Dilated Cardiomyopathy 1A (DCM1A / LMNA Cardiomyopathy): Comprehensive Disease Report

Summary

Dilated Cardiomyopathy 1A (DCM1A; OMIM #115200; MONDO:0011541) is an autosomal-dominant genetic dilated cardiomyopathy caused by heterozygous pathogenic variants in **LMNA**, the gene encoding the nuclear-envelope intermediate filament proteins lamin A and lamin C (1q22). DCM1A is one of the most clinically malignant forms of inherited dilated cardiomyopathy (DCM) because its hallmark is an **arrhythmia-first natural history**: cardiac conduction disease (AV block), atrial arrhythmias (atrial fibrillation with thromboembolic risk), and life-threatening ventricular tachyarrhythmias with high sudden-cardiac-death (SCD) risk typically **precede** overt left-ventricular systolic dysfunction and heart failure. LMNA accounts for roughly 5–6% of DCM and carries the worst prognosis among common DCM genotypes, including the highest heart-transplantation rate (27%) in genotype-phenotype meta-analyses.

Mechanistically, DCM1A arises from a **weakened, mechanically fragile nuclear lamina**. Under the repetitive mechanical strain of the beating heart, lamin A/C-deficient nuclei sustain stress-induced envelope damage, which activates a DNA-damage response, disrupts chromatin organization and mechanotransduction, and dysregulates downstream signaling. Key druggable nodes identified across mouse models and patient-derived iPSC-cardiomyocytes include aberrant **MAPK (ERK/JNK/p38)** and **AKT–mTOR/DUSP4** signaling with impaired autophagy, **PDGF** pathway activation driving calcium-handling arrhythmia, **reactive oxygen species (ROS)** elevation, and **LOXL2**-mediated extracellular-matrix remodeling causing fibrosis. Microtubule-dependent force transmission concentrates mechanical stress on fragile nuclei and is itself a candidate therapeutic target.

Clinical management is dominated by **early, risk-guided ICD implantation** (via validated risk scores such as the van Rijsingen criteria and the Wahbi LMNA-risk-VTA score), device therapy for conduction disease (pacing/CRT), guideline-directed heart-failure pharmacotherapy, anticoagulation for atrial fibrillation, exercise restriction (an actionable gene–environment

interaction), and heart transplantation for end-stage disease. Cardiac MRI with late gadolinium enhancement (LGE) is a key diagnostic and prognostic biomarker. **No disease-modifying therapy is approved.** The lead mechanism-targeted candidate, the oral p38α-MAPK inhibitor ARRY-371797 (PF-07265803), showed promise in a 48-week phase 2 study but the confirmatory phase 3 REALM-DCM trial (NCT03439514) was terminated for futility, underscoring the gap between preclinical validation and clinical efficacy in this disease.

Section-by-Section Report

1. Disease Information

Overview. DCM1A is an inherited dilated cardiomyopathy defined by left-ventricular dilatation and systolic dysfunction in the context of a pathogenic *LMNA* variant, distinguished from other DCM subtypes by prominent, early electrical disease. As stated in a 2026 CMR meta-analysis, *"Lamin A/C (LMNA) cardiomyopathy is an inherited form of dilated cardiomyopathy associated with high rates of arrhythmias, conduction disease and sudden cardiac death, often preceding overt heart failure"* PMID: 41966904.

Key identifiers. - **OMIM:** #115200 (CMD1A / DCM1A); LMNA gene OMIM 150330 - **MONDO:** MONDO:0011541 - **HGNC gene:** HGNC:6636 (LMNA); NCBI Gene 4000; UniProt P02545 - **ICD-10:** I42.0 (dilated cardiomyopathy, parent term) - **MeSH:** Cardiomyopathy, Dilated (D002311); Laminopathies - **Orphanet:** within "Familial isolated dilated cardiomyopathy" / laminopathy spectrum

Synonyms / alternative names. LMNA-related dilated cardiomyopathy; LMNA cardiomyopathy; lamin A/C cardiomyopathy; CMD1A; DCM-CD (dilated cardiomyopathy with conduction defect). The disease sits within the broader "laminopathy" spectrum.

Information source. The evidence base is largely aggregated disease-level: OMIM/Orphanet curation, multicenter cohorts, genotype-phenotype meta-analyses, mouse models, and patient-derived iPSC studies, supplemented by individual pedigree reports.

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2. Etiology

Primary cause — genetic. DCM1A is caused by heterozygous pathogenic variants in *LMNA* (lamin A/C), inherited in an autosomal-dominant pattern. LMNA is pleiotropic; the same gene causes a spectrum of "laminopathies": *"Laminopathies are associated with a wide range of disease phenotypes, including neuromuscular, cardiac, metabolic disorders and premature aging syndromes"* PMID: 27529282.

Genetic risk factors / risk stratification. Within LMNA carriers, specific features confer high arrhythmic risk. In a European cohort of 269 carriers, *"Independent risk factors for MVA were nonsustained ventricular tachycardia, left ventricular ejection fraction <45% at the first clinical contact, male sex, and non-missense mutations (ins-del/truncating or mutations affecting splicing). MVA occurred only in persons with at least 2 of these risk factors"* PMID: 22281253. **Non-missense variants** (truncating/ins-del/splice) are the highest-risk molecular class.

Environmental risk factors. Male sex is associated with higher penetrance and worse outcomes. Intense/competitive exercise is a recognized disease modifier (see Section 5 and gene–environment interaction below). Age is a major factor given age-related incomplete penetrance.

Protective factors. No established genetic protective variants are documented for DCM1A. The clearest modifiable protective actions are **avoidance of intense/competitive exercise** and early prophylactic device therapy.

Gene–environment interactions. Because pathophysiology is driven by mechanical stress on fragile nuclei, physical strain is biologically expected to accelerate disease. Guidelines single out LMNA (and PKP2): *"The recommendations to engage in intensive exercise and competitive sports are usually contingent on annual clinical surveillance, except for pathogenic variants in specific genes, such as lamin A/C or plakophilin-2"* PMID: 36929832 — restriction is advised even in genotype-positive, phenotype-negative carriers.

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3. Phenotypes

DCM1A phenotypes are dominated by electrical disease preceding structural/pump failure. Quantitative frequencies from a meta-analysis of 8,097 DCM patients: *"While 73 % of DCM patients with LMNA mutations showed cardiac conduction diseases, low voltage was the reported ECG hallmark in PLN mutation carriers. The frequency of ventricular arrhythmia in DCM patients with LMNA (50 %) and PLN (43 %) mutation"* PMID: 27576561.

Phenotype	HPO term (suggested)	Type	Frequency	Onset / course
Cardiac conduction defect / AV block	HP:0031546 / HP:0001678	Clinical sign (ECG)	~73%	Often first sign, 3rd–4th decade; progressive
Ventricular arrhythmia / NSVT	HP:0004308 / HP:0004757	Clinical sign	~50%	Adult; high SCD risk
Atrial fibrillation	HP:0005110	Clinical sign	Common	Adult; thromboembolic risk
Dilated cardiomyopathy / reduced LVEF	HP:0001644 / HP:0001635	Physical/ structural	Common, mean ~5th decade	Progressive to heart failure
Sudden cardiac death	HP:0001645	Outcome	Elevated	Adult; can precede HF
Congestive heart failure	HP:0001635	Clinical sign	Late	Progressive, end-stage
Skeletal myopathy (overlap EDMD/ LGMD1B)	HP:0003198	Sign	Variable/ subclinical	Childhood–adult

Characteristics. Age of onset is typically adult (mean DCM onset ~fifth decade), but conduction disease can begin in the 30s. Severity is variable but tends to be severe due to arrhythmia and SCD. Progression is progressive with superimposed episodic arrhythmic events.

Quality of life. Reduced functional capacity is measurable by 6-minute walk test and Kansas City Cardiomyopathy Questionnaire (KCCQ); actigraphy in the REALM-DCM trial confirmed reduced real-world physical activity correlating with KCCQ physical-limitation scores PMID: 41693767.

4. Genetic / Molecular Information

Causal gene. *LMNA* (lamin A/C; HGNC:6636; NCBI Gene 4000; UniProt P02545; chromosome 1q22; gene OMIM 150330; disease OMIM #115200). Lamin A and lamin C are produced by alternative splicing of *LMNA*.

Variant spectrum. In a cohort of 324 unrelated DCM patients, LMNA protein-altering variants occurred at **5.9%** frequency PMID: 18585512. The variant classes: *"Of the 18 alterations, 11 were missense (one present in 2 kindreds), 3 were nonsense, 3 were insertion/deletions, and 1 was a splice site alteration"* PMID: 18585512 — predominantly heterozygous point mutations distributed across the rod domain and Ig-fold. Recurrent pathogenic variants reported include R190W, R644C, R377H, R89L, and a V445E Ig-fold missense associated with LV non-compaction and reduced sodium current PMID: 25829471.

Variant classification (ACMG/AMP). LMNA variants span pathogenic, likely pathogenic, and VUS in ClinVar. **Non-missense** (truncating/ins-del/splice) alleles confer the highest arrhythmic risk: *"non-missense mutations (ins-del/truncating or mutations affecting splicing)"* PMID: 22281253.

Origin. Germline; typically inherited (familial), occasionally de novo.

Functional consequence. Mixed mechanism — haploinsufficiency/loss-of-function combined with dominant-negative effects on nuclear-lamina assembly. Mutant lamin can aggregate subjacent to the nuclear envelope PMID: 25829471.

Penetrance / expressivity. Incomplete and age-related: *"an incomplete and age-related penetrance"* PMID: 25837155; expressivity is highly variable within families.

Modifier genes / epigenetics. LMNA-linked chromatin disorganization implies epigenetic dysregulation; specific modifier alleles are not firmly established, though pedigrees with divergent sub-family phenotypes suggest modifiers PMID: 29947763. No recurrent chromosomal abnormality defines DCM1A.

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5. Environmental Information

- **Environmental/mechanical factors.** Mechanical strain on fragile nuclei is the dominant "environmental" accelerant. **Intense/competitive exercise** is discouraged in LMNA carriers (see Section 2 gene–environment interaction) PMID: 36929832.

- **Lifestyle.** Standard cardiovascular risk-factor control applies. Hypertension co-occurs frequently in DCM generally and may modulate severity.
- **Infectious agents.** Not causal for DCM1A. Note the important differential: LMNA-DCM can mimic cardiac sarcoidosis on imaging, and endomyocardial biopsy may be equivocal — genetic testing is essential to distinguish them PMID: 40225500.

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6. Mechanism / Pathophysiology

Upstream trigger — nuclear-envelope fragility. LMNA mutations weaken the nuclear lamina, increasing nuclear-envelope fragility. The causal chain is summarized as: *"LMNA mutations disrupt nuclear envelope stability, activating the DNA damage response (DDR) and compromising chromatin organization and mechanotransduction"* PMID: 39998502.

Mechanical force transmission. The LINC complex (nesprins/SUN proteins) couples the cytoskeleton to the lamina. Microtubule-dependent forces concentrate mechanical stress on lamin-deficient nuclei: *"Microtubule disruption prevented nuclear damage and preserved cardiac function in lamin A/C deficiency"* PMID: 41073815, identifying microtubule-mediated force as both driver and therapeutic target.

Downstream signaling — MAPK / AKT–mTOR / DUSP4. Aberrant ERK1/2 signaling induces DUSP4, activating AKT–mTOR and impairing autophagy: *"Dusp4 expression is enhanced in hearts with LMNA cardiomyopathy, and its overexpression in mice causes it by activating AKT-mTOR signaling that impairs autophagy"* PMID: 23048029.

Additional druggable nodes (iPSC-CM evidence). Patient-derived iPSC-cardiomyocytes reveal calcium-handling arrhythmia driven by PDGF: *"the mutant iPSC-CMs displayed aberrant calcium homeostasis that led to arrhythmias at the single-cell level. Mechanistically, we show that the platelet-derived growth factor (PDGF) signalling pathway is activated in mutant iPSC-CMs"* PMID: 31316208. ROS elevation contributes downstream PMID: 39143095, and LOXL2-mediated ECM remodeling drives fibrosis (simtuzumab as candidate inhibitor) PMID: 41841259.

Tissue damage. Myocardial fibrosis (LGE on CMR) is a central downstream lesion, correlating with wall-motion and conduction abnormalities PMID: 21689390.

Suggested GO / CL terms. GO:0006974 (DNA-damage response), GO:0071260 (cellular response to mechanical stimulus), GO:0006914 (autophagy), GO:0000165 (MAPK cascade), GO:0006979 (response to oxidative stress); CL:0000746 (cardiac muscle cell/cardiomyocyte), CL:0002548 (cardiac fibroblast).

Causal chain (ASCII):

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LMNA mutation
   │
   ▼
Weakened nuclear lamina (fragile nucleus)
   │  ── microtubule / LINC-transmitted mechanical force
   ▼
Nuclear-envelope damage → DNA-damage response + chromatin/mechanotransduction disruption
   │
   ├──► ERK/JNK/p38 MAPK ↑ → DUSP4 ↑ → AKT-mTOR ↑ → autophagy ↓
   ├──► PDGF pathway ↑ → aberrant Ca²⁺ handling → single-cell arrhythmia
   ├──► ROS ↑ (oxidative stress)
   └──► LOXL2 ↑ → ECM remodeling → myocardial fibrosis (LGE)
   │
   ▼
Conduction disease + atrial/ventricular arrhythmia  (EARLY)
   │
   ▼
LV dilatation + systolic dysfunction → heart failure  (LATE)
   │
   ▼
Sudden cardiac death / transplantation
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7. Anatomical Structures Affected

- **Primary organ:** heart (UBERON:0000948), specifically myocardium/left ventricle (UBERON:0002084), cardiac conduction system (UBERON:0004146).
- **Secondary involvement:** systemic (brain — cardioembolic stroke from AF PMID: 39687831); skeletal muscle in overlap laminopathies (paravertebral, glutei, quadriceps, posterior thigh; peroneus involvement helps distinguish EMD- from LMNA-related disease) PMID: 26573435.
- **Body systems:** cardiovascular (primary), musculoskeletal (overlap), nervous (secondary embolic).

- **Tissue/cell level:** cardiac muscle (striated) and conduction tissue; cardiomyocytes (CL:0000746) and cardiac fibroblasts (CL:0002548).
- **Subcellular:** nuclear envelope/nuclear lamina (GO:0005638 nuclear membrane; GO:0005652 nuclear lamina), nucleus (GO:0005634); secondary involvement of the microtubule cytoskeleton (GO:0005874).
- **Laterality:** left-ventricle predominant, biventricular in advanced disease.

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8. Temporal Development

- **Onset:** adult-onset predominantly; conduction disease may begin in the 3rd–4th decade, with DCM manifesting on average in the 5th decade. Insidious then progressive.
- **Progression / stages:** early = isolated conduction disease / arrhythmia; intermediate = LV dilatation with declining EF; advanced/end-stage = refractory heart failure requiring transplant. Natural history is progressive with superimposed episodic arrhythmic events. A five-generation pedigree documented sinus bradycardia/AV block I° at ~36.5 yr → paroxysmal then permanent AF → NSVT/SCD, with 17 SCDs at mean age 49.3 yr PMID: 29947763.
- **Patterns:** no spontaneous remission; disease is chronic and lifelong. Critical intervention windows exist for prophylactic ICD (before first malignant arrhythmia) and early CRT in conduction disease PMID: 38495409.

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9. Inheritance and Population

- **Epidemiology.** DCM overall affects ~1 in 2,500; LMNA accounts for ~5–6% of DCM (5.9% in a 324-proband cohort PMID: 18585512; 7.5% familial vs 3.6% idiopathic in Parks 2008).
- **Inheritance pattern:** autosomal dominant.
- **Penetrance:** incomplete, age-related PMID: 25837155.
- **Expressivity:** highly variable, even within families/pedigrees PMID: 29947763.
- **Natural history/survival:** markedly worse than non-carrier DCM — *"event-free survival at the age of 45 years was 31% versus 75% in non-carriers"* PMID: 12628721.
- **Sex ratio:** male-biased penetrance; DCM overall M:F ~2.4:1, and even among genotype-positive DCM: *"similar to patients with an identified DCM variant (0.31 [95% CI, 0.26-0.36]; M:F 2.22:1"* PMID: 39895490. Male sex is itself an arrhythmic risk factor.

- **Founder effects / consanguinity:** not a prominent feature (dominant disease); no strong founder population documented. The concept of "carrier frequency" for a dominant pathogenic variant maps to population variant prevalence — ~0.7% of general-population cohorts harbor any actionable inherited-cardiomyopathy variant across 13 genes PMID: 35544052.

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10. Diagnostics

Clinical/functional tests. - **ECG / Holter:** first-line — detects AV block, bradyarrhythmia, AF, NSVT (LOINC ECG panels). - **Echocardiography:** LV dilatation, reduced EF. - **Cardiac MRI with LGE:** key diagnostic/prognostic biomarker. *"Patients had LV myocardial fibrosis in 88% of cases. Segmental wall motion abnormalities correlated strongly with the degree of enhancement. Myocardial enhancement was associated with conduction abnormalities"* PMID: 21689390. Meta-analysis: *"The LGE risk ratio for patients with LMNA cardiomyopathy versus healthy controls was 14.39 (P<0.001)"* PMID: 41966904. Subclinical parametric-mapping changes (prolonged native T1/T2) are present even with preserved EF PMID: 40372342. - **Biomarkers:** NT-proBNP tracks heart-failure severity and treatment response. - **Biopsy:** endomyocardial biopsy may be equivocal and is not required; caution against relying on imaging alone when sarcoidosis is in the differential PMID: 40225500.

Genetic testing. Central to diagnosis. Approach: DCM multigene panel or whole-exome sequencing including *LMNA*; single-gene/cascade testing in families with a known variant. Genetic testing enables accurate etiologic diagnosis, treatment (early ICD), and cascade screening of relatives PMID: 40225500, PMID: 29497013.

Differential diagnosis. Cardiac sarcoidosis (imaging mimic), other genetic DCM (TTN, FLNC, RBM20, PLN, DSP), arrhythmogenic cardiomyopathy, ischemic cardiomyopathy.

Screening. Cascade genetic testing plus serial ECG/Holter/echo/CMR surveillance of at-risk relatives.

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11. Outcome / Prognosis

DCM1A has among the worst prognoses of genetic DCM.

Prognostic metric	Value	Source
Event-free survival at age 45 (carriers)	31% vs 75% non-carriers	PMID: 12628721
Cardiac conduction disease frequency	~73%	PMID: 27576561
Ventricular arrhythmia frequency	~50%	PMID: 27576561
Heart-transplant rate (highest of DCM genes)	27%	PMID: 27576561
LTVTA incidence in carriers	19.3–23.4%	PMID: 31155932

Prognostic factors / risk models. Two validated tools guide ICD decisions: - **van Rijsingen criteria** — malignant ventricular arrhythmia (MVA) occurs only with ≥2 of: NSVT, LVEF<45%, male sex, non-missense mutation PMID: 22281253. - **Wahbi LMNA-risk-VTA score** (n=839): *"Predictors of LTVTA in the derivation sample were: male sex, nonmissense LMNA mutation, first degree and higher atrioventricular block, nonsustained ventricular tachycardia, and left ventricular ejection fraction"*; C-index 0.776–0.800; available as an online calculator PMID: 31155932.

Mortality/morbidity. High SCD risk (often preceding heart failure), progressive heart failure, and thromboembolic stroke from AF. LGE burden is prognostic.

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12. Treatment

Standard of care = guideline heart-failure therapy + device therapy + anticoagulation + transplant, with **no approved disease-modifying drug**.

- **Pharmacotherapy (NCIT interventions):** ACE inhibitors/ARB/ARNI, beta-blockers, mineralocorticoid-receptor antagonists (guideline-directed HF therapy); anticoagulation for AF (stroke prevention).
- **Device therapy:** ICD for SCD prevention (lower threshold than general DCM, guided by risk scores); pacemaker/CRT for conduction disease. Early CRT may preserve EF and delay end-stage HF in LMNA carriers with a pacing/ICD indication PMID: 38495409.
- **Surgical:** heart transplantation for end-stage disease (highest rate among DCM genotypes).
- **Mechanism-targeted (experimental).** The p38α-MAPK inhibitor **ARRY-371797 (PF-07265803)**: *"ARRY-371797 (PF-07265803), a potent, selective, oral, small-molecule inhibitor of the p38α mitogen-activated protein kinase pathway, improved 6-minute walk test*

(6MWT) distance in 12 patients with symptomatic LMNA-related DCM in a 48-week, open-label, phase 2 study" PMID: 36114020, with reduced NT-proBNP and improved KCCQ PMID: 36718638. However, *"REALM-DCM was terminated after a planned interim analysis suggested futility"* PMID: 38979608 (phase 3, NCT03439514).

- **Emerging preclinical targets:** JNK/ERK inhibition, microtubule modulation, PDGFRB inhibition, antioxidants (ROS), and LOXL2 inhibition (simtuzumab) — all validated in models but not yet clinically established.

Personalized medicine. Genotype (non-missense vs missense) and the risk scores directly guide ICD timing and exercise counseling.

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13. Prevention

- **Primary prevention:** cannot prevent inheritance of a dominant variant; genetic counseling and reproductive options (PGD/prenatal testing) apply.
- **Secondary prevention: cascade genetic screening** of relatives + serial cardiac surveillance (ECG/Holter/echo/CMR) to detect subclinical disease early. CMR parametric mapping can detect preclinical involvement PMID: 40372342.
- **Tertiary prevention:** early/prophylactic ICD to prevent SCD (risk-score guided); anticoagulation to prevent stroke; **exercise restriction** to slow progression PMID: 36929832; guideline HF therapy to prevent decompensation.
- **Counseling:** genetic counseling for risk assessment and family planning is a cornerstone.

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14. Other Species / Natural Disease

- **Taxonomy / orthologs:** human *LMNA* (NCBI Gene 4000); mouse *Lmna* (NCBI Gene 16905); orthologs conserved across mammals. Disease mechanisms (nuclear-envelope biology, LINC complex) are evolutionarily conserved.
- **Natural disease in other species:** LMNA/laminopathy-type dilated cardiomyopathy is chiefly modeled experimentally rather than reported as a common spontaneous companion-animal disease; comparative relevance is largely via engineered models. (No specific spontaneous animal disease was confirmed in this investigation.)
- **Zoonotic potential:** none — genetic, non-transmissible.

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15. Model Organisms

Mouse models (mammalian). - **Lmna^H222P/H222P knock-in** — the workhorse autosomal EDMD/DCM model. ERK and JNK MAPK branches are abnormally activated in the heart; pharmacologic inhibition improves cardiac structure/function and fibrosis: *"Echocardiography and histological analysis demonstrated that treatment prevented left ventricular end-systolic dilatation, increased ejection fraction, and decreased myocardial fibrosis"* PMID: 21173351. ERK inhibition (PD98059) PMID: 18927124, JNK inhibition (SP600125) PMID: 20388542, and genetic Erk1 deletion PMID: 23933734 all improved outcomes. Emerin/Lmna double mutants dissect skeletal- vs cardiac-muscle contributions PMID: 31430335. - **Other alleles:** Lmna N195K, LMNA knockout — cardiac conduction/hemodynamic phenotypes.

Cellular / in vitro (iPSC-CMs). Patient-derived iPSC-cardiomyocytes recapitulate arrhythmia via aberrant Ca^{2+} handling and PDGF activation PMID: 31316208; frameshift-LMNA iPSC models show ROS-driven pathology PMID: 39143095 and LOXL2/ECM remodeling PMID: 41841259.

Phenotype recapitulation. Mouse models reproduce DCM, fibrosis, and MAPK activation well; iPSC-CMs capture cell-autonomous arrhythmia. **Key limitation:** MAPK inhibition rescued mice but the corresponding human phase 3 (REALM-DCM) failed PMID: 38979608 — a cautionary example of imperfect translational fidelity.

Mechanistic Model / Interpretation

DCM1A is best understood as a **mechanotransduction disease of the cardiomyocyte nucleus**. The primary defect — a structurally weakened nuclear lamina — renders the nucleus vulnerable to the relentless mechanical strain of cardiac contraction. Force is transmitted to the nucleus via the microtubule cytoskeleton and the LINC complex; where lamin A/C is deficient, this force produces stress concentrations and physical envelope damage. The cell responds with a DNA-damage response and pathological signaling — chiefly MAPK (ERK/JNK/p38) feeding DUSP4→AKT–mTOR with impaired autophagy, plus PDGF-driven calcium mishandling, ROS, and LOXL2-driven fibrosis.

Two clinical corollaries follow directly from this model. First, the **arrhythmia-first phenotype** reflects the special vulnerability of the conduction system and the arrhythmogenic consequences of Ca^{2+} dysregulation and progressive fibrosis, which manifest electrically before pump failure. Second, the **exercise-restriction recommendation** is a rational,

mechanism-derived intervention: reducing mechanical load reduces nuclear damage. The therapeutic disappointment of p38α inhibition despite strong mouse data suggests that MAPK is one downstream branch of a multi-nodal network; targeting the upstream mechanical driver (microtubules/LINC) or rational combinations (PDGFRB, LOXL2, ROS) may be required.

Evidence Base

PMID	Role in report	Support / challenge
41966904	Disease definition; LGE prognostic	Supports arrhythmia-first course; LGE RR 14.39
39998502	Phenotype spectrum; mechanism	Supports NE/DDR/mechanotransduction chain
22281253	Risk stratification	Supports van Rijsingen ≥2-factor rule
31155932	Risk score	Supports LMNA-risk-VTA (C-index 0.78–0.80)
18585512	Epidemiology/genetics	LMNA 5.9% of DCM; variant classes
12628721	Natural history	31% vs 75% event-free survival
39895490	Sex ratio	Male bias M:F 2.22:1
23048029	Mechanism	DUSP4–AKT-mTOR–autophagy
41073815	Mechanism/therapy	Microtubule force as driver/target
36114020	Therapy phase 2	p38α inhibitor 6MWT benefit
38979608	Therapy phase 3	**Challenges** MAPK strategy (futility)
21689390	Diagnostics	88% LGE fibrosis; ties to conduction
27529282	Pleiotropy	Laminopathy spectrum
27576561	Phenotype frequencies	73% conduction, 50% VA, 27% HTx
36929832	Gene–environment	Exercise restriction for LMNA
31316208	iPSC mechanism	PDGF/Ca^{2+} arrhythmia
21173351	Mouse model	MAPK inhibition rescues phenotype
25837155	Genetics	Incomplete, age-related penetrance

Limitations and Knowledge Gaps

1. **Translational gap:** The most striking limitation is that the leading mechanism-targeted therapy (p38α inhibitor) succeeded in mice and phase 2 but failed phase 3 (REALM-DCM), leaving no approved disease-modifying drug and questioning MAPK as a sufficient single target.
2. **Small trial sizes:** Phase 2 (n=12) and phase 3 (n=77) were small for a rare disease, limiting statistical power and generalizability.
3. **Risk-model refinement:** van Rijsingen and Wahbi scores are validated but derived largely from European cohorts; performance across ancestries and in genotype-positive/phenotype-negative carriers needs broader validation.
4. **Penetrance/modifiers:** Incomplete, age-related penetrance and variable expressivity remain poorly explained; specific genetic/epigenetic modifiers are not established.
5. **Epidemiology precision:** Exact population prevalence/incidence of DCM1A specifically (vs DCM overall) is not firmly quantified; carrier-frequency data derive from broad multigene screens.
6. **Animal disease:** Spontaneous natural DCM1A in non-human species is not well documented in this investigation.

Proposed Follow-up Experiments / Actions

1. **Combination-target trials:** Test rational combinations (e.g., MAPK + PDGFRB inhibition, or microtubule/LINC modulation + anti-fibrotic LOXL2 inhibition) in iPSC-CM and Lmna^H222P models before human trials, given the single-node p38 failure.
2. **Upstream mechanical targeting:** Pursue microtubule-directed or LINC-complex therapeutics that reduce nuclear mechanical damage at the source [PMID: 41073815].
3. **Anti-fibrotic strategy:** Advance LOXL2 inhibition (simtuzumab) evaluation informed by CMR-LGE endpoints as a biomarker [PMID: 41841259].
4. **Biomarker-guided prevention trials:** Use subclinical CMR (native T1/T2) to enroll genotype-positive/phenotype-negative carriers into early-intervention/prevention studies [PMID: 40372342].

5. **Prospective risk-model validation:** Validate LMNA-risk-VTA and van Rijsingen scores across diverse ancestries and integrate CMR-LGE quantitatively.
6. **Registry/natural-history studies:** Establish LMNA-specific registries to refine prevalence, penetrance, sex effects, and modifier discovery.
7. **Exercise-intervention evidence:** Prospectively test the effect of activity restriction on disease progression to move the recommendation from mechanistic inference to evidence-based guideline.

Report compiled from a 5-iteration autonomous investigation: 13 confirmed findings, 46 papers reviewed. Evidence types span human clinical cohorts, genotype-phenotype meta-analyses, mouse knock-in models, and patient-derived iPSC-cardiomyocyte studies.
