UC San Diego Health

Gene therapy for cardiomyopathy: practical considerations for patients

Quan M. Bui, MD
Assistant Professor of Medicine
Advanced Heart Failure/Transplant Cardiology
Division of Cardiovascular Medicine
University of California, San Diego

Monday, July 14, 2025

Disclosures

- Research Grants: AHA Career Development Award (2024-2027), Janice Wiesman Young Investigator (2023-2025)
- Consulting: Lexeo Therapeutics, Papillon Therapeutics

Outline

- Overview of genetic cardiomyopathies
- Current state of therapeutics: cancer vs heart failure
- Gene therapy
  - How it works
  - Delivery
  - Side effects and immunosuppression
  - Practical considerations
- Importance of genetic testing

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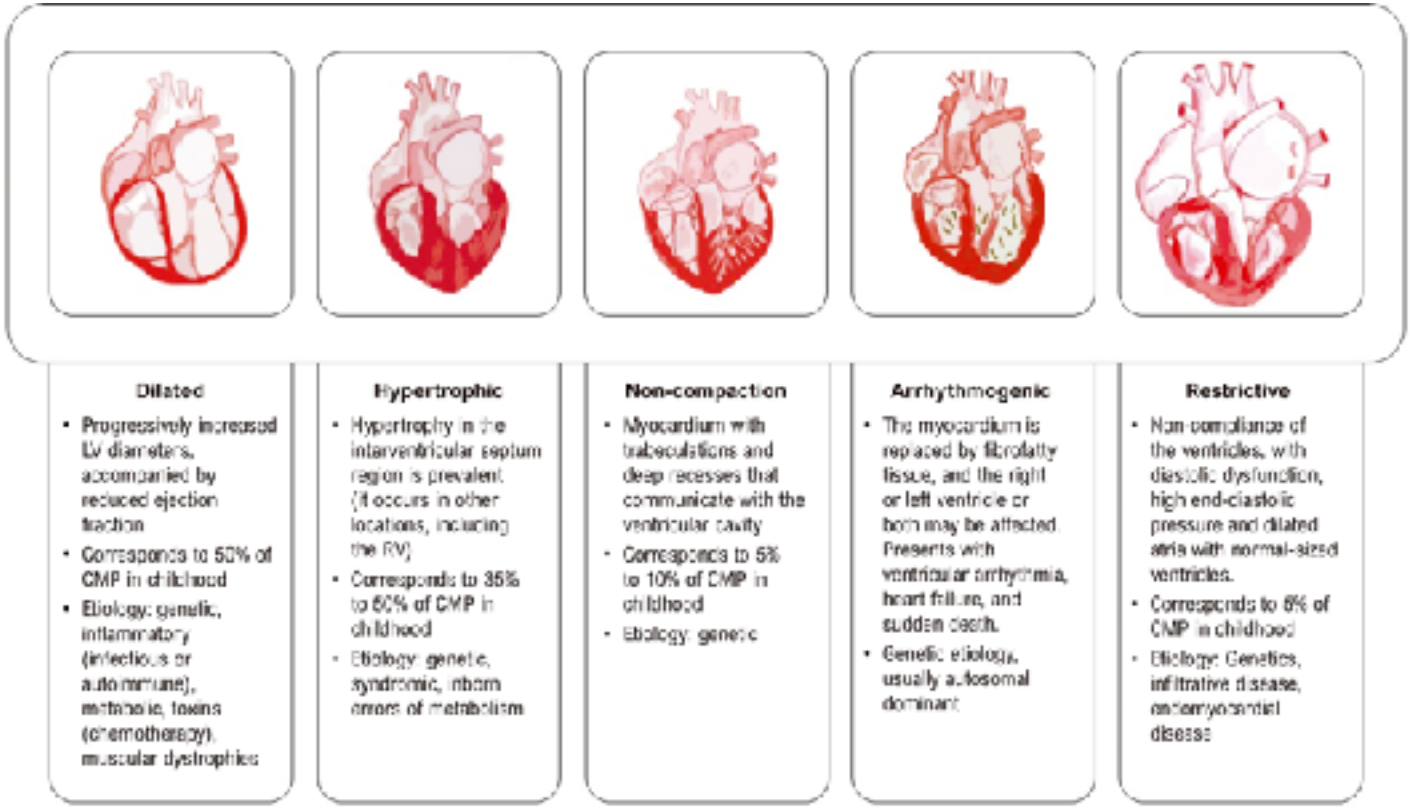
Cardiomyopathies: subset with underlying genetic cause



Dilated

- Progressively increased LV diameters, accompanied by reduced ejection fraction
- Corresponds to 50% of CMP in childhood
- Etiology: genetic, inflammatory (infectious or autoimmune), ischemic, toxins (chemotherapy), muscular dystrophies

Hypertrophic

- Hypertrophy in the interventricular septum region is prevalent (it occurs in other locations, including the RV)
- Corresponds to 35% to 60% of CMP in childhood
- Etiology: genetic, syndromic, inborn errors of metabolism

Non-compaction

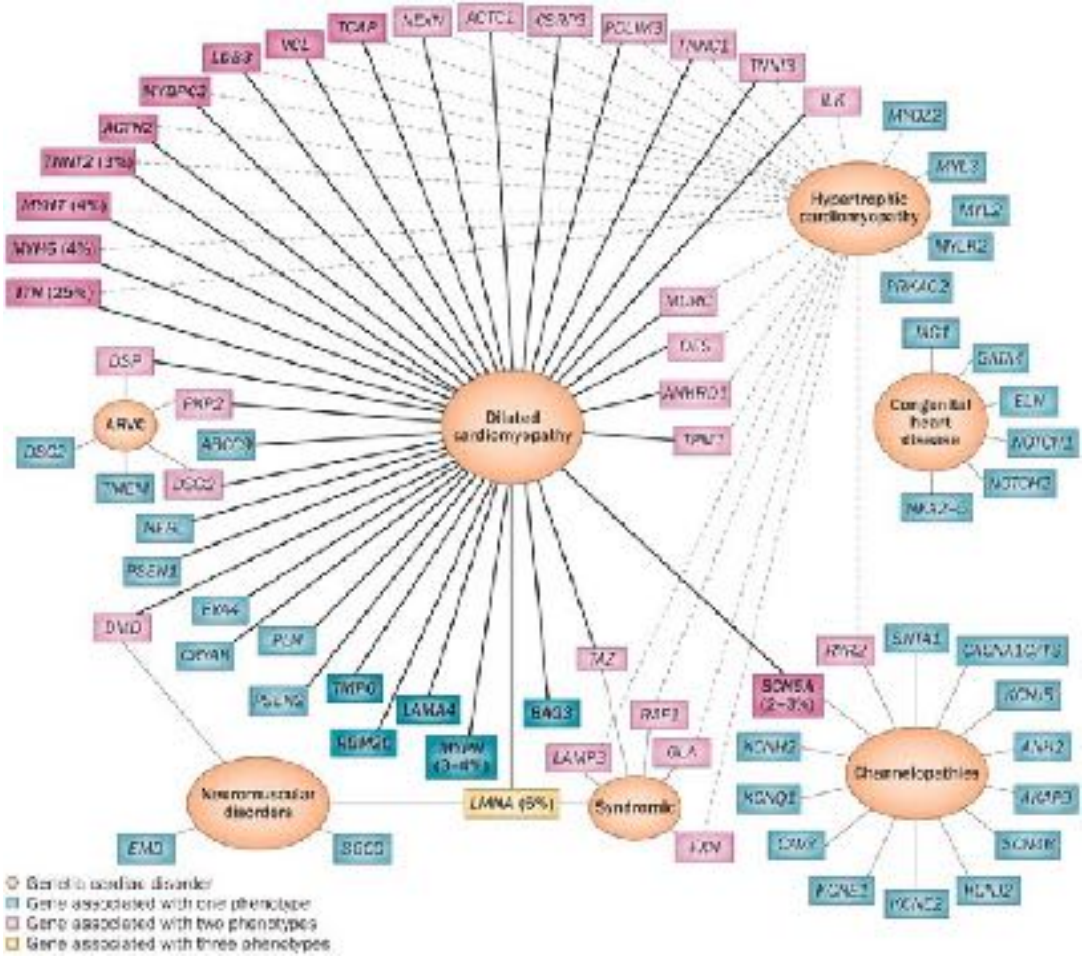
- Myocardium with trabeculations and deep recesses that communicate with the ventricular cavity
- Corresponds to 5% to 10% of CMP in childhood
- Etiology: genetic

Arrhythmogenic

- The myocardium is replaced by fibrofatty tissue, and the right or left ventricle or both may be affected. Presents with ventricular arrhythmia, heart failure, and sudden death.
- Genetic etiology, usually autosomal dominant

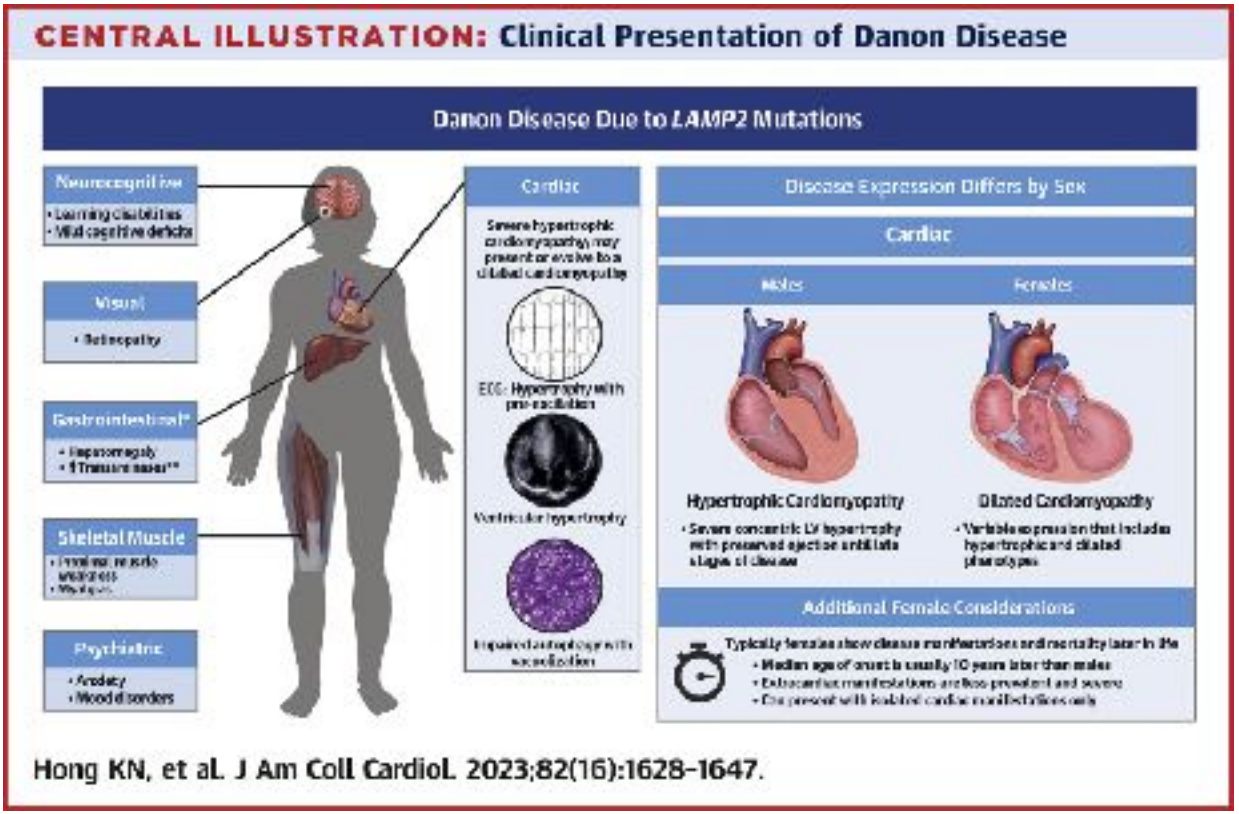
Restrictive

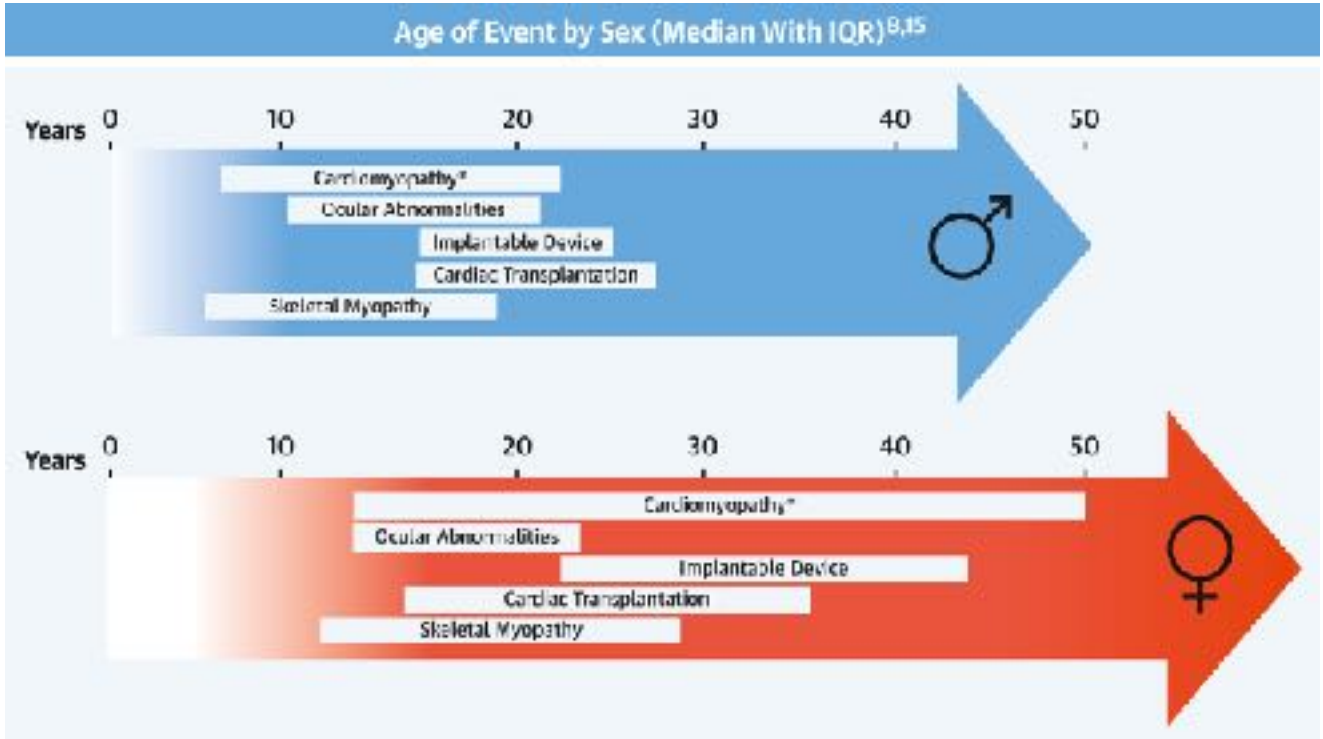
- Non-compliance of the ventricles, with diastolic dysfunction, high end-diastolic pressure and dilated atria with normal-sized ventricles.
- Corresponds to 6% of CMP in childhood
- Etiology: Genetics, infiltrative disease, endomyocardial disease



Torbey A et. al. Arq Bras Cardio 2024
Hershberger R et. al. Nature Cardio 2013

Danon disease: morbid genetic disease lacking effective treatment





Hong K et. al. JACC 2023

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Therapeutics in 2025: cancer vs heart failure

- **Cancer**
  - Treat as soon as disease detected, even in the **absence of symptoms**
  - Therapeutics based on tissue **genetics** and **endotype**

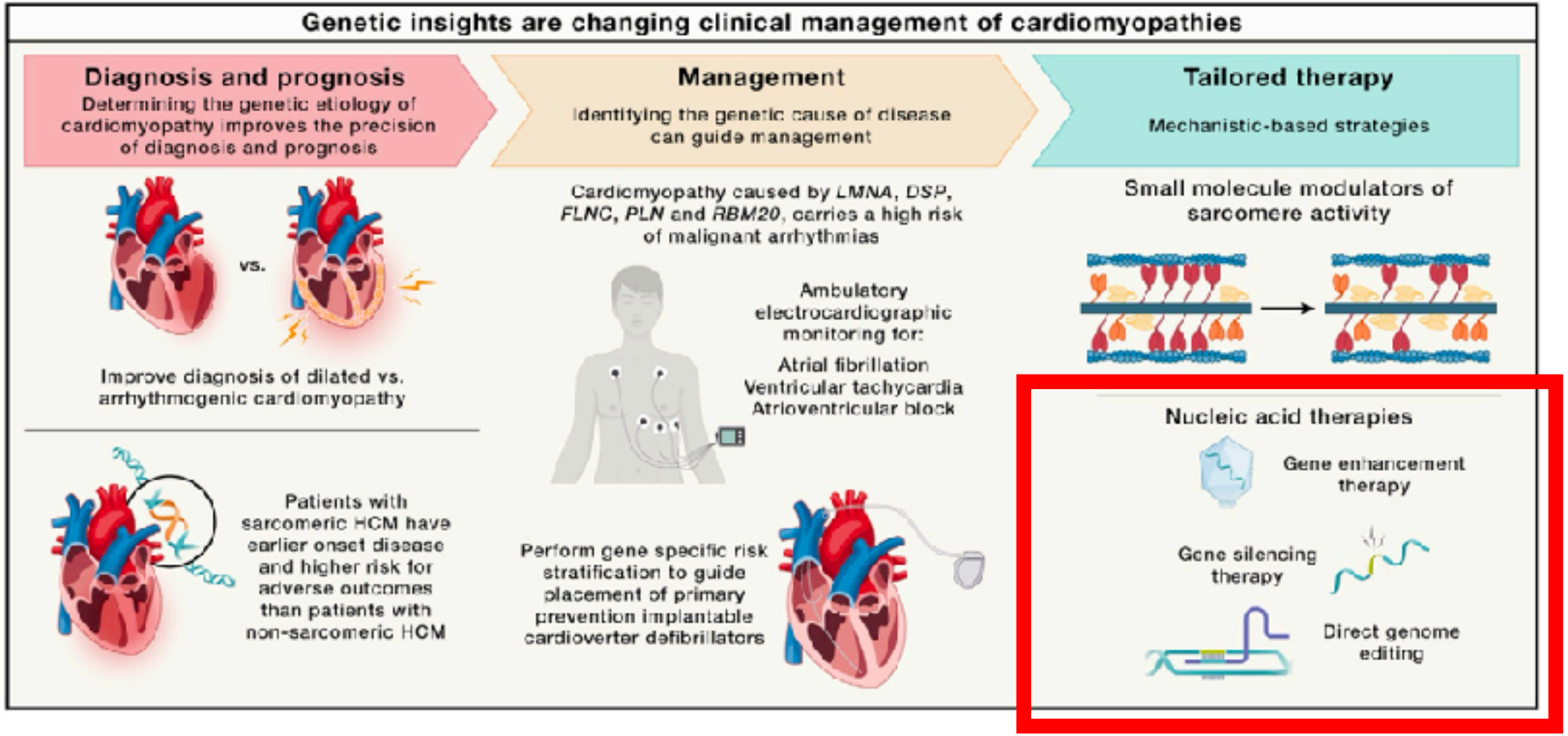
- **Heart Failure**
  - Therapies generally started once patients develop **symptoms**
  - Therapeutics based on **heart structure** and **phenotype**

- For genetic cardiomyopathies, **current treatments are repurposed heart failure medications to mitigate symptoms**.

- **Disease-targeted therapies** that **address the underlying genetic or molecular mechanisms** may offer more personalized and effective treatment.

*Slide adapted from Dr. Eric Adler

Gene therapy: tailored therapy for rare and genetic diseases



Parikh V et. al. Cell 2025

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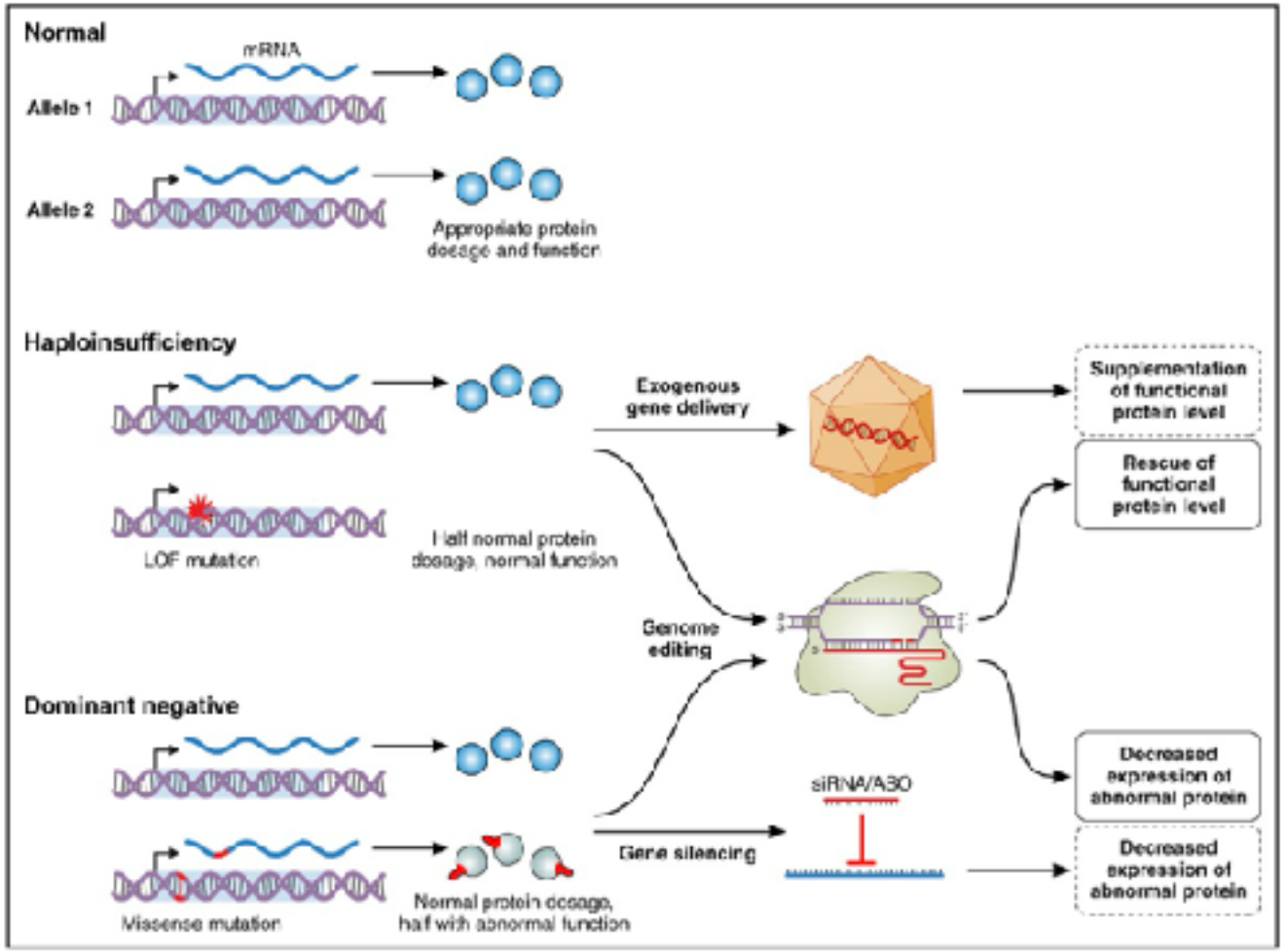
Gene therapy: how it works

- Every person has **two copies of each gene**.
- In a healthy person, **both copies work** to produce the **right amount of protein** the body needs

- **Problems:**
  - Not enough protein (haploinsufficiency)
    - *Strategy 1:* Deliver genetic material to heart cells to increase functional protein
    - *Strategy 2:* Genetic editing to correct mutation and increase functional protein
  - Harmful protein (dominant negative)
    - *Strategy 1:* Deliver genetic material to heart cells silence the harmful protein so that it is not made
    - *Strategy 2:* Genetic editing to correct the mutation and decrease harmful protein



Kim Y et. al. Circulation 2024

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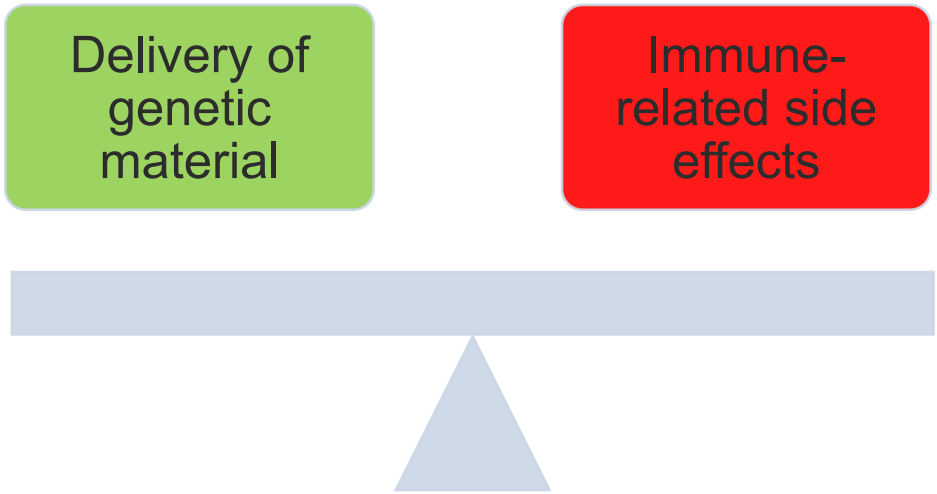
Gene therapy: delivery to the heart is the issue

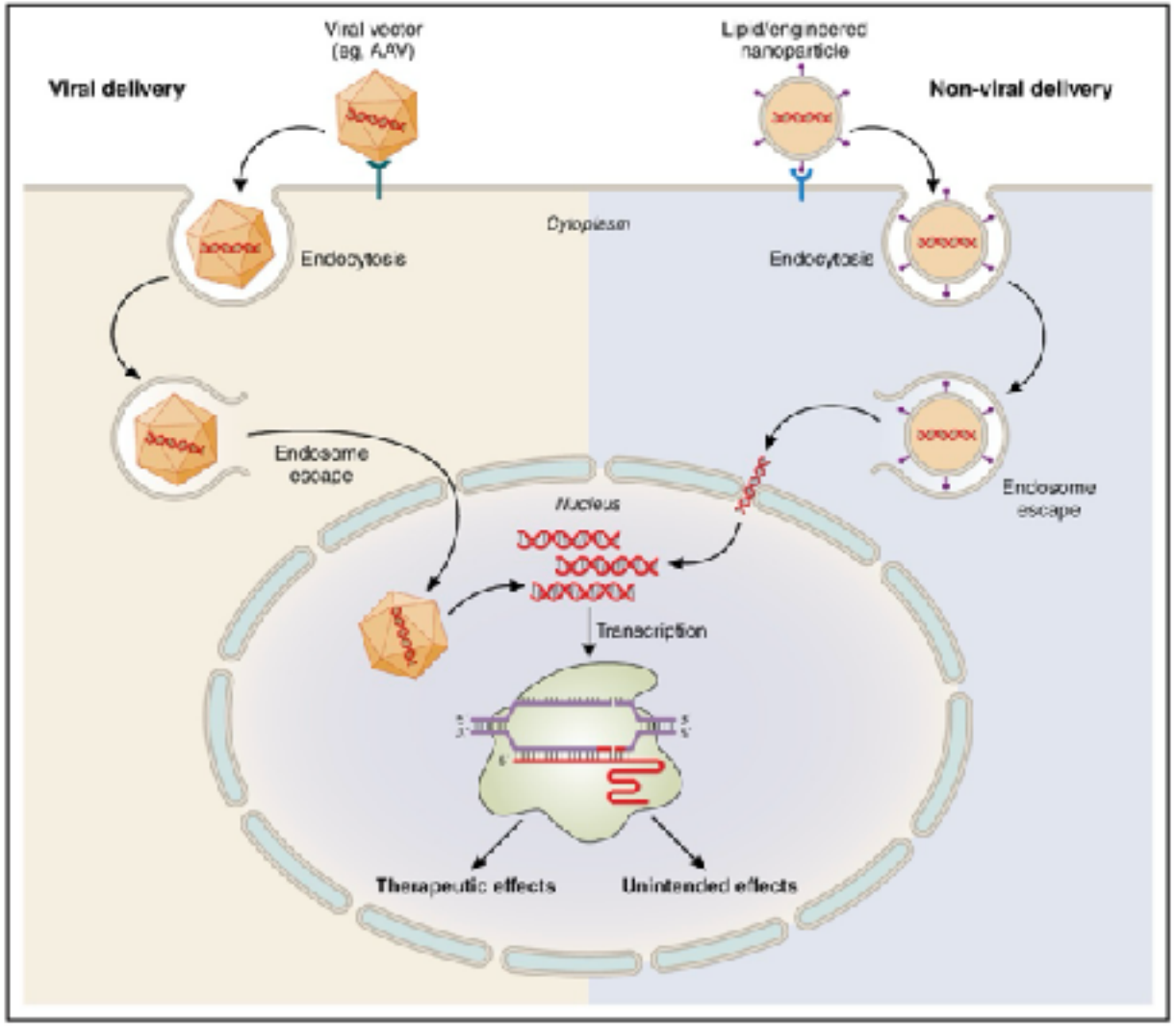
- *"There are only 3 problems in gene therapy: delivery, delivery, and delivery."* – Inder Verma
- Delivery of gene therapy to the the heart is especially hard.
- Need to get enough treatment into heart cells without triggering harmful immune reactions. It's a careful balancing act.



Gene therapy: delivery of the medicine

- Genetic medicines are unable to reach the heart on their own – need a delivery “vehicle”

- **Types of “vehicles”:**
  - Viral
    - Adeno-associated viruses (AAV) most common, can target different organs/tissue
  - Non-viral
    - Lipid nano-particles most common, targets liver mostly
    - Bio-conjugation (antibodies)
  - Delivery of gene therapy to the heart is challenging (viral vectors best currently)



Kim Y et. al. Circulation 2024

Delivery vehicles (viral): adeno-associated viruses/AAV

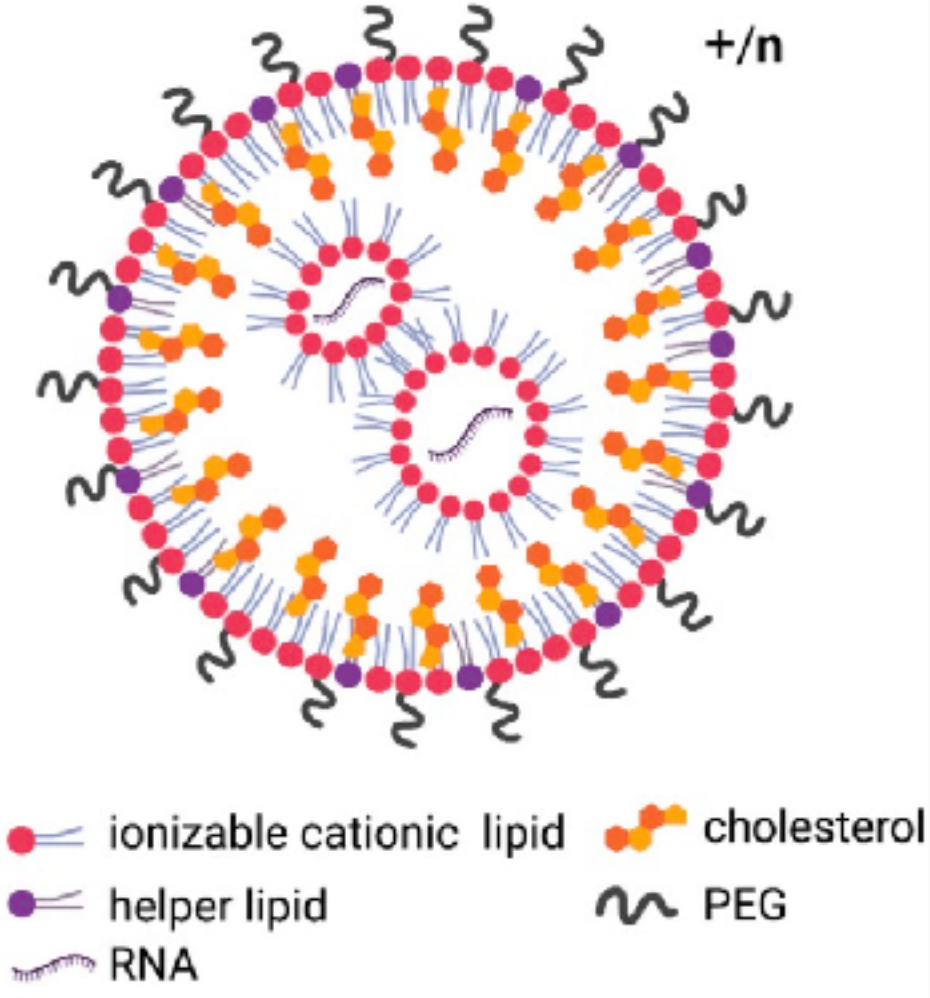
- **Composition:**
  - Made up of a protein shell (called a capsid) that carries a small piece of genetic material inside
  - AAV is genetically modified so that virus's own genes are removed ("inactive")
- **Advantages:**
  - Safe and well-studied: strong track record of safety in clinical trials, approved therapies
  - Specific tissue targeting: different types of AAVs can target various tissues, heart (AAV9)
  - Long-lasting effects: sustained gene expression
- **Challenges:**
  - Small packaging: carries limited sizes of genes
  - Pre-existing antibodies: reduce effectiveness, prevent future dosing
  - Immune-related side effects: triggered by response to AAV

	Adenovirus	Adeno Associated Virus
1 Expression & Genomic integration	High level Long-term expression Transient expression No genomic integration	Moderate level Long-term expression Transient expression No genomic integration
2 Transduction & Packaging capacity	Dividing and non-dividing cells 4-5 kb	Dividing and non-dividing cells 5kb
3 Immunogenicity	High Immunogenicity	Moderate Immunogenicity
Clinical trial	Yes	Yes

Bisserier M et. al. Cells 2022

Delivery vehicles (non-viral): lipid nanoparticles/LNP

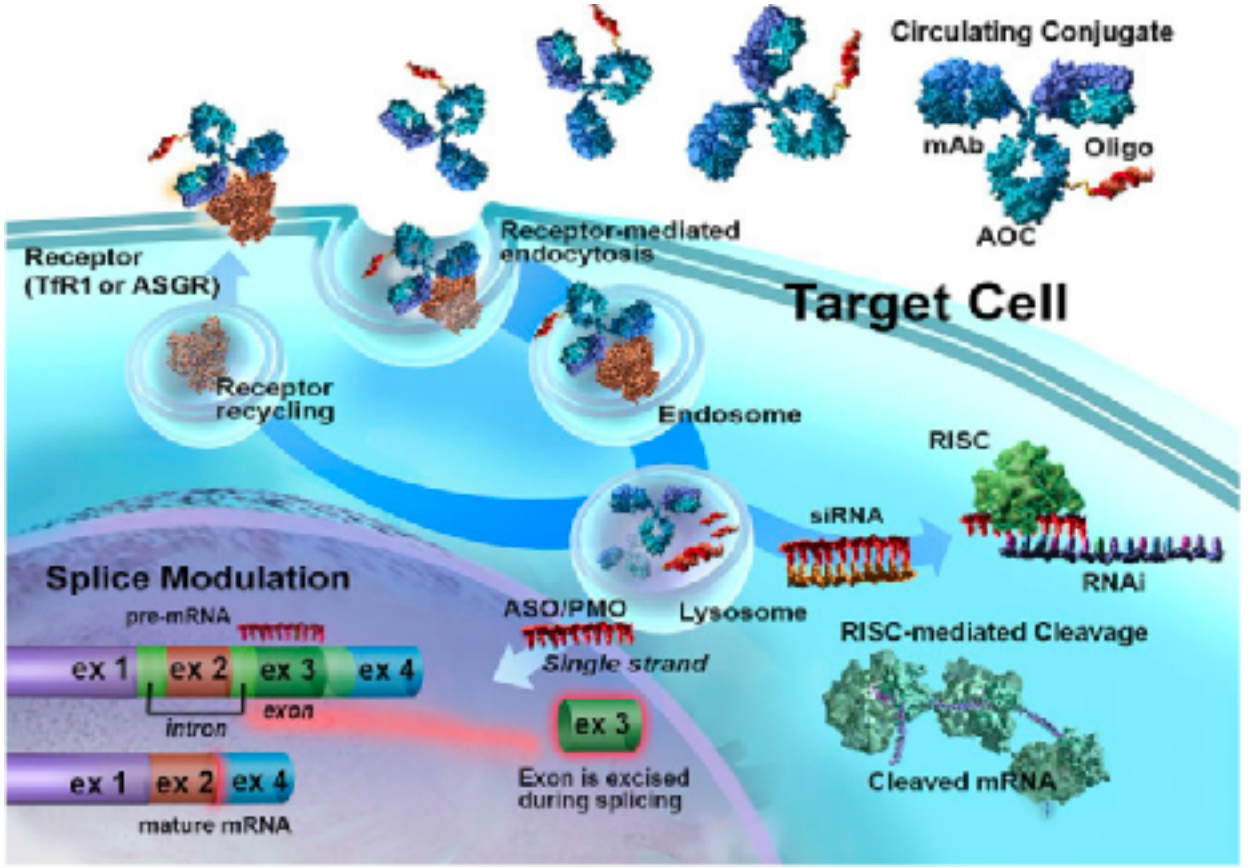
- **Composition:**
  - Made of lipids (fats) that self-assemble into a small sphere, carry genetic material, fuse with cell membranes to deliver its contents into cells
- **Advantages:**
  - Milder immune side-effects: compared to AAVs, more short-term immune reactions
  - Increased scalability: able to be mass produced
  - Repeat dosing possible: not limited by neutralizing antibodies
- **Challenges:**
  - Tissue targeting issues: difficult delivery to heart cells
  - Short-lived expression: more temporary effects rather than long-term



Zak M et. al. Pharmaceutics 2021

Delivery vehicles: bio-conjugation, antibodies

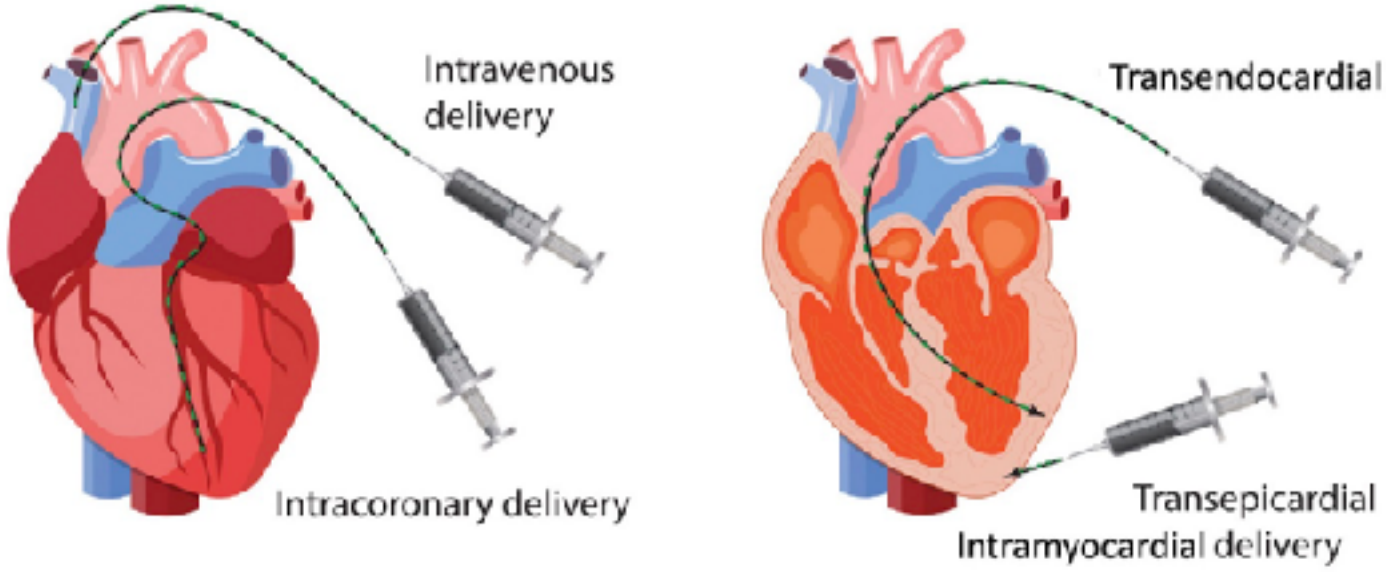
- **Composition:**
  - Engineered monoclonal antibody designed to bind a cell surface receptor (ie transferrin receptor 1 for cardiac cells)
- **Advantages:**
  - Tissue-specific delivery: directs therapy to heart cells, limiting off-target effects
  - Milder immune side-effects: compared to AAVs and LNPs
  - Repeat dosing possible: not limited by neutralizing antibodies
- **Challenges:**
  - Limited to RNA therapeutics: only able to perform gene silencing modulation. Unable to delivery DNA to nucleus
  - Short-lived expression: more temporary effects rather than long-term



Malecova B et. al. Nucleic Acids Res 2023

Gene therapy: systemic vs local administration to reduce side effects

- **Local administration** of gene therapy **reduces the dose** required for delivery, **~50-70 times**
- Pros:
  - Decreased risk of immune-related side effects
  - Avoid pre-treatment immunosuppression, including steroids
- Cons:
  - Unclear uptake of gene therapy into the cardiac cells
  - Requires invasive procedure



Parajuli SP et. al. Emerging Tech Heart Dis 2020

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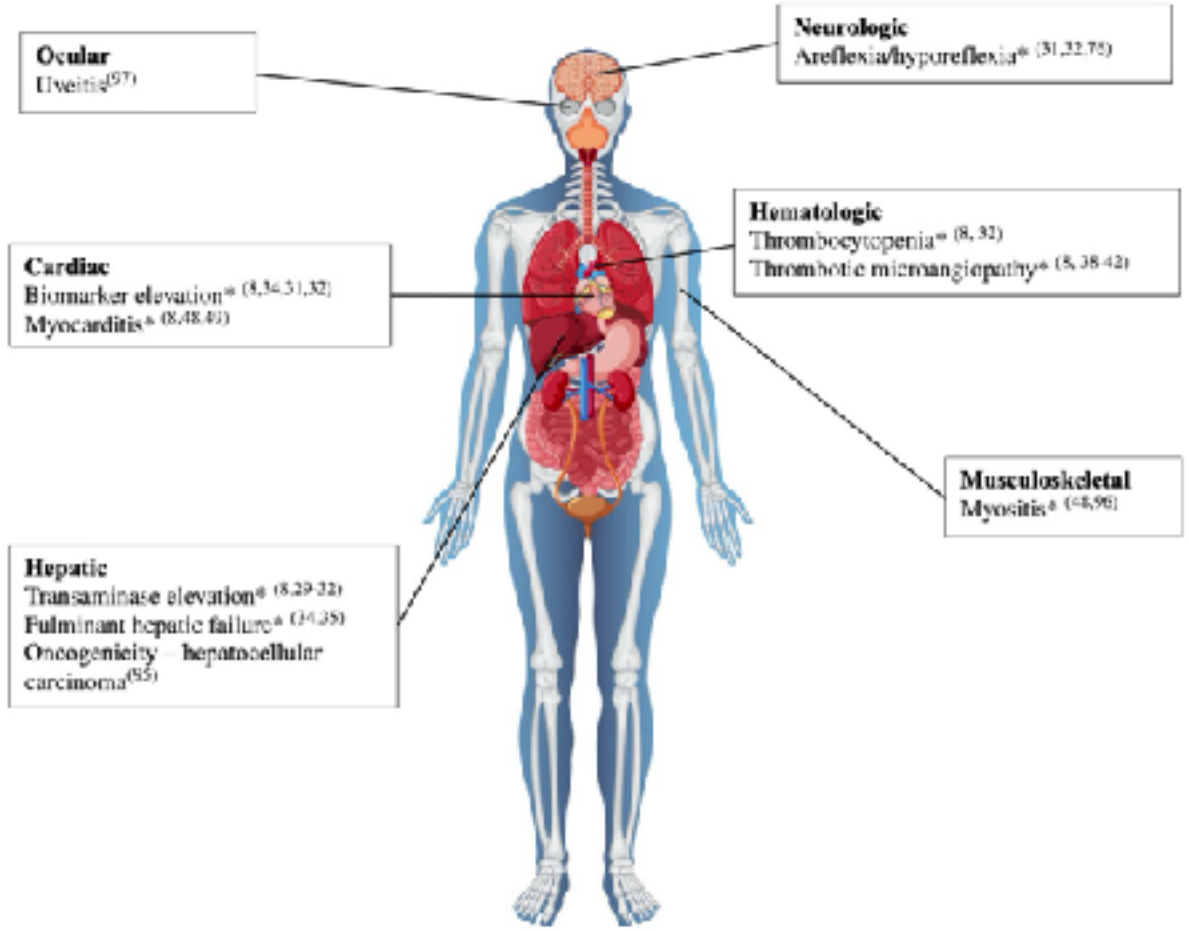
Gene therapy: immune-related side effects

- Body can **recognize delivery vehicles as foreign** and react, sometimes causing immune-related side effects
- *Mostly pertinent to viral vectors (AAV), but can also be seen with non-viral vectors (LNP) with higher doses associated with increased risk.*
- **Liver inflammation (i.e. hepatotoxicity)**
  - Most common, elevated liver tests
  - Usually mild, but can be severe
- **Heart inflammation (i.e. myocarditis)**
  - Rare, typically mild
  - Typically manifest as elevated cardiac enzymes
- **Blood issues (i.e. thrombotic microangiopathy)**
  - Rare, but can be severe
  - Leads to low blood counts and kidney problems



Satish T et. al. JACC:HF 2024
Argiro A et. al. JACC:HF 2024

Gene therapy: immunosuppression to reduce side effects

- Use of immunosuppression medications to **calm the immune system** so it doesn't overreact to gene therapy.
- Tailored to individual risk for immune-related side effects
- Immunosuppression can temporarily increase vulnerability to infections

- **Immunosuppression approaches**
  - Steroids (i.e. prednisone)
    - *Preventative:* started before and after gene therapy infusion
    - *Reactive:* if side effects appear after treatment
  - Advanced immunosuppression
    - Mammalian target of rapamycin (mTOR) inhibitors (i.e. sirolimus)
    - Calcineurin inhibitors (i.e. tacrolimus)
    - Anti-CD20 antibodies (i.e. rituximab)
    - Complement inhibitors (i.e. eculizumab)

Parikh V et. al. Cell 2025

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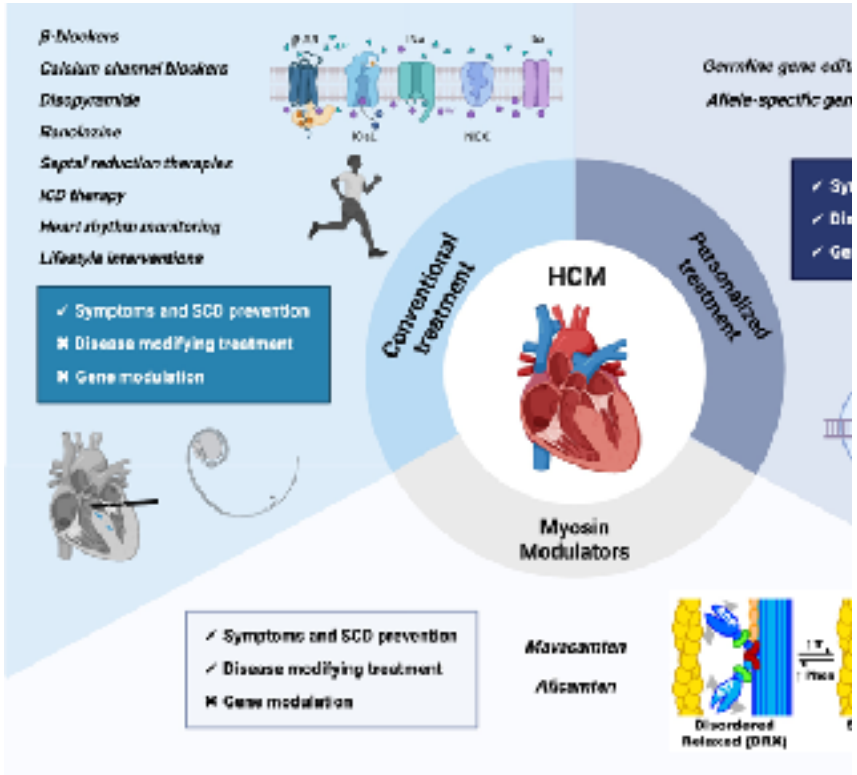
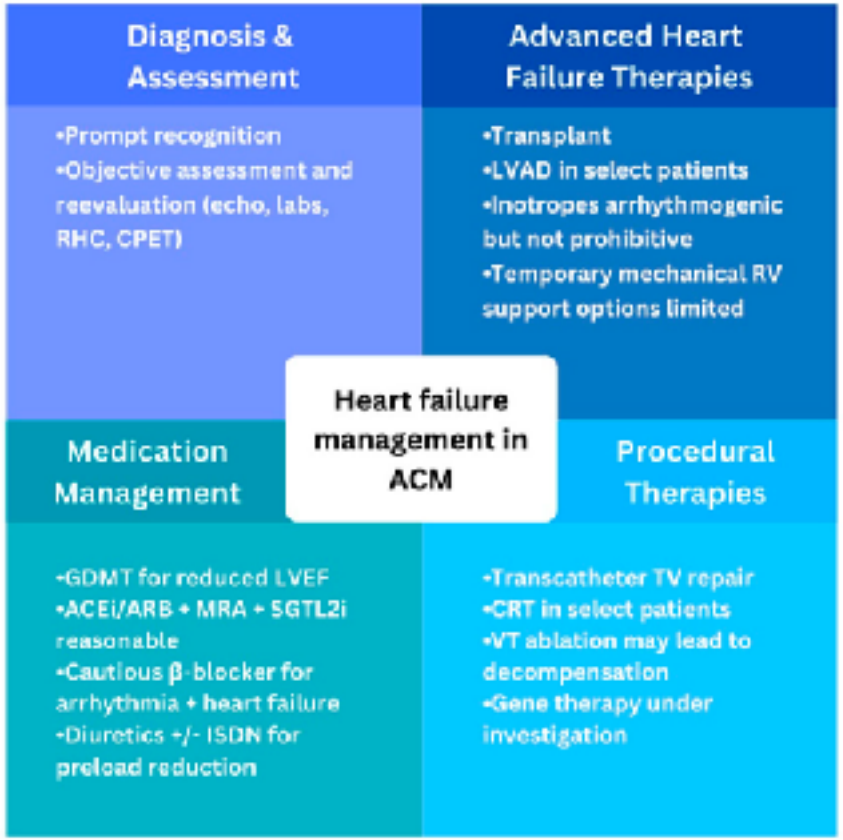
Gene therapy: practical considerations

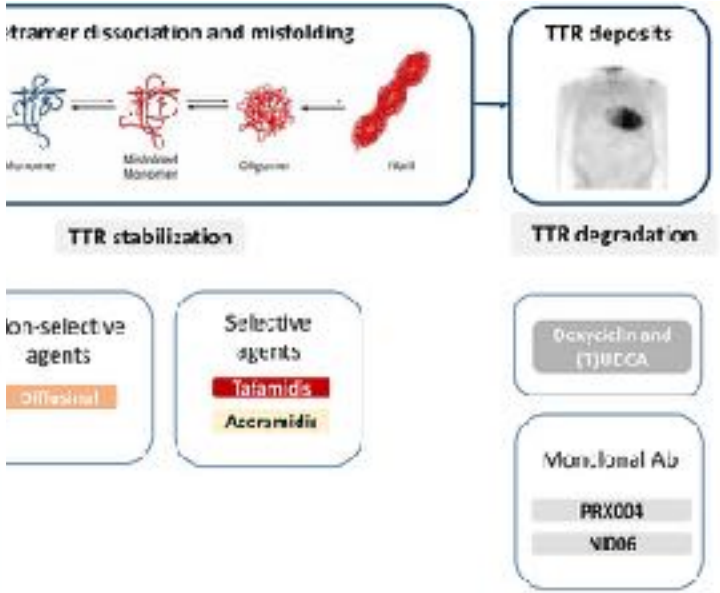
1. Unmet clinical need: How does gene therapy compare to other available treatments for my condition?
2. Delivery: What delivery system is used? Viral or non-viral? Systemic (IV) or local (intra-coronary) administration?
3. Side effects/safety: What are possible side effects? Dose? Immunosuppression?
4. Disease trajectory: Does my disease have a poor trajectory? What happens if gene therapy does not work? Eligible for another gene therapy clinical trial?
5. Effectiveness/clinical trial stage: How likely will this gene therapy work? Has it been tested in other people with heart disease?

Practical #1: cardiac disease with unmet clinical need?

- **Does my cardiac disease have an unmet clinical need?**
  - There are approved, <u>disease-targeted treatments</u> such as cardiac myosin inhibitors for hypertrophic cardiomyopathy and stabilizers/silencers for transthyretin cardiac amyloidosis.
  - Other diseases rely on <u>repurposed HF medications that relieve symptoms</u> with eventual need for heart transplant.







Ottaviani A et. al. J Clin Med 2023
Tomasoni D et. al. Front Card Med 2023

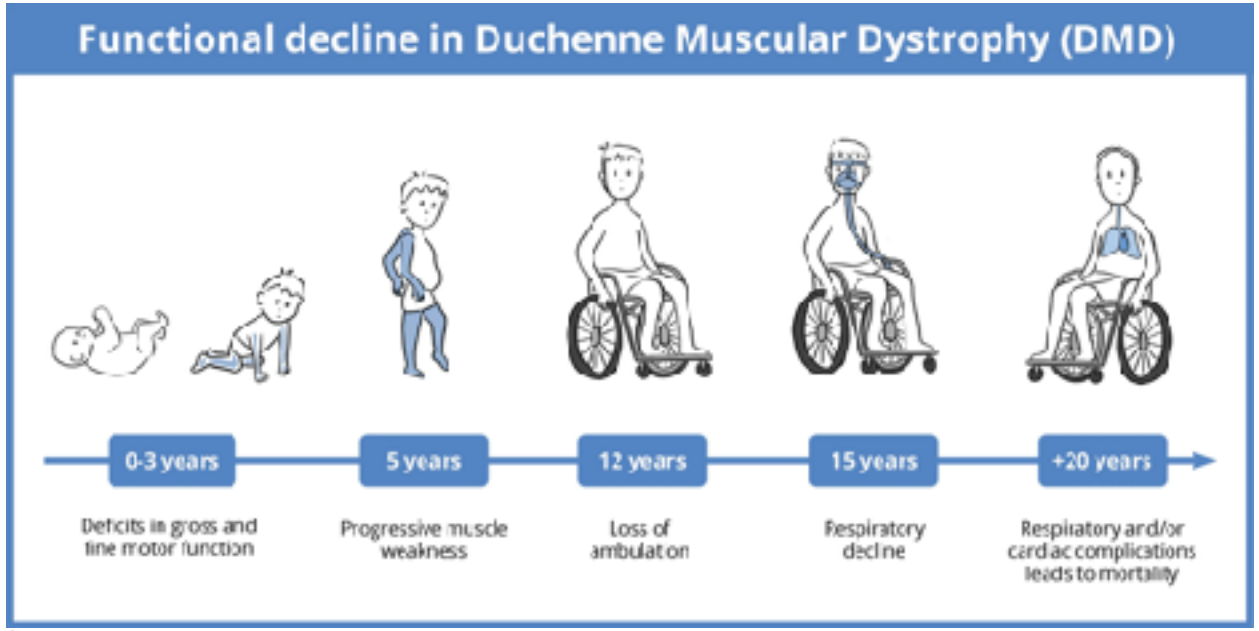
Practical #2: risks and safety of gene therapy?

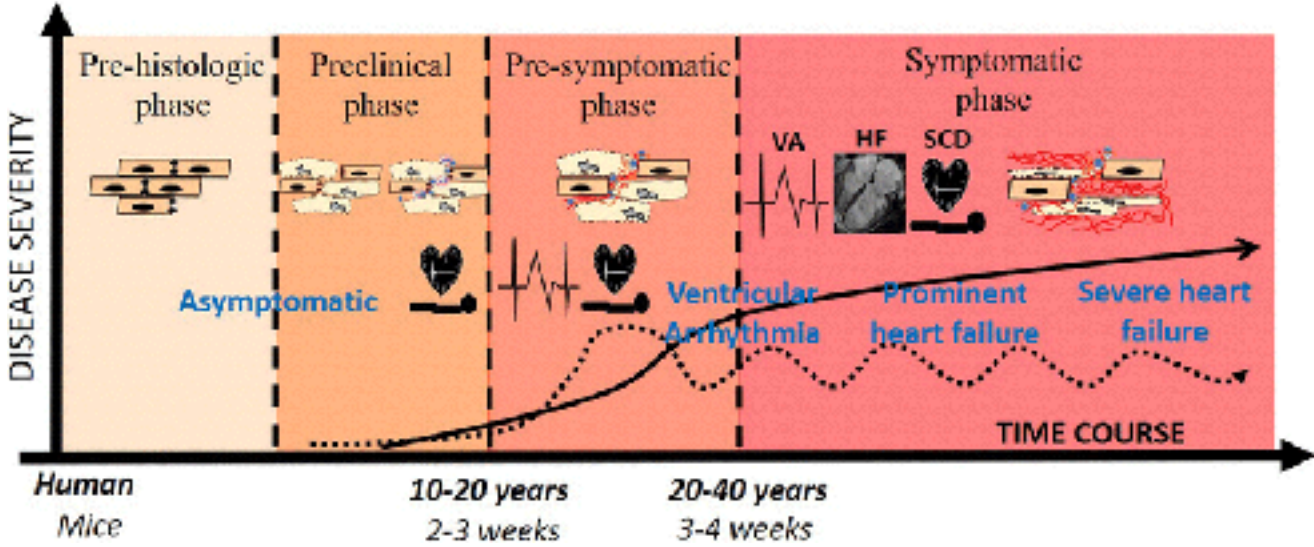
- **How safe is gene therapy? What are the most common side effects? Have there been any associated deaths?**
  - While gene therapy has been largely safe, there have been multiple deaths associated. These include rare metabolic disorders, Duchenne muscular dystrophy, spinal muscular atrophy, and Danon disease.
  - Some therapies are permanent so long-term side effects are important. There are always unknown risks. *Informed consent is critical.*

Rinde M et. al. Science Hist Inst 2019

Practical #3: disease trajectory?

- **How severe is my disease trajectory? If I get this gene therapy now, can I still qualify for future gene therapy trials or treatments?**
  - You should discuss with your provider about the pros and cons based on your specific condition and disease trajectory.
  - After one gene therapy (especially with viral vectors), the body may build immunity to the delivery system and become ineligible for future gene therapies.





Laurie E et. al. Biospective Imag 2025
Lin Y et. al. Basic Res Cariol 2021

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Gene therapy for Danon disease: a success story

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

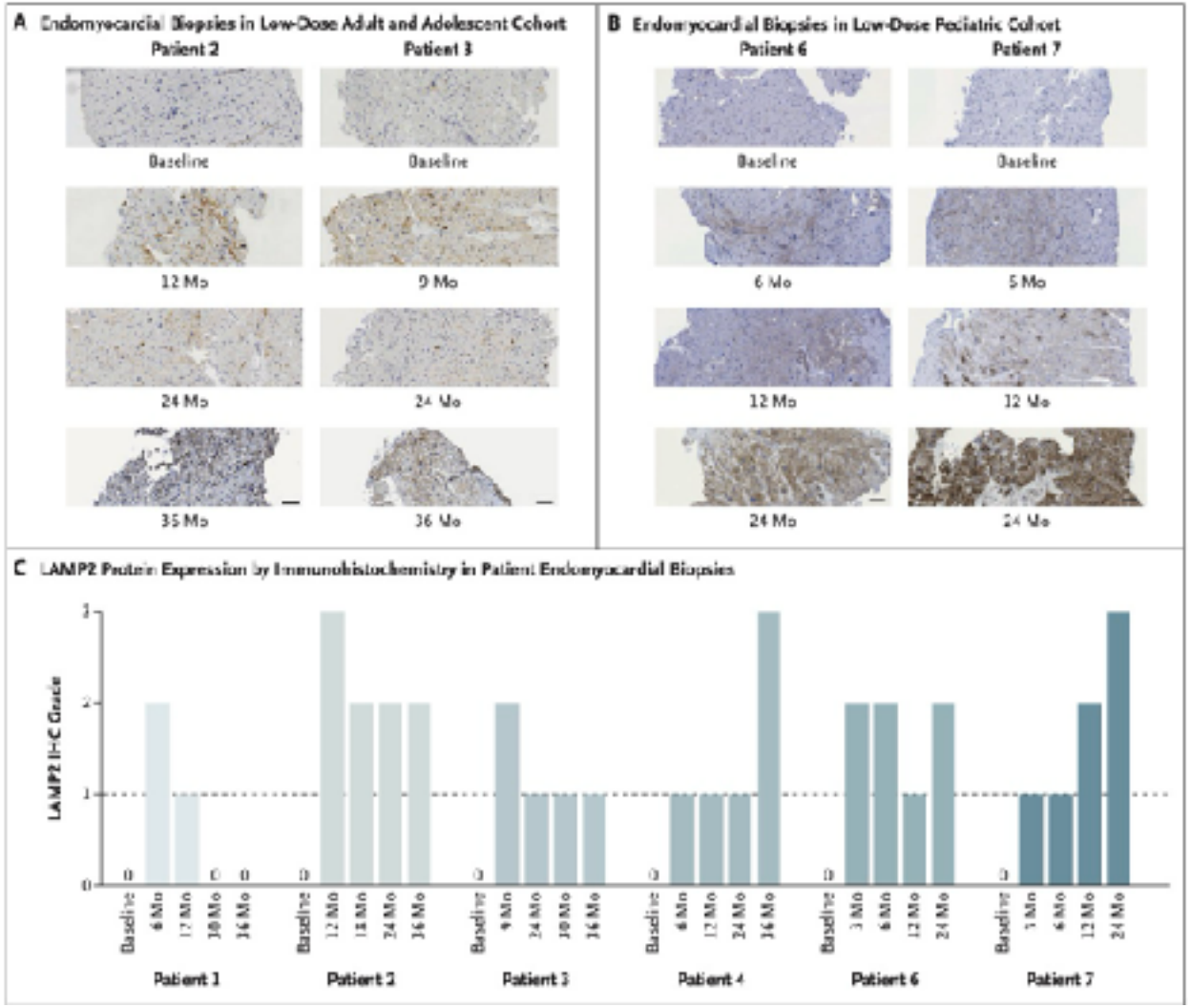
Phase 1 Study of AAV9.LAMP2B Gene Therapy in Danon Disease

B. Greenberg,[1] M. Taylor,[2] E. Adler,[1] S. Colan,[3] D. Ricks,[4] P. Yarabe,[4] P. Battiprolu,[4] G. Shah,[4] K. Patel,[4] M. Coggins,[4] S. Carou-Keenan,[4] J.D. Schwartz,[4] and J.W. Rossano[5,6]

"These boys, contrary to what was seen in the natural history studies ... are alive and doing well."

Barry H. Greenberg, MD, FHFSA

Healio



Greenberg B et. al. NEJM 2025

Gene therapy: many CVD-related ones in the pipeline

- ***There are over 100 gene therapies in development for CVD worldwide from the discovery stage to phase III development.

COMMENT | August 19, 2021

More than 80 gene therapies in CVD pipeline with heart failure among key indications

Several companies have recently invested resources in gene therapies within the cardiovascular disease (CVD) field.

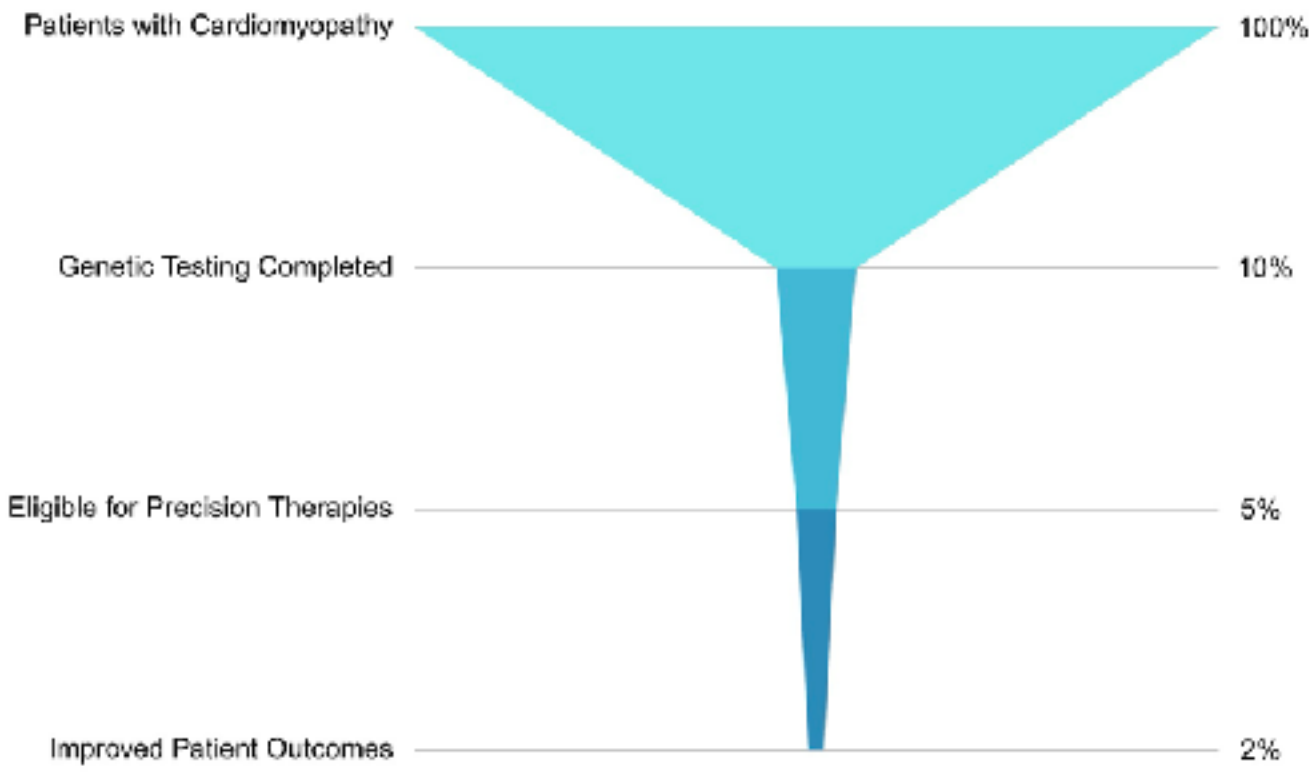
By GlobalData Healthcare

Gene therapy: representative list of cardiomyopathy-related ones

Cardiomyopathy	Gene	Delivery vehicle	Delivery route	Immunosuppression	Study phase	Disease-targeted therapies (FDA approved)
Hypertrophic	MYBPC3	AAV9	Systemic IV	Yes	Phase 1	Cardiac myosin inhibitors
Arrhythmogenic	PKP2	AAVrh.10/AAVrh.74/AAV9	Systemic IV	Yes	Phase 1/2	None
Arrhythmogenic	PLN	Antibody conjugation	Systemic IV	None	Pre-clinical	None
Dilated	BAG3	AAV9	Systemic IV	Yes	Phase 1/2	None
Dilated	LMNA	AAV9	Systemic IV	Yes?	Phase 1/2	None
Non-ischemic	I-1C	AAV2i8	Intra-coronary	None	Phase 2	None
Transthyretin	TTR	LNP	Systemic IV	None	Phase 3	TTR stabilizer/silencers
Danon Disease	LAMP2B	AAV9	Systemic IV	Yes	Phase 2	None

Call to action: ability to treat starts with the ability to identify

- Patient identification through **genetic testing** is the critical first step in **precision cardiovascular medicine and gene therapy**!



Conclusion

- Gene therapy is moving us toward **personalized treatment** based on your **genetic makeup** and the **root cause** of cardiomyopathy.
- **Delivery** remains one of the greatest challenges in gene therapy for cardiomyopathy. Achieving effective, cardiac delivery while minimizing risk is essential.
- **AAV vectors** offer the most efficient cardiac delivery but are associated with **immune-related risks** and may require **immunosuppression medications**.
- Emerging delivery technologies like **lipid nanoparticles and antibody-guided delivery** may offer safer and more targeted options in the future.
- When considering gene therapy, patients and providers must weigh **unmet clinical need**, **safety profile** and **disease trajectory**.
- **Choosing gene therapy is a big decision.** Talk to your care team and make sure you fully understand the risks, benefits, and alternatives.
- Genetic testing is the gateway to personalized treatment – improved uptake is an essential first step.
  - **“The ability to treat begins with the ability to identify.”**

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Please fill out “Patient Gene Therapy” survey!

- **Why You Are Being Asked to Participate**
  You are invited to take part in a research study because you are either:
  - A patient with a heart muscle disease (cardiomyopathy), or
  - A caregiver or family member of a patient with cardiomyopathy
- **Purpose of the Study**
  The goal of this study is to better understand how patients and their families think about gene therapy for heart muscle conditions. We hope this information will help us develop better educational tools and communication strategies for individuals with heart muscle disease considering gene therapy in the future.
- **What You Will Be Asked to Do**
  If you choose to participate, you will:
  1. Watch a short, introductory video about gene therapy (4 minutes)
  2. Complete a one-time survey (21 questions) that takes approximately 10 minutes

SCAN ME!