Journal of Neuromuscular Diseases xx (2021) x–xx
DOI 10.3233/JND-200596
IOS Press

Research Report

Laminopathies' Treatments Systematic Review: A Contribution Towards a 'Treatabolome'

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Pre-press 5 March 2021

Abstract.

Background: Variants in the *LMNA* gene, encoding lamins A/C, are responsible for a growing number of diseases, all of which complying with the definition of rare diseases. *LMNA*-related disorders have a varied phenotypic expression with more than 15 syndromes described, belonging to five phenotypic groups: Muscular Dystrophies, Neuropathies, Cardiomyopathies, Lipodystrophies and Progeroid Syndromes. Overlapping phenotypes are also reported. Linking gene and variants with phenotypic expression, disease mechanisms, and corresponding treatments is particularly challenging in laminopathies. Treatment recommendations are limited, and very few are variant-based.

Objective: The Treatabolome initiative aims to provide a shareable dataset of existing variant-specific treatment for rare diseases within the Solve-RD EU project. As part of this project, we gathered evidence of specific treatments for laminopathies via a systematic literature review adopting the FAIR (Findable, Accessible, Interoperable, and Reusable) guidelines for scientific data production.

Methods: Treatments for *LMNA*-related conditions were systematically collected from MEDLINE and Embase bibliographic databases and clinical trial registries (Cochrane Central Registry of Controlled Trials, clinicaltrial.gov and EudraCT). Two investigators extracted and analyzed the literature data independently. The included papers were assessed using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.

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ISSN 2214-3599

Results: From the 4783 selected articles by a systematic approach, we identified 78 papers for our final analysis that corresponded to the profile of data defined in the inclusion and exclusion criteria. These papers include 2 guidelines/consensus papers, 4 meta-analyses, 14 single-arm trials, 15 case series, 13 cohort studies, 21 case reports, 8 expert reviews and 1 expert opinion. The treatments were summarized electronically according to significant phenome-genome associations. The specificity of treatments according to the different laminopathic phenotypical presentations is variable.

Conclusions: We have extracted Treatabolome-worthy treatment recommendations for patients with different forms of laminopathies based on significant phenome-genome parings. This dataset will be available on the Treatabolome website and, through interoperability, on genetic diagnosis and treatment support tools like the RD-Connect's Genome Phenome Analysis Platform.

INTRODUCTION

Variants in the *LMNA* gene, encoding A-type lamins, are responsible for a growing number of rare monogenic diseases. A unique characteristic of the *LMNA* pathogenic variants is that they lead to a myriad of phenotypic expressions although they arise from the same gene. A complete explanation for this phenotypic variability still lacks at present despite the ever-growing amount of data from research [1–6]. A-type Lamins (lamins A and C) are intermediate filaments that build a meshwork at the inner face of the nuclear membrane after polymerization. They are also present in the nucleoplasm. They interact with the DNA, histones and chromatin in the nucleus, protect it from mechanical stress [7] and help in the maintenance of the nuclear shape while providing an anchorage to the endoplasmic reticulum through their interaction with other proteins like SUN1/SUN2 and the outer layers of the nuclear membrane [8].

The disorders that arise from changes to the *LMNA* gene have a varied phenotypic expression with more than 15 syndromes already described belonging to five phenotypic groups of pathologies, i.e. Muscular Dystrophies, Neuropathies, Cardiomyopathies, Lipodystrophies and Progeroid Syndromes [9]. Phenotypic overlaps are also reported between one or several laminopathic entities. The ubiquitous *LMNA* expression and the major role of A-type lamins in the functional organization of chromatin and the subsequent regulation of developmental genes probably play important roles in the pathophysiology of the different tissue-specific laminopathies [10]. In addition, the variable phenotypic expression arising from pathological *LMNA* variants could also result from epigenetic factors, modifier genes, altered expression levels and defective protein processing. Consequently, connecting gene and variants with phenotypic expression, disease mechanisms, and corresponding treatments is challenging in laminopathies. However, this approach could provide useful data to improve the guidelines and recommendations for the clinical management of these diseases, which remain under-recognized.

A recent paper on congenital myasthenia syndromes served as proof of concept of an innovative idea that consists of assembling a knowledge database of gene and variant-specific treatments for a significant entity group while preparing its future integration into electronic decision-support systems. This concept was baptized "Treatabolome" by the authors [11]. Subsequently, a standard methodology has been defined for other disease groups writing systematic literature reviews (SLR) of treatments in their expertise area [12]. The Treatabolome concept is developed within the Solve-RD EU project and addresses the need to identify and improve the visibility of the existing specific treatments for rare diseases. Several teams have collected gene and variant-specific treatments for different rare diseases in Findable, Accessible, Interoperable, and Reusable (FAIR)-compliant datasets [13]. This information will be freely available through the Treatabolome website to complement existing diagnostic tools and support clinical management.

The current paper is an attempt to collect knowledge of specific treatments for laminopathies. However, since pathogenic *LMNA* variants may trigger varied phenotypical presentations, laminopathies do not display univocal genome-phenome relationships, thus hindering the collection of variant-specific treatments. To adapt to these circumstances, we have decided to flag significant phenome-genome associations that trigger laminopathies' treatment recommendations.

We first collected 4783 papers through a systematic approach, then selected 78 studies reporting treatments for the diverse forms of laminopathies. From these data, we generated FAIR-compatible datasets to feed the Laminopathies' Treatabolome knowledge base. The corresponding complete dataset is provided as a Supplementary File S1.

List of Abbreviations

ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
ChEBI *https://www.ebi.ac.uk/chebi/*	Chemical Entities of Biological Interest
CENTRAL (Cochrane Central Registry of Controlled Trials) *https://www.cochranelibrary.com/central/about-central*	The Cochrane Central Register of Controlled Trials (CENTRAL) is a highly concentrated source of reports of randomized and quasi-randomized controlled trials
CHADS-VASC score	The CHADS2 score and its updated version, the CHA2DS2-VASc score, are clinical prediction rules for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation (AF), a common and serious heart arrhythmia associated with thromboembolic stroke
Clinicaltrials.gov	ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world
CMD1A	Familial Dilated Cardiomyopathy, type 1A (i.e. related to *LMNA*)
CRT-D	Cardiac Rehabilitation Therapy - Defibrillator
DCM	Dilated cardiomyopathy
Embase *www.embase.com*	Embase is the most comprehensive source for biomedical literature (36 + million records) from peer reviewed journals and conference abstracts
EDMD2	Emery-Dreifuss Muscular Dystrophy type 2
EudraCT *https://eudract.ema.europa.eu/*	EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) is the European database for all interventional clinical trials on medicinal products authorized in the European Union (EEA) and outside the EU/EEA if they are part of a Pediatric Investigation Plan (PIP) from 1 May 2004 onwards
EU	European Union
FAIR	Findable, Accessible, Interoperable, and Reusable. "The principles emphasize machine-actionability (i.e., the capacity of computational systems to find, access, interoperate, and reuse data with none or minimal human intervention) because humans increasingly rely on computational support to deal with data as a result of the increase in volume, complexity, and creation speed of data" *(see http://go-fair.org)*
FPLD2	Familial Partial Lipodystrophy type 2, Dunnigan Syndrome
HGPS	Hutchinson-Guilford Progeria Syndrome
ICD	Implantable Cardioversion Defibrillator
LMNA-CMD	*LMNA*-related congenital muscular dystrophy
MADA	Mandibulo Acral Dysplasia with Type A Lipodystrophy
MEDLINE *https://www.nlm.nih.gov/bsd/medline.html*	MEDLINE is the U.S. National Library of Medicine® (NLM) premier bibliographic database that contains more than 26 million references to journal articles in life sciences with a concentration on biomedicine. A distinctive feature of MEDLINE is that the records are indexed with NLM Medical Subject Headings (MeSH®)
OEBML *https://www.cebm.ox.ac.uk/resources/levels-of-evidence*	Oxford Evidence-Based Medicine Level
PCOS	Polycystic Ovary Syndrome
PRISMA *http://www.prisma-statement.org*	PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.
PROSPERO *https://www.crd.york.ac.uk/prospero/*	Website from the University of York, UK, that accepts registrations for systematic reviews, rapid reviews and umbrella reviews.
PubMed *https://pubmed.ncbi.nlm.nih.gov/*	PubMed® comprises more than 30 million citations for biomedical literature from MEDLINE, life science journals, and online books.
RD-Connect	The RD-Connect Project was a multidisciplinary project running from 2012 to 2018 that united partners from the EU and beyond to create an integrated global infrastructure for Rare Disease research.
SLR	Systematic literature review
Solve-RD *https://www.solve-rd.eu*	European research project aiming to solve the NGS-unsolved rare disease cases
Treatabolome	Publicly-available database of gene and variant-specific treatments, to be designed within the Solve-RD project

METHODS

Published treatments for *LMNA*-related conditions were collected and appraised following a research question shared by all Treatabolome systematic literature reviews [12]: "What treatments have been described for this condition/gene/variant; on which specific genetic variants have they been tested; and what is the strength of the associated supporting evidence?". This review follows the recommendations from the Cochrane Collaboration systematic reviews handbook [14] and the Centre for Reviews and Dissemination, namely by adopting the Systematic Review Protocol template of the PROSPERO tool [15]. The reporting of our findings follows the PRISMA reporting guidelines [16].

Search methods

We have searched the Cochrane Central Registry of Controlled Trials, clinicaltrial.gov and EudraCT (https://eudract.ema.europa.eu/eudract-web/login/login.faces) for clinical trials on *LMNA*-related diseases treatments. Simultaneously, we accessed MEDLINE and Embase through PubMed to extract any publications on the same subject. We did not impose a starting date for data collection that has included all references up to 31/12/2019. The searches were made in English, French, Spanish, Italian and Portuguese. We ran recurrent searches with the same search strategy that consisted of de-duplicating independent searches by each one the following expressions (all fields): "*LMNA*", "Lamin A/C", "A type Lamin", "Lamin A", "Lamin C" and "Laminopathy OR Laminopathies".

The search results were then reviewed by title and abstract, followed by a selective full-text data extraction. Inclusion and exclusion criteria are listed in Table 1. An electronic data capture form was built for this purpose by one of the authors (AA) using Filemaker Pro version 12 Software. This form was inspired by a publicly-available template from the Cochrane Collaboration Project [17] and followed the Methodological Expectations of Cochrane Intervention Reviews - the MECIR Standards [18]. We also complied with the Treatabolome Systematic Reviews' Methodology paper [12].

Table 1
Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Papers with any report of clinical use of a treatment for a *LMNA* gene-related disease, from single case reports to meta-analysis	Papers reporting preclinical treatments for *LMNA* gene-related diseases

RESULTS

The PRISMA flowchart (see Fig. 1) details the publication numbers at each stage of our selection.

After applying the described search strategy in PubMed, the initial starting number of papers was 11376 and the number went down to 4741 after de-duplication of entries with the following number of references for each search term:

- "*LMNA*": 1536 references
- "Lamin A/C": 2585 (932 duplicates eliminated: 1653)
- "A type Lamin": 3213 (2145 duplicates eliminated: 1068)
- "Lamin A": 2891 (2587 duplicates eliminated: 304)
- "Lamin C": 450 (437 duplicates eliminated: 13)
- "Laminopathy OR Laminopathies": 701 (534 duplicates eliminated: 167).

We then added 42 papers from additional sources (mainly expert bibliography references, besides ClinicalTrials.gov, EudraCT and Cochrane Library), reaching 4783 references eligible for Title/Abstract screening. At this stage, we excluded 624 references, mainly because they were unrelated to the LMNA gene. We full-text reviewed 4159 papers. We excluded 4081 papers, mainly for not addressing treatment findings or presenting only preclinical therapies in animal models and/or cell-culture experiments (see inclusion and exclusion criteria in Table 1). At the end of the process, 78 articles ended up in the qualitative analysis. These papers include 2 guidelines/consensus papers, 4 meta-analyses, 14 single-arm trials, 15 case series, 13 cohort studies, 21 case reports, 8 expert reviews and 1 expert opinion.

Two investigators extracted and analyzed the literature data independently. The treatments were summarized electronically according to significant phenome-genome associations. A complete list of the reported treatments is provided in Table 2.

The specificity of treatments according to the different *LMNA*-related diseases is variable. Some therapeutic approaches are specific for a unique phenotypical presentation. Others apply for laminopathic phenotypes that share a common clinical feature, as it happens regarding the risk of cardiac arrhythmia and

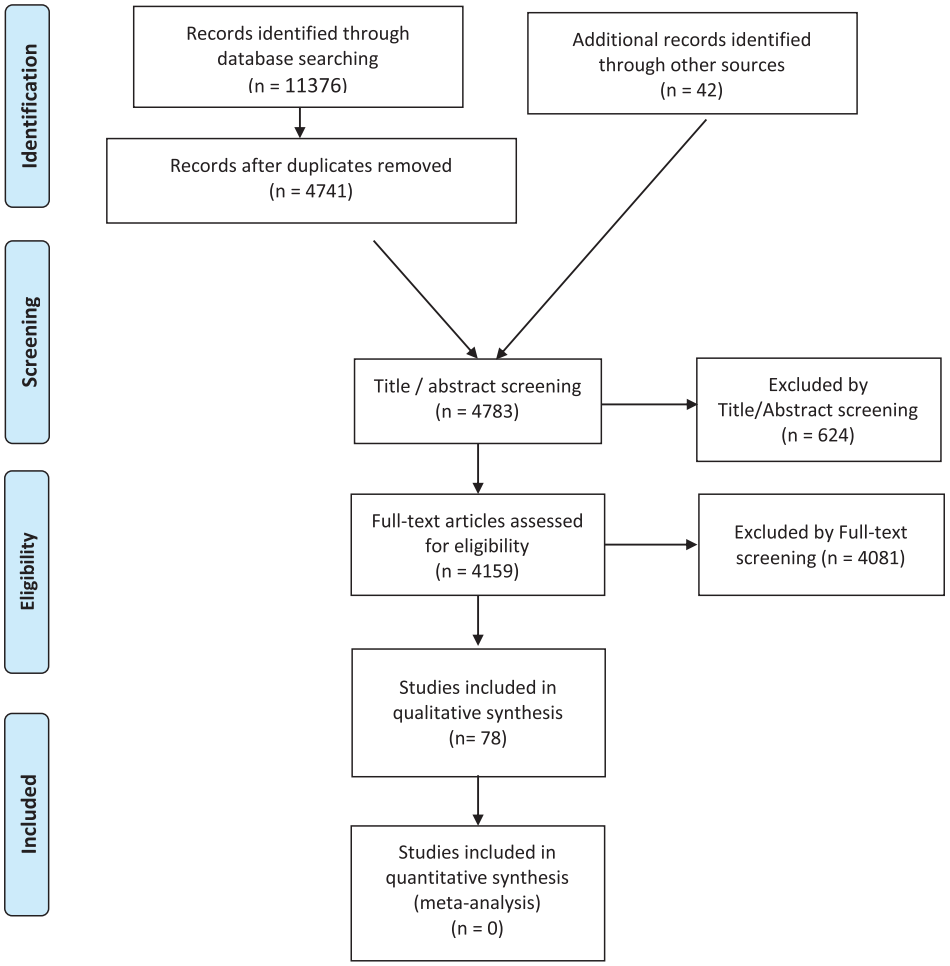

Fig. 1. Laminopathies' Treatabolome PRISMA Flow Diagram.

sudden death, present both in cardiomyopathies and in several other phenotypic groups of laminopathies. The Tables 3 to 4, specific of laminopathic phenotypes, are ordered according to the alphabetic order of the treatment or intervention names.

Treatabolome data for LMNA-related muscular phenotypes

The *LMNA*-related muscular phenotypes comprise a range of muscular dystrophies, i.e., the congenital muscular dystrophy (*LMNA*-CMD) [19], the Emery-Dreifuss muscular dystrophy (EDMD2) [20] and the Limb-Girdle Muscular Dystrophy type 1B [21]. These *LMNA*-muscular dystrophies differ in the age at onset of the muscular symptoms, the degree of joint contractures, when present, and, the severity, progression rate and topology of muscle wasting and weakness. But they all share a common feature, i.e. a life-threatening cardiac disease characterized by conduction and/or rhythm defects associated with dilated cardiomyopathy resulting in a high frequency of cardiac sudden death [1]. Of note, the cardiac involvement of *LMNA*-related muscular phenotypes is highly similar to the isolated *LMNA*-related cardiomyopathy presentation (CMD1A) [22, 23].

Currently, there are no specific treatments for *LMNA* related muscle weakness/wasting. Those treatments are common to all muscular dystrophies and neuropathies and, for that reason, are not included in the *LMNA* Treatabolome dataset. However, a frequent question asked by physicians following these patients pertains the management of joint contractures. Early joint contractures observed in the *LMNA*-related Emery-Dreifuss disease, which are not necessarily linked to muscle deficit, may benefit from direct

Table 2
Summary of reported laminopathy treatments

Treatment or intervention database	Treatment or intervention name	Treatment or intervention ID	Main Phenotype	Pubmed #
ChEBI	Corticosteroid	CHEBI: 50858	*LMNA*-CMD	26034236
MeSH	Anesthesia (Total Intravenous Anesthesia TIVA)	D000758	EDMD2	22973525
MeSH	Implantable Cardiac Defibrillator (ICD)	D017147	CMD1A	23811080, 17605093, 29173404, 26835025, 23946316, 22019351, 30287275, 12854972, 18926329, 30482687, 15551023, 22281253, 31155932, 28696268, 20627339, 23483212, 26385533, 30586772, 30518714, 15598919, 27993908, 27884249, 17605093, 29173404, 26835025, 23946316, 22019351, 30287275, 12854972, 18926329, 30482687, 15551023, 22281253, 31155932, 28696268, 20627339, 23483212, 26385533, 30586772, 30518714, 15598919, 27993908
MeSH	Transplant (heart)	D019737	CMD1A	31060954, 30287275, 18926329, 30482687
MeSH	Catheter Ablation	D017115	CMD1A	31060954, 29759522, 27506821
MeSH	Cardiac Pacing, Artificial	D002304	CMD1A	26620845
MeSH	CRT-D Cardiac Resynchronization Therapy	D058406	CMD1A	30891417
ChEBI	Anticoagulation	CHEBI: 50249	CMD1A	30191544, 30518714, 23073275
MeSH	rt-PA (alteplase)	D010959	CMD1A	30191544, 30518714, 23073275
MeSH	Percutaneous atrial appendage occlusion	D020517; Q000601[£]	CMD1A	29570041
ChEBI	Insulin	CHEBI: 145810	FPLD2	21168376
ChEBI	Pioglitazone	CHEBI: 8228	FPLD2	18728124
ChEBI	Pioglitazone Metformin Flutamide	CHEBI: 8228 CHEBI: 6801 CHEBI: 5132	FPLD2	18728124
ChEBI	Pioglitazone Metformin	CHEBI: 8228 CHEBI: 6801	FPLD2	17936664
ChEBI	Pioglitazone Metformin Insulin	CHEBI: 8228 CHEBI: 6801 CHEBI: 145810	FPLD2	19249234
ChEBI	Fenofibrate	CHEBI: 5001	FPLD2	19249234
ChEBI	Nicotinamide	CHEBI: 17154	FPLD2	12766116
ChEBI	Rosiglitazone	CHEBI: 50122	FPLD2	16241930, 22274718, 14510863
ChEBI	Liraglutide	CHEBI: 71193	FPLD2	29044799
MeSH	Roux en Y Gastric Bypass	D015390	FPLD2	27778252
MeSH	Noninvasive Ventilation	D063087	FPLD2	17893350, 19418082
ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	FPLD2 with hypoleptinemia	19727665, 31135595, 31194872, 30296183, 26584826, 25734254, 27710244, 30370487, 31620670, 24926953, 27692500, 30990519, 27207511, 31300002, 30539782, 23439261, 15791619, 22068254, 29644599, 27642538, 30805888, 29267953
MeSH	Surgery, Plastic	D013518	FPLD2	21561824, 21306965
ChEBI	Troglitazone (No market authorization for safety reasons)	CHEBI: 9753	FPLD2	10929166
ChEBI	Lonafarnib	CHEBI: 47097	HGPS	23012407, 29710166
ChEBI	Lonafarnib Pravastatin Zoledronic acid	CHEBI: 47097 CHEBI: 63618 CHEBI: 46557	HGPS	27400896
ChEBI	Alendronic acid / biphosphonates in general	CHEBI: 2567	HGPS	27400896
ChEBI	Growth Hormone (GH)	CHEBI: 37845	HGPS	31199775, 17642424, 9258264

CMD1A: Familial Dilated Cardiomyopathy, type 1A; EDMD2: Autosomal Dominant Emery-Dreifuss Muscular Dystrophy 2; FPLD2: Familial Partial Lipodystrophy, Dunningan Type; HGPS: Hutchinson-Gilford Progeria Syndrome; *LMNA*-CMD: *LMNA*-related congenital muscular dystrophy. [£]D020517 code for atrial appendage, Q000601 qualifier for surgery, no qualifier was found for percutaneous procedures.

Table 3
LMNA-related muscular syndromes treatment

Pubmed	Ref.	Clinical diagnosis ORDO	ORPHA code	Type of study	OCEBM	Number *LMNA* patients	HGVS cDNA	HGVS protein	Treatment database	Treatment or intervention name	Treatment or intervention ID	Clinical effect	Comments
22973525	Schuster et al., 2012 [90]	EDMD2	98853	Case report	5	1	NA	NA	MeSH	Anesthesia (Total Intravenous Anesthesia TIVA)	D000758	large	safe in this patient, presumed *LMNA* from phenotype
30518714	Wang et al., 2019 [91]	EDMD2	98853	Expert review	5	NA	NA	NA	ChEBI	Anticoagulation	CHEBI: 50249	large	prevention of stroke
26034236	Moraitis et al., 2015 [31]	*LMNA*-CMD	157973	Case report	5	1	c.91_93 delGAG	p.Glu31del	ChEBI	Corticosteroid	CHEBI: 50858	small	motor improvement
17605093	Antoniades et al., 2007 [34]	EDMD2	98853	Case series	4	15	c.908_909 delCT	p.Ser303 CysfsX27	MeSH	ICD	D017147	large	sudden cardiac death prevention
30518714	Wang et al., 2019 [91]	EDMD2	98853	Expert review	5	NA	NA	NA	MeSH	ICD	D017147	large	prevention of stroke

EDMD2: Autosomal Dominant Emery-Dreifuss Muscular Dystrophy 2; *LMNA*-CMD: *LMNA*-related Congenital Muscular Dystrophy.

surgical procedures when severe or responsible for high disability [24]. The most common joint contractures localizations are Achilles tendons, elbows and post-cervical muscles. There is published evidence on the surgical management of severe extension deformity of the cervical spine associated or not with scoliosis [24, 25] and also of severe upper extremity contractures. These were treated successfully with contracture release and musculotendinous lengthening [26] that improved range of motion without a significant sacrifice of strength. This literature is however limited. Some peri- or postoperative complications have been reported [27] and these patients should be managed by specific anesthetic and per operatory protocols [25, 28–30], preceded by careful full-spine analysis and preoperative evaluation.

In the case of *LMNA*-related congenital muscular dystrophy, there is scarce evidence that steroid therapy may bring some motor improvement [31]. Nevertheless, it has been included in our Treatabolome dataset but with a weak evidence-level (see Table 3). We have additional entries whose treatment is related to prevention of sudden cardiac death and that were included in Table 3, as the main phenotype is muscular. The prevention of sudden cardiac death is quite similar whether skeletal muscle is present or not (see Table 4).

Treatabolome data for LMNA-related sudden cardiac death prevention

A major *LMNA*-associated clinical problem is represented by the phenotypes that induce the risk of sudden cardiac death due to malignant arrhythmia (Table 4). Phenotypically, these arise either as isolated dilated cardiomyopathy or dilated cardiomyopathy associated with skeletal muscular dystrophy [32]. In principle, all laminopathies involving heart muscle bear a risk of cardiac arrhythmia and sudden death as demonstrated in a 2005 meta-analysis [32] and on published case series as well [33–37]. It is also established that mutations leading to haploinsufficiency (nonsense, indel, truncating insertions/deletions and splice site) carry the highest risk of sudden cardiac death [38]. An updated list of these mutations is supplied as Supplementary File S2. Defining the precise risk level has fueled different risk models published in the literature [39–45]. The different papers converge on an agreement that pacing does not prevent sudden cardiac death occurrence and the need for early cardiac defibrillator implantation (with or without resynchronization therapy)

Table 4
LMNA-related sudden cardiac death preventive treatment

Pubmed	Ref.	Clinical diagnosis ORDO	ORPHA code	Type of study	OCEBM evidence	Number of *LMNA* patients	HGVS cDNA	HGVS protein	Treatment or intervention database	Treatment or intervention name	Treatment or intervention ID	Clinical effect	Comments
23073275	van Rijsingen et al., 2013 [50]	CMD1A	300751	Case-control study	3	76	NA	NA	ChEBI	Anticoagulation	CHEBI: 50249	large	NA
30191544	Homma et al., 2018 [92]	CMD1A	300751	Case report	5	1	NA	NA	ChEBI	Anticoagulation	CHEBI: 50249	large	NA
27506821	Kumar et al., 2016 [49]	CMD1A	300751	Cohort study	4	25	NA	NA	MeSH	Catheter Ablation	D017115	moderate	NA
29759522	Roberts et al., 2017 [48]	CMD1A	300751	Case report	5	1	c.979C > G	p.Leu327Val	MeSH	Catheter Ablation	D017115	moderate	NA
31060954	Hasebe et al., 2019 [46]	CMD1A	300751	Cohort study	4	6	IVS3–10A > G 815_818 delins CCAGAC	p.?p.Asp272 AlafsX203	MeSH	Catheter Ablation	D017115	moderate	transient effects
26620845	Kato et al., 2016 [36]	CMD1A ARVD	300751 293910	Case series	4	2	c.2T > A c.1542G > A	p.Met1? p.Trp514*	MeSH	Cardiac Pacing, Artificial	D002304	small	does not prevent sudden cadiac death
30891417	Rudbeck-Resdal et al., 2019 [93]	CMD1A	300751	Case report	5	1	c.1411C.T	p.Arg471Cys	MeSH	CRT-D Cardiac Resynchroniza-tion Therapy	D058406	moderate	NA
12854972	MacLeoad et al., 2003 [94]	CMD1A	300751	Case report	5	1	c.908_909delCT	p.Ser303 CysfsX27	MeSH	ICD	D017147	large	NA
15598919	Desai et al., 2004 [95]	CMD1A	300751	Meta-analysis	1	1854	NA	NA	MeSH	ICD	D017147	large	NA
15551023	van Berlo et al., 2005 [32]	CMD1A	300751	Meta-analysis	1	299	NA	NA	MeSH	ICD	D017147	large	NA
18926329	Pasotti et al., 2008 [38]	CMD1A	300751	Cohort study	4	94	NA	NA	MeSH	ICD	D017147	large	NA
20627339	Meune et al., 2011 [96]	CMD1A	300751	Cohort study	4	19	NA	NA	MeSH	ICD	D017147	large	NA
26835025	Charron et al., 2012 [40]	CMD1A EDMD2 EDMD2	300751 264 98853	Expert review	5	NA	NA	NA	MeSH	ICD	D017147	large	NA
22019351	Keller et al., 2012 [35]	CD1A	300751	Case report	5	1	c.367_369delAAG	p.Lys123del	MeSH	ICD	D017147	large	NA
22281253	van Rijsingen et al., 2012 [41]	CMD1A	300751	Case series	3	149	NA	NA	MeSH	ICD	D017147	large	NA
23811080	Anselme et al., 2013 [42]	CMD1A	300751	Case series	4	47	c.16C > T c.748G > C c.1129C > T c.1130G > A c.1145G > A c.1589T > C	p.Gln6* p.Arg249Pro p.Arg377Cy p.Arg377His p.Arg482Gl p.Leu530Pro	MeSH	ICD	D017147	large	Innapropriate shocks

23946316	Disertori et al., 2013 [43]	CMD1A	300751	Expert review	5	NA	NA	NA	MeSH	ICD	D017147	large	NA
23483212	Ng & Kaye, 2013 [97]	CMD1A	300751	Case report	5	1	NA	NA	MeSH	ICD	D017147	large	NA
27884249	Kumar et al., 2016 [45]	CMD1A	300751	Cohort study	4	87	NA	NA	MeSH	ICD	D017147	large	NA
26385533	Olde Nordkampe et al., 2016 [88]	CMD1A	300751	Meta-analysis	1	462	NA	NA	MeSH	ICD	D017147	large	ICD implantation carries a significant risk of inappropriate shocks and in hospital & post discharge complications in relatively young patients with inherited arrhythmia syndromes
29173404	Atteya et al., 2017 [98]	CMD1A	300751	Expert review	5	NA	NA	NA	MeSH	ICD	D017147	large	NA
27993908	Golwhala et al., 2017 [99]	CMD1A	300751	Meta-analysis	1	1854	NA	NA	MeSH	ICD	D017147	large	NA
28696268	Halliday et al., 2017 [44]	CMD1A	300751	Expert review	5	NA	NA	NA	MeSH	ICD	D017147	large	NA
30586772	Kusumoto et al., 2019 [100]	CMD1A	300751	Cohort study	1	NA	NA	NA	MeSH	ICD	D017147	large	NA
30287275	Kwapich et al., 2019 [101]	CMD1A	300751	Case-control study	4	58	c.139G > T c.310C > G c.398G > T c.448A > G c.467G > A c.481G > A c.694G > C c.751C > T c.860del c.949G > A c.1157G > C c.1173dup c.1238del; c.1315C > T c.1357C > T c.1444C > T c.1445G > A c.1445G > T c.1930C > T	p.Asp47Tyr p.Leu104Val p.Arg133Leu p.Thr150Ala p.Arg156His p.Glu161Lys p.Gly232Arg p.Gln251* p.Ala287Valfs*193 p.Glu317Lys p.Arg386Thr p.Ser392Glnfs*34 p.Gly413Alafs*67 p.Arg439Cys p.Arg453Trp p.Arg482Trp p.Arg482Gln p.Arg482Leu p.Arg644Cys	MeSH	ICD	D017147	large	NA

(Continued)

Table 4
(Continued)

Pubmed	Ref.	Clinical diagnosis ORDO	ORPHA code	Type of study	OCEBM evidence	Number of *LMNA* patients	HGVS cDNA	HGVS protein	Treatment or intervention database	Treatment or intervention name	Treatment or intervention ID	Clinical effect	Comments
30482687	Peters et al., 2019 [47]	CMD1A	300751	Expert review	5	NA	NA	NA	MeSH	ICD	D017147	large	NA
31155932	Wahbi et al., 2019 [39]	CMD1A	300751	Cohort study	3	444	NA	NA	MeSH	ICD	D017147	large	innapropriate implantation of ICD
29570041	De Roeck et al., 2019 [102]	CMD1A	300751	Case report	5	1	c.235C>G	p.Leu85Val	MeSH	percutaneous atrial appendage occlusion	D020517 SU	large	NA
23360689	Chen et al., 2013[51]	CMD1A	300751	Case report	5	1	c.513+1 G>A	p.Lys152Lys	MeSH	rt-PA (alteplase)	D010959	large	NA
18926329	Pasotti et al., 2008 [38]	CMD1A	300751	Observational study	3	94	NA	NA	MeSH	Transplant (heart)	D019737	large	NA
31060954	Hasebe et al., 2019 [46]	CMD1A	300751	Cohort study	4	6	IVS3–10A>G 815_818 delins CCAGAC	p.? p.Asp272 AlafsX203	MeSH	Transplant (heart)	D019737	large	NA
30287275	Kwapich et al., 2019 [101]	CMD1A	300751	Case-control study	3	58	c.139G>T c.310C>G c.398G>T c.448A>G c.467G>A c.481G>A c.694G>C c.751C>T c.860del c.949G>A c.1157G>C c.1173dup c.1238del; c.1315C>T c.1357C>T c.1444C>T c.1445G>A c.1445G>T c.1930C>T	p.Asp47Tyr p.Leu104Val p.Arg133Leu p.Thr150Ala p.Arg156His p.Glu161Lys p.Gly232Arg p.Gln251* p.Ala287Valfs*193 p.Glu317Lys p.Arg386Thr p.Ser392Glnfs*34 p.Gly413Alafs*67 p.Arg439Cys p.Arg453Trp p.Arg482Trp p.Arg482Gln p.Arg482Leu p.Arg644Cys	MeSH	Transplant (heart)	D019737	large	NA
30482687	Peters et al., 2019 [47]	CMD1A	300751	Expert review	5	NA	NA	NA	MeSH	Transplant (heart)	D019737	large	NA

ARVD: Familial isolated arrhythmogenic ventricular dysplasia, right dominant form; CMD1A: Familial dilated cardiomyopathy with conduction defect due to *LMNA* mutation; FPLD2: Familial Partial Lipodystrophy, Dunnigan Type.

to improve patient's vital prognosis. The treatment does not delay progression to heart failure though, and when arrhythmia occurs under the latter condition, only cardiac transplantation extends survival [46]. Early referral for heart transplant is therefore advised in laminopathies [47].

There is evidence of some efficacy of radiofrequency catheter ablation for ventricular tachyarrhythmias [48, 49], which should delay referral to heart transplantation.

Atrial fibrillation and other atrial arrhythmias are common manifestations of laminopathies. They have been associated with high risk of stroke and other cardioembolic complications, therefore requiring the systematic use of curative anticoagulation, regardless to CHADS-VASC score [45, 50, 51].

Treatabolome data for LMNA-related lipodystrophies

The *LMNA*-related lipodystrophies central entity is the Familial Partial Lipodystrophy Type 2, also known as Dunnigan type lipodystrophy. It is characterized by loss of subcutaneous adipose tissue from the trunk, buttocks and limbs and accumulation of fat around face, neck, pelvis and axillae coexisting with muscle hypertrophy later accompanied by metabolic perturbations such as hypertriglyceridemia, low HDL cholesterol, hepatic steatosis, insulin-resistant diabetes, and early atherosclerosis. The phenotype is more marked in females, who also frequently develop ovarian hyperandrogenia leading to hirsutism, menstrual disturbances and decreased fertility [52]. A prevalence of the Dunnigan syndrome below 1/100 000 was reported, but is probably underestimated, since partial lipodystrophy is largely underdiagnosed [53, 54]. *LMNA*-related lipodystrophies are the most common forms of genetic lipodystrophies in Europe. In the great majority of cases they are inherited in an autosomal dominant fashion. The characteristic hotspot results from heterozygous mutations at the 482nd codon of the gene (p.Arg482Trp/Gln or Leu). However, other *LMNA* pathogenic variants can be found rarely as well, that may lead to typical partial lipodystrophic syndromes or mixed laminopathic phenotypes [55, 56].

These patients have severe cardiovascular risk through atherosclerosis. Female patients may suffer from Polycystic Ovarian Syndrome (PCOS), associated with reduced fertility, hirsutism and menstrual disturbances. Due to the multiple comorbidities associated with *LMNA*-related lipodystrophic syndromes, patients require multidisciplinary management. The first-line management of diabetes and dyslipidemia mainly follows the general population's guidelines, with dietary and lifestyle rules being fundamental. No cure is available for lipodystrophy itself (Table 5).

Rare studies report the effects of nonspecific antidiabetic medications such as metformin, thiazolidinediones and glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin in some patients with *LMNA*-related lipodystrophies. Usually, these are case reports of different combinations with low evidence level. One open-label prospective trial with the thiazolidinedione troglitazone, which is withdrawn from the market since 2000, found that the drug lowered HbA1C levels in FPLD patients [57]. Additional anecdotal evidence exists from case reports [58–61] regarding thiazolidinediones (pioglitazone, rosiglitazone) in different associations with insulin and/or metformin, that improve metabolic markers (leptin levels, HbA1C levels, insulin sensitivity), but could exacerbate faciocervical fat accumulation [58]. To note, all thiazolidinediones were withdrawn from the market in France, so checking locally their availability is advisable. GLP-1 receptor agonists have shown promises as a glucose-lowering therapy in a case report [62].

Lipid-lowering drugs are also used in accordance to guidelines for the general population in *LMNA*-related lipodystrophies [63].

A case report has shown that thiazolidinediones could improve PCOS in women with FPLD2 [64]. Obstructive Sleep Apnea Syndrome is a known complication of *LMNA*-related lipodystrophies that should benefit from Non-Invasive Ventilation as treatment [65, 66]. We suspect that more systematic sleep studies in these populations will potentially disclose sleep disturbed breathing as a frequent feature. Dunnigan lipodystrophy syndrome is also a stigmatizing disease and plastic surgery can be useful for some patients (liposuction of lipohypertrophic areas and/or reconstructive procedures for lipoatrophic areas). A few case reports have described such surgical treatments [67, 68]. Bariatric surgery [69] has been occasionally used in cases of Dunnigan syndrome associated with obesity.

LMNA-related lipodystrophic syndromes, especially when lipoatrophic features are prominent, are associated with decreased leptin levels which contribute to the metabolic alterations and their associated comorbidities. The hormone replacement therapy's efficiency using the orphan drug Metreleptin, a recombinant leptin agonist, has not been

Table 5
LMNA-related lipodystrophic syndromes treatment

Pubmed	Ref.	Clinical diagnosis ORDO	ORPHA code	Type of study	OCEBM evidence	Number of *LMNA* patients	HGVS cDNA	HGVS protein	Treatment or intervention database	Treatment or intervention name	Treatment or intervention ID	Clinical effect	Biomarker Effect[$]	Comments
23073275	van Rijsingen et al., 2013 [50]	CMD1A	300751	Case-control study	3	76	NA	NA	ChEBI	Anticoagulant	CHEBI: 50249	large	NA	NA
27506821	Kumar et al., 2016 [49]	CMD1A	300751	Cohort study	4	25	NA	NA	MeSH	Catheter Ablation	D017115	moderate	NA	NA
12766116	Herbst et al., 2003 [103]	FPLD2	2348	Case series	4	13	NA	NA	ChEBI	Fenofibrate	CHEBI: 5001	NA	moderate	NA
17642424	Sadeghi-Nejad et al., 2007 [84]	HGPS	740	Case report	5	1	c.1822G > A	p.G608S	ChEBI	Growth Hormone	CHEBI: 37845	small	NA	NA
9258264	Abdenur et al., 1997 [85]	HGPS	740	Case series	4	3	NA	NA	ChEBI	Growth Hormone; Nutritional Intervention	CHEBI: 37845	small	NA	does not stop athero-sclerosis
15598919	Desai et al., 2004 [95]	CMD1A	300751	Meta-analysis	1	###	NA	NA	MeSH	ICD	D017147	large	NA	NA
23483212	Ng & Kaye, 2013 [97]	CMD1A	300751	Case report	5	1	NA	NA	MeSH	ICD	D017147	large	NA	NA
27884249	Kumar et al., 2016 [45]	CMD1A	300751	Cohort study	4	87	NA	NA	MeSH	ICD	D017147	large	NA	NA
27993908	Golwala et al., 2017 [99]	CMD1A	300751	Meta-analysis	1	###	NA	NA	MeSH	ICD	D017147	large	NA	NA
31155932	Wahbi et al., 2019 [39]	CMD1A	300751	Cohort study	3	444	NA	NA	MeSH	ICD	D017147	large	NA	innapropriate implantation of ICD
21168376	Cardona-Hernandez et al., 2011 [104]	FPLD2	2348	Case series	5	1	c.29C > T	p.Thr10Ileu	ChEBI	Insulin	CHEBI: 145810	large	large	NA
15791619	Javor et al., 2005 [105]	FPLD2	2348	Case series	4	2	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	moderate	NA
19727665	Chong et al., 2010 [70]	FPLD2	2348	Observational study	3	48	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA
22068254	Chan et al., 2011 [106]	FPLD2	2348	Case series	4	19	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	moderate	NA
23439261	Safar Zadeh et al., 2013 [107]	FPLD2	2348	Cohort study	3	27	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	moderate	NA
24926953	Joseph et al., 2014 [108]	FPLD2	2348	Cohort study	5	82	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA
25734254	Diker-Cohen et al., 2015 [71]	FPLD2	2348	Cohort study	4	31	c.1444C > T c.1445G > A c.1445G > T	p.Arg482Trp p.Arg482Gln p.Arg482Leu	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA

27642538	Ajluni et al., 2016 [109]	FPLD2	2348	Cohort study	4	23	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA
27710244	Brown et al., 2016 [63]	FPLD2	2348	Expert review	5	NA	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA
27207511	Schlogl et al., 2016 [110]	FPLD2	2348	Cohort study	5	9	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA
26584826	Vatier et al., 2016 [72]	FPLD2	2348	Case-control study	4	9	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA
27692500	Vatier et al., 2017 [111]	FPLD2	2348	Cohort study	10	16	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	moderate	NA
30370487	Akinci et al., 2018 [69]	FPLD2	2348	Expert opinion	5	NA	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA
29644599	Brown et al., 2018 [112]	FPLD2	2348	Cohort study	4	66	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	moderate	NA
29267953	Hussain et al., 2018 [113]	NA	NA	Cohort study	4	7	c.29C>T	p.T10I	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	large	NA
31620670	Kinzer et al., 2019 [114]	FPLD2	2348	Cohort Study	4	5	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA
30990519	Lee et al., 2019 [115]	FPLD2	2348	Cohort study	4	42	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	moderate	NA
31135595	Melvin et al., 2019 [116]	FPLD2	2348	Expert review	5	NA	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA
30805888	Oral et al., 2019 [117]	FPLD2	2348	Cohort study	4	41	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	large	NA
30539782	Puschel et al., 2019 [118]	FPLD2	2348	Cohort study	4	10	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA
31194872	Sekizkardes, et al., 2019 [75]	FPLD2	2348	Cohort study	4	22	c.1444C>T c.1445G>A c.IVS8+5G>C c.1543A>G c.1662G>C c.1751G>A	pArg482Trp p.Arg482Gln p.Ileu497Valfs*20 p.Lys515Glu p.Arg541Pro p.Arg584His	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA
30296183	Vatier et al., 2019a [76]	FPLD2	2348	Case series	4	1	c.1444C>T	p.Arg482Trp	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	oestrogens contra-indicated
31300002	Vatier et al., 2019b [119]	FPLD2	2348	Cohort study	4	10	NA	NA	ChEBI	Leptin (Metreleptin Myalept)	CHEBI: 81571	small	small	NA
29044799	Banning et al., 2017 [62]	FPLD2	2348	Case report	5	1	c.1445G>A	p.Arg482Gln	ChEBI	Liraglutide	CHEBI: 71193	small	large	NA
12766116	Herbst et al., 2003 [103]	FPLD2	2348	Case series	4	13	NA	NA	ChEBI	Nicotinamide	CHEBI: 17154	NA	small	NA
17893350	Hegele et al., 2007 [65]	FPLD2	2348	Case series	4	2	c.1445G>A	p.Arg482Gln	MeSH	Noninvasive Ventilation	D063087	moderate	moderate	NA

(Continued)

Table 5
(Continued)

Pubmed	Ref.	Clinical diagnosis ORDO	ORPHA code	Type of study	OCEBM evidence	Number of *LMNA* patients	HGVS cDNA	HGVS protein	Treatment or intervention database	Treatment or intervention name	Treatment or intervention ID	Clinical effect	Biomarker Effect[$]	Comments
19418082	Patel et al., 2009 [66]	FPLD2	2348	Case report	5	1	c.1445G > A	p.Arg482Gln	MeSH	Noninvasive Ventilation	D063087	moderate	large	NA
18728124	Gambineri et al., 2008 [64]	FPLD2	2348	Case report	4	2	c.1445G > A	p.Arg482Gln	ChEBI	Pioglitazone 30 mg/d	CHEBI: 8228	moderate	NA	NA
17936664	Moreau et al., 2007 [59]	FPLD2	2348	Case report	5	1	NA	NA	ChEBI	Pioglitazone	CHEBI: 8228	small	large	NA
										Metformin	CHEBI: 6801			
18728124	Gambineri et al., 2008 [64]	FPLD2	2348	Case report	4	2	c.1445G > A	p.Arg482Gln	ChEBI	Pioglitazone 30 mg/d; Metformin 1700 mg/d; Flutamide 250 mg/d	CHEBI: 5132	moderate	NA	NA
19249234	Collet-Gaudillat et al., 2009 [60]	FPLD2	2348	Case report	5	1	NA	NA	ChEBI	Pioglitazone	CHEBI: 8228	small	large	NA
										Metformin	CHEBI: 6801			
										Insulin	CHEBI: 45810			
14510863	Owen et al., 2003 [58]	FPLD2	2348	Case report	5	1	c.1444C > T	p.Arg482Trp	ChEBI	Rosiglitazone	CHEBI: 50122	small	NA	NA
16241930	Ludtke et al., 2005 [120]	FPLD2	2348	Case report	5	1	c.1444C > T	p.Arg482Trp	ChEBI	Rosiglitazone	CHEBI: 50122	small	moderate	NA
22274718	Luedtke et al., 2012 [61]	FPLD2	2348	Cohort study	3	5	c.1444C > T	p.Arg482Trp	ChEBI	Rosiglitazone	CHEBI: 50122	small	moderate	NA
27778252	Grundfest-Broniatowski et al., 2017 [121]	FPLD2	2348	Case report	5	1	c.1445G > A c.1444C > T	p.Arg482Gln p.Arg482Trp	MeSH	Roux en Y Gastric Bypass	D015390	moderate	NA	NA
23360689	Chen et al., 2013 [51]	CMD1A	300751	Case report	5	1	c.513 + 1G > A	p.Lys171Lys + splice defect ?	MeSH	rt-PA (alteplase)	D010959	large	NA	NA
21561824	Calderoni et al., 2011 [67]	FPLD2	2348	Case report	5	1	NA	NA	MeSH	Surgery, Plastic	D013518	moderate	NA	NA
21306965	Hughes et al. 2011 [68]	FPLD2	2348	Case report	5	1	NA	NA	MeSH	Surgery, Plastic	D013518	moderate	NA	NA
10929166	Arioglu et al., 2000 [57]	FPLD2	2348	Cohort study	3	7	NA	NA	ChEBI	Troglitazone	CHEBI: 9753	small	small	NA

FPLD2: Familial Partial Lipodystrophy, Dunnigan Type; CMD1A: Familial dilated cardiomyopathy with conduction defect due to *LMNA* mutation. [$]Biomarkers effects are indicated only in this table V, as some were reported only for these class of phenotypes/symptoms/treatments. [###]Not possible to find how many patients with *LMNA*-related disease were reported in these meta-analyses.

studied in placebo-controlled studies. Still, several reports suggest that Metreleptin can be useful to improve glucose and lipid homeostasis and decrease hepatic steatosis in lipodystrophic syndromes, at least partly independently from its anorexigenic effects. Leptin-replacement therapy with Metreleptin has been assessed in two single-arm open-label trials [70–75]. They addressed heterogeneous populations with different genome-phenome associations, and Metreleptin seems to have some benefit in low-leptin populations in reducing triglycerides. Raised triglycerides are associated with cardiovascular risk and incidence of acute pancreatitis in these patients. No risk reduction figures of such outcomes are provided, though. A practice guideline reaches similar treatment recommendation for Metreleptin [63] as well as some case series and reports [72, 75, 76]. Although Metreleptin is more efficient in generalized than partial lipodystrophy, it could be useful in Dunnigan lipodystrophy, especially when metabolic alterations are severe and leptin levels very low at baseline [63, 71].

The increased cardiovascular risk in lipodystrophy should also lead to early screening and treatment of atherosclerotic events and rhythm and conduction disturbances. This has been mentioned in case reports, but specific recommendations are needed. [56].

Treatabolome data for LMNA-related progeroid syndromes

Although some progeroid syndromes still do not have a specific Orpha code, that is not the case of the archetypal *LMNA*-related progeroid presentation Hutchinson-Guilford Progeria Syndrome (HGPS) [77, 78]. It is an accelerated ageing developmental disorder that affects children at a young age, markedly reducing their life expectancy. Despite being born in apparent health, affected children fail to thrive before the first year of life and go on to develop the characteristic features that spare the cognitive development and that result in early cardiovascular death from a heart attack or stroke [79, 80]. Treatments described for the condition are summarized in Table 6.

Two clinical trials involving a farnesyl transferase inhibitor, named lonafarnib, have risen great expectations. The initial 2012 trial (*ClinicalTrials.gov, NCT02579044*) enrolled 26 subjects and was a non-randomized controlled trial [81]. At the conclusion, treated patients had improved weight, vascular stiffness, bone structure and audiological

Table 6
LMNA-related progeroid syndromes treatment

Pubmed	Ref.	Clinical diagnosis ORDO	ORPHA code	Type of study	OCEBM	Number *LMNA* patients	HGVS cDNA	HGVS protein	Treatment or intervention name	Treatment or intervention ID	Clinical effect
17935239	Kosho et al., 2007 [87]	MADA	90153	Case report	5	1	c.1585G>A	p.Ala529Thr	Alendronic acid biphosphonates in general	CHEBI: 2567	small
31199775	Toni et al., 2019 [122]	HGPS	740	Case report	5	1	c.433G>A	p.Glu145Lys	Growth Hormone	CHEBI: 37845	small
17642424	Sadeghi-Nejad et al., 2007 [84]	HGPS	740	Case report	5	1	c.1822G>A	p.Gly608Ser	Growth Hormone	CHEBI: 37845	small
9258264	Abdenur et al., 1997 [85]	HGPS	740	Case series	4	3	NA	NA	Growth Hormone; Nutritional Intervention (= no code)	CHEBI: 37845	small
23012407	Gordon et al., 2012 [81]	HGPS	740	Cohort study	3	26	c.1824C>T	p.Gly608Gly	Lonafarnib	CHEBI: 47097	small
29710166	Gordon et al., 2018 [82]	HGPS	740	Cohort study	3	63	c.1824C>T	p.Gly608Gly	Lonafarnib	CHEBI: 47097	small
27400896	Gordon et al., 2016 [83]	HGPS	740	Cohort study	3	37	c.1824C>T	p.Gly608Gly	Lonafarnib Pravastatin Zoledronic acid	CHEBI: 47097; CHEBI: 63618 CHEBI: 46557	small

MADA: Mandibulo Acral Dysplasia Type A with Lipodystrophy; HGPS: Hutchinson-Gilford Progeria Syndrome.

state. The treatment seemed to have a beneficial effect on survival but the findings were limited by the observational design [82]. A second trial (*Clinical Trials.gov, NCT00879034*) involving 37 patients followed, employing a combination of lonafarnib, pravastatin and zoledronic acid in which comparisons with lonafarnib monotherapy treatment revealed additional bone mineral density benefit [83]. There was no added cardiovascular benefit, leaving small hope that such an approach can improve survival. There is an ongoing Phase I/II trial combining lonafarnib and everolimus that estimates enrolling 80 patients and being completed by December 2021 (*ClinicalTrials.gov, NCT02579044*).

Growth hormone (GH) has been mentioned as a treatment that may favor growth in HGPS patients. An initial 3 cases report of GH and nutritional therapy as well as a more recent case report suggest that it brings mild transient benefits [84, 85]. A mixed case with empty sella has found no improvement in long term outcome [86]. The evidence, therefore, remains weak for recommending this therapy in HGPS.

Finally, a case report of *LMNA*-related case of Mandibulo Acral Dysplasia (MADA) recommends bisphosphonates to prevent the clastic activity with a rationale based on mechanism, so with a low level of evidence supporting the suggestion [87]. This entity is sometimes found in association with lipodystrophy.

DISCUSSION

The current systematic literature review of the Treatabolome pilot study research question ("What treatments have been described for this condition/gene/variant; on which specific genetic variants have they been tested; and what is the strength of the associated supporting evidence?") did not provide any accessible list of *LMNA* variant-specific treatments. As an example, *LMNA* variants reported as "malignant" because of their association with a high risk of sudden cardiac death require the same cardiological management as "unlabelled" variants, as they share the same potential risk. However, we could identify a list of inactivating mutations conferring a major risk of sudden cardiac death (Supplementary File S2). We recommend having in mind that although many papers based the assertion of variant pathogenicity on existing functional studies, a sizeable number have not indicated what scientific validation has been done for some of the previously undescribed variants. Keep in mind that variants reported in our Supplementary File S2 and this paper may have less than complete evidence regarding their pathogenicity.

In *LMNA*-triggered conditions, the specific treatment indications thus rather relate to significant genome-phenotype pairings. The evidence regarding these pairings are summarised in Tables 3 (*LMNA*-related muscular phenotypes treatment), 4 (Sudden Cardiac Death Prevention), 5 (*LMNA*-related lipodystrophy treatment) and 6 (*LMNA*-related progeroid syndrome treatment). Regarding the corresponding gene and variant information, we have included reported variants from case reports and series and some genetic hotspots for several diseases, bearing in mind there is no variant-specific relationship with the listed treatments.

Our view is that the data assembled in our tables are of relevance for the Treatabolome database. A growing number of non-specialized clinicians gain access to genetic results and the Treatabolome database provides fundamental information for the management of patients. The integration of a treatment-related early warning system in the context of the genetic diagnosis tools has the potential to reduce management delays and to improve standards of care for patients with rare diseases.

Regarding the risk of sudden cardiac death, although superficially solved by a blanket indication of implantation of a defibrillator, the timing and risk assessment for that therapy have yet to achieve a clear consensus. The use of a "risk factors" approach, derived from the study by van Rijsingen et al. [41], has been implemented in the European and North American guidelines from cardiology scientific societies on sudden death prevention. A recent publication [39] has proposed an algorithm that is available as an online calculator (*https://lmna-risk-vta.fr/)* and could reduce the risk for patients to die suddenly, along with the number of patients having unnecessary device placements. It is also noticeable that although life-saving, implantable cardioversion defibrillators (ICD) have unpleasant side-effects when patients receive inappropriate shocks. A meta-analysis estimates that about a fifth of patients have these complications [88] and analysis continues on the mechanisms that originate this unwanted side effect of treatment. This requires that a risk stratification strategy is clearly laid down, namely for asymptomatic candidates. Overall, the ratio between the benefit and risk of prophylactic ICD placements appear to be extremely favorable in the very arrhythmogenic condition and we recommend using the

online tool developed as described by Wahbi et al. [39] to assess the risk of sudden cardiac death prior to ICD implantation. The risk factors were identified in cardiology tertiary centers' *LMNA* patients, some of whom with neuromuscular involvement. The score was derived from a French nationwide cohort including all phenotypes, so one can reasonably conclude that the resulting sudden death risk stratification applies to any *LMNA* variant carriers. Therefore, we believe that it improves patient selection for implantation of ICD. Still, we recognize a limitation in Wahbi et al. paper's approach [39] because it has not been specifically addressed whether the clinical presentation (myopathy, neuropathy, lipodystrophy...) influences the risk for cardiac events beyond the genetic and cardiac risk factors, although the authors intend to study this in the future.

Another clear point is that pacing is inadequate for these patients and should be replaced by ICD [33]. Cardiac Rehabilitation Therapy coupled with defibrillator (CRT-D) may support patients awaiting transplant and is a valid treatment option [39, 41, 42] but its wide use is limited by this population's modest cardiac function response to CRT. There is no specific arrhythmogenic phenotype linked to the *LMNA* gene or its variants but general cardiological guidance for anticoagulation applies also in these cases.

In *LMNA*-related lipodystrophies, diet and exercise have to be strongly encouraged for prevention and treatment of metabolic complications. Nonspecific antidiabetic and lipid lowering treatments are largely used, and the numerous comorbidities (liver disease, cardiovascular risk, polycystic ovary syndrome, muscular symptoms, morphological and psychological consequences of the disease) require a multidisciplinary care. There was some success in reducing triglyceride levels and improving insulin resistance and glucose parameters by administering the orphan drug Metreleptin in patients with low leptin levels and severe metabolic alterations.

The literature about Progeroid Syndromes includes two non-randomized non-blinded controlled studies on the use of a farnesyl transferase inhibitor, lonafarnib, either in monotherapy or in association with pravastatin and zoledronic acid. The results show that weight, vascular stiffness, bone structure and audiological state (and bone density in the association trial) improve, but little or no effect on survival was observed. Reports on the use of Growth Hormone (GH) and nutritional measures unfortunately show only a transient advantage.

CONCLUSION

We have performed a systematic literature review to extract 'uploadable' data for Treatabolome dataset and to trigger the discussion on information management of laminopathies treatments. The corresponding dataset will integrate the Treatabolome platform and will be shared with interoperable data platforms like the Genome-Phenome Analysis Platform *(https://platform.rd-connect.eu/)*, allowing its incorporation in this and other clinical support tools. As examples of platforms that may consider looking into how to make interoperability with Treatabolome happen in the future, we have considered OPALE [89] the National French Registry for Laminopathies, UMD-*LMNA* (available at *www.umd.be/LMNA/*), LOVD (available at *http://www.dmd.nl/lmna_home.html*) and CMDIR (available at *https://www.cmdir.org)*. We are confident that others will arise in time, as the treatment component of all rare diseases is a concern of researchers, clinicians and patients alike.

ACKNOWLEDGMENTS

This publication is part of the Solve-RD project (http://solve-rd.eu/). The Solve-RD project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 779257.

The authors of this publication are members of the European Reference Network for Neuromuscular Diseases - Project ID N° 870177.

CONFLICTS OF INTEREST

None to declare.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JND-200596.

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