Life Science Caucus Meeting
June 28, 2022
7:30am

Co-chairs:
Senators Newton and Woodard
Representatives White and Reives

Meeting will begin shortly

Agenda

- Welcoming Remarks by Chairs
  - Senators Paul Newton and Mike Woodard
  - Representatives Donna White and Robert Reives
- Rare Disease Advisory Council remarks
  - Representative Becky Carney
- Transforming the Clinical Outcomes on Individuals with Rare Diseases: The Gene Therapy Journey
  - Dr. Priya Kishnani - Duke Undiagnosed Network
- The Path of Hope Begins with a Diagnosis
  - Dr. Vandana Shashi – Duke Undiagnosed Network
- An Overview of Cell and Gene Therapy Payment Policy
  - Dr. Marianne Hamilton Lopez –Duke Margolis
- The Patient Perspective
  - Nickey Hosey, SMA parent and patient advocate
  - Charlene Cowell, executive director, Hemophilia of North Carolina
- Q & A

Priya Kishnani, MD

Dr. Kishnani is Chief, Division of Medical Genetics, at Duke University Medical Center and the Medical Director of the YT and Alice Chen Pediatrics Genetics and Genomics Center which has a focus on developing new therapies for rare genetic disorders. Throughout her career, Dr. Kishnani's primary focus has been the translation of laboratory science into the clinical arena, especially in the area of such therapeutic interventions as enzyme replacement therapy, gene therapy and small molecules. Dr. Kishnani has propelled a translational research program at Duke with a T1-T4 impact, implementing bench-to-bedside approach, from the bedside back to the bench for further advances toward the diagnosis, treatment and management of patients with rare genetic diseases. Her primary clinical and research focus is in patients with Glycogen Storage diseases Types (I, II, III IV, VI and IX), Lysosomal Storage diseases, Hypophosphatasia, other inborn errors of metabolism and Down syndrome.

Spanning her career Dr. Kishnani has shown commitment to understanding the long-term complications and the natural history and evaluation of therapies of several GSDs, with a specific focus on GSD I, II, III, IV, VI and IX. An example of her work is in GSD II (Pompe disease) where she was responsible for the clinical translation from the bench and served as the lead investigator for the pivotal trials which led to FDA approval of Myozyme™ (2006)/Lumizyme™ (2010) as the first treatments for Pompe disease. She has also played a role in newborn screening efforts for rare diseases and played a pivotal role in getting Pompe, MPSI and MPSII added to the recommended uniform screening panel.

Vandana Shashi, MBBS, MD

I am a clinical geneticist and pediatrician. I obtained my medical degree from the University of Mysore, India and post-graduate training in Pediatrics from Mangalore University in India. Subsequently, I completed my residency in Pediatrics from the Bowman Gray School of Medicine, NC in 1992 and a fellowship in Clinical Genetics at the University of Virginia, VA, in 1995. I am board certified in Clinical Genetics. After working as a clinical geneticist at Wake Forest University in NC for 12 years, I joined the faculty at Duke University in 2008 and am a Professor of Pediatrics within the Division of Medical Genetics.

I have taken care of adult and pediatric patients with undiagnosed and rare disorders for the past 25 years. When the diagnosis is not readily apparent, I have observed families invest inordinate amounts of effort, time and finances to obtain a diagnosis. The majority of such undiagnosed patients (~85%) are thought to have an unidentified genetic disorder. As the PI of the Duke clinical site for the Undiagnosed Diseases Network (UDN), funded by the NIH, I evaluate patients with undiagnosed diseases and apply genomic sequencing to obtain diagnoses. I also run the Duke sequencing clinic. In both settings, rare ultra-rare genetic disorders are diagnosed, with resulting changes in medical management, and treatment and immense psychological relief from obtaining a diagnosis. I have delineated the phenotype and genetics of many genetic syndromes identified through sequencing, such as a new neurodevelopmental disorder with severe epilepsy NACC1 [OMIM#617393] and Shashi-Pena syndrome, due to truncating variants in ASXL2 [OMIM#617190]. Overall, under my leadership the Duke UDN site has been responsible for 18 new gene discoveries that are associated with ultra-rare genetic disorders and for the highest rate of diagnoses in the network.

I have also in the course of my clinical and research experience, observed that patients who lived in rural and medically underserved areas (MUA) tend not to participate in genomic medicine and thus experience disparities in outcomes. Not having a diagnosis results in patients/parents having difficulty in being effective advocates for themselves/their children and they suffer enormously- we found that ~40% of undiagnosed patients/parents meet criteria for depression/anxiety, most of which goes unnoticed, since they seldom express this unless asked. The Duke UDN site, under my leadership, was the first in the network to ascertain patients who had declined NGS (more likely to live in MUA and be non-White) to ask for their perspectives and we found that a number of practical as well as sociocultural factors underlie non-participation, such as low genomic knowledge. We are implementing telehealth to increase participation in medically underserved areas.

Marianne Hamilton Lopez, PhD

Marianne Hamilton Lopez, PhD, is the Senior Research Director of Biomedical Innovation and an adjunct associate professor and core faculty at the Duke-Margolis Center for Health Policy in Washington, DC. She leads the strategic design and direction of the Center's Biomedical Innovation portfolio, with a focus on medical products development and regulation, real world evidence, infectious disease preparedness, and payment, pricing, and coverage of drugs and medical devices. She also oversees the Value for Medical Products Consortium and partners with Duke University faculty, scholars, and external health experts to advance this work. Prior to joining Duke-Margolis, Dr. Hamilton Lopez was a senior program officer with the National Academy of Medicine's Leadership Consortium for a Value & Science-Driven Health System and led the Consortium's Science and Technology portfolio and Clinical Effectiveness Research Innovation and the Digital Learning Collaboratives. She was a Senior Manager at AcademyHealth; a Public Health Community Advisor for the United States Cochrane Center; and the Federal Women's Program Manager and American Indian/Alaska Native Employment Program Manager for the National Institutes of Health.

Rare Disease Innovations Institute

Transforming the clinical outcomes of individuals with Rare diseases: The Gene Therapy Journey

Cell & Gene Legislative Breakfast
June 28, 2022

Priya S. Kishnani, MD
Professor of Pediatrics
Division Chief, Medical Genetics
Duke University Medical Center

Disclosures

- PSK has received research/grant support from Sanofi Genzyme and Amicus Therapeutics.

- PSKhas received consulting fees and honoraria from Sanofi Genzyme, Amicus Therapeutics, Maze Moderna, Ultragenyx and Asklepios Biopharmaceutical, Inc. (AskBio).

- PSK is a member of the Pompe and Gaucher Disease Registry Advisory Board for Sanofi Genzyme, Amicus Therapeutics, and Baebies.
- PSK has Equity options and serves as a Consultant for Kriya Therapeutics

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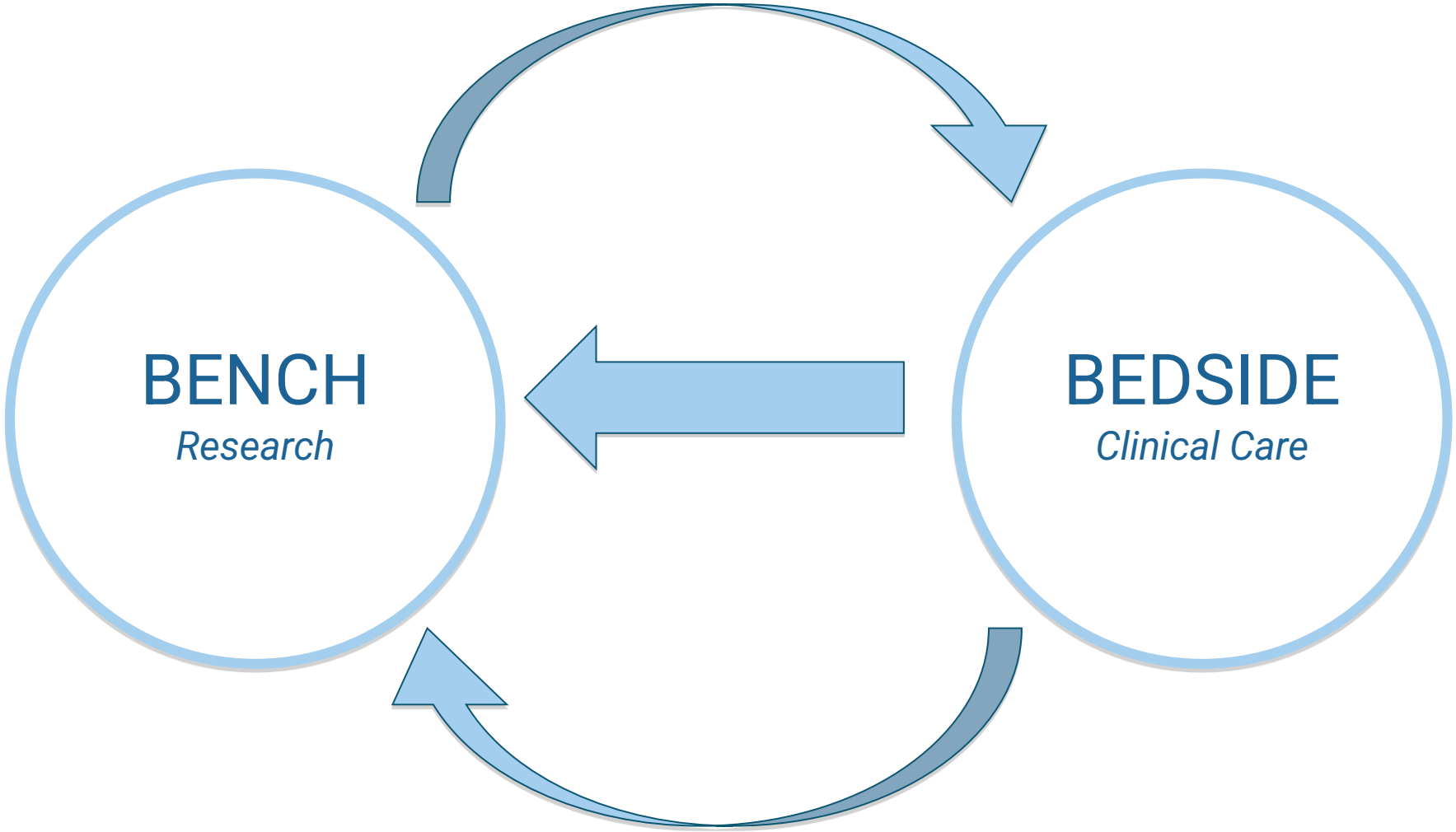
Integration of patient care and research
Multidirectional flow



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RARE DISEASES ARE NOT RARE

RARE DISEASE

Any disease affecting fewer than 5 in 10,000 people in Europe or fewer 200,000 people in the United States

About **7,000** rare diseases are known

think RARE DISEASES research

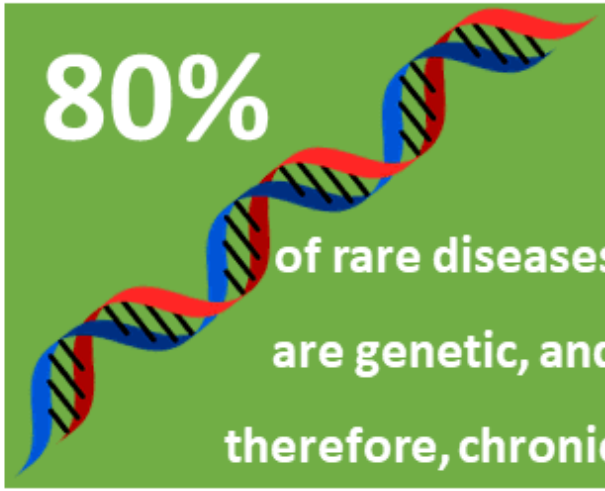
Around 1.4% of newborn children are affected by one of these diseases.

Many rare diseases result in premature deaths of infants and young children.

RARE DISEASES CURRENTLY AFFECT **5%** OF THE WORLDWIDE POPULATION

Most of RARE DISEASES lead to permanent disability

80% of rare diseases are genetic, and therefore, chronic



MORE THAN 90% of rare diseases are without an FDA-approved treatment

ALL PEDIATRIC CANCERS ARE RARE

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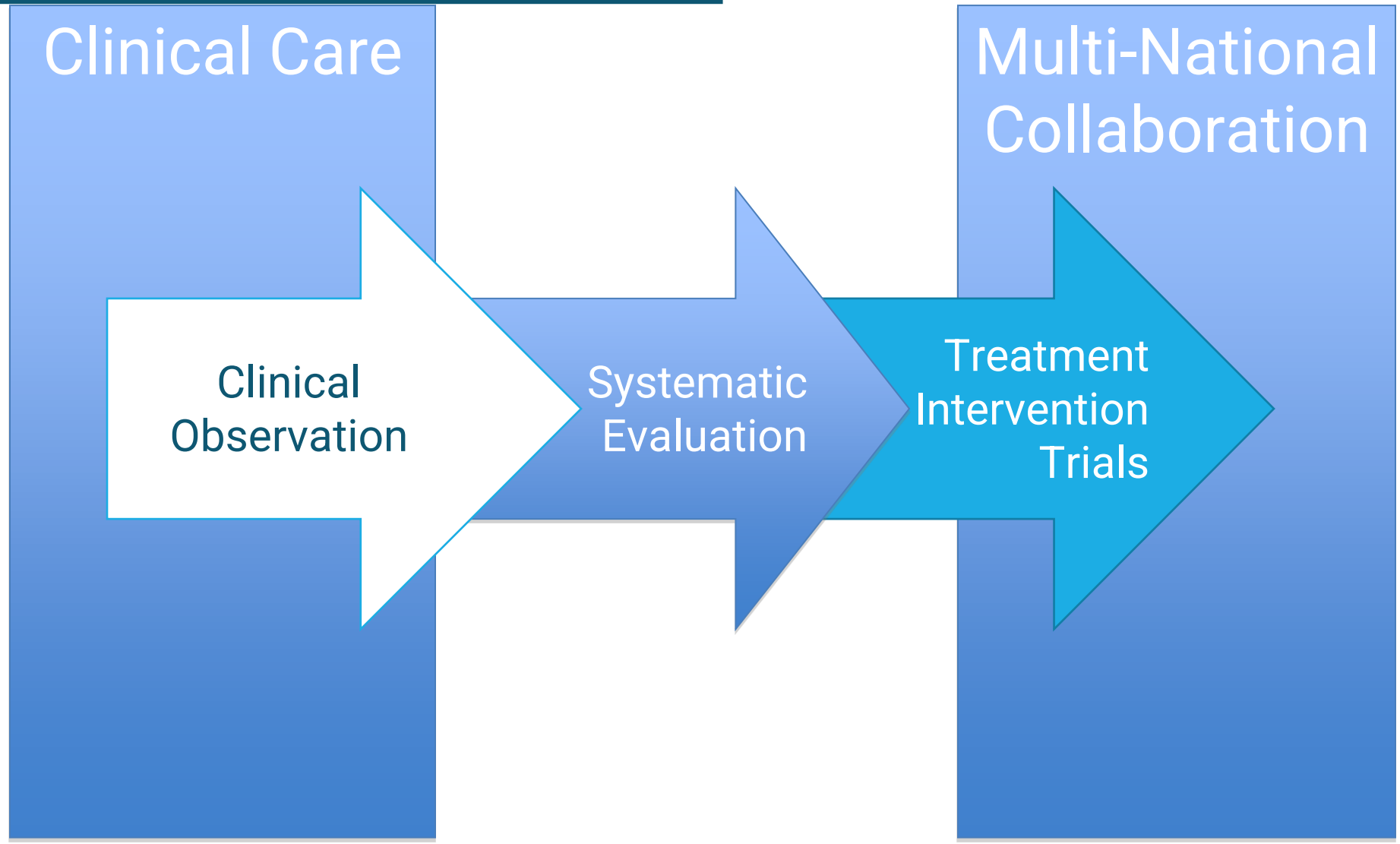
Figure adapted from MDPI; Images by M. Hassan, CoxinhaFotos

Discovery to clinical practice



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Pompe disease and the enzyme replacement therapy revolution

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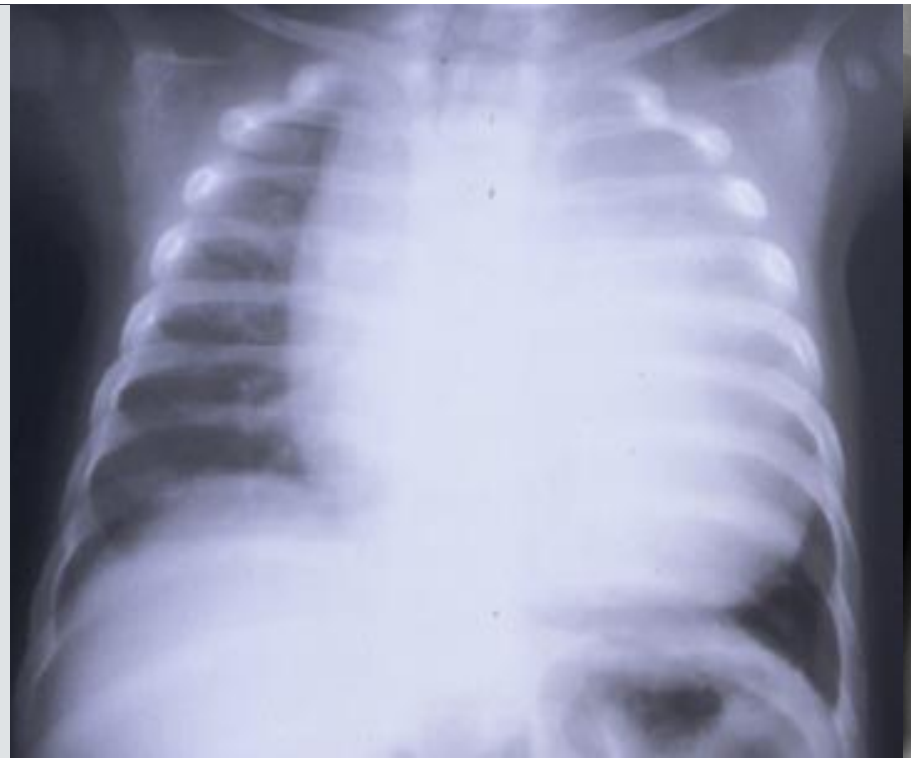
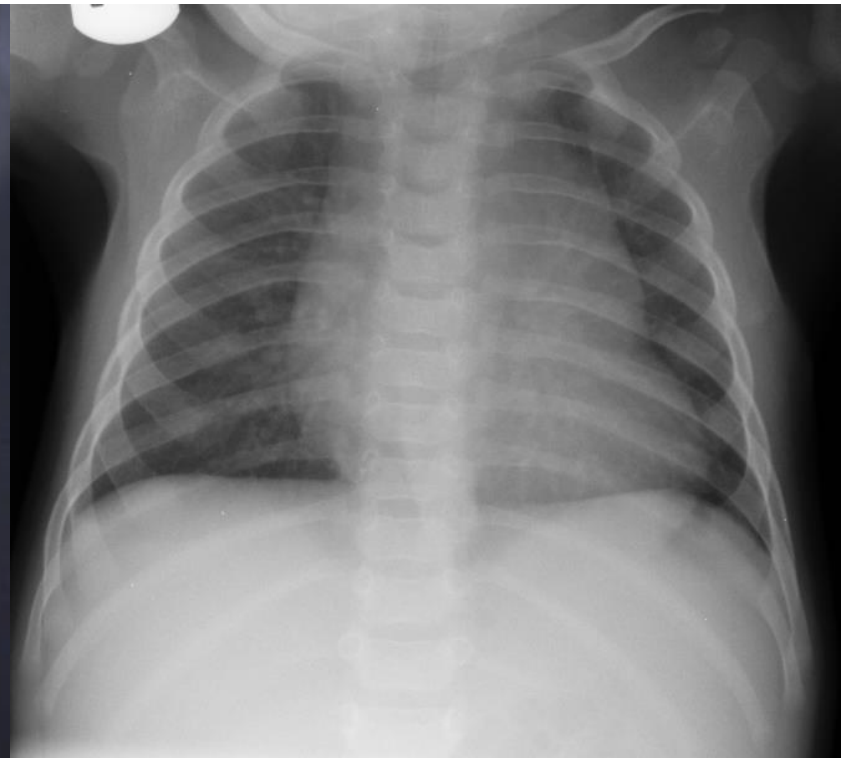


Chest X-ray
Baby affected by Pompe disease



Chest X-ray
Normal baby

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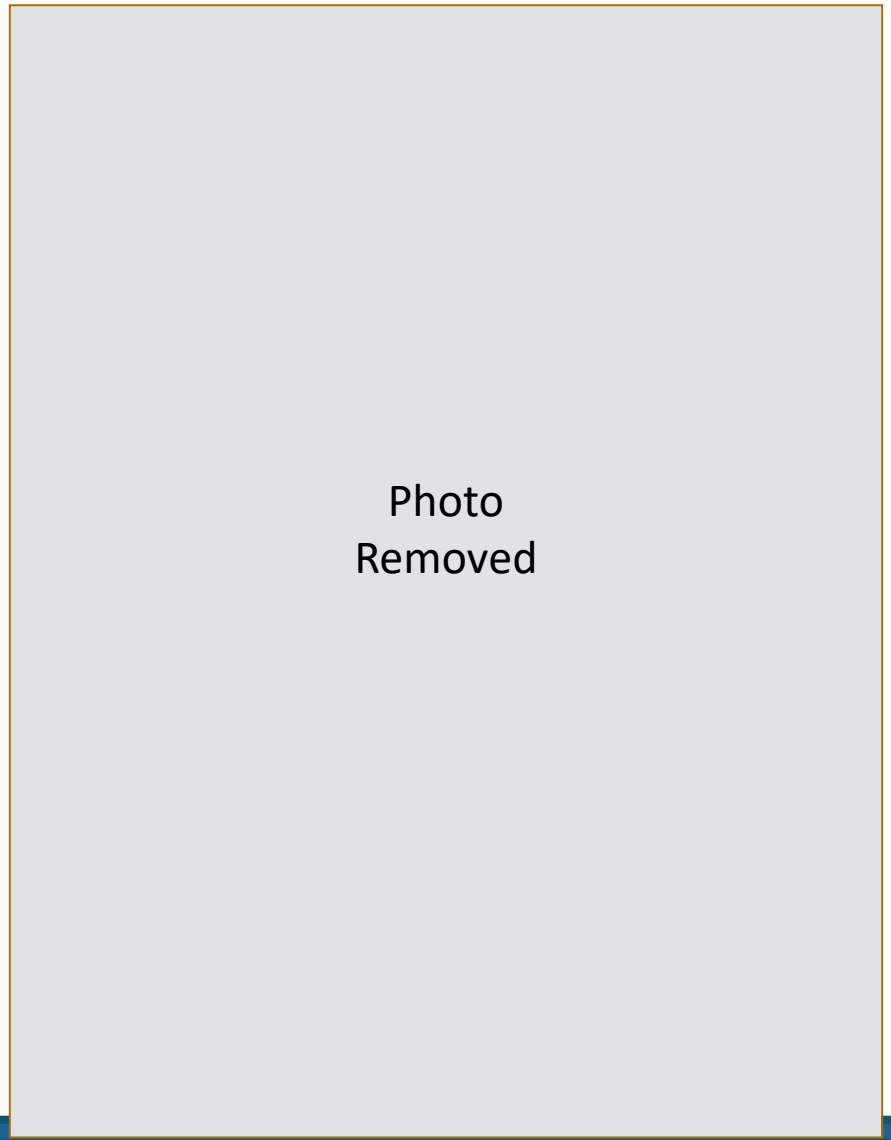
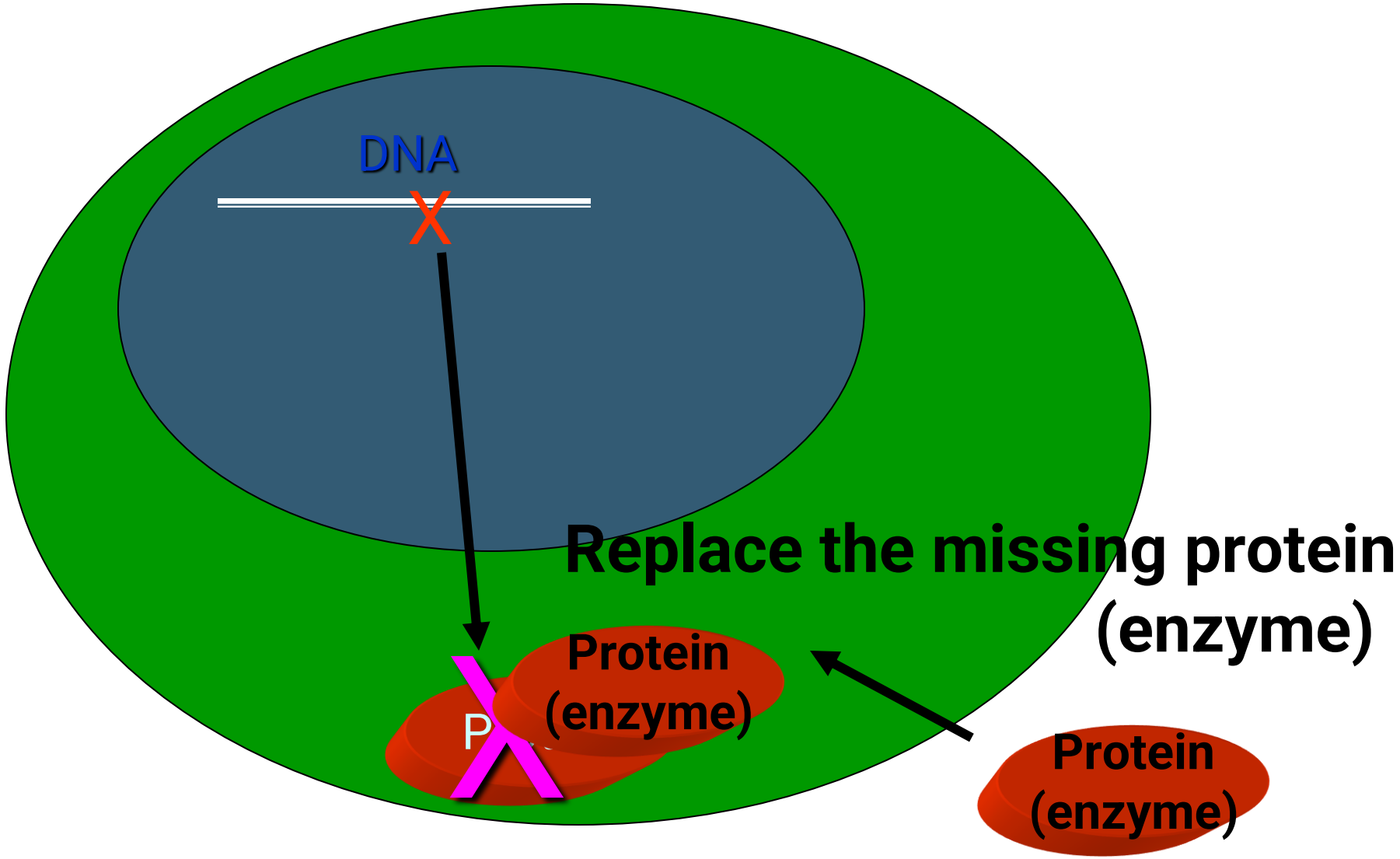
Baby Carmen



Mutations in the gene (DNA) result in defective or no enzyme



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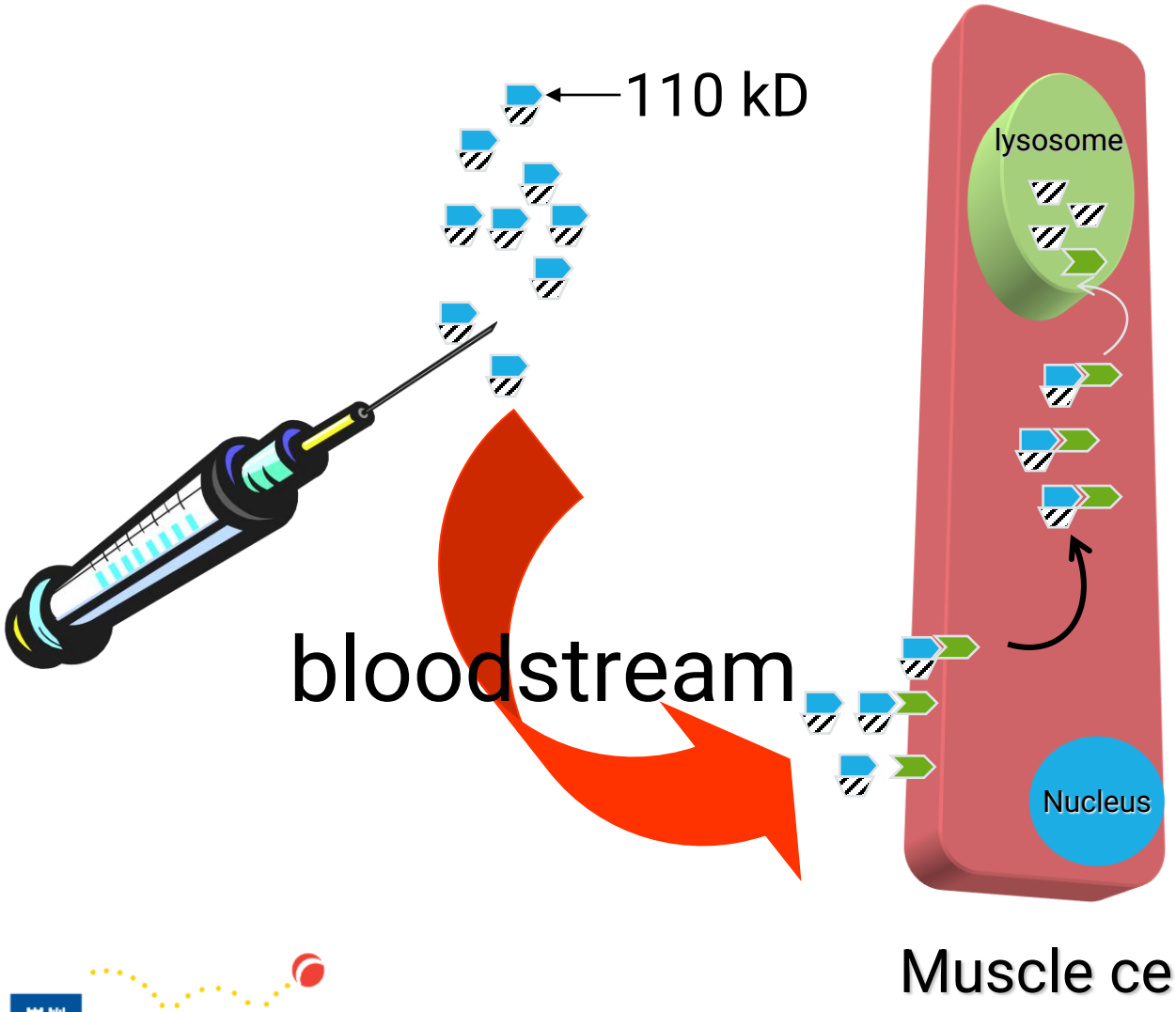
Intravenous injection of recombinant enzyme (human GAA) will correct enzyme deficiency in Pompe patients



Brothers with and without treatment

Baby R at 9 months

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Baby J at 9 months

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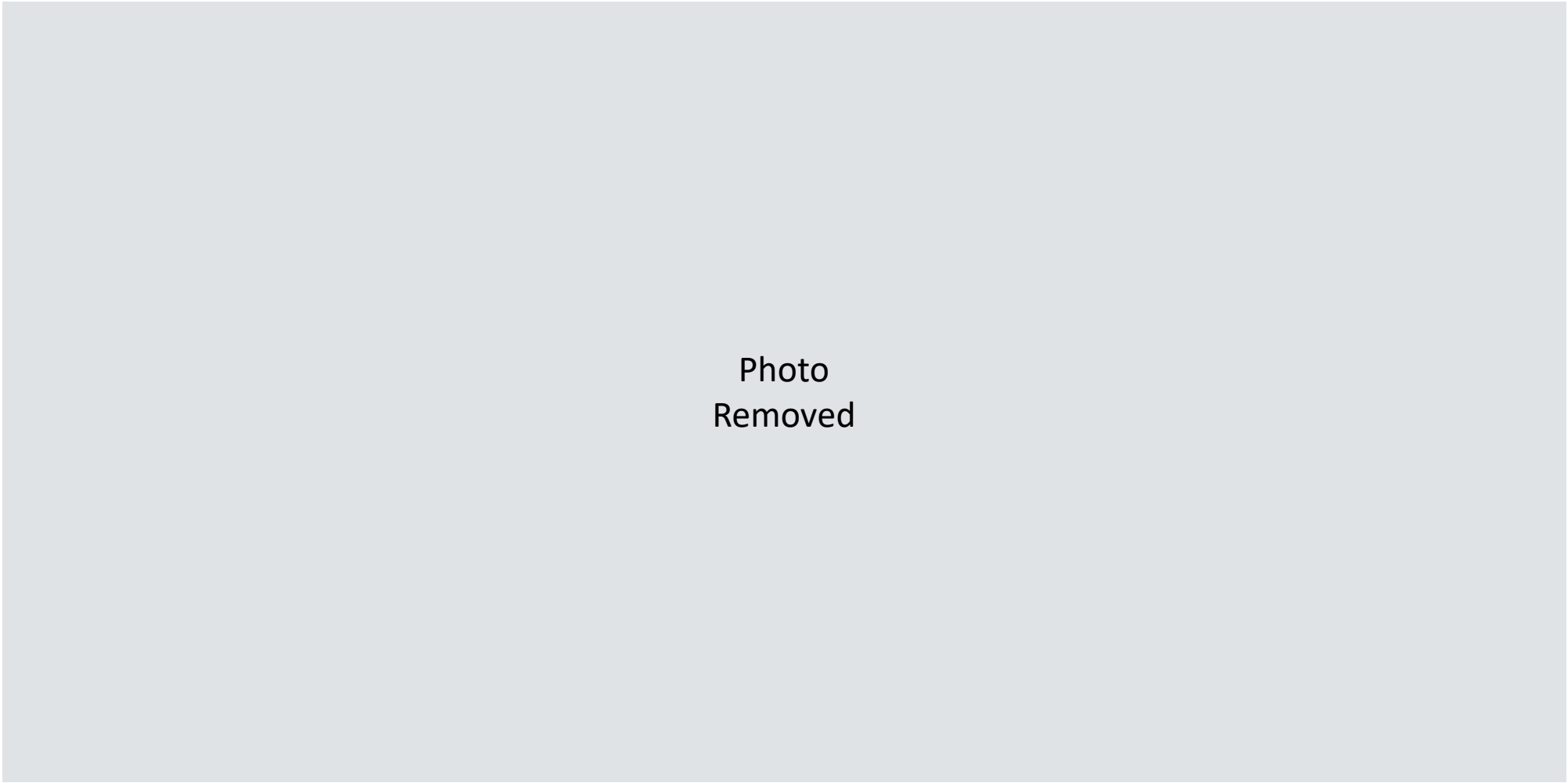
Babies lead the way for FDA approval of enzyme replacement therapy in 2006



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Newborn screening – a way to ensure a healthy start for our babies

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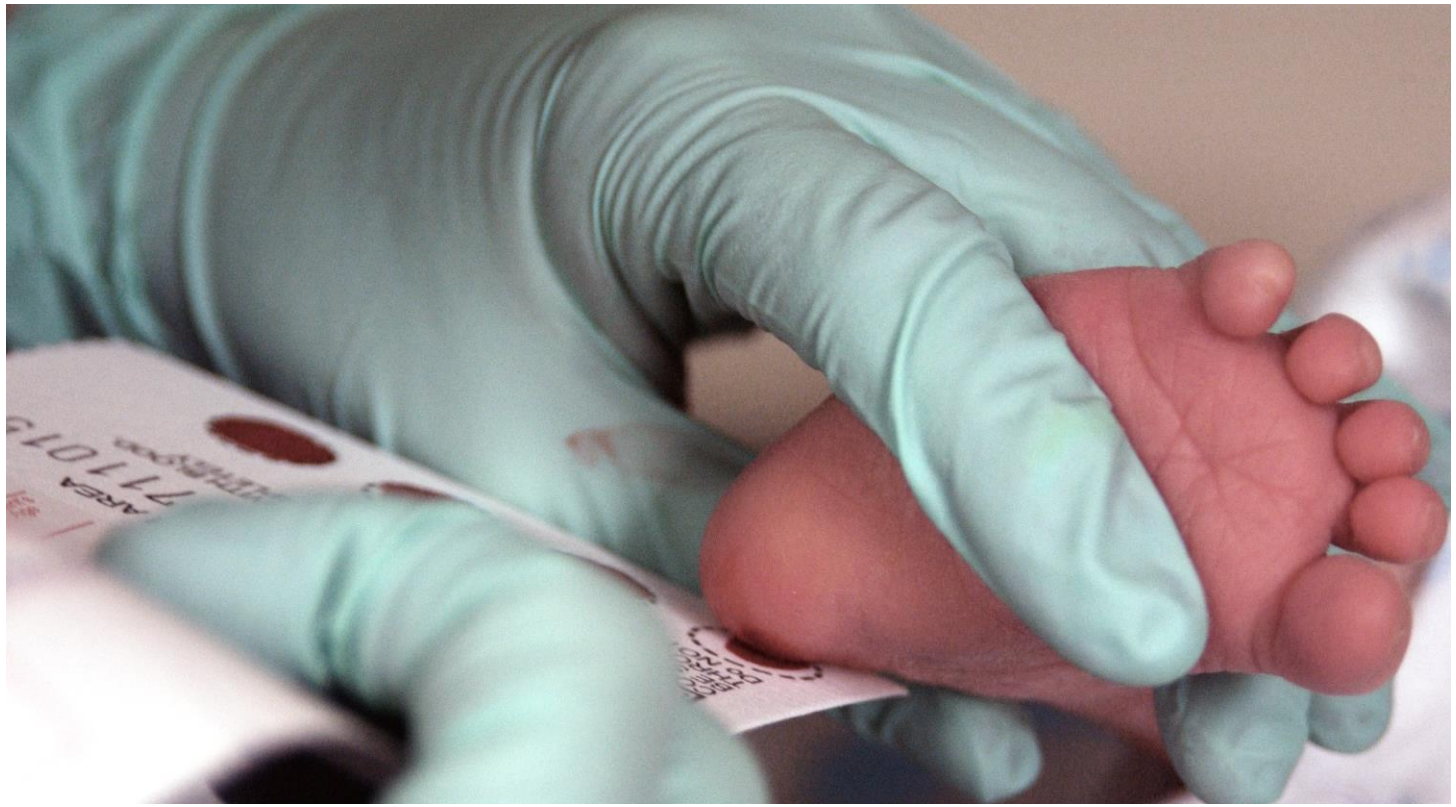

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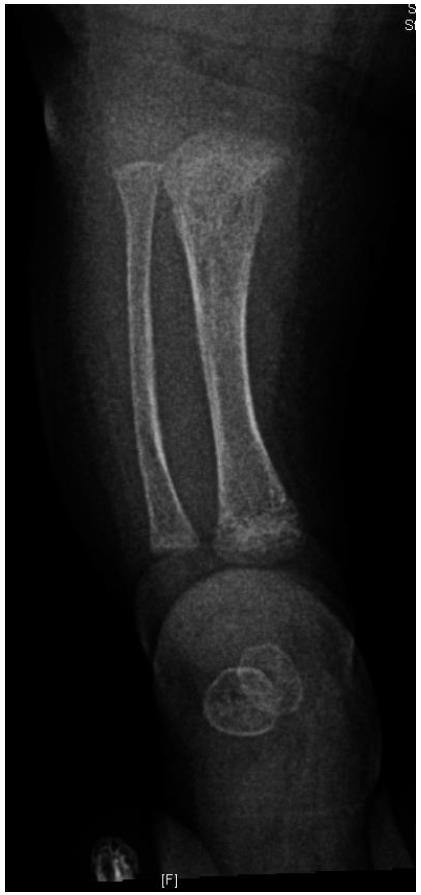
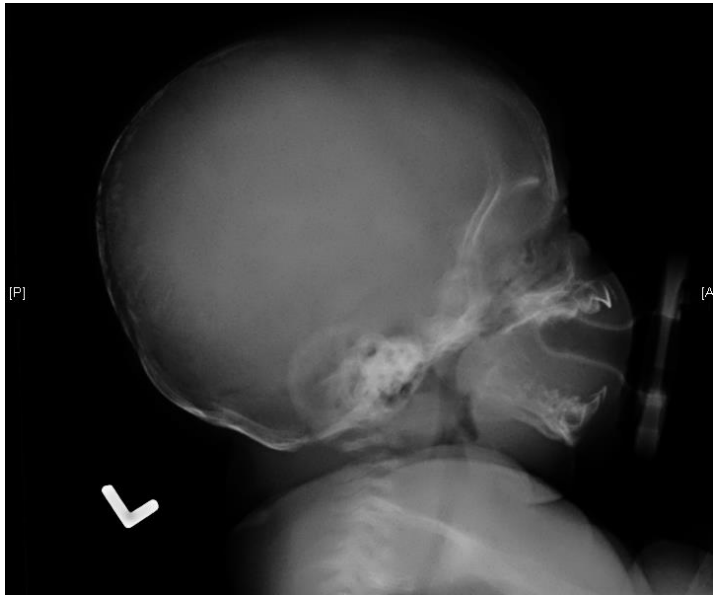
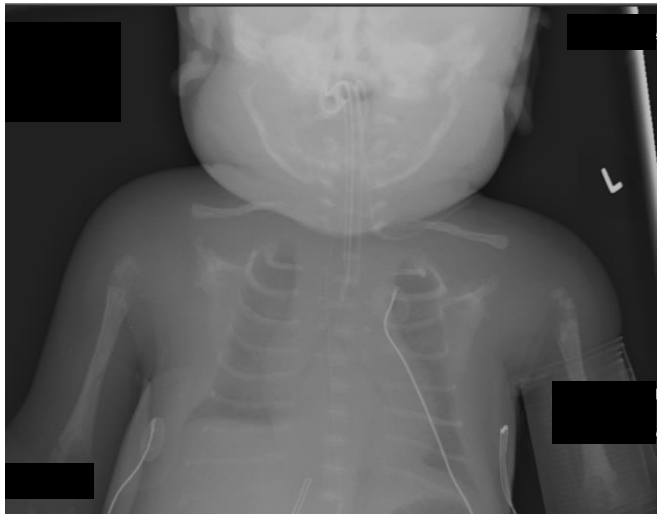
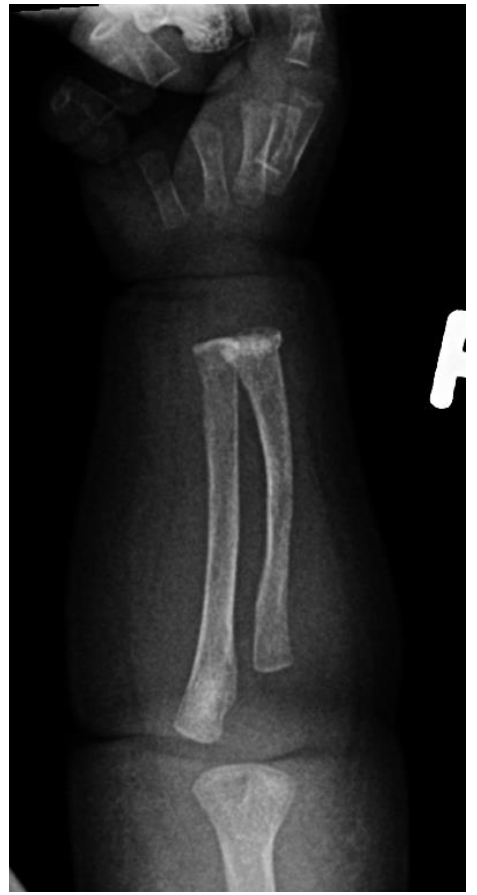
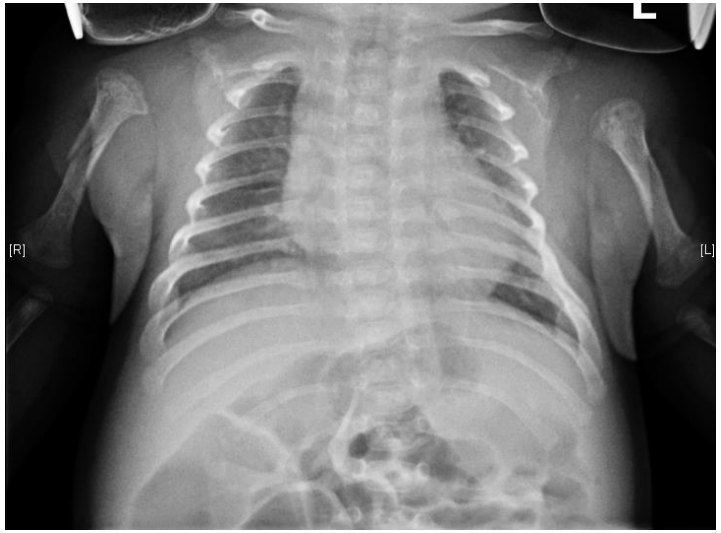
Hypophosphatasia

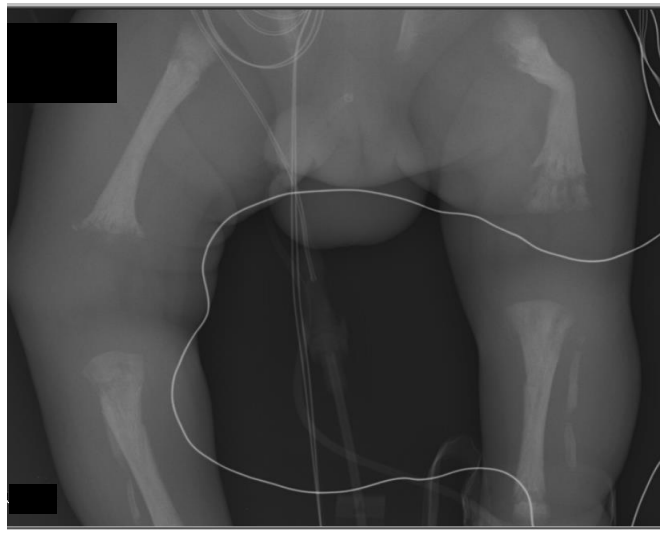




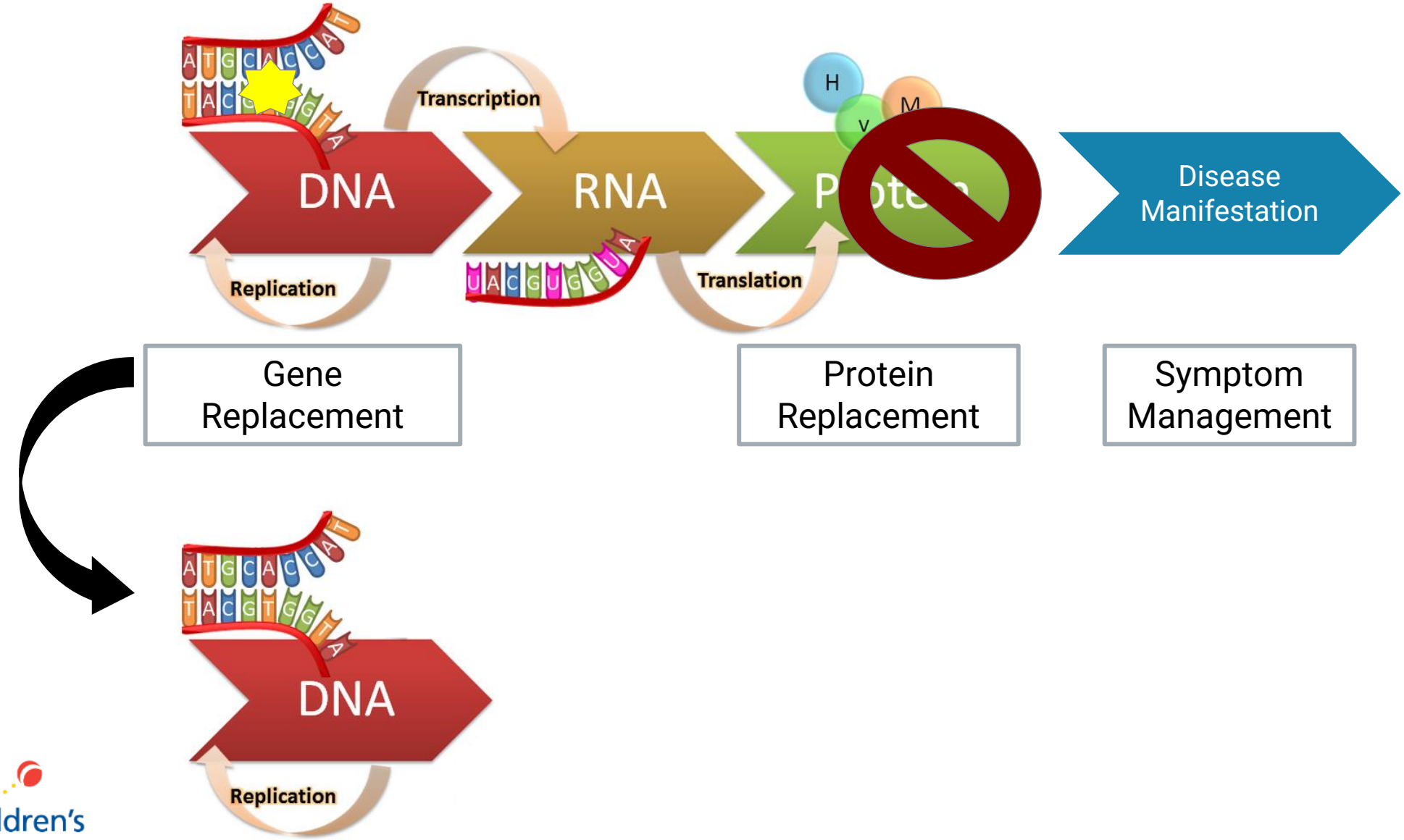




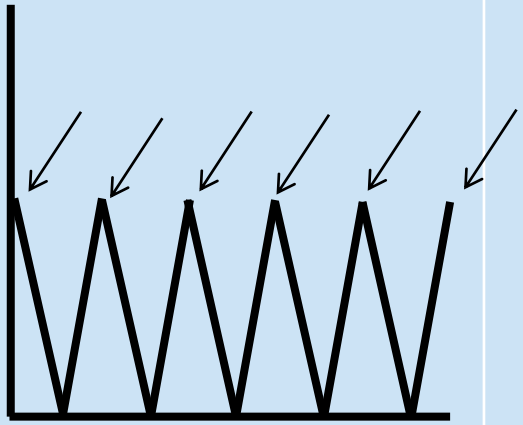
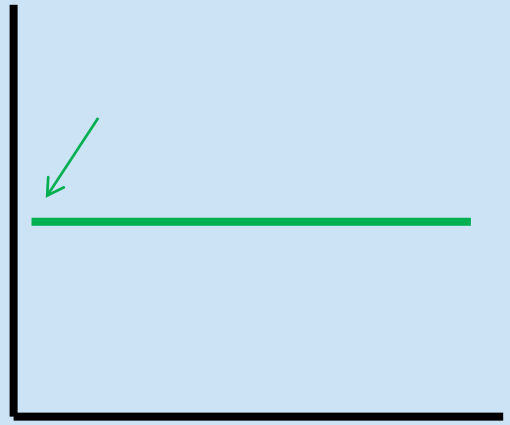




From management to a cure



Comparison of ERT and Gene Therapy: The concept

	ERT	AAV2/8LSPhGAA
Stability	Short half-life in blood	Continuous GAA in bloodstream
GAA delivery to muscle	Lack of uptake in skeletal muscle	Increased delivery to muscle
Immune Responses	High titer antibody response	Immune tolerance induction
Population	Some patients fail to respond	Larger patient population
Efficacy	Partial	More complete correction
Mortality	Yes	Decreased
Administration	Every 2 weeks 	Single dose 

Gene therapy research is rapidly advancing

2006 – 2010

FDA approves enzyme replacement therapy for Pompe disease

Myozyme and Lumizyme were approved to treat infantile-onset and late-onset Pompe disease

Lumizyme®

Myozyme®

2015

FDA approves enzyme replacement therapy for hypophosphatasia

Strensiq was approved to treat hypophosphatasia

Strensiq® (asfotase alfa) for injection

2019

FDA approves Zolgensma gene therapy to cure an spinal muscular atrophy (SMA)

zolgensma® (onasemnogene abeparvovec-xioi) suspension for intravenous infusion

2022

Ongoing preclinical and clinical gene therapy efforts at Duke Health Rare Disease Center through biotech partnerships

A focus on Pompe disease and Glycogen Storage Diseases type III, IV, VI, and IX

AskBio KRIYA

Early 2000s – 2020

Transitioning from an enzyme replacement era to a gene therapy revolution…

Continuing to improve enzyme replacement therapies (2nd generation) for Pompe disease and other lysosomal storage diseases – they continue to be life saving management strategies

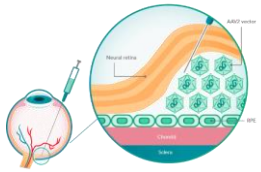
Gene therapy technologies rapidly improved facilitating **CURATIVE** strategies

2017

FDA approves Luxturna gene therapy to cure an inherited retinal dystrophy

The first in vivo gene therapy was approved for the treatment of RPE65 mutation-associated retinal dystrophy

LUXTURNA® voretigene neparvovec-rzyl for subretinal injection



Current Phase 1/2/3 gene therapy clinical trials for inherited disorders include:

- Pompe Disease
- Phenylketonuria (PKU)
- Wilson disease
- GSD type Ia
- Methylmalonic aciduria
- Ornithine transcarbamylase deficiency
- X-linked myotubular myopathy
- Duchenne Muscular Dystrophy
- Hemophilia B
- ***and more…!***

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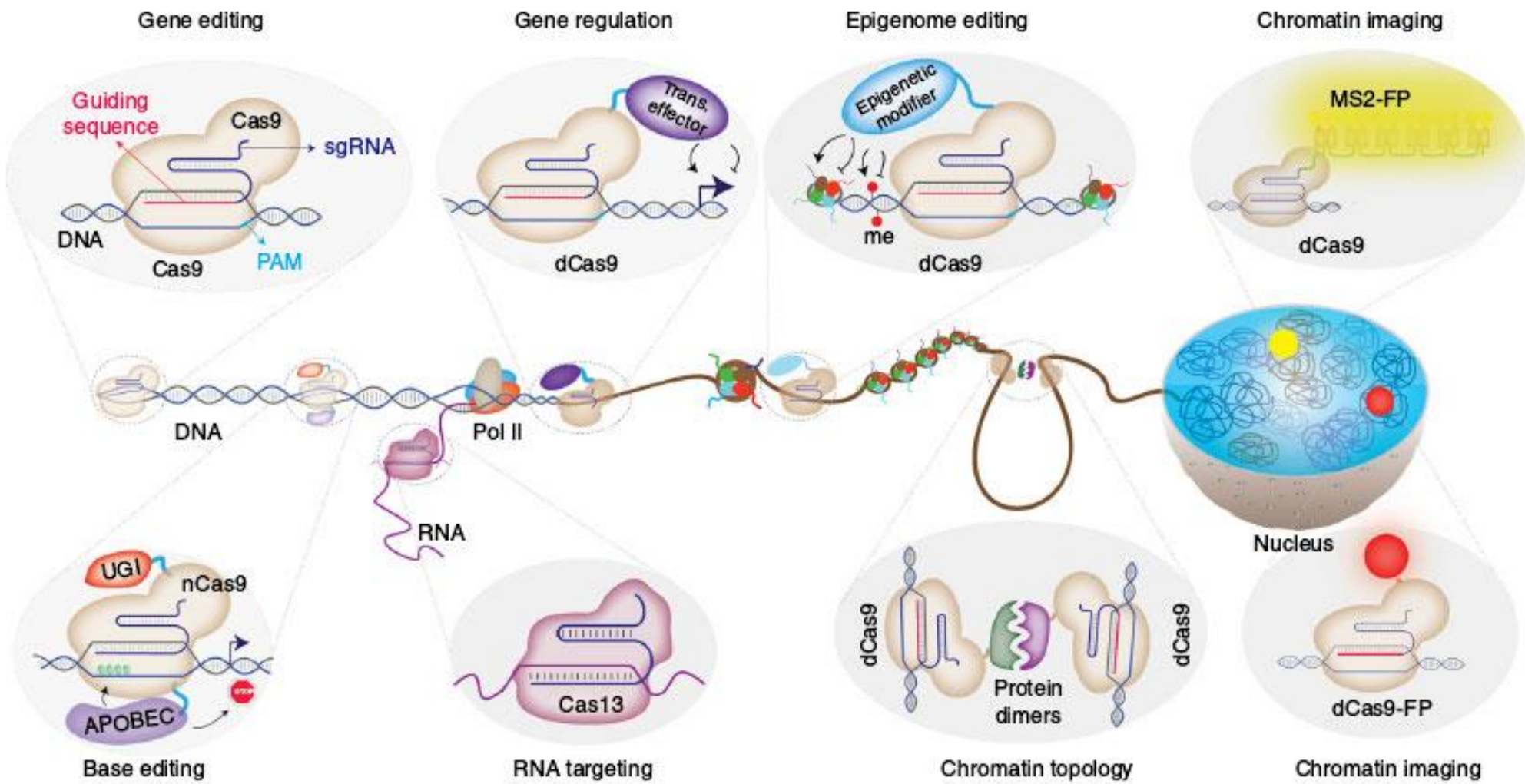
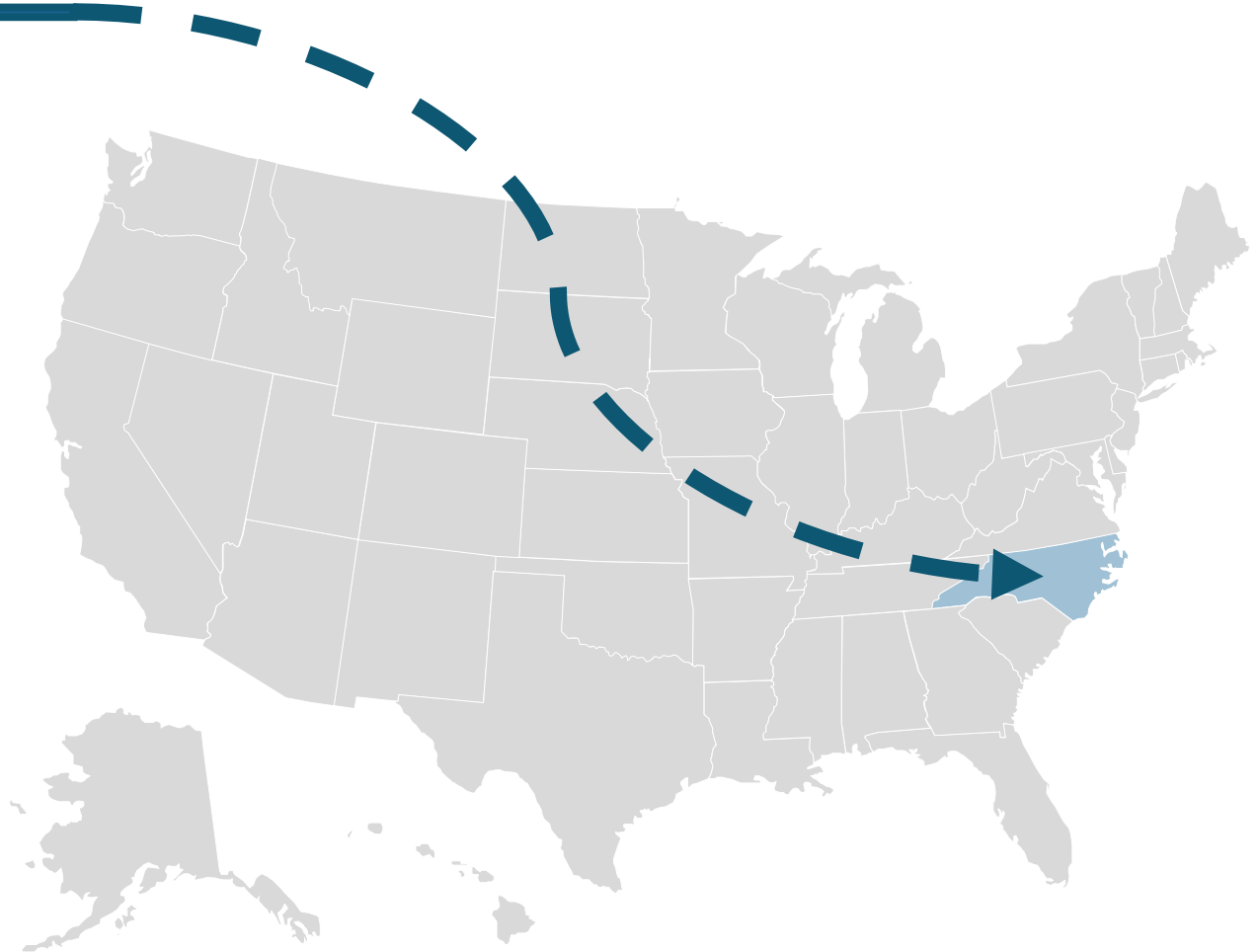
Future Gene Therapy – Gene/RNA Editing - CRISPR



An ongoing influx of patients coming to North Carolina for care and treatment

- Duke University and other allied rare disease programs are continuing to expand their gene therapy efforts
- More and more patients from around the world and the US are relocating to North Carolina for care
- Newborn screening is leading to increased diagnoses, allowing earlier access to care and improved patient outcomes



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Dedication to those we have lost

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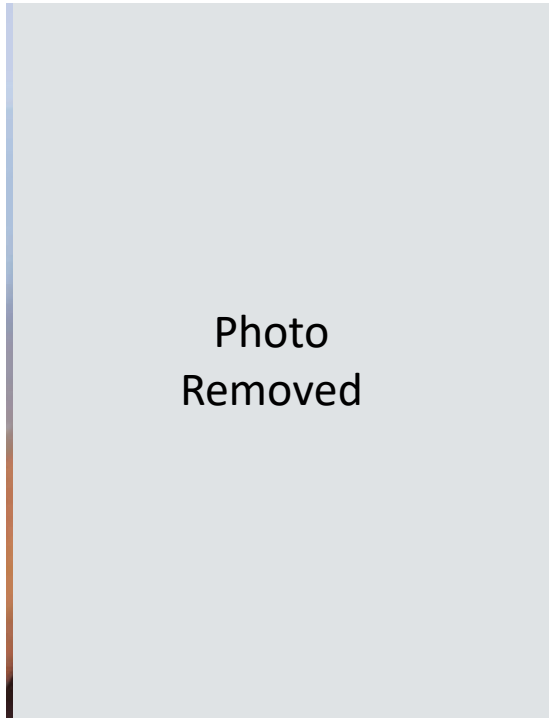

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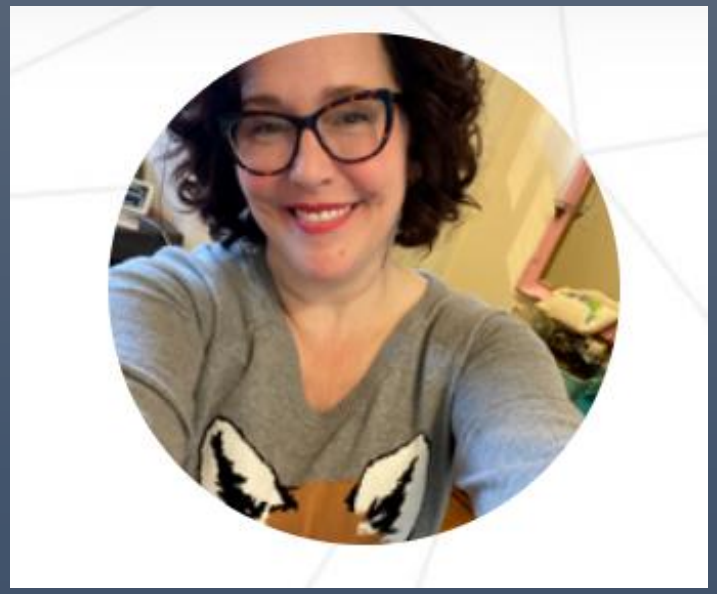
The path to hope begins with a diagnosis

Vandana Shashi, MBBS, MD
Division of Medical Genetics
Department of Pediatrics

The Problem of Rare Diseases

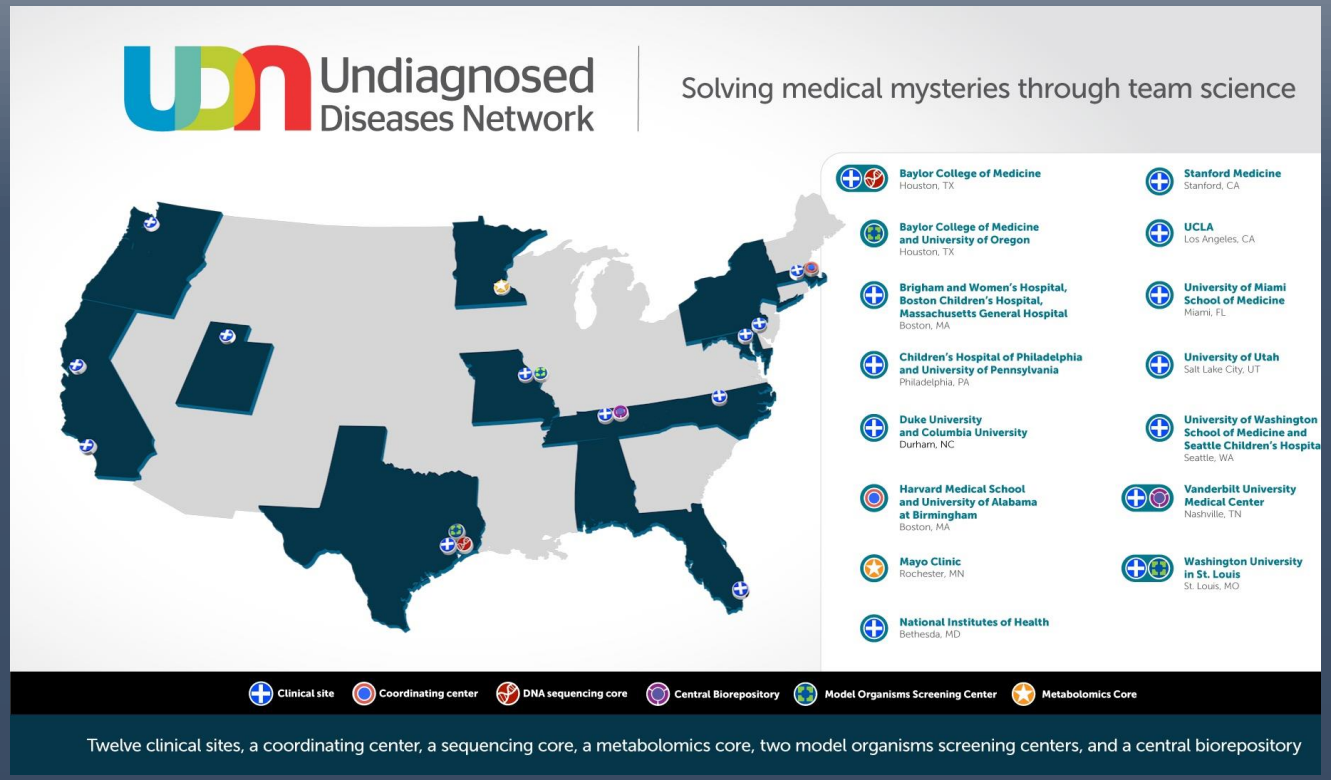
- Individually rare, collectively common
- About 7000 rare disorders- affect 6-8% of the US population: >500,000 affected in NC
- Exert personal and familial psychosocial and financial impact, and societal toll
- Difficult to diagnose
  - ~80% are genetic
  - Even with technological advances such as exome sequencing 60-75% remain undiagnosed



The Undiagnosed Diseases Network

Solving Medical Mysteries through Team Science

Background



- The Undiagnosed Diseases Network (UDN) created by the National Institutes of Health Common Fund in 2014
- Expanded in 2018: 12 clinical sites
  - Duke is the only clinical site in NC

UDN Objectives

Diagnose patients for whom all available clinical testing has failed (they mostly have rare/ultra-rare diseases)

Facilitate **research** into causes of undiagnosed diseases

Create an **integrated** and **collaborative** research community to improve patient management

Undiagnosed Diseases Network

UDN evaluations

Coordinated clinical evaluation by multiple specialists completed in 5 days

Tailored evaluations with standardized data collection for network sharing

Genomic sequencing: clinical lab and research reanalysis of sequence data
(~80% of undiagnosed diseases are rare or ultra-rare genetic disorders)

Incorporation of cutting-edge tools including RNA sequencing, model organisms, metabolomics

Undiagnosed Diseases Network

Key Metrics of Network and at Duke site

Applications received

Patients Accepted

Evaluations Completed

Number of Diagnoses

Diagnosis rate

Duke site's data are in parentheses and white

*18 new disease gene discoveries from the Duke site

Impact of the UDN

<u>Patients</u>

Diagnosis, new disease gene discoveries

Treatment changes (even without a diagnosis)

- New medications
- Clinical trials
- Screening for complications
- Membership in foundations, support groups, advocacy

The psychological relief of getting a diagnosis cannot be overstated

<u>Medical/Scientific community</u>

Continued innovation on diagnostic approaches to rare disease

- No patient is ever “closed” in the UDN

UDN best practices scalable

- Effective yet cost-efficient

Partnerships with biotech

- Disease mechanisms
- Innovative treatments

Impact of the UDN in NC

The UDN offers the best chance for diagnosis for NC patients who remain undiagnosed by standard methods (including exome sequencing)

UDN best practices can save costs while maximizing diagnoses

Scaling of UDN will benefit large numbers of NC patients and increase access in underserved areas

This can improve the lives of North Carolinians

UDN data can drive scientific innovations with biotech partnerships in NC

North Carolina Life Sciences Caucus

June 28, 2022

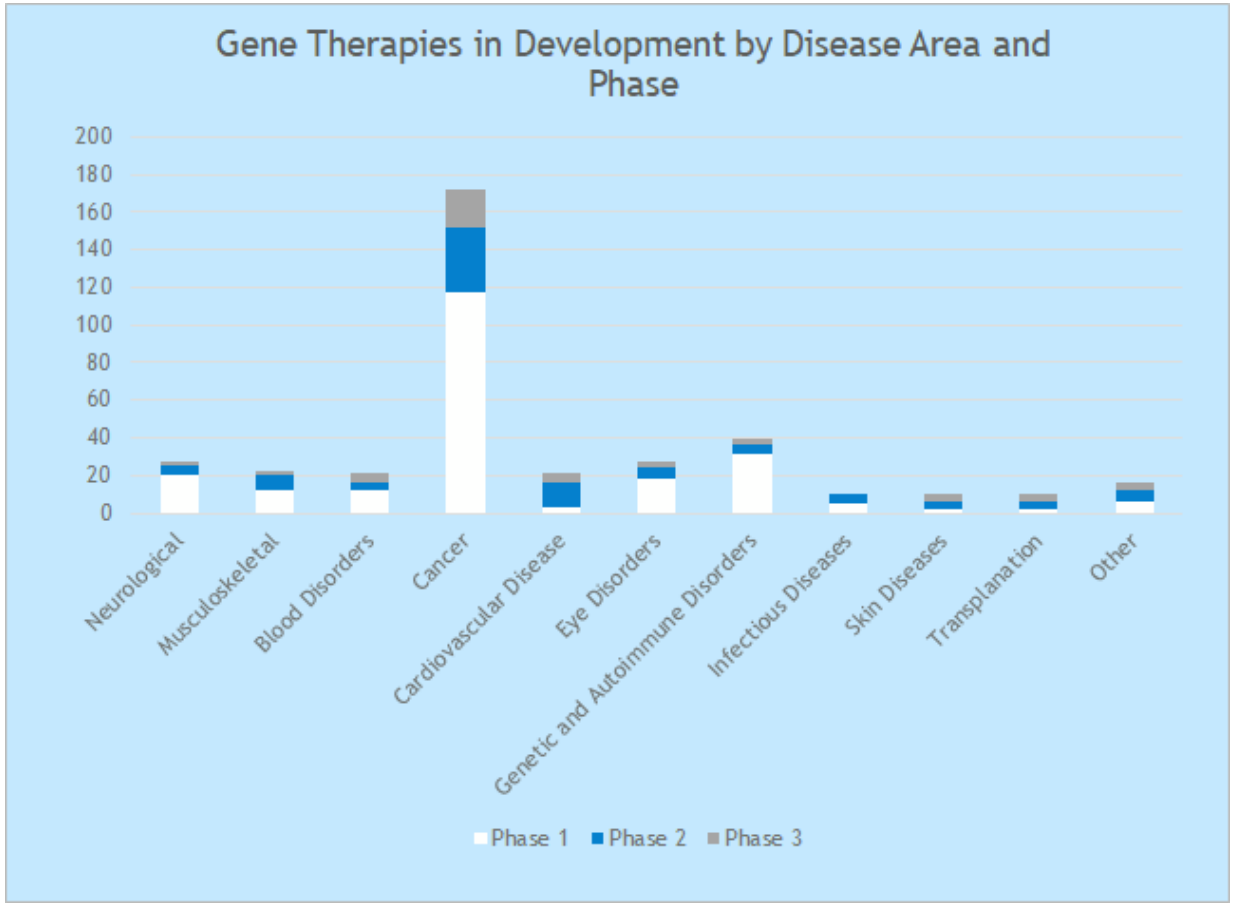
Duke-Margolis Disclaimers

Anti-Trust Compliance Policy: Call participants are committed to free and open competition in the marketplace and compliance with all applicable laws, including compliance with antitrust and competition laws. Meetings, communications and other activities are not intended in any way to limit the individual competitive decisions of the Members or to restrict competition among them. It is the responsibility of all call participants to be guided by this policy of strict compliance with the antitrust laws. Meetings, communications and other activities shall not be proposed for, or used for the purpose of, reaching or implementing any agreement concerning the competitive activities of others. Any call participant who has a question regarding compliance with the antitrust laws or any aspect of the meetings, communications or activities should promptly consult the participant's own legal counsel.

Antitrust Policy – Off limit topics: When participating in Collaborative activities, Members, Member representatives, and observers shall avoid discussing non-public, company-specific information relating to current or future competition in the marketplace. These include: Company-specific prices, pricing methods, pricing policies, pricing plans. Sensitive cost information, including reimbursement rates or methods, pharmacy costs, and salaries/compensation information. Marketing and strategic plans, market or competitive evaluations. Identity and other information about present or potential customers, healthcare providers or payers, including costs, prices, profitability, marketing plans, and product development plans. Research & development plans. Other confidential or proprietary activities, strategies, processes or procedures. Refusals to deal with any company or supplier. Strategies or plans to award business or remove business from a specific company, to participate or not participate in any particular business opportunity or type of business opportunity. Status of negotiations with present or potential customers, suppliers, payers or healthcare providers

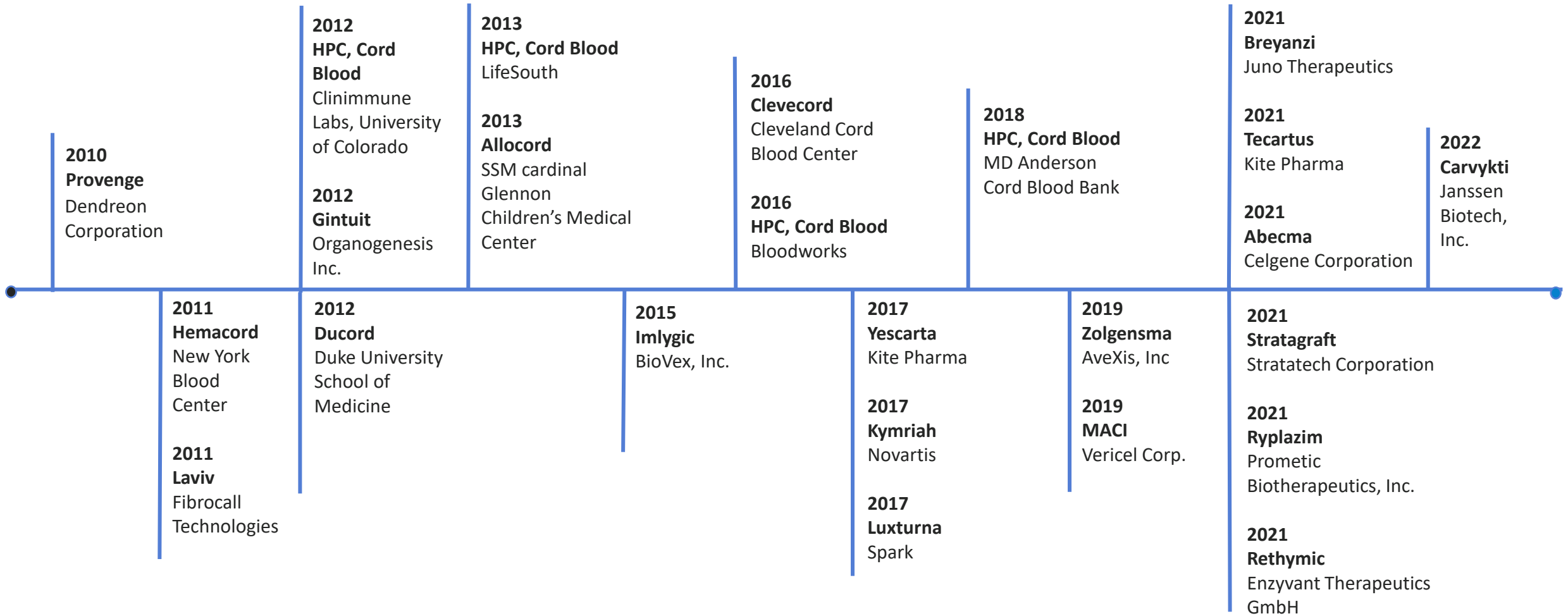
Landscape of the cell and gene therapy market

- **There are roughly 600 drugs in the pipeline.**
  - Of those 600 products, around 80 are in Phase 3 of development
- **Drugs likely to enter the market soon address:**
  - Severe/rare genetic diseases (e.g., SCID), Neurological Disorders (e.g., Alzheimer's), Retinal Diseases and Disorders (e.g., LHON)
  - Oncology (a predominant number of drugs are still in Phase 1 or 2), Blood and Immunological disorders (e.g., hemophilia)



Source data: America's Biopharmaceutical Companies' 2020 report **Charts are modified from the Medicines in Development 2020 Update.

FDA approvals of cell and gene therapies



Costs for gene and cell therapy products on the market today

- Cell and gene therapies offer potential cures for previously incurable diseases, but also carry extraordinarily high price tags.
- In addition to the high cost of the drug itself, these therapies are complex to administer and often require extensive care coordination before, during, and after administration.
- These treatments are administered primarily in hospital settings, which drives additional costs.

DRUG NAME	MANUFACTURER	INDICATION	COST
Luxturna (voretigene neparvovec-rzyl)	Spark	Inherited retinal disease	$850,000/ for both eyes
Kymriah (tisagenlecleucel)	Novartis	Acute lymphocytic leukemia Diffuse large B-cell lymphoma	$475,000 $373,000
Yescarta (axicabtagene ciloleucel)	Kite	Large B-cell lymphoma and Follicular lymphoma	$373,000
Zolgensma (onasemnogene abeparvovec-xioi)	AveXis	Spinal muscular atrophy	$2.125 million
Tecartus (brexucabtagene autoleucel)	Kite	Mantle cell lymphoma	$373,000
Breyanzi (lisocabtagene maraleucel)	BMS	Large B-cell lymphoma	$410,300
Abecma (idecabtagene vicleucel)	BMS and bluebird bio	Multiple myeloma	$419,500

Source data: "Cost management for sky-high, high-cost gene therapy." Prime Therapeutics. August 2021.

Payment challenges for cell and gene therapies

- **Budgetary impact of high upfront costs**
  - Current payment system in the US was designed to reimburse for chronic conditions, which are administered and paid for over time in periodic increments
  - Cell and gene therapies are typically administered one time and accrue benefits over time
  - Payers may not be able to absorb the high one-time cost and providers may not want to assume the reimbursement risk if rates don't cover total costs
- **Uncertainty regarding real-world clinical efficacy and long-term durability of the therapeutic benefit**
  - Evidence used for regulatory approval may have limited information on the long-term outcomes and durability associated with the treatment
  - Current treatments have been studied in relatively small numbers of patients over a short period of time
  - Payers may pose coverage restrictions when there is uncertainty of impact in different types of patients and as combination therapies
- **Uncertainty in recouping investment with multiple payers**
  - Cost savings from cell and gene therapies will likely be accrued downstream from the initial treatment
  - It is likely that a patient will switch health plans, so these savings may not accrue to the payer that assumed the original treatment cost, creating an additional hurdle for payers to cover and reimburse these therapies

Medicare payment policies for cell and gene therapy products

- In January 2016, CMS agreed to cover hematopoietic stem cell transplant to treat multiple myeloma myelofibrosis, and sickle cell disease through the CED mechanism
  - Reimbursement rate is below the procedure's true cost
- CMS finalized a new MS-DRG 018 for FY 2021 for hospital inpatient treatments using CAR T-cell products meant to increase payment predictability for these therapies
  - Proposed base payment for CAR-T cases in FY 2023 would increase from $246,955 (FY 2022) to $248,806
  - Overall financial impact will vary by hospital, but reimbursement rate still sometimes fails to cover total hospital costs, affecting provider uptake and patient access
  - Concerns over how CMS will address an inpatient therapy that maps to DRG 018 but has significantly different costs
- Products in pipeline are intended for much broader patient populations those currently available, potentially shifting industry away from heavy inpatient focus to more outpatient treatment
  - Shifting volume toward outpatient use may result in changes to the outpatient payment system

Commercial payer policies for cell and gene therapy products

- Commercial payers cover cell and gene therapies on a case by case basis
  - If they decide to cover the therapy, reimbursement rates will be similar to which Medicare pays for these treatments
- Commercial payers have greater flexibility to enter into **outcome-based agreements,** which align payment to observed outcomes and/or **annuity models** that spread the cost of the therapy out over time
  - Example: Harvard Pilgrim Health Care and Spark entered into an agreement to tie payments for the drug to measure improvement in patients at 30- to 90-day intervals and then again at the 30-month mark.
- Commercial payers have utilized **financing models** to manage spending, including risk pooling, stop-loss and reinsurance, supplier credit, and patient assistance subsidy
  - One example is Cigna's Embarc Benefit Protection platform, which carves out coverage for cell and gene therapies
    - Employers that adopt platform pay a per member, per month fee to participate
    - Program is designed to alleviate high cost-sharing for patients and prevent shock claims for employers

Medicaid policies for cell and gene therapy products

- State Medicaid programs face particularly acute challenges with coverage of high-cost treatments given requirements to cover products and limited tools for mitigating budgetary impacts
- Like private payers, Medicaid programs may engage in outcome-based agreements, also called value-based purchasing arrangements
  - Example Massachusetts Medicaid and AveXis entered into an outcome-based arrangement for Zolgensma, which will include evaluations and refunds over the course of five years based on the drug's effectiveness over time in treated patients
- Medicaid value-based purchasing arrangements for medical products are still relatively new and state experience with these arrangements is very limited
  - Medicaid organizations are much more engaged in looking for opportunities, in part because there is growing interest from manufacturers to engage in these arrangements
  - However, the extent to which states can carry out successful contracts is dependent on data capabilities that many do not have
- Currently, states have to request additional authorities from CMS to engage in value-based purchasing arrangements
  - A CMS final rule effective in July, 2022 allowing for multiple Medicaid best prices is intended to support payers entering into value-based purchasing negotiations. CMS recently released guidance to states on the final rule and engaging in VBP arrangements

Patient Voices

- Nickey Hosey, SMA parent and advocate

- Charlene Cowell, MPA, executive director, Hemophilia of North Carolina

Q&A/Discussion

Life Science Caucus Meeting
June 28, 2022
7:30am

Co-chairs:
Senators Newton and Woodard
Representatives White and Reives

Meeting adjourned