Protocole National de Diagnostic et de Soins (PNDS)

Laminopathies with cardiac presentation

Center de référence des maladies cardiaques héréditaires ou rares (*cardiomyopathies and rhythm disorders*) Hôpital de la Pitié-Salpêtrière, Paris

Center de référence des maladies neuromusculaires Nord/Est/Ile de France, Hôpital Cochin, Paris

CARDIOGEN national healthcare network

Version of October 21, 2022

Centre de Référence des Maladies Cardiaques Héréditaires ou Rares

cardiogen
filière nationale de santé
maladies cardiaques héréditaires ou rares

Table of contents

Summary for the attending physician

Introduction

Laminopathies are rare genetic disorders caused by mutations in the *LMNA* gene, which encodes two main proteins: lamin A and lamin C. The mode of transmission is almost always autosomal dominant. These proteins play a role in several cellular processes, notably in the formation of a filamentous network lining the inner surface of the cell nucleus. Phenotypic expression varies. Indeed, laminopathies can either affect specific tissues, such as striated skeletal and/or cardiac muscles, peripheral nerves or adipose tissue, or present as a systemic disease concomitantly affecting several organs. Among the various phenotypes, cardiac involvement is one of the most widespread and severe manifestations.

Laminopathy is a relatively rare disease, but it accounts for 5-9% of dilated cardiomyopathies, and clinicians need to be aware of its severe prognosis (justifying early therapeutic management) and genetic nature (requiring organized family management).

Cardiac manifestations

Cardiac damage caused by laminopathies is most often characterized by systolic dysfunction within the framework of dilated cardiomyopathy (DCM), associated with conductive and rhythmic disorders, and is frequently seen in young adults (25-45 years). Rhythmic manifestations most often precede the development of cardiomyopathy, and most often include conduction disorders that may extend to complete atrioventricular block, supraventricular arrhythmias and ventricular arrhythmias, which are associated with an increased risk of sudden cardiac death.

Extracardiac manifestations

Laminopathies can present as predominant or isolated cardiac involvement, but sometimes as multi-system involvement.

Skeletal muscle disorders include limb-girdle muscular dystrophy type 1B (LGMD1B) and Emery Dreifuss muscular dystrophy (EDMD). Metabolic and endocrine disorders are manifested by lipodystrophic syndromes such as Dunnigan's partial familial lipodystrophy (FPLD2). Peripheral neuropathies are expressed in a form of Charcot-Marie-Tooth disease type 2 (CMT2). Acro-mandibular dysplasia and Hutchinson-Gilford progeria (HGPS) are other exceedingly rare manifestations of laminopathy.

Diagnostics

Laminopathy should be suspected in the presence of a cardiological presentation associating dilated cardiomyopathy, conduction disorders, supraventricular or ventricular rhythm disorders, especially in the case of a familial form of cardiac damage or a history of sudden death at a young age in the family. Taken in isolation, these cardiological signs are not specific. Occasionally, the diagnosis may be made as part of a family work-up after the diagnosis has been confirmed in an index case. Suspicion is heightened by associated neuromuscular signs. More rarely, the presentation may be highly atypical, in the context of a very particular form of cardiac involvement (such as left ventricular non-compaction, arrhythmogenic right ventricular cardiomyopathy). Suspicion of laminopathy

should lead to genetic testing, and only the identification of a pathogenic variant of the *LMNA* gene will confirm the diagnosis. In the event of clinical suspicion, a full multidisciplinary medical evaluation is required at a center with expertise in this disease.

Evolution

The expression, severity and evolution of laminopathies with cardiac involvement vary from patient to patient, even within the same family. The disease most often begins between the ages of 25 and 45, but can appear as early as adolescence or as late as 50-60. The main life-threatening cardiovascular complications in patients with laminopathies and cardiac involvement are 1) ventricular rhythm disorders and, to a lesser extent, high-grade conductive disorders responsible for sudden death,
2) heart failure with reduced ejection fraction and 3) stroke, most often complicating atrial rhythm disorders.

Therapeutic management

The management of patients with laminopathies needs to be organized within dedicated expert centers, given its complexity and specific features compared with more common cardiomyopathies.

Pacemaker implantation is based on the usual criteria for the management of conductive disorders. With regard to the risk of ventricular rhythm disorders, the main therapeutic option for preventing sudden death is prophylactic defibrillator implantation (usually endocavitary), based on a risk score and the presence of cardiac damage. It is important to point out that, in the presence of recurrent ventricular rhythm disorders and impaired systolic function, rhythmological management should not delay the possibility of heart transplantation.

Drug therapy for laminopathies with systolic myocardial dysfunction is based on beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers/sacubitril, or gliflozins. Curative anticoagulation is imperative in the case of atrial rhythm disorders, regardless of the CHADS-VASC embolic risk score.

In cases of advanced muscular damage, several treatment options can be implemented in coordination with a multidisciplinary neuromuscular consultation, including motor and respiratory physiotherapy, mechanical aids and surgery for tendon retractions and severe scoliosis.

Follow-up

Carriers of LMNA variants in adulthood are generally advised to undergo cardiological evaluation at least once a year, even if they are asymptomatic and have no previously identified manifestations of the disease (especially from age 30 onwards in the latter case).

The minimum workup to be scheduled for annual assessments includes an ECG, transthoracic echocardiography and Holter ECG. Stress tests are performed every one to two years, and MRIs every 3 to 5 years. The purpose of these examinations is to adapt treatment according to progress.

A more frequent monitoring schedule is indicated for a significant proportion of patients with significant myocardial or rhythmological damage, and should be implemented on a case-by-case basis according to the individual characteristics of each patient.

Close cardiological monitoring is recommended during pregnancy, as it may require adaptation of treatment and modification of delivery methods.

As with any type of cardiomyopathy, competitive or recreational sports must be discussed, supervised and limited, given the high risk of sudden death.

In lipodystrophies associated with pathogenic LMNA variants, appropriate diet and non-intensive exercise should be strongly encouraged for the prevention and treatment of metabolic complications. Regular, moderate physical exercise, after a cardiovascular examination to ensure there are no contraindications, is recommended.

Family surveillance and genetic counseling

All first-degree relatives (parents, siblings, children) should be monitored from the age of 10, due to the hereditary nature of the disease and its often delayed cardiac expression. In addition to the search for symptoms, the work-up includes an ECG, echocardiography and a 24-hour Holter-ECG.

Genetic counseling should be offered to all patients with laminopathies. The aim is to explain the genetic origin of the disease, the mode of transmission (and thus identify relatives at risk), the benefits of family cardiological monitoring, and the possibility of molecular genetic testing. Genetic testing was initially proposed for case-index patients to establish the diagnosis of laminopathy-related heart disease, and predictive genetic testing can then be offered to first-degree relatives to guide cardiological monitoring (continuing it in the presence of the familial mutation, or stopping it in its absence).

Genetic counseling must be given, and genetic testing prescribed, by a physician with expertise in the disease, as part of a multidisciplinary team, including a clinical geneticist (mandatory for prescribing predictive genetic testing for relatives, list of Centers of Reference and Competence in Appendix 3 and on www.filiere-cardiogen.fr).

Action to be taken by the attending physician

If laminopathy is suspected, the attending physician or cardiologist should refer the patient to one of the Cardiogen reference or competence centers.

The role of the attending physician, in coordination with the specialist, is to ensure proper compliance with medication, specialized follow-up and family monitoring. Therapeutic education sessions can be set up to help patients and their families better understand the disease and its treatment, cooperate with caregivers, live as healthily as possible and maintain or improve their quality of life.

List of abbreviations

ANSM	National Agency for the Safety of Medicines and Health Products
AV	Ventricular arrhythmia
AVM	Malignant ventricular arrhythmia
BAV	Atrioventricular block
CMD	Dilated cardiomyopathy
CMNI	Non-ischemic cardiomyopathy
CMT2	Charcot-Marie-Tooth type 2
CPDPN	Multidisciplinary commissions for prenatal diagnosis
CVDA	Arrhythmogenic right ventricular cardiomyopathy
DAI	Automatic implantable defibrillator
DPN	Prenatal diagnosis
DSP	Desmoplakine
ECA	Angiotensin-converting enzyme
ECG	Electrocardiogram
EDMD	Emery-Dreifuss muscular dystrophy
FLNC	Filamine C
HAS	French Health Authority
HGPS	Hutchinson-Gilford progeria
MRI	Magnetic resonance imaging
LGMD1B	Limb-girdle muscular dystrophy type 1B
LMNA	Gene encoding lamins A and C
MAPK	Mitogen-activated protein kinase
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
FPLD2	Dunnigan's partial familial lipodystrophy
PNDS	National diagnosis and care protocol
TVNS	Non-sustained ventricular tachycardia
VG	Left ventricle
VSI	Variant of unknown significance or "unclassified" variant

1. Preamble

1.1 Objectives of the PNDS

The aim of this National Diagnostic and Care Protocol (PNDS) is to explain to the healthcare professionals concerned the optimal diagnostic and therapeutic management and care pathway of a patient suffering from laminopathy with cardiac involvement.

This PNDS covers adult-onset forms of laminopathy, and is limited to forms with cardiac involvement. It has been decided not to include childhood forms of the disease, which fall into very different nosological entities.

It is a pragmatic tool to which the attending physician, in consultation with other specialists, can refer for the management of this disease, particularly when drawing up the care protocol in conjunction with the consulting physician and the patient. The PNDS cannot, however, cover all specific cases, all comorbidities, all therapeutic particularities, hospital care protocols, etc... It cannot claim to be exhaustive in terms of possible management approaches, nor can it replace the individual responsibility of doctors towards their patients. This protocol does, however, reflect the essential structure of management of a patient suffering from laminopathy with cardiac involvement, and will be updated in line with the validation of new data.

1.2 NSDP method

After analysis of the international literature, the PNDS was drawn up following the "Méthode d'élaboration d'un protocole national de diagnostic et de soins pour les maladies rares" published by the Haute Autorité de Santé (HAS) in 2012 (methodological guide available on the HAS website: www.has-sante.fr), and discussed by a multidisciplinary group of experts. The group's proposals were submitted to a review group, which evaluated each of the proposals set out (Appendix 2). The corrected document was discussed and validated by the multidisciplinary group of experts.

In addition, the therapeutic proposals have been reviewed by the French National Agency for the Safety of Medicines and Health Products (ANSM).

1.3 Sales pitch

This document presents the results of the literature review carried out prior to the development of the PNDS for laminopathies with cardiac involvement. It is presented in the form of bibliographic summary tables and written, well-argued summaries.

2. Definition(s), epidemiology

2.1 Definition(s)

Laminopathies are rare genetic disorders caused by mutations in the *LMNA* gene, which encodes two main proteins: lamin A and lamin C. Laminins A and C (laminins A/C) participate in the formation of a filamentous network lining the inner surface of the cell nucleus, necessary for maintaining the structure of this nucleus (Maggi et al., 2016; Charron 2012; Crasto 2021; Wormann, 2007) (Figure 1). These proteins play a role in several cellular processes, and pathogenic *LMNA* gene variants are associated with a wide range of pathological phenotypes, from isolated tissue damage (cardiac or skeletal striated muscle, adipose tissue, peripheral nerve), to multi-systemic damage, which may be part of premature aging syndromes (Carboni et al., 2010). In 1999, *LMNA* gene variants were shown to be responsible for autosomal dominant Emery-Dreifuss muscular dystrophy (EDMD) (Bonne et al., 1999). Shortly afterwards, variants in the same *LMNA* gene were identified in families of patients with dilated cardiomyopathies, conductive disorders and sudden death, without significant skeletal muscle involvement (Fatkin et al., 1999).

Progressively, numerous other phenotypes linked to damage to this gene have been identified, including limb-girdle muscular dystrophy type 1B (LGMD1B), Dunnigan's familial partial lipodystrophy (FPLD2, dedicated PNDS: Vigouroux C et al, 2021), a form of Charcot-Marie-Tooth disease type 2 (CMT2), acromandibular dysplasia (Sakka et al., 2021), or Hutchinson-Gilford progeria (HGPS) (Fatkin et al., 1999; Kovalchuk et al., 2021). Loss of *LMNA* function has been reported as a primary cause of renal disease (Park et al., 2020).

In families with adult-onset cardiac disease, including dilated cardiomyopathy, this cardiac condition is highly penetrant. However, penetrance of cardiac disease in individuals carrying the genetic variants varies with patient age. The overall penetrance of cardiac disease varies from 57% (Pasotti et al., 2008) to 64% (Perrot et al., 2009) depending on the study, and is very high in subjects aged over 35 (between 88% (Pasotti et al., 2008) and 100% (Quarta et al., 2012)). Cardiac involvement can manifest as electrical conduction disorders (atrioventricular block or sinus dysfunction), which may require pacemaker implantation, sometimes as early rhythm disorders (supraventricular or ventricular tachycardia/arrhythmia), and dilated cardiomyopathy (DCM), which often appears secondarily. DCM is classically defined by dilatation of the left ventricle (LV), or both ventricles, associated with systolic dysfunction, in the absence of abnormal loading conditions or coronary artery disease that may be causing the systolic dysfunction (Pinto et al., 2016).

In laminopathies with lipodystrophy (FPLD2) or progeroid syndromes, cardiovascular involvement may manifest as early and severe arteriosclerosis, valvular and/or arterial calcifications and/or CMD. These particular forms of laminopathy are rarely revealed by cardiovascular involvement (Vigouroux et al., PNDS 2021).

2.2 Epidemiology

The most common cardiac condition leading to the diagnosis of laminopathy is dilated cardiomyopathy. An increasing number of patients with CMD, formerly known as "Idiopathic", benefit from exploration by genetic testing (Pinto et al 2016), especially since the recognition of frequent familial forms of CMD, which make up around 20-50% of CMD cases (Pinto et al 2016).

In patients with DCM, the prevalence of pathogenic *LMNA* gene variants ranges from 5% to 9% depending on the study (Parks et al., 2008; Perrot et al., 2009; Taylor et al., 2003; Haas 2015).
In patients with familial CMD, the prevalence of the *LMNA* gene varies from 6% to 28% depending on the study (Parks et al., 2008; Taylor et al., 2003; Perrot et al; 2009; Hasselberg et al., 2018).

The prevalence of the gene in patients associating CMD with conductive disorders (mainly BAV) varies from 33% to 45%, depending on the study (Fatkin et al., 1999; Hasselberg et al., 2018; Skjølsvik et al., 2020).

Pathogenic *LMNA* gene variants are still an under-diagnosed cause of cardiomyopathies and rhythm disorders. In contrast, *LMNA* mutations are rarely the cause of isolated atrial fibrillation (Brauch et al., 2009).

2.3 Pathophysiology

Mutations in the *LMNA* gene are at the root of laminopathies, a group of disorders characterized by phenotypically heterogeneous manifestations.

To date, a total of 623 mutations in the *LMNA* gene have been described and associated with over 15 different phenotypes (Figure 2) (Crasto 2020 & *http://www.umd.be/LMNA* & HGMD-Pro database). Indeed, laminopathies can either affect specific tissues, including skeletal and/or cardiac striated muscle, peripheral nerves or adipose tissue, or present as a systemic disease concomitantly affecting several organs, as in premature aging syndromes. However, there are a growing number of descriptions of overlapping phenotypes, suggesting the presence of a true continuum within the disease (Crasto et al., 2020).
Among the various phenotypes, cardiac involvement is one of the most widespread and severe manifestations.

Cardiac damage is characterized at cellular level by alterations to the nuclear membrane of myocytes, with shape anomalies and dehiscence of cell nuclei (van Berlo et al., 2005, Maggi et al, 2016, Crasto et al, 2020), and histologically by diffuse myocardial fibrosis, sometimes fibrolipid degeneration of the atrioventricular junction and sometimes sub-sarcolemmal glycogen deposits. Some cases of fibro-adipocytic infiltrate similar to arrhythmogenic right ventricular dysplasia have also been described (van Tintelen et al., 2007). Cardiac forms of laminopathy are inherited in an autosomal dominant fashion.

Altered cardiomyocyte development and maturation has been identified as a prenatal feature in a mouse model of laminopathy. These data highlight early epigenetic modifications in lamin A/C-mediated pathology.

and could suggest a new therapeutic perspective for cardiomyopathy (Johnston et al., 2021).

2.4 Distinct phenotypes

Pathogenic variants of the *LMNA* gene can cause a large number of different diseases, which can present in a variety of forms (Captur et al., 2018).

Cardiac damage caused by laminopathies is most often characterized by dilated cardiomyopathy (DCM) associated with conductive disorders and supraventricular and ventricular rhythm disturbances, and is frequently seen in young adults (25-45 years of age). The diagnosis of CMD is usually defined by systolic dysfunction, corresponding to a left ventricular ejection fraction (LVEF) <50%, associated with left ventricular dilatation adjusted for age and body surface area, after exclusion of other usual causes of clinically detectable systolic dysfunction such as coronary artery disease (Jordan et al., 2021; Pinto 2016). In patients with laminopathies, left ventricular dilatation is not always present and patients may have non-dilated hypokinetic cardiomyopathy, with isolated LVEF decrease (Pinto 2016).

Myocardial involvement may present under a different phenotypic aspect. Several cases of arrhythmogenic right ventricular cardiomyopathies related to a variant of the *LMNA* gene have beeń reported with clinical pictures that are rhythmologically, radiologically and histologically close (Quarta et al., 2012; van Tintelen et al., 2007) to those observed in arrhythmogenic right ventricular dysplasias related to mutations in genes encoding desmosomal proteins.

The rhythmic manifestations of these pathologies are frequent, and most often precede the development of cardiomyopathy by an average of ten years (van Berlo et al 2005, Kumar et al 2016) and most often can include conduction disorders that can range from atrioventricular block to atrial palsy (sinus dysfunction), supraventricular arrhythmias (73%) (Taylor et al., 2003), and ventricular arrhythmias which are associated with an increased risk of sudden cardiac death (Kumar, Baldinger, et al., 2016; van Rijsingen et al., 2012).

On the other hand, an increased risk (risk ratio around 5) of arterial and venous thrombosis is also associated with *LMNA* (van Rijsingen, Bakker, et al., 2013). This risk is higher than in patients with other causes of DCM.

The phenotype of arrhythmogenic dilated cardiomyopathy may be observed in patients with purely cardiac laminopathies or associated with other manifestations such as skeletal muscle damage, lipodystrophy, metabolic disorders and/or signs of accelerated aging. Signs of accelerated atheroma or arterial and/or valvular calcification, sometimes extensive and responsible for significant morbidity and mortality, have been reported mainly in lipodystrophic and metabolic forms. Certain forms of FPLD2 or complex phenotypes of laminopathies can sometimes be revealed by cardiovascular involvement (PNDS Dunnigan lipodystrophic syndrome: Mosbah H et al Orphanet J Rare Dis 2022, Treiber G Eur J Endocrinol 2021).

Cardiac expression in children is very rare. It has been described in congenital muscular dystrophies or early forms of Emery Dreyfuss syndrome. In one

series including 3 children, atrial arrhythmia was the mode of cardiac presentation in all three patients. Symptoms of heart failure, including diarrhea and peripheral edema, preceded a rapid decline in left ventricular ejection fraction (Heller et al., 2017).

3. Diagnostic criteria and natural history of the disease

3.1 Introduction to the issues

Laminopathy is suspected in the presence of a cardiological presentation associating several cardiac disorders of varying degrees (dilated cardiomyopathy, conduction disorders, supra-ventricular or ventricular rhythm disorders), sometimes associated with skeletal muscle damage, especially when the subject is a young adult and there is a family background. Cardiological signs are not specific, and the diagnosis of laminopathy can only be made after genetic testing and identification of a pathogenic variant of the *LMNA* gene.

Laminopathy is a relatively rare disease, but one that clinicians should be aware of, as it is associated with a very severe prognosis (justifying early and aggressive therapeutic management) and a genetic disease (leading to organized family management).

3.2 Natural history and cardiac complications

The natural history of cardiac involvement in adult forms of laminopathy has been described in various epidemiological and clinical studies (Kumar, Baldinger, et al., 2016; van Rijsingen et al., 2012).

The main cardiac features were described in the seminal study of CMD and conduction disorders associated with *LMNA* mutations (Fatkin et al., 1999). Of 39 patients with cardiac involvement (mean age at onset: 38 years, extremes 19 to 53 years) from 5 families, 34 patients (87%) had atrioventricular block (AVB) or sinus node dysfunction, 23 (59%) had atrial fibrillation or flutter, and 25 (64%) had DCM (heart transplantation in 6). Of note, 21 patients (54%) were implanted with a pacemaker due to a high-grade conduction defect. In this study, 20 additional relatives were mutation carriers but without cardiac anomalies, all under 30 years of age. In Taylor's series, left ventricular dilatation was more moderate than in other cases of CMD with left ventricular ejection fraction (Taylor et al., 2003).

Clinical features were compiled in a meta-analysis of 299 mutation carriers from families with CMD, EDMD or LGMD1B (van Berlo et al., 2005). Rhythm disorders (supra-ventricular or ventricular arrhythmia) and conduction disorders occurred early in life (including 2 children < 10 years) and were highly penetrant: 74% in 20-30 year-olds, then 92% in patients over 30 (Figure 3). The ECG typically showed low P-wave amplitude, PR interval prolongation and normal QRS duration. A pacemaker was implanted in 3% of patients aged 10-20 years, and then worn in 44% of patients after age 30. Heart failure was reported at older ages, in 10% of patients < 30 years, and progressively increased to 64% of patients over 50 years. Ventricular arrhythmia has been suggested to be fairly common in

this meta-analysis, since almost half of sudden deaths (16 patients or 46%) occurred in patients with pacemakers (van Berlo et al., 2005). Studies on small numbers have observed that ventricular arrhythmia or appropriate defibrillator therapy can occur before myocardial dysfunction/CMD (Hookana 2008; Meune 2006) and sometimes as the first cardiac manifestation before a conduction defect (Fernandez 2008; Ehlermann 2011).

Another multicenter retrospective study involving 122 *LMNA* mutation carriers followed for 7 years found a high incidence of arrhythmic and non-arrhythmic progression and adverse events during long-term follow-up (Kumar S, Baldinger, S et al JACC 2016). The prevalence of clinical events largely increased during follow-up: BAV, 46% to 57%; atrial arrhythmia, 39% to 63%; ventricular arrhythmia, 16% to 34%; and LV systolic dysfunction, 44% to 57%. Implantable automatic defibrillators were placed in 59% of patients. End-stage heart failure developed in 19% of patients, and 13% died (Kumar S et al. 2016). Again, electrical abnormalities with rhythm or conduction disorders often precede myocardial dysfunction.

In patients with laminopathy, the initial presentation of the disease may be a marker of a different natural history. A study of 40 patients with laminopathy observed that patients with an initial neuromuscular presentation had earlier symptoms compared with those with an initial cardiological presentation, developed rhythm disorders (AF and/or flutter: 28 years on average vs. 41 years) earlier and required a pacemaker earlier (30 years vs. 44 years) even though the overall prevalence of these events was similar in both groups (Ditaranto et al., 2019). In this study, however, the overall prevalence of dilated cardiomyopathy and sustained ventricular rhythm disturbances was lower in patients with initial neuromuscular presentation (Ditaranto et al., 2019).

Impaired myocardial contractility is associated with progressive myocardial fibrosis, which is found very early on histology and MRI, even in asymptomatic patients with normal echocardiography (van Tintelen et al., 2007, Alfarih 2019, Ehlermann et al., 2011). Fibrosis of the myocardial septum has been associated with PR interval prolongation and a higher frequency of ventricular arrhythmias. Localized fibrosis in the interventricular septum could be the mechanism behind reduced septal function, atrioventricular block and ventricular arrhythmias in subjects with a Lamin A/C mutation (Hasselberg et al., 2014).

Finally among the cardiovascular complications of laminopathies, one study observed that patients with *LMNA* mutation were independently associated with an increased risk of arterial and venous thromboembolic complication compared to a cohort of patients with idiopathic CMD (van Rijsingen et al., 2013).

Cardiac mortality in laminopathies. In a meta-analysis of 299 *LMNA* mutation carriers, cardiac death was observed in 76 patients (mean age 46), and sudden death was more frequent than death from heart failure (46% of cardiac deaths versus 12% respectively) (van Berlo et al., 2005). Interestingly, the rate of sudden death was similar in patients with an isolated cardiac phenotype and those with a mixed cardiac and skeletal muscle phenotype. A slightly more recent study of a European cohort of 269 carriers of the

LMNA (van Rijsingen et al., 2012) confirmed the high risk of ventricular arrhythmia: 18% of patients developed sudden death, requiring resuscitation or appropriate defibrillator treatment. In patients with an implanted defibrillator at inclusion, the rate of appropriate treatment during follow-up was 13% per year in secondary prevention and 8% per year in primary prevention. Overall, however, cardiac mortality due to sudden death was lower than cardiac death due to heart failure (31% vs. 47% respectively) (van Rijsingen et al., 2012). In the largest cohort of patients with laminopathies assembled to date, Wahbi et al. analyzed 444 patients in the derivation cohort and 145 patients in the validation cohort (Wahbi et al., 2019). During follow-up of 3.6 years and 5.1 years respectively, it was observed that 86 patients (19.3%) and 34 patients (23.4%) experienced severe ventricular arrhythmia, respectively, a rate of 3.9% per year. Events included 31 appropriate defibrillator therapies (36%), 14 sudden cardiac deaths (16%) and 41 (47%) ventricular tachycardias with hemodynamic repercussions (Wahbi et al., 2019).

Prognosis of laminopathies within dilated cardiomyopathies. Other studies have compared the cardiological prognosis of cohorts of patients with dilated cardiomyopathy (DCM) according to underlying causes. In a cohort of 105 patients with DCM, cumulative survival was significantly shorter in *LMNA* mutation carriers than in non-carriers (36). At age 45, 55% of mutation carriers had a cardiovascular death or heart transplant, compared with 11% of non-carriers (p
= 0.0001 for overall comparison of cumulative survival).

In a fairly large recent study of 487 CMD patients (Gigli et al., 2019), a positive genetic test was found in 37% of patients, with a higher percentage (43%) in familial forms. Overall mortality did not differ according to the presence or absence of mutations, although mutation carriers tended to have more heart failure and ventricular arrhythmias. Carriers of *LMNA* gene mutations, and those of desmosome genes, are at highest risk of sudden death and life-threatening ventricular arrhythmias, irrespective of left ventricular ejection fraction.(Gigli et al., 2019). In a meta-analysis of 8,000 patients with CMD (Kayvanpour E et al., 2017), it was found that heart transplantation rates on the one hand, and the rate of sudden death/ventricular rhythm disorders on the other, were highest in *LMNA* mutation carriers compared with other genes, particularly in comparison with sarcomere genes. The overall clinical course of laminopathies is thus characterized by a particularly severe cardiac prognosis.

3.3 Diagnostic criteria

3.3.1 Cardiac and extracardiac factors leading to suspicion of the diagnosis

Laminopathy should be suspected above all in the presence of a cardiological presentation associating, to varying degrees, dilated cardiomyopathy, conduction disorders and supra-ventricular or ventricular rhythm disorders. Taken in isolation, these cardiological signs are not specific. One study evoked a somewhat peculiar ECG with signs of septal remodeling (QRS abnormalities in V1-V3 such as QS aspect or fragmented QRS or low R wave progression) that seems to distinguish *LMNA* gene variant carriers from healthy controls and patients with other causes of cardiomyopathies (L. Ollila et al., 2017). MRI frequently reveals a medio-parietal septal fibrosis pattern that is non-specific

of an *LMNA* mutation but may increase diagnostic suspicion (Alfari 2019, Peretto 2020).
Suspicion will be heightened if associated neuromuscular signs are present (especially if Emery-Dreifuss muscular dystrophy or limb-girdle muscular dystrophy type 1B), but their presence is not essential to suspect the diagnosis. In blood biology, CPK levels are often normal or only moderately increased (Fatkin et al., 1999). Suspicion will also be heightened in young adults and if there is a family background. More rarely, the presentation may be very atypical in the context of a very particular form of cardiac involvement (such as left ventricular non-compaction, arrhythmogenic right ventricular cardiomyopathy) or extra-cardiac laminopathy (such as partial lipodystrophy or progeria) (see section 3.7).

3.3.2 Genetic confirmation of diagnosis

Suspicion of laminopathy should lead to genetic testing, and only identification of a pathogenic variant of the *LMNA* gene will confirm the diagnosis.
Historically, the landmark study by Bonne et al. identified four mutations in the *LMNA* gene in five families with Emery-Dreyfuss myopathy: one nonsense mutation and three missense mutations (1999). These results constitute the first identification of mutations in a component of the nuclear lamina as a cause of hereditary muscle pathology (Bonne G et al., 1999). Shortly afterwards, the study by Fatkin et al. described five missense mutations in 11 families with isolated CMD: four in the alpha-helical stem domain of the lamin A/C gene, and one in the tail domain of lamin C. These mutations were associated with CMD. These mutations were associated with progressive conduction system disease (sinus bradycardia, atrioventricular conduction block or atrial arrhythmias) and dilated cardiomyopathy. None of the mutation carriers suffered from tendon retraction or skeletal muscle deficits at the time. Serum creatine kinase levels were normal in family members with lamin stem mutations, but slightly elevated in some family members with a defect in the lamin C tail domain (Fatkin et al., 1999).

3.3.2.1 LMNA gene (diagnostic value)

The *LMNA* gene is located on chromosome 1q21.2-q21.3, spans approximately 24 kb and is composed of 12 exons that encode, via alternative splicing, four isoforms of so-called A-type lamins (A, AΔ10, C and C2). The 2 major isoforms are lamins A and C (Crasto et al 2020; Charron et al 2012) (Figure 2). Laminins A and C are identical for their first 566 amino acids but differ in their C-terminal domains (Crasto et al 2020; Charron et al 2012). Laminins A and C are expressed in terminally differentiated somatic cells but are absent from early-phase embryos. The A/C lamins then assemble to form polymers which, together with the B-type lamins, constitute the nuclear lamina. One of the functions of lamins is to provide structural support for the nucleus and maintain the mechanical integrity of cells by linking the nucleoskeleton to the cytoskeleton. Other studies also suggest a complex role for lamins in nuclear pore function, chromatin organization, DNA replication and transcriptional regulation (Crasto et al 2020; Charron et al 2012) (Figure 1).

In practice, *LMNA* gene analysis is carried out by sequencing the coding regions (exons and flanking intronic junctions), usually from DNA extracted from a blood sample, either via a targeted analysis of the *LMNA* gene (Sanger technique) in the presence of a strong clinical suspicion of laminopathy, or via an analysis of a panel of genes (high throughput sequencing).

NGS) in the assessment of dilated cardiomyopathy, conduction disorders, rhythm disorders or extracardiac warning signs. The panel typically comprises between 40 and 80 genes.
Identification of a pathogenic variant (CGPA pathogenicity class 5 or 4) (more commonly referred to as a "mutation") enables the diagnosis of laminopathy. This step is therefore essential to the diagnosis. This result may have other very practical clinical implications in the management of the patient and his family, which are discussed below. Genetic testing can also be carried out post-mortem (ideally using fresh frozen tissue, notably spleen or liver) after sudden cardiac death or acute heart failure, with a significant medical impact of the procedure even if cardiomyopathy is suspected at autopsy, as the genetic results provide important additional information useful in the care of relatives (Marey et al., 2020).

We note that the *LMNA* gene is confirmed as having a causal role in CMD following the work of the ClinGen consortium, and is one of 19 genes that have a high level of evidence and are routinely recommended in panels for the genetic evaluation of CMD (Jordan et al., 2021).

Beyond the role of the *LMNA* gene in so-called "monogenic" or Mendelian inherited forms, the *LMNA* gene has also been implicated in common multifactorial forms of dilated heart disease via frequent variants with modest effect (Yin et al., 2015).

3.3.2.2 Variant(s) identified

Within the *LMNA* gene there is a large genetic variability with 623 different pathogenic variants (Crasto et al 2020; and *UMD-LMNA* mutation database, http://www.umd.be/LMNA/; and database HGMD-Pro https://my.qiagendigitalinsights.com/bbp/view/hgmd/pro/all.php).

All types of mutations are reported (Bertrand et al 2011): missense mutation which is the most frequent mechanism (72% of the first 301 published mutations of the *LMNA* gene), insertion/deletion not shifting the reading frame (in-phase) during translation (9%), insertion/deletion shifting the reading frame (out-of-phase) during translation and resulting in the formation of a probable truncated protein (9%), splice consensus site mutations (7%) and direct nonsense mutations corresponding to a stop codon (5%).

Genotype-phenotype relationships are not fully understood, partly due to the limited availability of three-dimensional structure (Scharner et al., 2014). However, mutations affecting tissues other than striated muscle are generally linked to specific amino acid residues or specific exons (Figure 2). In contrast, striated muscle-related mutations (68% are missense mutations) are distributed throughout the gene without clear relationships or hotspots for the different cardiac/skeletal clinical entities. What's more, the three cardiac/skeletal clinical entities (EDMD, CMD with conduction disorders, LGMD1B) can coexist within the same family. Interestingly, analysis of the *UMD-LMNA* database for patients with cardiac laminopathies revealed that 33% of patients with isolated cardiac disease carry mutations potentially leading to truncated proteins (nonsense, out-of-frame ins/del, splice site), whereas only 8% of patients with cardiac/skeletal defects carry this type of mutation (Bertrand et al, 2011).

In common cardiac forms of laminopathy, the mechanism of genetic variants affects the prognosis of cardiac damage with a greater risk of sudden death in the presence of truncating variants compared to missense variants (van Rijsingen et al 2012; Wahbi et al 2019) and this needs to be incorporated into prognostic stratification (see related section).

In a patient with suspected cardiac laminopathy, the presence of an *LMNA* variant previously reported in patients with other laminopathy phenotypes should prompt investigations to be extended to include corresponding metabolic, skeletal muscle and/or progeroid disorders.

Sequence variants that create or eliminate splice sites, but outside the canonical consensus sites, are often classified as variants of unknown significance (VSI) due to the imperfect understanding of their consequence on RNA splicing signals and the cumbersome nature of functional testing. Some authors have developed computational tools to better classify VSIs likely to alter splicing, and used a minigene assay to functionally confirm splicing-altering sequence variants. This strategy can improve the classification of pathogenic variants (Ito et al., 2017). However, it is not applicable to other types of VSI, such as missense variants, in the absence of a dedicated functional assay.

3.3.2.3 Transmission mode

The usual forms of adult cardiac involvement in laminopathies are autosomal dominant, meaning that the variant is found in the heterozygous state (one mutated copy on both copies of the chromosome pair concerned), is usually inherited from one of the two parents, and can be passed on to first-degree relatives with a 50% probability, regardless of male or female sex. Some rare extracardiac forms of laminopathy may be recessively inherited, such as acromandibular dysplasia with lipodystrophy (Sakka 2021; Perrot 2006).

3.3.3 Initial cardiac workup

Objective. The general objectives are to establish the diagnosis of laminopathy-related cardiac damage, rule out differential diagnoses, understand the mechanism of symptoms, assess the severitý of the disease and stratify the prognosis, in order to provide the elements that will enable therapeutic indications to be set.
In addition, patients and their families need to be informed about the natural history of the disease, its possible evolution, its therapeutic management, its mode of transmission, how to monitor relatives and, lastly, about patient associations and ongoing research.

Professionals involved. Initial patient care is multidisciplinary. It is best coordinated by a hospital doctor from an expert center in the network of rare heart disease reference or competence centers. The main medical professionals who interact with the general practitioner are: a cardiologist specialized in heart failure, a rhythmologist, a cardiac imaging specialist, a neurologist specialized in myology, a clinical geneticist, biologists (particularly molecular biologists), and other specialists such as sports physicians, cardio- vascular rehabilitation physicians, obstetrician-gynecologists, cardiac surgeons and pathologists,

the endocrinologist-diabetologist for mixed forms with metabolic impairment. The main paramedical players are the genetic counselor, psychologist and social worker.

Initial cardiological workup.

The clinical examination will mainly look for signs of heart failure, and also for extra-cardiological signs.

The ECG is an important examination, looking for atrioventricular block (especially PR interval measurement), bundle branch block (especially complete LBBB), anterior planing of the R wave, and atrial or ventricular extrasystoles.

Echocardiography is the diagnostic test of choice for dilated cardiomyopathy. It will look for LV systolic dysfunction (LVEF < 50%, global strain abnormality) and LV dilatation, which is itself often less marked or absent in laminopathies than in other causes of DCM (Taylor et al., 2003). Right ventricular dilatation and dysfunction are much less frequent. In some cases, atrial dilatation dominates ventricular dilatation (Marchel, et al., 2021).

In particular, cardiac MRI allows measurement of LV and VD dimensions, volumes, segmental kinetics and EF with high reproducibility. MRI can also be used to characterize myocardial tissue and, in particular, to search for late enhancement (after gadolinium injection), often of septal localization (Alfari 2019, Peretto 2020). The presence of late enhancement is associated with the occurrence of severe ventricular arrhythmias in non-ischemic cardiomyopathies (NICM) in general.
Cardiac imaging in cine-MRI mode can be used to detect early cardiac changes that cannot be detected with conventional echocardiography in *LMNA* mutation carriers (Alfari 2019, Peretto 2020).

Holter-ECG is a major test for detecting conduction disorders (AVB, sinus dysfunction), atrial rhythm disorders and ventricular rhythm disorders (especially unsustained VT bursts).
Exercise testing, often coupled with measurement of maximal oxygen consumption, enables functional capacity to be assessed, as well as a detailed analysis of the cardiac, vascular and extra-cardiovascular factors that may limit it. The test can also be used to detect exercise-induced rhythm disorders.

Invasive hemodynamic exploration by cardiac catheterization is sometimes necessary in patients with heart failure, in order to discuss invasive therapies such as circulatory support or heart transplantation.

In addition to the standard work-up, blood biology should include analysis of natriuretic peptides (such as NT-proBNP), CPK, iron levels in the case of heart failure, and a search for atherosclerotic risk factors (lipid and glycemic work-up). In a small cohort (53 patients), elevated troponins and natriuretic peptides were associated with ventricular arrhythmias (Chmielewski, 2020).

3.3.4 Initial extracardiac workup

In addition to myocardial damage and rhythmological manifestations, *LMNA* gene mutations can be associated with a wide range of pathological phenotypes, including skeletal muscle (limb-girdle muscular dystrophies type 1B and Emery Dreifuss), metabolic and endocrine (lipodystrophic syndromes such as Dunnigan's familial partial lipodystrophy), peripheral neuropathic (Charcot-Marie-Tooth disease type 2), acromandibular dysplasia or progeroid syndromes (Hutchinson-Gilford progeria) (Fatkin et al., 1999; Kovalchuk et al., 2021).
The aim of the initial extracardiac work-up is to look for the presence of these other associated clinical manifestations and, if necessary, to refer patients to a specialist physician for specific management, ideally in a reference center specializing in the management of rare neuromuscular or metabolic diseases (including the PRISIS network).

The extracardiac work-up indicated for all *LMNA* variant carriers, to determine whether there is an indication for referral to a practitioner in a specialty other than cardiology, includes :

- A search for personal or family medical history and/or symptoms that may fit into these nosological frameworks, such as myalgias, muscle-deficit symptoms, history of tendon retractions, atypical diabetes (non-autoimmune diabetes in young, overweight subjects), hypertriglyceridemia, fatty liver, personal or family history of acute pancreatitis, polycystic ovary syndrome in women.
- Clinical examination for skeletal muscle abnormalities, lipodystrophy (low quantity or absence of subcutaneous adipose tissue, either generalized or affecting the limbs in particular, and contrasting with preservation or accumulation of adipose tissue in the face, neck and supra-clavicular regions), *acanthosis nigricans* (thickened, brownish skin in the axillary, cervical and inguinal folds), peripheral neurological damage, dysmorphic signs (premature alopecia, drooping shoulders, scleroderma-like skin, abnormal skin pigmentation), atheromatous manifestations (chest pain, particularly on exertion, vascular murmur, reduced pulse).
- Certain complementary tests should be carried out systematically, such as a CPK assay (part of the first-line work-up for dilated cardiomyopathy), a lipid panel (EAL: lipid anomaly explorations with total cholesterol, HDL-cholesterol, direct LDL-cholesterol, triglycerides), measurement of the liver enzymes ASAT, ALAT, GGT, fasting glycemia.

If there is the slightest suspicion of extra-myocardial involvement, other, more detailed investigations will be carried out, depending on the context (electromyogram, muscle imaging, more complete metabolic work-up with, in particular, if there is no diabetes, an orally induced hyperglycemia (OIGH) with measurement of glycemia and insulinemia at times 0, 30 min, 60 min, 90 min and 120 min after oral intake of 75g glucose, liver ultrasound, screening for atheromatous manifestations, and gynecological consultation in women, and the patient will be referred to a rare neuromuscular or metabolic disease reference center.

3.3.5 Cardiovascular risk stratification strategies

The main life-threatening cardiovascular complications in patients with laminopathies and cardiac involvement are 1) ventricular rhythm disorders and, to a lesser extent, high-grade conductive disorders responsible for sudden death, 2) heart failure with reduced ejection fraction, and 3) stroke, most often complicating atrial rhythm disorders.
Cardiovascular risk stratification studies were essentially developed to assess the risk of sudden death and help select patients who could benefit from ICD implantation in primary prevention. Two strategies have been developed and validated on large cohorts of patients, and are therefore applicable for decision-making in clinical practice. They are detailed in the chapter dedicated to therapeutic aspects. They use the results of simple explorations, theoretically available to any patient as part of routine management: ECG, cardiac echography, Holter ECG and genetic test result (*LMNA* variant type: "false sense" or "other than false sense").

Risk stratification for heart failure relies primarily on close monitoring for early detection of signs of myocardial damage, such as reduced left ventricular ejection fraction, impaired right ventricular systolic function, elevated blood biomarkers of heart failure, and the presence of myocardial fibrosis on MRI. Assessment of the risk of stroke complicating atrial rhythm disorders is based on their systematic investigation by Holter ECG or more prolonged monitoring devices. If a sustained supra-ventricular arrhythmia is identified, curative anticoagulation is systematically initiated, independently of the usual thrombo-embolic risk assessment tools such as the CHADS-VASC score. These points are discussed in detail in the chapter on therapeutics.

3.4 Differential diagnosis

Variants in other genes may be associated with a similar clinical presentation.

- Variants of the EMD gene (on the X chromosome, coding for emerin) are responsible for Emery-Dreifuss muscular dystrophy (EDMD), sometimes with CMD. Atrial arrhythmias are common in patients with muscular dystrophy associated with mutations in the EMD or *LMNA* genes; however, they occur earlier in patients with mutations in the *EMD* gene. Ventricular arrhythmias are very common (60
%) and earlier in the *LMNA* group compared with the *EMD* group (Marchel, et al., 2021). The difference in the frequency of cardiac arrhythmias in the *LMNA* and *EMD* groups indicates the need for accurate genetic diagnosis in patients with muscular dystrophy. On the other hand, atrioventricular conduction abnormalities and/or early onset of atrial arrhythmia may be a red flag to look for laminopathy in young, healthy patients with no known previous neurological diagnosis. Only 35% of EDMD cases are genetically elucidated and associated with mutations in the *EMD* or *LMNA* gene, suggesting the existence of other major genes (Gueneau et al., 2009).
- Mutations in the *FHL1* gene sometimes cause X-linked Emery-Dreifuss muscular dystrophy, but the associated cardiomyopathy is most often hypertrophic cardiomyopathy.
- Mutations in desmoplakin (*DSP*) genes and filamin C null variants (*FLNC*) also lead to arrhythmogenic cardiomyopathy. The phenotype associated with these *DSP/FLNC* mutations on MRI is often characteristic, with a fibrosis-like appearance.

of subepicardial annulus, usually distinguishing them from laminopathies (Augusto et al., 2020). These MRI aspects will be taken into account in future diagnostic criteria for arrhythmogenic left ventricular cardiomyopathy.

3.5 Diagnosis and patient information

It's all about the announcement of chronic heart disease, the possibility of extracardiac involvement (essentially skeletal muscle in the absence of signs pointing to a lipodystrophic or progeroid syndrome), and finally the genetic origin, with the need to offer genetic counseling to the closest relatives. This is a consultation dedicated to a specific time, and must involve a multidisciplinary team, notably cardiology and genetics. The announcement consultation explains the disease and the principles of medical management, the organization of information to relatives, and must provide information or links to relevant patient associations (La ligue contre la cardiomyopathie).

3.6 Genetic counseling / genetic testing and family screening

Genetic counseling has a threefold objective (Charron et al., 2011; Wilde et al., 2022):

- Complete information on the pathology and its cause, particularly in the index case newly diagnosed with laminopathy-related heart disease.
- Help organize cardiology screening for relatives,
- And organize molecular genetic testing of relatives.

3.6.1 Information

The aim of this information is to answer questions from the index case (first patient in the family identified as having laminopathy) or family members, and to inform them about: the genetic origin of the disease; its autosomal dominant mode of transmission (and therefore identification of relatives at risk within the family); the usually delayed cardiac expression (usually starting only in adulthood, often after the age of twenty but sometimes only around 40 to 50), often discreetly earlier in men than in women, and highly variable from one person to another in the family in its chronology or diversity of manifestations; the very rare possibility of incomplete penetrance (i.e., being a carrier of the mutation but not declaring heart disease); if necessary, discuss childbearing and how to monitor a pregnancy and the unborn child. The consultation begins with a review of the family history, including a family tree spanning at least three generations.

It is also an opportunity to **introduce patient associations** (by providing contact details), to provide written material on the disease and its genetic origin, or to give contact details for the network or reference center that has put them online (www.filiere-cardiogen.fr or www.cerefcoeur.fr).

3.6.2 Family cardiology screening

Screening of relatives is essential because of (a) their genetic origin and the risk of transmission, which is 50% in all first-degree relatives, regardless of sex, and (b) the medical implications of early cardiological diagnosis (Charron 2010). Initial cardiological screening of relatives can be carried out in parallel with predictive genetic testing of the relative, or depending on the results of his or her predictive test.

If a relative does not wish to undergo genetic testing despite medical advice, then cardiological screening of at-risk relatives within the family should include, as a minimum, an ECG, echocardiography and 24-hour Holter-ECG. For these common forms of laminopathy with cardiac expression in adults, cardiological screening usually begins at age 10-12, and is repeated (if genetic testing is still not performed) every 2-3 years between ages 10 and 20, then every 2-5 years thereafter, usually up to age 60 (Charron 2010).

By law, **relatives cannot be contacted directly by the medical team** in charge of the *case-index*, but only via the *case-index*, after the latter has been informed of the importance of this approach and his or her responsibility in preventing the disease within the family. A written information sheet (available on the reference center's website) can be handed out, to make it easier to pass on information to the family. Refusal by the index case to inform its family may engage its civil liability under Decree n2013-527 of June 20, 2013. In complex cases, the use of a special partial information procedure may be discussed.

3.6.3 General organization of molecular genetic testing (or prescription procedures)

Under current regulations, genetic testing of a relative is part of a process known as "genetic counseling" (article l 1131-1-2 of the French Public Health Code). Prescribing a genetic test, and the genetic counselling that accompanies it, require special expertise and often special organization in the form of multidisciplinary consultations, involving a range of health professionals trained to deal with the medical and non-medical, particularly psychological, socio-professional and sometimes ethical implications of the genetic test result, while respecting the legislative framework for genetic testing.

In the case of a patient with cardiomyopathy (propositus or index case), the request for genetic testing must be accompanied by informed consent signed by the patient, attestation of this consent by the prescribing clinician, the prescription for the specific genetic test requested, the family tree and the minimum clinical information required for appropriate management by the molecular genetics laboratory, which must itself be certified.

The genetic test must be prescribed for the index case by a doctor with expertise in the field, who will then be able to explain the result and its consequences. Prescription of the predictive (or presymptomatic) test is more restrictive, and must be carried out by doctors working as part of a multidisciplinary team declared as such to the Biomedicine Agency (Decree no. 2008-321 of April 4, 2008 on the examination of a person's genetic characteristics or their identification by genetic fingerprinting for medical purposes).

3.6.4 Genetic screening of relatives and predictive testing

The request concerns a relative who has not yet declared the disease, but who is at risk of declaring it due to the often delayed expression (age-related penetrance), and the involvement is important because the test will guide the monitoring procedures for the relative. Predictive genetic testing (also known as presymptomatic testing) is targeted to search directly for the anomaly.

identified in the index case. It can only be proposed if a pathogenic variant (class 4 or 5) has been identified in the index case. The relative without the familial mutation is reassured and can discontinue specific medical surveillance for laminopathy, whereas the relative with the mutation should benefit from regular cardiological surveillance so that management can be initiated as soon as appropriate (Charron et al., 2011, Wilde et al., 2022).

In the context of these common forms of laminopathy with cardiac expression in adults, systematic genetic screening of first-degree relatives is recommended from the age of 10-12 (or earlier in the case of a proven early form in the family), and concerns all first-degree relatives of the case-index, whatever their sex, in this autosomal dominant disease. 1er degree relatives who do not wish to know their genetic status with regard to the disease must continue to undergo regular cardiological surveillance.

3.6.5 Prenatal and pre-implantation diagnosis

Various options can be discussed in the case of procreation and a couple's wish not to transmit the disease, including that of prenatal diagnosis (PND) or preimplantation diagnosis (Palojoki et al., 2010; Kuliev et al., 2012). PGD is authorized in France for particularly serious and incurable diseases, and is governed by law (Code de la Santé Publique - Article L2131-1). Pluridisciplinary Prenatal Diagnosis Commissions (CPDPN) rarely accept DPN requests from couples for cardiomyopathies, but more readily in cases of myopathy or complex forms of laminopathy. However, after a favorable opinion from the CPDPN, it may be carried out on a case-by-case basis, particularly in particularly severe forms of the disease, on the basis of family history or the presence of mutation(s) known to have deleterious effects. Pre-implantation diagnosis (PGD), as part of medically assisted procreation aimed at selecting and implanting an egg free of the family mutation during *in vitro* fertilization, is subject to the same legislation as PND.

3.7 Special situations

This PNDS focuses on laminopathies with a cardiac presentation, and in particular on forms that usually reveal themselves in adulthood (although they can sometimes affect children from the age of 10, particularly adolescents). Within this framework, there may be special clinical situations due to the type of extracardiac or systemic manifestations observed, or due to atypical features in the cardiac presentation of the disease.

In addition, it is important to note that there are also a number of very specific clinical forms which are not covered in this document, and which are frequently diagnosed in the neonatal period or in childhood (including before the age of 10), such as progerias, restrictive dermopathies or congenital muscular dystrophies.

3.7.1. Special situations due to extracardiac manifestations

Apart from cardiomyopathies, *LMNA* gene mutations may be associated with various extracardiac or systemic phenotypes, including Emery Dreyfuss or limb-girdle muscular dystrophies, Dunnigan-type familial partial lipodystrophy, Hutchinson Gilford syndrome, and autosomal recessive Charcot Marie Tooth type 2 disease, among others (Rankin et al., 2008). In all these clinical forms, cardiomyopathy and electrical damage have been reported to be possible, justifying in principle the initiation of

specific cardiological management. On the other hand, there are no studies to confirm that certain clinical forms are associated, independently of other clinical or genetic characteristics, with a lower or higher cardiac risk of cardiomyopathy.

3.7.2. Special situations with atypical cardiac presentations

Alongside the typical clinical form previously described in this document, characterized by the association of dilated cardiomyopathy with mainly atrioventricular conductive disorders and atrial and/or ventricular rhythm disorders, several other clinical forms have been reported less frequently in laminopathies.
First, there are several other forms of cardiomyopathy associated with *LMNA* variants: left ventricular non-compaction (*LMNA* gene mutations identified in 5% of cases) (Sedaghat-Hamedani et al., 2017; Richard et al. 2019), left ventricular apical aneurysm and ventricular rhythm disorders without initial ventricular dilatation or systolic dysfunction (Forissier et al., 2003), isolated apical left ventricular hypoplasia (Pica et al., 2014), arrhythmogenic right ventricular cardiomyopathy (ARVC).

Around 4% of *LMNA* pathogenic variants have been identified in patients with ARVC of definite or probable diagnosis (Quarta et al., 2012), usually associated with conductive disorders. Thus, the lamin A/C gene is usually associated with genes encoding desmosomal proteins in genetic panels for the assessment of ARVC (Kato et al., 2016).

Moreover, in the context of very specific entities with extracardiac presentation, cardiological involvement has sometimes been described. In particular, lipodystrophic syndromes associated with *LMNA* gene variants are associated with early atheroma, particularly coronary, which justifies systematic screening and management of cardiovascular risk factors, and ischemia testing at the slightest doubt (cf PNDS Dunnigan lipodystrophic syndrome: Mosbah H et al Orphanet J Rare Dis 2022). Progeroid laminopathic syndromes put patients at risk of early and severe atheroma, dilated cardiomyopathy and valvular calcification. Several complex forms of laminopathy associating lipodystrophic, metabolic, progeroid, and/or muscular and cardiac signs have been described (Mosbah H et al Orphanet J Rare Dis 2022; Treiber G Eur J Endocrinol 2021; Araújo-Vilar et al, 2008; Francisco et al, 2017; Marian et al, 2017).

4 Therapeutic management

4.1 Objectives

Therapeutic management aims to improve symptoms, stabilize disease progression, treat and prevent complications, and manage specific situations such as pregnancy.

4.2 Professionals involved (and coordination arrangements)

The management of patients with laminopathies should be organized within dedicated reference centers, given its complexity and specific features compared with cardiomyopathies of other causes. It should involve a cardiology team with specific expertise in cardiomyopathies. Depending on the type of extracardiac manifestations potentially present, patients should also be referred to specific reference centers (neuromuscular, metabolic, etc.).

in particular). Diagnosis and genetic counseling must involve a multidisciplinary team, particularly cardiology and genetics (paragraph 3.5). This specialized care should be organized in conjunction with the patient's GP.

4.3 Therapeutic management

4.3.1 Conduction disorders

Atrioventricular conductive disturbances were reported on ECG in 32 to 57% of patients at mean ages of 40 and 41 years, respectively (Wahbi 2019, Kumar 2016). The risk of progression of these conductive disorders to complete atrioventricular block is high, and has been reported for 15-18% of the total patient population in these same cohorts. The decision to preventively implant a pacemaker is based on the usual criteria for the management of conductive disorders, with no specificity in the context of laminopathies. In a meta-analysis of patients implanted with pacemakers for conductive disorders, a sudden death rate of 11% (10 out of 84 patients) was reported (van Berlo 2005). These sudden deaths in patients with pacemakers are essentially due to ventricular rhythm disorders, and justify the implantation of defibrillators (endocavitary, not subcutaneous) as first-line treatment rather than pacemakers when there is an indication for permanent pacing (Meune et al, 2006).

4.3.2 Atrial rhythm disorders

Atrial fibrillation and flutter are frequent manifestations of laminopathy. They may be present in the early stages of the disease, before the appearance of significant myocardial abnormalities, or in the late stages in the context of heart failure. Whether paroxysmal or permanent forms of arrhythmia, they are associated with a high risk of ischemic stroke and other cardio-embolic complications, necessitating the routine use of curative anticoagulation, irrespective of CHADS-VASC embolic risk score (Atalaia et al., 2021; Kumar, Baldinger, et al., 2016; van Rijsingen, Bakker, et al., 2013). There are no studies comparing sinus rhythm maintenance strategies (cardioversion and/or ablation) versus ventricular rate control. Given the significant risk of onset or deterioration of systolic ventricular function and heart failure in patients with laminopathies, a sinus rhythm maintenance strategy is probably preferable. Ablation procedures for the treatment of atrial fibrillation appear to be associated with lower efficacy than those obtained in the general population, probably even lower in advanced stages of the disease associated with significant atrial electrical remodeling with a diffuse arrhythmogenic substrate. In one of the few series of atrial fibrillation ablation in laminopathies, the risk of early recurrence was high (7 out of 8 cases, mean delay 4 months) (Chauvel, 2021). The use of antiarrhythmic drugs to prevent recurrence should follow the same prescribing rules as in the general population, while respecting the contraindications that left ventricular dysfunction, conductive disorders or ventricular hyperexcitability may represent for certain molecules.

4.3.3 Ventricular rhythm disorder

Preventing sudden death is a major challenge in the management of patients with laminopathies. The main mechanism of sudden death is the onset of ventricular rhythm disorders (tachycardias and ventricular fibrillations), which can occur while the left ventricular ejection fraction is preserved. The main therapeutic option for

to prevent sudden death is the prophylactic implantation of conventional (endocavitary) rather than subcutaneous defibrillators, given the high risk of patients developing high-grade conductive disorders at the same time. Patient selection for ICD implantation in primary prevention should be based on very specific criteria that have been validated in this pathology, and not on the LVEF <35% criterion generally used for dilated cardiomyopathy, which is not sensitive enough. In secondary prevention (recovered cardiac arrest, sustained ventricular rhythm disorders), the indication for an ICD in this condition is clear-cut.

An initial study of 19 patients supported this strategy, showing that systematic implantation of an implantable automatic defibrillator in cases where a pacemaker is indicated for severe conductive disorders (HV>70ms and/or complete BAV and/or severe sinus dysfunction) has the potential to prevent a high number of sudden deaths: over a median follow-up of 34 months, 8 patients (42%) implanted on these criteria received an appropriate internal electric shock (Meune et al., 2006). Another study including 47 patients with conductive disorders (sinus dysfunction, high-grade BAV or association of PR>240ms with left bundle branch block or NSVT) fitted with an ICD showed that 11 patients (52%) received an appropriate internal electric shock over a median follow-up of 62 months (Anselme et al., 2013).

Subsequently, two large-scale studies developed and validated the two strategies currently recommended for selecting patients for ICD implantation in primary prevention. **The first strategy is** based on the search for the following 4 independent risk factors associated with the occurrence of malignant ventricular arrhythmias: male sex, NSVT (non-sustained VT) on Holter ECG, LVEF <45%, nonfalse-sense *LMNA* mutations (van Rijsingen, 2012). It has been shown in a European cohort (269 patients, mean follow-up 43 months) (van Rijsingen, 2012) and secondarily validated in a French cohort (101 patients, follow-up 3.4 years) (Thuillot, 2019) that patients with at least 2 of these risk factors have a sufficiently high risk of event to justify ICD implantation, whereas patients with 0 or 1 risk factor have a low enough risk to be content with cardiological monitoring (van Rijsingen, 2012; Thuillot, 2019). In the external validation study, the C-index was calculated at 0.76 (Thuillot, 2019). The special case of male patients with a non-false-sense mutation should prompt discussion of the indication for an ICD on a case-by-case basis only (depending on the presence of phenotypic expression of the disease at the cardiac level and the quantitative estimate of the level of risk described below) and not systematically, even if they have de facto 2 risk factors present. **The second strategy is** based on the use of modeling with an algorithm to obtain a quantitative estimate of the absolute risk of malignant arrhythmia at 5 years, available via an online calculator (https://LMNA-risk-vta.fr/) by filling in the following items: gender, atrioventricular block (absent, 1er degree, high grade), NSVT (ventricular triplets or beyond, HR ≥120 bpm), LVEF, non-false sense mutation type (Wahbi, 2019). The study was conducted in an initial cohort of 444 patients (C-index 0.77) and replicated in a second population of 145 patients (C index 0.827) (Wahbi, 2019).- The question of the risk threshold for ventricular arrhythmia justifying ICD implantation remains a difficult one, with a threshold of 10% at 5 years often applied by a majority of teams specializing in the management of genetic cardiomyopathies.
In practical terms, it seems reasonable to combine these two approaches to guide the decision to implant an ICD, bearing in mind that a direct comparison of these approaches was carried out and was in favor of a better prediction of events with the quantitative approach using the calculator. Most recently, the ESC 2022 recommendations have

have been published advocating prophylactic implantation of an ICD in laminopathies in the event of a rhythmic risk score ≥10% at 5 years combined with the presence of LV EF <50% or atrioventricular block or VTns (Zeppenfeld K et al., 2022). Finally, the decision to implant an ICD, particularly in a young patient, will have very important implications in terms of follow-up, potential impact on quality of life and ICD-related morbidity, with around 30% of complications (inappropriate shocks, infections, lead breaks) expected at 5 years. It is therefore crucial to take into account the patient's choice, after informing him or her of the risks and benefits. Different wishes may be expressed by patients with the same level of risk, particularly in intermediate-risk situations.

In the presence of recurrent ventricular rhythm disorders, particularly despite antiarrhythmic drug treatment, it may be worth considering proposing an ablation procedure to correct the arrhythmogenic substrate. Arrhythmia is indeed usually due to scar-mediated reentry or branch-to-branch reentry (Kumar et al., 2015). In a multicenter study, the fate of patients with laminopathies and refractory ventricular tachycardia was described (Kumar, Androulakis, et al., 2016), which is often associated with modest ablation efficacy with a high recurrence rate (91%), frequent progression to end-stage heart failure (44%) and high mortality (26%). These disappointing results are probably due to the presence of difficult access to the arrhythmogenic substrate, which can be diffuse, localized at the basal portion of the septum and intramural in location (Hasebe et al 2019). Given the high probability of recurrence of ventricular tachycardia indicating a poor prognosis, Sidhu et al. advise aggressive strategies including amiodarone and management by an expert center accustomed to treating the mid-myocardial substrate by catheter ablation after an episode of ventricular tachycardia (Sidhu et al. 2020).
It is important to point out that, in the presence of recurrent ventricular rhythm disorders with impaired systolic function, rhythmological management should not delay the possibility of heart transplantation.

4.3.4 Cardiomyopathy and heart failure

The management of *LMNA-associated* systolic dysfunction and heart failure should follow the general recommendations for the use of disease-modifying drug therapies that have demonstrated a benefit in terms of morbidity and mortality, such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers/sacubitril, or gliflozins, although the specific efficacy of these treatments in this population is unknown (Chen et al., 2019).

Cardiac resynchronization by multisite pacing can be offered to patients with laminopathies meeting the general population criteria for recommending this treatment (McDonagh, 2021), as a positive response to this treatment has been observed in 38-62% of patients in terms of stabilization of left ventricular ejection fraction and progression of clinical heart failure (Sidhu K, 2022**).**

In the presence of severe heart failure or significant systolic dysfunction (left or right ventricular), and given that progression is often more rapid than for cardiac pathologies of other causes, patients with laminopathies must be rapidly referred to a center with expertise in the management of heart failure, to optimize pharmacological treatment and assess the possible indication for permanent circulatory assistance or transplantation. The aim of rapid referral is to

increase the likelihood of successful management of end-stage heart failure, and limit the risk of serious complications before the project is completed.

4.3.5 Venous thromboembolic complications

The increased risk of venous thromboembolic disease associated with laminopathies that has been observed in some preliminary clinical studies with moderate patient numbers should prompt us to be proactive in terms of venous thromboprophylaxis in primary prevention and should be taken into account in the use of anticoagulants in secondary prevention (van Rijsingen, Bakker, et al., 2013).

4.3.6 Sport restrictions and healthy living

As with any type of cardiomyopathy, and a fortiori when there's a high risk of sustained ventricular rhythm disorders, competitive or recreational sports should be discussed in depth, given the high risk of sudden death.

In the case of laminopathies, there are a number of both experimental and clinical observational data suggesting the deleterious effect of sustained sporting activity over the long term with greater progression of myocardial disease damage. In a mouse model of laminopathy, an earlier development of dilated cardiomyopathy was shown upon exposure to heavy physical activity (Cattin et al., 2016). Competitive sport has also been identified as an independent marker for the occurrence of sudden death or severe events associated with heart failure (Pasotti et al., 2008), and cumulative lifetime physical activity has been independently associated with the development of systolic left ventricular dysfunction and higher NT-proBNP values (Skjølsvik et al., 2020; Tomczak, 2020). In view of these various data, it would seem necessary to contraindicate competitive sport in patients with cardiac expression of laminopathy (especially in cases of CMD or ventricular hyperexcitability) and to recommend restricting sustained physical activities over the long term (especially those with high intensity) (Pelliccia, 2020), while avoiding an excessive sedentary lifestyle, which has a deleterious effect in terms of the progression of heart failure in the general population. In relatives who carry the familial mutation but have not yet developed cardiac expression, competitive sport should be discussed on a case-by-case basis, but is generally not recommended (Pelliccia, 2020).

4.3.7 Extracardiac disorders

In lipodystrophies associated with pathogenic *LMNA* variants, appropriate diet and non-intensive physical exercise must be strongly encouraged for the prevention and treatment of metabolic complications. A balanced diet, adapted to body mass index, limits high-glycemic index sugars and saturated fatty acids as much as possible, and favors complex carbohydrates, fiber and mono- and polyunsaturated fatty acids. Regular physical exercise is recommended, following a cardiovascular examination to ensure there are no contraindications. Metformin can be prescribed as soon as moderate fasting hyperglycemia (> 1g/L) or glucose intolerance to oral hyperglycemia has been diagnosed. Other antidiabetic treatments are frequently used. The LDL-cholesterol target for primary prevention is < 1g/L (2.58 mmol/L) in the absence of diabetes, and < 0.7g/L in the presence of diabetes, which frequently justifies the prescription of statins. Fibrates are also used in cases of hypertriglyceridemia. Contraception must be adapted to the metabolic risk. The frequent co-morbidities associated with insulin resistance (hepatic disease, cardiovascular risk, polycystic ovary syndrome, symptoms of diabetes, etc.) must be taken into account.

(cf. PNDS Dunnigan's lipodystrophic syndrome: Mosbah H et al Orphanet J Rare Dis 2022). The possible use of metreleptin, an orphan leptin analogue, will be discussed on a case-by-case basis at the PRISIS network multidisciplinary consultation meeting.

Patients with suspected lipodystrophy should undergo metabolic investigations, including an OGTT if they do not have diabetes, lipid abnormalities (total cholesterol, HDL-cholesterol, direct LDL-cholesterol, triglycerides), a liver ultrasound, and a gynecological consultation in women (cf. 3.3.4). They should also be screened for muscular damage (myalgia, muscle weakness, tendon retractions). Careful cardiac monitoring is required for all patients with pathogenic *LMNA* variants.

At present, there is no specific treatment to improve amyotrophy and muscle strength degradation. The treatments used are often symptomatic and common to all muscular dystrophies and neuropathies (Atalaia et al., 2021). Myalgia and muscle cramps are treated by analgesic therapy (according to pain intensity, localization, context, associated factors, patient age and comorbidities), decontracting treatments and analgesic massage. In the case of more advanced muscular damage, several treatment options can be implemented in coordination with a neuromuscular multidisciplinary consultation: 1) motor physiotherapy with stretching, massage and gentle muscle strengthening to prevent and stabilize tendon retractions and muscle decline, 2) mechanical aids (canes, orthoses, walkers and wheelchairs) as required to maintain walking for as long as possible, 3) surgery for tendon retractions (especially Achilles) and severe scoliosis, 4) respiratory physiotherapy if necessary, with cough assistance or even non-invasive ventilation.

The use of depolarizing muscle relaxants (succinylcholine) and volatile anesthetics (halothane, isoflurane) should be avoided during surgical procedures when there is obvious muscle damage (theoretical risk of malignant hyperthermia).

In *LMNA-linked* congenital muscular dystrophy, some patients appear to respond dramatically to corticosteroid treatment, with stabilization or even improvement in muscular performance (walking, running, headstand) (unpublished). Further studies are underway to support these preliminary results.

The literature on progeroid syndromes includes two non-randomized, blinded, controlled studies on the use of a farnesyl transferase inhibitor, lonafarnib, either as monotherapy or in combination with pravastatin and zoledronic acid. Results show improvements in weight, vascular rigidity, bone structure and audiological status (and bone density in the combination trial), but little or no effect on survival. Reports on the use of growth hormone (GH) and nutritional measures unfortunately show only a transient benefit (Atalaia et al., 2021). Ambrosi described 7 patients from the same family with limb-girdle muscular dystrophy 1B who underwent heart transplantation (Ambrosi et al., 2009). These patients had no more early or late postoperative complications than other heart transplant recipients.

during an average follow-up of 8 years (from 1 to 17 years). Notably, there were no cases of rhabdomyolysis, and skeletal muscle symptoms were not significantly altered. Mild skeletal muscle involvement is not a contraindication to heart transplantation.

4.3.8 Innovative therapeutic perspectives

New therapeutic approaches are being developed for the treatment of cardiomyopathies associated with laminopathies at more or less advanced stages, both experimental and clinical, and could strengthen the therapeutic arsenal for laminopathies in the years to come.
Some are exploring novel pharmacological approaches aimed primarily at blocking pathophysiological pathways over-expressed in this disease. These include 1) a selective oral inhibitor of the p38 mitogen-activated protein kinase (MAPK) pathway (Wu et al., 2011) which is currently the subject of an international multicenter phase III clinical trial (www.clinicalTrials.gov identifier NCT03439514), 2) 'mTOR pathway inhibitors which have shown improved remodeling and systolic function in mouse models of laminopathy, and 3) PDGFR blockers with the potential to correct certain rhythmic manifestations in in vitro models (Crasto et al., 2020).
Other treatments based on more innovative approaches are currently being studied at pre-clinical stages by academic or private research teams. These approaches are most often "mutation-specific", aiming, for example, to correct the haploinsufficiency associated with certain mutations (gene therapy) or to correct the genetic defect itself in a specific way (gene correction, CrisprCas9). In the long term, they could have the potential to offer truly curative treatments for these patients, particularly if administered at the earliest stages of cardiac involvement in these pathologies. It remains uncertain how long it will be before this type of treatment, with satisfactory efficacy and safety profiles, becomes available in the clinic.

4.3.9 Pregnancy

There is little information on the risk associated with pregnancy in women with *LMNA* gene mutation. A study of a limited number of women (n=5) showed a favorable outcome in the early stages of cardiomyopathy and in the absence of heart failure (Palojoki et al., 2010).
These women were related to patients with overt cardiac disease, and no life-threatening arrhythmias were observed during their pregnancies. In a recent series of 89 pregnant women with *LMNA* gene mutation (Castrini, 2022), new arrhythmias were observed in 9% of cases, but there were no severe maternal or fetal complications, nor was the previous pregnancy history a pejorative factor. Close cardiological monitoring is recommended during pregnancy, including echocardiographic measurements of left ventricular dimensions and ejection fraction, Holter-ECG and measurement of plasma NT-proBNP concentrations. Monitoring intervals depend on the patient's symptoms and clinical manifestations.

4.4 Therapeutic education

The aim of a therapeutic education program is to help patients and their families better understand their disease and treatment, cooperate with their caregivers, live as healthily as possible and maintain or improve their quality of life (WHO).

Patients with laminopathies benefit in particular from FTE adapted to heart failure and defibrillator, depending on the patient.

5 Follow-up

5.1 Objectives

The aim is to regularly monitor the progress of the disease and treatments, so as to periodically adjust the management modalities. This is all the more justified in view of the progressive nature of cardiac damage in laminopathies, and the high incidence of annual complications (particularly malignant arrhythmias, around 4% per year for patients included in the French national registry, hence the need for regular reassessment of the risk of sudden death and the possible indication for implanting an ICD for primary prevention, in order to improve the overall strategy for preventing sudden death).
The frequency and methods of follow-up must take into account the initial workup, the patient's classification (low risk, high risk), the patient's response to the treatments used, and the patient's condition (age, pregnancy, associated pathology or preoperative workup, for example).

5.2 Professionals involved (and coordination arrangements)

Patient follow-up is coordinated, at best, by a hospital doctor from the CMD reference and/or competence center, who is the identified referent for the patient and the treating physician, in close collaboration with the latter.

Other specialists intervene at the request of the doctor in charge (see section 3.3.3 & 3.3.4).

Pacemakers and defibrillators are monitored in a specialized environment. Psychological support is often very useful, due to family and/or personal experience of the disease.

School doctors (personalized schooling project) and occupational physicians can be involved.

5.3 Frequency and content of consultations

Carriers of *LMNA* variants in adulthood are generally advised to undergo cardiological assessment at least once a year, even if they are asymptomatic and have no previously identified manifestations of the disease (in the latter case, the assessment becomes annual, especially from the age of 30 onwards). As explained in the section on genetic diagnosis, for minors who are carriers or at risk of being carriers of *LMNA* variants, follow-up is systematically indicated from the age of 10, even if the penetrance of cardiac damage is lower in this age group than in adults. Follow-up before the age of
18 years can be scheduled at least once a year if phenotypic manifestations are present, and every two years if no phenotype is identified.
A more frequent monitoring schedule is indicated for a significant proportion of patients with significant myocardial or rhythmological damage, and should be implemented on a case-by-case basis according to the individual characteristics of each patient.
Clinical examination should include detailed questioning and a physical examination, particularly to check for heart failure.

5.4 Additional tests (other prescriptions during follow-up)

The cardiological examinations recommended during follow-up are :

- 12-lead ECG ;
- Echocardiography ;
- Exercise test; either alone or coupled with measurement of gas exchange ($_{VO2}$)
- Holter ECG.
- Cardiac MRI
- Blood biology including natriuretic peptide assay.

The minimum workup to be scheduled for annual assessments includes an ECG, transthoracic echocardiography and Holter ECG. An exercise test, either alone or coupled with a VO2 gas exchange measurement, is performed every one to two years, depending on the cardiological assessment. These tests enable us to update our assessment of the risk of ventricular arrhythmia, evaluate myocardial systolic function and look for atrial rhythm disorders and paroxysmal conduction abnormalities. In the presence of proven myocardial or rhythmological abnormalities, these investigations may be repeated more frequently, with the frequency depending on the patient's specific clinical context.

A natriuretic peptide (BNP or NT-proBNP) assay may be considered during follow-up to raise awareness of myocardial damage and guide management of established heart failure. Cardiac MRI may be considered during follow-up to reassess myocardial damage in terms of systolic function (myocardial deformation, ejection fraction), atrial and ventricular remodeling and tissue characterization, including quantification of fibrosis (late enhancement, native T1, ECV). Repeat MRIs can be envisaged at intervals of 3 to 5 years (further apart than simpler investigations such as ECG and ultrasound).

6.figures

Figure 1. schematic presentation of lamin interactions with inner nuclear membrane (INM) proteins and nucleoplasmic proteins (adapted from reference Charron 2012). A/C lamins interact with several transcription factors (c-fos, Rb) and regulate several important signaling pathways such as the Rb/E2F or Rb/MyoD differentiation pathways, the AP-1 and TGFb proliferation pathways. ONM: outer nuclear membrane, BAF: Barrier to Autointegrative Factor, LAP: Lamin Associated Protein, Rb: Retinoblastoma protein, AP-1: Activator Protein 1, TGFb: Transforming Growth Factor b.

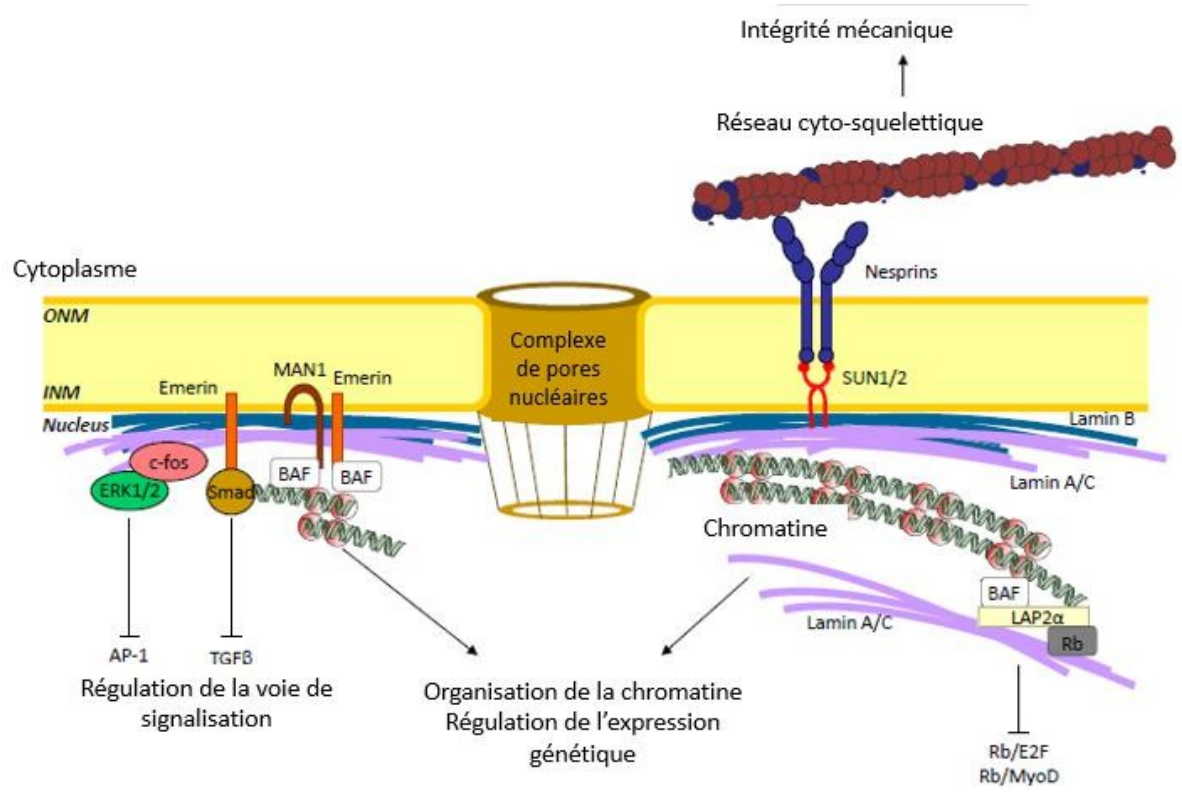


Figure 2. Distribution of *LMNA* mutations in prelamine A and lamin C (adapted from Bertrand et al. 2011) Schematic representation of the *LMNA* gene and its two main isoforms: prelamine A and lamin C. *LMNA* mutations associated with striated muscle are represented by black lines and are located along the molecules. *LMNA* mutations leading specifically to adipose tissue abnormalities are represented by dotted lines and are mainly located in the N- and C-terminal domains, with a hotspot in the Ig-like domain at Arg482. Mutations associated with premature aging syndromes (progeria) are shown in light grey. They are also mainly located in the N- and C-terminal domains, with a hotspot at position 608 and position 527 (acromandibular dysplasia). The position of the single *LMNA* mutation, p.R298C, leading to axonal neuropathy, is also indicated.

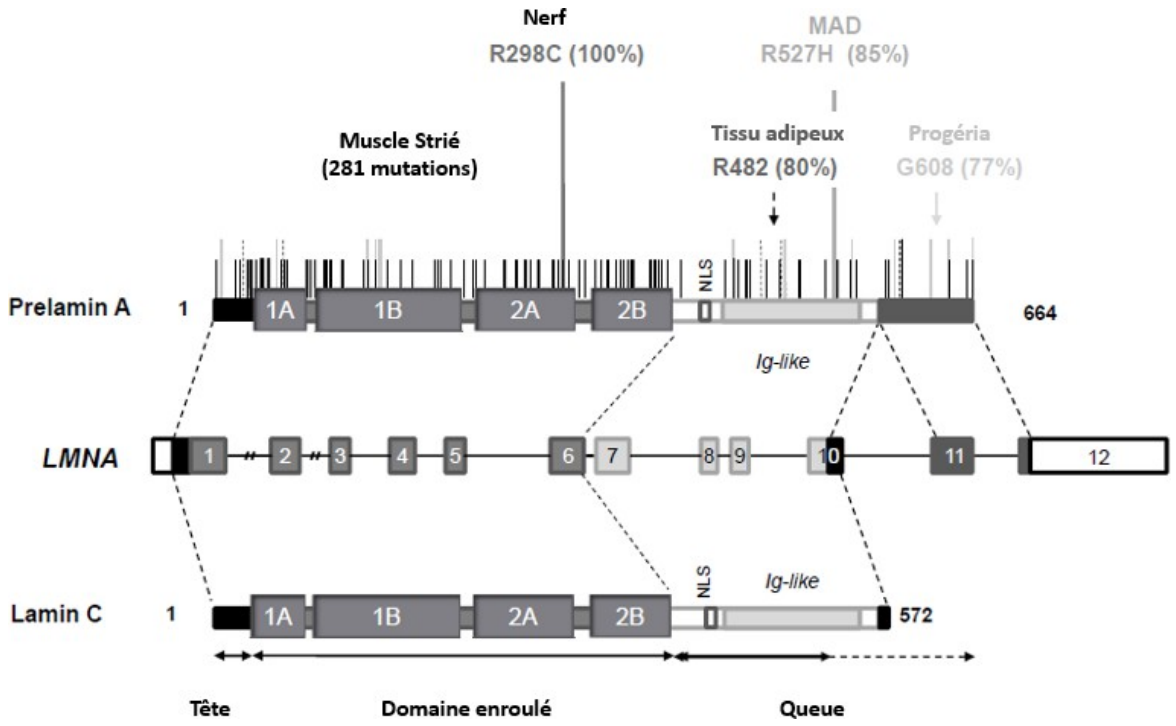


Figure 3. Age-dependent penetrance of a major cardiac event in 299 *LMNA* mutation carriers (from van Berlo et al. 2005) (a) Age-dependent penetrance of rhythm disorders (conduction defect, supraventricular or ventricular arrhythmia) and pacemaker implantation. (b) Age-dependent penetrance of heart failure.

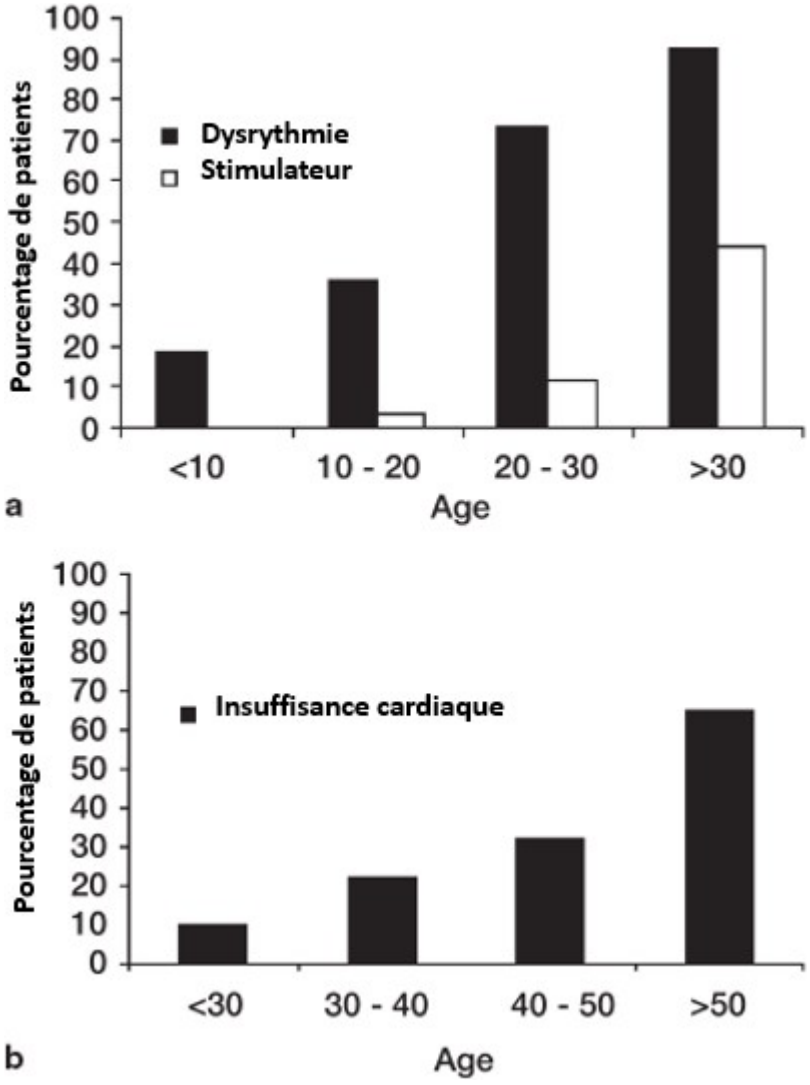
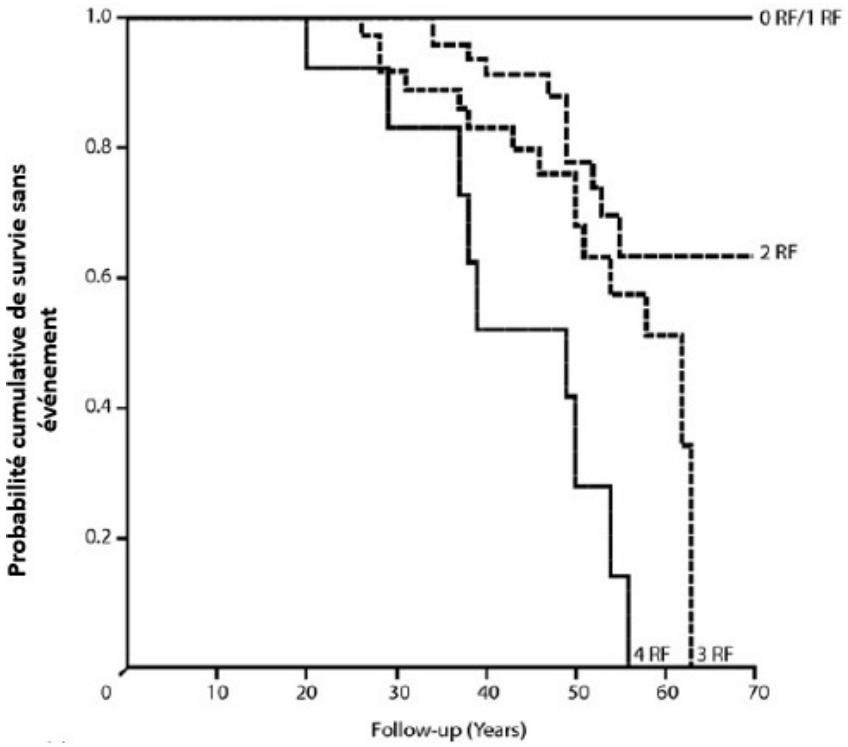


Figure 4. Event-free survival (without malignant ventricular arrhythmia) in 269 *LMNA* mutation carriers (adapted from van Rijsingen, JACC 2012) Kaplan- Meier event-free survival stratified by 4 independent risk factors (RF): nonsustained ventricular tachycardia, left ventricular ejection fraction <45% at first visit to cardiologist, being male and nonfalse-sense mutations (ins-del/troncating or mutations affecting splicing). Event: occurrence of malignant ventricular arrhythmias, defined as appropriate treatment with an automatic implantable defibrillator, cardiopulmonary resuscitation or sudden cardiac death.



7 Care network

Filière nationale de santé CARDIOGEN (hereditary or rare heart diseases):
www.filiere-cardiogen.fr/ & www.filiere-cardiogen.fr/public/annuaire/

Reference and competence center for hereditary or rare cardiomyopathies and cardiac rhythm disorders
www.cerefcoeur.fr

Detailed list of teams in appendix 3.

FILNEMUS national health network (rare neuromuscular diseases) www.filnemus.fr

8 Association network

- French cardiomyopathy patients' association: "la Ligue contre la cardiomyopathie": 6, rue du Houssay, 28800 MONTBOISSIER; tel.: 06 86 41 41 99
  fax: 02 37 47 23 22; ligue-cardiomyopathie@orange.fr

- The French Muscular Dystrophy Association AFM-Téléthon

9 Appendices

Appendix 1 Literature search and article selection

Databases searched : *PubMed, LegiFrance*
Search period: *last 20 years* Languages used:
English
Method and keywords used: *"LMNA, cardiomyopathy, LMNA pathways Lamin A/C, mutation, identification, physiopathology, sudden cardiac death, treatment, child" in the titles and abstracts of the documentary resources.*
Number of references selected:*111*
Article selection criteria: *Relevance according to the expertise of the PNDS coordinators*

Appendix 2 PNDS expert panel

This work was coordinated by :

- *1* Pr Philippe Charron, coordinator of the Reference Centre for Hereditary or Rare Cardiomyopathies and Cardiac Rhythm Disorders, APHP, Hôpital de la Pitié-Salpêtrière, Paris
- *2* Pr Karim Wahbi, Cardiology Department, Reference Centre for Neuromuscular Diseases; APHP, Hôpital Cochin, Paris

Multidisciplinary review group for the PNDS

- *1 Frédéric Sacher,* Centre de référence des maladies rythmiques héréditaires du CHU de Bordeaux (CMARY), Bordeaux
- *2 Estelle Gandjbakhch,* Centre de référence des cardiomyopathies et des troubles du rythme cardiaque héréditaires ou rares, APHP, Hôpital de la Pitié-Salpêtrière, Paris
- *3 Rabah Ben Yaou,* Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Institut de Myologie, Sorbonne Université, Paris, France.
- *4 Corinne Vigouroux,* Centre de référence maladies rares (PRISIS) (Pathologies Rares de l'Insulino-Sécrétion et de l'Insulino-Sensibilité), Hôpital Saint-Antoine, Paris
- *5 Nicolas Piriou,* Université de Nantes, CHU Nantes, Centre National de la Recherche Scientifique, Institut National de la Santé et de la Recherche Médicale, Institut du Thorax, France
- *6 Pascale Richard,* Assistance Publique Hôpitaux de Paris (APHP), Unité Fonctionnelle Cardiogénétique et Myogénétique, Service de Biochimie Métabolique, APHP, Hôpital de la Pitié-Salpêtrière, Paris, France.
- *7 Pierre Sabouret, private cardiologist,*14 Bis Boulevard de l'Hôpital, 75005 Paris
- *8 Gabriel Nemes*, general practitioner, Paris
- *9 "Ligue contre la Cardiomyopathie"* patient association*, Léa de Bellaigue*

Appendix 3 Contact details for reference and competence centers and patient association(s)

Reference centers

First name , Last name	Address	Phone	E-mail
Prof. Philippe CHARRON	Reference center for hereditary or rare cardiomyopathies and cardiac rhythm disorders CRMR coordinator	01 42 16 13 47	philippe.charron@aphp.fr
Prof. Karim WAHBI	Reference center for neuromuscular pathologies Cochin	01 58 41 16 53	Karim.wahbi@aphp.en
Prof. Nicolas MANSENCAL	APHP Ambroise-Paré Centre de reference Paris	01 49 09 56 19	nicolas.mansencal@apr.aphp.fr
Prof. Antoine LEENHARDT	APHP Bichat Constituent reference center Paris	01 49 95 82 06	antoine.leenhardt@aphp.fr
Prof. Albert HAGEGE	APHP HEGP Reference center constitutive Paris	01 56 09 37 13	albert.hagege@aphp.en
Pr Thibaud DAMY	Henri Mondor Reference center constitutive Paris	01 49 81 22 53	thibaud.damy@aphp.en
Prof. Damien BONNET	APHP Necker Constituent reference center Paris	01 44 49 43 40	damien.bonnet@aphp.fr
Prof. Vincent PROBST	Reference center for hereditary or rare cardiac rhythm disorders de l'Ouest, Nantes	02.40.16.57.14	vincent.probst@chu-nantes.fr
Pr SACHER Frédéric	CMARY reference center for hereditary rhythmic diseases of the Bordeaux University Hospital	05 57 65 63 56	cmary@chu-bordeaux.fr
Prof. Philippe CHEVALIER	Reference center for hereditary or rare cardiac rhythm disorders du Sud/Sud-Est , Lyon	04 72 35 76 89	philippe.chevalier@chu-lyon.fr

Competence centers

Region	First name , Last name	Discipline	Address	Phone	E-mail
Brittany	Prof. Jacques MANSOURATI	Cardiomyopathy, Rhythm disorder	Brest University Hospital	02 98 34 73 73	jacques.mansourati@chu-brest.fr
	Pr Erwan DONAL Pr Philippe MABO	Cardiomyopathy, Rhythm disorder	CHU Rennes, Pontchaillou Hospital	02 99 28 37 55	erwan.donal@chu-rennes.fr
Bourgogne Franche Com	Dr Jean-Christophe EICHER Dr Gabriel LAURENT	Cardiomyopathy, Rhythm disorder	Dijon University Hospital, François Mitterrand Hospital, Dijon	03 80 29 35 36	jean-christophe.eicher@chu-dijon.fr
Center - Loire Valley	Prof. Laurent FAUCHIER Prof. Dominique BABUTY	Cardiomyopathy, Rhythm disorder	CHRU TROUSSEAU, Towers	02 47 47 46 50	lfau@med.univ-tours.fr
Great East	Prof. Nicolas SADOUL	Cardiomyopathy, Rhythm disorder	Nancy University Hospital	03 83 15 49 29	n.sadoul@chu-nancy.fr
	Dr François LESAFFRE	Cardiomyopathy, Rhythm disorder	Reims University Hospital, Robert Debré Hospital	03 26 78 90 03	flesaffre@chu-reims.fr
	Dr Elise SCHAEFER	Cardiomyopathy, Rhythm disorder	Hautepierre Hospital, Strasbourg	03 88 12 81 20	elise.schaefer@chru-strasbourg.fr

Hauts de France	Prof. Christophe TRIBOUILLOY	Cardiomyopathy, Rhythm disorder	CHU Amiens-Picardie, Amiens	03 22 08 72 40	tribouilloy.christophe@chu-amiens.fr
	Dr Pascal DE GROOTE Prof. Didier KLUG	Cardiomyopathy, Rhythm disorder	Lille University Hospital, Heart-Lung Institute	03 20 44 57 21	pascal.degroote@chru-lille.fr didier.klug@chru-lille.fr
	Dr Benedicte GODIN, Prof. Frédéric ANSELME	Cardiomyopathy, Rhythm disorder	Rouen University Hospital	02 32 88 81 11	benedicte.godin@chu-rouen.fr federic.anselme@chu-rouen.fr
New Aquitaine	Pr Patricia REANT	Cardiomyopathy	Bordeaux University Hospital, Haut-Lévêque, Pessac	05 57 65 69 69	patricia.reant@chu-bordeaux.fr
	Dr Maxime De GUILLEBON Dr Prune GAILLARD	Rhythm disorder	CH de Pau	05 59 92 48 83	
	Dr Rodrigue GARCIA	Rhythm disorder	Cardiovascular Center Poitiers University Hospital	05 49 44 37 29	
	Dr Alain ALARNAOUT	Rhythm disorder	La Rochelle Hospital	05 46 45 66 41	
Normandy	Dr Marion GERARD	Cardiomyopathy, Rhythm disorder	Caen University Hospital	02 31 27 25 69	gerard-m@chu-caen.fr
Occitanie	Pr François ROUBILLE ; Pr Jean luc PASQUIE	Cardiomyopathy, Rhythm disorder	Montpellier University Hospital, Arnaud de Villeneuve Hospital	04 67 33 61 85, 04 67 33 61 87	f-roubille@chu-montpellier.fr
	Dr Pierre WINUM ; Prof. Patrick MESSNER	Rhythm disorder	Nîmes Carémeau University Hospital, NÎMES	04 66 68 31 15	
	Prof. Philippe MAURY	Cardiomyopathy, Rhythm disorder	TOULOUSE University Hospital, Purpan Hospital	05 61 32 33 16	maury.p@chu-toulouse.fr
Pays de la Loire	Prof. Jean-Noël TROCHU	Cardiomyopathy,	Thorax Institute, Laennec Hospital, Nantes	02 40 16 57 14	jeannoel.trochu@chu-nantes.fr
	Dr Jean Marc DUPUIS	Rhythm disorder	Angers University Hospital	02 41 35 45 47	
Provence Alpes-Côte d'azur	Prof. Gilbert HABIB Prof. Jean-Claude DEHARO	Cardiomyopathy, Rhythm disorder	Marseille University Hospital Timone Hospital	04 91 38 75 88 05 04 91 38 60 93	gilbert.habib@mail.ap-hm.fr
	Dr David BERTORA	Cardiomyopathy,	Nice University	04 92 03 77 33	bertora.d@chu-nice.f

	Dr Guillaume THEODORE	Rhythm disorder	Hospital, Pasteur Hospital	04 92 03 77 33	theodore.g@chu-nice.fr
Rhône-Alpes Auvergne	Pr Antoine Da COSTA	Rhythm disorder	CHU de St-Etienne - Hôpital Nord	04 77 82 86 79	
	Dr Gilles BARONE-ROCHETTE Dr Pascale DEFAYE	Cardiomyopathy, Rhythm disorder	Grenoble Alpes University Hospital, Grenoble	04 76 76 51 72 04 76 76 54 37	GBarone@chu-grenoble.fr PDefaye@chu-grenoble.fr
	Prof. Romain ESCHALIER	Rhythm disorder	CHU Gabriel Montpied Clermont-Ferrand	04 73 75 14 12	
FRENCH OVERSEAS DEPARTMENTS AND TERRITORIES	Dr Laurent LARIFLA	Cardiomyopathy, Rhythm disorder	CHU de la Guadeloupe, Pointe À Pitre	05 90 89 14 20	laurent.larifla@chu-guadeloupe.fr
	Dr Olivier GEOFFROY	Rhythm disorder	Saint-Pierre University Hospital, Reunion Island	02 62 35 91 00	olivier.geoffroy@chu-reunion.fr

Other care providers :

NAME, First name	Address	Phone	E-mail
League against cardiomyopathy: http://www.ligue-cardiomyopathie.com/cardiomyopathie/	6, rue du Houssay, 28800 MONTBOISSIER	06 86 41 41 99	league-cardiomyopathy @orange.fr
French Muscular Dystrophy Association AFM-Téléthon: www.afm-telethon.fr/fr	47 Bd de l'Hôpital, 75013 Paris	0 800 35 36 37	
The association of defibrillator, http://www.apodec.com/	4 Place Louis Armand - 75012 PARIS	07 77 75 67 35	contact@apodec.fr
Filière nationale de santé Cardiogen, hereditary or rare heart diseases: Website: https://www.filiere-cardiogen.fr	CHU Pitié-Salpêtrière-genetics department 47-83 bvd de l'hôpital 75013 PARIS	: 01 42 16 12 88	contact@filiere-cardiogen.fr
Le Centre National de Ressources Psychologiques : Filière Cardiogen psychologist for any questions about psychological support or referrals,	CHU Pitié-Salpêtrière-service de génétique 47-83 bvd de l'hôpital 75013 PARIS	01 42 16 13 62	psychologists@filiere-cardiogen.fr

Appendix 4 Multidisciplinary working group consultation procedures

Meetings by videoconference

Date	Type of meeting	Present	Objectives
June 28, 2021	Videoconferencing	Philippe Charron, Karim Wahbi, Nathalie Baudry, Enguerrand Caley	Framing the project
September 29, 2021	Videoconferencing	Philippe Charron, Karim Wahbi, Nathalie Baudry, Enguerrand Caley	Item selection
November 19, 2021	Videoconferencing	Philippe Charron, Karim Wahbi, Nathalie Baudry, Enguerrand Caley	Item selection
December 17, 2021	Videoconferencing	Philippe Charron, Karim Wahbi, Nathalie Baudry, Enguerrand Caley	Outline of the PNDS text

January 31, 2022	Videoconferencing	Philippe Charron, Karim Wahbi, Nathalie Baudry, Enguerrand Caley	PNDS text discussion
January to October 2022	Regular e-mail exchanges and contacts telephone	Philippe Charron, Karim Wahbi, Nathalie Baudry, Enguerrand Caley	Integration of proofreaders' comments and finalization of various documents

10 References

Alfarih M, Syrris P, Arbustini E, Augusto JB, Hughes A, Lloyd G, Lopes LR, Moon JC, Mohiddin S, Captur G. Familial cardiomyopathy caused by a novel heterozygous mutation in the LMNA gene (c.1434dupG): a cardiac MRI-augmented segregation study. Acta Myol. 2019 Sep 1;38(3):159-162. PMID: 31788659; PMCID: PMC6859410.

Al-Saaidi, R. A., Rasmussen, T. B., Birkler, R. I. D., Palmfeldt, J., Beqqali, A., Pinto, Y. M., Nissen, P. H., Baandrup, U., Mølgaard, H., Hey, T. M., Eiskjaer, H., Bross, P., & Mogensen, J. (2018). The clinical outcome of LMNA missense mutations can be associated with the amount of mutated protein in the nuclear envelope. European Journal of Heart Failure, 20(10), 1404-1412. https://doi.org/10.1002/ejhf.1241

Ambrosi, P., Mouly-Bandini, A., Attarian, S., & Habib, G. (2009). Heart transplantation in 7 patients from a single family with limb-girdle muscular dystrophy caused by lamin A/C mutation. International Journal of Cardiology, 137(3), e75-76. https://doi.org/10.1016/j.ijcard.2009.04.036

Anselme, F., Moubarak, G., Savouré, A., Godin, B., Borz, B., Drouin-Garraud, V., & Gay, A. (2013). Implantable cardioverter-defibrillators in lamin A/C mutation carriers with cardiac conduction disorders. Heart Rhythm, 10(10), 1492-1498. https://doi.org/10.1016/j.hrthm.2013.06.020

Araújo-Vilar, D., Lado-Abeal, J., Palos-Paz, F., Lattanzi, G., Bandín, M. A., Bellido, D., Domínguez-Gerpe, L., Calvo, C., Pérez, O., Ramazanova, A., Martínez-Sánchez, N., Victoria, B., & Costa-Freitas, A. T. (2008). A novel phenotypic expression associated with a new mutation in LMNA gene, characterized by partial lipodystrophy, insulin resistance, aortic stenosis and hypertrophic cardiomyopathy. Clinical Endocrinology, 69(1), 61-68. https://doi.org/10.1111/j.1365-2265.2007.03146.x

Arimura, T., Onoue, K., Takahashi-Tanaka, Y., Ishikawa, T., Kuwahara, M., Setou, M., Shigenobu, S., Yamaguchi, K., Bertrand, A. T., Machida, N., Takayama, K., Fukusato, M., Tanaka, R., Somekawa, S., Nakano, T., Yamane, Y., Kuba, K., Imai, Y., Saito, Y., ... Kimura, A. (2013). Nuclear accumulation of androgen receptor in gender difference of dilated cardiomyopathy due to lamin A/C mutations. Cardiovascular Research, 99(3), 382-394. https://doi.org/10.1093/cvr/cvt106

Atalaia, A., Ben Yaou, R., Wahbi, K., De Sandre-Giovannoli, A., Vigouroux, C., & Bonne, G. (2021). Laminopathies' Treatments Systematic Review: A Contribution Towards a "Treatabolome. Journal of Neuromuscular Diseases, 8(3), 419-439. https://doi.org/10.3233/JND-200596

Augusto, J. B., Eiros, R., Nakou, E., Moura-Ferreira, S., Treibel, T. A., Captur, G., Akhtar, M. M., Protonotarios, A., Gossios, T. D., Savvatis, K., Syrris, P., Mohiddin, S., Moon, J. C., Elliott, P. M., & Lopes, L. R. (2020). Dilated cardiomyopathy and arrhythmogenic left ventricular cardiomyopathy: A comprehensive genotype-imaging phenotype study. European Heart Journal. Cardiovascular Imaging, 21(3), 326-336. https://doi.org/10.1093/ehjci/jez188

Ben Yaou, R., Bécane, H.-M., Demay, L., Laforet, P., Hannequin, D., Bohu, P.-A., Drouin-Garraud, V., Ferrer, X., Mussini, J.-M., Ollagnon, E., Petiot, P., Penisson-Besnier, I., Streichenberger, N., Toutain, A., Richard, P., Eymard, B., & Bonne, G. (2005). [Autosomal dominant limb-girdle muscular dystrophy associated with conduction defects (LGMD1B): A description of 8 new families with the LMNA gene mutations]. Revue Neurologique, 161(1), 42-54. https://doi.org/10.1016/s0035-3787(05)84972-0

Bertrand AT, Chikhaoui K, Ben Yaou RB, Bonne G. Clinical and genetic heterogeneity in laminopathies. Biochem Soc Trans 2011;39:1687-1692.

Brauch, K. M., Chen, L. Y., & Olson, T. M. (2009). Comprehensive mutation scanning of LMNA in 268 patients with lone atrial fibrillation. The American Journal of Cardiology, 103(10), 1426-1428. https://doi.org/10.1016/j.amjcard.2009.01.354

Captur, G., Arbustini, E., Bonne, G., Syrris, P., Mills, K., Wahbi, K., Mohiddin, S. A., McKenna, W. J., Pettit, S., Ho, C. Y., Muchir, A., Gissen, P., Elliott, P. M., & Moon, J.

C. (2018). Lamin and the heart. Heart (British Cardiac Society), 104(6), 468-479. https://doi.org/10.1136/heartjnl-2017-312338

Carboni, N., Mura, M., Marrosu, G., Cocco, E., Marini, S., Solla, E., Mateddu, A., Maioli, M. A., Piras, R., Mallarini, G., Mercuro, G., Porcu, M., & Marrosu, M. G. (2010). Muscle imaging analogies in a cohort of patients with different clinical phenotypes caused by LMNA gene mutations. Muscle & Nerve, 41(4), 458-463. https://doi.org/10.1002/mus.21514

Cattin, M.-E., Ferry, A., Vignaud, A., Mougenot, N., Jacquet, A., Wahbi, K., Bertrand, A. T., & Bonne, G. (2016). Mutation in lamin A/C sensitizes the myocardium to exercise-induced mechanical stress but has no effect on skeletal muscles in mouse. Neuromuscular Disorders: NMD, 26(8), 490-499. https://doi.org/10.1016/j.nmd.2016.05.010

Charron Philippe, Michael Arad, Eloisa Arbustini, Cristina Basso, Zofia Bilinska, Perry Elliott, Tiina Helio, Andre Keren, William J McKenna, Lorenzo Monserrat, Sabine Pankuweit, Andreas Perrot, Claudio Rapezzi, Arsen Ristic, Hubert Seggewiss, Irene van Langen, Luigi Tavazzi. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2010 Nov;31(22):2715-26. doi: 10.1093/eurheartj/ehq271. Epub 2010 Sep 7.

Charron P, Arbustini E, Bonne G. Arrhythm Electrophysiol Rev. 2012 Sep;1(1):22-28. doi: 10.15420/aer.2012.1.22. PMID: 26835025

Chauvel R, Derval N, Duchateau J, Denis A, Tixier R, Welte N, André C, Ramirez FD, Nakashima T, Nakatani Y, Kamakura T, Takagi T, Krisai P, Cheniti G, Vlachos K, Bourier F, Takigawa M, Kitamura T, Sacher F, Hocini M, Jaïs P, Haïssaguerre M, Pambrun T. Persistent atrial fibrillation ablation in cardiac laminopathy: Electrophysiological findings and clinical outcomes. Heart Rhythm. 2021 Jul;18(7):1115-1121. doi: 10.1016/j.hrthm.2021.03.040. Epub 2021 Mar 31. PMID: 33812085

Chen, S. N., Sbaizero, O., Taylor, M. R. G., & Mestroni, L. (2019). Lamin A/C Cardiomyopathy: Implications for Treatment. Current Cardiology Reports, 21(12), 160. https://doi.org/10.1007/s11886-019-1224-7

Chmielewski, P., Michalak, E., Kowalik, I., Franaszczyk, M., Sobieszczanska-Malek, M., Truszkowska, G., Stepien-Wojno, M., Biernacka, E. K., Foss-Nieradko, B., Lewandowski, M., Oreziak, A., Bilinska, M., Kusmierczyk, M., Tesson, F., Grzybowski, J., Zielinski, T., Ploski, R., & Bilinska, Z. T. (2020). Can Circulating Cardiac Biomarkers Be Helpful in the Assessment of LMNA Mutation Carriers? Journal of Clinical Medicine, 9(5), E1443. https://doi.org/10.3390/jcm9051443

Cowan, J., Li, D., Gonzalez-Quintana, J., Morales, A., & Hershberger, R. E. (2010). Morphological analysis of 13 LMNA variants identified in a cohort of 324 unrelated patients with idiopathic or familial dilated cardiomyopathy. Circulation. Cardiovascular Genetics, 3(1), 6-14. https://doi.org/10.1161/CIRCGENETICS.109.905422

Crasto, S., My, I., & Di Pasquale, E. (2020). The Broad Spectrum of LMNA Cardiac Diseases: From Molecular Mechanisms to Clinical Phenotype. Frontiers in Physiology, 11, 761. https://doi.org/10.3389/fphys.2020.00761

Decaudain, A., Vantyghem, M.-C., Guerci, B., Hécart, A.-C., Auclair, M., Reznik, Y., Narbonne, H., Ducluzeau, P.-H., Donadille, B., Lebbé, C., Béréziat, V., Capeau, J., Lascols, O., & Vigouroux, C. (2007). New metabolic phenotypes in laminopathies: LMNA mutations in patients with severe metabolic syndrome. The Journal of Clinical Endocrinology and Metabolism, 92(12), 4835-4844. https://doi.org/10.1210/jc.2007-0654

DeWitt, E. S., Chandler, S. F., Hylind, R. J., Beausejour Ladouceur, V., Blume, E. D., VanderPluym, C., Powell, A. J., Fynn-Thompson, F., Roberts, A. E., Sanders, S. P., Bezzerides, V., Lakdawala, N. K., MacRae, C. A., & Abrams, D. J. (2019). Phenotypic Manifestations of Arrhythmogenic Cardiomyopathy in Children and Adolescents. Journal of the American College of Cardiology, 74(3), 346-358. https://doi.org/10.1016/j.jacc.2019.05.022

Ditaranto, R., Boriani, G., Biffi, M., Lorenzini, M., Graziosi, M., Ziacchi, M., Pasquale, F., Vitale, G., Berardini, A., Rinaldi, R., Lattanzi, G., Potena, L., Martin Suarez, S., Bacchi Reggiani, M. L., Rapezzi, C., & Biagini, E. (2019). Differences in cardiac phenotype and natural history of laminopathies with and without neuromuscular onset. Orphanet Journal of Rare Diseases, 14(1), 263. https://doi.org/10.1186/s13023-019-1245-8

Duparc, A., Cintas, P., Somody, E., Bieth, E., Richard, P., Maury, P., & Delay, M. (2009). A cardio-neurological form of laminopathy: Dilated cardiomyopathy with permanent partial atrial standstill and axonal neuropathy. Pacing and Clinical Electrophysiology: PACE, 32(3), 410-415. https://doi.org/10.1111/j.1540-8159.2008.02254.x

Ehlermann, P., Lehrke, S., Papavassiliu, T., Meder, B., Borggrefe, M., Katus, H. A., & Schimpf, R. (2011). Sudden cardiac death in a patient with lamin A/C mutation in the absence of dilated cardiomyopathy or conduction disease. Clinical Research in Cardiology: Official Journal of the German Cardiac Society, 100(6), 547-551. https://doi.org/10.1007/s00392-011-0289-0

Fatkin, D., MacRae, C., Sasaki, T., Wolff, M. R., Porcu, M., Frenneaux, M., Atherton, J., Vidaillet, H. J., Spudich, S., De Girolami, U., Seidman, J. G., Seidman, C., Muntoni, F., Müehle, G., Johnson, W., & McDonough, B. (1999). Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. The New England Journal of Medicine, 341(23), 1715-1724. https://doi.org/10.1056/NEJM199912023412302

Fernandez X, Dumont CA, Monserrat L, Hermida-Prieto M, Castro-Beiras A. Sudden death in a patient with lamin A/C gene mutation and near normal left ventricular systolic function. Int J Cardiol 2008;126:136-137.

Forissier, J.-F., Bonne, G., Bouchier, C., Duboscq-Bidot, L., Richard, P., Wisnewski, C., Briault, S., Moraine, C., Dubourg, O., Schwartz, K., & Komajda, M. (2003). Apical left ventricular aneurysm without atrio-ventricular block due to a lamin A/C gene mutation. European Journal of Heart Failure, 5(6), 821-825. https://doi.org/10.1016/s1388- 9842(03)00149-1

Francisco, A. R. G., Santos Gonçalves, I., Veiga, F., Mendes Pedro, M., Pinto, F. J., & Brito, D. (2017). Complex phenotype linked to a mutation in exon 11 of the lamin A/C gene: Hypertrophic cardiomyopathy, atrioventricular block, severe dyslipidemia and diabetes. Revista Portuguesa De Cardiologia: Orgao Oficial Da Sociedade Portuguesa De Cardiologia = Portuguese Journal of Cardiology: An Official Journal of the Portuguese Society of Cardiology, 36(9), 669.e1-669.e4. https://doi.org/10.1016/j.repc.2016.07.018

Bonne G, Di Barletta MR, Varnous S, Bécane HM, Hammouda EH, Merlini L, Muntoni F, Greenberg CR, Gary F, Urtizberea JA, Duboc D, Fardeau M, Toniolo D, Schwartz K. (1999). Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. Nature Genetics, 21(3).

Ghosh, S., Renapurkar, R., & Raman, S. V. (2016). Skeletal myopathy in a family with lamin A/C cardiac disease. Cardiovascular Diagnosis and Therapy, 6(5), 417-423. https://doi.org/10.21037/cdt.2016.03.10

Gigli, M., Merlo, M., Graw, S. L., Barbati, G., Rowland, T. J., Slavov, D. B., Stolfo, D., Haywood, M. E., Dal Ferro, M., Altinier, A., Ramani, F., Brun, F., Cocciolo, A., Puggia, I., Morea, G., McKenna, W. J., La Rosa, F. G., Taylor, M. R. G., Sinagra, G., & Mestroni, L. (2019). Genetic Risk of Arrhythmic Phenotypes in Patients With Dilated Cardiomyopathy. Journal of the American College of Cardiology, 74(11), 1480-1490. https://doi.org/10.1016/j.jacc.2019.06.072

Gueneau, L., Bertrand, A. T., Jais, J.-P., Salih, M. A., Stojkovic, T., Wehnert, M., Hoeltzenbein, M., Spuler, S., Saitoh, S., Verschueren, A., Tranchant, C., Beuvin, M., Lacene, E., Romero, N. B., Heath, S., Zelenika, D., Voit, T., Eymard, B., Ben Yaou, R., & Bonne, G. (2009). Mutations of the FHL1 gene cause Emery-Dreifuss muscular dystrophy. American Journal of Human Genetics, 85(3), 338-353. https://doi.org/10.1016/j.ajhg.2009.07.015

Haas J, Frese KS, Peil B, Kloos W, Keller A, Nietsch R, Feng Z, Müller S, Kayvanpour E, Vogel B, Sedaghat-Hamedani F, Lim WK, Zhao X, Fradkin D, Köhler D, Fischer S, Franke J, Marquart S, Barb I, Li DT, Amr A, Ehlermann P, Mereles D, Weis T, Hassel

S, Kremer A, King V, Wirsz E, Isnard R, Komajda M, Serio A, Grasso M, Syrris P, Wicks E, Plagnol V, Lopes L, Gadgaard T, Eiskjær H, Jørgensen M, Garcia-Giustiniani D, Ortiz-Genga M, Crespo-Leiro MG, Deprez RH, Christiaans I, van Rijsingen IA, Wilde AA, Waldenstrom A, Bolognesi M, Bellazzi R, Mörner S, Bermejo JL, Monserrat L, Villard E, Mogensen J, Pinto YM, Charron P, Elliott P, Arbustini E, Katus HA, Meder

B. Atlas of the clinical genetics of human dilated cardiomyopathy. Eur Heart J. 2015 May 7;36(18):1123-35a. doi: 10.1093/eurheartj/ehu301. Epub 2014 Aug27. PMID: 25163546

Hasebe, Y., Fukuda, K., Nakano, M., Kumagai, K., Karibe, A., Fujishima, F., Satake, H., Kondo, M., Wakayama, Y., & Shimokawa, H. (2019). Characteristics of ventricular tachycardia and long-term treatment outcome in patients with dilated cardiomyopathy complicated by lamin A/C gene mutations. Journal of Cardiology, 74(5), 451-459. https://doi.org/10.1016/j.jjcc.2019.03.019

Hasselberg, N. E., Edvardsen, T., Petri, H., Berge, K. E., Leren, T. P., Bundgaard, H., & Haugaa, K. H. (2014). Risk prediction of ventricular arrhythmias and myocardial function in Lamin A/C mutation positive subjects. Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology: Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology, 16(4), 563-571. https://doi.org/10.1093/europace/eut291

Hasselberg, N. E., Haland, T. F., Saberniak, J., Brekke, P. H., Berge, K. E., Leren, T. P., Edvardsen, T., & Haugaa, K. H. (2018). Lamin A/C cardiomyopathy: Young onset, high penetrance, and frequent need for heart transplantation. European Heart Journal, 39(10), 853-860. https://doi.org/10.1093/eurheartj/ehx596

Heller, F., Dabaj, I., Mah, J. K., Bergounioux, J., Essid, A., Bönnemann, C. G., Rutkowski, A., Bonne, G., Quijano-Roy, S., & Wahbi, K. (2017). Cardiac manifestations of congenital LMNA-related muscular dystrophy in children: Three case reports and recommendations for care. Cardiology in the Young, 27(6), 1076-1082. https://doi.org/10.1017/S1047951116002079

Hoorntje, E. T., Bollen, I. A., Barge-Schaapveld, D. Q., van Tienen, F. H., Te Meerman, G. J., Jansweijer, J. A., van Essen, A. J., Volders, P. G., Constantinescu, A. A., van den Akker, P. C., van Spaendonck-Zwarts, K. Y., Oldenburg, R. A., Marcelis, C. L., van der Smagt, J. J., Hennekam, E. A., Vink, A., Bootsma, M., Aten, E., Wilde, A. A., ... van Tintelen, J. P. (2017). Lamin A/C-Related Cardiac Disease: Late Onset With a Variable and Mild Phenotype in a Large Cohort of Patients With the Lamin A/C p.(Arg331Gln) Founder Mutation. Circulation. Cardiovascular Genetics, 10(4), e001631. https://doi.org/10.1161/CIRCGENETICS.116.001631

Hussain, I., Jin, R. R., Baum, H. B. A., Greenfield, J. R., Devery, S., Xing, C., Hegele, R. A., Carranza-Leon, B. G., Linton, M. F., Vuitch, F., Wu, K. H. C., Precioso, D. R., Oshima, J., Agarwal, A. K., & Garg, A. (2020). Multisystem Progeroid Syndrome With Lipodystrophy, Cardiomyopathy, and Nephropathy Due to an LMNA p.R349W Variant. Journal of the Endocrine Society, 4(10), bvaa104. https://doi.org/10.1210/jendso/bvaa104

Ito, K., Patel, P. N., Gorham, J. M., McDonough, B., DePalma, S. R., Adler, E. E., Lam, L., MacRae, C. A., Mohiuddin, S. M., Fatkin, D., Seidman, C. E., & Seidman, J. G. (2017). Identification of pathogenic gene mutations in LMNA and MYBPC3 that alter RNA splicing. Proceedings of the National Academy of Sciences of the United States of America, 114(29), 7689-7694. https://doi.org/10.1073/pnas.1707741114

Johnston, J. R., Selgrade, D. F., & McNally, E. M. (2021). Epigenetic reprogramming to prevent genetic cardiomyopathy. The Journal of Clinical Investigation, 131(1), 143684. https://doi.org/10.1172/JCI143684

Jordan, E., Peterson, L., Ai, T., Asatryan, B., Bronicki, L., Brown, E., Celeghin, R., Edwards, M., Fan, J., Ingles, J., James, C. A., Jarinova, O., Johnson, R., Judge, D. P., Lahrouchi, N., Lekanne Deprez, R. H., Lumbers, R. T., Mazzarotto, F., Medeiros Domingo, A., ... Hershberger, R. E. (2021). Evidence-Based Assessment of Genes in Dilated Cardiomyopathy. Circulation, 144(1), 7-19. https://doi.org/10.1161/CIRCULATIONAHA.120.053033

Kato, K., Takahashi, N., Fujii, Y., Umehara, A., Nishiuchi, S., Makiyama, T., Ohno, S., & Horie, M. (2016). LMNA cardiomyopathy detected in Japanese arrhythmogenic right ventricular cardiomyopathy cohort. Journal of Cardiology, 68(4), 346-351. https://doi.org/10.1016/j.jjcc.2015.10.013

Kayvanpour E, Sedaghat-Hamedani F, Amr A, Lai A, Haas J, Holzer DB, Frese KS, Keller A, Jensen K, Katus HA, Meder B. Genotype-phenotype associations in dilated cardiomyopathy: meta-analysis on more than 8000 individuals. Clin Res Cardiol. 2017 Feb;106(2):127-139. doi: 10.1007/s00392-016-1033-6. Epub 2016 Aug 30. PMID: 27576561

Koikkalainen, J. R., Antila, M., Lötjönen, J. M. P., Heliö, T., Lauerma, K., Kivistö, S. M., Sipola, P., Kaartinen, M. A., Kärkkäinen, S. T. J., Reissell, E., Kuusisto, J., Laakso, M., Oresic, M., Nieminen, M. S., & Peuhkurinen, K. J. (2008). Early familial dilated cardiomyopathy: Identification with determination of disease state parameter from cine MR image data. Radiology, 249(1), 88-96. https://doi.org/10.1148/radiol.2491071584

Kovalchuk, T., Yakovleva, E., Fetisova, S., Vershinina, T., Lebedeva, V., Lyubimtseva, T., Lebedev, D., Mitrofanova, L., Ryzhkov, A., Sokolnikova, P., Fomicheva, Y., Kozyreva, A., Zhuk, S., Smolina, N., Zlotina, A., Pervunina, T., Kostareva, A., & Vasichkina, E. (2021). Case Reports: Emery-Dreifuss Muscular Dystrophy Presenting as a Heart Rhythm Disorders in Children. Frontiers in Cardiovascular Medicine, 8, 668231. https://doi.org/10.3389/fcvm.2021.668231

Kuliev A, Pomerantseva E, Polling D, Verlinsky O, Rechitsky S. PGD for inherited cardiac diseases. Reprod Biomed Online. 2012 Apr;24(4):443-53. doi: 10.1016/j.rbmo.2011.12.009. Epub 2012 Jan 8. PMID: 22386593.

Kumar, S., Androulakis, A. F. A., Sellal, J.-M., Maury, P., Gandjbakhch, E., Waintraub, X., Rollin, A., Richard, P., Charron, P., Baldinger, S. H., Macintyre, C. J., Koplan, B. A., John, R. M., Michaud, G. F., Zeppenfeld, K., Sacher, F., Lakdawala, N. K., Stevenson, W. G., & Tedrow, U. B. (2016). Multicenter Experience With Catheter Ablation for Ventricular Tachycardia in Lamin A/C Cardiomyopathy. Circulation. Arrhythmia and Electrophysiology, 9(8), e004357. https://doi.org/10.1161/CIRCEP.116.004357

Kumar, S., Baldinger, S. H., Gandjbakhch, E., Maury, P., Sellal, J.-M., Androulakis, A. F. A., Waintraub, X., Charron, P., Rollin, A., Richard, P., Stevenson, W. G., Macintyre, C. J., Ho, C. Y., Thompson, T., Vohra, J. K., Kalman, J. M., Zeppenfeld, K., Sacher, F., Tedrow, U. B., & Lakdawala, N. K. (2016). Long-Term Arrhythmic and Nonarrhythmic Outcomes of Lamin A/C Mutation Carriers. Journal of the American College of Cardiology, 68(21), 2299-2307. https://doi.org/10.1016/j.jacc.2016.08.058

Kumar, S., Stevenson, W. G., & John, R. M. (2015). Arrhythmias in dilated cardiomyopathy. Cardiac Electrophysiology Clinics, 7(2), 221-233. https://doi.org/10.1016/j.ccep.2015.03.005

Liu, N., Zheng, M., Li, S., Bai, H., Liu, Z., Hou, C. H., Zhang, S., & Pu, J. (2017). Genetic Mechanisms Contribute to the Development of Heart Failure in Patients with Atrioventricular Block and Right Ventricular Apical Pacing. Scientific Reports, 7(1), 10676. https://doi.org/10.1038/s41598-017-11211-2

Maggi, L., Carboni, N., & Bernasconi, P. (2016). Skeletal Muscle Laminopathies: A Review of Clinical and Molecular Features. Cells, 5(3), E33. https://doi.org/10.3390/cells5030033

Magno, S., Ceccarini, G., Pelosini, C., Ferrari, F., Prodam, F., Gilio, D., Maffei, M., Sessa, M. R., Barison, A., Ciccarone, A., Emdin, M., Aimaretti, G., & Santini, F. (2020). Atypical Progeroid Syndrome and Partial Lipodystrophy Due to LMNA Gene p.R349W Mutation. Journal of the Endocrine Society, 4(10), bvaa108. https://doi.org/10.1210/jendso/bvaa108

Marchel, M., Madej-Pilarczyk, A., Tymińska, A., Steckiewicz, R., Kochanowski, J., Wysińska, J., Ostrowska, E., Balsam, P., Grabowski, M., & Opolski, G. (2021). Echocardiographic Features of Cardiomyopathy in Emery-Dreifuss Muscular Dystrophy. Cardiology Research and Practice, 2021, 8812044. https://doi.org/10.1155/2021/8812044

Marchel, M., Madej-Pilarczyk, A., Tymińska, A., Steckiewicz, R., Ostrowska, E., Wysińska, J., Russo, V., Grabowski, M., & Opolski, G. (2021). Cardiac Arrhythmias in Muscular Dystrophies Associated with Emerinopathy and Laminopathy: A Cohort Study. Journal of Clinical Medicine, 10(4), 732. https://doi.org/10.3390/jcm10040732

Marey, I., Fressart, V., Rambaud, C., Fornes, P., Martin, L., Grotto, S., Alembik, Y., Gorka, H., Millat, G., Gandjbakhch, E., Bordet, C., de la Grandmaison, G. L., Richard, P., & Charron, P. (2020). Clinical impact of post-mortem genetic testing in cardiac death and cardiomyopathy. Open Medicine (Warsaw, Poland), 15(1), 435-446. https://doi.org/10.1515/med-2020-0150

Marian, A. J. (2017). Non-syndromic cardiac progeria in a patient with the rare pathogenic p.Asp300Asn variant in the LMNA gene. BMC Medical Genetics, 18(1), 116. https://doi.org/10.1186/s12881-017-0480-x

McDonagh Theresa A, Marco Metra, Marianna Adamo, Roy S Gardner, Andreas Baumbach, Michael Böhm, Haran Burri, Javed Butler, Jelena Čelutkienė, Ovidiu Chioncel, John G F Cleland, Andrew J S Coats, Maria G Crespo-Leiro, Dimitrios Farmakis, Martine Gilard, Stephane Heymans, Arno W Hoes, Tiny Jaarsma, Ewa A Jankowska, Mitja Lainscak, Carolyn S P Lam, Alexander R Lyon, John J V

McMurray, Alexandre Mebazaa, Richard Mindham, Claudio Muneretto, Massimo Francesco Piepoli, Susanna Price, Giuseppe M C Rosano, Frank Ruschitzka, Anne Kathrine Skibelund, 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J . 2021 Sep 21;42(36):3599-3726. PMID: 34447992

McPherson, E., Turner, L., Zador, I., Reynolds, K., Macgregor, D., & Giampietro, P. F. (2009). Ovarian failure and dilated cardiomyopathy due to a novel lamin mutation. American Journal of Medical Genetics. Part A, 149A(4), 567-572. https://doi.org/10.1002/ajmg.a.32627

Meune, C., Van Berlo, J. H., Anselme, F., Bonne, G., Pinto, Y. M., & Duboc, D. (2006). Primary prevention of sudden death in patients with lamin A/C gene mutations. The New England Journal of Medicine, 354(2), 209-210. https://doi.org/10.1056/NEJMc052632

Mosbah H, Donadille B, Vatier C, Janmaat S, Atlan M, Badens C, Barat P, Béliard S, Beltrand J, Ben Yaou R, Bismuth E, Boccara F, Cariou B, Chaouat M, Charriot G, Christin- Maitre S, De Kerdanet M, Delemer B, Disse E, Dubois N, Eymard B, Fève B, Lascols O, Mathurin P, Nobécourt E, Poujol-Robert A, Prevost G, Richard P, Sellam J, Tauveron I, Treboz D, Vergès B, Vermot-Desroches V, Wahbi K, Jéru I, Vantyghem MC, Vigouroux C. Dunnigan lipodystrophy syndrome: French National Diagnosis and Care Protocol (PNDS). Orphanet J Rare Dis. 2022 Apr 19;17(Suppl 1):170. doi: 10.1186/s13023-022-02308-7. PMID: 35440056; PMCID: PMC9019936.

Nishiuchi, S., Makiyama, T., Aiba, T., Nakajima, K., Hirose, S., Kohjitani, H., Yamamoto, Y., Harita, T., Hayano, M., Wuriyanghai, Y., Chen, J., Sasaki, K., Yagihara, N., Ishikawa, T., Onoue, K., Murakoshi, N., Watanabe, I., Ohkubo, K., Watanabe, H., ... Kimura, T. (2017). Gene-Based Risk Stratification for Cardiac Disorders in LMNA Mutation Carriers. Circulation. Cardiovascular Genetics, 10(6), e001603. https://doi.org/10.1161/CIRCGENETICS.116.001603

Olde Nordkamp, L. R. A., Postema, P. G., Knops, R. E., van Dijk, N., Limpens, J., Wilde, A. A. M., & de Groot, J. R. (2016). Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: A systematic review and meta-analysis of inappropriate shocks and complications. Heart Rhythm, 13(2), 443-454. https://doi.org/10.1016/j.hrthm.2015.09.010

Ollila, L. H., Nikus, K., Parikka, H., Weckström, S., & Helio T. (2021). Timing of pacemaker and ICD implantation in LMNA mutation carriers. Open Heart, 8(1), e001622. https://doi.org/10.1136/openhrt-2021-001622

Ollila, L., Nikus, K., Holmström, M., Jalanko, M., Jurkko, R., Kaartinen, M., Koskenvuo, J., Kuusisto, J., Kärkkäinen, S., Palojoki, E., Reissell, E., Piirilä, P., & Heliö, T. (2017). Clinical disease presentation and ECG characteristics of LMNA mutation carriers. Open Heart, 4(1), e000474. https://doi.org/10.1136/openhrt-2016-000474

Otomo, J., Kure, S., Shiba, T., Karibe, A., Shinozaki, T., Yagi, T., Naganuma, H., Tezuka, F., Miura, M., Ito, M., Watanabe, J., Matsubara, Y., & Shirato, K. (2005). Electrophysiological and histopathological characteristics of progressive atrioventricular block accompanied by familial dilated cardiomyopathy caused by a

novel mutation of lamin A/C gene. Journal of Cardiovascular Electrophysiology, 16(2), 137-145. https://doi.org/10.1046/j.1540-8167.2004.40096.x

Palojoki, E., Kaartinen, M., Kaaja, R., Reissell, E., Kärkkäinen, S., Kuusisto, J., & Heliö, T. (2010). Pregnancy and childbirth in carriers of the lamin A/C-gene mutation. European Journal of Heart Failure, 12(6), 630-633. https://doi.org/10.1093/eurjhf/hfq059

Parent, J. J., Towbin, J. A., & Jefferies, J. L. (2015). Left ventricular noncompaction in a family with lamin A/C gene mutation. Texas Heart Institute Journal, 42(1), 73-76. https://doi.org/10.14503/THIJ-13-3843

Park, J., Levin, M. G., Haggerty, C. M., Hartzel, D. N., Judy, R., Kember, R. L., Reza, N., Regeneron Genetics Center, Ritchie, M. D., Owens, A. T., Damrauer, S. M., & Rader, D. J. (2020). A genome-first approach to aggregating rare genetic variants in LMNA for association with electronic health record phenotypes. Genetics in Medicine: Official Journal of the American College of Medical Genetics, 22(1), 102-111. https://doi.org/10.1038/s41436-019-0625-8

Parks, S. B., Kushner, J. D., Nauman, D., Burgess, D., Ludwigsen, S., Peterson, A., Li, D., Jakobs, P., Litt, M., Porter, C. B., Rahko, P. S., & Hershberger, R. E. (2008). Lamin A/C mutation analysis in a cohort of 324 unrelated patients with idiopathic or familial dilated cardiomyopathy. American Heart Journal, 156(1), 161-169. https://doi.org/10.1016/j.ahj.2008.01.026

Pasotti, M., Klersy, C., Pilotto, A., Marziliano, N., Rapezzi, C., Serio, A., Mannarino, S., Gambarin, F., Favalli, V., Grasso, M., Agozzino, M., Campana, C., Gavazzi, A., Febo, O., Marini, M., Landolina, M., Mortara, A., Piccolo, G., Viganò, M., ... Arbustini, E. (2008). Long-term outcome and risk stratification in dilated cardiolaminopathies. Journal of the American College of Cardiology, 52(15), 1250-1260. https://doi.org/10.1016/j.jacc.2008.06.044

Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, Collet JP, Corrado D, Drezner JA, Halle M, Hansen D, Heidbuchel H, Myers J, Niebauer J, Papadakis M, Piepoli MF, Prescott E, Roos-Hesselink JW, Graham Stuart A, Taylor RS, Thompson PD, Tiberi M, Vanhees L, Wilhelm M; ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. Eur Heart J. 2021 Jan 1;42(1):17-96. doi: 10.1093/eurheartj/ehaa605. PMID: 32860412

Peretto, G., Di Resta, C., Perversi, J., Forleo, C., Maggi, L., Politano, L., Barison, A., Previtali, S. C., Carboni, N., Brun, F., Pegoraro, E., D'Amico, A., Rodolico, C., Magri, F., Manzi, R. C., Palladino, A., Isola, F., Gigli, L., Mongini, T. E., ... Italian Network for Laminopathies (NIL). (2019). Cardiac and Neuromuscular Features of Patients With LMNA-Related Cardiomyopathy. Annals of Internal Medicine, 171(7), 458-463. https://doi.org/10.7326/M18-2768

Peretto, G., Sala, S., Lazzeroni, D., Palmisano, A., Gigli, L., Esposito, A., De Cobelli, F., Camici, P. G., Mazzone, P., Basso, C., & Della Bella, P. (2020). Septal Late Gadolinium Enhancement and Arrhythmic Risk in Genetic and Acquired Non-Ischaemic Cardiomyopathies. Heart, Lung & Circulation, 29(9), 1356-1365. https://doi.org/10.1016/j.hlc.2019.08.018

Perrot, A., Hussein, S., Ruppert, V., Schmidt, H. H. J., Wehnert, M. S., Duong, N. T., Posch, M. G., Panek, A., Dietz, R., Kindermann, I., Böhm, M., Michalewska-Wludarczyk, A., Richter, A., Maisch, B., Pankuweit, S., & Ozcelik, C. (2009). Identification of mutational hot spots in LMNA encoding lamin A/C in patients with familial dilated cardiomyopathy. Basic Research in Cardiology, 104(1), 90-99. https://doi.org/10.1007/s00395-008-0748-6

Perrot, A., Sigusch, H. H., Nägele, H., Genschel, J., Lehmkuhl, H., Hetzer, R., Geier, C., Leon Perez, V., Reinhard, D., Dietz, R., Josef Osterziel, K., & Schmidt, H. H.-J. (2006). Genetic and phenotypic analysis of dilated cardiomyopathy with conduction system disease: Demand for strategies in the management of presymptomatic lamin A/C mutant carriers. European Journal of Heart Failure, 8(5), 484-493. https://doi.org/10.1016/j.ejheart.2005.11.004

Pica, S., Ghio, S., Raineri, C., Scelsi, L., Turco, A., & Visconti, L. O. (2014). [Mutation of the lamin A/C gene associated with left ventricular apical hypoplasia: A new phenotype for laminopathies?]. Giornale Italiano Di Cardiologia (2006), 15(12), 717-719. https://doi.org/10.1714/1718.18778

Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M, Duboc D, Gimeno J, de Groote P, Imazio M, Heymans S, Klingel K, Komajda M, Limongelli G, Linhart A, Mogensen J, Moon J, Pieper PG, Seferovic PM, Schueler S, Zamorano JL, Caforio AL, Charron P. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases.Eur Heart
J. 2016 Jun 14;37(23):1850-8. doi: 10.1093/eurheartj/ehv727. Epub 2016 Jan 19. PMID: 26792875

Quarta, G., Syrris, P., Ashworth, M., Jenkins, S., Zuborne Alapi, K., Morgan, J., Muir, A., Pantazis, A., McKenna, W. J., & Elliott, P. M. (2012). Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy. European Heart Journal, 33(9), 1128-1136. https://doi.org/10.1093/eurheartj/ehr451

Raman, S. V., Sparks, E. A., Baker, P. M., McCarthy, B., & Wooley, C. F. (2007). Mid-myocardial fibrosis by cardiac magnetic resonance in patients with lamin A/C cardiomyopathy: Possible substrate for diastolic dysfunction. Journal of Cardiovascular Magnetic Resonance: Official Journal of the Society for Cardiovascular Magnetic Resonance, 9(6), 907-913. https://doi.org/10.1080/10976640701693733

Rankin, J., Auer-Grumbach, M., Bagg, W., Colclough, K., Nguyen, T. D., Fenton-May, J., Hattersley, A., Hudson, J., Jardine, P., Josifova, D., Longman, C., McWilliam, R., Owen, K., Walker, M., Wehnert, M., & Ellard, S. (2008). Extreme phenotypic diversity and nonpenetrance in families with the LMNA gene mutation R644C. American Journal of Medical Genetics. Part , 146A(12),1530-1542. https://doi.org/10.1002/ajmg.a.32331

Richard P, Ader F, Roux M, Donal E, Eicher JC, Aoutil N, Huttin O, Selton-Suty C, Coisne D, Jondeau G, Damy T, Mansencal N, Casalta AC, Michel N, Haentjens J, Faivre L, Lavoute C, Nguyen K, Tregouët DA, Habib G, Charron P. Targeted panel sequencing in adult patients with left ventricular non-compaction reveals a large genetic

heterogeneity. Clin Genet. 2019 Mar;95(3):356-367. doi: 10.1111/cge.13484. Epub 2018 Dec 27. PMID: 30471092.

Rudenskaya, G. E., Polyakov, A. V., Tverskaya, S. M., Zaklyazminskaya, E. V., Chukhrova, A. L., Groznova, O. E., & Ginter, E. K. (2008). Laminopathies in Russian families. Clinical Genetics, 74(2), 127-133. https://doi.org/10.1111/j.1399-0004.2008.01045.x

Sakka R 1 , Marmouch H 2 , Trabelsi M 3 , Achour A 4 , Golli M 4 , Hannachi I 5 Kerkeni E 6 , Monastiri K 7 , Maazoul F 3 , M'rad R 3 Mandibuloacral dysplasia type A in five tunisian patients. Eur J Med Genet . 2021 Feb;64(2):104138. doi: 10.1016/j.ejmg.2021.104138. Epub 2021 Jan 8.

Sammani, A., Kayvanpour, E., Bosman, L. P., Sedaghat-Hamedani, F., Proctor, T., Gi, W.-T., Broezel, A., Jensen, K., Katus, H. A., Te Riele, A. S. J. M., Meder, B., & Asselbergs, F. W. (2020). Predicting sustained ventricular arrhythmias in dilated cardiomyopathy: A meta-analysis and systematic review. ESC Heart Failure, 7(4), 1430-1441. https://doi.org/10.1002/ehf2.12689

Scharner, J., Lu, H.-C., Fraternali, F., Ellis, J. A., & Zammit, P. S. (2014). Mapping disease-related missense mutations in the immunoglobulin-like fold domain of lamin A/C reveals novel genotype-phenotype associations for laminopathies. Proteins, 82(6), 904-915. https://doi.org/10.1002/prot.24465

Sébillon, P., Bouchier, C., Bidot, L. D., Bonne, G., Ahamed, K., Charron, P., Drouin-Garraud, V., Millaire, A., Desrumeaux, G., Benaïche, A., Charniot, J.-C., Schwartz, K., Villard, E., & Komajda, M. (2003). Expanding the phenotype of LMNA mutations in dilated cardiomyopathy and functional consequences of these mutations. Journal of Medical Genetics, 40(8), 560-567. https://doi.org/10.1136/jmg.40.8.560

Sedaghat-Hamedani, F., Haas, J., Zhu, F., Geier, C., Kayvanpour, E., Liss, M., Lai, A., Frese, K., Pribe-Wolferts, R., Amr, A., Li, D. T., Samani, O. S., Carstensen, A., Bordalo, D. M., Müller, M., Fischer, C., Shao, J., Wang, J., Nie, M., ... Meder, B. (2017). Clinical genetics and outcome of left ventricular non-compaction cardiomyopathy. European Heart Journal, 38(46), 3449-3460. https://doi.org/10.1093/eurheartj/ehx545

Sepehrkhouy, S., Gho, J. M. I. H., van Es, R., Harakalova, M., de Jonge, N., Dooijes, D., van der Smagt, J. J., Buijsrogge, M. P., Hauer, R. N. W., Goldschmeding, R., de Weger, R. A., Asselbergs, F. W., & Vink, A. (2017). Distinct fibrosis pattern in desmosomal and phospholamban mutation carriers in hereditary cardiomyopathies. Heart Rhythm, 14(7), 1024-1032. https://doi.org/10.1016/j.hrthm.2017.03.034

Sidhu, K., Han, L., Picard, K. C. I., Tedrow, U. B., & Lakdawala, N. K. (2020). Ventricular tachycardia in cardiolaminopathy: Characteristics and considerations for device programming. Heart Rhythm, 17(10), 1704-1710. https://doi.org/10.1016/j.hrthm.2020.05.023

Sidhu K, Castrini AI, Parikh V, Reza N, Owens A, Tremblay-Gravel M, Wheeler MT, Mestroni L, Taylor M, Graw S, Gigli M, Merlo M, Paldino A, Sinagra G, Judge DP, Ramos H, Mesubi O, Brown E, Turnbull S, Kumar S, Roy D, Tedrow UB, Ngo L, Haugaa K, Lakdawala NK. The response to cardiac resynchronization therapy in LMNA cardiomyopathy. Eur J Heart Fail. 2022 Apr;24(4):685-693. doi: 10.1002/ejhf.2463. Epub 2022 Mar 14. PMID: 35229420; PMCID: PMC9106891.

Skjølsvik, E. T., Hasselberg, N. E., Dejgaard, L. A., Lie, Ø. H., Andersen, K., Holm, T., Edvardsen, T., & Haugaa, K. H. (2020). Exercise is Associated With Impaired Left Ventricular Systolic Function in Patients With Lamin A/C Genotype. Journal of the American Heart Association, 9(2), e012937. https://doi.org/10.1161/JAHA.119.012937

Smith, G. C., Kinali, M., Prasad, S. K., Bonne, G., Muntoni, F., Pennell, D. J., & Nihoyannopoulos, P. (2006). Primary myocardial dysfunction in autosomal dominant EDMD. A tissue doppler and cardiovascular magnetic resonance study. Journal of Cardiovascular Magnetic Resonance: Official Journal of the Society for Cardiovascular Magnetic Resonance, 8(5), 723-730. https://doi.org/10.1080/10976640600723862

Taylor, M. R. G., Fain, P. R., Sinagra, G., Robinson, M. L., Robertson, A. D., Carniel, E., Di Lenarda, A., Bohlmeyer, T. J., Ferguson, D. A., Brodsky, G. L., Boucek, M. M., Lascor, J., Moss, A. C., Li, W. L. P., Stetler, G. L., Muntoni, F., Bristow, M. R., Mestroni, L., & Familial Dilated Cardiomyopathy Registry Research Group (2003). Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. Journal of the American College of Cardiology, 41(5), 771-780. https://doi.org/10.1016/s0735-1097(02)02954- 6

Theresa A McDonagh, Marco Metra, Marianna Adamo, Roy S Gardner, Andreas Baumbach, Michael Böhm, Haran Burri, Javed Butler, Jelena Čelutkienė, Ovidiu Chioncel, John G F Cleland, Andrew J S Coats, Maria G Crespo-Leiro, Dimitrios Farmakis, Martine Gilard, Stephane Heymans, Arno W Hoes, Tiny Jaarsma, Ewa A Jankowska, Mitja Lainscak, Carolyn S P Lam, Alexander R Lyon, John J V McMurray, Alexandre Mebazaa, Richard Mindham, Claudio Muneretto, Massimo Francesco Piepoli, Susanna Price, Giuseppe M C Rosano, Frank Ruschitzka, Anne Kathrine Skibelund, ESC Scientific Document Group, 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, Volume 42, Issue 36, 21 September 2021, Pages 3599-3726, https://doi.org/10.1093/eurheartj/ehab368

Thuillot, M., Maupain, C., Gandjbakhch, E., Waintraub, X., Hidden-Lucet, F., Isnard, R., Ader, F., Rouanet, S., Richard, P., & Charron, P. (2019). External validation of risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers. European Journal of Heart Failure, 21(2), 253-254. https://doi.org/10.1002/ejhf.1384

Treiber G, Flaus Furmaniuk A, Guilleux A, Medjane S, Bonfanti O, Schneebeli S, Bernard C, Le-Moullec N, Bakiri F, Pholsena M, Rollot O, Vatier C, Jarlet E, Jéru I, Lascols O, Darcel F, Domun B, Venault A, Venault S, Jacquemont ML, Doray B, Maiza JC, Cogne M, Vigouroux C, Nobécourt E. A recurrent familial partial lipodystrophy due to a monoallelic or biallelic LMNA founder variant highlights the multifaceted cardiac manifestations of metabolic laminopathies. Eur J Endocrinol. 2021 Aug 27;185(4):453-
462. doi: 10.1530/EJE-21-0282. PMID: 34292171.

Tomczak, C. R. (2020). Stepping Closer, But Not Stepping Too Much, Toward Exercise Recommendations for Lamin A/C Genotype-Positive Patients. Journal of the American Heart Association, 9(2), e015464. https://doi.org/10.1161/JAHA.119.015464

Van Berlo, J. H., de Voogt, W. G., van der Kooi, A. J., van Tintelen, J. P., Bonne, G., Yaou, R. B., Duboc, D., Rossenbacker, T., Heidbüchel, H., de Visser, M., Crijns, H. J. G. M., & Pinto, Y. M. (2005). Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: Do lamin A/C mutations portend a high risk of sudden death? Journal of Molecular Medicine (Berlin, Germany), 83(1), 79-83. https://doi.org/10.1007/s00109-004-0589-1

Van Rijsingen, I. A. W., Arbustini, E., Elliott, P. M., Mogensen, J., Hermans-van Ast, J. F., van der Kooi, A. J., van Tintelen, J. P., van den Berg, M. P., Pilotto, A., Pasotti, M., Jenkins, S., Rowland, C., Aslam, U., Wilde, A. A. M., Perrot, A., Pankuweit, S., Zwinderman, A. H., Charron, P., & Pinto, Y. M. (2012). Risk factors for malignant ventricular arrhythmias in lamin a/c mutation carriers a European cohort study. Journal of the American College of Cardiology, 59(5), 493-500. https://doi.org/10.1016/j.jacc.2011.08.078

Van Rijsingen, I. A. W., Bakker, A., Azim, D., Hermans-van Ast, J. F., van der Kooi, A. J., van Tintelen, J. P., van den Berg, M. P., Christiaans, I., Lekanne Dit Deprez, R. H., Wilde, A. A. M., Zwinderman, A. H., Meijers, J. C. M., Grootemaat, A. E., Nieuwland, R., Pinto, Y. M., & Pinto-Sietsma, S.-J. (2013). Lamin A/C mutation is independently associated with an increased risk of arterial and venous thromboembolic complications. International Journal of Cardiology, 168(1), 472-477. https://doi.org/10.1016/j.ijcard.2012.09.118

Van Rijsingen, I. A. W., Nannenberg, E. A., Arbustini, E., Elliott, P. M., Mogensen, J., Hermans-van Ast, J. F., van der Kooi, A. J., van Tintelen, J. P., van den Berg, M. P., Grasso, M., Serio, A., Jenkins, S., Rowland, C., Richard, P., Wilde, A. A. M., Perrot, A., Pankuweit, S., Zwinderman, A. H., Charron, P., ... Pinto, Y. M. (2013). Gender-specific differences in major cardiac events and mortality in lamin A/C mutation carriers. European Journal of Heart Failure, 15(4), 376-384. https://doi.org/10.1093/eurjhf/hfs191

Van Tintelen, J. P., Tio, R. A., Kerstjens-Frederikse, W. S., van Berlo, J. H., Boven, L. G., Suurmeijer, A. J. H., White, S. J., den Dunnen, J. T., te Meerman, G. J., Vos, Y. J., van der Hout, A. H., Osinga, J., van den Berg, M. P., van Veldhuisen, D. J., Buys, C. H. C. M., Hofstra, R. M. W., & Pinto, Y. M. (2007). Severe myocardial fibrosis caused by a deletion of the 5' end of the lamin A/C gene. Journal of the American College of Cardiology, 49(25), 2430-2439. https://doi.org/10.1016/j.jacc.2007.02.063

Wahbi, K., Ben Yaou, R., Gandjbakhch, E., Anselme, F., Gossios, T., Lakdawala, N. K., Stalens, C., Sacher, F., Babuty, D., Trochu, J.-N., Moubarak, G., Savvatis, K., Porcher, R., Laforêt, P., Fayssoil, A., Marijon, E., Stojkovic, T., Béhin, A., Leonard-Louis, S., ... Duboc, D. (2019). Development and Validation of a New Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies. Circulation, 140(4), 293-302. https://doi.org/10.1161/CIRCULATIONAHA.118.039410

Wilde AAM, Semsarian C, Márquez MF, Sepehri Shamloo A, Ackerman MJ, Ashley EA, Sternick EB, Barajas-Martinez H, Behr ER, Bezzina CR, Breckpot J, Charron P, Chockalingam P, Crotti L, Gollob MH, Lubitz S, Makita N, Ohno S, Ortiz-Genga M, Sacilotto L, Schulze-Bahr E, Shimizu W, Sotoodehnia N, Tadros R, Ware JS, Winlaw

DS, Kaufman ES; Document Reviewers, Aiba T, Bollmann A, Choi JI, Dalal A, Darrieux F, Giudicessi J, Guerchicoff M, Hong K, Krahn AD, MacIntyre C, Mackall JA, Mont L, Napolitano C, Ochoa JP, Peichl P, Pereira AC, Schwartz PJ, Skinner J, Stellbrink C, Tfelt-Hansen J, Deneke T. Expert Consensus Statement on the State of Genetic Testing for Cardiac Diseases.Heart Rhythm, from European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS). 2022 Apr 4:S1547-5271(22)01697-6.

Worman HJ, Bonne G. "Laminopathies": a wide spectrum of human diseases. Exp Cell Res. 2007 Jun 10;313(10):2121-33. doi: 10.1016/j.yexcr.2007.03.028. Epub 2007 Mar 30. PMID: 17467691; PMCID: PMC2964355.

Wu, W., Muchir, A., Shan, J., Bonne, G., & Worman, H. J. (2011). Mitogen-activated protein kinase inhibitors improve heart function and prevent fibrosis in cardiomyopathy caused by mutation in lamin A/C gene. Circulation, 123(1), 53-61. https://doi.org/10.1161/CIRCULATIONAHA.110.970673

Yin, J., Yang, J., Ren, F. X., Sun, C. M., Li, L. D., Han, L. Y., Cai, S. L., Zhang, C. H., Zhang, Z. Q., Zhang, Z. T., & Wang, H. (2015). Association of the LMNA gene single nucleotide polymorphism rs4641 with bdilated cardiomyopathy. Genetics and Molecular Research: GMR, 14(4), 15427-15434. https://doi.org/10.4238/2015.November.30.20

Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, Eckardt L, Friede T, Haugaa KH, Hocini M, Lambiase PD, Marijon E, Merino JL, Peichl P, Priori SG, Reichlin T, Schulz-Menger J, Sticherling C, Tzeis S, Verstrael A, Volterrani M; ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022 Aug 26:ehac262. doi: 10.1093/eurheartj/ehac262. Epub ahead of print. PMID: 36017572.