DMD
Research Overview
End Duchenne Tour
2018

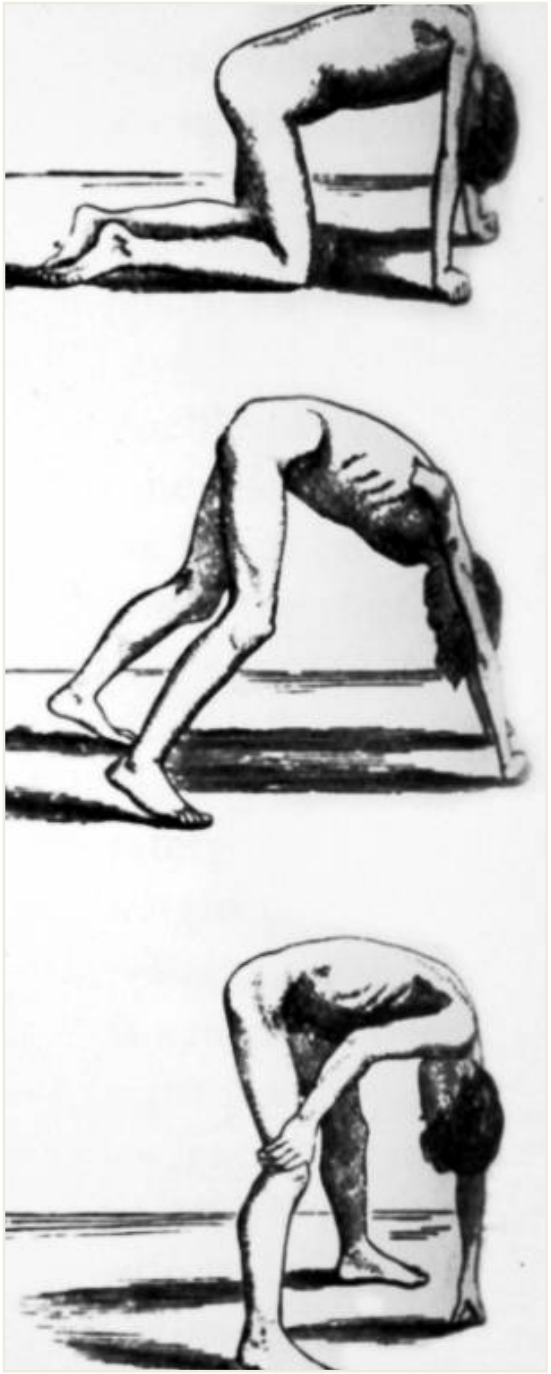
Susan T. Iannaccone, MD

Associate Director

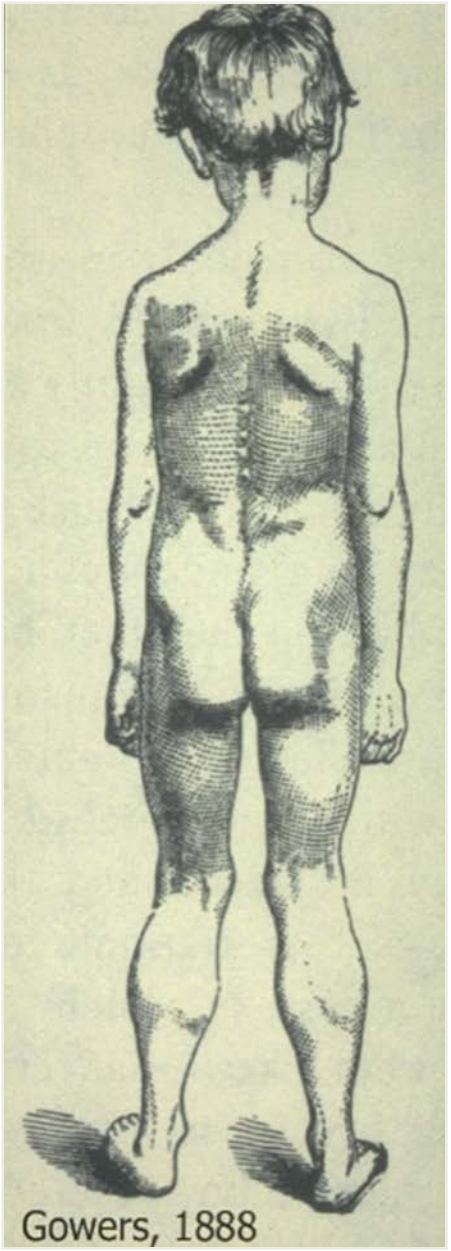
UTSW Wellstone MDC

Disclosures for STI

- Research funding from PTC Therapeutics, Sarepta, FibroGen, Regeneron, Mallinkrodt, Capricor
- DSMB for Catabasis
- Ad Board for AveXis, Biogen, Sarepta
- Supported by NIH and MDA funding
- Thanks to Pat Furlong and Amanda Wilkison for slides, Eugenio Mercuri for WMS update



Early descriptions,
19th century

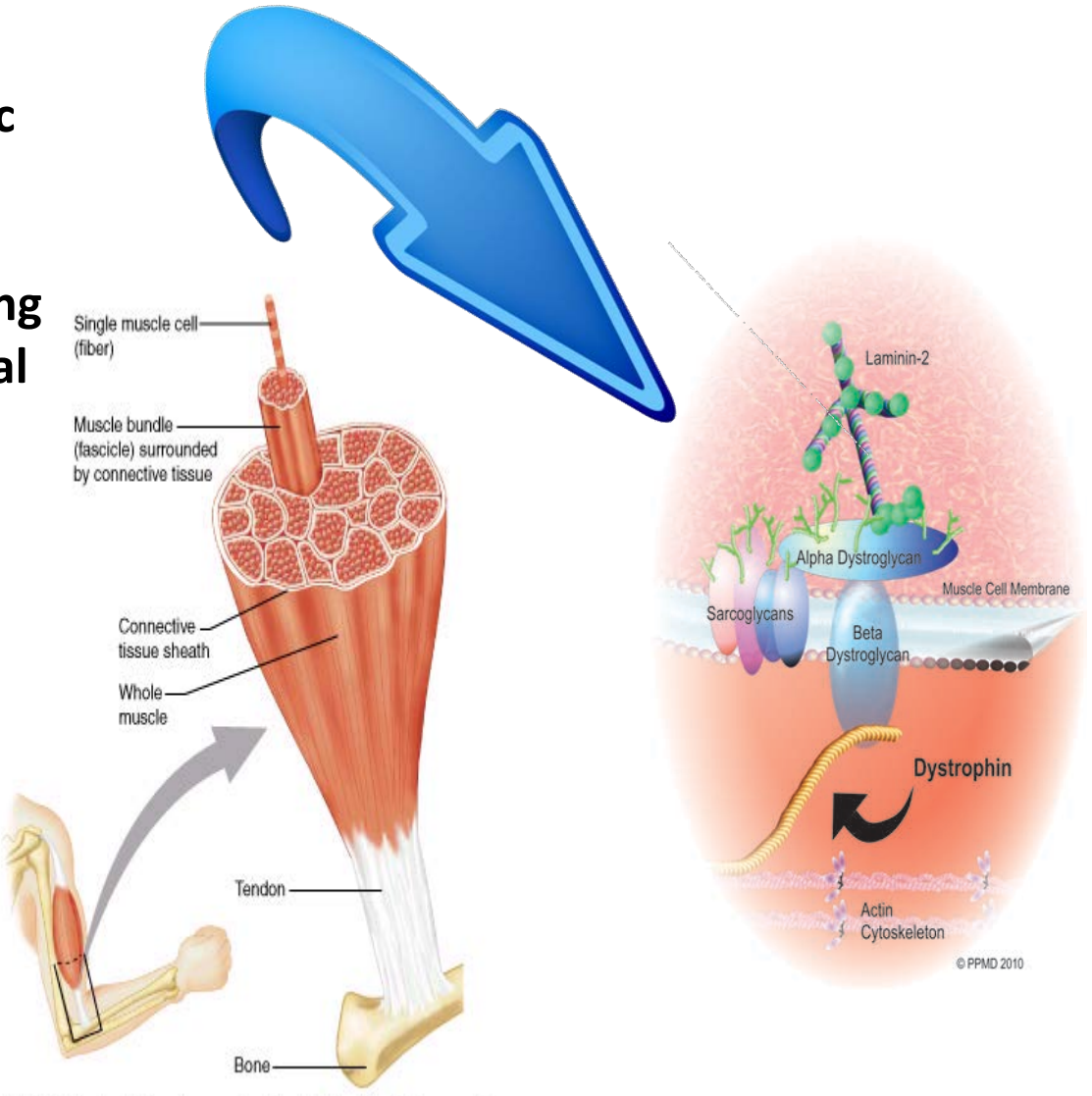


Duchenne/Becker MD

- Incidence: 1-3 in 10,000 male births
- Carrier frequency: 1 in 2000
- New mutations: 30%
- Mutation rate: 1 in 30,000
- CK >100X nl

Starting at the Beginning

Due to a genetic mutation, the dystrophin protein is missing or not functional in Duchenne

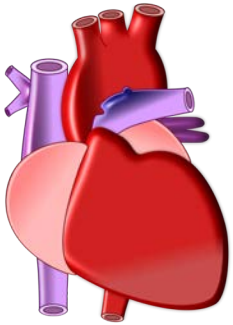


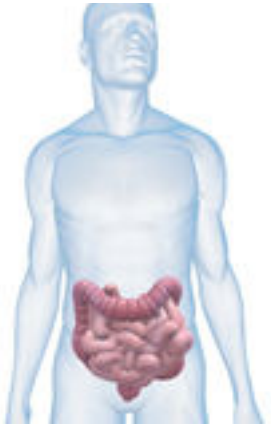
Diagnosis of DMD

- Clinical phenotype
- CK
- DNA
  - Deletion/duplication (up to 70%)
  - Sequencing
- NBS

DMD: Multisystem Disease

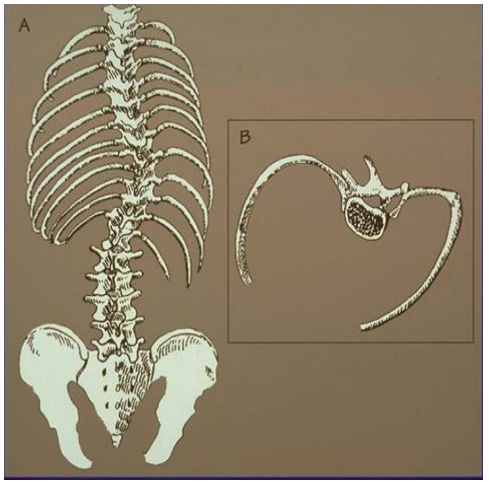
- Skeletal myopathy
- Encephalopathy
  - Behavior disorder
  - Cognitive deficit
  - Learning differences
- Cardiomyopathy
- Smooth muscle
  - Vessels
  - GI tract

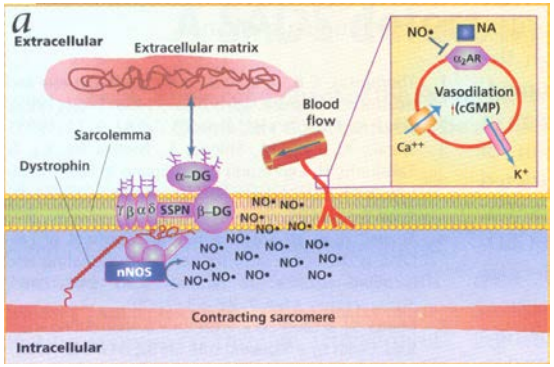




DMD: Complications

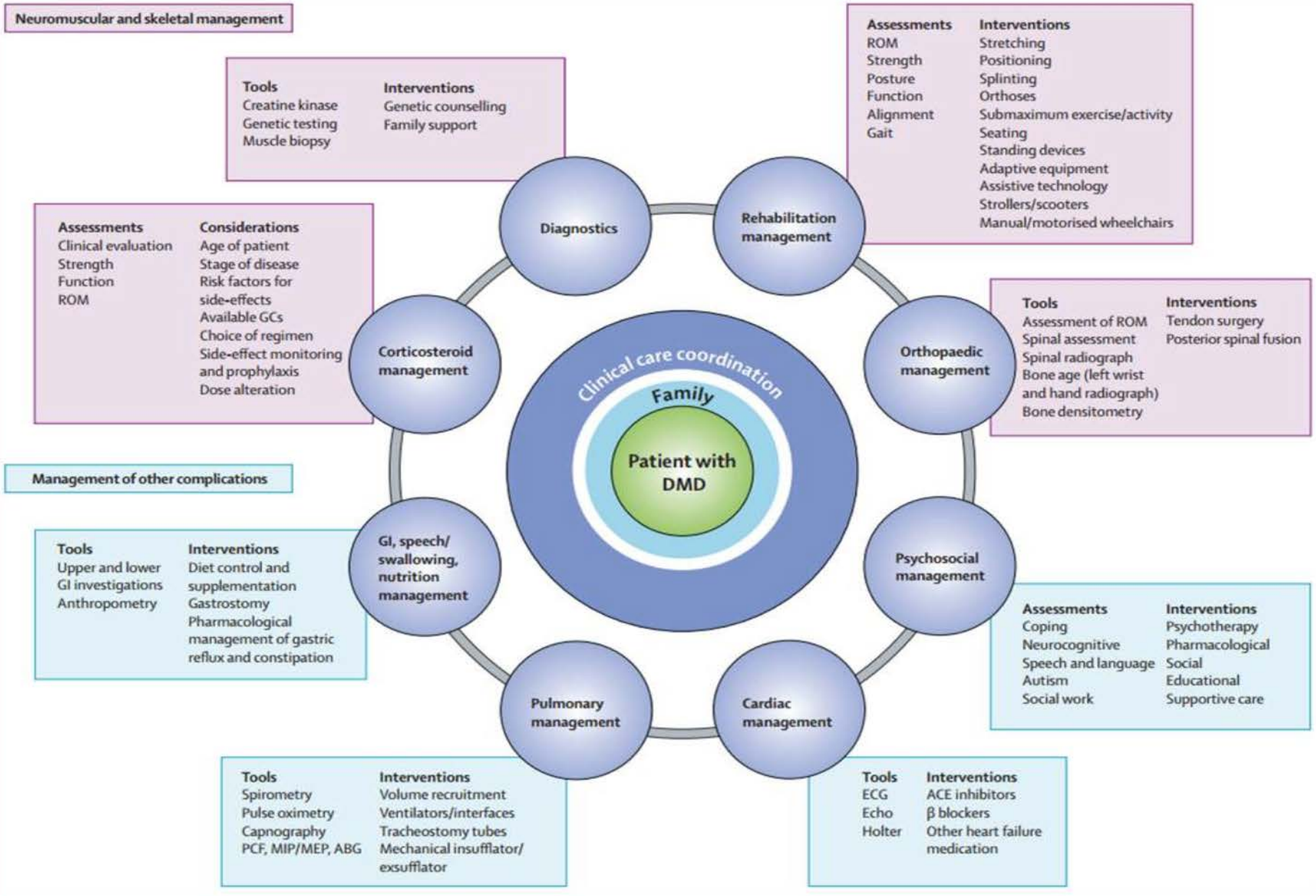
- **Orthopedic**
  - Contractures
  - Scoliosis
  - Chest wall deformity
- **Pulmonary**
  - Restrictive lung disease
  - Obstructive sleep apnea
- **Pain**
  - With exercise
  - With immobility

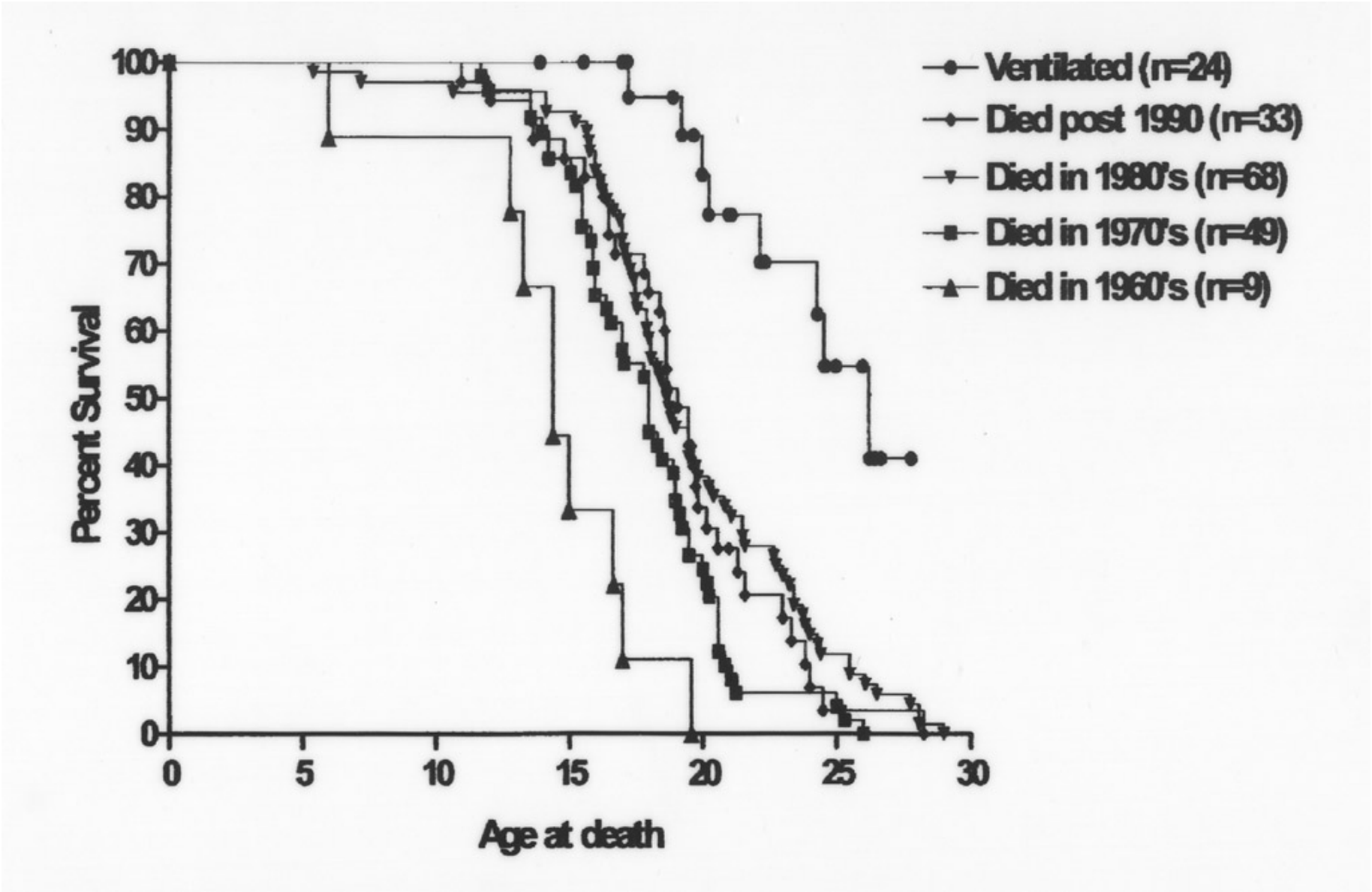




DMD: Multisystem Disease and Complications

- **Multidisciplinary clinic**
  - **One stop shopping**
  - **Specialists with expertise in DMD**
  - **Team approach**
- **Challenges**
  - **Cost/reimbursement**
  - **Space**
  - **Other commitments for providers**


Neuromuscular and skeletal management
Tools
Creatine kinase
Genetic testing
Muscle biopsy
Interventions
Genetic counselling
Family support
Assessments
ROM
Strength
Posture
Function
Alignment
Gait
Interventions
Stretching
Positioning
Splinting
Orthoses
Submaximum exercise/activity
Seating
Standing devices
Adaptive equipment
Assistive technology
Strollers/scooters
Manual/motorised wheelchairs
Diagnostics
Rehabilitation management
Assessments
Clinical evaluation
Strength
Function
ROM
Considerations
Age of patient
Stage of disease
Risk factors for side-effects
Available GCs
Choice of regimen
Side-effect monitoring and prophylaxis
Dose alteration
Corticosteroid management
Orthopaedic management
Tools
Assessment of ROM
Spinal assessment
Spinal radiograph
Bone age (left wrist and hand radiograph)
Bone densitometry
Interventions
Tendon surgery
Posterior spinal fusion
Clinical care coordination
Family
Patient with DMD
Management of other complications
Tools
Upper and lower GI investigations
Anthropometry
Interventions
Diet control and supplementation
Gastrostomy
Pharmacological management of gastric reflux and constipation
GI, speech/ swallowing, nutrition management
Psychosocial management
Assessments
Coping
Neurocognitive
Speech and language
Autism
Social work
Interventions
Psychotherapy
Pharmacological
Social
Educational
Supportive care
Pulmonary management
Cardiac management
Tools
Spirometry
Pulse oximetry
Capnography
PCF, MIP/MEP, ABG
Interventions
Volume recruitment
Ventilators/interfaces
Tracheostomy tubes
Mechanical insufflator/ exsufflator
Tools
ECG
Echo
Holter
Interventions
ACE inhibitors
β blockers
Other heart failure medication



From Eagle et al, Neuromusc Disorders, 2002

Treatment of DMD

- "Standard of Care:
  - Multi disciplinary care
  - Expert subspecialty care
- Steroids
  - Benefits
    - Life expectancy
    - Lung function
    - Cardiac function
    - Scoliosis
  - Prednisone vs Emflaza
  - Daily vs pulse/weekend dosing

Treatment of DMD

Chronology	
1843	First clinical description
1982	Linkage to Xp21
1986	Dystrophin gene cloned and protein predicted, antibodies to protein
1988	CIDD first reports of prednisone efficacy
1990s 2000s 2016 2017	Attempts to identify “mini-gene” Exon skipping Ataluren (gentamycin like mechanism) Drisapersen Eteplirsen now EXONDYS 51 Gene editing “CRISPR/cas9” EMFLAZA More ASOs More steroid-iike drugs Other

What is a Clinical Trial?

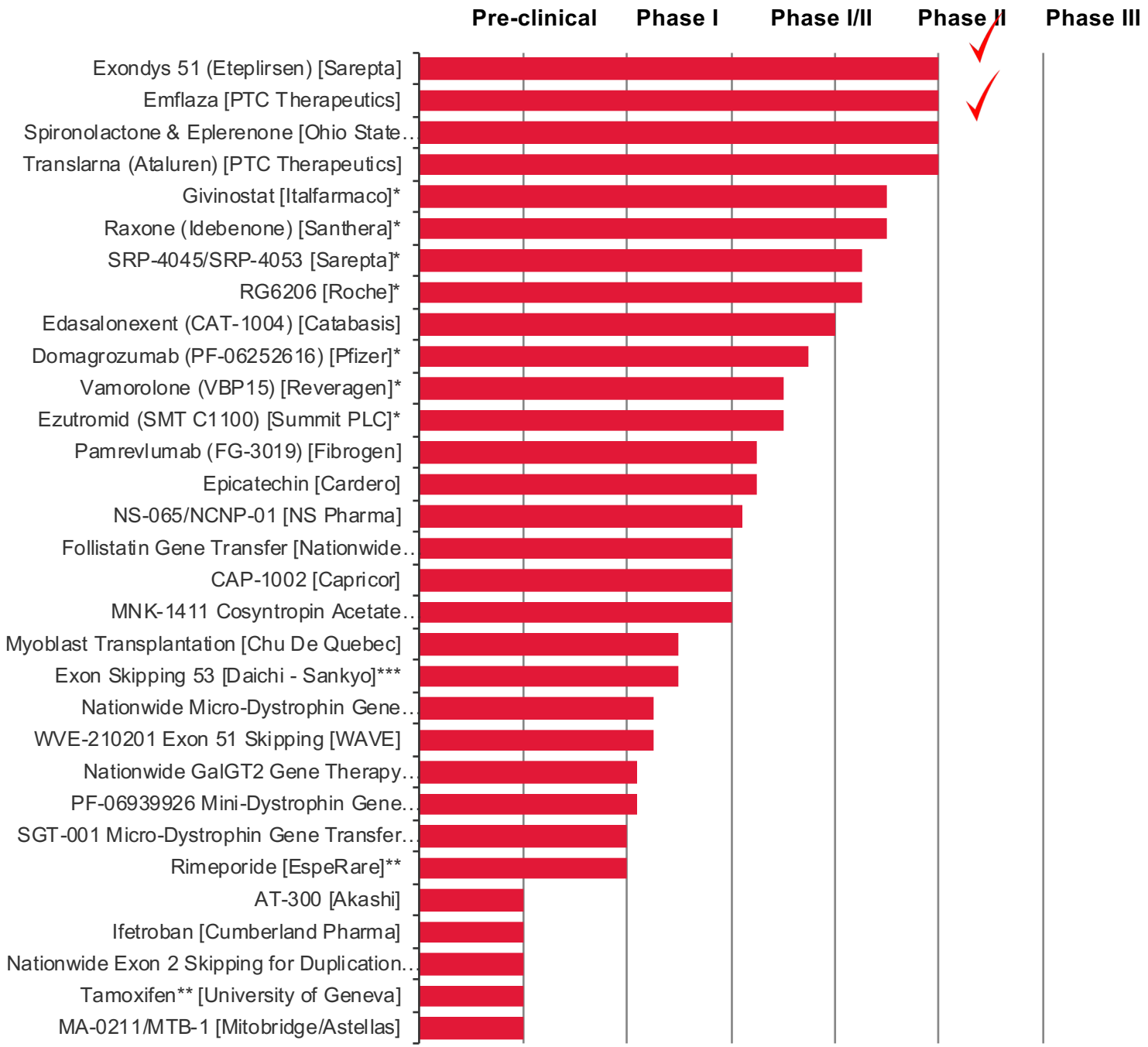
- A trial is an experiment, not a therapy
- Risks and benefits
  - Data Safety Monitoring Boards (DSMB)
  - May assess safety and data during the trial
- Important to pay attention to the informed consent/assent

Study Types

- Phases of Clinical Trials
  - Pre-clinical
    - Lab and animal studies
    - Non-human primates for safety
  - Phase I:
    - First in humans
    - Dosing
    - Small n
    - Assess safety
  - Phase IIa:
    - Assess dose requirements
    - IIa and Iib overlap…..

Study Types

- **Phase IIb**
  - **Assess efficacy; "Pivotal"**
  - **Can combine a and b, testing both efficacy and toxicity**
  - **Larger than phase I**
- **Phase III**
  - **Classical randomized control placebo trial 1000-3000 subjects**
    - **In rare disease, this number can be much smaller**
- **Phase IV**
  - **Post-Marketing**
  - **Monitor long term effects**


Pre-clinical
Phase I
Phase I/II
Phase II
Phase III
Exondys 51 (Eteplirsen) [Sarepta]
Emflaza [PTC Therapeutics]
Spironolactone & Eplerenone [Ohio State..
Translarna (Ataluren) [PTC Therapeutics]
Givinostat [Italfarmaco]*
Raxone (Idebenone) [Santhera]*
SRP-4045/SRP-4053 [Sarepta]*
RG6206 [Roche]*
Edasalonexent (CAT-1004) [Catabasis]
Domagrozumab (PF-06252616) [Pfizer]*
Vamorolone (VBP15) [Reveragen]*
Ezutromid (SMT C1100) [Summit PLC]*
Pamrevlumab (FG-3019) [Fibrogen]
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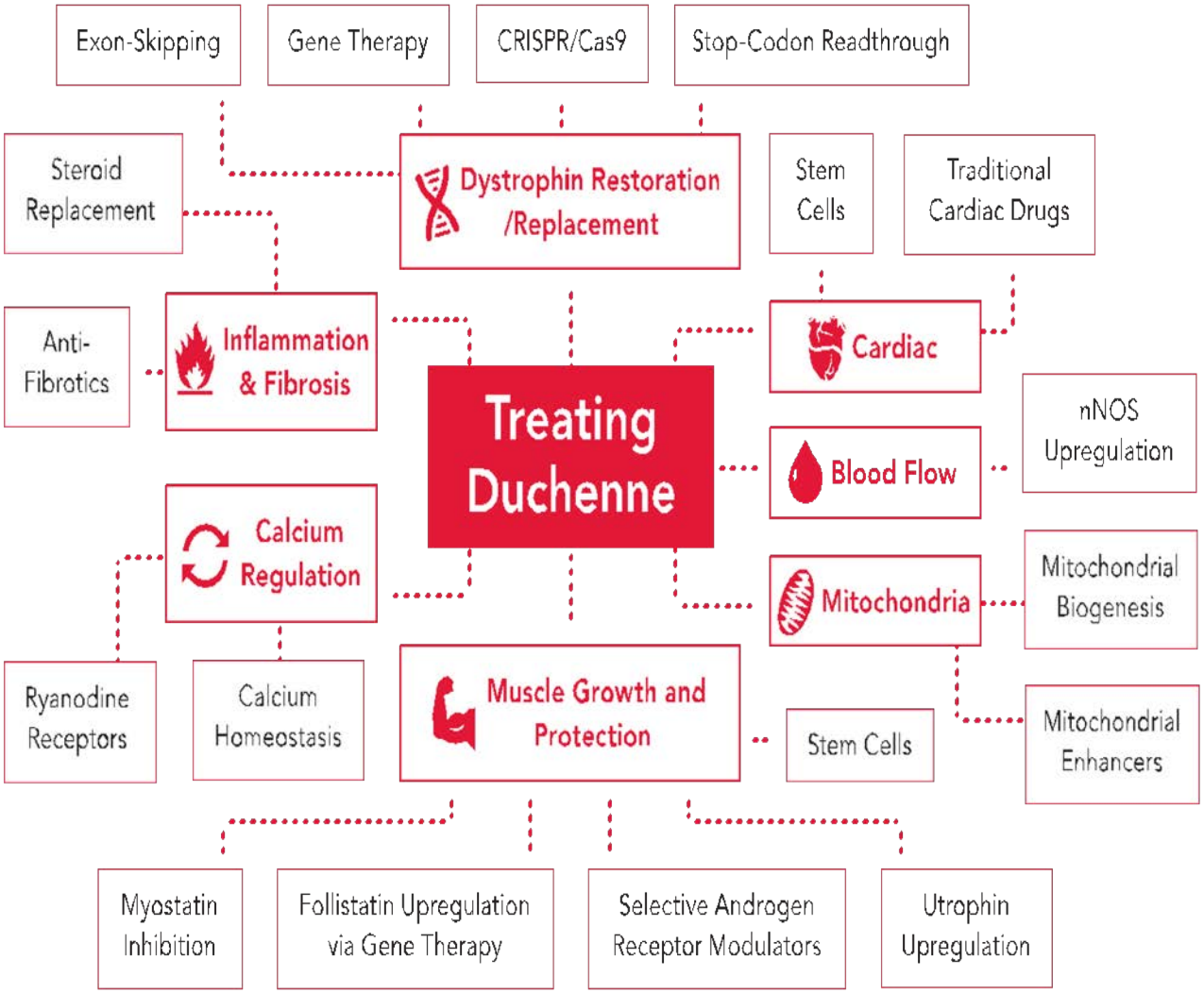
Myoblast Transplantation [Chu De Quebec]
Exon Skipping 53 [Daichi - Sankyo]***
Nationwide Micro-Dystrophin Gene..
WVE-210201 Exon 51 Skipping [WAVE]
Nationwide GalGT2 Gene Therapy..
PF-06939926 Mini-Dystrophin Gene..
SGT-001 Micro-Dystrophin Gene Transfer..
Rimeporide [EspeRare]**
AT-300 [Akashi]
Ifetroban [Cumberland Pharma]
Nationwide Exon 2 Skipping for Duplication..
Tamoxifen** [University of Geneva]
MA-0211/MTB-1 [Mitobridge/Astellas]

Clinical Trials in Duchenne



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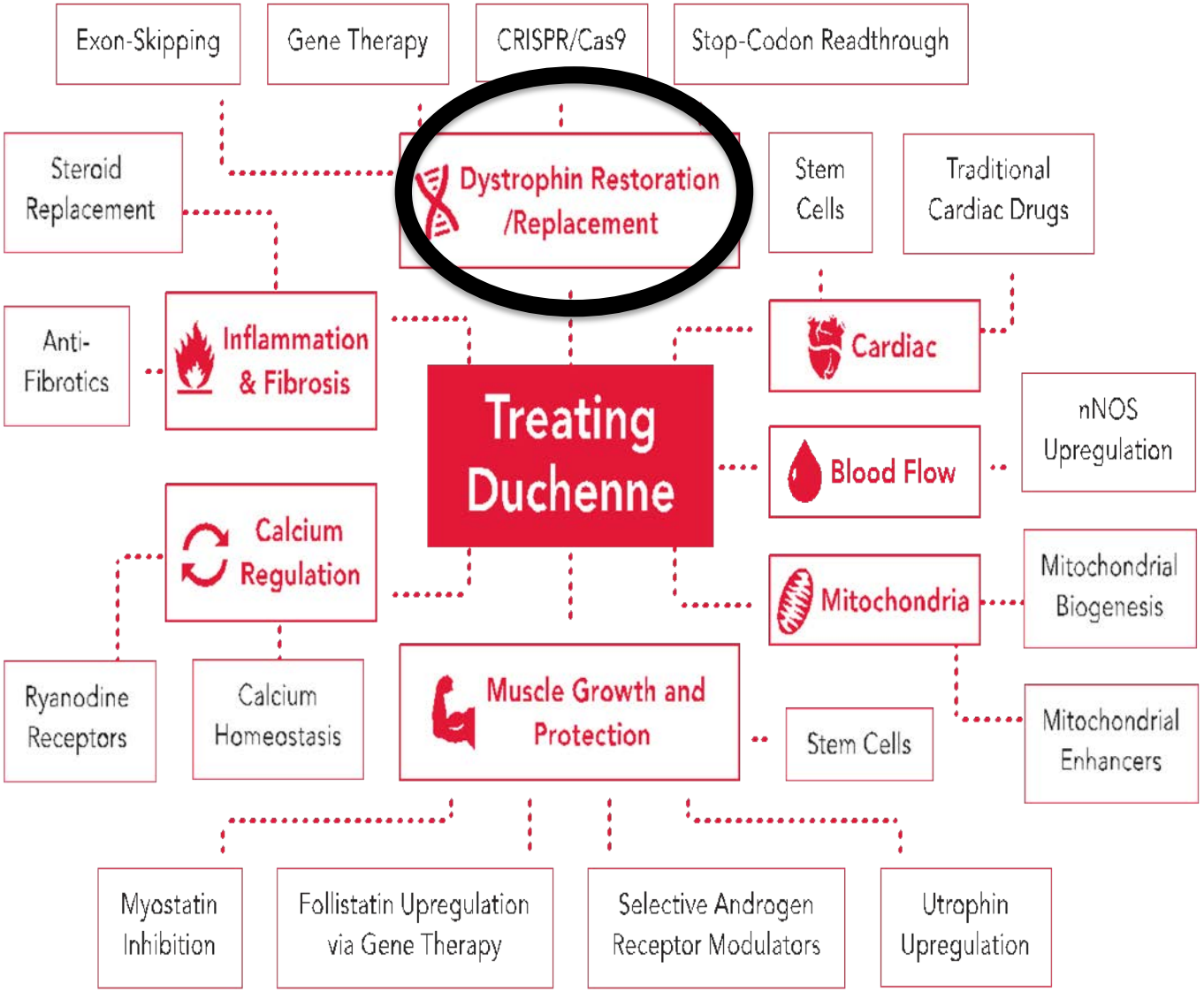


ASO (AON)

- Modified pieces of DNA/RNA
- Hybridize to target
  - preRNA
  - Sequence complement
- Exclude/include target exons
  - convert “out of frame” to “in frame” deletions
  - “DMD” to “BMD”

Dystrophin Restoration and Replacement

- **Exon Skipping (skip over the missing/defective part of the gene)**
  - **Exon 45 and 53**
  - **(Golodirsen, Casimersen)**
    - **Essence (Sarepta)**
    - **7-13yo, ambulatory, steroids >6mos**
  - **Exon 53**
    - **NS Pharma NS-065/NCNP-01**
    - **4-9yo, ambulatory, steroids >6mos**
- **WAVE Life Sciences**
  - **Exon 51 WVE-210201**
  - **5-18 years, recruiting**

SAREPTA THERAPEUTICS

NS Pharma

WAVE™ LIFE SCIENCES

Dystrophin Restoration and Replacement

- **Stop Codon (nonsense) Read through**
  - **Translarna (PTC)**
    - **EMA: Approval**
    - **Phase 3 extension study now**
      - **>5, ambulatory, steroids >12 mos**

PTC THERAPEUTICS™
Translating Science • Transforming Lives

Sarepta ASO/PMO/PPMO

- Eteplirsen
  - EXONDYS 51
- SRP 4045
- SRP 4053
- New drug with better cardiac distribution
- PPMO 2019
  - SRP 5053
  - SRP 5051

Toxicity of ASO

- **Acute toxicities in vivo:**
  - **Activation of the complement cascade**
  - **Inhibition of the clotting cascade**
- **Sub-chronic toxicity**
  - **Immune stimulation (splenomegaly, lymphoid hyperplasia and diffused multi-organ mixed mononuclear cell infiltrate)**
- **Mild and self-limiting toxicities at high plasma ASO concentrations**
  - **Thrombocytopenia**
  - **Increased LFT's**
  - **Hyperglycemia**

CHALLENGES

- Toxicity
- Administration
  - Route, frequency
- Distribution
  - Skeletal muscle
  - Cardiac muscle
  - CNS/BBB
- Expression
  - Amount
  - Duration

Gene Therapies

- AAV virus to deliver microdystrophins with the “business ends” of the dystrophin
- Studies will determine the most efficient microdystrophin
- Effect is thought to last ~10 years
- Single dose
  - Working to avoid the formation of antibodies to the virus
  - Goal – re-dosing

Gene Therapies

- **SGT-001**
  - **Solid GT**
  - **Micro-dystrophin**
  - **4-17 years**
  - **Recruiting**
- **PF-06939926**
  - **Pfizer**
  - **Mini-dystrophin**
  - **5-12 years**
  - **recruiting**

Gene Therapy

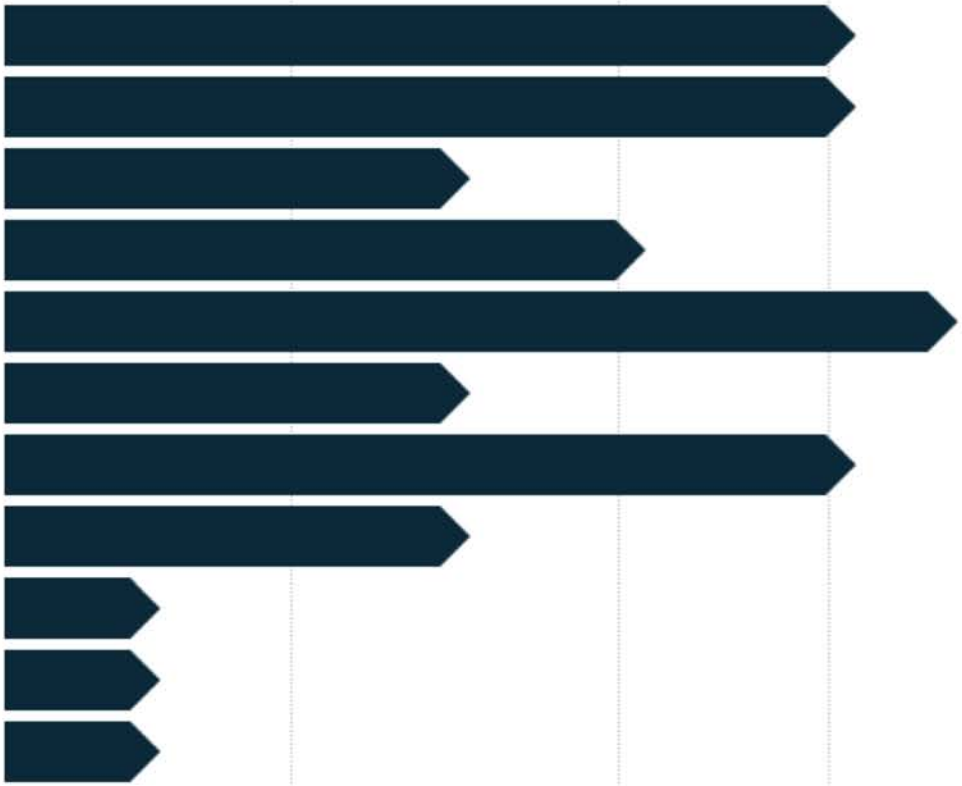
- **Microdystrophin**
  - **Nationwide Children's Hospital**
  - **Exons 18-58**
  - **Muscle specific**
    - **Doesn't cross blood brain barrier**
  - **Ages**
    - **6 patients, 4 -7 years**
  - **4 patients have been dosed**

Gene Therapy

- **GALGT2 - rAAVrh74.MCK.GALGT2**
  - **4 years and older**
  - **recruiting**

- **Exon 2 Duplication Strategy**
  - **Preclinical**
  - **Nationwide Children's Hospital**
  - **Only study looking at duplications**
  - **Specific *only* to duplications in exon 2**
  - **Pre-clinical**

GENE THERAPY



GENE EDITING

SAREPTA THERAPEUTICS

Internal

External Collaborations

*Candidate received accelerated approval in the U.S., confirmatory studies required

**Other exon targets in development: 43, 44, 50, and 55

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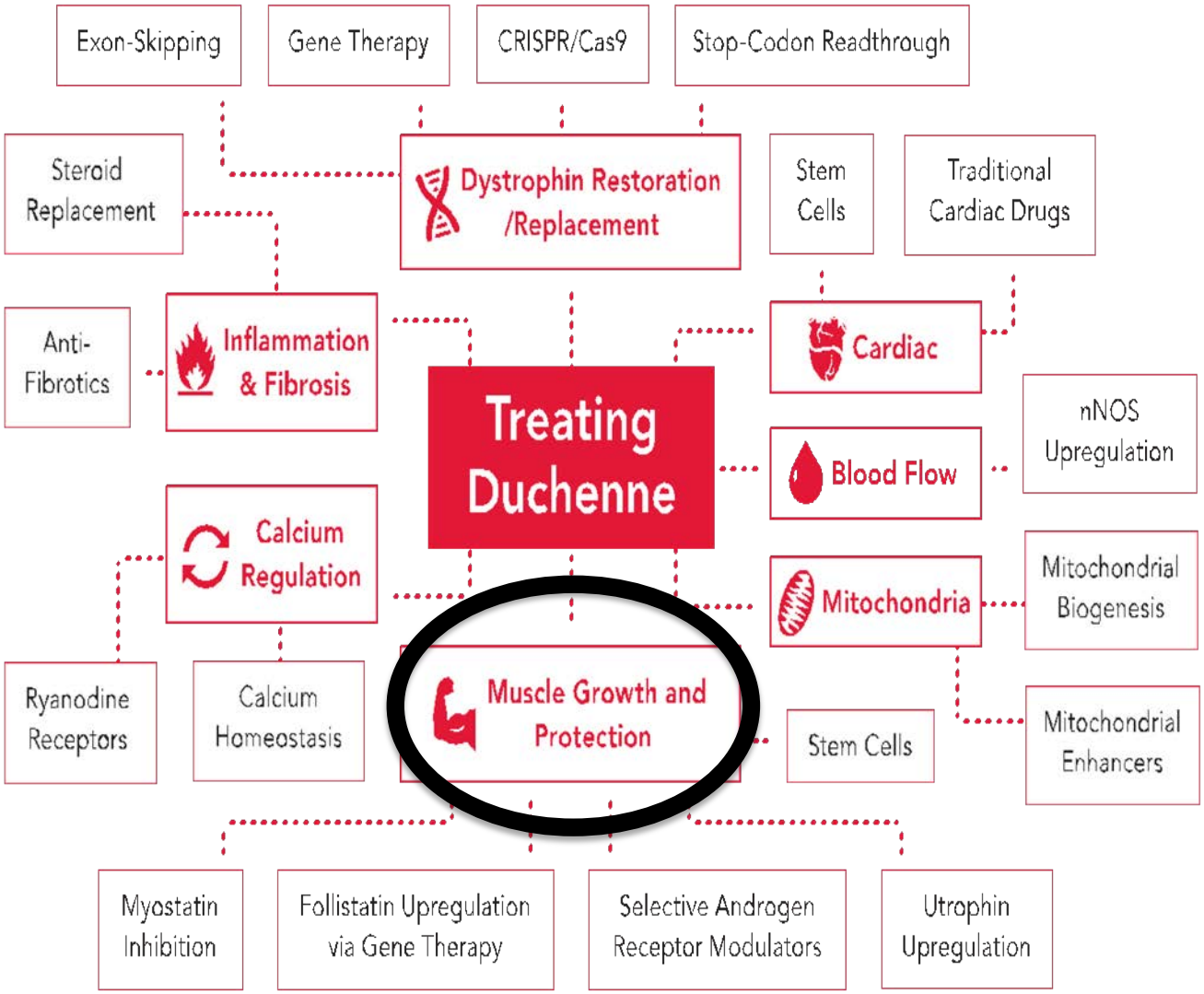


Muscle Growth and Regeneration

- **Biglycan (TVN-102)**
  - **Tivorsan Pharma**
  - **Pre-clinical**

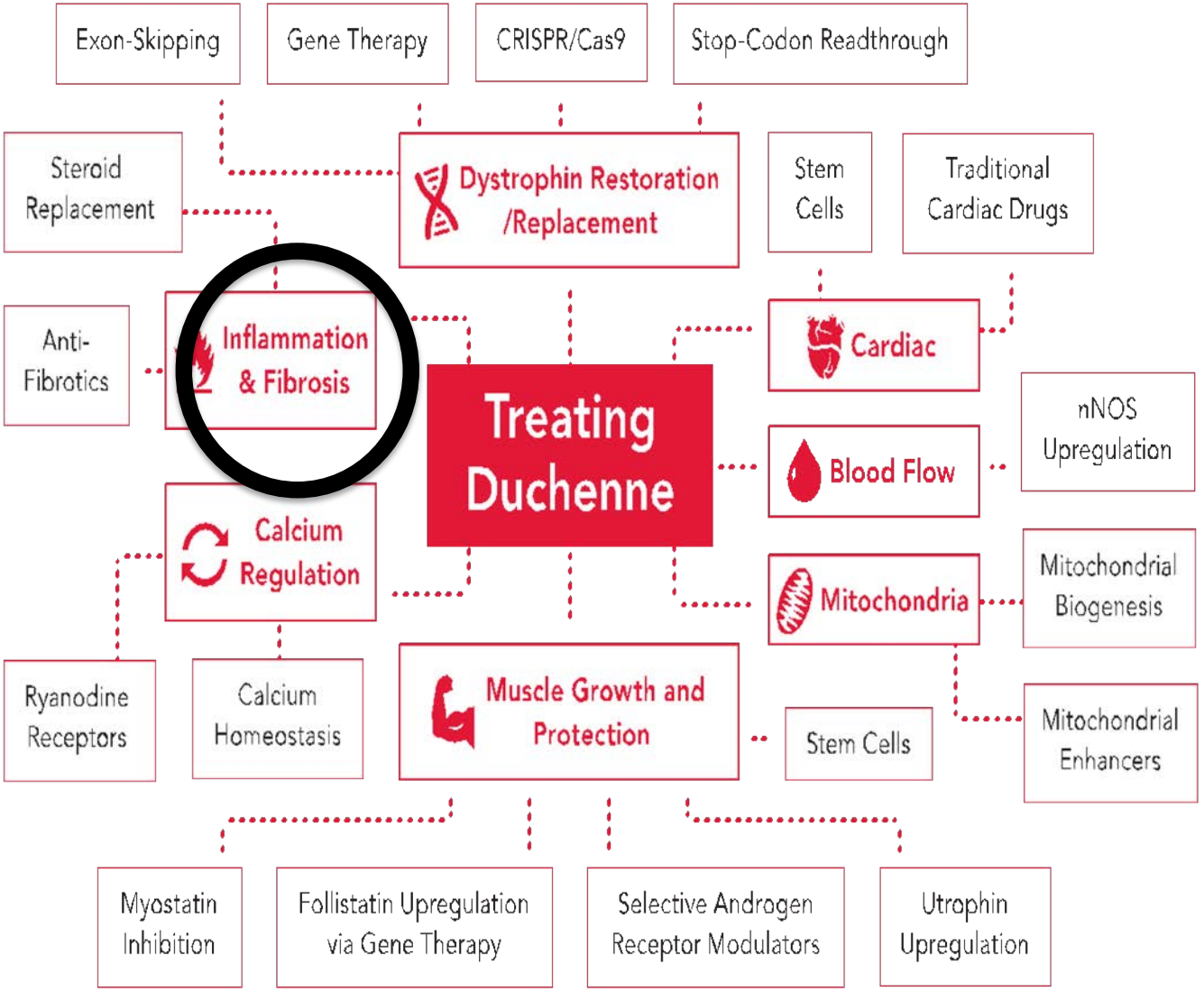
Muscle Growth and Regeneration

- **Myostatin Inhibition**

  - **Domagrozumab**
    - **Pfizer, Phase 2**
    - **STUDY TERMINATED**

  - **BMS 986089 (now Roche)**
    - **BMS/Roche, Phase 1**
    - **6-11yo, ambulatory, steroids >6mos**

Clinical Trials in Duchenne



Anti-inflammatory

- **Mallinckrodt**
  - **Pre-clinical**
  - **MK1411**
- **Pamrevlumab**
  - **FG-3019, Fibrogen, anti-fibrotic**
  - **Antibody to connective tissue growth factor**
  - **Phase 2**
  - **>12yo, non-ambulatory, steroids >6mos**

Mallinckrodt Pharmaceuticals

FIBROGEN

Anti-inflammatory

- **Givinostat**
  - **Italfarmaco, HDAC inhibitor**
  - **Phase 3**
  - **>6yo, ambulatory, steroids >6mos**

Anti-inflammatory

- **Edasalonexent**
  - **Catabasis, Phase 2a;**
  - **NFkB inhibitor, anti-fibrotic**
  - **4-7yo, ambulatory, steroid naïve**
- **Vamorolone**
  - **ReveraGen, Phase 2;**
  - **Steroid alternative**
  - **4-<6yo, ambulatory, steroid naive**

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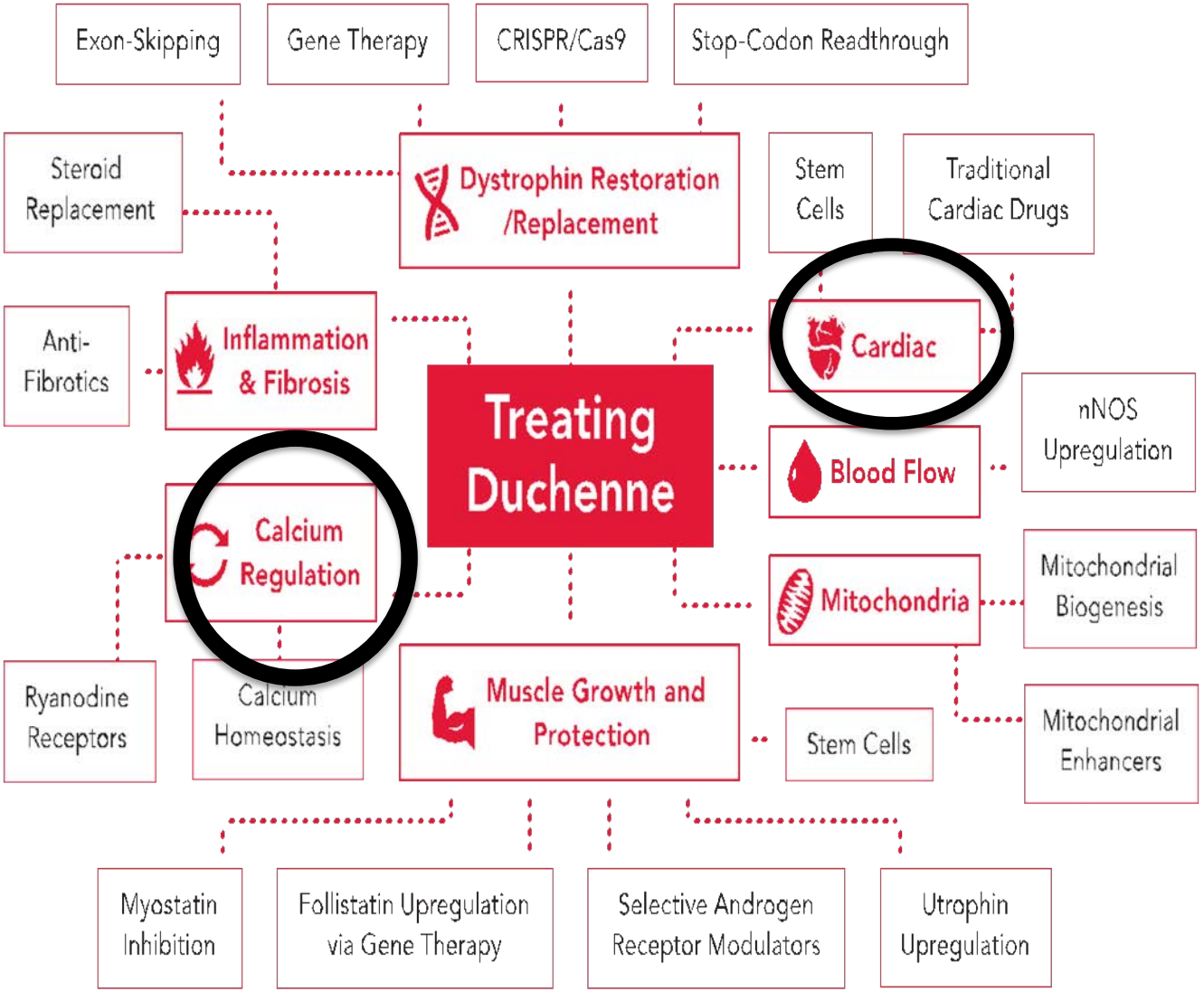
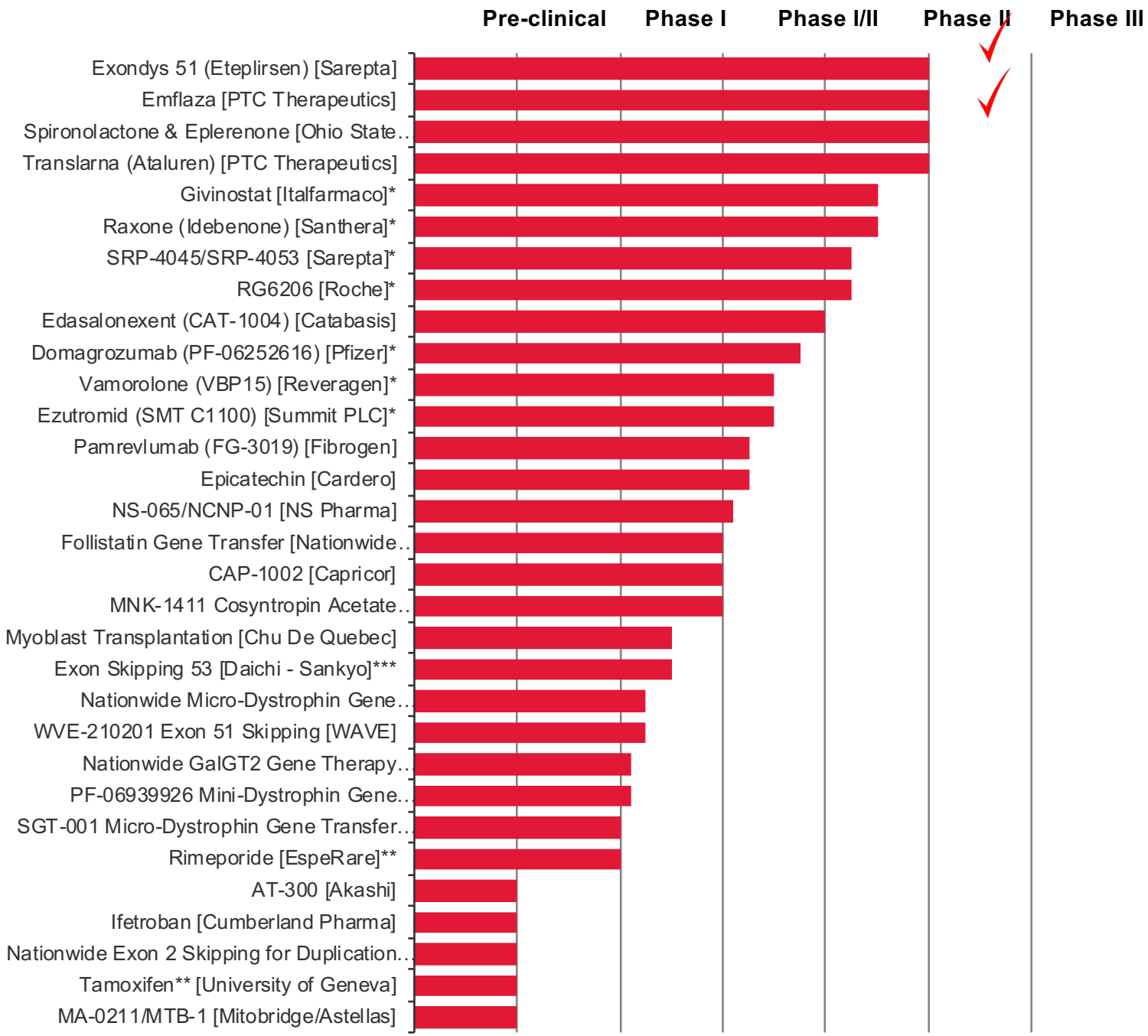


CELL BASED THERAPY

- **HOPE-2**
- **Capricor**
- **CAP-1002**
  - **Allogenic cardiosphere-derived cells (CDCs)**
  - **Release extracellular vesicles/exosomes/growth factors**
  - **Retained in lungs**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