Wilson's Disease
POLICY NETWORK

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Policy brief on Wilson's disease

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About the Wilson's Disease Policy Network

The Wilson's Disease Policy Network has been established with the aim of driving greater awareness, momentum and engagement from policymakers across Europe to address care gaps and policy barriers for people living with Wilson's disease. The Network is led by a multidisciplinary Steering Committee comprising patient representatives, healthcare professionals, academics and industry experts.

The following organisations have endorsed this policy brief:

ASSOCIATION BERNARD PEPIN POUR LA MALADIE DE WILSON

ASOCIACIÓN ESPAÑOLA DE FAMILIARES Y ENFERMOS DE WILSON

centre de référence maladies rares

ELPA European Liver Patients' Association

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Contents

Executive summary 5

01 About Wilson's disease 7

02 What does best-practice care for Wilson's disease look like? 9

03 What are the main barriers to improving care for people living with Wilson's disease? 10

Delays in diagnosis lead to poor health outcomes 10

Access to multidisciplinary care in Europe is unequal 13

Treatment non-adherence contributes to the worsening of health outcomes 17

Gaps in the collection and use of data on Wilson's disease hinder progress 19

Lack of comprehensive rare disease policy at the national and EU levels hampers equitable access 22

Gaps in capacity for Wilson's disease organisations affect their ability to drive advocacy at both the national and European levels 24

04 What can be done? 27

Priority actions 28

References 32

Executive summary

Wilson's disease is a rare genetic condition that can have a devastating impact on the lives of the people affected and their families. The disease affects the body's ability to metabolise copper, resulting in a range of potentially severe liver, neurological and psychiatric symptoms.[1 2] Neurological symptoms, in particular, can prevent a person from being able to work and can affect their ability to carry out everyday activities such as speaking, walking or writing.[3] This can have a significant psychological and financial impact on people living with Wilson's disease, their families and carers.[4-6]

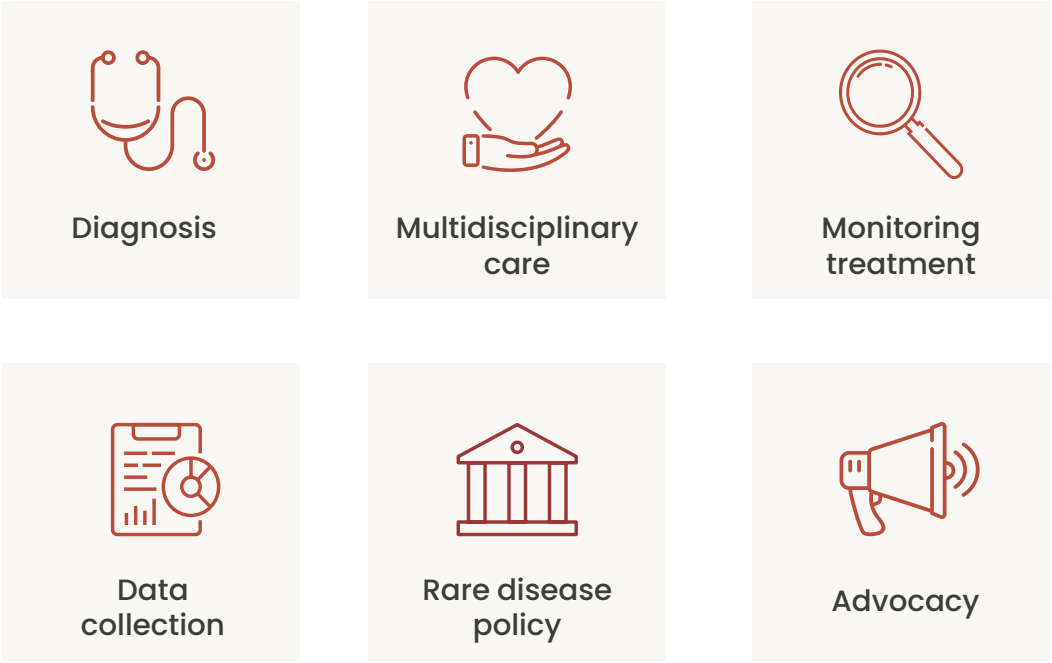
If Wilson's disease is diagnosed early and treated effectively, a person living with the condition can live a long and healthy life. People who receive an early diagnosis, timely initiation of lifelong treatment and long-term regular monitoring can have a similar quality of life and life expectancy to the general population.[7]

In reality, unacceptable gaps in care and systemic barriers prevent many people living with Wilson's disease from accessing the care they need. As Wilson's disease is rare, awareness among healthcare professionals can be low.[8] This contributes to unnecessary delays in diagnosis, with misdiagnosis being a common problem.[9] In addition, health systems often do not recognise, or are unable to coordinate, the full range of care and support services that a person living with Wilson's disease may need to ensure they are treated, monitored and supported in a long-term, holistic way.

As Wilson's disease is rare, awareness among healthcare professionals can be low.

In this report, we outline six priority areas that must be addressed to ensure everyone living with Wilson's disease is able to experience a high quality of life. In identifying the priority areas, we have drawn on the published literature and interviews with leading stakeholders to identify opportunities that policymakers, healthcare professionals and patient organisations could harness to drive change. Organisations need to work together to ensure health systems meet the long-term needs of people living with Wilson's disease.

Priority areas for action



01 About Wilson's disease

Wilson's disease is a rare but serious condition that can leave people with a wide range of severe symptoms. The most common symptoms associated with Wilson's disease affect the liver and brain (Box 1).[1 10] The disease's impact on the liver can range from liver disease with no noticeable symptoms to cirrhosis and acute liver failure.[1] Neurological symptoms can include speech problems, tremors and other movement disorders, including walking impairment and handwriting difficulties.[1 11 12] People living with Wilson's disease can also present with psychiatric symptoms including personality disorders, behavioural disturbances, mood disorders and, in rare cases, psychosis.[10 13]

Box 1. What is Wilson's disease?

Wilson's disease is a rare, inherited disorder – caused by a mutation in the *ATP7B* gene – that can affect a person's ability to metabolise copper.[2 14 15] This can result in an accumulation of copper in the liver and brain, leading to a wide range of clinical presentations – including liver, neurological and psychiatric symptoms, and dark rings in the eye (Kayser-Fleischer rings).[1 2] Wilson's disease can present at any age, but most people are diagnosed between the ages of 5 and 35.[16]

Treatment primarily involves attempts to reduce copper accumulation by using chelating agents to promote the excretion of copper and/or zinc salts to prevent copper absorption.[1] In cases of severe liver disease, liver transplantation can also be a treatment option.[1]

If left untreated, Wilson's disease is usually fatal.[15-17] However, if it is diagnosed early and treated appropriately, a person living with Wilson's disease can have a similar life expectancy to that of the general population.[7]

As a rare disease, Wilson's disease affects a relatively small number of people in Europe, although its genetic nature means that some regions have higher levels among their populations. Current prevalence estimates vary between region and country, but suggest that between 1 in 66,000 and 1 in 30,000 people in Europe have Wilson's disease.[18-20] It is important to note, however, that studies have found prevalence of the genetic mutations associated with Wilson's disease to be up to three or four times higher than this.[18] This suggests the disease may be underdiagnosed[21] and/or that some people with the *ATP7B* mutation do not actually develop Wilson's disease symptoms.[22] Although most countries have similar levels of Wilson's disease among the whole population, there can be regional variation, with some pockets of higher prevalence in communities such as in Sardinia in Italy and the Canary Islands in Spain.[14 23]

Wilson's disease can lead to adverse economic outcomes, particularly for people who experience neurological and psychiatric symptoms. A study conducted in Poland found that people living with Wilson's disease who presented with neurological symptoms were less likely to progress through education and less able to work than the general population.[5] Some people have symptoms that prevent them from being able to work full time and may require social or disability government support.[5] In some countries, government disability support is significantly below the legal minimum salary requirements, making people who live with Wilson's disease financially dependent on their families.[6] Furthermore, owing to the variable coverage of reimbursement for Wilson's disease diagnosis and treatment across Europe, people may have to pay out-of-pocket costs, resulting in an additional economic burden.[9,24] Some people may also require specialist support services to prevent their symptoms from worsening, such as physiotherapy or speech therapy. Where these are not covered by health insurance, the personal financial costs are even greater.[6]

> **"Physiotherapy and speech therapy are really important for preventing some neurological symptoms from getting worse, but these can be unaffordable for many families."**
>
> David Martín Miguel, Asociación Española de Familiares y Enfermos de Wilson

The neurological symptoms of Wilson's disease can prevent people from carrying out everyday activities, leading to dependence on family members and psychological distress. Untreated neurological symptoms of Wilson's disease can make it difficult to perform everyday activities, such as speaking, eating, drinking, washing and driving.[3] This results in some people requiring extensive assistance from carers or family members. This can have an enormous impact on the quality of life of families and carers. In addition, the dependence on others caused by living with a debilitating illness, combined with experiencing the disease itself, can lead to significant psychological distress and loss of self-worth for the person with Wilson's disease.[4]

> **"Wilson's disease is not just a physical disease – it can cause a great deal of emotional turmoil, with people feeling distress, loneliness and guilt.**
>
> Caroline Roatta, Association Bernard Pépin pour la Maladie de Wilson

02 What does best-practice care for Wilson's disease look like?

The impact of Wilson's disease on people's lives can be reduced if people living with the condition have access to best-practice care at every stage. Figure 1 outlines the steps in the Wilson's disease patient pathway and an overview of what should be expected at each step from a 'gold standard' approach to care.

Figure 1. Best-practice care at each step of the Wilson's disease pathway

Referral

- Person presents with liver, neurological and/or psychiatric symptoms to a clinician in primary care, or via other routes such as a hepatologist, neurologist, psychiatrist or nutritionist.
- Clinician has a good awareness of rare conditions and suspects presentation to be Wilson's disease.
- Person with suspected Wilson's disease referred to a specialist for diagnosis.

Diagnosis

- Diagnosis involves a combination of clinical, biomarker, genetic and radiological assessments.
- Each result contributes to the person's Leipzig score, which establishes likelihood of Wilson's disease as the diagnosis.
- Family screening carried out alongside referred cases in children and pre-symptomatic people related to the person living with Wilson's disease.
- In areas with known high prevalence of Wilson's disease, detection can be through population screening.

Ongoing care

- Selection of the appropriate pharmacological or surgical treatment (possible liver transplantation in severe cases) on a case-by-case basis, taking symptom combination and the person's needs and preferences into account.
- Management of Wilson's disease by a multidisciplinary team that provides clinical and social care, and considers the complexity and wide range of possible symptoms and their impact on the person's life.
- Monitoring carried out regularly to evaluate treatment efficacy, safety and adherence, with care plans adjusted as needed.
- More frequent monitoring conducted for groups at particular risk of non-adherence, such as young people and people without symptoms.
- For some people with severe and chronic symptoms, additional regular treatment (such as physiotherapy or speech therapy) may be required.

03 What are the main barriers to improving care for people living with Wilson's disease?

Many people living with Wilson's disease do not have access to best-practice care and face barriers and unmet needs at each stage of the care pathway.

Delays in diagnosis lead to poor health outcomes

What is the challenge?

Delays in diagnosis and misdiagnosis of Wilson's disease are common and can have a devastating impact on the lives of people living with the condition. A 2012 survey across six European countries found that half of people diagnosed with Wilson's disease waited more than six months for a diagnosis, and a fifth waited between one year and three years.[9] Just under half of people who eventually received a diagnosis of Wilson's disease reported being initially misdiagnosed.[9] Delays are considerably longer for people who first present with neurological and psychiatric symptoms.[10] These delays can lead to the worsening of symptoms[25] and ultimately a permanently lower quality of life.[7]

Limited awareness of Wilson's disease among primary care clinicians and the complexity of its symptoms are key drivers of delays and misdiagnoses. The low prevalence of Wilson's disease means many healthcare professionals are unlikely to suspect it when people present with symptoms.[8] In addition, several symptoms of Wilson's disease are similar to those of other, more common disorders, such as other liver diseases or Parkinson's disease.[9 13] This is further complicated by the presence of psychiatric symptoms.

Diagnosing Wilson's disease is complicated by the lack of a 'gold standard' test. There is no single test that can establish a diagnosis for Wilson's disease.[26] Diagnosis involves a healthcare professional considering a number of clinical assessments combined with biomarker testing.[1 7 27] Differences in access to certain tests, and in levels of clinical awareness, mean that the path to diagnosis can be highly variable.[26] It can also involve both false negatives and false positives of Wilson's disease.[28] Genetic testing can be used to confirm suspected Wilson's disease and limit the number of misdiagnoses, but is not widely available.[16 28]

Why should it be addressed?

Although diagnosis can be distressing, the earlier it happens the sooner the person can begin their treatment, preventing progression of the disease and improving health outcomes. For people living with Wilson's disease, health outcomes are considered to be best when treatment is initiated within the first month of symptoms occurring.[25] Screening the family members of people already diagnosed with Wilson's disease is the most effective way of diagnosing asymptomatic people and initiating treatment as early as possible.[16]

> **"A Wilson's disease diagnosis can be very disruptive, not just for the person who receives the diagnosis but also for their family, who must find out how to live and rebuild their lives."**
>
> Caroline Roatta, Association Bernard Pépin pour la Maladie de Wilson

Reducing delays in diagnosis and treatment can have an economic impact. Wilson's disease can progress to acute liver failure, which may require liver transplantation.[29-31] A study in Germany which examined hospitalisations for Wilson's disease in 2017 found that, although fewer than 10% of inpatients received a liver transplant, this accounted for almost 50% of the total annual inpatient costs associated with the disease.[32] Earlier diagnosis would reduce the chance of the disease progressing to this stage. It may also lessen the need to rely on additional long-term therapy, such as physiotherapy and speech therapy, for people whose neurological symptoms have worsened while undiagnosed.[6] For people who are of working age, reducing delays in diagnosis means a lower chance of developing severe neurological symptoms that could make them both financially dependent and unable to contribute to the economy.

What opportunities are there to address this challenge?

Increasing clinical awareness may be the key to improving the speed of appropriate referral and, ultimately, of accurate diagnosis. Raising the profile of Wilson's disease within clinical undergraduate programmes and ongoing continuing professional development schemes could build a broader knowledge base within the healthcare professional community. Specific attention should be given to the healthcare professionals with whom people living with Wilson's disease symptoms are most likely to engage, such as primary care clinicians, hepatologists, neurologists, psychiatrists and psychologists. This may also include ophthalmologists (as the presence of Kayser-Fleischer rings in the eye – dark rings around the iris – can be an indication of Wilson's disease)[16] and gynaecologists, as disturbed ovarian function and changes in the menstrual cycle can be a presentation of Wilson's disease.[33]

Increasing the availability of biomarker testing, particularly genetic testing, may improve the speed of diagnosis. Genetic testing can play an important role in the diagnosis of Wilson's disease, but availability remains variable across different countries owing to differences in capacity and funding.[16 28] Cross-border genetic testing may be a route to mitigating these challenges. In 2015, the European Commission recommended that 'access to genetic testing – whether provided locally or on a cross-border basis – should be ensured' in Member States to obtain an accurate and timely diagnosis of people with a genetic rare disease, and that this be built into national rare disease plans.[34]

New diagnostic tools may contribute to earlier diagnosis and lower rates of misdiagnosis. There are funding opportunities at the European Union (EU) level to support this. The European Joint Programme on Rare Diseases (EJP RD) and its successor, the European Partnership on Rare Diseases, aim to provide funding for rare disease innovation, with the latter specifically identifying rare disease diagnostics as a priority.[35] This may provide an avenue for researchers to develop a gold standard Wilson's disease biomarker test and simplify the diagnostic process.

Newborn screening may also play a role in future diagnosis, but more research is needed. Newborn screening is not currently available for Wilson's disease, but a recent study demonstrated that the *ATP7B* peptide (variations of which cause Wilson's disease) could be measured to a high degree of accuracy using a dried blood spot.[36] This opens the door for the possibility of newborn screening for Wilson's disease in the future, but more research is needed before it can be incorporated into national newborn screening programmes.[37]

Access to multidisciplinary care in Europe is unequal

What is the challenge?

People living with Wilson's disease – as with any rare disease with complex symptoms – must have access to a wide range of healthcare professionals, but that is often lacking. The complexity and mix of symptoms make it necessary for many people living with Wilson's disease to be cared for by a number of different healthcare professionals. This is most efficiently achieved when delivered as part of a coordinated multidisciplinary team (MDT).[10 38-41] While best-practice, high-quality multidisciplinary care is available through various centres of expertise across Europe,[42] these are not established in all countries[43] and access to multidisciplinary care for Wilson's disease can vary between countries and centres.

Current European clinical practice guidelines for the management of Wilson's disease tend not to cover all aspects of the condition, which may be contributing to gaps in the availability of multidisciplinary care. Current Wilson's disease guidelines published by the European Association for the Study of the Liver (EASL)[16] and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[30] are comprehensive regarding the management of liver conditions, but limited on the care of neurological and psychiatric symptoms.[44] The need for a multidisciplinary approach is outlined in UK national guidelines for Wilson's disease published by the British Association for the Study of the Liver's Rare Diseases Special Interest Group in April 2022[45] – this could set a precedent for future Wilson's disease guidelines.

The complexity and mix of symptoms make it necessary for many people living with Wilson's disease to be cared for by a number of different healthcare professionals.

The psychiatric and psychological needs of people living with Wilson's disease are especially neglected. Anecdotal evidence suggests that, across Europe, access to psychiatric care is severely limited for people living with Wilson's disease. In addition, there are no European guidelines for the management of psychiatric symptoms, despite the fact that most people living with the condition experience these symptoms throughout the course of their illness.[10] Some people, as well as their families, may require psychological support as part of their disease management – this is also absent from current guidelines.[46] It should be noted that people who present with psychiatric symptoms have a very different care pathway from those who initially present with liver or neurological symptoms and develop psychiatric symptoms later. The lack of guidelines on both recognition and management of psychiatric symptoms, therefore, has a variable and wide-ranging impact on people living with the disease.

> **"Having contact with psychologists, social workers and patient associations can be really helpful for dealing with distress caused by living with Wilson's disease."**
>
> Caroline Roatta, Association Bernard Pépin pour la Maladie de Wilson

People living with Wilson's disease may also require neurological rehabilitation, but this is often not available. For people with neurological symptoms, rehabilitation services such as physiotherapy and speech therapy are an important part of care. However, access to this support is often lacking.[47] This may be a consequence of neurological rehabilitation not being included in current guidelines.

Why should it be addressed?

Improving access to multidisciplinary care could improve health outcomes for people living with Wilson's disease across Europe. Optimal care of Wilson's disease involves a multidisciplinary approach that supports access to a broad range of specialists, including hepatologists, neurologists, psychiatrists, nutritionists, psychologists, speech therapists and physiotherapists. Such care has the potential to lead to good life expectancy,[48] similar to that of the general population.[7]

A multidisciplinary approach can also help to alleviate the need for people to visit multiple different specialist centres, contributing to better continuity of care. Providing access to multiple specialists in one place can ease the travel burden for people living with Wilson's disease and increase the likelihood of regular attendance at follow-up appointments.[49 50] This is critical to monitoring treatment adherence or changes in symptoms.

What opportunities are there to address this challenge?

EASL is currently updating its Wilson's disease guidelines, which presents an opportunity to incorporate the holistic management of neurological and psychiatric aspects of care and achieve truly multidisciplinary guidelines. The updated guidelines should emphasise the importance of multidisciplinary care and outline the holistic management of a wide array of symptoms characteristic of the condition. They should include clear guidance on aspects of Wilson's disease care that are underrepresented in current guidelines, particularly psychiatric and neurological manifestations, and the services needed to support the management of these symptoms, such as speech therapy, physiotherapy and psychological therapies. The European Reference Network on Hepatological Diseases (ERN RARE-LIVER) working group on Wilson's disease (Box 2) is involved in updating the EASL guidelines.[28 51] ERN RARE-LIVER and other ERNs advocate for the delivery of multidisciplinary care and should therefore support its inclusion in guidelines.

Box 2. European Reference Networks

European Reference Networks (ERNs) were launched in 2017 by the European Commission with the aim of increasing access to highly specialised care for complex conditions.[52] They involve bringing together a network of centres of expertise which seek to promote multidisciplinary working in rare disease care.[53] There are three ERNs of relevance to Wilson's disease: rare liver diseases (ERN RARE-LIVER), rare neurological diseases (ERN-RND) and hereditary metabolic disorders (MetabERN). At present, it appears that the majority of ERN Wilson's disease activity is conducted by ERN RARE-LIVER, which has established a dedicated working group.[54] The ERNs are expected to work together across diseases.[52] A number of ERN-affiliated centres of expertise are currently providing specialised Wilson's disease services, but these are not available in every country, meaning that many people living with Wilson's disease do not benefit.[42 43]

The European Rare Disease Research Coordination and Support Action consortium (ERICA) seeks to promote cross-ERN collaboration and may present another opportunity to improve access to multidisciplinary care for Wilson's disease. ERICA was established with the aim of facilitating inter- and intra-ERN disease networks.[55] While some efforts are being made to increase collaboration between relevant ERNs, intensifying this may provide a platform for improving access to multidisciplinary care for people living with Wilson's disease across Europe by pooling and facilitating access to expertise from a range of clinical areas.

Greater awareness from and involvement of psychiatrists, psychologists, physiotherapists and speech therapists is needed to ensure the psychiatric and neurological needs of people living with Wilson's disease are addressed. It can be challenging to identify and involve these specialists in the management of people living with Wilson's disease,[56] contributing to gaps in care. Increasing awareness among a wider range of specialists and communicating the importance of their expertise in the management of Wilson's disease has the potential to increase their involvement and help address these gaps.

Treatment non-adherence contributes to the worsening of health outcomes

What is the challenge?

Despite the risks associated with discontinuing Wilson's disease treatment, rates of adherence to treatment remain worryingly low. Wilson's disease requires lifelong treatment to avoid serious complications and premature death, but 20–45% of people do not follow their treatment regimen for an extended period of time.[1 5 57 58] One of the reasons for non-adherence is a range of severe side effects associated with some of the current treatment options for some people. These can actually include the worsening of neurological symptoms in 10–50% of people.[16 59] Treatment side effects have been reported to lead to approximately 30% of people living with Wilson's disease discontinuing their treatment.[16] Other reasons include inconvenient dosing regimen, cost and people forgetting to take their medication.[59-61]

Certain populations are at increased risk of discontinuing their treatment or not taking it as directed by a healthcare professional. People with psychiatric presentations and asymptomatic people have been identified as being at particular risk, in addition to people going through major life changes such as adolescence, pregnancy, menopause/andropause and ageing.[5 7 10]

> **"There are key moments in life when someone with Wilson's disease deserves extra attention. People who are transitioning through adolescence, making decisions about contraception or having children, [or experiencing] menopause/ andropause and ageing need tailored resources to help them to understand how to navigate these life stages with the disease and avoid the risks of non-adherence to medication and depression, which can be higher."**
>
> Caroline Roatta, Association Bernard Pépin pour la Maladie de Wilson

Why should it be addressed?

Efforts to increase levels of treatment adherence have the potential to significantly improve health outcomes. People living with Wilson's disease who do not continue to take their medication are at greater risk of disease progression and, ultimately, death.[60] Disease progression leading to the worsening of neurological symptoms can also limit people's ability to work and carry out everyday activities.[3] Measures taken to improve adherence to treatment can have a positive impact on people's health outcomes and quality of life.[62]

What opportunities are there to address this challenge?

Greater recognition of enhanced monitoring for at-risk populations in clinical guidelines may improve the low levels of treatment adherence. There is agreement among clinicians involved in Wilson's disease that some groups of people are more likely to stop taking their medication than others, but no clear recommendations for the closer monitoring of treatment adherence are laid out in current guidelines.[5 7 10] The expected update to the EASL guidelines[28 51] should formally outline which populations are at greater risk of treatment non-adherence and specify recommendations for more intensive monitoring to mitigate potential issues. Specific attention should be paid to young people transitioning from child to adult services, as the risks associated with transition are not addressed in current paediatric or adult guidelines.[16 30]

Patient organisations can provide visibility of the risks of non-adherence to people living with Wilson's disease. Patient organisations can offer an opportunity for people living with Wilson's disease with varying symptoms to share their experiences with one another.[6] For example, people at an early stage of their disease may not be aware of the severity of the neurological symptoms experienced by others. By providing a forum for people living with Wilson's disease to meet, patient organisations allow people to see the extent to which symptoms can deteriorate as a result of treatment non-adherence.[6]

Gaps in the collection and use of data on Wilson's disease hinder progress

What is the challenge?

There are important gaps in the available data on Wilson's disease. There is limited research into the impact of Wilson's disease on the lives of the people affected and their families, as well as a lack of comprehensive clinical monitoring and outcomes data. A multi-country patient survey was conducted as part of the EuroWilson initiative, which has now ended; while these data were comprehensive, they are now ten years old.[9]

Wilson's disease registries can provide valuable sources of data, but they have only been established in a few European countries and vary in methodology and criteria. Registries are a key component of the data collection ecosystem, gathering information on aspects such as prevalence, disease stage, diagnosis, treatment and socioeconomic features, and how these may change over time or differ by region.[63 64] Having an understanding of these factors can improve rates of diagnosis and timely access to treatment. However, national Wilson's disease registries have only been established in a limited number of countries in Europe and there are no comprehensive international registries currently active.[24] Experts have also raised concerns around the inconsistency of methodology and criteria to guide data collection practices in Wilson's disease registries.

Why should it be addressed?

Comprehensive data would allow the Wilson's disease community to identify and advocate for the changes needed to improve health outcomes and quality of life for people living with Wilson's disease. A full understanding of Wilson's disease prevalence and service provision allows for more accurate identification of gaps in care, the development of evidence-based guidelines and, ultimately, improvements in health outcomes. Registries are acknowledged by the EU and clinical community as key instruments for health service planning and improving outcomes for people with rare diseases.[63 65] In the case of Wilson's disease, a lack of data across the care continuum has made the development of guideline recommendations difficult, with many based on expert opinion rather than rigorous randomised clinical trials.[14]

For diseases with low prevalence, such as Wilson's disease, data pooling and cross-national data sharing are crucial to allow high-quality clinical research to be conducted. Owing to the limited number of people affected by rare diseases, research is reliant on multinational registries to generate sufficient data to produce significant findings for clinical trials.[66]

Evidence on the impact of Wilson's disease on people's lives can help organisations to raise awareness of the disease and advocate for improvements. By having a greater understanding of how Wilson's disease affects each person, patient organisations would be able to better monitor the situation in Europe and advocate for the needs of the people they represent. For example, understanding the specific impact of the disease on people's ability to participate in education and employment may support advocacy efforts to improve access to benefits, such as social security and carer support. While some research has been done in this area, it has been relatively small in scale, so larger studies and surveys are needed.[67]

What opportunities are there to address this challenge?

Wilson's disease patient organisations are in an excellent position to collect comprehensive information on the lived experience of the people they represent. National organisations may be able to work together to collect consistent data through a shared patient survey covering multiple countries. Umbrella organisations such as EURORDIS-Rare Diseases Europe (EURORDIS) and the European Liver Patients' Association (ELPA) may be able to provide guidance on how this survey could be funded, developed and rolled out.

The development of quality standards for national Wilson's disease registries may reduce the variability of data collection across Europe. ERNs are involved in the development of registries for rare diseases.[68] ERN RARE-LIVER coordinates the R-Liver registry, which includes a number of rare liver diseases and could be expanded to include Wilson's disease.[69] ERNs may also play a central role in developing national standards for data collection. These standards could improve the interoperability of national registries and allow for data sets to be combined to generate a more robust picture of Wilson's disease. In addition to this, work being carried out by Orphanet to revise its classifications of rare diseases may also increase levels of interoperability between registries through improved codification of rare diseases.[70]

Positive steps have been taken but a more long-term and sustainable approach to registry coordination and funding is needed. To maintain a registry as an active resource for data collection and analysis, long-term funding is required. Unfortunately, current funding mechanisms mean that while intensive short-term funding may lead to the creation of a registry, the lack of a sustainable funding source often results in the registry coming to an end.[70] Despite variable levels of funding for registry creation, there have been significant efforts in recent years to establish national registries – for example in France, Poland and Spain – which should be recognised as contributing to improvements in the collection of Wilson's disease data.[71-74] A multinational registry is also being established by Yale University in the US and will include Germany and the UK.[75] More work is needed, however, to improve registry funding, coverage and standards across Europe.

Lack of comprehensive rare disease policy at the national and EU levels hampers equitable access

What is the challenge?

Almost all EU countries have a national rare disease plan, but many of these require updating. Following a centralised push by the European Commission in 2009, EU countries were asked to adopt a national plan for rare diseases.[76 77] As of April 2022, two Member States were still without a national rare disease plan and seven had plans that had expired. In addition, a number of national plans are 'open-ended' and are not time-bound to the commitments or priorities within them, making it difficult to evaluate whether they have been successful.[76] The majority also have no dedicated funding, putting the plans at risk of not being adequately resourced.[76]

The lack of a European collective policy framework for rare diseases to address gaps in care remains an unmet need. While there has been important progress in the rare disease space at the EU level, including, critically, the implementation of the ERNs, gaps remain from a policy perspective. There is no longer an expert group or Joint Action on rare diseases at the EU level. While there are some EU-level initiatives which support constructive multi-stakeholder dialogue and facilitate debate between Member States, including the ERNs and the EJP RD, commentators have noted a 'relative vacuum' when it comes to a truly comprehensive rare disease policy-focused initiative.[78]

Why should it be addressed?

A comprehensive national rare disease plan provides a framework to support stakeholders in driving the changes needed for more equitable access to care. Countries that have a national plan for rare diseases are more likely to have policies that cover the whole pathway, from diagnosis to treatment and long-term management.[79] This means that there are fewer gaps in the overall rare disease strategy,[79] which may contribute to more equitable access to services. National plans have also contributed to growth in the number of rare disease registries in Europe.[80]

A European-level rare disease strategy is an important tool for addressing the significant challenges faced by people with rare diseases, such as Wilson's disease. People in Europe living with rare diseases, including Wilson's disease, continue to face long diagnostic delays and limited or unequal access to high-quality care and treatment.[81 82] An overarching European policy framework could act as a vital tool to coordinate and guide national rare disease plans that could address gaps in service provision and improve health outcomes.

What opportunities are there to address this challenge?

National-level advocacy aimed at policymakers is central to driving the implementation or renewal of national rare disease plans. Communicating the needs of people with rare diseases, including Wilson's disease, to policymakers through persuasive, evidence-based campaigns can help to position the development or renewal of national rare disease plans as a healthcare priority in European countries. National rare disease umbrella organisations or disease-specific patient advocacy groups are well placed to work together to carry out these activities, but may require support in terms of capacity or the development of messaging materials to bolster engagement efforts.

Momentum is growing at the EU level to strengthen rare disease policy. The European Commission has committed to revising its rare disease strategy by 2023,[83] and the European Parliament has called for an EU action plan for rare diseases.[84] The current and upcoming presidencies of the Council of the European Union have recognised the importance of prioritising rare diseases.[82 85]

Leading rare disease advocacy organisations are also calling for substantial strengthening of EU policy. The Rare 2030 foresight study, led by EURORDIS, called for the creation of a European collective strategy for rare diseases.[82] The study's main recommendation is the establishment of a European policy framework for rare diseases to guide national strategies, secure government investment, and improve access to early diagnosis and timely treatment.[82] The Network of Parliamentary Advocates for Rare Diseases, a group of European and national members of parliament which advocates to improve the lives of people living with a rare disease, has pledged to put a new European policy framework for rare diseases in place.[83] This is a promising commitment, and it will be important for the Wilson's disease community and its allies to continue their work to ensure the framework is successfully delivered.

A European-level rare disease strategy is an important tool for addressing the significant challenges faced by people with rare diseases, such as Wilson's disease.

Gaps in capacity for Wilson's disease organisations affect their ability to drive advocacy at both the national and European levels

What is the challenge?

The ability of Wilson's disease patient groups to take part in meaningful policy engagement and advocacy is often challenged by a lack of capacity and resources. Where they exist, national Wilson's disease patient organisations provide invaluable information and support for individuals and their families. However, they are often small organisations that are run predominantly by volunteers.[86 87] This naturally restricts their time and capacity to carry out broader activities, including policy engagement.

There is no dedicated Wilson's-disease-specific organisation spearheading advocacy efforts at the EU level, and many countries lack a national disease-specific association. There is, however, excellent work being carried out by some international umbrella organisations such as ELPA and the Global Liver Institute (GLI) to raise awareness of Wilson's disease, support national patient organisations and deliver impactful advocacy activities. Some Wilson's disease organisations are also members of EURORDIS.[88] Many countries do not have national-level Wilson's disease patient organisations, which may limit the strength of Wilson's-disease-specific advocacy at the national level.

Why should it be addressed?

Active and consistent advocacy is vital to ensure the challenges experienced by people living with Wilson's disease are well represented in policy debates at both the national and European levels. Although a European-level policy on Wilson's disease may not be feasible, it is important that the needs of people living with the condition are represented among wider rare disease policies.

A strong advocacy base can give a voice to people living with Wilson's disease to communicate their needs. An active patient community can support and empower people to make decisions about their own care. This strong support network can give people living with Wilson's disease the confidence and channels to raise concerns over access to the best-practice care that they need.

What opportunities are there to address this challenge?

There is significant drive at the European level to seek improvements for people with rare diseases, and many Wilson's disease patient organisations would benefit from deepening their collaboration to take advantage of this. There is increasing recognition among leading EU stakeholders that more must be done to support people with rare diseases. Now is the time to engage with European policymakers and ensure Wilson's disease is well represented in future rare disease initiatives. By working together, advocates would be able to pool resources and present a shared voice and vision for Wilson's disease in Europe.

There are opportunities for Wilson's disease patient organisations to engage directly with ERNs through European patient advocacy groups (ePAGs) and ERN RARE-LIVER's Wilson's disease working group; ePAGs have been set up for each ERN to help ensure that people living with rare diseases are able to contribute to the work of ERNs. Each ePAG is made up of elected patient advocates who have a permanent mandate to represent member organisations by participating in their respective ERN's board and subclinical committees. As it stands, only one Wilson's disease patient organisation is listed as an ePAG in an ERN (for rare liver diseases).[89] There is significant potential for more Wilson's disease voices to be heard within the governance structures of ERNs. More Wilson's disease patient organisations may also benefit from connecting with the ERN RARE-LIVER Wilson's disease working group, which is co-led by the German Wilson's disease patient organisation Morbus Wilson.[54]

There are EU funding opportunities to support stakeholders seeking to bring together members of the rare disease community and strengthen collaboration. The Networking Support Scheme of the EJP RD offers funding for rare disease stakeholders to encourage sharing of knowledge on rare diseases or rare cancers in new or expanding research networks through networking events.[90] Patient advocacy organisations are among the groups of stakeholders that can apply for up to €30,000 in funding per event.[91] A Wilson's disease networking event would provide an opportunity to take steps toward uniting the advocacy community for the condition and providing a foundation for future collaboration.

New guidance has the potential to make patient organisations more influential in EU research projects. The EJP RD has developed a 'guide on patient partnerships in rare diseases research projects' aimed at people with rare diseases, researchers, policymakers and funders to communicate the importance of having patient organisation participation at the heart of research projects, and to support applicants to describe the role and added value of patient partnerships in research proposals.[90 92] This is an opportunity to amplify the voices of people living with Wilson's disease through future rare disease research.

Building national, cross-stakeholder Wilson's disease coalitions may provide an opportunity to collaborate with a wider network of relevant partners. National coalitions may focus on one disease or a broader disease area and can involve a range of stakeholders, from policymakers to clinicians and people living with the disease(s). ELPA is currently rolling out national coalitions for liver health that bring together non-governmental organisations, people living with liver disease, clinical experts and media partners to identify the main challenges faced by people with liver diseases in each country.[93] Implementing a similar model for Wilson's disease, or building Wilson's disease into these existing coalitions, could provide a platform for broad collaboration across the health sector and an opportunity to develop tailor-made solutions to national Wilson's disease issues.

More Wilson's disease patient advocacy organisations may also benefit from connecting with European-level umbrella organisations that can provide training, knowledge sharing and advocacy support. Umbrella organisations such as EURORDIS, ELPA, GLI, Liver Patients International and the European Federation of Neurological Associations provide an opportunity to enhance capacity and expertise through knowledge sharing, networking opportunities and training programmes.[93-95] This may help to mitigate capacity challenges faced by Wilson's disease patient advocacy organisations. It may also offer an opportunity to feed into wider rare disease advocacy efforts carried out by umbrella organisations with a greater presence in the European rare disease space.

04 What can be done?

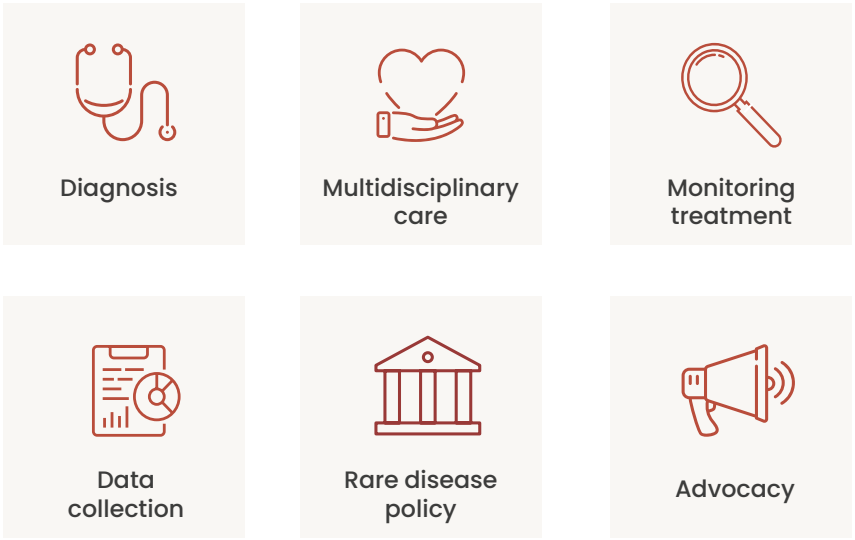
People living with Wilson's disease face a range of unacceptable barriers, which may have wide-reaching consequences on their health outcomes and quality of life. Delays in receiving a diagnosis of Wilson's disease are common across Europe, and can lead to a deterioration of symptoms and worse health outcomes. These delays are driven by a combination of limited clinical awareness and the complex diagnostic process. Once the disease has been diagnosed, it is crucial that people receive the most appropriate treatment, multidisciplinary care, and financial and social support, but access to these elements is variable across European countries. A lack of psychiatric support and neurological rehabilitation is often a particular area of concern. Although lifelong treatment is required for Wilson's disease, some individuals struggle to maintain it, which can result in the worsening of symptoms.

A number of systemic issues relating to data collection, rare disease policy and capacity for patient advocacy are hampering progress. A comprehensive evidence base on Wilson's disease is a requirement of effective planning for future services and advocacy, but data collection is currently variable between countries and there is no active multinational registry in place. Data on the lives of people living with Wilson's disease from sources such as patient surveys are also lacking. National rare disease strategies represent an opportunity to mitigate some of the challenges specific to Wilson's disease, as well as addressing health system deficiencies in rare disease service provision. Some countries in Europe do not have a national rare disease plan and, where those plans do exist, many do not have dedicated funding and/or require updating. A European policy framework for rare diseases is needed to coordinate and align national strategies. Patient advocacy is a key tool to communicate the needs of people living with Wilson's disease to policymakers and to inform rare disease strategies, but capacity within Wilson's disease organisations is often limited. Opportunities must be taken to build this capacity.

Priority actions

The barriers and unmet needs facing people living with Wilson's disease in Europe must be urgently addressed through joint and concerted action from stakeholders, including policymakers, organisations supporting people living with Wilson's disease, healthcare professionals and the research community.

Priority areas for action



Diagnosis: delays in diagnosis must be addressed to improve health outcomes

- **Raise awareness of Wilson's disease** among healthcare professionals working in both community and hospital settings, to ensure accurate and timely diagnosis.
- **Increase the availability of biomarker testing, particularly genetic testing,** to improve timeliness of diagnosis.
- **Develop new diagnostic tools** to support accurate and definitive diagnosis of Wilson's disease.
- **Fund new research** to explore the feasibility of newborn screening.

Multidisciplinary care: people living with Wilson's disease must be supported by a multidisciplinary approach with access to a range of specialist services that they may require

- **Incorporate underrepresented aspects** of Wilson's disease care into the updated clinical guidelines from EASL. These include the management of neurological and psychiatric symptoms, and associated support services such as speech therapy, physiotherapy and psychological therapies.
- **Promote collaboration between the ERNs** through the ERICA consortium, with the aim of improving access to multidisciplinary care for Wilson's disease.
- **Raise awareness of the importance of psychiatry, psychology, physiotherapy and speech therapy in Wilson's disease** to increase the number of relevant specialists involved in the condition's care and ensure that an individual's financial situation is not a barrier to them accessing these specialists.

Monitoring treatment: tackling non-adherence is vital to limit disease progression

- **Seek greater recognition of enhanced monitoring for at-risk groups** in clinical practice guidelines, and support its implementation to improve treatment adherence.
- **Encourage people to share their experiences of Wilson's disease with others living with the condition,** to increase visibility of the risks of treatment non-adherence.

Data collection: a robust and comprehensive evidence base on Wilson's disease is needed to support advocacy, policy, planning and monitoring

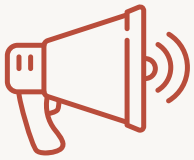
- **Collect data on the experiences of people living with Wilson's disease** through patient surveys, and use the findings to drive change via advocacy activities.
- **Develop methodology and criteria standards** for national Wilson's disease registries to reduce the variability of data collection across Europe and promote interoperability to produce a more robust Wilson's disease evidence base.
- **Encourage a more long-term and sustainable approach** to registry coordination and funding.

Rare disease policy: national and European rare disease policy should be strengthened and must be relevant to the needs of people living with Wilson's disease

- **Drive the implementation and renewal of national rare disease plans** through advocacy aimed at policymakers while ensuring the plans represent the needs of people living with Wilson's disease.
- **Ensure the needs of people living with Wilson's disease are well represented as part of ongoing EU advocacy activities** to support the implementation of the Rare 2030 foresight study recommendations.

Advocacy: opportunities should be harnessed at the European level to build advocacy capacity

- **Support Wilson's disease organisations** to take advantage of the significant drive at the European level to seek improvements for people living with rare diseases.
- **Encourage Wilson's disease organisations** to engage directly with ERNs through ePAGs and the ERN RARE-LIVER Wilson's disease working group.
- **Exploit current EU network funding opportunities** that aim to bring together members of the rare disease community and strengthen collaboration.
- **Leverage new guidance on partnerships with patients** to give people with Wilson's disease more influence in research projects.
- **Build national cross-stakeholder Wilson's disease (or broader) coalitions** to create a wider network of relevant partners to support improvements.
- **Encourage Wilson's disease patient organisations** to connect with European-level umbrella organisations to strengthen capacity, training and advocacy support.



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