International CardiOmyopathy Network | ICON

MANIFESTO FOR THE FUTURE OF CARDIOMYOPATHY CARE

2023

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The Health Policy Partnership

About the International Cardiomyopathy Network

The International Cardiomyopathy Network (ICoN) is a newly established association of medical, scientific and lay stakeholders with the mission of improving the health of people affected by cardiomyopathy and related diseases. ICoN plans to undertake a rolling programme to transform the cardiomyopathy landscape in Europe through clinical education and patient engagement, so that more people with cardiomyopathy can access the treatment and support that they need when they need it.

About this report

The manifesto has been developed based on desk research and structured interviews with experts in cardiomyopathy and relevant fields, including people living with the condition and their family members, healthcare professionals and industry representatives.

Research and drafting were led by Karolay Lorenty, Kirsten Budig and Ed Harding at The Health Policy Partnership. The Steering Committee, as co-authors, closely guided the development of the vision and priority actions in the manifesto.

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FOREWORD

Cardiomyopathies are a diverse and complex group of heart muscle diseases which can have a devastating impact on the lives of people of all ages. Collectively, they are the most common form of inherited cardiovascular disease, affecting around 1 in 200–300 people, and are a major cause of sudden cardiac death in the young.

While most cardiomyopathies cannot be cured, there are medications and implantable devices that can alleviate symptoms and improve prognosis. With the right kind of specialist treatment, information and support, most people affected by cardiomyopathy are able to face the challenges of living with cardiomyopathy and adjust to a changed life. However, best-practice care is still limited by poor awareness and unequal access to specialist teams. There is also a need to improve the links between clinical research and experimental medicine – despite considerable scientific progress in the field of cardiomyopathies, translation into patient benefit has been slow and poorly targeted.

The **International Cardiomyopathy Network (ICoN)** was established in 2019 as a multi-stakeholder group that seeks to improve the health of people affected by cardiomyopathy. Its long-term goals include better and more effective training of healthcare professionals, improvement in the wellbeing of people affected by cardiomyopathy, and increased awareness of cardiomyopathy among the general public and policymakers.

In this manifesto, we lay out our key priorities for the first phase of our plan to establish ICoN as a leading voice in the world of cardiomyopathy. We seek to encourage and support transnational and local initiatives that enhance the ability of clinicians to diagnose and treat cardiomyopathy, and we seek to promote research priorities for cardiomyopathy guided by the needs of affected people and families.

PROFESSOR PERRY ELLIOTT, Chair, International Cardiomyopathy Network (ICoN)

EXECUTIVE SUMMARY

Cardiomyopathy is a complex disease of the heart muscle that is partly determined by genetic factors and affects people of all ages, with varying levels of severity. As a chronic disease affecting the heart muscle, most types of cardiomyopathy have a strong genetic component. However, both genetic and environmental factors determine the time of onset and severity of symptoms in each person, leading to a wide range of manifestations.[1]

The high complexity of cardiomyopathy puts it at the forefront of emerging precision medicine approaches for cardiovascular disease. Personalised treatments that affect disease progression are being developed as our understanding of the genetic basis of cardiomyopathy improves.[2,3] Ultimately, this may encourage the cardiovascular field more generally to adopt the precision medicine approaches that have succeeded in other disease areas such as cancer.[4]

Cardiomyopathy contributes to major public health issues. Dilated cardiomyopathy is a major cause of heart failure[5] and hypertrophic cardiomyopathy is a leading cause of sudden cardiac death.[6] More than half of people who need a heart transplant have cardiomyopathy.[7,8]

For decades, the field of cardiomyopathy has faced challenges in diagnosis, genetic testing and effective treatments. Delayed diagnosis and misdiagnosis are common with cardiomyopathy,[9] and only a small portion of people with cardiomyopathy are ever diagnosed.[10] Despite advances in genetics, it remains difficult to predict disease progression,[11] and treatment has barely changed in the past few decades.[11]

As a community, our vision is that every person with, or at risk of, cardiomyopathy has timely access to optimal care that addresses their unique needs and improves their lives.

1. A TIMELY AND ACCURATE DIAGNOSIS

OBJECTIVES	PRIORITY ACTIONS
Increased awareness of and education about cardiomyopathy	Provide high-quality resources with information on cardiomyopathy targeted to specific audiences
A culture of early referral to cardiomyopathy specialist services	Promote communication and collaboration between primary care and cardiomyopathy specialist services

2. SPECIALIST CARE

OBJECTIVES	PRIORITY ACTIONS
Greater availability of and access to specialist services for cardiomyopathy	Assess the availability of cardiomyopathy specialist services across countries
Widespread access to genetic testing for people with cardiomyopathy	Create multi-stakeholder groups to advocate for wider access to genetic testing across countries
Increased genetic knowledge among healthcare professionals	Provide genetics education and training for healthcare professionals
Consensus-based, universal interpretation of genetic results	Promote multi-stakeholder collaboration for the universal interpretation of genetic results

3. PERSONALISED TREATMENT

OBJECTIVES	PRIORITY ACTIONS
Personalised treatments that halt disease progression in people with cardiomyopathy	Establish a research agenda for targeted investment in the development and clinical implementation of treatments for cardiomyopathy
Personalised care plans that improve quality of life	Promote greater collaboration between healthcare professionals and patient organisations to holistically support people with cardiomyopathy

4. PERSON-CENTRED, DATA-DRIVEN RESEARCH

OBJECTIVES	PRIORITY ACTIONS
Improved design of clinical trials for cardiomyopathy	Strengthen collaboration between people with cardiomyopathy, healthcare professionals, researchers and industry
Sustainable data infrastructures for cardiomyopathy care	Promote the integration of cardiomyopathy data across care services, research centres and countries

5. ACTIVE PATIENT ADVOCACY

OBJECTIVES	PRIORITY ACTIONS
An empowered cardiomyopathy patient advocacy community	Provide and signpost training and support opportunities for people with cardiomyopathy and relatives who are interested in advocacy
Shared decision-making across the cardiomyopathy care pathway	Provide joint decision-making resources to healthcare professionals and people with cardiomyopathy and their families
Active participation from people with cardiomyopathy in their own care	Develop and promote tools and technologies that facilitate self-monitoring and self-care

CARDIOMYOPATHY: TIME FOR A PARADIGM SHIFT

Cardiomyopathy is a complex disease of the heart muscle. It is a chronic disease that arises because of structural problems with the heart muscle, which include thickening of the heart walls, scarring and changes in the elasticity and strength of the muscle tissue.[12] There are several types of cardiomyopathy, with a wide range of clinical features (*Table 1*); the most common types are hypertrophic and dilated cardiomyopathy.[13]

Cardiomyopathy can be genetically inherited and affects people of all ages. Up to 40% of people with cardiomyopathy have a known family history of the disease:[13] genetic inheritance accounts for 30–60% of cases of hypertrophic cardiomyopathy[14] and 33% of cases of dilated cardiomyopathy.[15] In many cases, however, the cause remains unknown.[5] It is important to note that the genetics involved in cardiomyopathy means that there are differences in the strategies required for diagnosis and treatment of the different types of cardiomyopathy. This is different from other cardiovascular conditions that are primarily caused by prolonged exposure to risk factors such as high blood pressure and high cholesterol, as well as other lifestyle and environmental drivers.[16]

Both genetic and environmental factors affect when, how and whether cardiomyopathy will manifest. The onset, progression and severity of cardiomyopathy symptoms are determined by genetic and environmental factors.[1] Some people carrying a pathogenic genetic variant (variation in the DNA sequence) associated with hypertrophic cardiomyopathy will develop severe symptoms when they are young, whereas others will experience few or no symptoms throughout their life.[1 17]

The symptoms among people with cardiomyopathy are variable. Cardiomyopathy presents with a wide variety of symptoms, including breathlessness, chest pain, palpitations, fainting and swelling. The condition often leads to severe manifestations, including heart failure and sudden cardiac death, even in people with minimal or no symptoms.[18] Cardiomyopathies may progress towards heart failure, and a large proportion of sudden cardiac deaths are known to arise in people with cardiomyopathy.[5 6]

CARDIOMYOPATHY IS A PATHFINDER FOR PRECISION MEDICINE IN CARDIOVASCULAR DISEASES

A 'one size fits all' strategy has long been the norm for cardiovascular disease care, but a more personalised approach is emerging. Most healthcare for cardiovascular diseases has been based on the assumption that people with common signs and symptoms share the same disease mechanism and therefore will respond similarly to treatment.[19] Diagnostic procedures and treatments typically address symptoms, but insufficiently target the root cause of disease or halt disease progression (*Table 2*). In contrast, molecular diagnostics, genomics and precision medicine are becoming more widely adopted in disease areas such as cancer.[4] The advances seen elsewhere give a powerful impetus for cardiovascular disease care to evolve dramatically – to intervene earlier, give the right care to the right person, improve quality of life and save lives.

The high complexity of cardiomyopathy puts it at the forefront for developments in precision medicine. Complex chronic diseases that do not have a single cause, such as cardiomyopathy, require a new approach that takes into consideration people's individual characteristics and needs.[19] Improved understanding of the genetic basis of cardiomyopathy is propelling the development of sophisticated approaches and tailored treatments that could help achieve better outcomes.[2 3] Experts have highlighted that advances in precision medicine for cardiomyopathies can also present learning opportunities for other cardiovascular diseases.[20]

Table 1. Types of cardiomyopathy[12]

Type of cardiomyopathy	Clinical features
Hypertrophic (HCM)	Increased wall thickness of the heart muscle
Dilated (DCM)	Dilatation of the heart muscle and reduced contractility
Non-dilated left ventricular (NDLVC)	Scarring and fatty tissue replacement of the heart muscle
Arrhythmogenic right ventricular (ARVC)	Abnormal structural changes of the heart muscle along with ventricular arrhythmia (abnormal heart rhythm in the lower chambers of the heart)
Restrictive (RCM)	Stiff walls of the heart muscle

Table 2. Traditional management of cardiomyopathy[18]

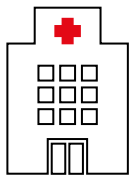
Type of treatment	Details
Medication	Heart failure medication to alleviate symptoms and improve outcomes
Device therapy	Implantable cardioverter defibrillator (ICD) and pacemaker to prevent sudden cardiac death in people at high risk
Surgery	Invasive therapy or heart transplantation to restore cardiac function
Lifestyle changes	Weight control and improving diet, as well as limiting tobacco and alcohol consumption; in some cases, prohibition of competitive sport or other types of exercise

WHAT IS AT STAKE: THE IMPACT OF CARDIOMYOPATHY

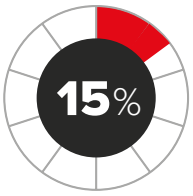
Cardiomyopathy is a major cause of heart failure and sudden cardiac death. Dilated cardiomyopathy is a principal cause of heart failure,[5] which itself is a complex syndrome affecting one in five people[21] and the leading cause of preventable hospitalisations in Europe.[22] Hypertrophic cardiomyopathy (one of the most prevalent types of the disease) is a leading cause of sudden cardiac death.[6] Sudden cardiac deaths are a major public health issue, accounting for up to one in every four deaths.[23]

More than half of all people who need a heart transplant have cardiomyopathy. Studies have shown that, in Germany, cardiomyopathies account for 60% of all heart transplants and 68% of heart transplants in children under 15 years old.[25] In France, cardiomyopathy accounts not only for half of all heart transplants, but also for one third of defibrillator implantations and one third of mechanical circulatory support devices.[7]

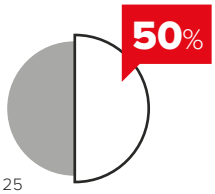
Cardiomyopathy accounts for **1 in 10 hospitalisations** for heart failure in France.[7]



Cardiomyopathy is responsible for up to **15% of sudden cardiac deaths** in the US.[24]



Cardiomyopathy leads to more than **50% of heart transplants** among adults and children in European countries.[7 25]



DID YOU KNOW?

Inequalities in cardiomyopathy care across Europe lead to stark **geographical and gender disparities**.

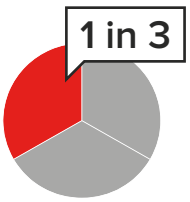
In eastern Europe, the rate of major cardiovascular events for people with cardiomyopathy is more than two times higher than in southern Europe.[26] Women with cardiomyopathy are diagnosed later than men, even when they have more symptoms; they also receive a device implantation less frequently than men, even with similar risk of sudden cardiac death.[27] Probably as a result of delayed or inappropriate treatment, women with cardiomyopathy have worse survival than men.[28 29]

THE STATUS QUO: KEY CHALLENGES IN RESEARCH AND CLINICAL PRACTICE

CHALLENGE: **Cardiomyopathy often remains undetected, leading to missed opportunities for timely treatment.** Only a small proportion of people with hypertrophic cardiomyopathy are ever diagnosed, with experts suggesting a 'tip of the iceberg' phenomenon where healthcare professionals are only exposed to people with more severe signs and symptoms within the broader disease spectrum.[10] Symptoms of cardiomyopathy, such as breathlessness and chest pain, overlap with those of other conditions, leading to frequent misdiagnosis. People with cardiomyopathy induced by pregnancy (peripartum cardiomyopathy) often receive a delayed diagnosis due to the overlap of signs and symptoms with normal pregnancy.[9]

CHALLENGE: **Access to genetic counselling and testing for cardiomyopathy varies widely between European countries.** Genetic counselling is performed inconsistently; while it can be performed in up to 83% of cases, in most European countries it only happens in 50% of cases or fewer.[32] Similarly, there are wide variations in the provision of genetic testing. While almost half of people with cardiomyopathy in southern and western European countries receive genetic testing, this occurs for fewer than one in six people in eastern Europe.[32] There are also discrepancies between people with different types of cardiomyopathy. For example, genetic testing was performed less frequently in people with dilated cardiomyopathy than in those with other types,[32] even though dilated cardiomyopathy is currently considered to have genetic causation in up to one third of cases.[15]

People with transthyretin amyloid (ATTR) cardiomyopathy (caused by the build-up of amyloid protein) can **wait for up to seven years** for a diagnosis, with misdiagnosis taking place in around half of cases.[30 31]



Of people with cardiomyopathy in Europe, only **one in three** receive genetic testing.[13 32]

DID YOU KNOW?

Genetic testing can uncover **silent cardiomyopathy**.

There are people who carry a pathogenic genetic variant associated with cardiomyopathy, but who do not currently have clinical symptoms. Family screening allows the early detection of cardiomyopathy in asymptomatic individuals who may be at risk of heart failure or sudden cardiac death.[33] Of the relatives of people diagnosed with cardiomyopathy who carry a genetic mutation, around half will develop the disease.

CHALLENGE: **It remains difficult to predict disease progression in people with cardiomyopathy.** Scientific and clinical studies have attempted to understand how different genetic variants affect disease presentation and progression.[11] But the disease mechanism of many genetic variants remains unknown and it has been challenging to identify reliable markers that predict disease onset and progression, making it hard to assess which people are most at risk.[10] Although genetic testing helps with the identification of an underlying cause once a person is diagnosed with cardiomyopathy, it remains difficult to predict the progression of disease across a very diverse population.

CHALLENGE: **For decades, there have been few developments in treatments for cardiomyopathy.** In the past 30 years, treatment for cardiomyopathy has barely changed.[11] Current strategies and international guidelines are based on medicines commonly used for other diseases; they can alleviate symptoms, but do not target the disease mechanism or restore cardiac function in people with cardiomyopathy.[34] For example, people with non-obstructive hypertrophic cardiomyopathy do not respond well to conventional heart failure treatment and have worse outcomes than those with obstructive hypertrophic cardiomyopathy.[34]

Most treatments for cardiomyopathy do not target the underlying disease mechanism and do not repair heart damage.[34]

OUR VISION FOR THE FUTURE OF CARDIOMYOPATHY

Every person with, or at risk of, cardiomyopathy must have timely access to optimal care that addresses their unique needs and improves their quality of life.

This includes access to:

A TIMELY AND ACCURATE DIAGNOSIS

SPECIALIST CARE

PERSONALISED TREATMENT

PERSON-CENTRED, DATA-DRIVEN RESEARCH

ACTIVE PATIENT ADVOCACY

A TIMELY AND ACCURATE DIAGNOSIS

OBJECTIVE I.

Increased awareness of and education about cardiomyopathy

There is a lack of awareness and education regarding cardiomyopathy. Misconceptions about cardiomyopathy are common, even among healthcare professionals, leading to misdiagnoses and delayed diagnoses.[31] Rare cardiomyopathies such as arrhythmogenic right ventricular cardiomyopathy (ARVC) receive even less attention and often remain undiagnosed.[35] Besides healthcare professionals, there is also poor awareness of cardiomyopathy among the general public.

PRIORITY ACTION:

Provide high-quality resources with information on cardiomyopathy targeted to specific audiences. This includes the development of new platforms that direct current and future healthcare professionals, people with cardiomyopathy, their families and the general public to existing high-quality educational resources. Topics should include diagnostic red flags relevant to different care settings and knowledge relevant to the interpretation of genetic results. Information should be accessible to different audiences within the healthcare community who do not specialise in cardiomyopathy. It will also be essential that there are country-specific sources to overcome language barriers.

There are many cardiologists who are not aware of cardiomyopathies. It is a big problem. Many people do not know that cardiomyopathy can cause young people to die suddenly.

RUTH BILLER *with personal experience of cardiomyopathy and Chair of German patient organisation for ARVC*

OBJECTIVE 2.

A culture of early referral to cardiomyopathy specialist services

Early recognition of markers of cardiomyopathy is vital to facilitate timely diagnosis and treatment. It is essential that healthcare professionals are aware of diagnostic clues, as these should guide the selection of additional tests and enable a final diagnosis (*Case study 1*).[36] Diagnostic markers may include personal characteristics (such as age and sex), family history, signs and symptoms, imaging and laboratory findings, as well as other risk factors. Detailed evaluation of clinical symptoms and signs in people with unexplained heart dysfunction can facilitate diagnosis[37] and help differentiate cardiomyopathy from other conditions, for example, Fabry disease or Friedreich's ataxia.[38 39] In the case of peripartum cardiomyopathy, assessing risk is also vital to set preventive measures – women with more than six risk markers are at 800 times higher risk of developing peripartum cardiomyopathy than women with six or fewer risk markers.[40]

> ***The number one obstacle to improved diagnosis of cardiomyopathy is awareness among general physicians and cardiologists. Sometimes there is a lack of urgency or understanding that an individual should be referred for further evaluation.***
>
> **PROFESSOR PERRY ELLIOTT**, *Director of clinical research for heart muscle disease*

Lack of early access to specialist services hampers the early and accurate diagnosis of cardiomyopathy. The presentation of cardiomyopathy can overlap with other common conditions (such as anxiety), which can lead to underdiagnosis and misdiagnosis, particularly in non-specialist services such as primary care.[9] An inherited cardiomyopathy can also be missed if the family history of cardiovascular disease is not considered. A study by Cardiomyopathy UK found that general practitioners (GPs) asked about the family history of cardiovascular disease in only 29% of people.[41]

PRIORITY ACTION:

Promote communication and collaboration between primary care and cardiomyopathy specialist services. Establishing partnerships between specialist services and primary care networks can help to raise awareness of cardiomyopathy and establish infrastructures for referrals. Educational resources should be tailored to presentations that primary care professionals can encounter in their practice. Resources should also indicate when initial signs or a family history of heart disease require referral to a specialist cardiomyopathy service.

Case study 1.

Developing a screening tool to accelerate the diagnosis of transthyretin-related amyloidosis cardiomyopathy

The problem.
Transthyretin-related amyloidosis (ATTR) cardiomyopathy is often undiagnosed or misdiagnosed.[42 43] The delays in receiving a correct diagnosis lead to rapid disease progression and organ dysfunction, despite the availability of inexpensive, non-invasive diagnostic tools and effective treatment.

The opportunity.
Studies suggest ATTR cardiomyopathy may be a common cause of heart failure with preserved ejection fraction.[30] A study in Italy found that half of ATTR cardiomyopathy diagnoses occurred following a medical evaluation for heart failure,[44] indicating that targeting people known to have heart failure could accelerate diagnosis.

The solution.
A working group of experts developed a screening tool to help healthcare professionals recognise the red flags of ATTR cardiomyopathy. They identified that men aged over 65 and women aged over 70 with increased heart wall thickness and heart failure and other diagnostic red flags require further investigation.[43]

SPECIALIST CARE

OBJECTIVE 3:

Greater availability of and access to specialist services for cardiomyopathy

Despite the need for specialist care, many people with cardiomyopathy do not have access to these services. The diagnosis and management of cardiomyopathy is complex; it requires specialist care involving multidisciplinary teams and a large variety of diagnostic tools.[45 46] Every person living with cardiomyopathy should be linked to a specialist service. However, there are marked differences in the number of available specialist services and tools across regions. For example, although cardiac magnetic resonance imaging is a key component of diagnosis and management, it is performed in less than one third of people with cardiomyopathy due to limited availability across Europe.[47] Children and young people living with the condition can also face unique barriers. Some families report that there is no single service that specialises in paediatric cardiomyopathy in their local region, so they have to move from one centre to another as part of their child's care.[48]

For more on **cardiomyopathy multidisciplinary teams**, see the spotlight on page 31.

PRIORITY ACTION:

Assess the availability of cardiomyopathy specialist services across countries. A map of all cardiomyopathy-related services (including imaging, diagnostic services, genetic services and genetic counselling) will help to assess access to specialist services. This will identify regions that are in most need of expertise and resources to provide guideline-recommended care for cardiomyopathy.

Develop national expert networks and advocacy initiatives to engage local health policymakers. Expert networks can play a key role in improving access to specialist care, facilitating the exchange of best practice across centres and establishing benchmark criteria to improve quality of care. For example, these networks can make the case for the establishment of new cardiomyopathy specialist services to local and national health decision-makers (such as national governments, health departments, insurers and payers).

DID YOU KNOW?

2019 marked the foundation of the **Greek National Network of Precision Medicine in Cardiology and the Prevention of Sudden Death in the Young**, a partnership between hospitals and research institutions. Besides being involved in the creation of registries and screening for high-risk families, the network has also supported the training of healthcare professionals and the development of specialist units throughout the country.

OBJECTIVE 4:

Widespread access to genetic testing for people with cardiomyopathy

Access to genetic testing is not consistent across Europe, although it can facilitate the diagnosis and management of cardiomyopathy. Genetic testing can help to differentiate cardiomyopathy from other diseases with overlapping symptoms, leading to a faster, more accurate diagnosis and risk assessment.[12] It can also help healthcare professionals to choose the most appropriate treatment and follow-up measures. However, reimbursement for genetic testing is not consistent across Europe.[32] Experts have highlighted that underusage is also caused by the lack of clarity regarding the clinical implications of genetic testing and gaps in the knowledge of healthcare professionals.

For more on the debate on **genetic testing**, see the spotlight on page 30.

For more on **genetic testing after sudden death**, see the spotlight on page 31.

PRIORITY ACTION:

Create multi-stakeholder groups to advocate for wider access to genetic testing across countries. Due to the large variations in access to genetic testing and the local and national regulations, it is imperative that national advocacy groups engage with their health policymakers. A strong case must be developed to showcase the advantages and opportunities that arise for people with cardiomyopathy and their care once genetic testing is made more widely available.

OBJECTIVE 5:

Increased genetic knowledge among healthcare professionals

Education and training in cardiogenetics are often not available for non-specialists, despite the fact that most people with cardiomyopathy will be treated by a non-specialist. Healthcare professionals need a clear understanding of the types of genetic tests currently available for cardiovascular disease, the appropriate interpretation of results and their clinical implications. Even the appropriate selection of a genetic test tailored to an individual can be complicated, as the composition of gene panels varies across laboratories and different testing approaches have their own benefits and limitations.[49 50] Ideally, genetic counsellors or clinical geneticists should form part of the cardiomyopathy multidisciplinary team;[51 52] usually, however, they are only available in specialist cardiomyopathy centres. Therefore, it is essential that other healthcare professionals, such as cardiologists, have education in cardiogenetics.[51 52] Across Europe, genetic counselling is provided by cardiologists in 85% of cases, despite the lack of training available.[32]

For more on **genetic counselling**, see the spotlight on page 32.

PRIORITY ACTION:

Provide genetics education and training for healthcare professionals. For example, a collaborative international learning network would help to fill the gaps of expertise in genetic counselling and cardiogenetics for healthcare professionals. The network could develop training programmes and competency-based frameworks, as well as organise events to facilitate learning and exchange of best practice. For genetic counselling, innovative delivery models could be developed and implemented to help alleviate the workload of healthcare professionals.

OBJECTIVE 6:

Consensus-based, universal interpretation of genetic results

Genetic tests are crucial in selecting treatment for cardiomyopathy, yet consensus on the interpretation of results is lacking. Depending on the way genetic results are interpreted, they can be classified as benign, pathogenic or of uncertain significance.[50] Their interpretation can change over time and needs to be periodically reviewed. There are general clinical guidelines for variant interpretation, but they avoid specific instructions to allow for adaptations – leading to different approaches in different laboratories.[53] Although there are reference sources for interpretation of variants in the public domain,[54] many new variants are observed in laboratories that generate a proprietary variant interpretation, rather than sharing their data. Genetic variants may be reclassified as more or less pathogenic following initial classification, so it is vital that interpretation takes into account the most up-to-date information.[55]

In some countries, every single lab looks at the data through their own lens. That means that a physician could diagnose a person as having a pathogenic mutation, while another physician diagnoses a variant of unknown significance – all because they're working with different labs. The first physician can prescribe treatment, but the other can't even though it is the same mutation.

GABRIEL BROOKS, *Chief Medical Officer at a life sciences company*

PRIORITY ACTION:

Promote multi-stakeholder collaboration for the universal interpretation of genetic results. Experts have called for collaboration and data sharing to ensure the consistent interpretation of genetic results.[53 56] A multi-stakeholder group could develop consensus-based guidelines for the interpretation of genetic results specific to cardiomyopathy. Strategies should be established to ensure that all relevant clinical and experimental data and the most up-to-date information on the classification of genetic variants are in the public domain.

DID YOU KNOW?

In Norway, genetic testing is financed entirely by the health system. Since 2003, there has only been **one national laboratory for genetic testing** for all people with cardiomyopathies in the country: the Unit for Cardiac and Cardiovascular Genetics at Oslo University Hospital.[57] This ensures that all families receive the same classification for their genetic variant. The laboratory has performed genetic testing on more than 4,400 people with a cardiomyopathy diagnosis as well as 3,000 relatives.

PERSONALISED TREATMENT

OBJECTIVE 7:

Personalised treatments that halt disease progression in people with cardiomyopathy

Recent advances in cardiomyopathy have shone a light on disease mechanisms and new treatment approaches. For decades, the complexity in clinical presentation of cardiomyopathies has made it very difficult for management strategies to progress.[58] In recent years, scientific advances have led to the identification of multiple genes associated with the disease, as well as a variety of biological pathways underlying the genetic subtypes that are involved in its development.[59] This increased understanding of underlying mechanisms has led to establishing disease markers and prompted the development of new treatments for cardiomyopathy.

Despite this encouraging progress, the development of new treatments for cardiomyopathy is only in its early stages and limited in scope. Current clinical trials focus on specific population groups, such as people with obstructive hypertrophic cardiomyopathy.[60] It is essential that a range of treatments for cardiomyopathy, both pharmacological and non-pharmacological (such as device and surgical treatments), are available.[58 61] A wider variety of options would mean a timely treatment decision can be made based on the unique needs of each individual.

From the patient perspective, a high priority is new treatments for cardiomyopathy. The treatments available do not work on the mechanism of action of the disease, they just work by lowering symptoms. We also need better surgical options.

MATTEO PINCIROLI, *with personal experience of cardiomyopathy and Chair of a global patient group for cardiomyopathy*

PRIORITY ACTION:

Establish a research agenda for targeted investment in the development and clinical implementation of treatments for cardiomyopathy. For example, a multi-stakeholder forum could be created to assess current priorities, establish a research agenda and co-develop research projects to ensure equal access to effective treatments. The forum should involve multidisciplinary representation, including people with cardiomyopathy and patient advocates, researchers (in basic science as well as clinical and translational research), healthcare professionals, industry representatives and funders.

To find out more about **the dawn of treatments for cardiomyopathy**, see the spotlight on page 21.

DID YOU KNOW?

Beyond genomics, **next-generation omics-based approaches** (the study of proteins, lipids and other molecules) can improve the understanding of what processes lead to cardiomyopathy and how the disease progresses.[62] In turn, the increased understanding can help to identify biomarkers that facilitate the assessment of risk and can help develop new treatments.

Network-based approaches provide insights into the complex processes that underlie the development and progression of cardiomyopathy, allowing the identification of biomarkers and the development of new treatments.[63] For example, a study using network medicine identified subgroups of people with hypertrophic cardiomyopathy at a lower risk of sudden cardiac death, who would otherwise be unnecessarily implanted with an implantable cardioverter defibrillator (ICD).[64]

OBJECTIVE 8:

Personalised care plans that improve quality of life

Cardiomyopathy has a huge impact on the daily lives of people with the condition, as well as their families and loved ones. People with cardiomyopathy who undergo an ICD implantation can experience device-related complications, such as shocks and infections.[65] Following diagnosis, children and adults with cardiomyopathy are also at higher risk of mental health conditions, such as anxiety and depression.[66 67] It can also have additional complications for people at key stages of their lives, such as when they are leaving school, starting university, starting a new job or considering pregnancy.[68] Cardiomyopathy can decrease the level of physical activity that a person takes part in, leading to obesity and an increased risk of further cardiovascular disease.[69] As a leading cause of sudden cardiac death in young people, cardiomyopathy can also leave families or loved ones in grief and struggling to process an unexpected death.[70]

There is a need for tailored guidance and comprehensive support for people with cardiomyopathy and their families or loved ones. Multidisciplinary teams for cardiomyopathy care should include psychological support and refer to a specialist as required.[71] Psychosocial support for mental health and key life events is also crucial, especially in young people with cardiomyopathy. Women with cardiomyopathy may also require tailored advice regarding planning or prevention of pregnancy.[72] It is also critical that healthcare professionals provide tailored recommendations around physical exercise;[73] studies have found that people with cardiomyopathy are less physically active than the general population regardless of age or the presence of symptoms.[69] This may be due to self-imposed restrictions or untailored advice from healthcare professionals.[74]

> ***The psychological impact of cardiomyopathy needs to be taken into account more. It not only affects yourself, but your whole family and children. And yet, nearly no psychological support is offered.***
>
> **RUTH BILLER**, *with personal experience of cardiomyopathy and Chair of German patient organisation for ARVC*

PRIORITY ACTION:

Promote greater collaboration between healthcare professionals and patient organisations to holistically support people with cardiomyopathy. Patient organisations can raise awareness among healthcare professionals about aspects of living with cardiomyopathy that are important for people with the diagnosis and modifiable. Resources could be created jointly, with information on tailored cardiomyopathy care including different aspects such as mental health and lifestyle. This would help healthcare professionals to provide tailored recommendations to people with cardiomyopathy, referring them when needed to specialist services as well as patient organisations and peer-to-peer groups for further support.

PERSON-CENTRED, DATA-DRIVEN RESEARCH

OBJECTIVE 9:

Improved design of clinical trials for cardiomyopathy

Clinical trials for cardiomyopathy must be person-centred and representative of the population. Clinical trials should include appropriate markers of stages as the disease progresses that are important to people with cardiomyopathy, such as quality of life and other patient-reported outcome measures.[35 75 76] Furthermore, differences in genetics, presentation, management and outcomes across population groups must be taken into account.[77 78]

PRIORITY ACTION:

Strengthen collaboration between people with cardiomyopathy, healthcare professionals, researchers and industry. Partnerships between patient organisations, healthcare professionals, researchers and industry could increase the participation of people with cardiomyopathy in research. Improved collaboration could also ensure that the priorities of those living with the condition are a core part of clinical trials. It is also essential that the people involved in clinical trials are representative of the population, considering age, sex and ethnic differences in cardiomyopathy.

When I started in this field, we had no idea we were ever going to do randomised trials. So when the time came, about less than 10 years ago, the community was very unprepared. It is difficult to choose endpoints to assess clinical efficacy in these lifelong conditions, and the search is still ongoing.

PROFESSOR IACOPO OLIVOTTO,
Professor of cardiovascular medicine

DID YOU KNOW?

Clinical trials of new treatments for cardiomyopathy are rarely performed in children, leading to the use of treatments that do not have evidence in this age group.[68] Experts have highlighted that conducting clinical trials with children has additional challenges, such as the need for more centres involved to gather enough data as well as perceived concerns regarding ethical considerations and the willingness of families to participate. However, as revealed in interviews, many families want to be engaged in clinical trials, and obtaining robust evidence for the effectiveness of treatments in children with cardiomyopathy is crucial to them.[68]

OBJECTIVE 10:

Sustainable data infrastructures for cardiomyopathy care

Capturing cardiomyopathy data is critical to improving care. Linking phenotype and genotype data of cardiomyopathy can provide important information for clinical practice.[11] Vast amounts of phenotype data are generated in routine care, such as personal characteristics or imaging and lab results.[79] Algorithms can be used in large data sets, combining data from multiple sources to identify patterns. For example, algorithms could classify people with cardiomyopathy into subgroups with a shared disease mechanism that may respond similarly to treatment, helping to guide clinical decision-making. The data can also be used for research to assess the performance of clinical processes and improve quality of care (*Case study 2*).[79]

PRIORITY ACTION:

Promote the integration of cardiomyopathy data across care services, research centres and countries. A common cardiomyopathy data platform could be developed using existing data sets and integrating them in real time. The platform would allow researchers to download, add and analyse cardiomyopathy data in their efforts to improve quality of care, and in developing new treatments for people with cardiomyopathy. A key stepping stone for an international platform will be to promote data sharing across cardiomyopathy services.

Case study 2.

Using big data on routine electronic health records

The problem.
Limited knowledge about cardiomyopathies hinders improvements in care. Patient registries often have fixed timepoints for data collection and a lot of routine care data are disregarded.[80]

The solution.
At the University Medical Centre Utrecht and Bergman Clinics in the Netherlands, the UNRAVEL Research Data Platform is embedded in routine practice to facilitate research.[81,82] It aims to improve care for people with cardiomyopathy and their relatives by providing a standardised database that allows big data analytics.[80] The platform combines:

- **routine electronic health records**, including cardiological, electrophysiological, imaging and genetic data, as well as clinical notes and investigations using text-mining tools
- **a standardised blood biobank and cardiac tissue database**, following a consent process and standardised protocol for sample storage.

The impact.
The UNRAVEL Research Data Platform allows automatic collection of data over a period of time. Besides being efficient, this also enables data integration into a detailed picture of the clinical pathway. The platform makes it possible to assess interventions and measure outcomes during routine healthcare.[80]

ACTIVE PATIENT ADVOCACY

OBJECTIVE II:

An empowered cardiomyopathy patient advocacy community

Patient organisations have a huge role to play in overcoming the issues that affect people with cardiomyopathy. Too often, decisions regarding policy, healthcare and treatment development are made without consulting those who are affected most – the people living with cardiomyopathy and their families. In some cases, people with cardiomyopathy have developed initiatives to change local policies that greatly influence their daily life.[48] But some challenges persist. For example, in some regions of Italy, people who have received an ICD implantation struggle to renew their driving licence.

There is a disconnect. Life science companies have not been speaking with people with cardiomyopathy. Healthcare professionals speak to people with cardiomyopathy one on one, but they rarely speak to patient associations. This needs to change. We need to find ways to interact and understand each other.

MATTEO PINCIROLI, *with personal experience of cardiomyopathy and Chair of a global patient group for cardiomyopathy*

PRIORITY ACTION:

Provide and signpost training and support opportunities for people with cardiomyopathy and relatives who are interested in advocacy. Patient organisations play a critical role in ensuring that people with cardiomyopathy (and their families or loved ones) who wish to get involved in advocacy efforts can access the knowledge and skills necessary to engage different stakeholders, so they can drive the change they want to see. Patient organisations can boost empowerment by providing training that is specific to the challenges that people with cardiomyopathy face.

OBJECTIVE I2:

Shared decision-making across the cardiomyopathy care pathway

Healthcare professionals should enable people to actively engage in decisions about their care. People with cardiomyopathy should be fully informed about their treatment options and the risks involved. Decisions regarding treatment should be shared between people with cardiomyopathy and healthcare professionals.[83] Healthcare professionals must take into account the person's experience of perceived risk and take appropriate measures to resolve disagreements when needed.

If we're not able to communicate to patients what we mean by risk, we are in real trouble. Shared decision-making appears in lots of documents, but it's often a tick-box exercise with a lack of exploration on what decision-making should look like.

PROFESSOR JUAN PABLO KASKI, *Director of the Centre for Paediatric Inherited and Rare Cardiovascular Disease at University College London and Great Ormond Street Hospital*

PRIORITY ACTION:

Provide joint decision-making resources to healthcare professionals and people with cardiomyopathy and their families. Healthcare professionals and patient organisations should jointly determine what shared decision-making looks like for people with cardiomyopathy, a consensus which can shape the development of resources and tools.[68] Shared decision-making tools help people with cardiomyopathy feel better informed and gain clarity on what is important to them.[84] The cardiomyopathy community can be inspired by the materials and training developed for people with other cardiovascular diseases, including evidence-based information for the different options available as well as the personal values that should be considered and clarified when making a decision.[85 86]

OBJECTIVE I3:

Active participation from people with cardiomyopathy in their own care

People with cardiomyopathy play an important role in the long-term monitoring and management of their condition. While genetic testing allows healthcare teams to identify increasing numbers of people at risk of cardiomyopathy, there is uncertainty regarding disease progression that requires long-term monitoring.[55] People with cardiomyopathy and their families can be empowered to be active participants in their own monitoring and care, so they can alert healthcare professionals to any signs or symptoms and receive appropriate care when they need it.

PRIORITY ACTION:

Develop and promote tools and technologies that facilitate self-monitoring and self-care. Technologies that facilitate self-monitoring and communication with healthcare professionals may be key for the sustainability of health systems. For example, wearables have the potential to improve risk assessment by providing comprehensive data, and evidence from heart failure shows that they can improve the management of the condition.[87] In light of these technologies, experts have highlighted that people with cardiomyopathy could play a key role in self-monitoring at home, as already happens in other diseases.[55 87]

SPOTLIGHTS ON KEY TOPICS IN CARDIOMYOPATHY CARE

THE DAWN OF TREATMENTS FOR HYPERTROPHIC CARDIOMYOPATHY

Recent advances in the development of pharmacological treatments for hypertrophic cardiomyopathy target disease mechanisms. One promising treatment for hypertrophic cardiomyopathy that targets the disease mechanism is cardiac myosin inhibitors.[61] Myosin is a protein that uses energy to generate muscle contraction. Studies have shown that genetic variants associated with hypertrophic cardiomyopathy result in excessive availability of myosin, and therefore, excessive contraction of the heart muscle. Cardiac myosin inhibitors work by inhibiting the protein, allowing normal contraction of the heart muscle. In 2021, a clinical trial showed that a cardiac myosin inhibitor safely reduced blood flow restriction and the severity of symptoms, while improving the quality of life in people with obstructive hypertrophic cardiomyopathy.[88 89] This led to its approval by the US Food and Drug Administration and the European Medicines Agency.[90 91] Other cardiac myosin inhibitors have also shown promising results in clinical trials.[92]

Gene therapies have the potential to become an effective treatment for hypertrophic cardiomyopathy, but there are still issues that need to be resolved before the therapies become widely available. In recent years, there have been advances in gene therapies such as gene replacement and genome editing studies.[93] Gene therapies have the potential to slow or even reverse the course of hypertrophic cardiomyopathy with a single treatment. Currently, there is one ongoing clinical trial for hypertrophic cardiomyopathy.[94] However, experts have highlighted that many unresolved questions remain regarding the suitability of gene therapies, such as costs and legal considerations.[95] It will be important to initiate discussion among people with cardiomyopathy, healthcare professionals and policymakers before gene therapies become widely available.

GENETIC TESTING

Genetic testing can facilitate accurate diagnosis and risk assessment, leading to early initiation of suitable therapies. Genetic testing can help to differentiate primary cardiomyopathies from other diseases with overlapping symptoms, meaning that diagnoses and risk assessments are more accurate.[50] Consequently, healthcare professionals can discuss the most suitable treatment options with people with cardiomyopathy. This is particularly important when a disease-modifying treatment is available. In other cases, in which a pathogenic variant has been identified, it can also help to make treatment decisions that prevent complications, such as ICD implantation for people with high-risk genetic variants.[71]

Genetic testing contributes to the understanding of cardiomyopathy. It can generate data that can be used in research, improving our understanding of genetic variants and disease mechanisms. It can support the development of disease-modifying treatment and, over time, increase our understanding of the clinical implications of specific genetic variants.[96]

Genetic testing helps early diagnosis of relatives with cardiomyopathy and allows the introduction of appropriate follow-up measures. Once a genetic cause has been identified in an individual, this information is communicated to relatives who may also be at risk of developing cardiomyopathy.[50] As a result, relatives may be diagnosed with cardiomyopathy over 10 years earlier.[13] If a clear genetic cause for cardiomyopathy is found in the family, genetic testing in relatives can help to accelerate diagnosis and treatment of people who may have otherwise been missed. For those who have a negative genetic result, it releases them from worry and the need for long-term follow-up.

Further research is needed to overcome the barriers to implementing genetic testing. Some experts suggest that further knowledge is required regarding the most appropriate treatment and the best time to start it following genetic test results for cardiomyopathy.[97] People may receive a result from genetic testing that is not definite,[53] which can make it difficult to understand the clinical relevance of many genetic variants. Inheritance of cardiomyopathy is complex and the interpretation of genetic results may change as more evidence accumulates.[98] Further research into who should have access to genetic testing is also required, whether that is only people who have already received a diagnosis for cardiomyopathy and their close relatives, or also those who are at high risk (such as people with heart failure).[99]

GENETIC TESTING AFTER SUDDEN DEATH

Genetic testing following sudden death can reveal a cardiovascular cause and help to detect cardiomyopathy in relatives. Sudden unexpected death is investigated using forensic procedures to find the cause. There are variations across countries, but autopsies can be conducted to investigate the potential involvement of third parties or self-inflicted death, as well as to identify the underlying pathological cause. Many unexplained sudden death cases are attributable to cardiac reasons.[100] There is evidence that genetic testing could help to increase the proportion of explained cases by 9%.[101] A study in Canada found that 6% of cardiac arrest survivors without a previous diagnosis of cardiomyopathy carried a pathogenic genetic variant in a cardiomyopathy gene. The researchers used genetic testing, identifying that more than half of variants (57%) were in genes associated with cardiomyopathy. The confirmation of a genetic cause for a sudden death can lead to genetic testing of family members and the early identification of cardiomyopathy.[102]

THE CARDIOMYOPATHY MULTIDISCIPLINARY TEAM

Clinical decision-making for cardiomyopathy relies on clinical judgement, local expertise and patient preference.[103] A dedicated multidisciplinary team has emerged as the best strategy to provide tailored care for people with cardiomyopathy, optimising care across the care pathway. The team plays a key role in undertaking personalised risk assessment, providing treatment and ensuring the application of the latest research.[103-105]

Multidisciplinary teams for cardiomyopathy require a wide range of experts (clinicians and nurses), such as those in:[105]

cardiology	genetics	pharmacy	medical specialties	psychology and social work
including specialists in adult and paediatric cardiomyopathy, heart failure, cardiac surgery, electrophysiology, imaging and echocardiography	including clinical genetics, molecular genetics, genetic counselling and inherited cardiac disease	to manage complex polypharmacy and medication-to-medication interactions and side effects	such as neurology, obstetrics, haematology, oncology, nephrology (kidney care), dermatology, opthalmology and gastro-enterology	to provide psychosocial support to people with cardiomyopathy and their families or loved ones

THE IMPORTANCE OF GENETIC COUNSELLING

Genetic counselling is an essential component of cardiomyopathy care. The complexity of genetic test results and their meaning for people with cardiomyopathy requires genetic counselling, which helps people understand and adapt to the implications of their genetic disease (*Table 3*).[52] Although it is not its main goal, genetic counselling can also play a key role in addressing the psychological impact of a diagnosis on families with or at risk of cardiomyopathy. For example, people may experience anxiety and uncertainty surrounding the diagnosis, as well as guilt for passing on the gene to their children.[52 106] Studies show that genetic counselling has psychological benefits, such as increasing perceived personal control and decreasing anxiety.[107]

The use of innovative delivery models could be explored to facilitate the provision of some aspects of genetic counselling. Group genetic counselling can effectively reduce anxiety in people with cardiomyopathy and is well received as a replacement for one-to-one counselling.[108] In Germany, a study showed that providing pre-test genetic counselling via a webinar was as effective as one-to-one counselling for people with cardiomyopathy. Pre-test genetic counselling was also shown to reduce genetic counsellor time and help overcome attendance issues associated with in-person appointments, demonstrating a high quality of care and optimisation of resources.[109] However, it is important to note that while these models help to deliver genetic counselling, they cannot entirely replace tailored counselling and support.[98]

Table 3. The benefits of genetic counselling before and after genetic testing[52 106 110]

Before genetic testing, genetic counselling:
◦ empowers people with cardiomyopathy and families with the necessary information, such as the benefits and limitations of genetic testing
◦ helps establish expectations around genetic testing (including the risk that it does not provide clinically meaningful results), facilitating the decision-making on when or whether genetic testing should take place
◦ helps people with cardiomyopathy understand how useful the information would be for their children and other relatives, and develop a clear plan regarding the involvement of children in the disclosure of results
◦ provides education about the disease (for example, via booklets or meetings for people with cardiomyopathy and their families), addressing any concerns
◦ ensures the appropriate use of genetic tests.
After genetic testing, genetic counselling:
◦ helps families understand the genetic results, addressing any questions and misunderstandings
◦ helps to identify relatives at risk of the disease and develop a communication plan to share the results with them
◦ provides guidance on how to communicate with children, such as sharing information in stages to facilitate understanding.

SHARED DECISION-MAKING

Healthcare professionals must ensure bilateral communication with people with cardiomyopathy. Healthcare professionals should provide sufficient time and space for people with cardiomyopathy, allowing and encouraging them to actively participate in consultations. For example, they can ask open questions to enable the person to talk about their symptoms and experience. Healthcare professionals should listen to and show interest in the subjective experience of the person's cardiomyopathy, their symptoms and disease evolution over time, allowing them to express their doubts and any additional details.[111]

People with cardiomyopathy, and their families and loved ones, should be fully informed about their condition and care. They should be fully informed about their treatment options and the risks involved. For example, they need to understand the benefits of ICD implantation as well as potential device-related complications (such as inappropriate shocks, infections or bleeding).[65] It is essential that healthcare professionals communicate the risks to families and loved ones in a way that is easy to understand.[68] This is particularly important in younger people with cardiomyopathy, who are at a higher risk of having complications and will have the device for a longer period of time.[10] In the case of peripartum cardiomyopathy, people with cardiomyopathy and their partners should receive careful counselling about long-term prognosis and undergo risk stratification if further pregnancies are considered.[112]

Decisions regarding the care for cardiomyopathy should take into account the perspective of the person with the condition. Healthcare professionals should fully acknowledge the current gaps in knowledge and subjectivity of risk assessment for cardiomyopathy.[83] This uncertainty has ethical implications – when setting a threshold for an 'acceptable risk', it must be asked: 'Acceptable to whom?'[83] Decisions regarding treatment should be shared rather than only take into account the healthcare professional's perspective, which is based on measures such as calculated risk or financial costs. Instead, healthcare professionals must take into account the patient's experience of perceived risk and take appropriate measures to resolve disagreements when needed.[83] There is strong evidence that shared decision-making tools help people with cardiomyopathy feel better informed and gain clarity on what is important to them.[84]

NETWORK STATEMENT

This manifesto is a call to action. For too long, cardiomyopathies have been viewed as rare, incurable disorders of peripheral interest to most health systems. As a result, many people receive inadequate care and advice.

In this first step to a better deal for patients and families, ICoN seeks to promote sustainable partnerships that can shape and exploit the exciting possibilities offered by recent developments in science and personalised medicine for the benefit of all.

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In memoriam: Claudio Rapezzi

Professor Claudio Rapezzi, one of the founding members of ICoN, sadly passed away before the publication of this manifesto. Claudio was a man of keen intellect, good humour and kindness, and had been a pillar of the cardiomyopathy community for more than three decades. He made a substantial scientific contribution to the field, but will be most remembered as an inspirational teacher and mentor. This document reflects his lifelong passion to improve the lives of people affected by cardiomyopathy.

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