidance and referral pathways, delays in diagnosis are almost inevitable.

Consequences of diagnostic delays

Delays in diagnosis can lead to increased pain, uncertainty, and worsening outcomes. [9, 57, 58] Misdiagnosis is particularly dangerous when it leads to inappropriate treatment. For example, HPP is frequently mistaken for osteoporosis, leading to patients being prescribed bisphosphonate therapy. [31] Bisphosphonates can worsen bone hypomineralisation and increase the risk of atypical femoral fractures. [31] One case study reported a patient who suffered multiple atypical subtrochanteric femoral fractures after four years of bisphosphonate treatment. [32] Data from the Global Registry study shows that 17.6 per cent of individuals with HPP had previously received bisphosphonates. [15]

Accurate diagnosis is crucial not only to avoid harm but also to ensure appropriate management. It also facilitates family screening for this genetic condition. Identifying one case can help detect the condition in relatives, allowing for earlier monitoring and treatment to improve long-term outcomes. [31]

For people living with HPP, a timely diagnosis is the first step toward appropriate management and a better quality of life. Addressing these challenges requires a shift in how rare diseases are recognised and diagnosed.

CARE WITHOUT **COORDINATION**

Effective management of HPP requires a broad range of supportive interventions to relieve symptoms and maintain daily function. Many individuals rely on pain management, allied health services, dental care, assistive equipment, and surgery to manage the physical burden of the condition. [14]

Key supportive interventions include:

Pain management
Analgesics and non-pharmacological strategies, such as physiotherapy, and physical activity, play a crucial role in managing pain and improving comfort. [59]

Allied health support
Allied health services help individuals maintain mobility, independence, and daily function. Physiotherapy and exercise physiology support mobility, occupational therapy aids daily function, and mental health services address emotional challenges. [60, 61]

Dental care
Regular dental monitoring and interventions, such as specialised dental treatments or implants, may be necessary to preserve oral health and function. [62]

Assistive equipment and prosthetics
Individuals may require mobility aids, orthotics, or prosthetic devices to support movement, stability, and daily activities. [61]

Surgical intervention
Procedures such as fracture repairs, cranial surgery, and “rodding” for long bone fractures are often necessary and most effective when combined with rehabilitation. [14]

Given HPP’s variability, management must be tailored to each individual and their symptoms, severity, and evolving needs. However, there is no national model of care for HPP, no dedicated clinics, and no care coordinators to guide individuals through finding and managing their complex care needs. People living with HPP manage their condition within a health system that is not designed to support them.

Limited access to coordinated paediatric care

Children with HPP are typically cared for by endocrinologists and paediatricians at specialist hospitals, with some clinics providing care coordination to assist with referrals and specialist communication. However, access to coordinated care varies across Australia, and funding for these services is often limited.

In some states, long wait times for essential allied health services further delay critical interventions, making it even harder to manage HPP effectively.

> *In our paediatric clinic, we try to coordinate care and link in allied health services, like physiotherapy as needed. But that's not the case for everyone. Funding for such things is very limited.*
>
> **– Professor Craig Munns, Paediatric Endocrinologist**

Significant gaps in adult care

Adults with HPP face even greater challenges than children, as they are largely responsible for managing and funding their own care. Unlike paediatric patients, who may receive some level of coordinated care, adults must independently navigate multiple specialists and allied health providers to piece together their own multidisciplinary support. This fragmented system places a significant burden on individuals and families. [14, 29]

The transition from paediatric to adult care is particularly difficult. Many young people move from a structured, team-based model to a system where they must identify and access services on their own. This often results in delayed treatment and missed opportunities to improve quality of life. [14, 29]

> *Regardless of how much physical disability or how many symptoms people were experiencing, the mental burden of navigating the healthcare system was a constant issue identified by patients. Patients often have to explain their condition to each new doctor or health professional they see — over and over again. It's incredibly challenging because of the lack of awareness among health professionals, many of whom have never heard of the condition. This leaves patients in the position of having to educate their own care providers, which is completely the wrong way around.*
>
> **– Associate Professor David Scott, exercise scientist and research fellow**

The rare nature of HPP further complicates access to appropriate care. Finding healthcare professionals with the specialised expertise to manage the condition can be incredibly difficult, if not impossible. [14, 29] Even when individuals locate knowledgeable providers, there is no guarantee of continuity or

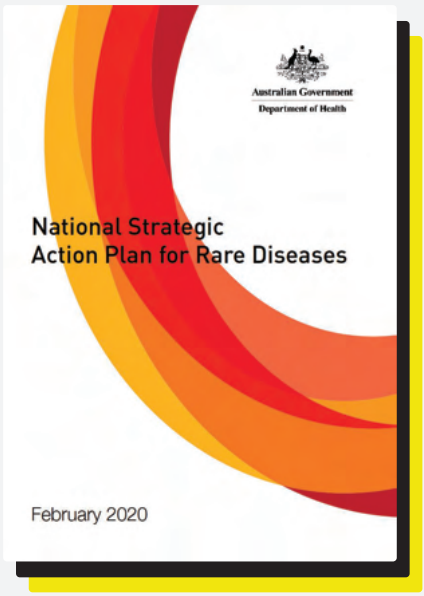
access to the full range of necessary services. This challenge is not unique to HPP but is shared by many Australians living with rare conditions, who often struggle within a healthcare system that is not designed to meet their complex needs.

> *I've had to explain to [clinicians], in my limited language around what HPP is, because a lot of the time they've not heard of it or they've heard of it, but they don't necessarily understand it.*
>
> **– Trudy, living with HPP**

The need for a nationally coordinated approach

The challenges faced by Australians with HPP reflect broader systemic issues affecting rare disease communities. *The National Strategic Action Plan for Rare Diseases* highlights these issues and calls for a nationally coordinated, patient-centred approach to improve diagnosis, treatment access, and integrated care. [7] While progress has been made, further investment and reform are needed to progress these to ensure people with HPP, and all rare diseases, receive the comprehensive and coordinated care they deserve. [63]

National Strategic Action Plan for Rare Diseases (2020)



The *National Strategic Action Plan for Rare Diseases* provides the overarching policy framework to improve outcomes for Australians living with rare conditions, including HPP. It identifies three key pillars: awareness and education, care and support, and research and data. [7] The Plan calls for a nationally coordinated approach to rare disease care, including early and accurate diagnosis, integrated multidisciplinary models, and equitable access to treatment and support. [7] It also highlights the critical role of patient organisations in driving system reform, shaping policy, and ensuring lived experience informs care delivery. [7] Each of the recommendations in this report aligns with priorities in the Action Plan and aims to support its implementation.

People with HPP face a fragmented and uncoordinated system that fails to meet the needs of a complex, lifelong condition — a reality shared by many Australians living with rare diseases.

UNLOCKING **ACCESS TO INNOVATION**

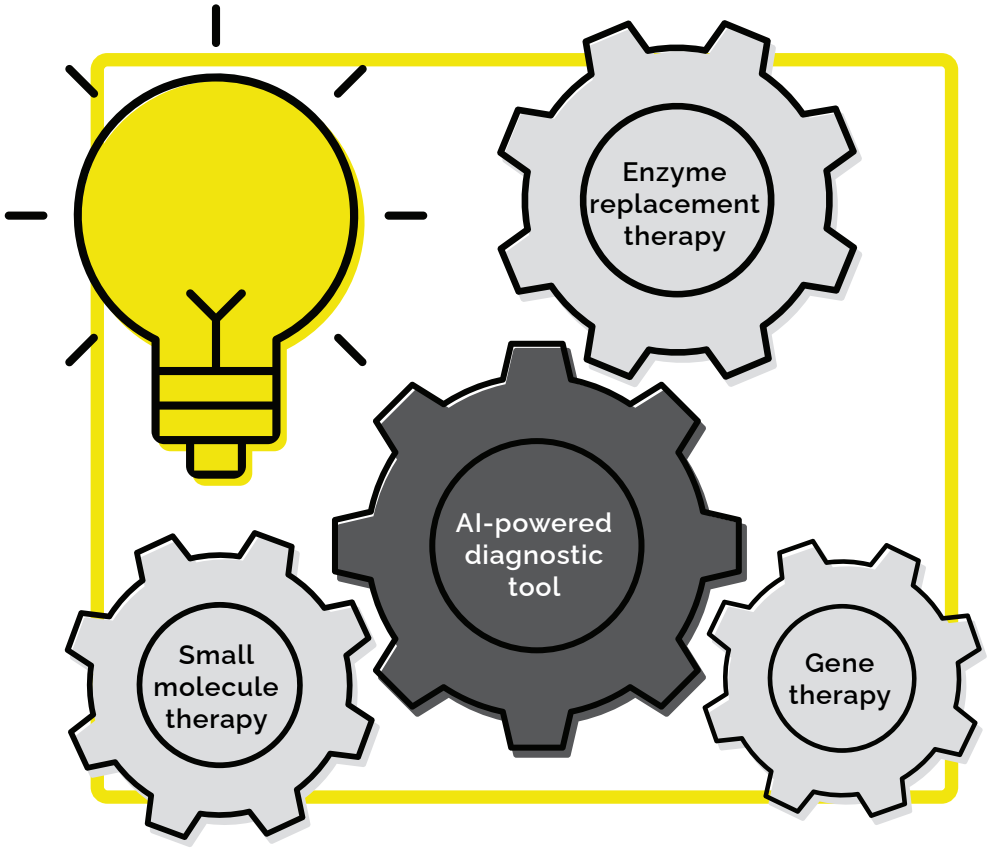
Significant advancements in the diagnosis and treatment of HPP are on the horizon, offering hope for earlier detection, more convenient care, and better long-term outcomes.

Diagnostic innovation

New tools are being developed to support earlier and more accurate diagnosis of HPP. These include AI-assisted technologies that analyse imaging to detect bone abnormalities and monitor disease progression. [33] Such tools could improve both early identification of HPP and long-term care monitoring and planning.

Emerging therapies

Several new treatments for HPP are under development with most seeking to target the underlying cause and reduce impact on the patient. These include enzyme replacement therapies, gene therapies and small molecules. [33-40] These innovations mark a major milestone in the management of this complex condition, offering patients hope for better future living with HPP.



The future of HPP diagnosis and treatment: What's on the horizon?

Diagnostic innovation

Monash University researchers have developed ALIGNOGRAM1.0, an AI-powered diagnostic tool that analyses X-rays to measure bone disorganisation, a key biomarker for HPP. Early trials have demonstrated its ability to monitor improvements in bone structure in response to treatment. This tool has the potential to enhance early diagnosis and ongoing monitoring of HPP, offering a more efficient and accurate way to track disease progression. [33]

Treatment innovation

Enzyme replacement therapy (ERT)

By replacing the missing or deficient TNSALP enzyme responsible for impaired mineralisation, ERT has demonstrated in clinical trials that it can help to restore key biological processes involved in bone development and maintenance, reducing symptoms and complications of HPP. [64-67] Clinical studies have shown that ERT can lead to substantial benefits for patients with severe forms of HPP, particularly when initiated early. Reported improvements include:

- **Survival:** 7-year survival increased from 27 per cent (untreated) to 87 per cent (treated) in patients with perinatal- and infantile-onset HPP. [68]
- **Bone health:** Rickets severity scores decreased in treated children. [69]
- **Respiratory function:** Reduced need for respiratory support. [69, 70]
- **Quality of life:** People with HPP reported less pain and fatigue, better sleep, reduced anxiety and depression, and improved daily life participation with treatment. [71]
- **Cognitive and motor function:** Children showed gains in motor skills (e.g., head control, sitting, walking) and cognitive abilities (e.g., object identification, classification). Most caught up with their peers in motor and cognitive development as strength and bone stability improved. [13, 69]

At the time of writing this report there was one ERT registered and reimbursed in Australia for selected patients, with two more undergoing various stages of development and clinical trials globally. [34-37, 64]

Small molecule therapy

An orally administered small molecule therapy for HPP is currently undergoing Good Laboratory Practice toxicology studies, with clinical trials anticipated to begin in 2025. This investigational treatment targets a novel mechanism to reduce levels of PPi, a key contributor to impaired bone mineralisation in HPP. [38]

Gene therapy

A gene therapy for HPP is currently in preclinical development. It uses an adeno-associated virus vector to deliver the gene encoding TNSALP, the enzyme deficient in individuals with HPP. This approach is designed as a one-time intramuscular injection. No clinical trials have commenced to date. [39, 40]

These innovations hold immense potential to transform the future of HPP care. However, without reform to Australia's framework for funding decisions for medicines, vaccines, and medical technologies - health technology assessment (HTA), these innovations risk remaining out of reach for the very people who need them most.

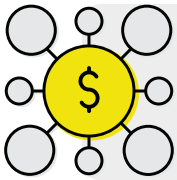
Barriers to accessing innovation

Current HTA processes remain rigid and outdated, often unable to accommodate the complexity, urgency, and rarity of conditions like HPP. [41] The HTA process, which determines public funding of treatments in Australia, often relies on traditional cost-effectiveness models[3] and large clinical trials, which are difficult conditions for rare disease treatments to meet. [41] Within this system, the Life Saving Drugs Program (LSDP)[4] provides a funding pathway only for life-saving treatments in ultra-rare disease[5] populations, excluding interventions that may significantly improve quality of life or reduce long-term disability. [41]

Key challenges include:

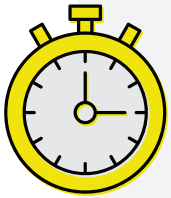
Limited clinical trial data and use of real-world evidence (RWE): Small patient populations limit the ability to conduct large randomised controlled trials (RCTs). As a result, HTA applications for rare disease therapies often rely on observational data[6] and RWE,[7] which are undervalued. [41, 72, 73]

Uncertainty in population size: The true prevalence of rare diseases like HPP is often underestimated, making it harder to demonstrate treatment need and impact. [41, 72, 73]



Traditional cost-effectiveness models: High drug development costs and small patient groups make rare disease therapies appear less cost-effective under traditional HTA methods. [41, 72, 73]

Failure to recognise transformative benefits: HTA processes tend to favour and fund life-saving over life-changing treatments. Therapies that reduce pain, improve mobility, prevent complications or reduce disability may be undervalued and in many cases not funded at all. [41, 72, 73]



Long lead times to review and fund life-saving therapies: Even when a therapy for a rare disease is considered life-saving, the time to review and fund it is unnecessarily delayed by at least 12 months in Australia. The treatment must first apply for funding through the Pharmaceutical Benefits Scheme (PBS)[8] and undergo assessment by the Pharmaceutical Benefits Advisory Committee (PBAC)[9]. If the therapy is accepted as clinically effective but rejected for PBS listing due to cost-effectiveness issues, the sponsor must then develop a new application to meet the submission criteria for the LSDP. [41] The LSDP Expert Panel then assesses the application. This creates a clunky, lengthy, and labour-intensive process.

[3]Cost-effectiveness models assess whether a treatment provides good value by comparing its cost to the health benefits it delivers

[4]The LSDP is an Australian Government initiative that provides subsidised access to high-cost medicines for people with very rare and life-threatening conditions, where no alternative treatments are available and the medicine has not been recommended for listing on the Pharmaceutical Benefits Scheme (PBS) due to cost-effectiveness concerns.

[5]A disease that affects an extremely small percentage of the population, typically less than 1 in 50,000 people

[6]Information gathered outside of controlled trials, such as patient registries and clinician-reported outcomes

[7]Data collected from everyday clinical practice, including treatment effectiveness, patient experiences, and long-term outcomes

[8]The PBS is a program run by the Australian Government that provides subsidised prescription medicines to residents, ensuring affordable access to necessary treatments.

[9]The PBAC is an independent expert body that evaluates the clinical effectiveness and cost-effectiveness of medicines and makes recommendations to the Australian Government on whether they should be publicly funded.

> *We absolutely have HPP patients who could benefit from treatment, but because of the restrictive criteria (for the LSDP), if we can't clearly prove their symptoms began in childhood, they miss out.*
>
> **– Professor Ravi Savarirayan, Clinical Geneticist**

These systemic challenges have been acknowledged in recent government reports. Both *The New Frontier – Delivering Better Health for All Australians (2021)* and *Accelerating Access to the Best Medicines for Australians Now and into the Future (2024)* recommend reforms to improve the HTA process for rare disease therapies, such as using a broader range of data and considering factors beyond cost. [5, 6] What is needed now is the implementation of these recommendations so that Australians with rare diseases can have timely access to life-saving and life-changing treatments.

The New Frontier – Delivering Better Health for All Australians (2021)

A parliamentary report recommending reforms to the healthcare system to ensure faster access to new medicines and technologies, including those for rare diseases. It outlines 31 recommendations, including the establishment of a Centre for Precision Medicine and Rare Diseases. [5]

Accelerating Access to the Best Medicines for Australians Now and into the Future (2024)

A report presenting 50 recommendations to reform Australia's HTA system, aiming for faster access to new medicines. It acknowledges that current HTA processes are not fit-for-purpose for rare diseases and calls for greater flexibility in evidence requirements, including the use of RWE. [6]

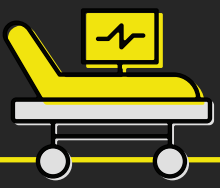
Australia must adopt a more flexible and patient-centred approach to HTA that embraces RWE, acknowledges unmet need, and incorporates lived experience. Without these changes, Australians with HPP will be excluded from treatments that could fundamentally change their lives. Ensuring affordable and equitable access is critical to improving outcomes for people with HPP and addressing broader failings in the rare disease system.

Access to treatment transformed Anita's life[10]

Anita has lived with the effects of HPP for most of her life, but it took decades to receive a diagnosis. As a child growing up in the Netherlands, she experienced some pain and lost her teeth at an early age. Despite seeking answers, no one could explain her symptoms. After moving to Australia, her symptoms remained a mystery. A bone biopsy in the 1980s raised suspicion, but no diagnosis followed.

In 1985, she sustained a severe fracture from a minor injury, leading to further investigations and her first major surgery in 1992. Despite regular visits to specialists, Anita was told no treatment was available. She continued to suffer fractures and increasing physical limitations, with no medical interventions beyond surgery to repair the damage.

Anita has endured **29 surgeries** over the past **30 years.**



Over **80 days** in hospital and **5 years** of recovery time from surgeries.

Approximately **$233,925 cost** to health system for surgeries alone.

Anita's condition deteriorated over the decades. A broken wrist from lifting a cup of tea was one of many fractures. Over time, she became reliant on a rollator, then a hoist, and eventually, in October 2015 she lost the ability to stand, walk, or manage basic daily activities like personal care due to extreme bone fragility and pain. She relied entirely on her husband, Gary, to assist with showering, dressing, and even using the toilet.

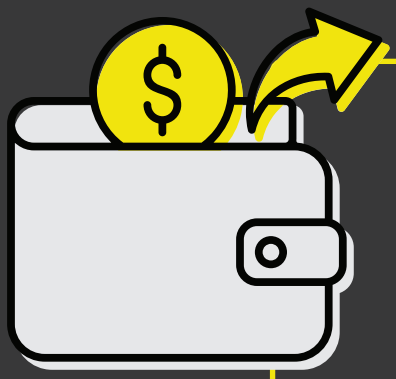
Gary **retired** early at **52 years** old to become Anita's full-time carer.

An estimated **1.3 million** income lost due to retirement before age 65.

Now supported by a **level 4 Aged Care Package.**

Recognising the progressive nature of her condition, her endocrinologist advised Anita and Gary to prepare for a future with increased mobility challenges. Though they initially couldn't afford major home modifications, they eventually moved to a wheelchair-accessible home in 2000 - one of the best decisions they made.

[10]Costs associated with this patient were estimated using a mixed-methods approach reflecting the Australian healthcare context (see Appendix A).



Out of pocket expenses have included:

Purchase and relocation to a home that was wheelchair accessible

A **$40,000** vehicle was purchased specifically to accommodate **$20,000** in wheelchair-accessible modifications

$71,000 was spent to install a home pool for Anita's rehabilitation, reducing the 4-hour daily commitment required to access a public pool with a lift chair

The emotional toll of an invisible condition

The emotional toll was immense. Anita experienced severe physical decline, repeated trauma, and loss of independence. At her lowest point, she feared she wouldn't survive. Gary became her lifeline, helping her shower, dress, eat, and move. Their children also struggled with the emotional strain of watching their mother suffer.

> *"I felt hopeless. There was nothing anyone could do for me, and I just had to keep breaking my bones."*

Gary, too, faced significant challenges. He gave up work in 2006 to become Anita's full-time carer. The responsibility of lifting, showering, and assisting her with all aspects of personal care took a toll on his own well-being. Gary recalls how she needed to be fed because she couldn't even cut her own food, a heartbreaking loss of dignity and autonomy.

Accessing treatment

At 65 years old, after decades of fractures and surgeries, Anita began treatment with an emerging therapy that had the potential to slow bone deterioration. Since starting treatment, Anita's condition has improved, allowing Gary some respite. Before access to treatment, Anita was in constant pain and required hoist transfers for every movement, making even the simplest tasks agonising. Gary can now leave the house for short periods without constant worry, and they can once again enjoy outings together. The ability to regain small but meaningful aspects of normal life has been life-changing.

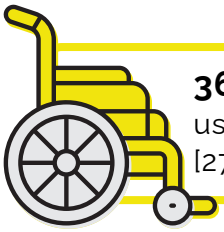
CARRYING THE **BURDEN ALONE**

HPP has a wide-reaching and lifelong impact, affecting not only physical health but also emotional well-being, independence, and financial security. Symptoms typically involve multiple body systems, with progressive disability, frequent fractures, chronic pain, and mobility challenges that worsen over time. [27, 28] These challenges limit participation in school, work, and everyday activities, contributing to a reduced quality of life.

The ongoing physical burden

The physical burden of HPP is significant and lifelong, often beginning in infancy and persisting into adulthood. Infants and children with HPP can experience skeletal deformities, fractures, and respiratory complications that require frequent medical intervention and hospital stays. [27, 28] One study found that 81 per cent of infants diagnosed with HPP were hospitalised within their first 5 years of life. [26] Nearly 50 per cent of children aged six months or older experience early tooth loss, and 33 per cent develop bone deformities. [15] Developmental delays and craniosynostosis can also occur leading to long-lasting neurological complications. [15]

Among paediatric patients living with HPP



36 per cent use wheelchairs. [27]

32 per cent rely on crutches. [27]

27 per cent require canes for mobility support. [27]

Mobility challenges are common, with many children relying on wheelchairs, crutches or canes. These difficulties often persist as children grow older, progressing into chronic pain, muscle weakness, and reduced mobility. [16] Such limitations disrupt daily life and independence, necessitating ongoing support and intervention. Research shows that approximately 75 per cent of adults report ongoing pain, [15] and 86 per cent experience at least one fracture, with an average of nearly 13 fractures per person. [27] Fractures may heal poorly or not at all, contributing to long-term complications and mobility loss. As a result, using assistive devices becomes the norm for many. [27, 28]

Among adults living with HPP

27 per cent rely on crutches. [27]

21 per cent require walkers or canes for mobility support. [27]

A study of 212 patients found the average disability score[11] for people with HPP was double that of the general population, reflecting substantial restrictions in self-care, work, and mobility. [28] Even in milder cases, symptoms such as early tooth loss, osteoporosis, and persistent bone pain interfere with daily life, limiting independence and participation in education and employment. [27, 74]

Annie's story – HPP affects far more than bones

"The flares can be extreme, lasting several weeks at a time, and it's quite frightening because it stops you from doing things that are just normal for everyone else - like just a short walk around the block or managing the grocery shopping."

Chronic pain in her shoulders, neck, biceps, and hamstrings can make even simple activities, like standing, walking, or sleeping difficult. The unpredictability of symptom severity and location makes management challenging, as few interventions provide her with lasting relief.

Annie experiences dental fractures, nail growth issues, and hair thinning. A broken toe two years ago took an extended time to heal, and after seven weeks in a medical boot, she developed Complex Regional Pain Syndrome (CRPS). The nerve pain, swelling, and motor function challenges associated with CRPS have persisted, even as some symptoms have improved.

Navigating emotional and psychosocial challenges

The emotional toll of HPP is significant yet often overlooked. The unpredictability of symptoms, prolonged diagnostic delays, and progressive loss of function contribute to mental health struggles. More than half of people living with HPP report that their condition negatively impacts their psychological well-being. [28] Children frequently experience fatigue (68 per cent), headaches (63 per cent), and depression (40 per cent). [74] Mobility impairments further contribute to social isolation in childhood, while adults often struggle with the long-term emotional impact of managing a rare, poorly understood condition. [28, 74]

[11]Health Assessment Questionnaire Disability Index is a validated tool used to measure a person's level of functional ability and the degree of difficulty they experience in performing everyday activities, with higher scores indicating greater disability.

More than half of patients report their health negatively affects their **physical and mental well-being**. [28]

Children with HPP report experiencing **fatigue (68 per cent)**, **headaches (63 per cent)**, and **depression (40 per cent)**. [74]

The uncertainty surrounding diagnosis adds to this burden. Prolonged diagnostic delays cause stress, frustration, and anxiety, especially when unnecessary procedures fail to provide clarity or relief. This distress is further exacerbated by knowing that effective treatments exist but are not accessible to all who may benefit - a frustration shared by both those with HPP and their clinicians.

> *It's incredibly frustrating when we diagnose a rare disease, know there's a treatment that targets the underlying cause, and yet we can't use it. You can't imagine how disheartening it is to have a solution in front of you but be unable to offer it to your patient.*
>
> **– Professor Peter Ebeling, Endocrinologist**

The impact of HPP extends beyond individuals to caregivers, particularly parents of children with severe forms of the disease. Navigating a fragmented healthcare system with limited clinical awareness is exhausting, and the emotional strain of witnessing a child's suffering can lead to burnout. Parents may also experience guilt associated with passing on a hereditary condition, deepening the emotional toll. [28, 74]

> *HPP is an invisible condition in so many ways, and very few people or doctors understand it. When people have a visual indication that you are injured or in pain, like a cast or a wheelchair, there is more likely a level of understanding or relatability. But when it's chronic pain, spasms, or difficulty doing simple daily activities that can't be controlled, it's not surprising that people can't understand. I can barely understand it myself!*
>
> **– Annie, living with HPP**

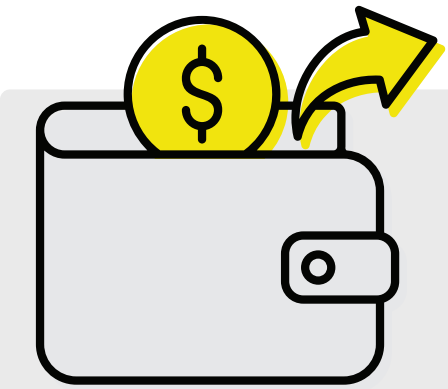
The rarity of HPP adds to feelings of isolation. Without patient advocacy networks or formal support groups, opportunities for peer connection are limited, making it difficult for patients and caregivers to find others who truly understand their experiences.

> *It's cruel in so many ways. You grieve for the person you once were and the life that seemed so much easier when you look back.*
>
> **– Annie, living with HPP**

Financial strain

The financial burden of HPP is significant. Families face ongoing medical expenses, the cost of mobility aids, and home modifications to accommodate accessibility needs (see Anita's story on page 34). Many caregivers also face a loss of income as they reduce their work hours or leave their jobs to meet the demands of caregiving.

The need for multidisciplinary care, which includes visits to endocrinologists, orthopaedic specialists, dentists, and allied health professionals, significantly increases the financial burden on both individuals and the healthcare system (see Tom's case study on page 22 and Anita's story on page 34). While these specialists are critical for managing HPP, out-of-pocket costs can be overwhelming, placing further pressure on families.



Costs of managing HPP for Annie[11]

For Annie the out-of-pocket costs of managing her HPP have been substantial. Since her diagnosis in 2019 her out of pocket health cost is estimated at **$18,324**. These costs have included multiple visits to specialists like endocrinologists and immunologists each year, GP visits, bone density scans, regular physiotherapy and psychological support.

Funded access to care and support is also fraught with challenges. A recent study of Australians with skeletal dysplasia found that individuals with significant mobility and functional impairments faced challenges accessing the National Disability Insurance Scheme (NDIS), largely due to limited assessor understanding and a lack of rare disease-specific guidance. [75] For people with HPP, who often face delays in diagnosis and limited awareness even among clinicians, the burden of proving eligibility for essential financial support can be overwhelming. This lack of recognition increases the personal strain of navigating already fragmented care, reinforcing the need for more structured pathways and informed assessment processes for rare diseases.

[11]Costs associated with this patient were estimated using a mixed-methods approach reflecting the Australian healthcare context (see Appendix A).

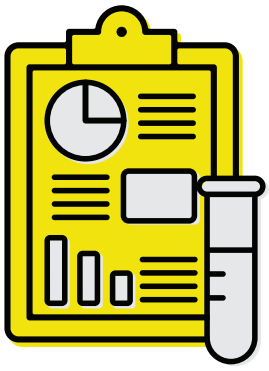
RECOMMENDATIONS

This report demonstrates how HPP exposes critical gaps in Australia's rare disease care, while also presenting a clear blueprint for reform. It illustrates how the challenges faced by Australians living with HPP — delayed diagnosis, limited treatment access, and fragmented care — are echoed across the rare disease community. Australia's healthcare system is not yet equipped to meet the needs of people with rare conditions, but targeted, small-scale reforms could deliver lasting improvements for the more than 2 million Australians affected. [4]

Addressing these issues requires a comprehensive, patient-centred approach: faster and more accurate diagnoses, access to innovative therapies, and integrated multidisciplinary care. These changes must be informed by the lived experience of those affected.

Currently, Australians with HPP lack a dedicated patient advocacy group, limiting their ability to amplify their plight and influence decisions about their care and wellbeing. This absence also reduces opportunities for peer support and participation in research and policy development. Establishing a formal advocacy forum would provide a platform for individuals and families to share their experiences, guide research priorities, and inform care pathways. *The National Strategic Action Plan for Rare Diseases (Priority 3.1)* [7] stresses the importance of empowering patient organisations to drive system improvements. Embedding the patient voice in HPP policy, care, and research is essential. It will be critical to enabling the success of the solutions proposed in this report.

The following recommendations outline practical actions to improve outcomes for people with HPP, grounded in clinical and lived experience, and aligned with key national policies, including the *National Strategic Action Plan for Rare Diseases*, the *New Frontier, and Accelerating Access report recommendations*. [5-7] Together, they provide a roadmap for a more equitable, coordinated, and patient-driven approach to rare disease care in Australia.



RECOMMENDATION 1

Standardise pathology reporting to include alerts when ALP falls below normal range, to enable early recognition and referral of suspected HPP.

HPP is difficult for GPs to recognise due to its highly variable symptoms and overlap with more common conditions. Persistently low ALP is a key biomarker for HPP, [54] yet it is often overlooked in routine pathology reports. Many clinicians are unaware that low ALP could indicate a rare disease, leading to missed diagnoses, repeated medical visits, and years of uncertainty before receiving the correct diagnosis.

To improve early recognition and reduce diagnostic delays, pathology reporting should be standardised to include automatic alerts when ALP falls below the

normal range. These alerts should be integrated into pathology provider reports or triggered through GP practice software, prompting clinicians to investigate further, consider HPP, and refer to specialist care earlier. This system should be developed collaboratively between The Royal Australian College of General Practitioners (RACGP), The Royal College of Pathologists of Australasia (RCPA), pathology providers, and specialist groups, ensuring the alert is accompanied by an explanatory note and publicly available resources for both clinicians and people with HPP (see Recommendation 2).

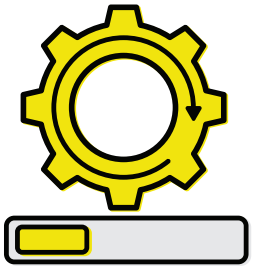
RECOMMENDATION 2

Develop Australian specific clinical guidelines and patient education materials for HPP and make them publicly available on the Rare Awareness Rare Education (RARE) Portal.

Currently, there are no Australian-specific clinical guidelines or patient education resources for HPP. This lack of guidance creates uncertainty for those with the condition and clinicians, leading to missed opportunities for early diagnosis and effective management. People with HPP struggle to navigate their condition and understand treatment options, while clinicians often lack the knowledge necessary to manage HPP effectively.

To address this, Australian-specific clinical guidelines and patient education materials must be developed and made publicly available. The RARE Portal, a key initiative of the *National Strategic Action Plan for Rare Diseases*, provides a trusted platform to host these resources. Making them available through this channel will ensure these resources are easily accessible to individuals with HPP, their families, healthcare professionals, and researchers. [7, 76]

In addition to supporting clinical care, accessible education resources can empower people with HPP to better manage their health, particularly those with milder or asymptomatic forms. Reliable information can improve self-efficacy and guide safe, beneficial health behaviours such as physical activity and diet, ultimately enhancing quality of life and strengthening care pathways.



RECOMMENDATION 3

Progress HTA Review recommendations relevant to accessing therapies for rare and ultra-rare diseases, like HPP.

Current HTA processes do not effectively accommodate rare diseases, as traditional assessment frameworks rely on large-scale clinical trials and cost-effectiveness models that rare disease treatments struggle to meet. This results in significant barriers to accessing affordable life-changing therapies. The HTA Review (i.e. *Accelerating Access to the Best Medicines for Australians Now and into the Future* report) recognised these challenges and proposed 50 key recommendations to improve the system. [6]

To ensure timely and equitable access to therapies for rare and ultra-rare diseases, it is essential to prioritise the implementation of the following recommendations:

- Incorporating RWE and real-world data (RWD) to support treatment access decisions where traditional clinical trial data is limited or unfeasible (recommendations 27 - 31, 35, 37, 39). [6]
- Applying an explicit values framework that considers disease severity, patient burden, and unmet need when evaluating funding decisions (recommendations 26, 42). [6]
- Embedding structured patient and clinician input into HTA processes to ensure decisions reflect lived experiences and real-world impact (recommendations 24, 25, 33). This includes empowering patients, families, and carers to participate meaningfully in the HTA process. While progress has been made through the development of the Enhanced Consumer Engagement Process, it must remain a priority. [6]
- Streamlining and fast-tracking HTA processes for ultra-rare conditions where delays can have life-altering consequences or there is high unmet need (recommendations 8, 14, 20, 44, 45, 46). While the HTA Review acknowledged the need for a more streamlined application pathway, the government should also support expanding the LSDP to include life-changing, not just life-saving, medicines for ultra-rare diseases. [6]

Advancing these reforms is crucial to ensuring that Australians living with rare diseases, such as HPP, are not denied access to innovative and effective therapies due to outdated and inflexible assessment frameworks. By implementing the HTA Review recommendations, Australia can establish a more equitable system that acknowledges and addresses the unique challenges posed by rare diseases.

RECOMMENDATION 4

Fund the development of a national model for rare disease centres of expertise, including access to bone disease specialist care, care coordination and virtual service delivery for HPP patients.

HPP is a complex, multisystem disease that requires coordinated care from multiple specialists. However, Australia currently lacks a structured model for HPP care, leading to fragmented services and limited access to expertise. The *National Strategic Action Plan for Rare Diseases* acknowledges the need for integrated multidisciplinary care and nationally coordinated care networks. [7]

While successful care models for rare diseases exist internationally and within Australia, they need to be assessed for feasibility and adapted to suit the Australian healthcare system.

Example of rare disease care models

Several global and local examples demonstrate the value of multidisciplinary and virtual care approaches for rare diseases:

- **Rare Care Centre in Perth, Australia**: Designed to address challenges faced by families with rare and undiagnosed diseases, this model offers two core services: a statewide cross-sector care coordination service and the Nurse Navigator program. [77]
- **European Reference Networks (ERNs)**: These virtual networks connect healthcare providers and specialists across Europe to manage rare, low-prevalence, and complex diseases. ERNs facilitate collaboration, enabling specialists to share expertise and provide advice on diagnosis and treatment options. [78]
- **Children's National Rare Disease Institute (CNRDI) in the United States**: This institute serves as a "medical home" for families seeking advanced care for children with rare genetic, metabolic, and undiagnosed disorders. It coordinates multidisciplinary care, integrating specialists from diverse fields. [79]

Developing a fit for purpose model for Australia

A national rare disease centre of expertise should integrate specialist care, care coordination, research, and virtual service delivery for HPP and other rare diseases. Organisations such as Rare Voices Australia could lead or play a central role in guiding the development of this model, drawing on deep sector knowledge and established partnerships across the rare disease landscape. Key considerations for developing this model include:

- Feasibility and scalability within the existing healthcare system.
- Access to bone disease expertise.
- A virtual care network to improve access, particularly for rural and regional patients.
- Collaboration between clinicians, patient support services, and advocacy groups to enable specialist knowledge sharing and patient access to expert guidance.
- Multidisciplinary teams, including allied health professionals, to ensure comprehensive, coordinated care.
- Care coordinators to help patients navigate services and identify appropriate specialists and support networks.
- Integrated research to support evidence generation for improving care and emerging therapies/management strategies.
- Educational outreach for medical school curricula content and continuing education for healthcare providers (GPs and specialists) to increase awareness and understanding of rare diseases.
- A sustainable funding strategy to support long-term implementation, which could include seeking funding pathways from established national research funding schemes, such as the National Health and Medical Research Council (NHMRC) Centres of Research Excellence and the Medical Research Future Fund (MRFF).

Considering the challenges of forming a patient-led group, integrating an advocacy forum within the proposed national centre of expertise would enable collaboration between patients, clinicians, and researchers. This would facilitate RWD collection, strengthen the evidence base for treatment access, and create a structured platform for patient education and peer support.

By investing in a purpose-built model, Australia can develop a national framework that improves patient outcomes, reduces healthcare inefficiencies, drives research advancements, and ensures equitable access to specialist care and support for those living with HPP and other rare diseases.

The time for action is now. Reforming care for Australians with HPP offers a practical, politically attractive opportunity to deliver on rare disease reform — while setting a precedent for system-wide improvements. With leadership and patient partnership, we can build a health system that no longer leaves people with rare diseases behind in the shadows.

ABBREVIATIONS

Abbreviation	Description
ALP	Alkaline Phosphatase
ALPL	Alkaline Phosphatase Liver/Bone/Kidney
CNRDI	Children's National Rare Disease Institute
CRPS	Complex Regional Pain Syndrome
ERN	European Reference Networks
ERT	Enzyme Replacement Therapy
GP	General Practitioner
HPP	Hypophosphatasia
HTA	Health Technology Assessment
IPAN	Institute for Physical Activity and Nutrition
LSDP	Life Saving Drugs Program
NDIS	National Disability Insurance Scheme
NHMRC	National Health and Medical Research Council
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PEA	Phosphoethanolamine
PLP	Pyridoxal 5'-Phosphate
PPi	Inorganic Pyrophosphate
RACGP	The Royal Australian College of General Practitioners
RARE Portal	Rare Awareness Rare Education Portal
RCPA	The Royal College of Pathologists of Australasia
RCT	Randomise Controlled Trial
RWD	Real-World Data
RWE	Real-World Evidence
TNSALP	Tissue-Nonspecific Alkaline Phosphatase

APPENDIX A – **METHODOLOGY FOR COST ESTIMATES**

Healthcare costs

Costs associated with each patient were estimated using a mixed-methods approach reflecting the Australian healthcare context. Where hospital admissions or surgical interventions were described, costs were assigned using AR-DRG cost weights from the National Hospital Cost Data Collection (NHCDC) version 11.0 (2020–21), sourced from the Independent Health and Aged Care Pricing Authority (IHACPA). For outpatient services, diagnostics, and consultations, Medicare Benefits Schedule (MBS) item numbers were used to identify rebates, and typical out-of-pocket expenses were determined using the Medicare Cost Finder. This approach ensured that both public funding and patient-borne costs were captured to provide an estimate of each patient's healthcare utilisation and financial burden.

Income loss

Income loss for patient and carers was estimated through time loss multiplied by Australian median wage as reported by Australian Bureau of Statistics, 2023, Earnings and Working Conditions data.

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DISCLAIMER

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Authors: Renae Beardmore, Deanna Mill, and Theresa Doueihi

Report design: Adam Sorgini

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(02) 6198 3440

www.evohealth.com.au

Level 1, 18 National Circuit,
Barton ACT, Australia 2600

evohealth