# And Now For Something Completely Different

## Standing up a new program that is waaay outside the box

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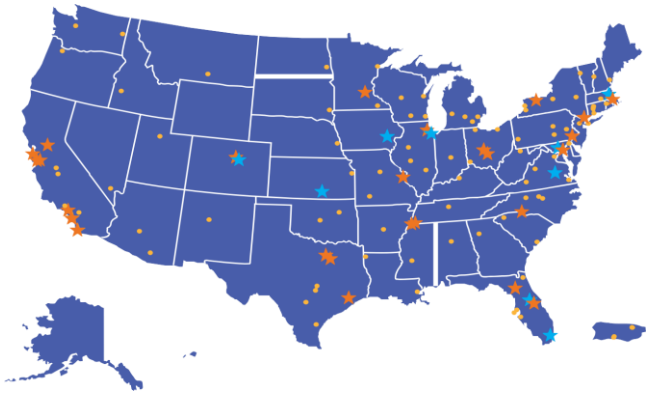
Prompts: “outside the box” “steampunk”

# MDA Research & Care

The Muscular Dystrophy Association was founded in the 1950's by concerned parents who wanted to development treatments for their children who were living with neuromuscular disease.

## MDA Care Centers

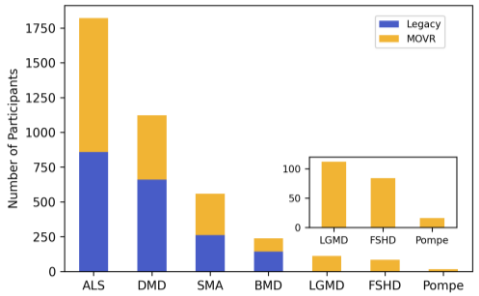
- 150 Care Centers supported across the US
- 60,000 individuals seen annually



## Research Grants

- $1B projects funded
- 7000 Individual investigators funded
- 2000 new investigators trained and supported

## MOVR Clinical Database



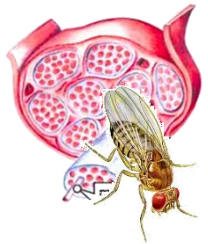

- Over 4000 individuals enrolled
- 7 Disease areas
- 12,000 encounters documented

## New Therapies

- 18 drugs approved for neuromuscular diseases
- 9 Drugs developed directly from MDA funding

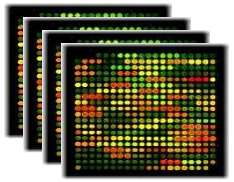
# MDA Research Program Focused on “De-Risking” Drug Development

| 5-10 Years | 2 Years | 2 Years | 2 Years | 6 Years |
|---|---|---|---|---|
| Academic Institutions ⟷ | Small Biotechnology Companies | | ⟷ | Larger Companies |



**Basic Research**

- MDA Research Grant
- MDA Development Grant
- MDA Idea Award
- Funding Conferences
- Holding Conferences



**Target Identification & Drug Screening**

- MDA Infrastructure Grant (tools, techniques and services)
- MDA Research Grant

**“Proof-of-Concept” Testing**

- MDA Research Grant
- MDA Idea Award
- MDA Development Grant


**Translational Research**

- MDA Venture Philanthropy
- MOVR Registry

**Clinical Trials**

- MDA Clinical Trial Grants
- MDA Clinical Research Network Grants
- MDA Clinical Fellowship
- MOVR Registry
- MDA Care Center Network

# Needs Assessment

## The Ultra-Rare Neuromuscular Disease Problem

## Muscular dystrophies

The muscular dystrophies are a group of diseases that cause weakness and degeneration of the skeletal muscles.

Becker muscular dystrophy (BMD)

Congenital muscular dystrophies (CMD)

- Collagen VI CMDs (Bethlem, Ullrich)
- CMD, dynamin2-related
- CMD, telethonin-related
- CMDs with hypoglycosylation of dystroglycan
- CMDs with integrin deficiency
- Fukuyama CMD
- Lamin A/C/LMNA-related dystrophy
- Merosin/LAMA2-deficient CMD (MDC1A)
- Muscle-eye-brain diseases (MEBs)
- Rigid spine syndromes
- Walker-Warburg syndromes (WWS)

Duchenne muscular dystrophy (DMD)

Emery–Dreifuss muscular dystrophy (EDMD)

- Types 1-7

Facioscapulohumeral muscular dystrophy (FSHD)

- Types 1-2

Limb–girdle muscular dystrophies (LGMD)

- Types 1A-1F
- Types 2A-2Y

Myotonic dystrophy (DM)

- DM1
- DM2

Oculopharyngeal muscular dystrophy (OPMD)

## Motor neuron diseases

In motor neuron disease, nerve cells called motor neurons progressively lose function, causing the muscles they control to become weak and then nonfunctional.

ALS (amyotrophic lateral sclerosis)

- Familial
- Sporadic

Spinal–bulbar muscular atrophy (SBMA)

Spinal muscular atrophy (SMA)

- Types 1-4
- Distal SMA

## Ion channel diseases

Diseases associated with defects in proteins called ion channels typically are marked by muscular weakness, absent muscle tone, or episodic muscle paralysis.

Andersen–Tawil syndrome

Hyperkalemic periodic paralysis

Hypokalemic periodic paralysis

- HypoKPP Types 1-3
- Thyrotoxic HypoKPP

Myotonia congenita

- Thomsen myotonia
- Becker myotonia

Paramyotonia congenita

Potassium–aggravated myotonia

## Mitochondrial diseases

Mitochondrial diseases occur when structures that produce energy for a cell malfunction.

Friedreich's ataxia (FA)

MDA covers all mitochondrial myopathies, including the following:

Mitochondrial myopathies

- Kearns-Sayre syndrome (KSS)
- Leigh syndrome (subacute necrotizing encephalomyopathy)
- Mitochondrial DNA depletion syndromes
- Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)
- Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
- Myoclonus epilepsy with ragged red fibers (MERRF)
- Neuropathy, ataxia and retinitis pigmentosa (NARP)
- Pearson syndrome
- Progressive external opthalmoplegia (PEO)

## Myopathies

A myopathy is a disease of muscle in which the muscle fibers do not function properly, resulting in muscular weakness.

Congenital myopathies

- Cap myopathies
- Centronuclear myopathies
  - Centronuclear myopathy, BIN1-related
  - Centronuclear myopathy, DMN2-related
  - Centronuclear myopathy, RYR1-related
  - Centronuclear myopathy, TTN-related
- Congenital myopathies with fiber type disproportion
- Core myopathies
  - Central core disease
  - Multiminicore myopathies
- Myosin storage myopathies
- Myotubular myopathy
- Nemaline myopathies
  - NEM1-10

Distal myopathies

- Distal anoctaminopathy
- Distal myopathy with caveolin defect
- Distal myopathy with myotilin defect
- Distal myopathy with nebulin defect
- Distal myopathy with VCP defect
- Distal myopathy, alpha-B crystallin-related
- Distal myopathy, dynamin 2-related
- Distal myopathy, filamin C-related
- GNE myopathy/Nonaka myopathy/ hereditary inclusion-body myopathy (HIBM)
- Laing distal myopathy
- Markesbery-Griggs late-onset distal myopathy
- Miyoshi myopathy
- Udd myopathy/tibial muscular dystrophy
- Vocal cord and pharyngeal distal myopathy
- Welander distal myopathy

Endocrine myopathies

- Hyperthyroid myopathy
- Hypothyroid myopathy

Inflammatory myopathies

- Dermatomyositis
- Inclusion-body myositis
- Polymyositis

Metabolic myopathies

- Acid maltase deficiency (AMD, Pompe disease)
- Carnitine deficiency
- Carnitine palmitoyltransferase deficiency
- Debrancher enzyme deficiency (Cori disease, Forbes disease)
- Lactate dehydrogenase deficiency
- Myoadenylate deaminase deficiency
- Phosphofructokinase deficiency (Tarui disease)
- Phosphoglycerate kinase deficiency
- Phosphoglycerate mutase deficiency
- Phosphorylase deficiency (McArdle disease)

Myofibrillar myopathies (MFM)

- MFM, alpha-B crystallin-related
- MFM, BAG3-related
- MFM, desmin-related
- MFM, filamin C-related
- MFM, LDB3/ZASP-related
- MFM, myotilin-related
- MFM, SEPN-related
- Spheroid body myopathy

Scapuloperoneal myopathy

## Neuromuscular junction diseases

Neuromuscular junction disorders result from the destruction, malfunction or absence of one or more key proteins involved in the transmission of signals between muscles and nerves.

Congenital myasthenic syndromes (CMS)

Lambert–Eaton myasthenic syndrome (LEMS)

Myasthenia gravis (MG)

## Peripheral nerve diseases

In peripheral nerve diseases, the motor and sensory nerves that connect the brain and spinal cord to the rest of the body are affected, causing impaired sensation, movement or other functions.

Charcot–Marie–Tooth disease (CMT)

- CMT-1
- CMT-2
- CMT-4
- CMT-X/X-linked CMT
- Dejerine-Sottas disease

Giant axonal neuropathy (GAN)

7 major categories of NMDs in MDA's Program =
330 individual diseases officially "covered" by MDA
(partial list shown here)

MDA Muscular Dystrophy Association

# Only 17 Diseases in MDA's program likely affect over 1000 people each in the US

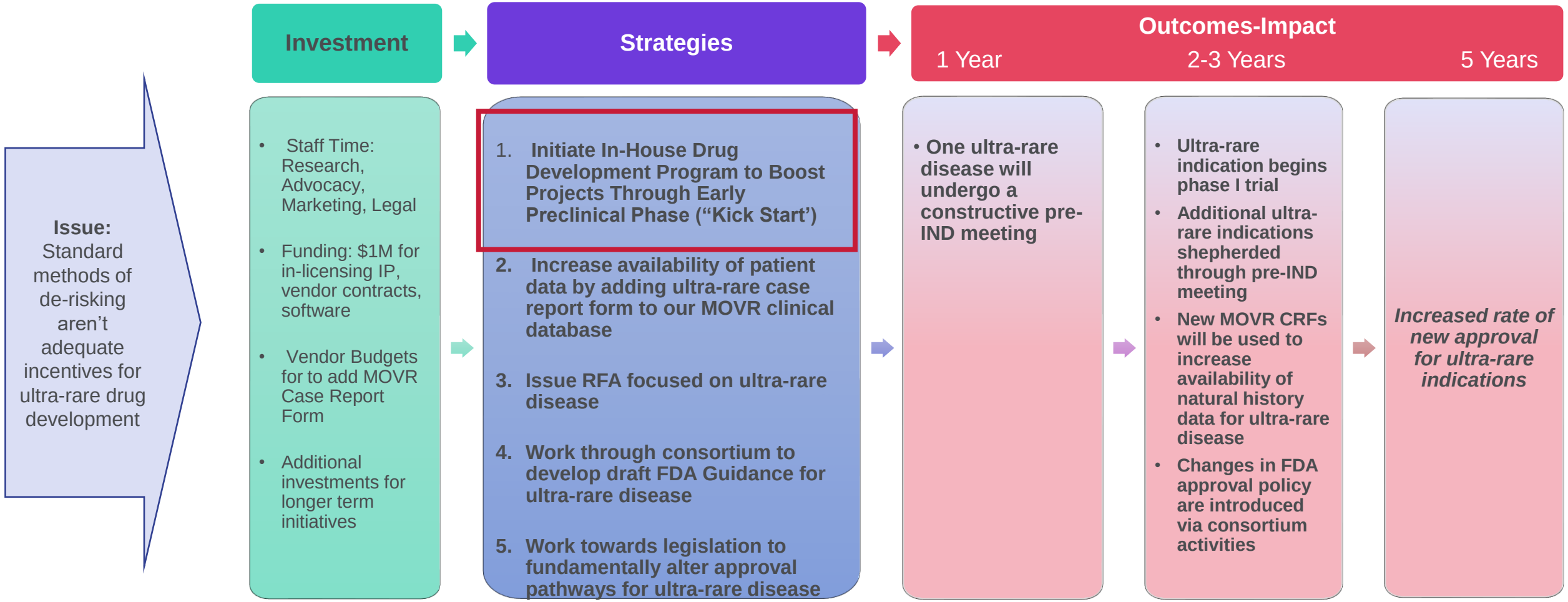
There are over 300 neuromuscular diseases individually defined by genetic cause (when applicable) covered in MDA's program; The majority of people served by MDA (306,657) have one of these 17 diseases. The remaining 335 disorders may still impact between as many as 100,000 people collectively.

| | Indication | % US Population | US Prevalence |
|---|---|---|---|
| 1 | CMT1A | 0.02290 | 75,169 |
| 2 | Myasthenia Gravis | 0.02020 | 66,287 |
| 3 | DM1/DM2* | 0.01262 | 41,429 |
| 4 | HNPP (CMT) | 0.00885 | 29,033 |
| 5 | Sporadic ALS | 0.00473 | 15,511 |
| 6 | FSHD | 0.00454 | 14,914 |
| 7 | DMD/BMD | 0.00347 | 11,375 |
| 8 | SMA | 0.00293 | 9,612 |
| 9 | CMTX | 0.00271 | 8,883 |

| | Indication | % US Population | US Prevalence |
|---|---|---|---|
| 10 | FA | 0.00252 | 8,286 |
| 11 | CMT1B | 0.00214 | 7,026 |
| 12 | CMT2A2 | 0.00174 | 5,700 |
| 13 | OPMD | 0.00100 | 3,314 |
| 14 | EDMD | 0.00100 | 3,314 |
| 15 | LGMD2A | 0.00100 | 3,282 |
| 16 | Leigh Syndrome (SURF1) | 0.00075 | 2,462 |
| 17 | CMT4C | 0.00032 | 1,060 |

*Preliminary studies suggest that DM1 prevalence may be up to five times higher than this older estimate

# How do we De-Risk Ultra-Rare Drug Development?



# MDA Kickstart Is an In-House Incubator for Ultra-Rare Gene Therapy Projects

**Goal:** De-risk technically feasible ultra-rare projects by completing a constructive pre-IND meeting with FDA

**Initial Budget:** $1.12M

**Project Criteria:**

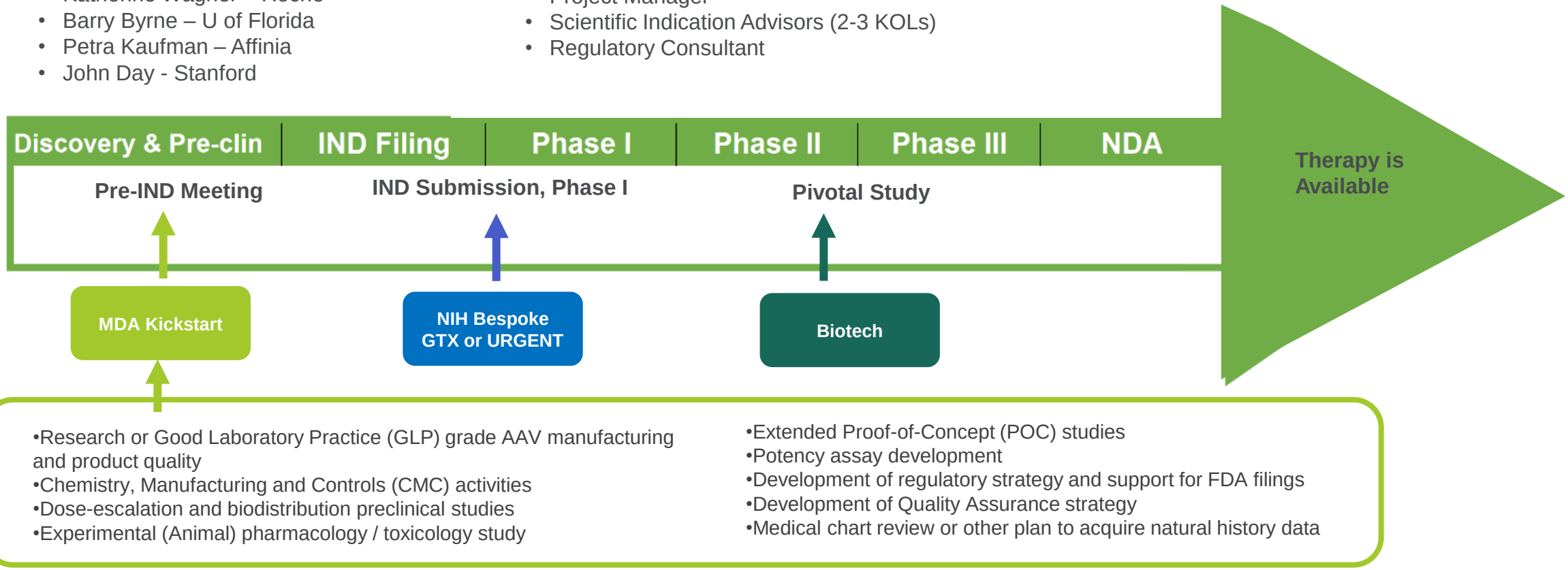
- AAV-based gene therapy approach for condition affecting less than 1000 people in the US
- No disease-modifying therapy available; high unmet medical need
- Straight-forward gene replacement strategy, technically feasible (high likelihood of success)
- Construct design completed
- Proof-of-concept data using in vitro or in vivo models available

**Sustainability--Multiple Paths**: equity stake, share of licensing revenue, share of pediatric voucher sales

# Kickstart will Provide the Initial Data Package for Constructive Pre-IND Meeting

**Kickstart Advisory Committee**:
- Dan Levy – Pfizer
- Katherine Wagner – Roche
- Barry Byrne – U of Florida
- Petra Kaufman – Affinia
- John Day - Stanford

**Kickstart Project Team**:
- Project Lead – MDA Staff
- Project Manager
- Scientific Indication Advisors (2-3 KOLs)
- Regulatory Consultant



# Details

- Gaining Board Support:
  - Timing is everything
  - Clear explanation of the problem
  - Convincing solution
  - Generating excitement
- Key Questions:
  - How to scale?
  - How to manage risk?
  - How to manage project and project data?
- Fuzzy Challenges:
  - Comfort with ambiguity
  - OK with being opportunistic
- Advice:
  - Socialize idea thoroughly first with all stakeholders