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National Organization for Rare Disorders

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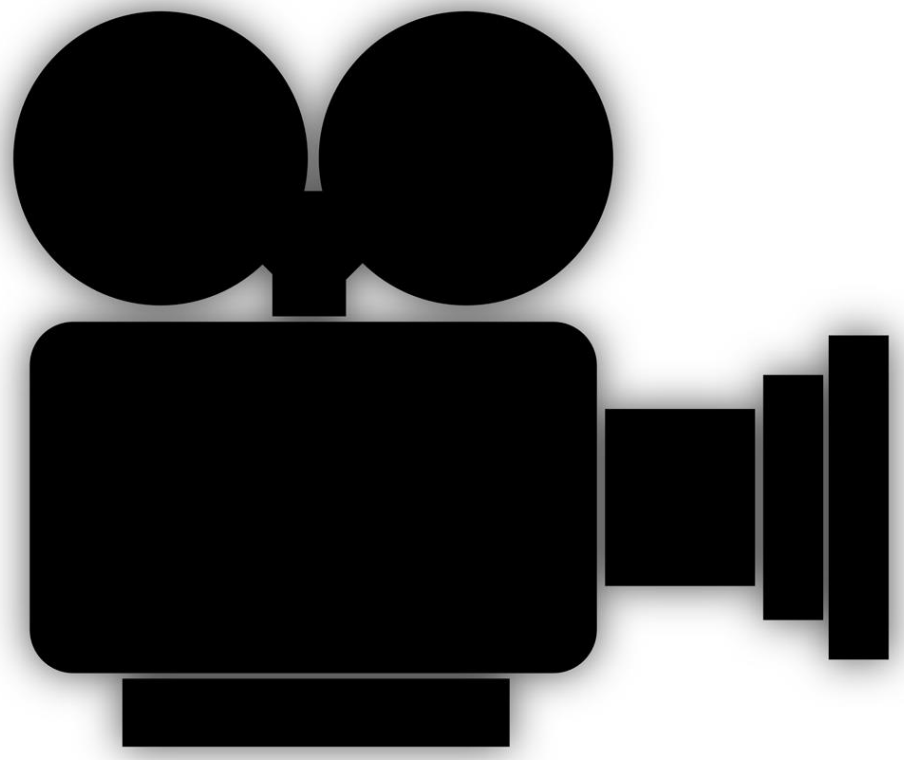
Gene Therapy: Yesterday, Today and Tomorrow

For sound, stream audio through your speakers.
If you are having trouble accessing sound, please send a message using the chat box in the lower left hand corner.

Alone we are rare. Together we are strong.®

This webinar is being recorded.



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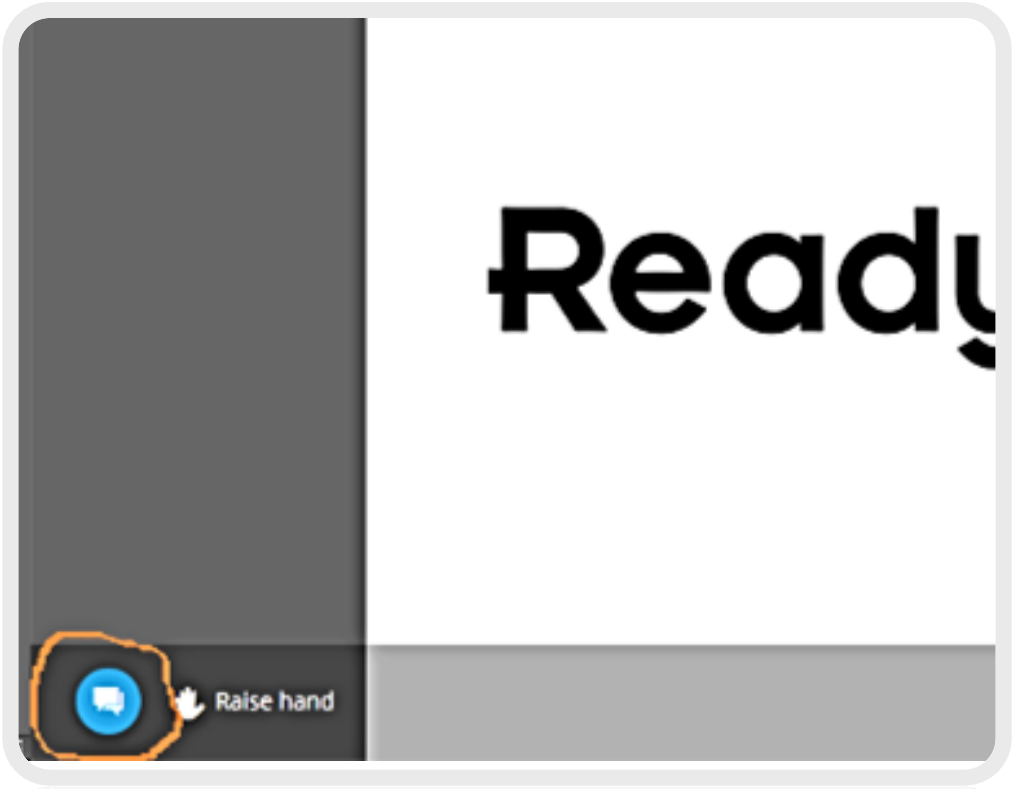
Question and Answer Session

Submit your questions using the chat function. It can be found at the **lower left hand corner** of the window.



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NORD, an independent nonprofit, is leading the fight to improve the lives of **rare disease patients and families.**

We do this by supporting patients and organizations, accelerating research, providing education, disseminating information and driving public policy.

What: Two days of learning, networking, innovation and more
When: October, 21-22 2019
Where: Washington, DC
Venue: Marriott Wardman Park, 2660 Woodley Rd. NW Washington, D.C. 20008

Register today:
https://bit.ly/2ZksRG8

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Gene Therapy Webinar Series

Today's webinar is the first webinar in an exciting five-part series on gene therapy from NORD in collaboration with the American Society for Gene and Cell Therapy (ASGCT.)

Mark your calendar for the rest of the series:

- **The Science Behind Gene Therapy -** Wednesday, September 25
    - 3:00-4:00pm EST
- **The FDA's Role in Gene Therapy -** Wednesday, October 30
- **Understanding the Gene Therapy Process and Aftercare -** Wednesday, November 20
- **Life After Gene Therapy -** Wednesday, December 18

Dates subject to change

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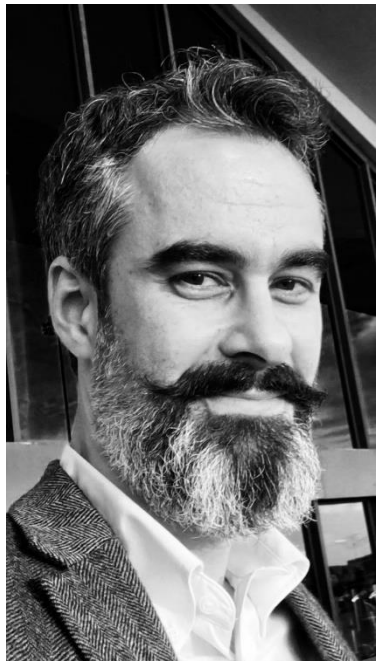
Speakers

Phillip Tai, Ph.D.
Instructor, Horae Gene Therapy Center
UMass Medical School



Cenk Sumen, Ph.D.
Chief Technology Officer, Stemson Therapeutics
Adjunct Professor, NYU Tandon School of Engineering

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Gene Therapy: Yesterday, Today, Tomorrow

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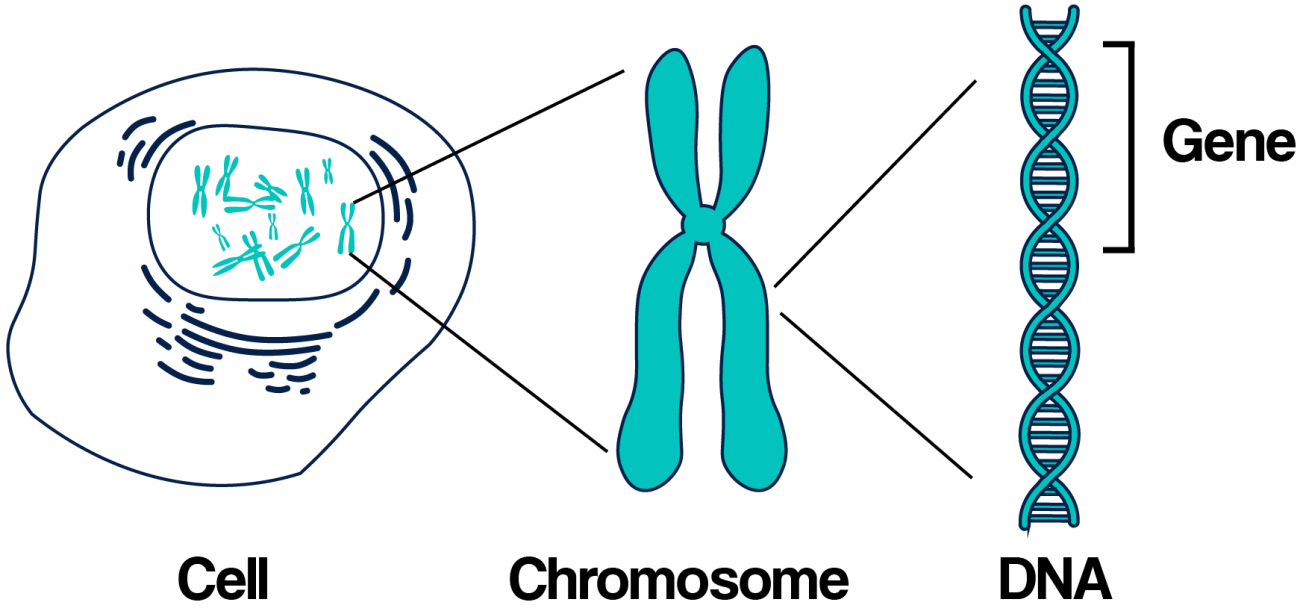
Starting with the Basics

Each **cell** in our body contains inherited genetic material. This genetic material is called **DNA** and contains important instructions for how our bodies work.



https://kintalk.org/genetics-101/

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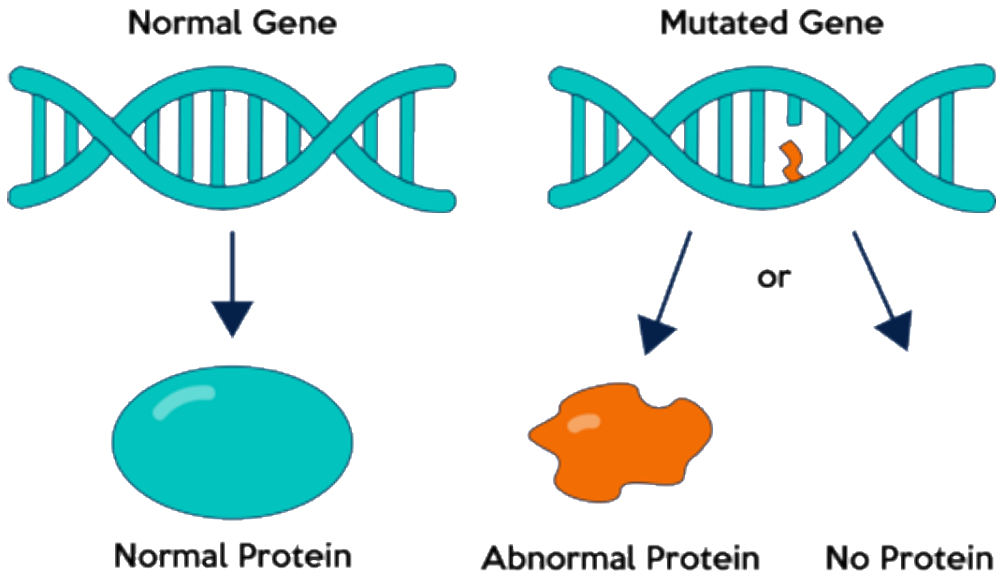
Starting with the Basics

Genes are made up of DNA, which are the blueprints to build the enzymes or proteins that perform various crucial bodily functions.

- **Gene mutations**
  - Occur as cells age, exposed to certain chemicals, or are inherited.
  - *Small* changes to DNA within and surrounding genes can have large impacts on cellular function and such as breathing, walking, and digesting food.



https://kintalk.org/genetics-101/

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What is gene therapy?

It is the introduction, removal, or change of genetic material within patient cells. This transfer of genetic material into the cells of a patient repairs a gene or compensates for the loss of a gene to treat a specific disease.

Gene therapy mechanism of action

Once inside the cell, the agent will correct the faulty gene by:

- Reducing levels of *disease-causing* proteins
- Increasing production of *disease-fighting* proteins
- Producing *new or modified* proteins

Jan. 11, 1999

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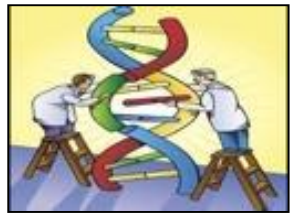
How does gene therapy work?



- Gene replacement
  - ✓ Replaces non-working mutant gene (***loss-of-function genetic disease***) with a healthy one.

- Gene silencing
  - ✓ Inactivates a mutated gene that becomes toxic to cells (***gain-of-function genetic disease***).

- Gene addition
  - ✓ Overexpression of an “foreign” gene to impact disease state.

- Gene editing
  - ✓ Permanent manipulation of a gene in a patient’s genome.

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Delivery mechanism

https://www.asgct.org

- Typically, genetic material is transferred into the target cell using a “vector”, which is a carrier of the gene.
- The most promising vectors are derived from viruses because they have evolved to enter cells very efficiently.
- All viral genes are removed and replaced by our engineered genes.

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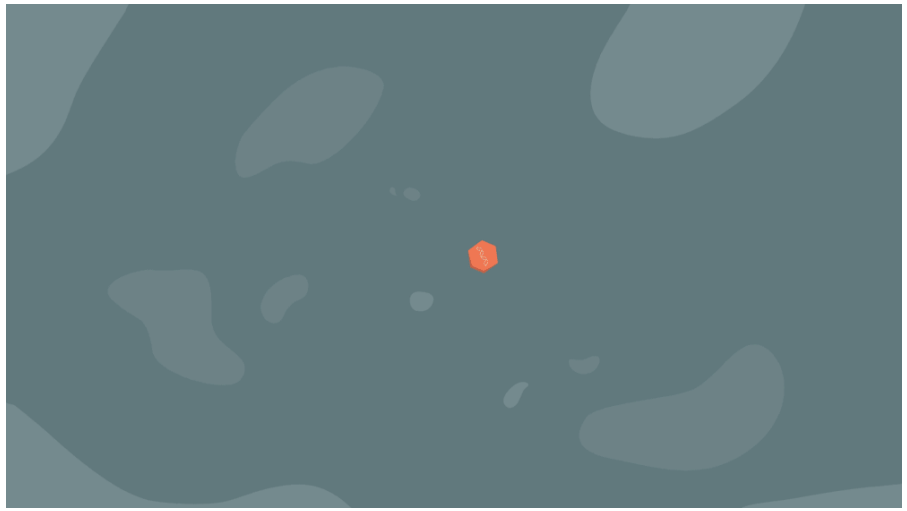
Delivery mechanism



https://www.asgct.org

Once inside the cell, the gene will make functional protein or target the disease-causing faulty gene.

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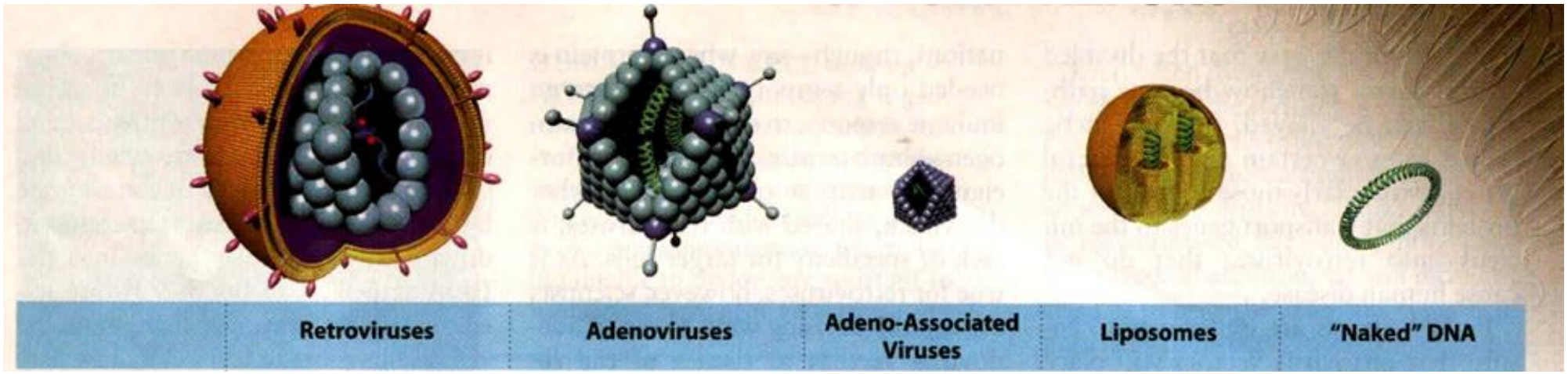
Gene Delivery Vehicles

Viral Vectors

Non-viral Vectors



RNA viruses

DNA viruses

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History of Gene Therapy

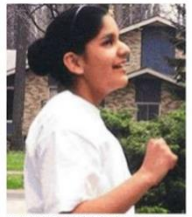
- In 1970, the first gene therapy trial in humans was administered. involved two sisters who had a rare genetic disease called hyperargininemia. Trial to test whether the Shope papilloma virus could limit arginine levels, but failed. It was discovered that the Shope papilloma genome does not encode for arginase production.

- In 1980, a gene therapy trial on two patients with beta-thalassemia. Martin Cline tried to insert the gene needed for normal production of hemoglobin into extracted bone marrow cells of the patients' and infused the cells back into the patients. However, the experiment failed to produce positive results.

- In December 1988, the National Institute of Health's Recombinant DNA Advisory Committee (RAC) approved a clinical trial to introduce a foreign gene into humans. This study resulted in no growth of tumors at the injection site, and this indicated that gene transfer with engineered viruses can be used safely.

History of clinical viral vector gene therapies

Jesse Gelsinger
(Sept 17,1999)



In 1990 Ashanti de Silva became the first patient to receive gene therapy for ADA deficiency. Shown here at age 13, she continues to lead a healthy, active life.
Photo: Courtesy of Van de Silva

Gene Therapy
-The path to today & beyond……

LUXTURNA (1st In vivo Gene Tx approved by FDA 10/22/2017)
1st ex vivo Gene Tx approved by FDA (8/30/2017)
Glybera approved by EMA (2012)
AAV8 to treat hemophilia B (2011)
AAV2 gene transfer to treat LCA (2008)
Discovery of AAV8 (2002)
Gene therapy for chronic pain (2009)

1990 1995 2000 2005 2010 2015 2020

First human gene therapy for ADA via retrovirus (Sept 14,1990)
First AAV for CFTR (November 1995)
First adenovirus for cystic fibrosis (1993)
Oncolytic Herpes simplex virus for Viral therapy of cancer(2000)
HVTN502 by Merck (2004)
Gendicin by Sibiono Gene Tech, China (2004)
Two cases of leukemia in patients receiving retroviral X-linked SCID
First lentivirus against HIV (2003)
Oncorine by Sunway Biotech, China (2006)
CAR-T-cell therapy (2011)
Clinical trial for X-linked ALD (2014)

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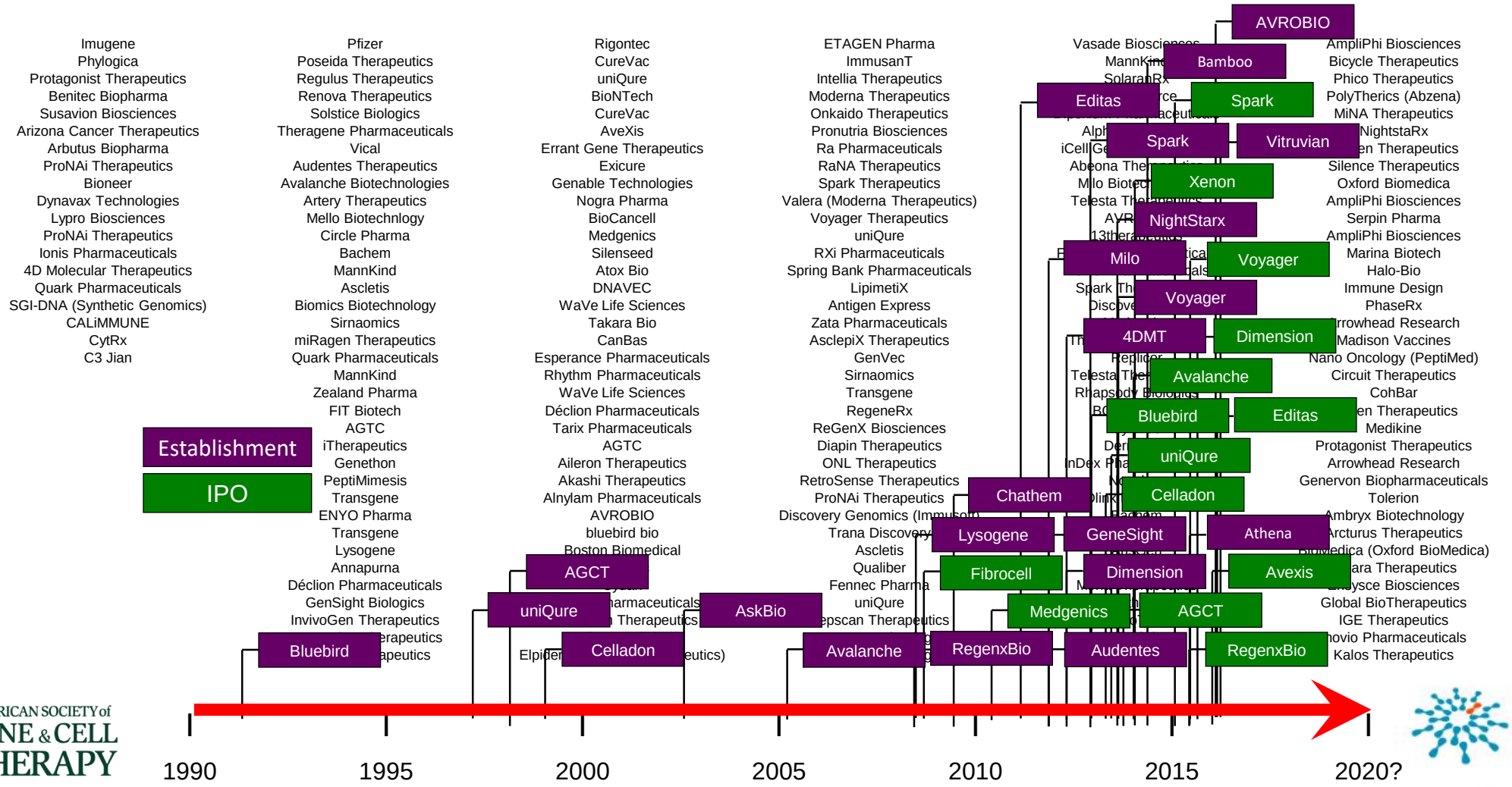
Trends in Gene Therapy



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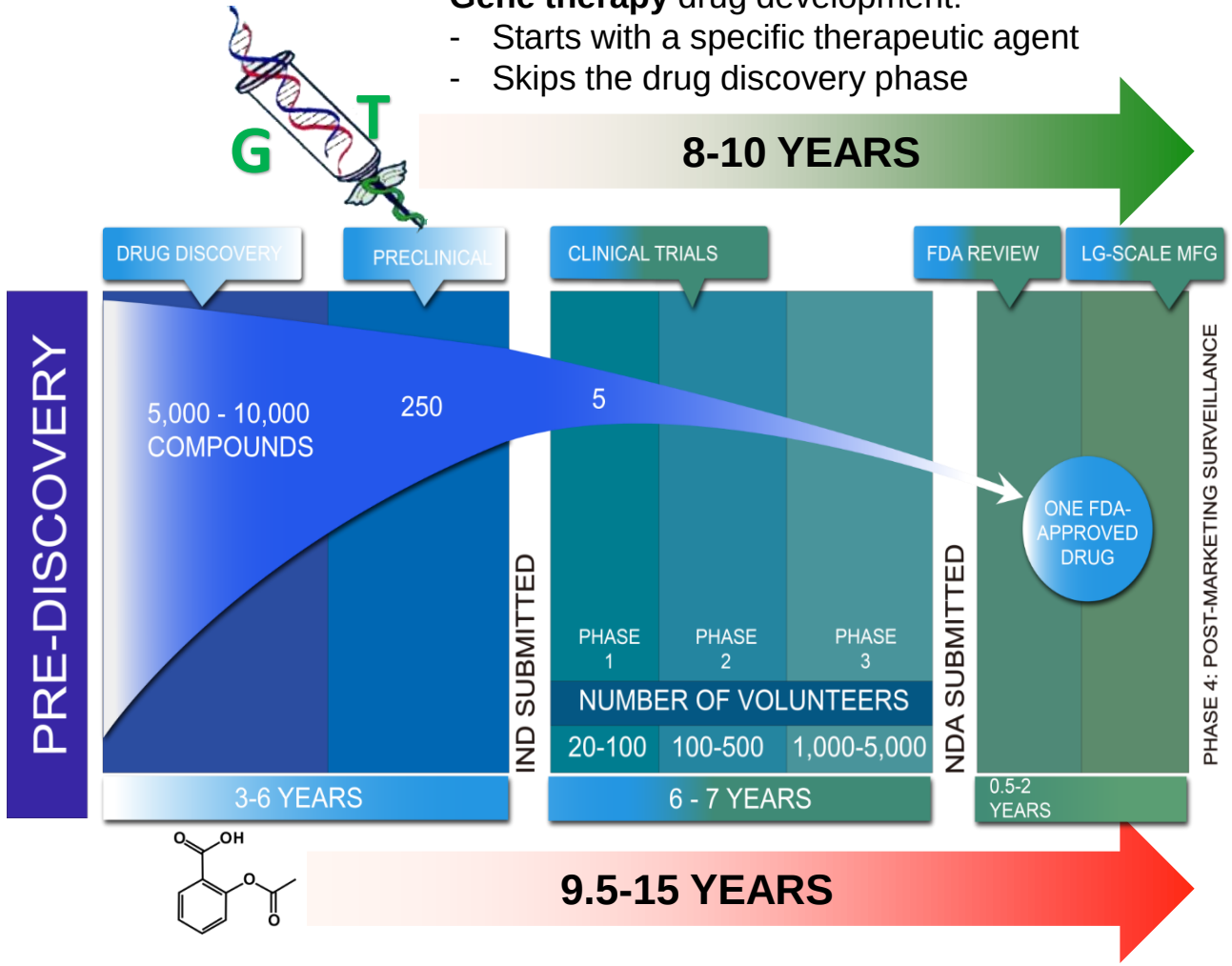
The promise of gene therapy

Gene therapy drug development:
- Starts with a specific therapeutic agent
- Skips the drug discovery phase



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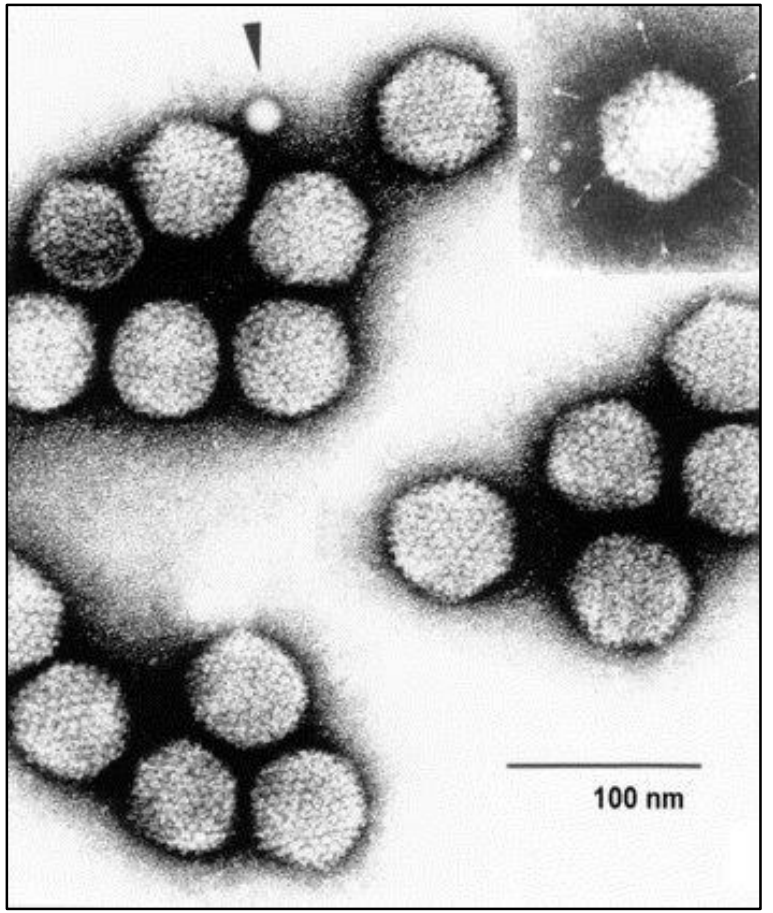
Adeno-Associated Virus (AAV)

- AAV is believed by many to be the future of gene therapy, especially following the Zolgensma approval.
- First discovered in 1960s by Bob Atchison as a contaminant in adenovirus preparations.



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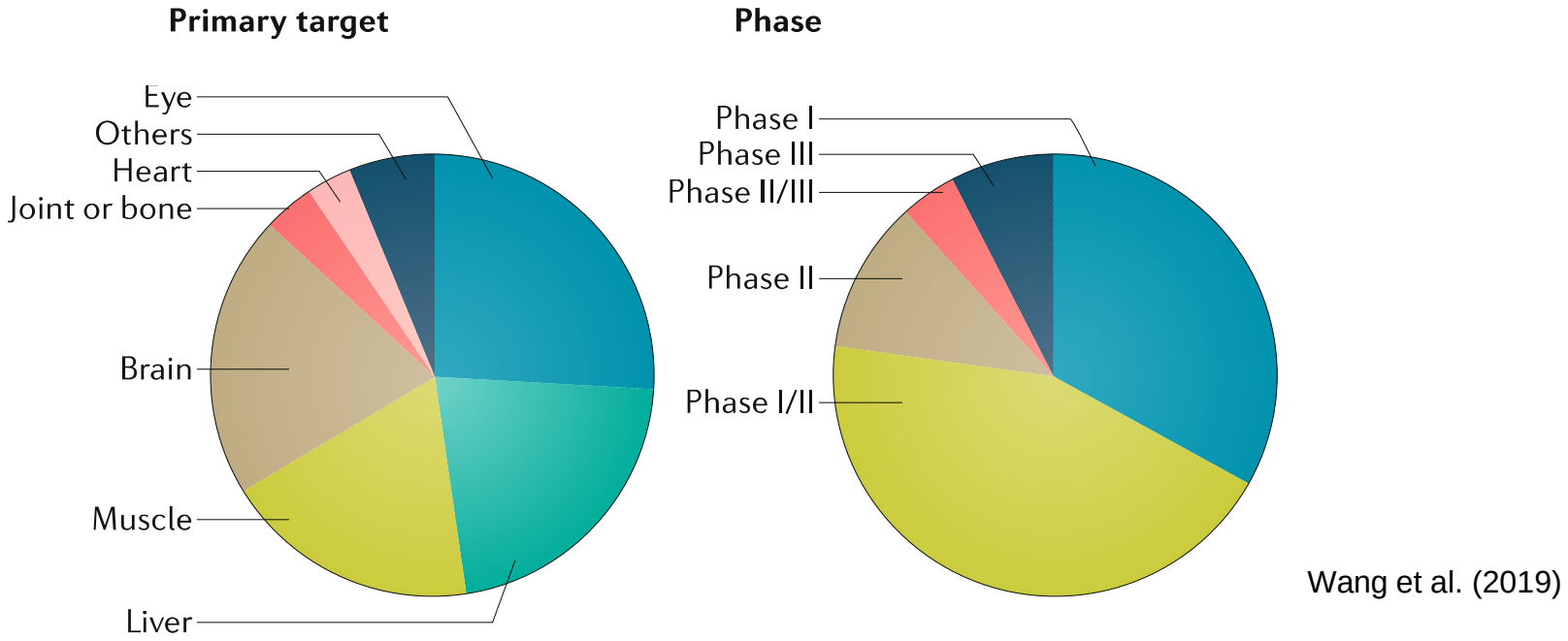
AAV Gene Therapies in Development



Wang et al. (2019)

- There are over 400 active and recruiting clinical trials for gene and cell therapy in the US
- Information can be found at: https://app.emergingmed.com/asgct/home//

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Why has it been difficult to develop gene therapies?

- Limited patient populations for rare disease trials
- Length of clinical trial process
  - Preclinical and clinical trials to determine safety an efficacy take a long time
- Uncertain of durability at this time
- Halts, but does not typically reverse, damage

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Unique Benefits of Gene Therapy

- Unmet need: treating rare, debilitating diseases that have few to no treatment options
- Approved therapies to date have high efficacy
- Aims for single administration
- Targets the cause of disease
- Can reduce or eliminate need for other costly treatments (e.g., hemophilia and sickle cell disease)
- Potential positive effect on indirect and intangible costs (e.g., ability to work)

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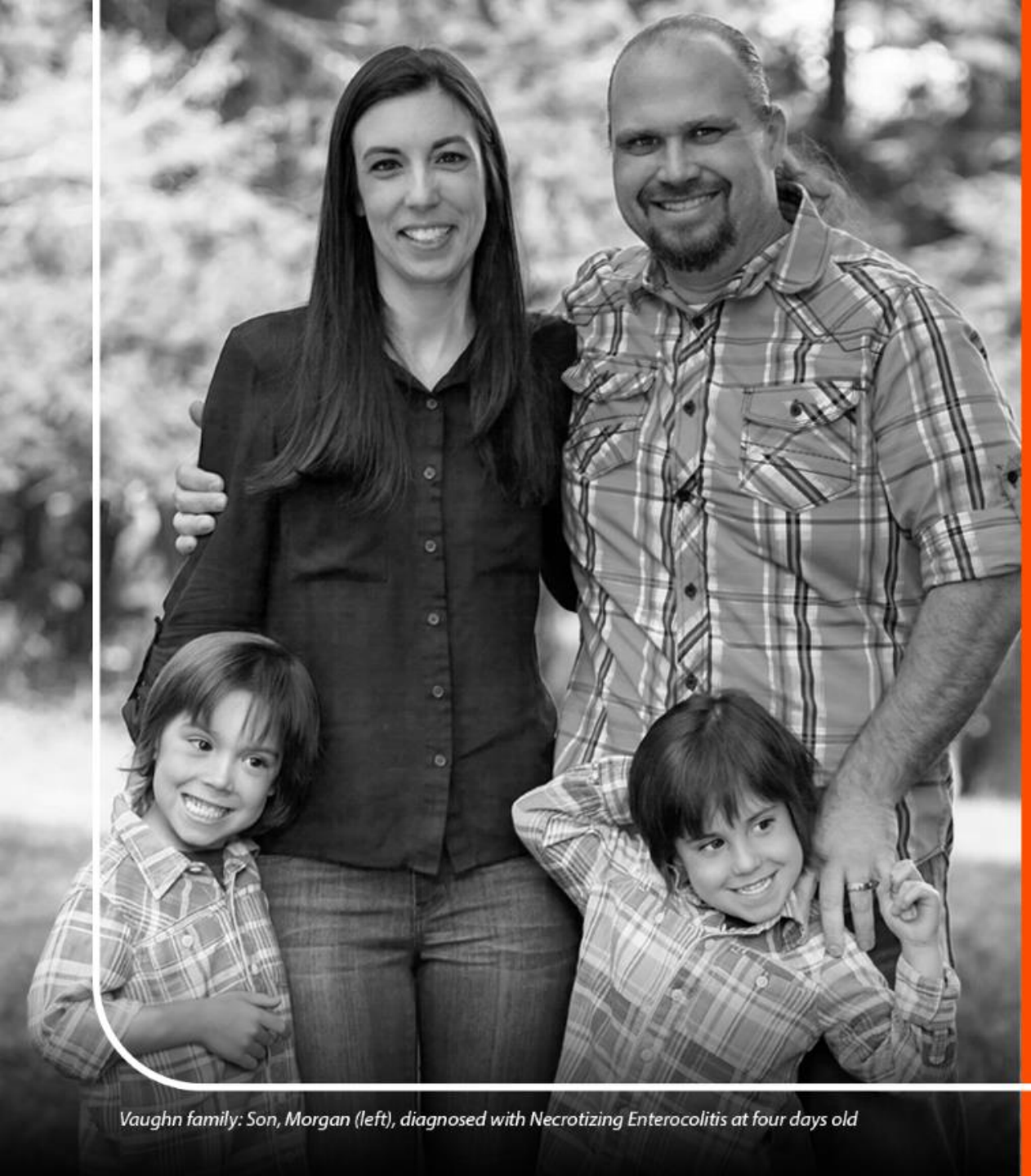

Vaughn family: Son, Morgan (left), diagnosed with Necrotizing Enterocolitis at four days old

Gene therapy - state of the industry and future trends

Cenk Sumen, Ph.D.

Chief Technology Officer, Stemson Therapeutics

Adjunct Professor, NYU Tandon School of Engineering

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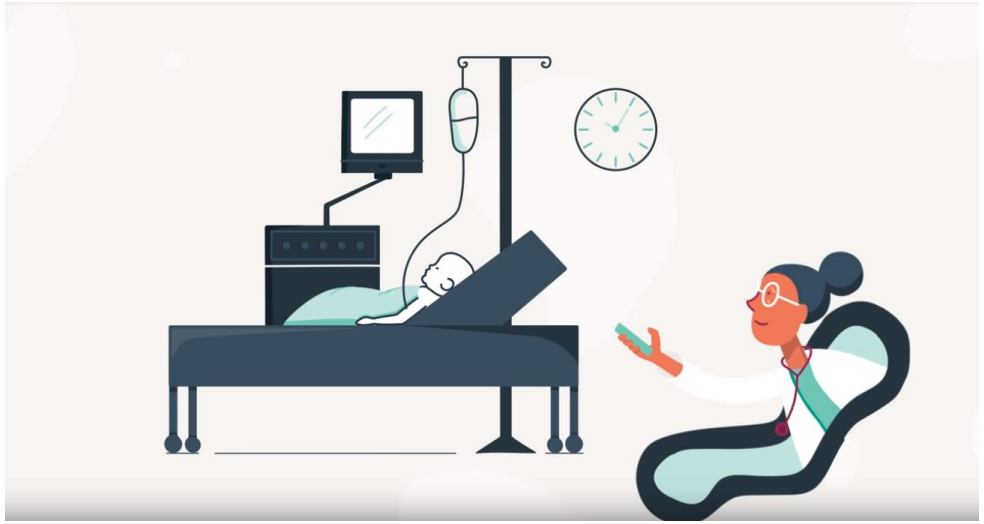
Why is gene therapy so valuable?

- Efficacy
- One-time intervention
- Can potentially prevent a lifetime of expensive and/or painful treatments



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Approved Gene Therapies

Listed below are some of the major gene therapy approvals in the US and EU:

- 2016 EMA approval of Strimvelis for ADA-SCID
- 2017 FDA approval of Kymriah for certain B-cell acute lymphoblastic leukemia
- 2017 FDA approval of Yescarta for certain B-cell lymphoma
- 2017 FDA approval of Luxturna for certain Leber Congenital Amaurosis
- 2019 FDA approval of Zolgensma for Spinal Muscular Atropy
- 2019 EMA approval of Zynteglo for beta thalassemia

Strimvelis

KYMRIAH® (tisagenlecleucel) Suspension for IV infusion

YESCARTA™ (axicabtagene ciloleucel) Suspension for IV infusion

LUXTURNA™ voretigene neparvovec-rzyl for subretinal injection

zolgensma® (onasemnogene abeparvovec-xioi)

bluebirdbio®

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Most Recent FDA Approval

- Approval of Zolgensma (AveXis/Novartis treatment) for very rare SMA Type 1 based on systemic AAV9 delivery of a working SMN1 gene to motor neurons
- Why treat children under 2 years of age? Damage accumulates and currently cannot be reversed
- This approval demonstrates a lot of promise with the AAV vector

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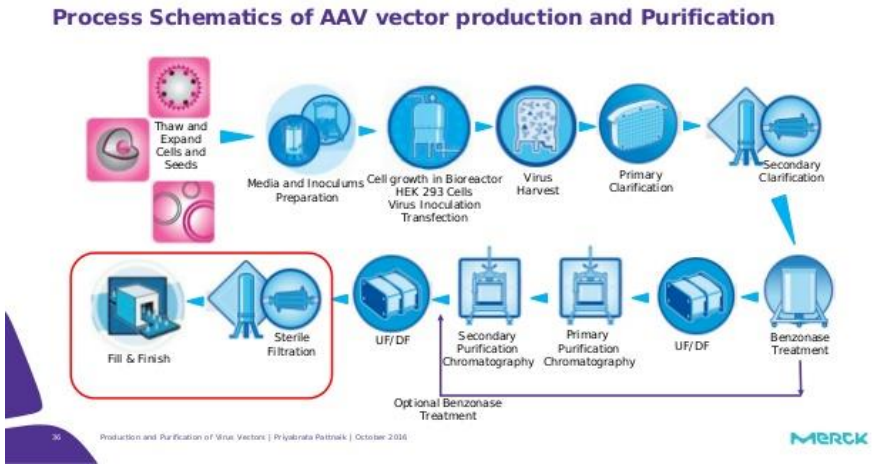
Current Challenges for Gene Therapy Manufacturing

- Manufacturing is complex and time intensive
- Potential capacity constraints
  - Some therapies require a high dose that is difficult to mass produce.
    - For example: the dosage for Zolgensma is 10^14 viral genomes per kg
    - This is more viral particles than cells in your body



A technician servicing a bioreactor.

Image source: Getty Images.

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Patients Come First

- Creating a system to support families and build the necessary infrastructure to be able to provide access and care before and after therapy
- Patients should contact their health insurance provider to determine coverage and out of pocket costs. Manufacturers of gene therapies often offer patient support services to assist in navigating the process.

Patient support programs should:

- Provide dedicated, individualized support to patient families and caregivers
- Support reimbursement and financial coordination among stakeholders

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Future Direction of Gene Therapy

- Ensuring access for patients globally
- Collaboration between stakeholders to make therapies affordable and accessible to patients
- Capacity scale-up for AAV manufacturing
- Gene therapy factories of the future
- Automation, AI, logistics, single use systems
- Streamlined regulatory landscape
- Other vectors and technologies for gene therapy
- Determining how many of the >5,000 genetically-based rare diseases can we treat with gene therapy

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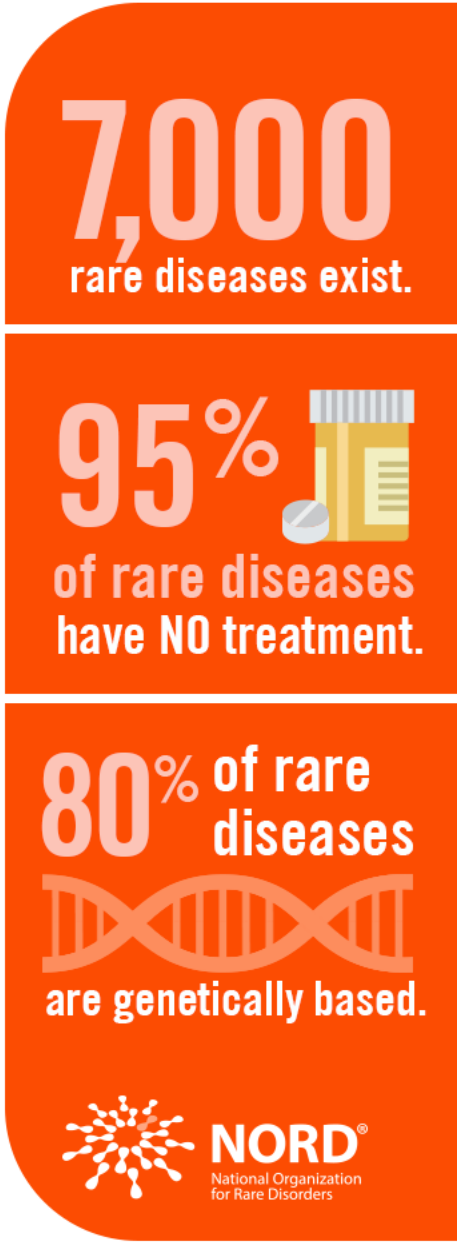

Resources for Patients and Caregivers

Clinical Trials

Clinicaltrials.gov

National Institutes of Health

https://ghr.nlm.nih.gov/primer/therapy/genetherapy

Food and Drug Administration

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products

ASGCT

https://www.asgct.org/education/gene-therapy-basics

NORD

https://rarediseases.org/video-topic/research-science/#watch-39678

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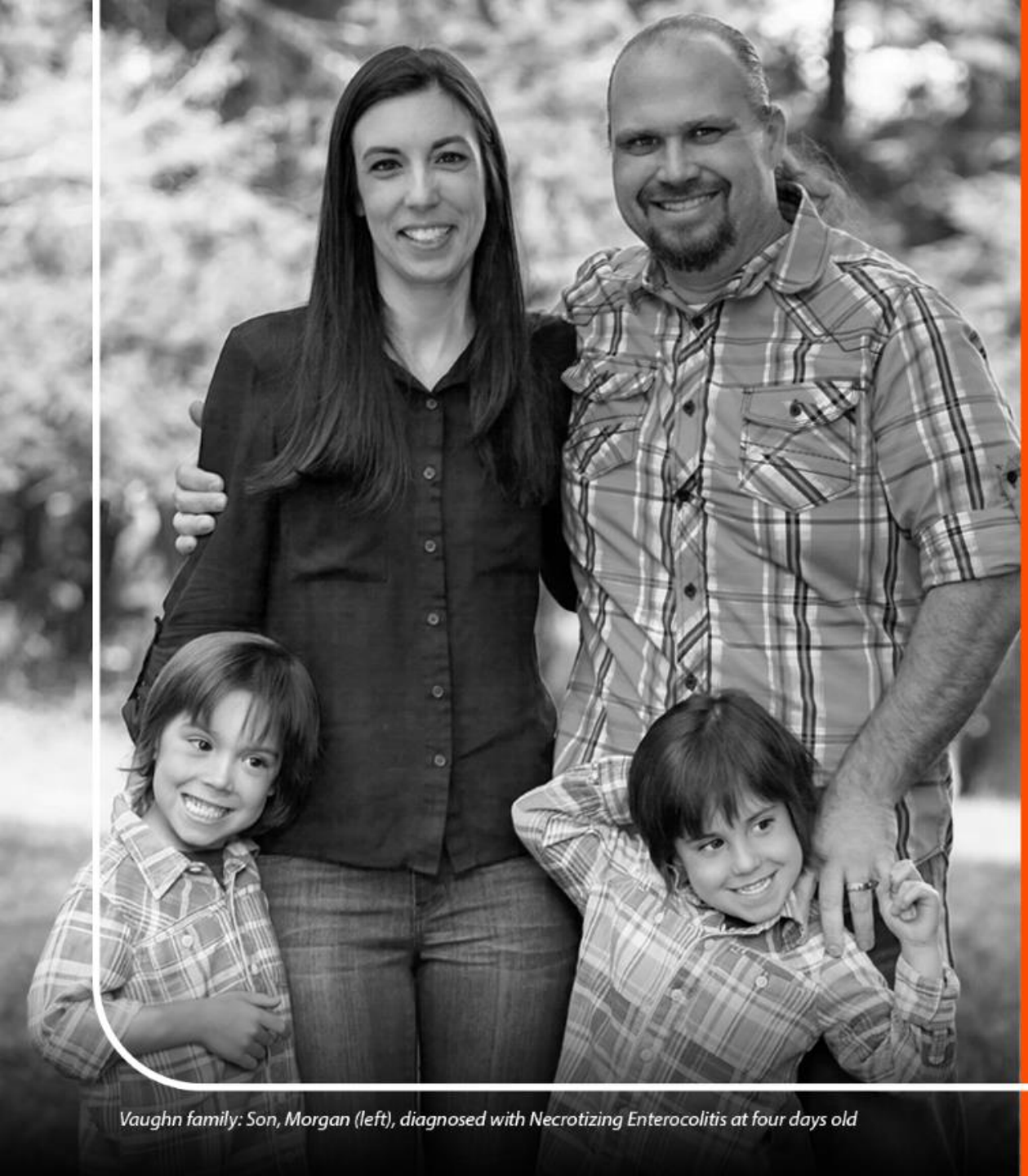

Vaughn family: Son, Morgan (left), diagnosed with Necrotizing Enterocolitis at four days old

Question and Answer Session

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Dr. Sumen and Dr. Tai will answer them in the order in which they came in and based on relevance to the discussion.

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