# Gene Therapy in Neurology: from benchside promise to clinical practice

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MEDICINE *of* THE HIGHEST ORDER

UNIVERSITY *of* ROCHESTER MEDICAL CENTER

11 August 1967, Volume 157, Number 3789 SCIENCE



# Will Society Be Prepared?

New information is being obtained in the field of biochemical genetics at an extremely rapid rate. Thus far, this knowledge has had relatively little effect upon man. More information must be obtained before practical application will be possible, and the technical problems that must be overcome are formidable. However, when these obstacles have been removed this knowledge will greatly influence man's future, for man then will have the power to shape his own biologic destiny. Such power can be used wisely or unwisely, for the betterment or detriment of mankind.

**Marshall W. Nirenberg**

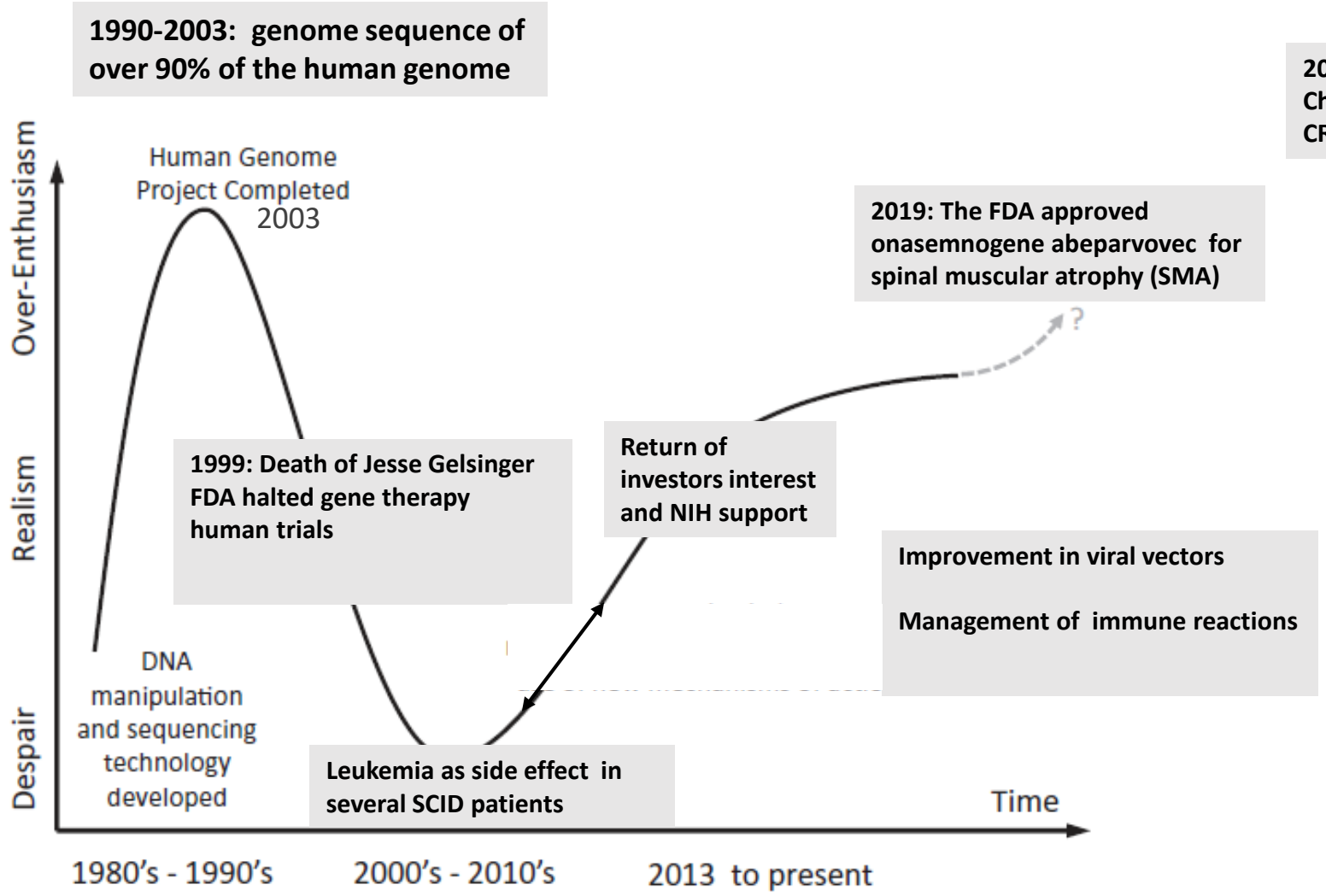
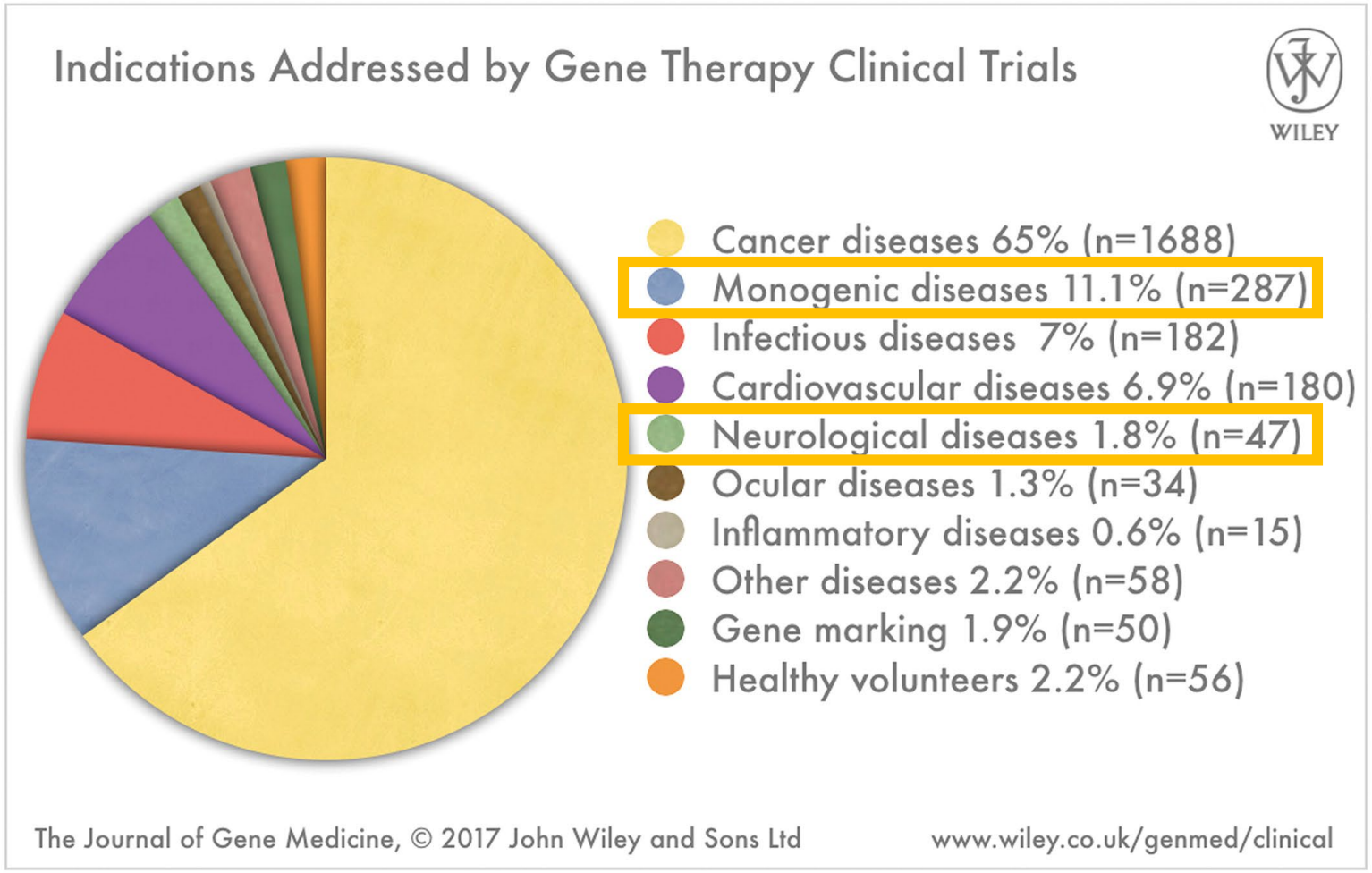
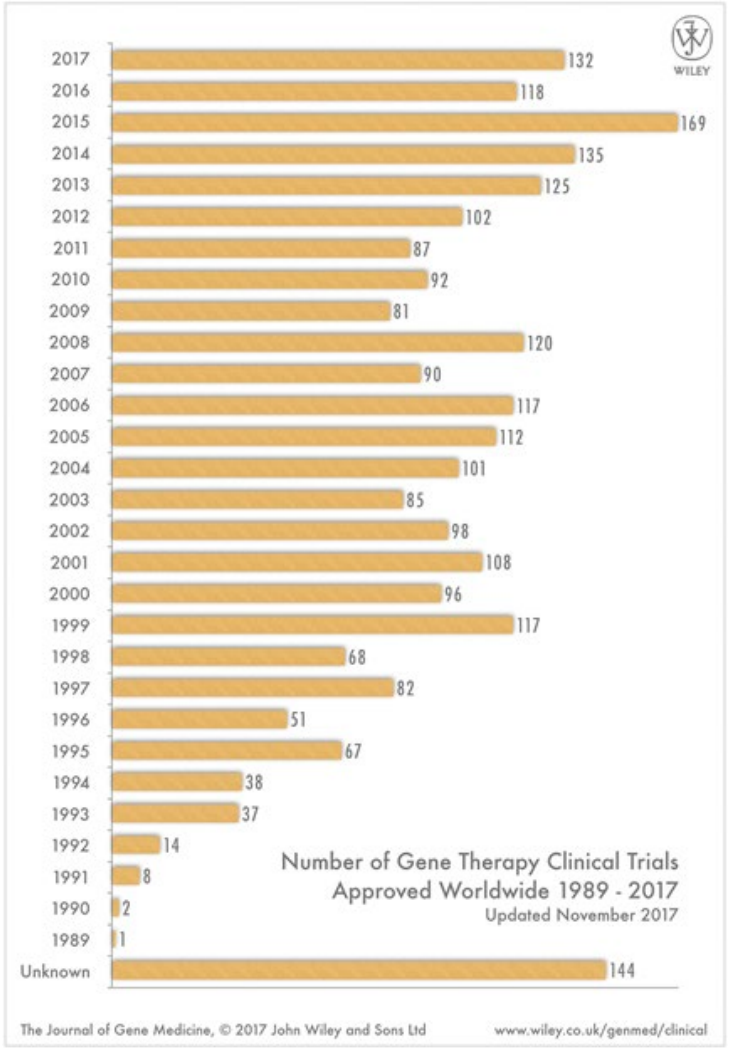


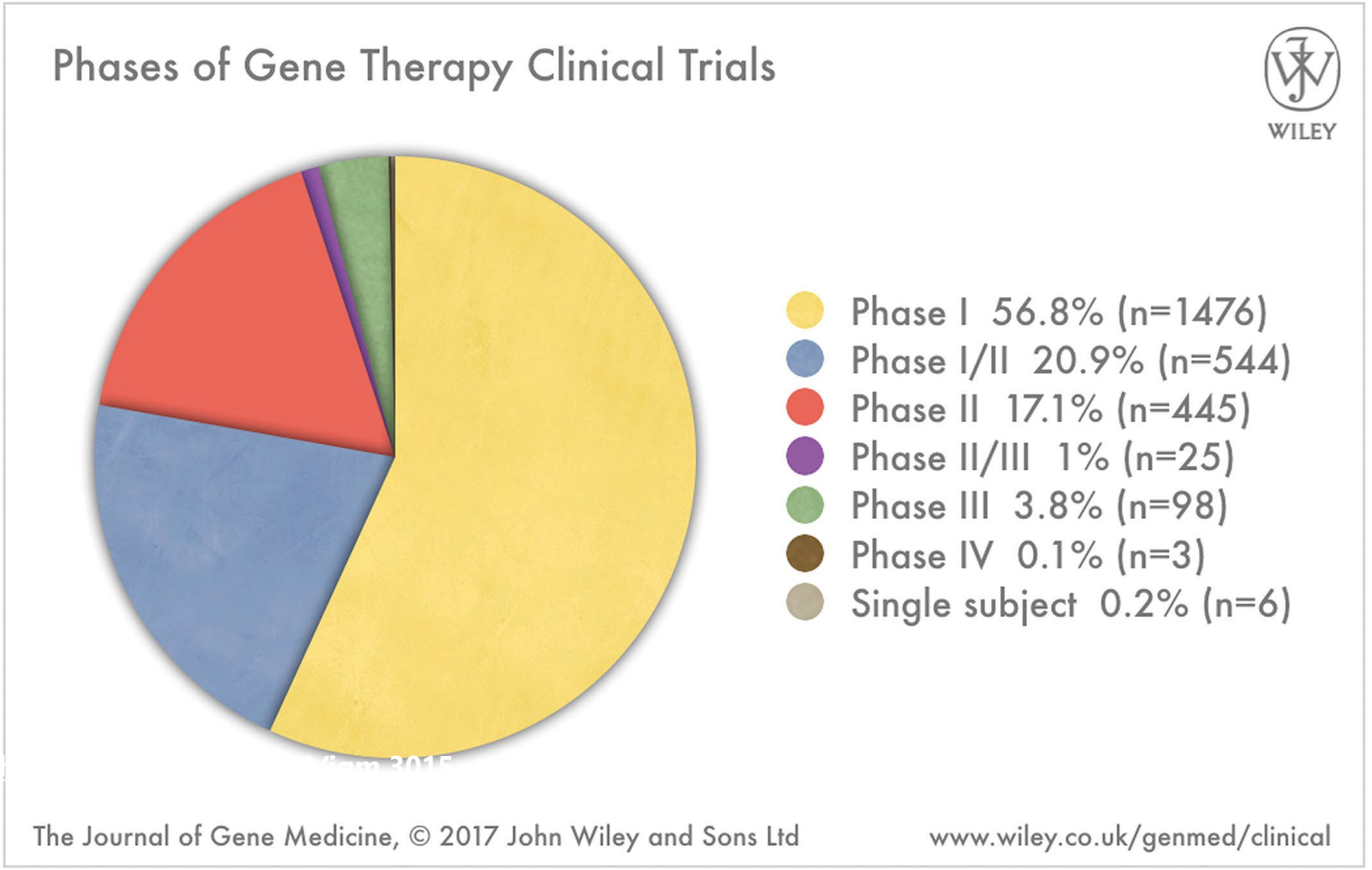

**FIGURE 1** A view of the "hype cycle" the field of gene therapy has traversed

# Diseases targeted by gene therapy

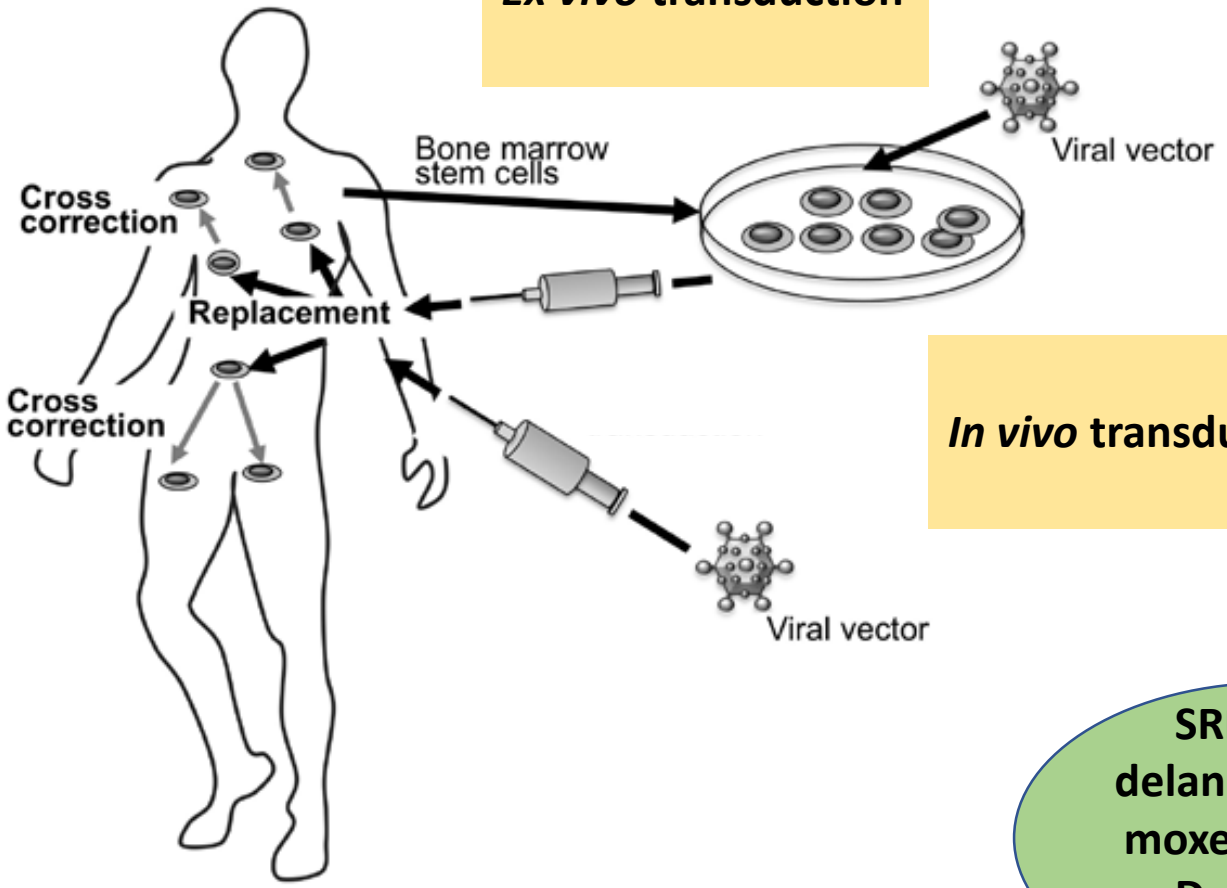


# Steady increase in trials and proportion of late phase trials



# Type of Gene Therapies: *ex vivo* and *in vivo*




***Ex vivo* transduction**

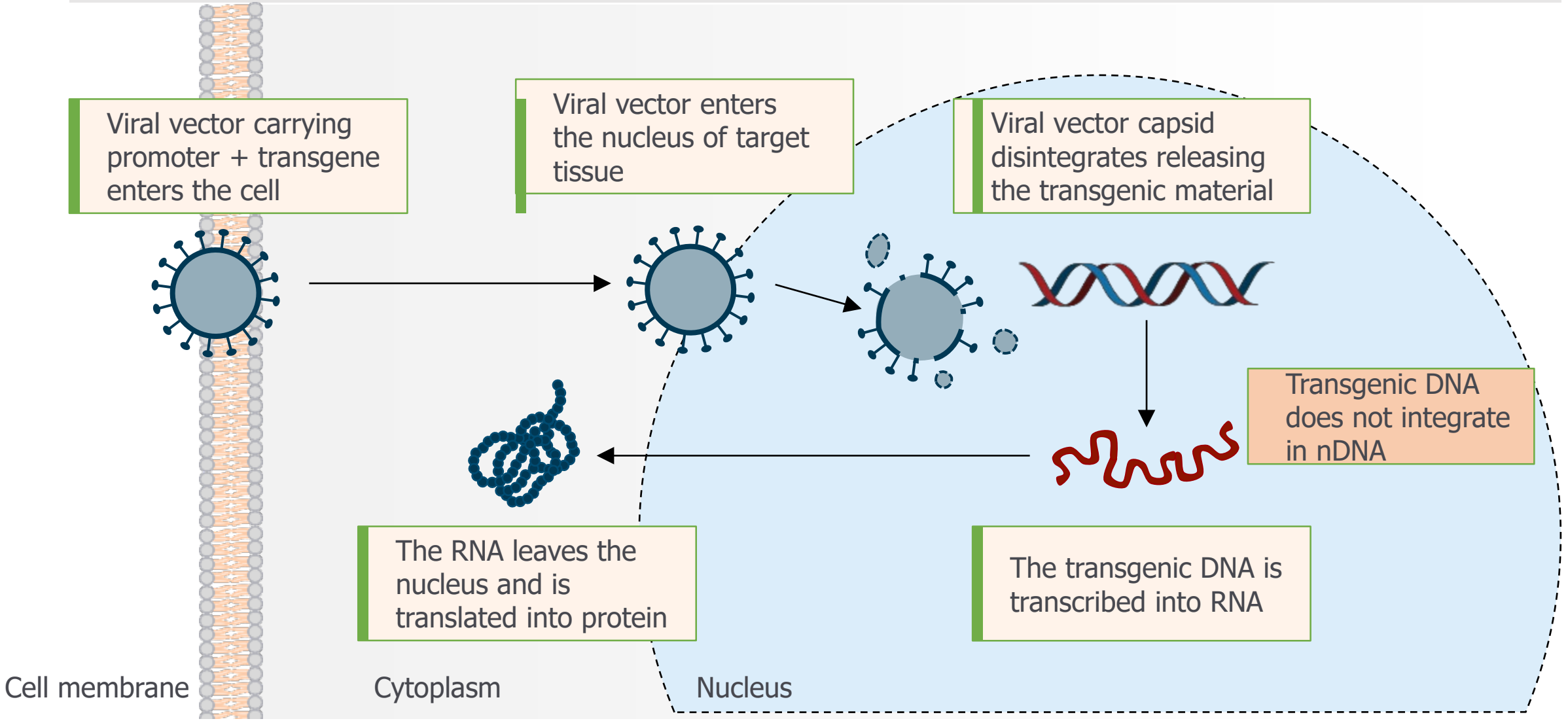
- **CAR T-Cell Drugs**
- **Zynteglo: βthalassemia**
- **Skysona: cerebral adrenoleukodystrophy**

***In vivo* transduction**

- **Zolgensma: Spinal Muscular Atrophy (SMA) (2019)**
- **Luxturna: genetic retinal disease *RPE*65 (2017)**

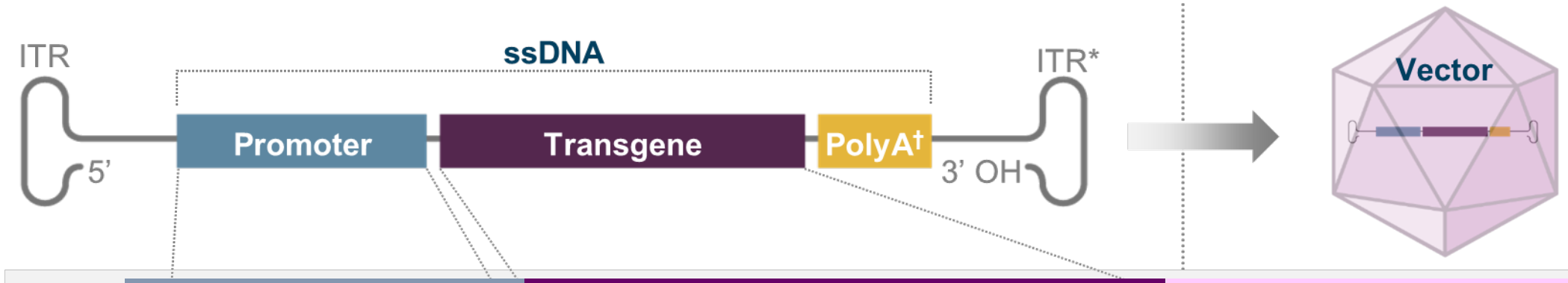
**SRP-9001-delandistrogene moxeparvovec: Duchenne 2023**

# Principles of in vivo IV Gene Therapy



# AAV-Based Gene Transfer Therapy

Adeno-associated virus (AAV)




**Tissue expression and specificity**

**Full transgene**

**Engineered mini- or micro-trans genes**

**Safety and Transduction**

- Non-pathogenic
- Mostly non-integrating
- Target tropism
- High transduction efficiency with IV delivery
- Payload capacity

***ITRs are required for genome replication and packaging; †PolyA signals the end of the transgene to the cellular machinery that transcribes (ie, copies) it.**
**ssDNA = single-stranded DNA**

# The Rochester Way: Neurology Department Pioneering Patient- Centered Neurological Care and Experimental Therapeutics since 1966

What it takes to go from bench to clinic

## Patient-Centered Research

- Discoveries from basic and translational research need to be tested in clinical trials to affect patient care

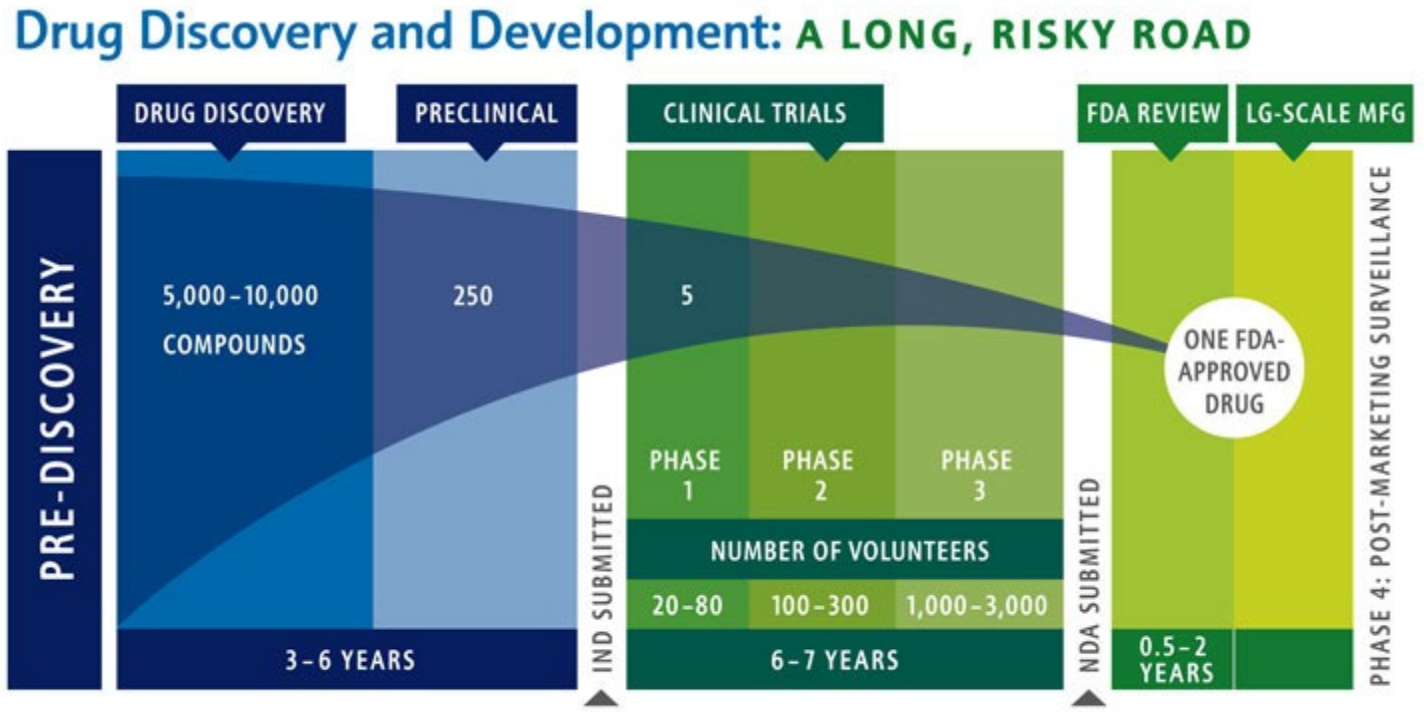
## Clinical Research and Trials Expertise

- Natural History Studies
- Outcome Measures
- Trial readiness

## Commitment to Rare Diseases

- There are 7,000 rare diseases
- 30 million Americans living with a rare disease- 1 out of 10 people
- 8 out of 10 are genetic
- 95% of Rare Diseases Lack an FDA Approved Treatment
- 1 of 2 Patients Diagnosed with a Rare Disease is a Child

# Traditional Drug Development Path: not well suited for Rare Diseases and Gene Therapy




Source: Pharmaceutical Research and Manufacturers of America

**Approval does not equal access**

- Access to Highly Specialized Centers with institutional Support
- High Pricing: Insurance and Policies variation among payers
- Avoid Health Inequality

# Gene-Based Therapies for Neuromuscular Diseases

Spinal Muscular Atrophy

Duchenne Muscular Dystrophy

Myotonic Dystrophy

Fascioscapular muscular dystrophy (FSHD)

Limb-Girdle-Muscular Dystrophies

Pompe Disease

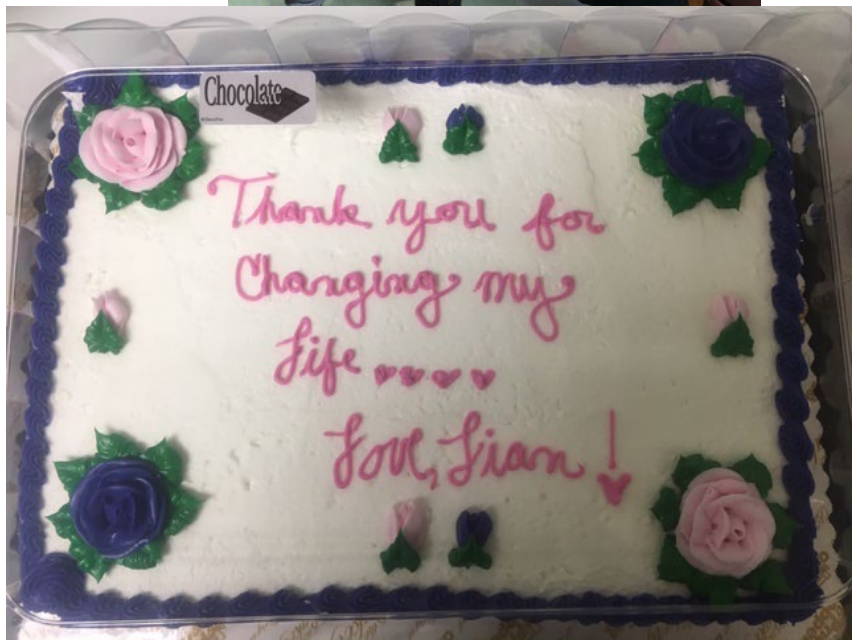
Hereditary Neuropathy: Charcot-Marie-Tooth (CMT)

ALS

Giant Axonal Neuropathy

# First Patient treated with Gene Therapy for Spinal Muscular Atrophy at URMC

December 18, 2018

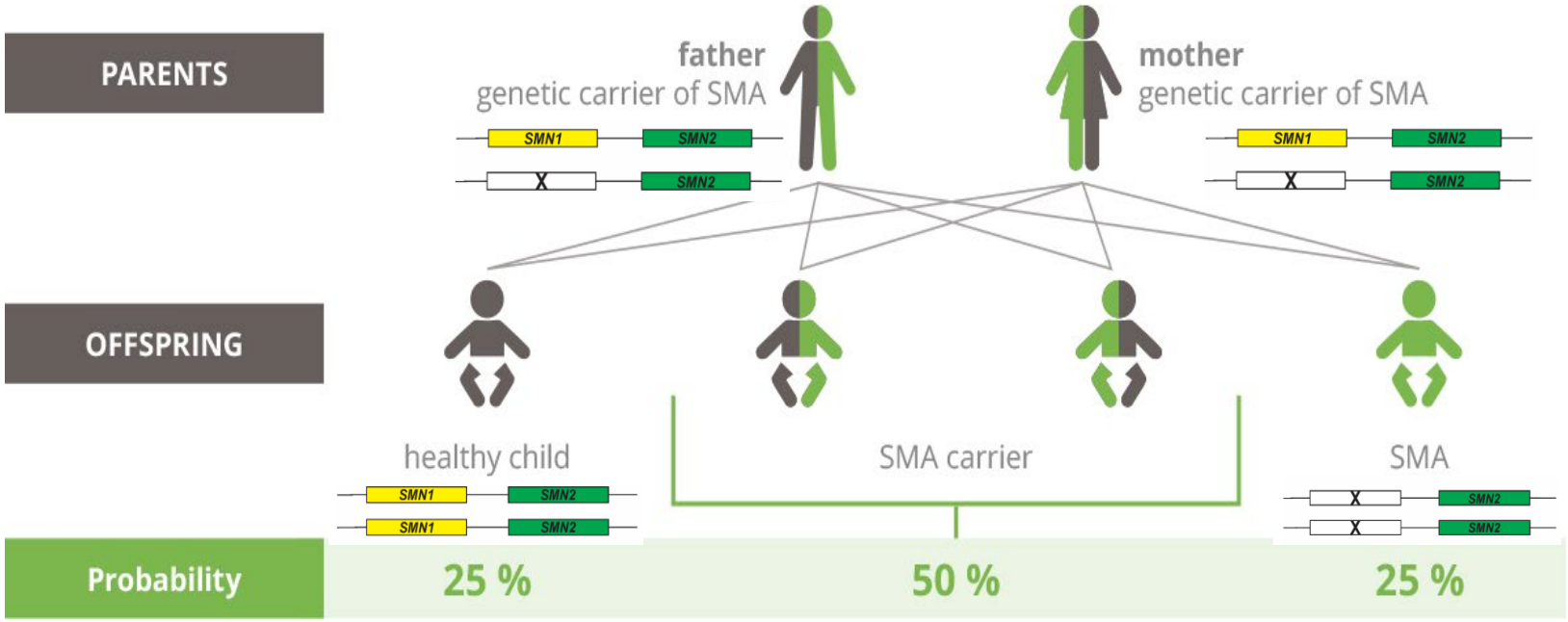


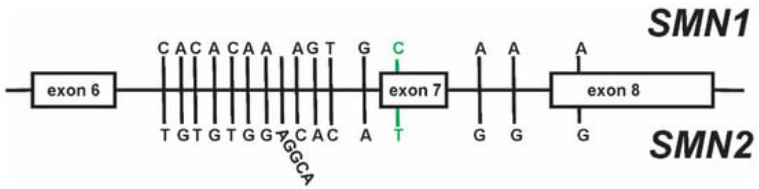

# How SMA Changed Everything

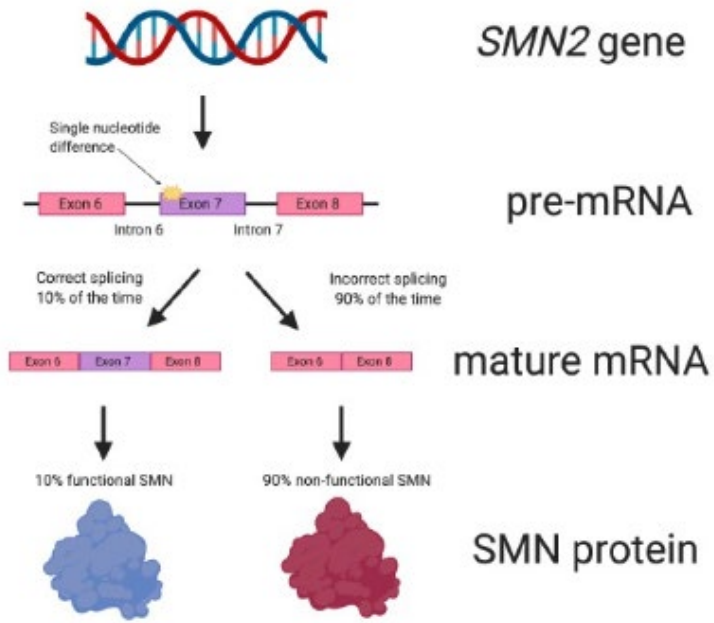
Bo Lee, M.D.

Assistant Professor of Neurology and Pediatrics

# SPINAL MUSCULAR ATROPHY



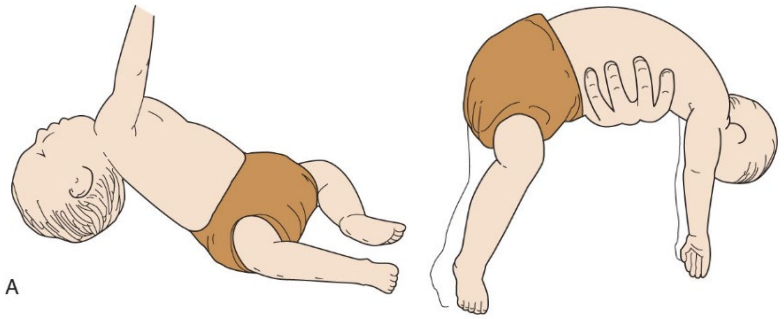



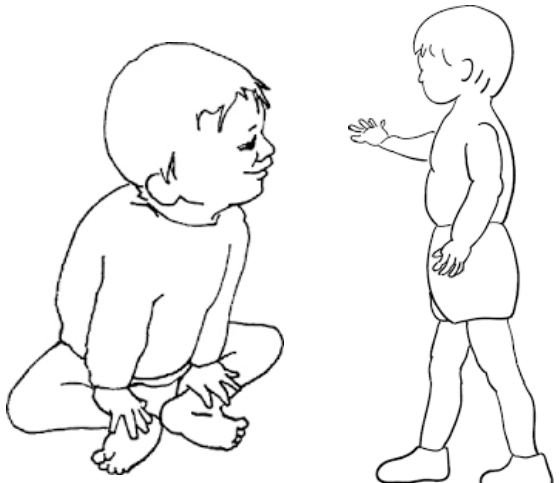
Classification of Spinal Muscular Atrophy

| | Age of Onset | Highest Achieved Motor Milestone | Life Expectancy* | Proportion of Patients With SMA | *SMN2* Copies |
|---|---|---|---|---|---|
| Type 0 | Birth | Never sitting | <6 months | <1% | 1 |
| Type I | <6 months | Never sitting | 8-24 months | 50%-60% | 2-3 |
| Type II | 6-18 months | Sitting | 20s-30s | 30% | 2-4 |
| Type III | 18 months-30 years | Walking | Normal | 10% | 3-5 |
| Type IV | >30 years | Walking | Normal | 5% | 3-5 |

*Without disease-modifying treatment or mechanical ventilation.

Nicolau S et al. Spinal Muscular Atrophy. Semin Pediatr Neurol. 2021. 37:100878



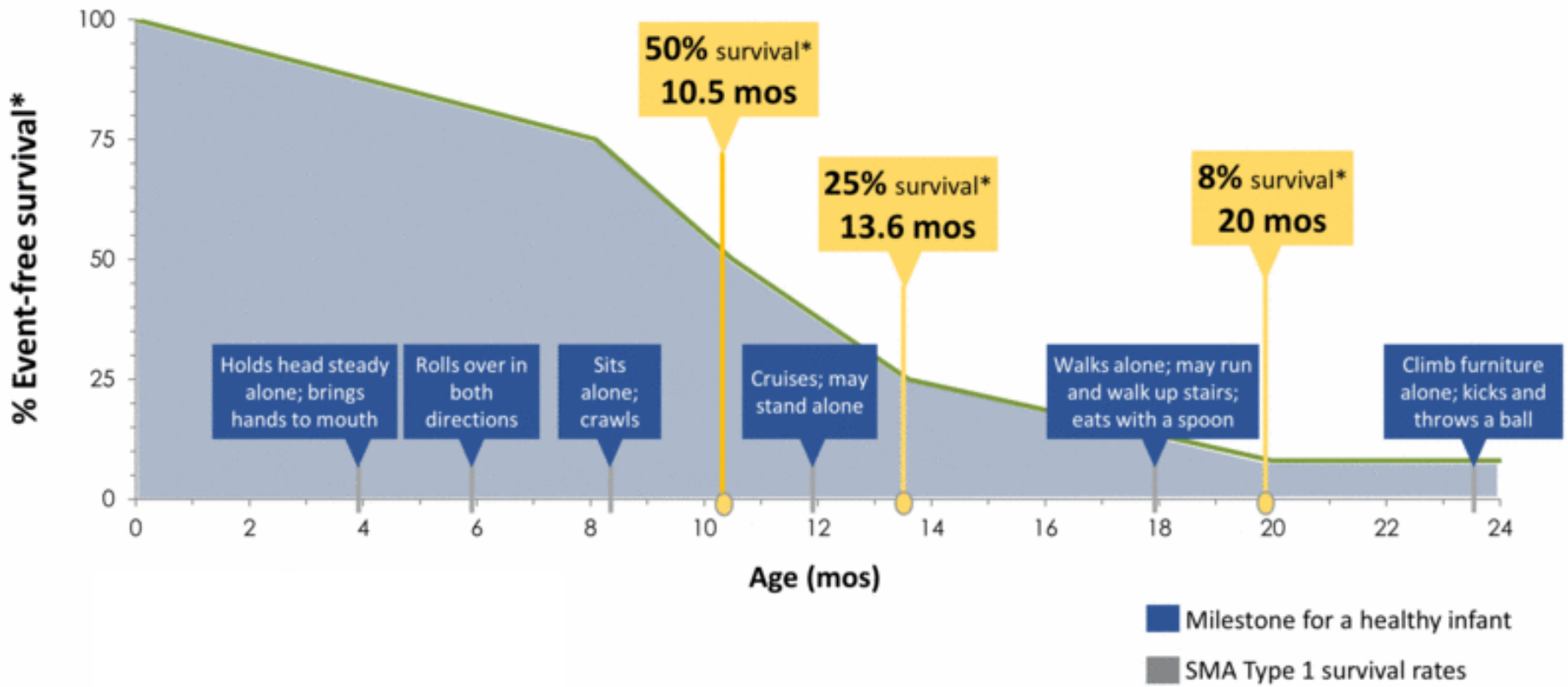





- Leading genetic cause of infant death
- Estimated incidence of 1 in 10,000 live births in the US

# Natural History of SMA Type 1

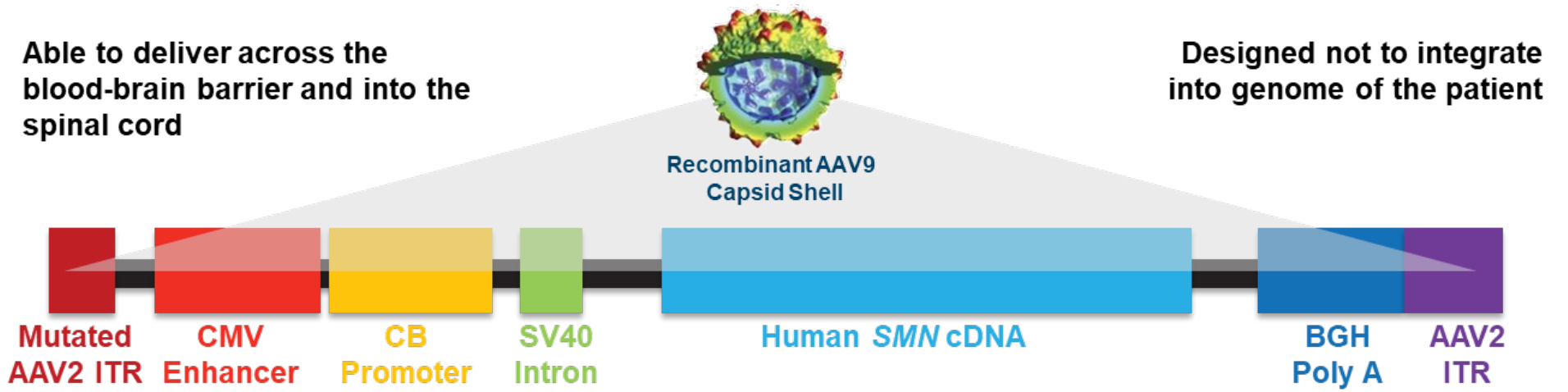
**90% of SMA Type 1 patients will not survive to the age of 2**




*Survival = no death, or no need for ≥16-hr/day ventilation continuously for ≥2 weeks, in the absence of an acute reversible illness

Finkel RS, et al. Neurology 2014;83:810–7 Pediatric NM Clinical Research Network for SMA

# Gene therapy for SMA: Onasemnogene abeparvovec



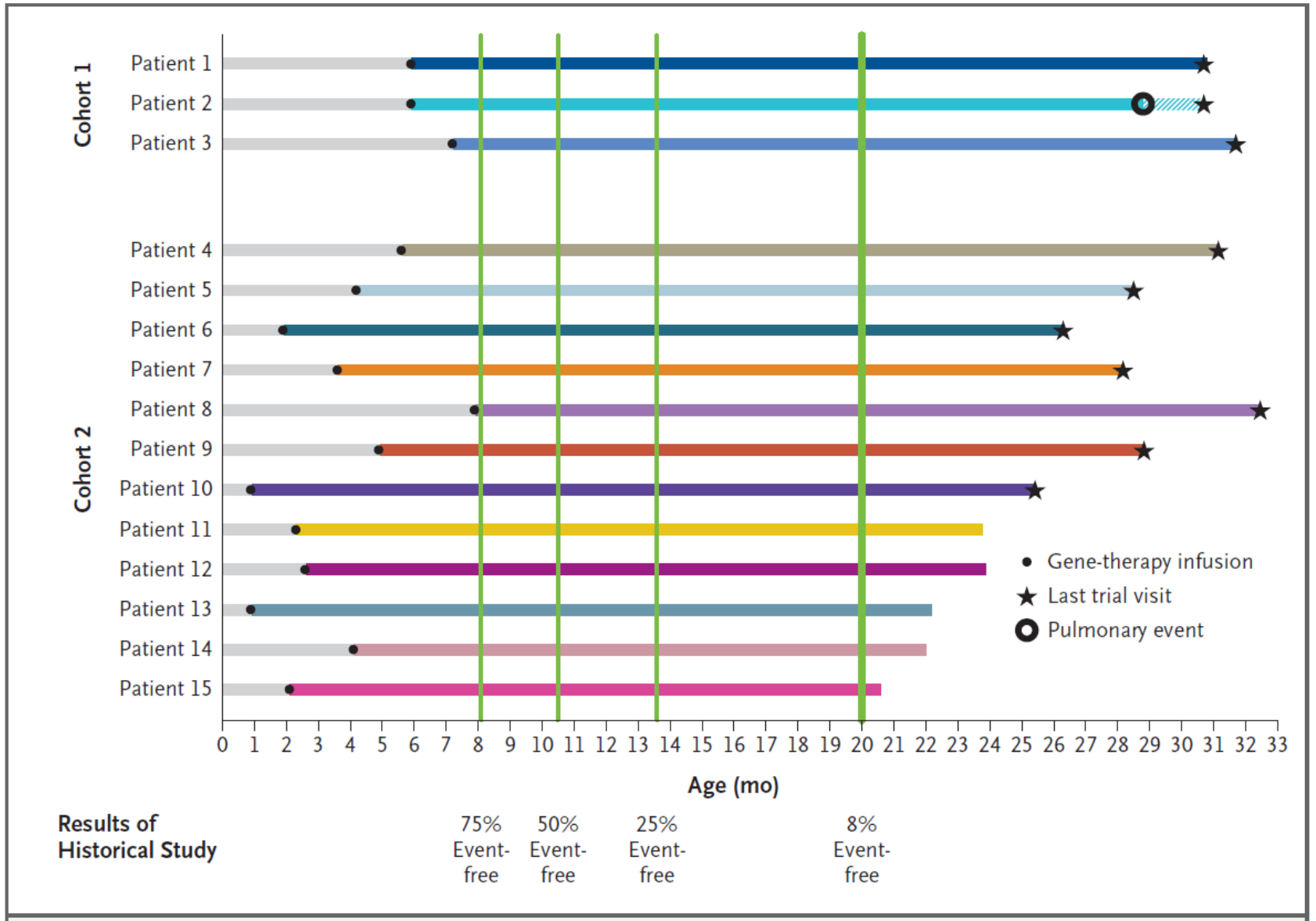

| Continuous Promoter | Human *SMN* Transgene | Self-Complementary AAV Inverted Terminal Repeats (scAAV ITR) |
|---|---|---|
| • Hybrid CMV enhancer and CB promoter activates the transgene to allow for continuous and sustained SMN protein expression | • Full copy of a stable, functioning human *SMN* gene that is introduced into the cell's nucleus | • The scAAV ITR increases the speed at which the double-stranded transgene is transcribed and the resulting protein is produced |

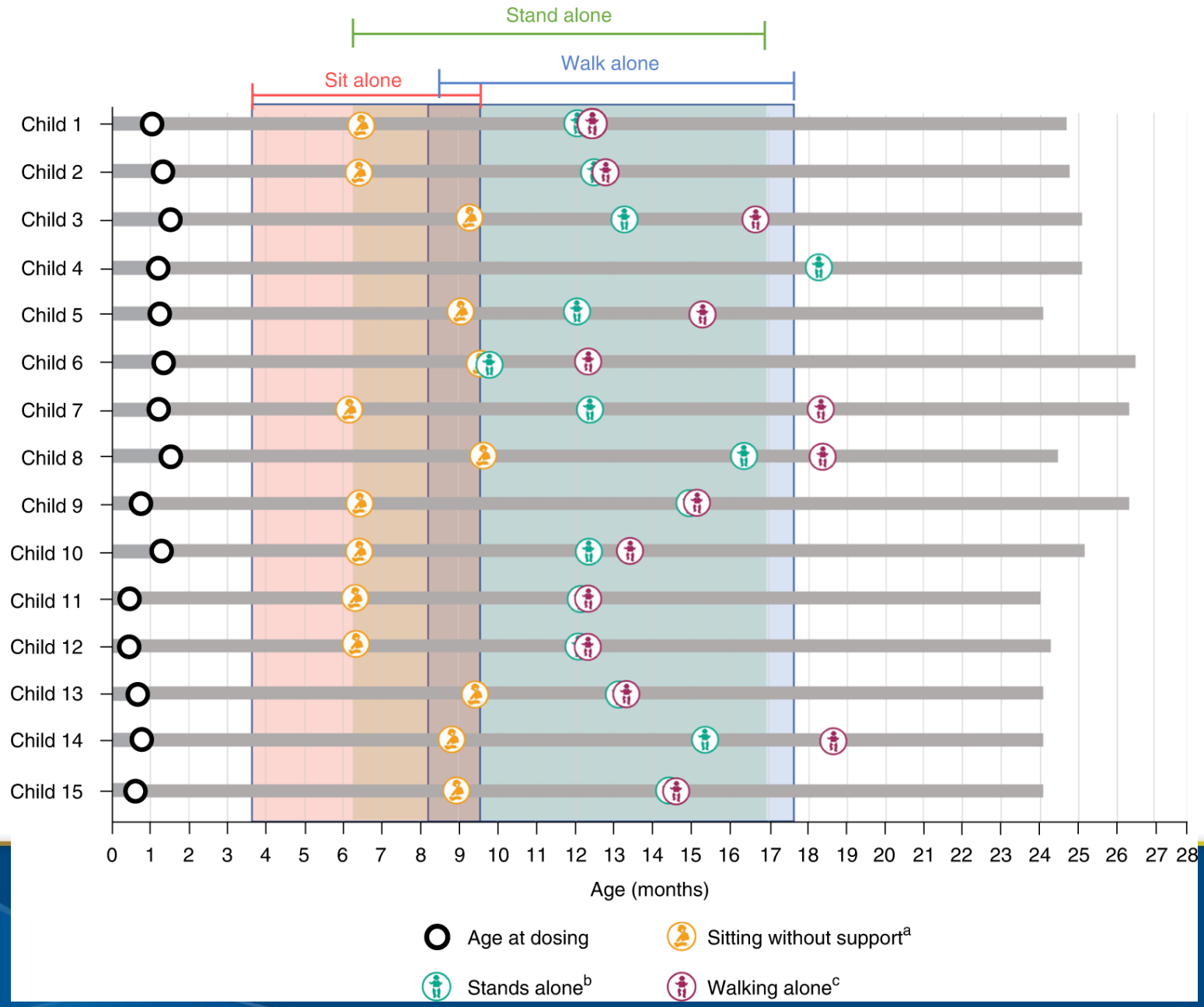
ORIGINAL ARTICLE

# Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

Jerry R. Mendell, M.D., Samiah Al-Zaidy, M.D., Richard Shell, M.D., W. Dave Arnold, M.D., Louise R. Rodino-Klapac, Ph.D., Thomas W. Prior, Ph.D., Linda Lowes, P.T., Ph.D., Lindsay Alfano, D.P.T., Katherine Berry, P.T., Kathleen Church, M.S.W., John T. Kissel, M.D., Sukumar Nagendran, M.D., et al.

**Patient #10: VIDEO**





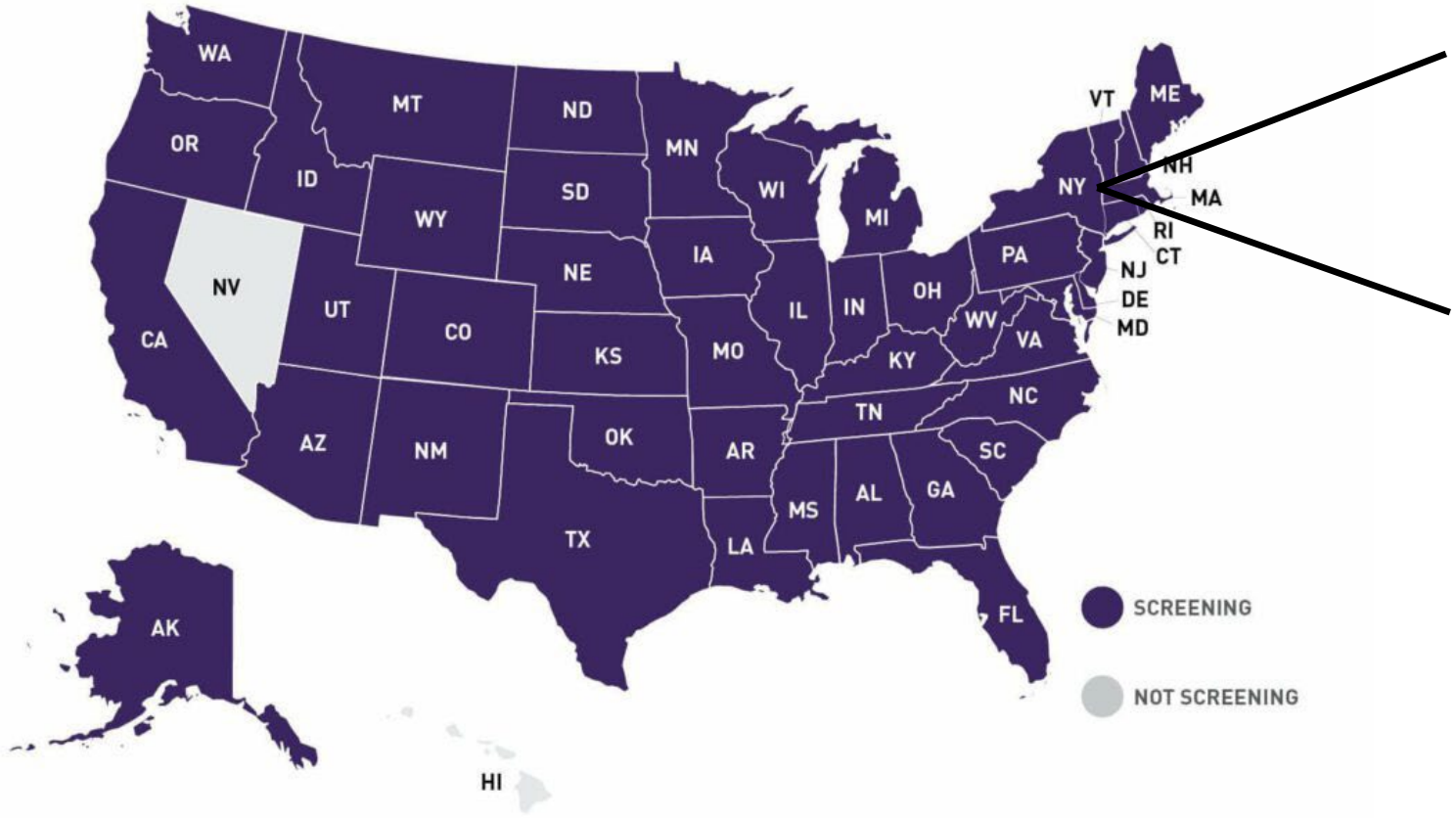

nature medicine

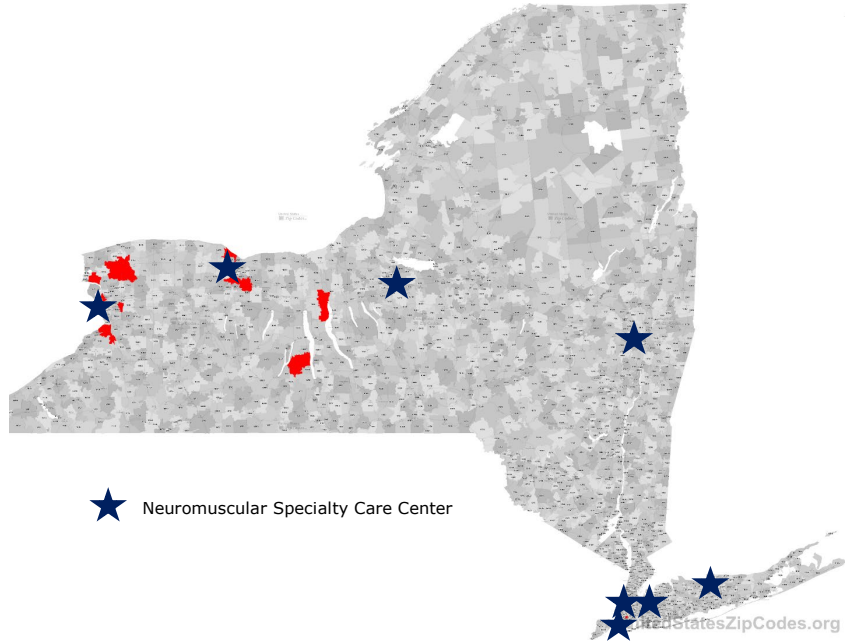
## Onasemnogene abeparvovec for presymptomatic infants with two copies of *SMN2* at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial

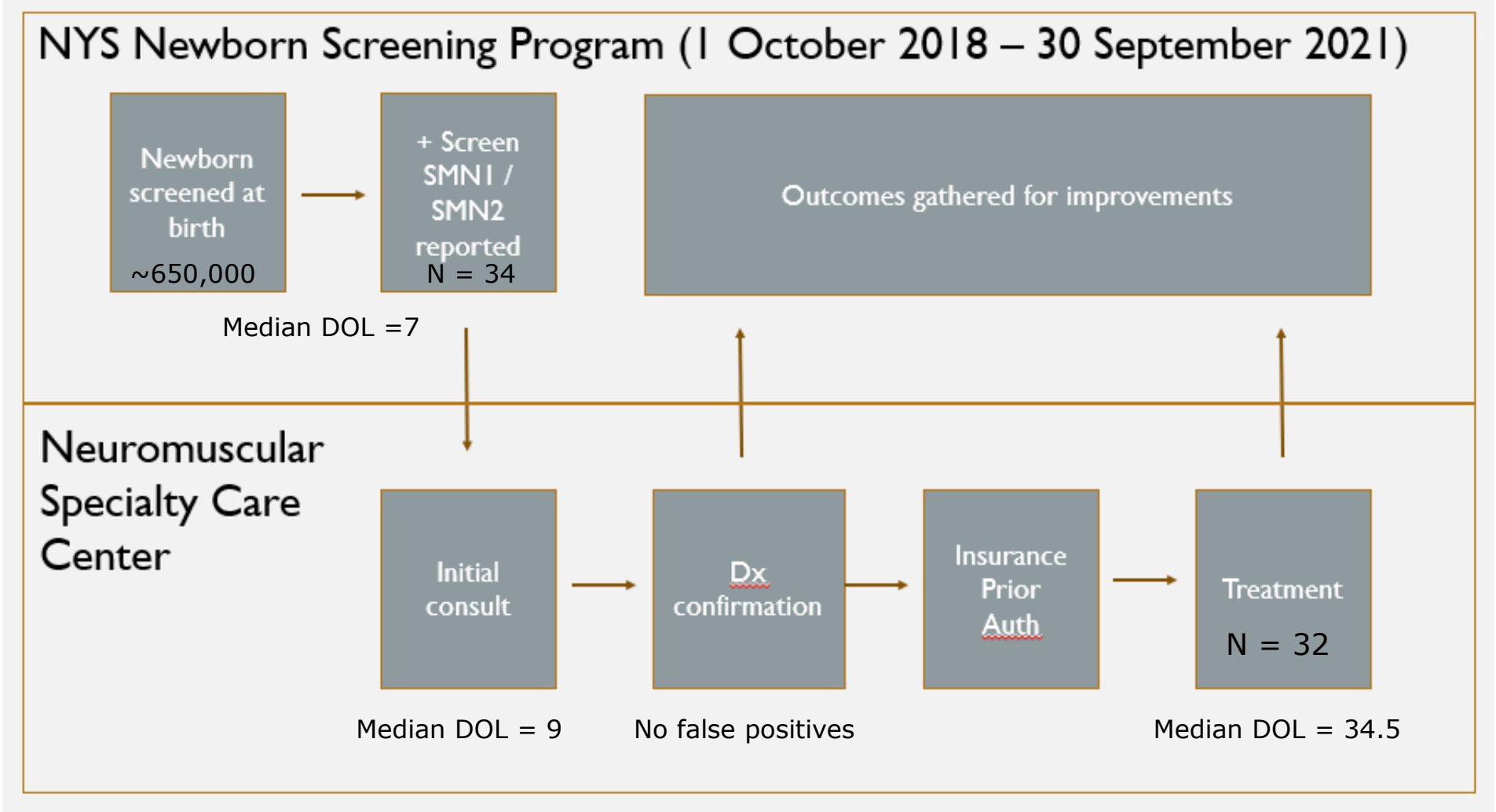
Kevin A. Strauss[1,2,3], Michelle A. Farrar[4,5], Francesco Muntoni[6,7], Kayoko Saito[8], Jerry R. Mendell[9,10], Laurent Servais[11,12], Hugh J. McMillan[13], Richard S. Finkel[14,15], Kathryn J. Swoboda[16], Jennifer M. Kwon[17], Craig M. Zaidman[18], Claudia A. Chiriboga[19], Susan T. Iannaccone[20], Jena M. Krueger[21], Julie A. Parsons[22], Perry B. Shieh[23], Sarah Kavanagh[24], Sitra Tauscher-Wisniewski[24], Bryan E. McGill[25] and Thomas A. Macek[24]

# STATES SCREENING & NOT SCREENING FOR SMA

48 States Currently Screen for SMA | 99% of Newborn Babies in the U.S. are Screened




NYS Newborn Screening Program (1 October 2018 – 30 September 2021)
Newborn screened at birth
~650,000
+ Screen SMN1 / SMN2 reported
N = 34
Median DOL =7
Outcomes gathered for improvements
Neuromuscular Specialty Care Center
Initial consult
Dx confirmation
Insurance Prior Auth
Treatment
N = 32
Median DOL = 9
No false positives
Median DOL = 34.5

# Pediatric Neuromuscular Care Model: How SMA Changed Everything

## OLD MODEL (prior to 2016)

- Clinical Diagnosis and Genetic Confirmation
- Diagnostic Delay
- Multidisciplinary supportive care, **no disease modifying treatments**

## NEW MODEL

- Diagnosis through NBS
- **Deliver gene therapy: "*Time is muscle*"**
- Manage adverse events
- High cost drugs
- New expertise, new infrastructure, new collaborations

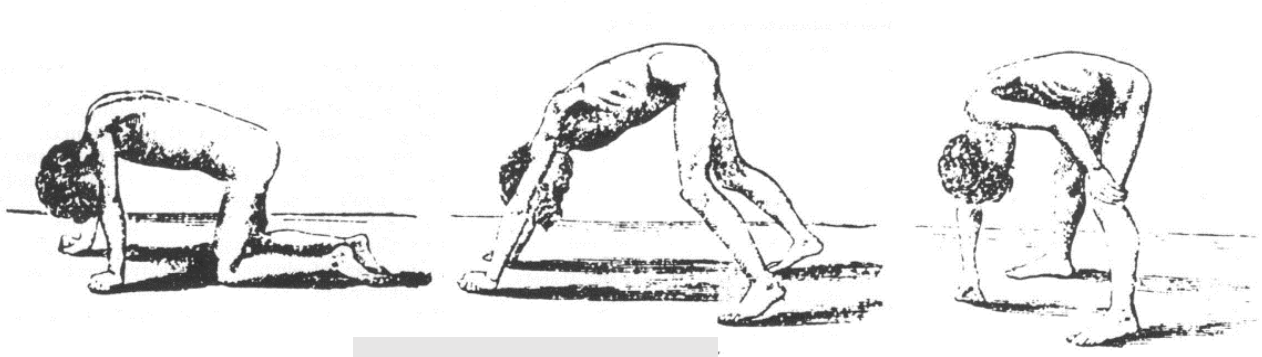
# Duchenne Muscular Dystrophy and Gene Therapy

Samuel Mackenzie, M.D., Ph.D.

Assistant Professor of Neurology, Neuroscience and Pediatrics

# Motor Signs and Symptoms of DMD

- Delayed walking
- Waddling gait, toe walking
- Difficulty walking, running, jumping, and negotiating stairs
- Lordosis
- Frequent falls
- Gowers sign
- Enlarged calves



**Gowers sign**

**Timed rise from supine**

# Damage Starts In Utero, Is Progressive, and Leads to Early Death

## Birth – 2 years of age

**Birth**
Creatine Kinase
> 2,000 (U/L)

**Poor head control**

**Can't sit without support**

**Standing, cruising late**

**Walk**
15 – 18 months

Autistic spectrum, delayed speech

### 3 – 4 yoa

- Increased CK
- Genetic diagnosis

### 5 – 7 yoa

- Motor delay
- Toe walking
- Difficulty stair climbing
- Positive Gowers' sign

### 8 – 11 yoa

- Walking difficulty
- Tires easier
- Wheelchair at times
- Frequent falls

### Early Teens

- Loss of ambulation
- Full-time wheelchair use
- Increased arms weakness

### Teens

- Reduced forced vital capacity
- Need for ventilatory support
- Reduced activities of daily living

### Teens to Twenties

- Cardiac dysfunction
- Heart failure
- Death

# Children with Duchenne Suffer Irreparable Harm Highlighting Urgent Need for Effective Therapies

**Based on US incidence and prevalence**

**~ 400 lose ambulation each year**

**2,000 more will lose ambulation over 5 years**

**Median survival 28 years**

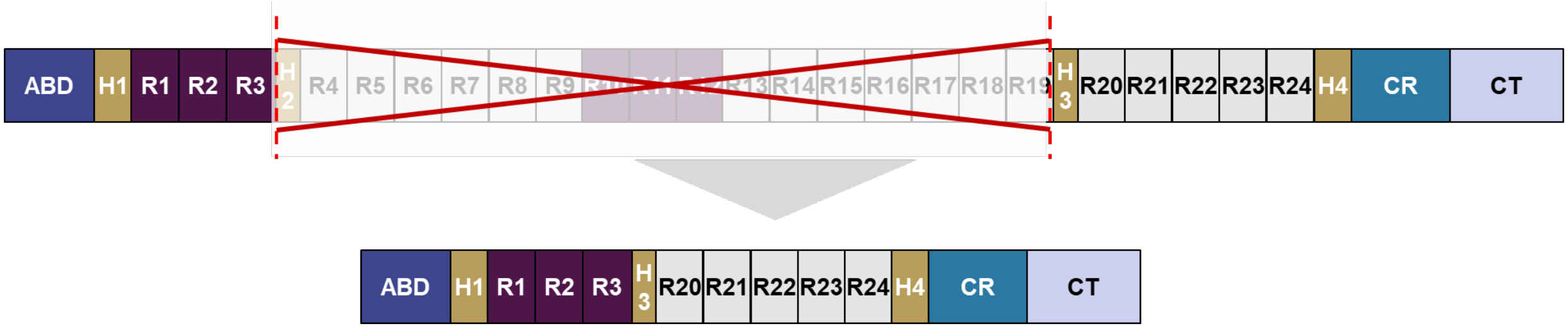
**> 400 patients in US die each year**

**2,228 patients will die over 5 years**

McDonald et al. 2018; Passamano et al. 2012; Broomfield et al. 2021; Paramsothy et al. 2022

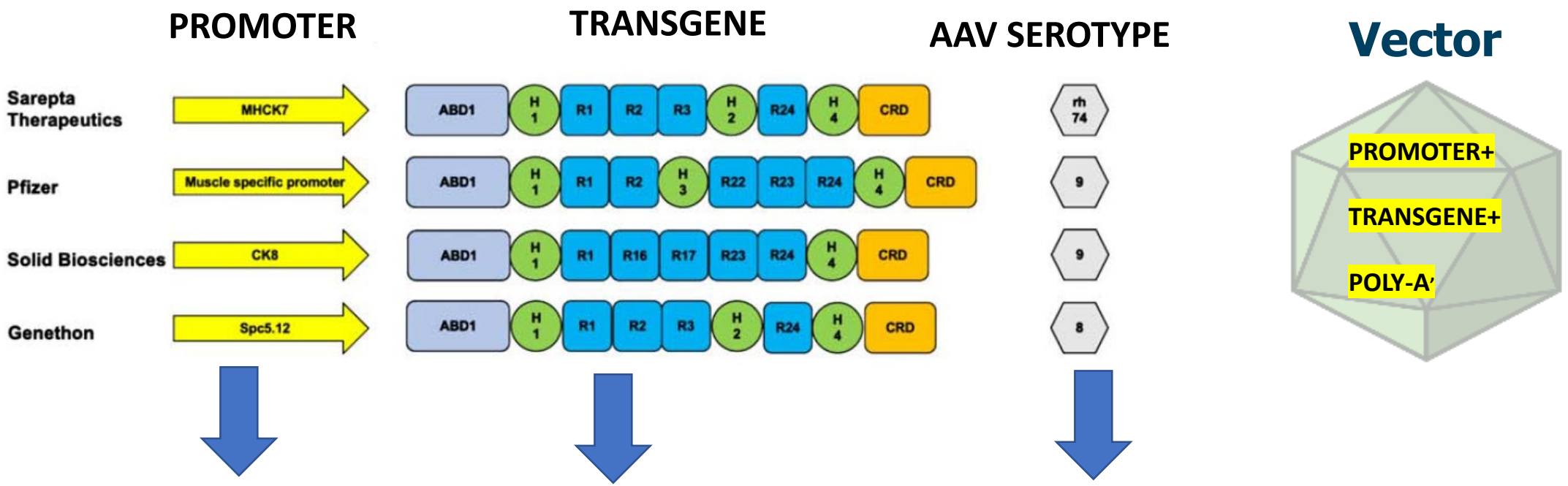
# Natural History Demonstrates that Large Portions of Dystrophin Protein Are Less Critical

- First discovered by Professor Kay Davies in 1990
  - Mild Becker muscular dystrophy (BMD) patient who, surprisingly, could still ambulate at age 61
- Genetic testing confirmed patient missing nearly half their dystrophin protein
  - Missing 46% of dystrophin coding region (Del 17 – 48)[1], specifically large stretch of spectrin-like repeats in middle




1. England et al. 1990
Evidence includes 2 additional mildly affected individuals in the pedigree

# Gene Therapy for Duchenne

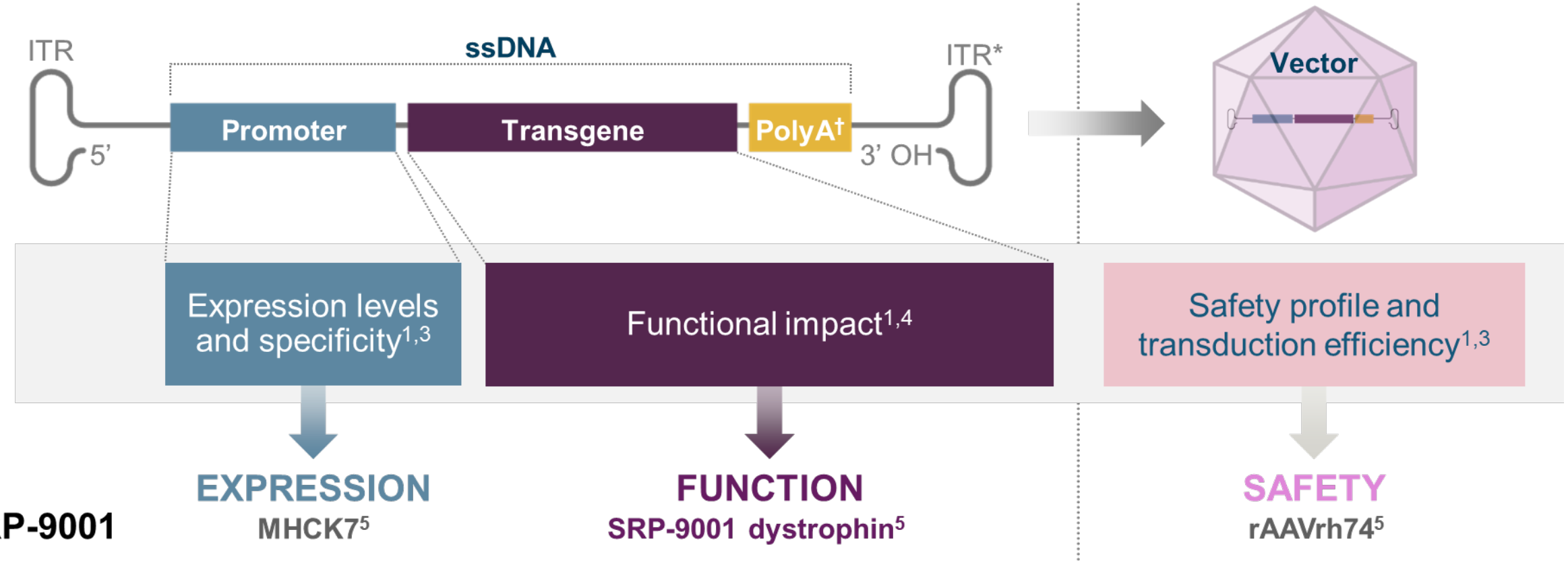



**Tissue Expression and Specificity**

**Function**
proved to greatly prevent muscle damage in transgenic *mdx* mice and NHP

**Safety and Transduction**
- non-pathogenic
- mostly non-integrating
- strong muscle and heart tropism
- high transduction efficiency with IV delivery
- Payload capacity

# SRP-9001: AAV-Based Investigational Gene Transfer Therapy for Treatment of DMD[1,2]

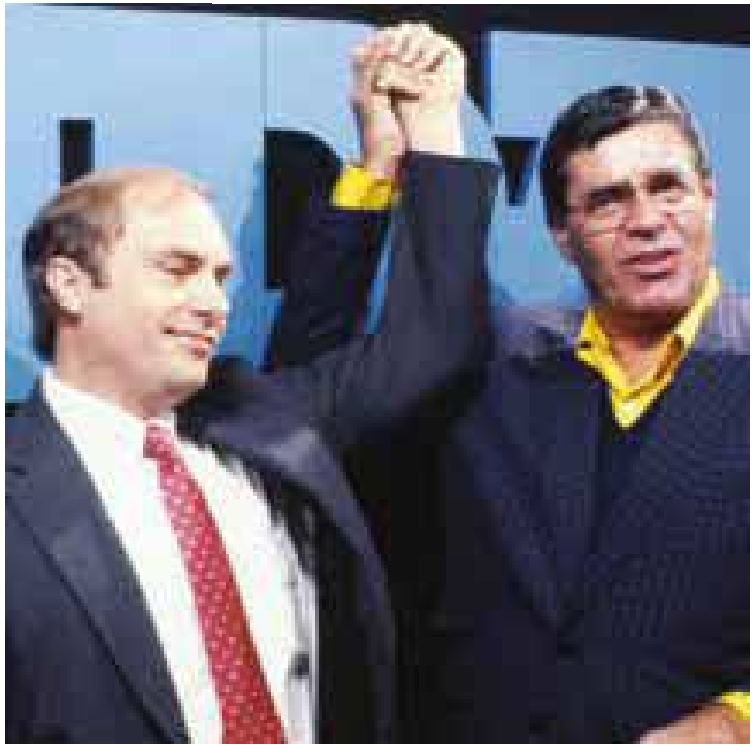



*ITRs are required for genome replication and packaging; †PolyA signals the end of the transgene to the cellular machinery that transcribes (ie, copies) it.
AAV = adeno-associated virus; AAVrh74 = recombinant human adeno-associated virus 74; ITR = information transfer rate; ssDNA = single-stranded DNA

1. Asher et al. 2020; 2. US National Library of Medicine 2013; 3. Zheng and Baum 2008; 4. Chandler and Venditti 2016; 5. Mendell et al. 2020

# DYSTROPHIN

## A Triumph of Reverse Genetics and the End of the Beginning



*''The achievements of Kunkel and his colleagues have introduced a new era of research that should be useful and exhilarating''*

Dr. Rowland Editorial: “Dystrophin”, NEJM 1988

Louis Kunkel and Jerry Lewis announcing the identification of the dystrophin gene Oct. 16, 1986

ELEVYDIS first gene therapy for Duchenne Dystrophy approved June 22, 2023

18 months post-gene therapy (age 7)

First patient dosed in Phase 3 trial at Rochester

## RARE DISEASE TYPES

**7,000+**

Identified rare diseases, with more being discovered every day.

## THE CAUSE

**80%**

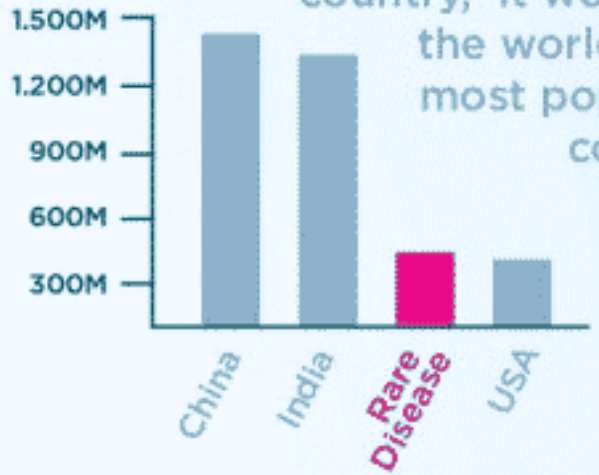
of rare diseases are caused by faulty genes.

## RARE DISEASE EFFECT

**30** MILLION AMERICANS

**350** MILLION WORLDWIDE

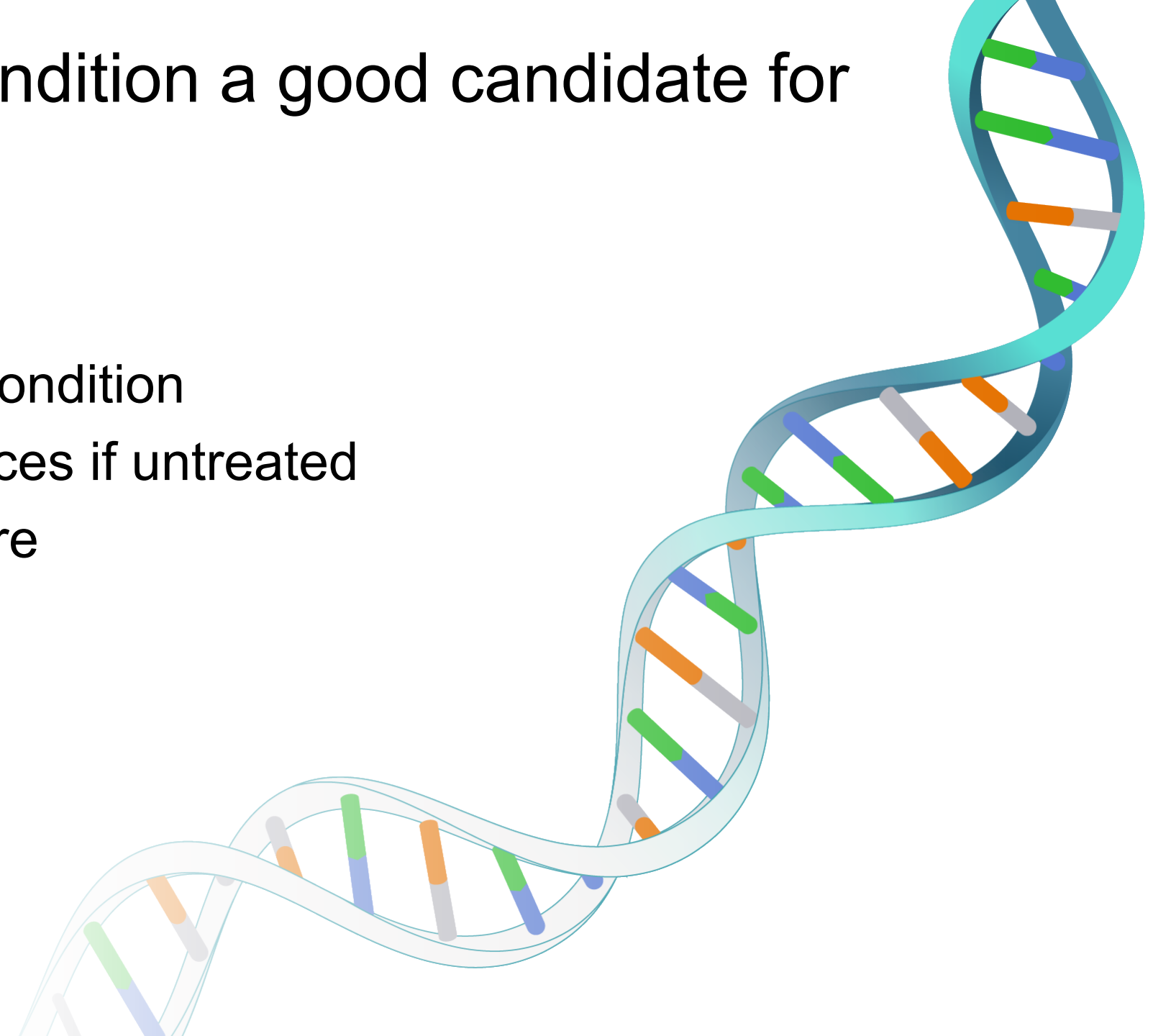
If all of the people with rare diseases lived in one country, it would be the world's 3rd most populous country.




*World Rare Disease Day*

# What makes a condition a good candidate for gene therapy?

- Small gene
- “Loss of function” condition
- Severe consequences if untreated
- Rare but not too rare



# TANGO2-deficiency disorder








- ✓ Small gene
- ✓ “Loss of function” condition
- ✓ Severe consequences if untreated
- ✓ Rare but not too rare

*TANGO2 Research Foundation*

# A research roadmap

# THANK YOU

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