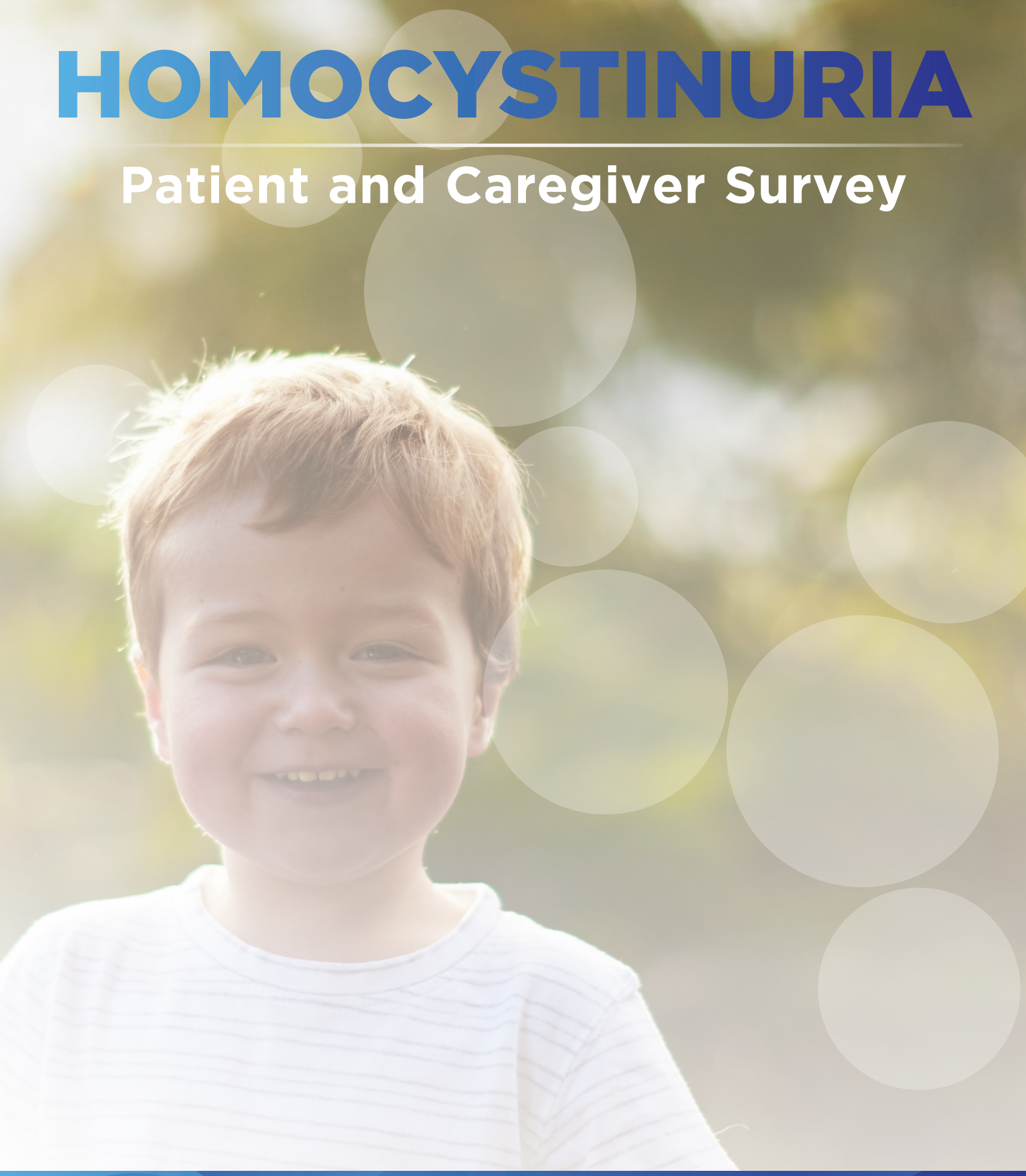
HOMOCYSTINURIA

Patient and Caregiver Survey



Experiences of Diagnosis and Beyond

HCU Network Australia
HCUNetworkAustralia.org.au

EHOD
European Network and Registry for Homocystinurias and Methylation Defects

CONTENTS

IN SEARCH OF A DIAGNOSIS 3

A DIAGNOSIS IS ONLY PART OF THE JOURNEY 4-5

KEY FINDINGS 6-8

LEARNING POINTS 9

A survey driven by individual experiences

This unique online survey – designed and undertaken by HCU Network Australia – provides insight into the lived experiences of people with homocystinuria, both during and beyond the often long and frustrating diagnostic journey.

HCU Network Australia is one of the very few support groups specific for people with homocystinuria. Initially formed to help support Australian families living with cystathionine beta-synthase (CBS) deficiency, it has since gained members from around the world and those with other forms of this rare, inherited, metabolic disorder.

Between May 2018 and April 2019, 143 people living with homocystinuria from 22 countries around the world shared their diagnosis experiences and satisfaction with current medical care and treatments. These valuable insights highlight the problems faced by individuals and families living with homocystinuria and provides learning points for the medical community – so that improvements in diagnosis, care and treatments can be made.

WHAT IS HOMOCYSTINURIA?

The homocystinurias are a group of inherited metabolic disorders where high levels of an amino acid called homocysteine build-up in the body causing a range of health problems.

The genetic faults that lead to homocystinuria are present at birth, but problems do not always develop immediately, and milder forms may present later in life. Symptoms can often be vague and difficult to detect.

There are different forms of homocystinuria with their own specific genetic causes, clinical symptoms and treatment needs. The most common forms are:

CBS Cystathionine beta-synthase (CBS) deficiency also known as classical homocystinuria or HCU.

RMD Remethylation defects (RMD) – the most common being methylenetetrahydrofolate reductase (MTHFR) deficiency and cobalamin metabolism defects (cobalamin C [cblC] deficiency being the most common of these).

In search of a diagnosis

1 UNLESS HOMOCYSTINURIA IS DETECTED DURING NEWBORN SCREENING, THERE WILL OFTEN BE A LONG DELAY WITH MANY PHYSICIANS INVOLVED BEFORE A DIAGNOSIS IS MADE.

Newborn babies can be screened for rare genetic, hormone-related, and metabolic conditions that can cause serious health problems. Newborn screening is well suited to treatable diseases, such a homocystinuria, whose clinical diagnosis is often delayed. Not all forms of homocystinuria are detected during screening tests and not all countries have newborn screening programs.

- Newborn screen was available to only 30% of those surveyed.
- Overall, only **20%** of people with homocystinuria were diagnosed following newborn screening.
- Nearly **ALL** (93%) of those detected following screening only needed to see 1-2 physicians before a diagnosis was confirmed.

For the remainder (those not detected following newborn screening or where screening was not available), diagnosis relies on a combination of symptoms plus biochemical and genetic testing. The majority (80%) of people were diagnosed in this way, with many requiring the involvement of numerous physicians and long delays before a correct diagnosis was finally made.

1 in 3 people needed to see 5 or more physicians before getting the correct diagnosis.

1 in 8 had to wait more than 15 years for a diagnosis.

1 in 10 needed to see a significant number (over 11) of physicians before this happened.

2 DELAYS IN DIAGNOSIS WERE THOUGHT TO BE MAINLY DUE TO IGNORANCE OF THE DISEASE.

People with homocystinuria and carers clearly felt that diagnosis and subsequent treatments are significantly delayed by the limited knowledge many doctors (general practitioners [GPs] and specialists) have about this rare disease. Difficulties accessing testing, getting test results and long waiting times to see medical specialists were also thought to contribute to delays.

- **68%** thought a lack of knowledge about the disease caused the delay in diagnosis.
- **34%** linked delays to problems within the medical system.

3 EVEN WHEN THE DIAGNOSIS IS MADE, THE WAY IT IS COMMUNICATED IS SOMETIMES POOR.

While most people were satisfied with the way they were told about their diagnosis, the survey showed there is still room for physicians (and other healthcare professionals) to improve their communication skills and provide more information and support at the time of diagnosis.

1 in 4 people received their diagnosis either by telephone or letter.

1 in 4 felt they had not been given enough information about the disease.

1 in 4 families were offered support from a psychologist.

Few were informed about support groups, even though most were keen to join them and receive more information about their disease.

- Only **50%** of people had found a support group in their country.
- Almost **ALL** (98%) were interested in being kept informed of current research and clinical trials.

Some were unable to name their disease or provide important information, such as their plasma homocysteine values, used in making critical clinical decisions.

- Written information about CBS deficiency and RMDs is available in most European languages.

Diagnosis is only part of the journey

4 MOST ARE NOW LOOKED AFTER BY A METABOLIC SPECIALIST.

The majority (90%) of people attended a specialist clinic. Most (83%) are seeing a metabolic specialist along with a range of other specialists, including geneticists, GPs, haematologists, pedestrians and neurologists.

2 in 3 people considered their medical care good or excellent.

2% reported they had no medical professional helping them manage their condition.

5 FRUSTRATIONS WITH MEDICAL CARE AND TREATMENTS ARE COMPOUNDED WHEN A DIAGNOSIS IS EVENTUALLY MADE, AND FAMILIES LEARN THE CONDITION IS TREATABLE.

There is no cure for homocystinuria – but it is possible to manage the condition with dietary restrictions, supplements, and medication. If the diagnosis is made in childhood and treatment started early enough health complications may be prevented.

- Families were more satisfied with the diagnostic process, treatment and medical care when homocystinuria was detected following newborn screening.
- Older respondents were generally more satisfied with their treatment and medical care.
- Communication between healthcare professionals/medical clinics and families living with homocystinuria could be improved.

6 PHYSICIANS, OTHER HEALTHCARE PROVIDERS AND COMPANIES PRODUCING MEDICATIONS AND SUPPLEMENTS CAN LEARN MORE ABOUT THE TREAMENT-RELATED PROBLEMS MANY FAMILIES HAVE TO FACE.

About 13% of people living with homocystinuria reported being very dissatisfied with their treatments and 49% considered treatment only partly satisfactory. This may reflect the type of homocystinuria diagnosed or problems around availability/cost of treatments.

- Treatment is easy and effective for vitamin B6-responsive CBS deficiency, but dietary treatment is difficult for other types of CBS deficiency.
- Treatment is not very effective for people with RMDs.
- People with cobalamin defects may dislike their hydroxocobalamin injections.

1 in 3

More than 1 in 3 reported problems with the availability or cost of treatments.

Taking the amino acid mixtures was reported to cause more problems than dietary protein restrictions – the **amino acid mixtures available for CBS deficiency being less palatable than those for other disorders such as phenylketonuria.**

- Only **50%** of people always took their amino acid mixture.
- Taking the amino acid mixture caused more conflict and restricted activities more than dietary protein restrictions.
- Nearly everyone (98%) reported sticking to their dietary protein restrictions – **BUT 80% said it was hard, time-consuming and caused unhappiness.**

7 TREATMENT OF THE HOMOCYSTINURIAS WAS NOT ALWAYS IN LINE WITH CURRENT RECOMMENDATIONS.

Current treatment recommendations include:

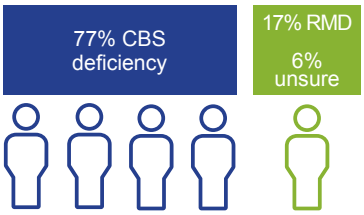
- Protein restriction is not recommended in RMD.
  - 1 person with a RMD was on a low-protein diet.
- Vitamin B12 treatment is not recommended for CBS deficiency unless it is needed to supplement nutritional deficiencies.
  - 10 people with CBS deficiency were on parenteral (non-oral) vitamin B12 treatments and may have been receiving painful injections unnecessarily.
- Dietary management of CBS deficiency can be highly successful with a low-protein diet supplemented with a methionine-free amino acid mixture generally recommended.
  - Some people with CBS deficiency were on a low-protein diet without the amino acid mixture.

Standardised testing of vitamin B6 (pyridoxine) responsiveness in CBS deficiency is currently recommended and can help tailor treatment.

- Oral vitamin B6 (pyridoxine) is only indicated in vitamin B6-responsive forms of CBS deficiency.
  - Approximately two-thirds of the vitamin B6-nonresponsive CBS deficient people also took oral vitamins.
- A low-methionine diet (severe protein restriction and methionine-free amino acid supplements) is recommended for vitamin B6-nonresponsive CBS deficient people.
  - 1 in 4 were on a normal diet.

Key Findings

Who took part in the survey?



- Most people surveyed had or were caring for someone with homocystinuria due to CBS deficiency (classical homocystinuria) – which is the most common form of homocystinuria.
- RMD diagnoses were mostly either due to MTHFR deficiency or cobalamin C (clbC) disease.
- Worryingly, **1 in 17** people surveyed were unsure of their diagnosis.

SUMMARY OF HOMOCYSTINURIA DIAGNOSES	
CBS deficiency	77%
RMD	17%
clbC	7%
MTHFR deficiency	5%
clbE	2%
clbG	2%
clbF	1%
Unsure of diagnosis	6%

1 WHEN ASKED ABOUT THEIR DIAGNOSIS...

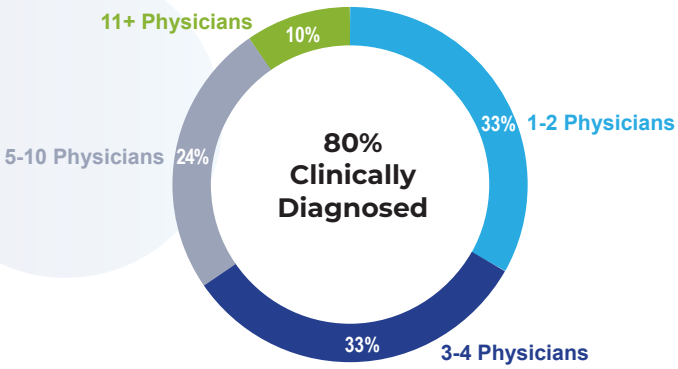
Most reported being diagnosed clinically through a combination of symptoms along with biochemical and genetic testing.

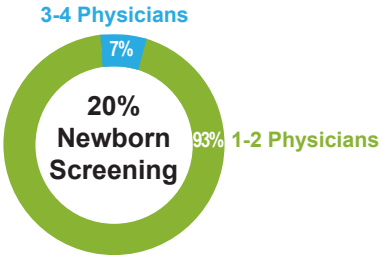
80% CLINICALLY DIAGNOSED
- Half were adults before diagnosis was made.
- 1 in 8 took more than 15 years.
- 1 in 10 saw more than 11 physicians.

20% NEWBORN SCREENING
- Only available to 30% surveyed.
- 93% only needed to see 1-2 physicians.

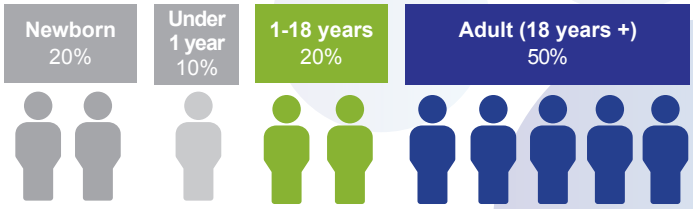
When newborn screening is available, it can dramatically reduce the number of physicians seen and the time taken before a diagnosis is made.

- Newborn screening was available to only 30% of those surveyed AND not all homocystinurias are detected by screening tests.
- The majority of those detected following newborn screening only needed to see 1-2 physicians before a diagnosis was made.





The diagnostic journey can be long for some people – half of those surveyed were adults before a diagnosis was made.



1 in 8
waited **15+ years**
before a diagnosis was made.

1 in 10
saw **11+ physicians**
before getting their diagnosis.

2 WHEN ASKED ABOUT DELAYS IN DIAGNOSIS...

Top reported reasons for delays were:

68% LACK OF KNOWLEDGE
- GPs 25%.
- Medical specialists 30%.
- Families 13%.

34% THE MEDICAL SYSTEM
- Access to testing 18%.
- Test result delays 8%.
- Long waiting times for specialists 8%.

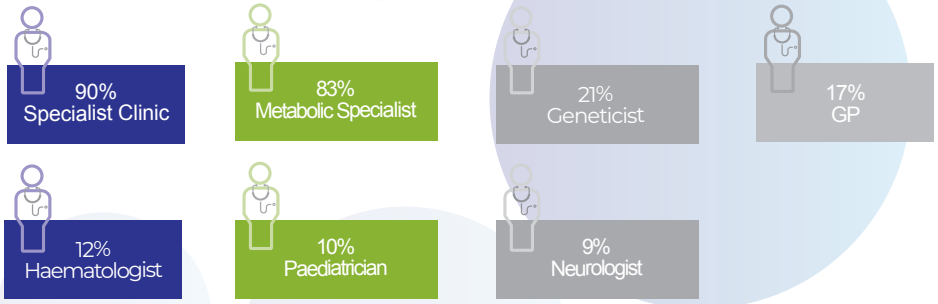
3 WHEN ASKED ABOUT HOW THE DIAGNOSIS WAS COMMUNICATED...

Most were satisfied – but there is room for improvement.

- 24% were given, their diagnosis by phone or letter.
- 24% wanted more information about their disease.
- Only 26% were offered psychological support.
- Only 21% were given information about support groups.

4 WHEN ASKED ABOUT THEIR CURRENT SUPPORT AND MEDICAL CARE...

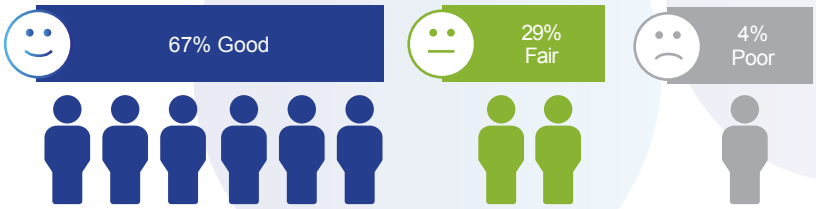
Most were being looked after by a metabolic specialist and attended a specialist clinic.



2% see no healthcare professional.

5 OPINIONS ON MEDICAL CARE AND SUPPORT...

Most thought their care and support was good – particularly if the disease was diagnosed following newborn screening – but communications with medical clinic staff can be a problem.



- 20% had difficulty talking to staff at medical clinics.
- 20% had difficulty getting answers from different clinics.

6 WHEN IT COMES TO TREATMENT...

Reported satisfaction with treatment regimens is likely to be linked to the type of homocystinuria diagnosed and the problems around availability/cost of treatments.

TREATMENT RELATED PROBLEMS

- High cost.
- Availability problems.
- Palatability of protein substitutes.

Learning Points

How can we improve the diagnosis and treatment of homocystinurias?

MAKING A DIAGNOSIS

Measure homocysteine concentrations in:

- Children with neurodevelopmental problems.
- People with heterogeneous symptoms including: thromboembolism, dislocation of the optic lens, haemolytic uraemic syndrome and psychiatric disease.

A simple **blood test** of total homocysteine can help indicate **HCU**.

TREATMENT DOES NOT ALWAYS FOLLOW CURRENT RECOMMENDATIONS

- Protein restriction is not recommended in RMD.
- Parenteral vitamin B12 should not be necessary in CBS deficiency.
- Dietary management of CBS deficiency can be highly successful with a low-protein diet supplemented with a methionine-free amino acid mixture generally recommended.
- Standardised testing of vitamin B6 (pyridoxine) responsiveness in CBS deficiency is currently recommended.
- Oral vitamin B6 (pyridoxine) is only indicated in vitamin B6-responsive CBS deficient people.
- Low-methionine diets are recommended for vitamin B6-nonresponsive CBS deficient people.

COMMUNICATING A DIAGNOSIS

- Improve communication skills between healthcare professionals and people with homocystinuria/caregivers.
- Provide more information at the time of the diagnosis.
- Provide more support at the time of the diagnosis.

Source: Morrison T, et al. Orphanet J Rare Dis. 2021;16(1):124

This is an open access article distributed under the terms of the Creative Commons CC BY license. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

Information provided is for educational purposes only.
Please consult your doctor regarding any symptoms you might be experiencing.

For more information, visit HCUNetworkAustralia.org.au
HCU Network Australia, PO Box 7484 Baulkham Hills, NSW 2153

EXPERIENCES OF DIAGNOSIS AND BEYOND

HCU Network Australia

https://www.hcunetworkaustralia.org.au

info@hcunetworkaustralia.org.au

HCUNetworkAustralia

world HOMOCYSTINURIAS awareness day 18 may

SPONSORS

GOLD

TRAVERE THERAPEUTICS

aeglea

SILVER

CODEXIS®

BRONZE

synlogic