Revolutionizing Healthcare: Exploring Gene Therapy and Innovative Payment Models

February 13, 2024

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Sponsored by BioMarin & Ultragenyx

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What We'll Cover Today

- Guide you through the science behind gene therapy
- Explore the political environment and barriers to outcomes-based arrangements (OBAs) designed to facilitate access to gene therapies
- Advocate for state and federal policies that will pave the way for adoption of innovative payment models

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Science of Gene Therapy

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Senior Medical Director

Hematology

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Developed and funded by BioMarin

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Gene Therapy
History and Research

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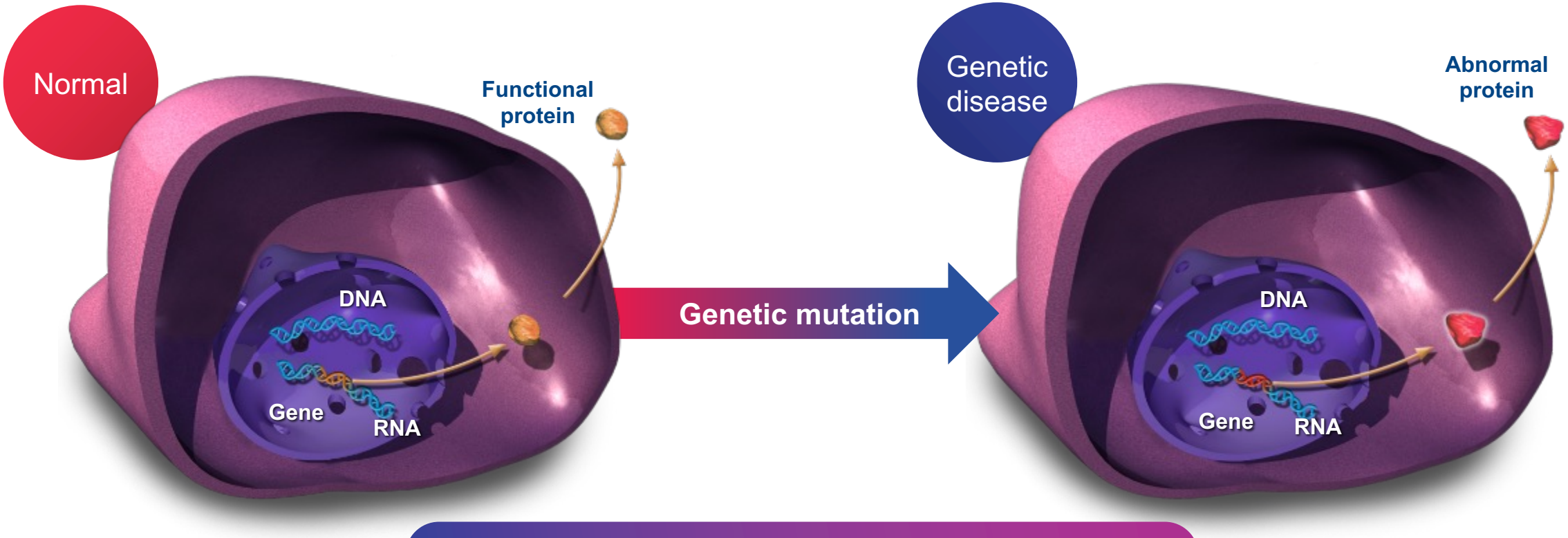
Genetic mutations may cause abnormal protein production



A single variant gene can lead to:[1]

- Production of no protein
- Production of nonfunctional protein
- Overproduction of a disease-causing protein

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1. Lodish H *et al.* Section 8.1, Mutations: types and causes. In: *Molecular Cell Biology*. 4th ed. New York: WH Freeman; 2000

Principles of gene therapy

Rather than treating downstream symptoms, gene therapy is designed to enable the body to endogenously produce a functional protein to overcome the disease

Gene therapy allows a rebalancing of protein products in the body:

- Reduction of proteins causing disease
- Increase of proteins fighting disease
- Production of new, modified or missing proteins

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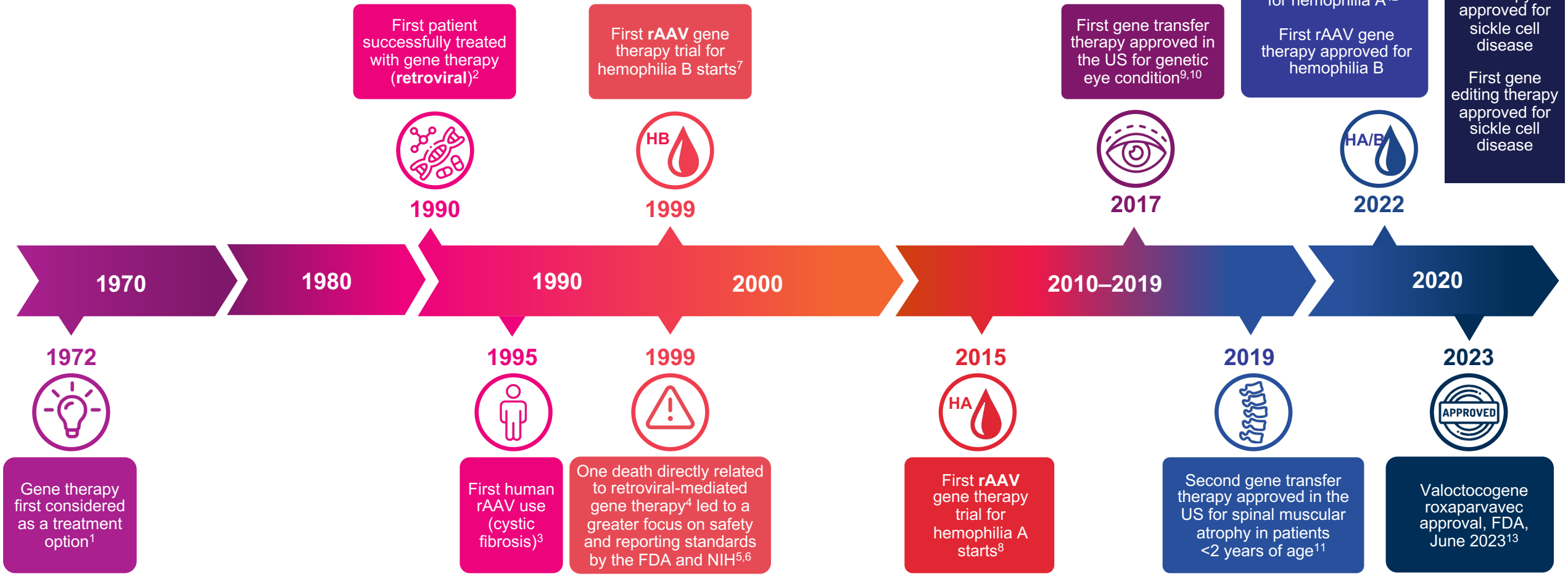
1. Pierce GF, Iorio A. *Haemophilia* 2018;24(Suppl.6):60–7

Over 50 years of gene therapy research



FDA, US Food and Drug Administration; HA, hemophilia A; HB, hemophilia B; NIH, National Institute of Health; rAAV, recombinant adeno-associated virus
1. Friedmann T *et al. Science* 1972;175:949–55; 2. Blaese RM *et al. Science* 1995;270:475–80; 3. Wang D *et al. Nat Rev Drug Discov* 2019;18:358–78; 4. Sibbald B. *CMAJ* 2001;164:1612; 5. Cotrim AP, Baum BJ. *Toxicol Pathol* 2008;36:97–103; 6. Collins FS, Gottlieb S. *N Engl J Med* 2018;379:1393–5; 7. Hough C, Lillicrap D. *J Thromb Haemost* 2005;3:1195–205; 8. Biomarin Pharmaceutical. https://www.biomarin.com/our-company/about-us/company-milestones/. Accessed August 2023; 9. Luxturna Prescribing Information. Spark Therapeutics, Inc. 2017; 10. FDA. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss. Accessed August 2023; 11. Zolgensma Prescribing Information. AveXis, Inc. 2022. https://www.novartis.com/us-en/sites/novartis_us/files/zolgensma.pdf. Accessed August 2023; 12. EMA. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/roctavian. Accessed August 2023; 13. https://investors.biomarin.com/2023-06-29-U-S-Food-and-Drug-Administration-Approves-BioMarins-ROCTAVIAN-TM-valoctocogene-roxaparvovec-rvox-,-the-First-and-Only-Gene-Therapy-for-Adults-with-Severe-Hemophilia-A. Accessed August 2023

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The number of gene therapies under investigation has steadily increased in recent years

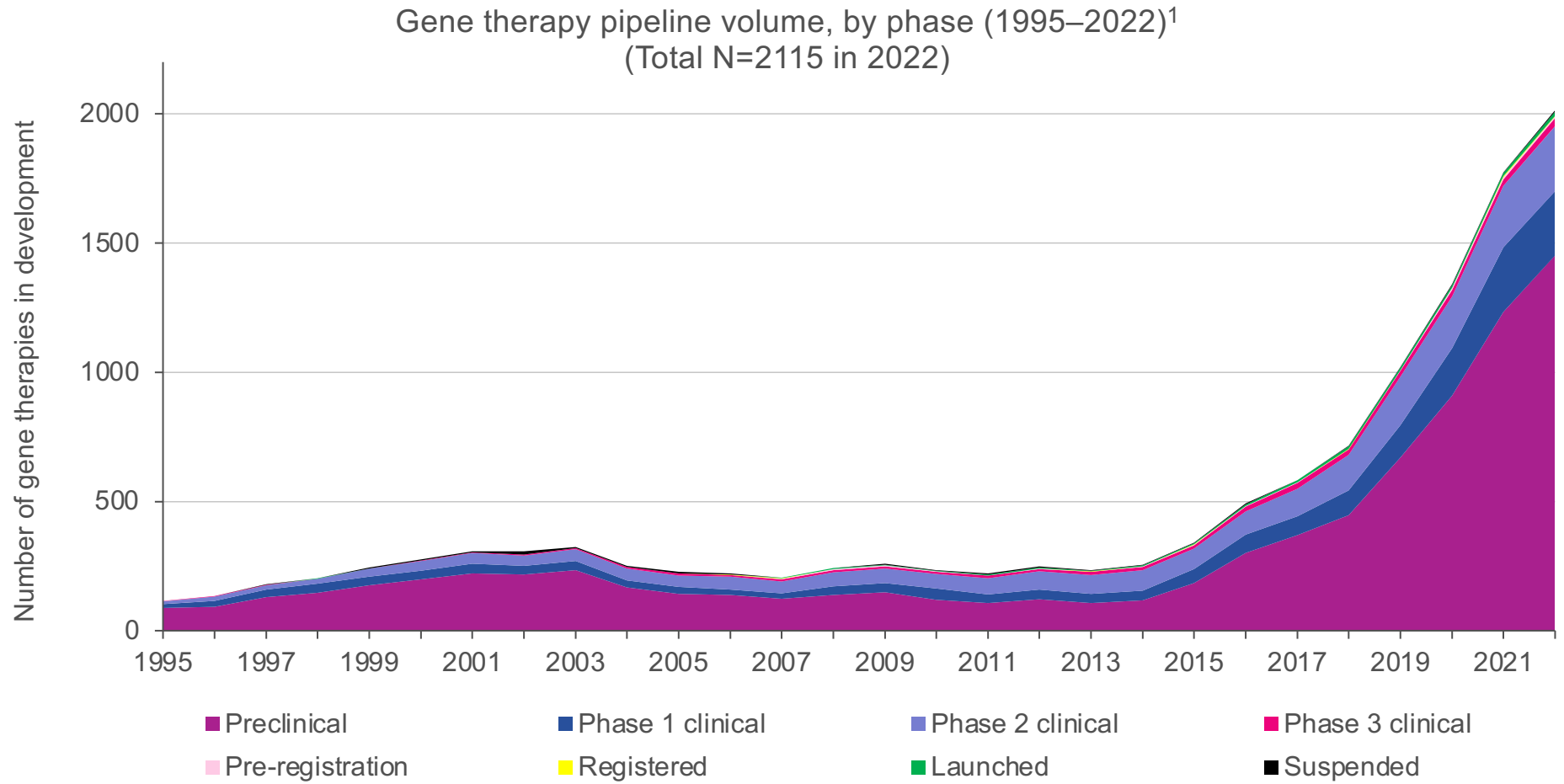

Figure derived from PharmaProjects database

1. PharmaProjects, 12 July 2022

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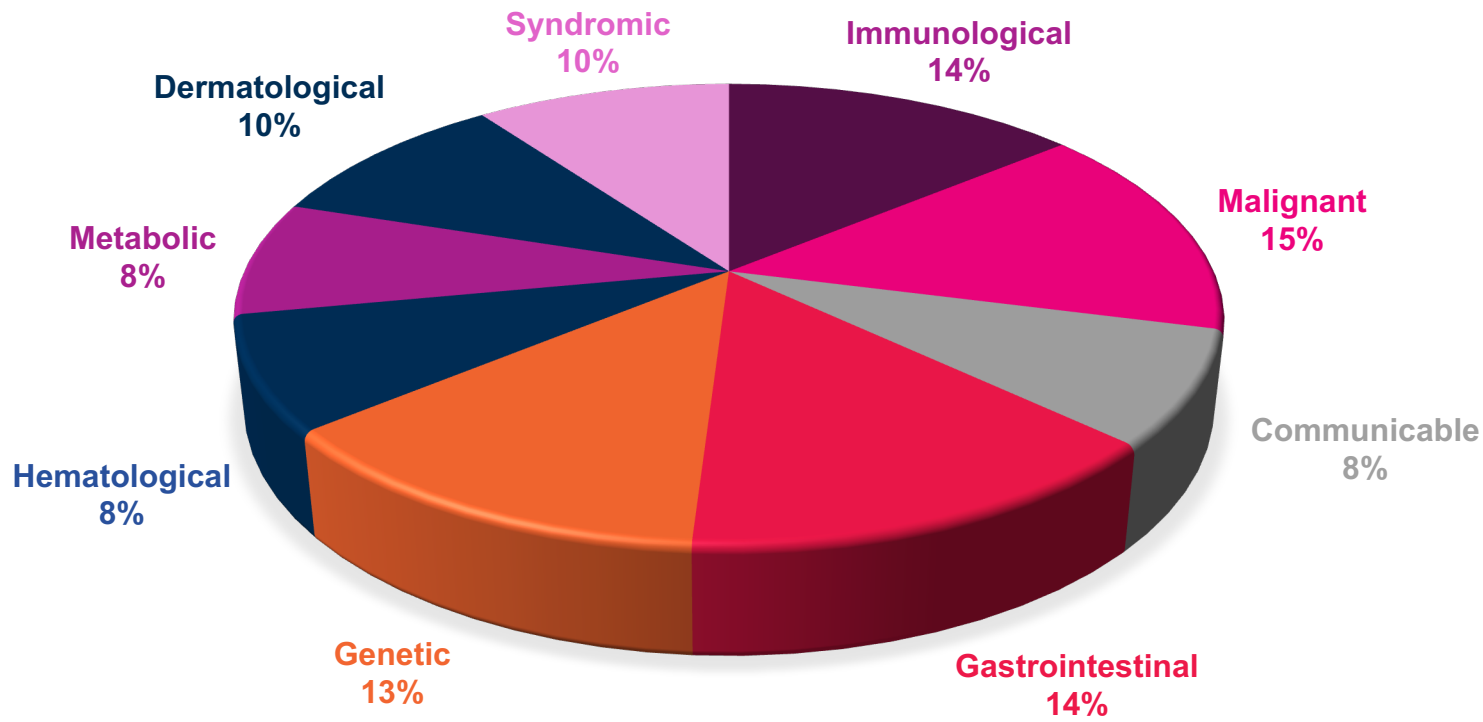
Gene therapy disease treatment landscape

Gene therapy studies, by disease category (to 2019)[1]



The future of gene therapy: As of 2022, 5363 clinical trials in gene therapy from 58 different countries are listed in the US Government's clinical trial database[2]

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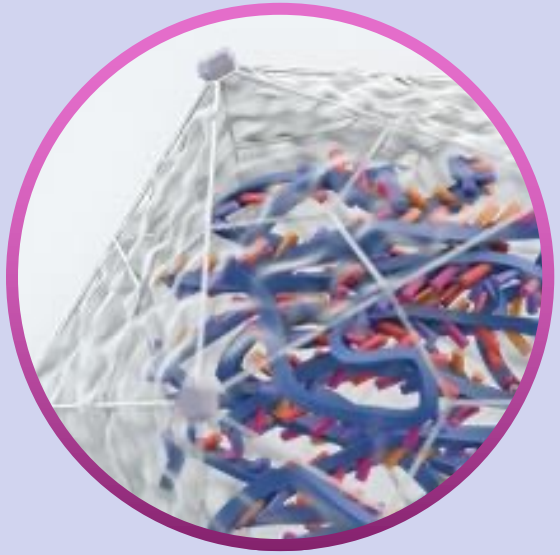
1. Goswami R et al. Front Oncol 2019;9:297; 2. ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/results?cond=&term=gene+therapy&cntry=&state=&city=&dist=. Accessed August 2023)

Types of gene therapy



Gene transfer

Gene editing

Cell therapy

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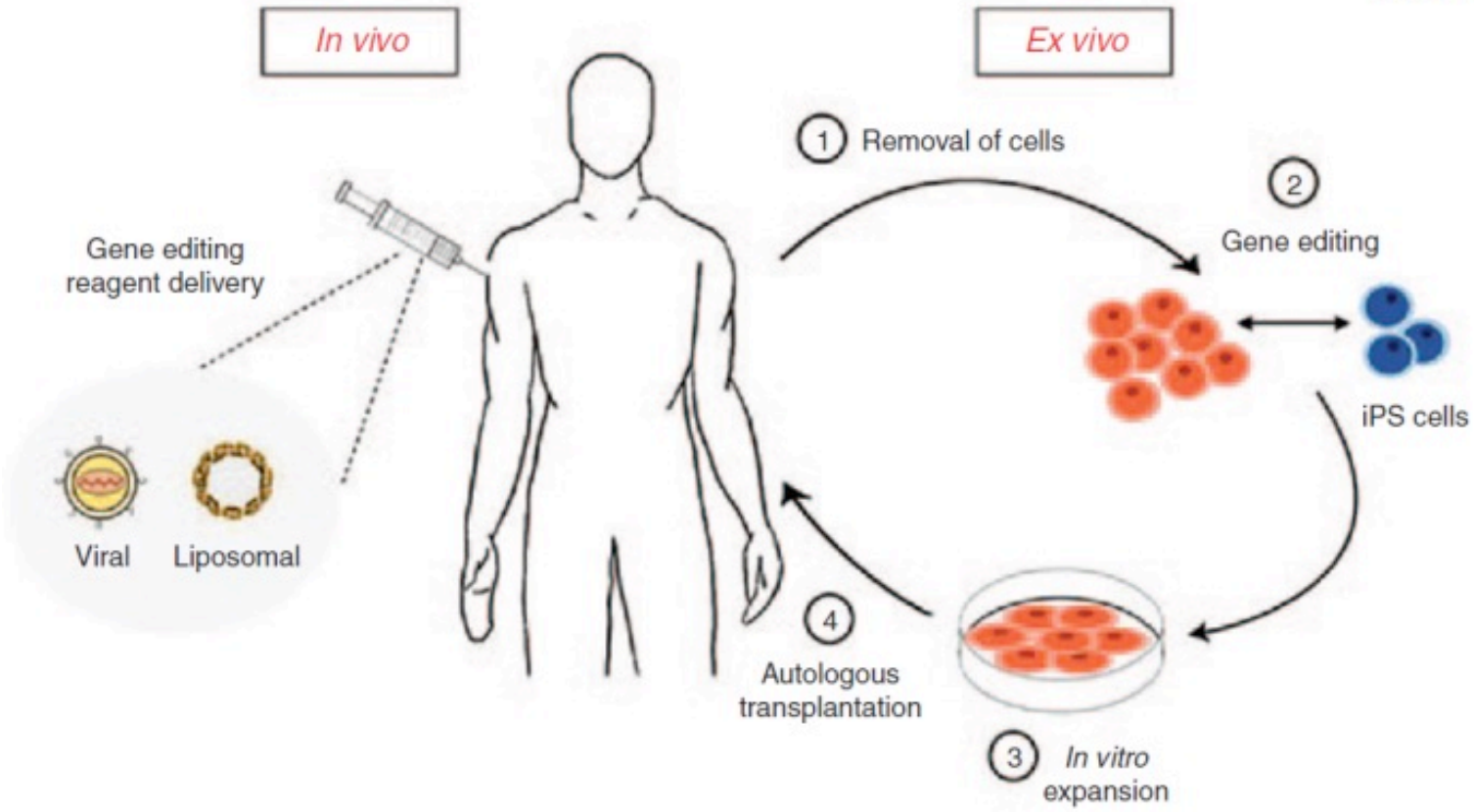
1. Pipe SW. *Pediatr Blood Cancer* 2018;65:e26865; 2. Cornu TI *et al. Nat Med* 2017;23:415–23

Gene Editing

Gene editing



Gene editing is a gene therapy approach that relies on designer nucleases to recognize and cut specific DNA sequences, and subsequently exploits innate cellular DNA repair pathways.

Prakash1et al. Molecular Therapy 2016, 24(3): 465-474.

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Cell Therapy

Cell therapy

Cell therapies, the so-called living drugs, can harness similar genetic engineering techniques to enhance or modify their natural capabilities.

Currently, such reprogramming is commonly applied to white blood cells or hematopoietic stem cells, creating powerful therapeutic strategies in oncology and immunology settings.

The most prevalent example of genetically engineered cell therapies is chimeric antigen receptor T cells (CAR-Ts).

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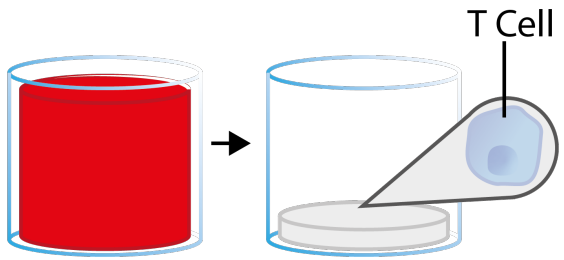
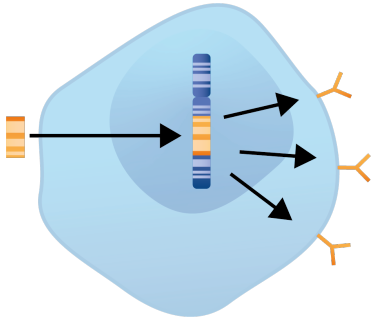
1. Chancellor et al. Molecular Therapy 2023 31(12): 3376-3338.

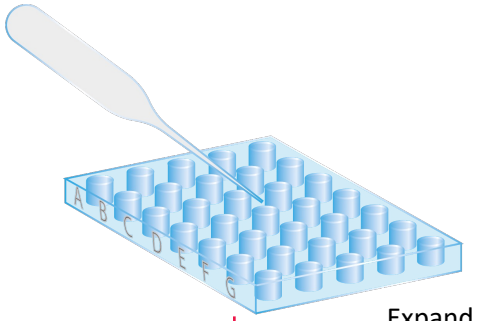
CAR-T Therapy Procedure



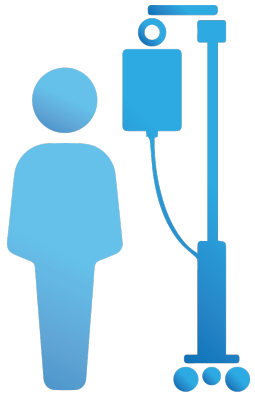
Isolate T cells from patient's blood



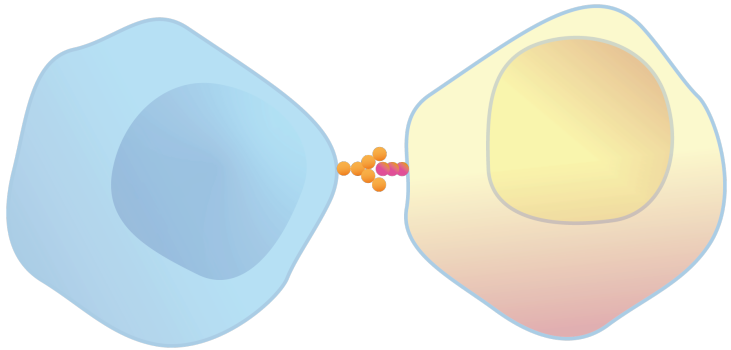
Perform *ex vivo* gene transfer to deliver CAR gene to T cells



Expand CAR-expressing T cells in culture



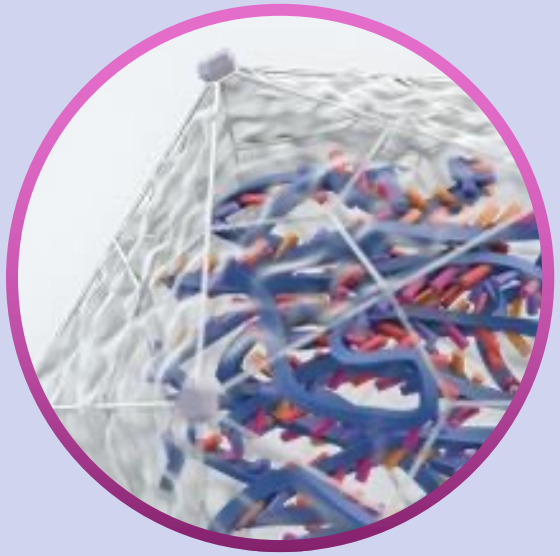
Deliver CAR T cells to the patient



CAR T cells recognise and attack cancer cells

CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T-cell.

Gene Transfer



Gene transfer

- Delivery of new genetic material (DNA or RNA) into a target cell.
  - Supplements those cells with a functional copy of the defective gene, allowing for endogenous protein production.
- New genetic material is delivered via vehicles, called vectors, to circumvent the barriers created by extracellular and intracellular elements.
- Potentially beneficial for genetic conditions with a single mutation that can lead to abnormal protein production.
  - Examples: hemophilia, Huntington's disease, spinal muscular atrophy

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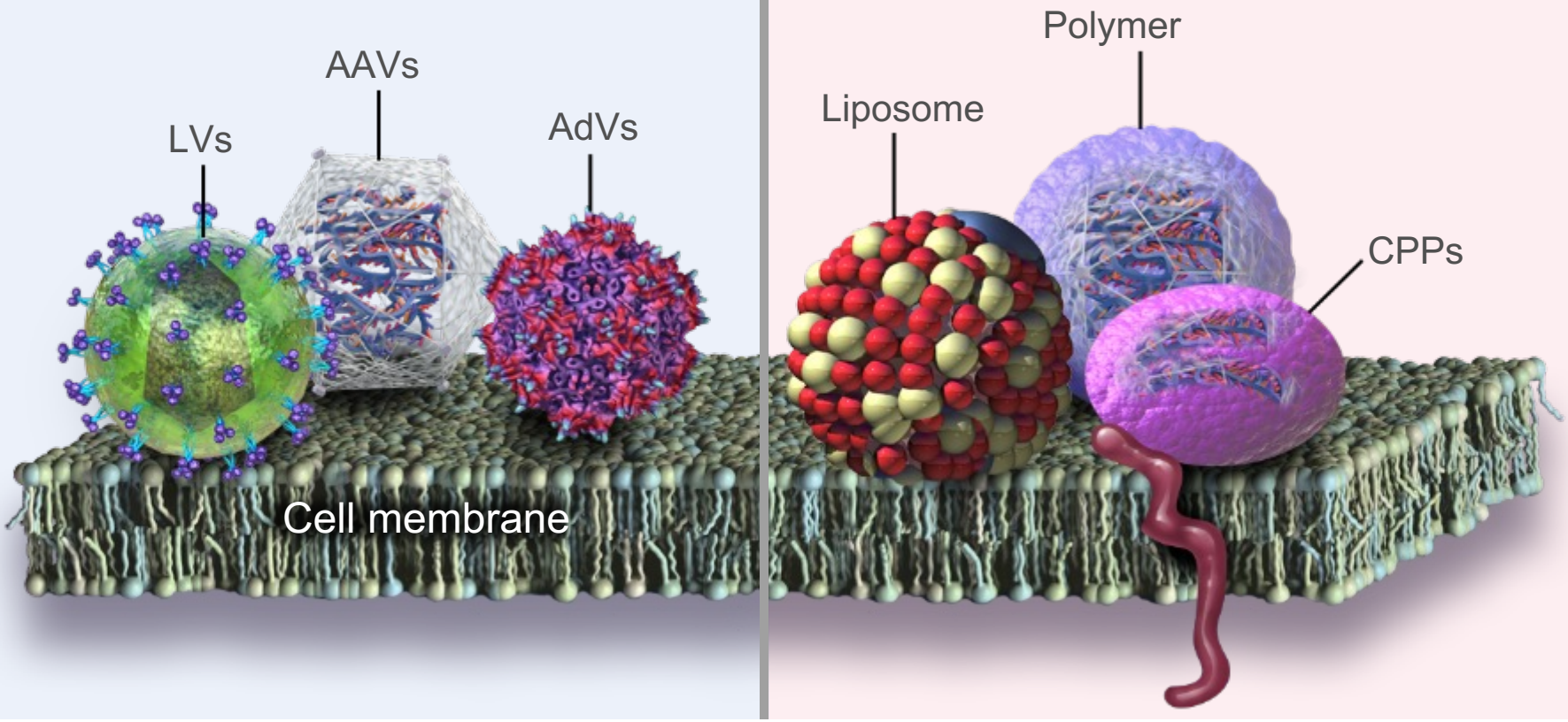
1. Pipe SW. *Pediatr Blood Cancer* 2018;65:e26865; 2. Cornu TI *et al. Nat Med* 2017;23:415–23

Viral and non-viral vectors for gene delivery

Viral vectors:
AAVs, AdVs and LVs, etc

Non-viral vectors:
polymers, liposomes and CPPs, etc



AAV, adeno-associated virus; AdV, adenovirus; CPP, cell-penetrating peptides; LV, lentivirus
Wang L *et al. Int J Mol Sci* 2016;17:626

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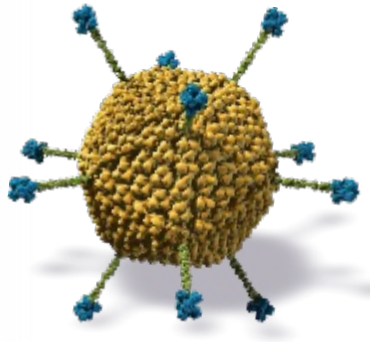
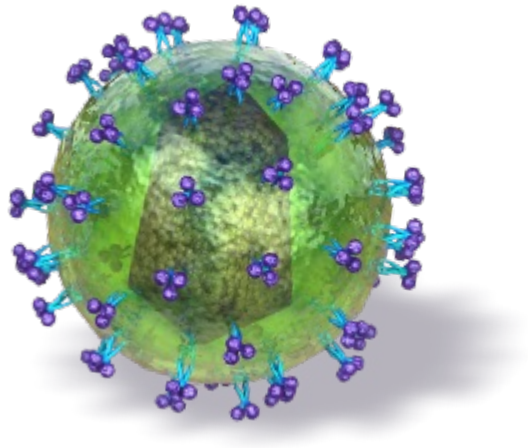
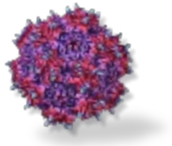
Gene transfer using viral vectors

Optimal characteristics of viral vectors

- Replication defective
- Minimal immunogenicity
- Low pre-existing immunity
- Tissue-specific tropism
- Efficient cellular transduction
- Non-integrating or targeted genomic integration







Viruses offer evolutionary advantages that can be harnessed for gene delivery

1. Yin H *et al. Nat Rev Genet* 2014;15:541–55; 2. Hardee CL *et al. Genes (Basel)* 2017;8:65; 3. Dunbar CE *et al. Science* 2018;359:eaan4672;
4. Nayerossadat N *et al. Adv Biomed Res* 2012;1:27

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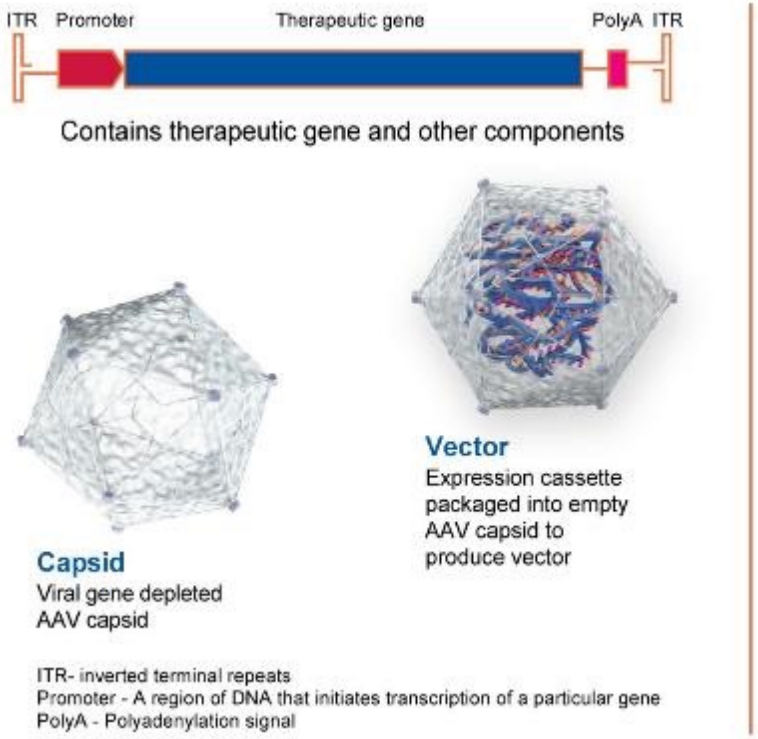
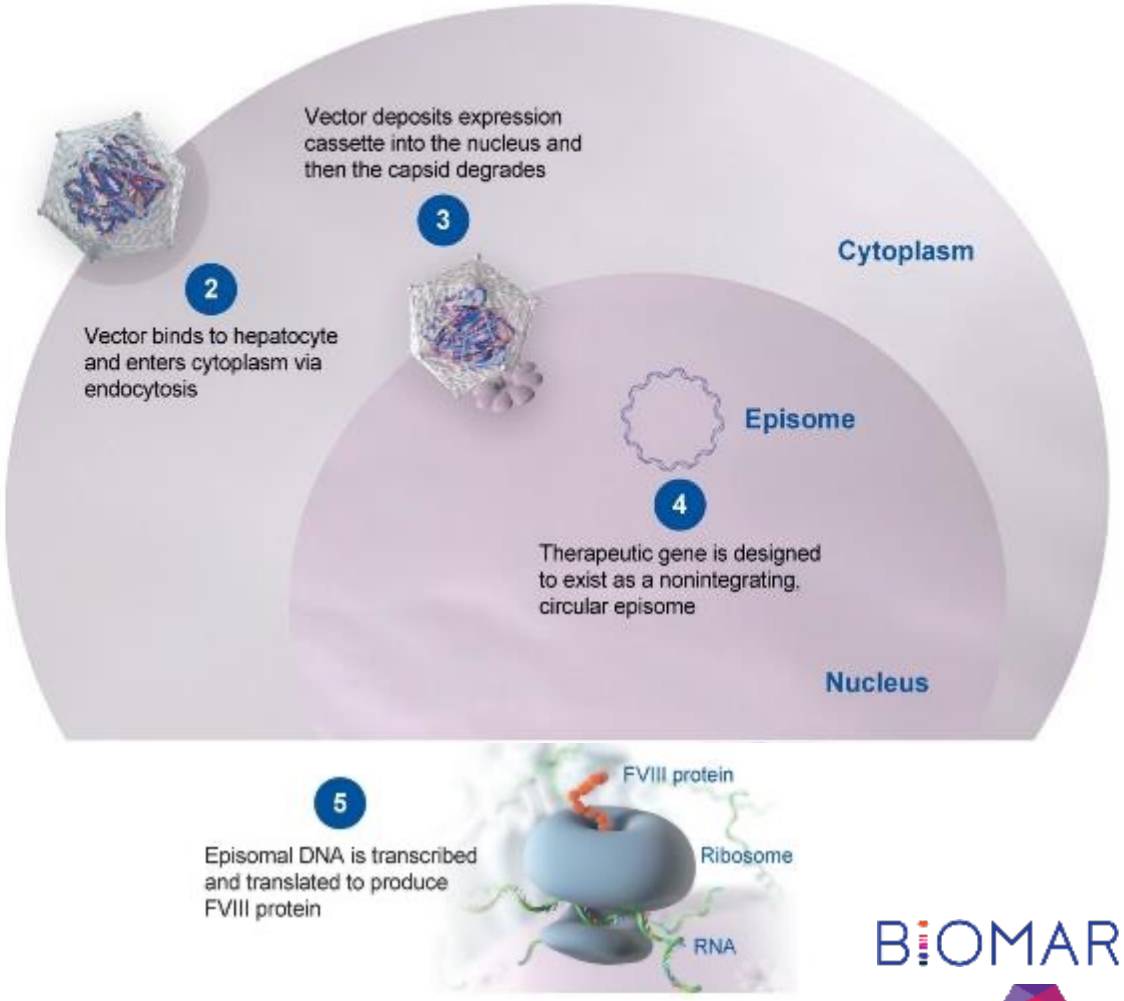
AAV-mediated gene transfer mechanism of action





ITR, inverted terminal repeat

1. Coura RdS *et al. Genet Mol Biol* 2008;31:1–11; 2. Sen D *et al. Sci Rep* 2013;3:1832

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Learn more about **canine studies** on durability, safety and vector integration

AAV-mediated integration events into the host genome

- Majority of rAAV DNA persists in human cells as extrachromosomal episomes[1]
- AAV-mediated integration events occur; the associated risks are not established[1]
- Integration rate is thought to vary by transgene, serotype and many other factors[2]
- As of 2016, over 130 rAAV-based clinical trials have been conducted with no reported cases of rAAV-mediated genotoxicity[3]

Future research and long-term follow-up studies are ongoing to determine the clinical outcomes of integration

AAV, adeno-associated virus; AAV-cFVIII; adeno-associated virus canine factor VIII; rAAV, recombinant adeno-associated virus

1. Wang D *et al. Nat Rev Drug Discov* 2019;18:358–78; 2. Cole J, Skopek TR. *Mutat Res* 1994;304:33–105; 3. Gil Farina I *et al. Mol Ther* 2016;24:1100–5; 4. Nguyen GN *et al. Blood* 2019;134(Suppl.1):611; 5.Batty P *et al. Res Pract Thromb Haemost* 2020;4(Suppl.1).

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Thank You

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Polling Question

- Have you ever met with your state or federal legislator?
- Do you plan to take part in legislative visits during rare disease week (February 25-28)?
- Where will these visits take place?
  - Capitol Hill, Washington, DC
  - District offices
  - State Capitol

FEDERAL ADVOCACY

Sloan Salzburg

Vice President
Council for Affordable Health Coverage
Campaign for Transformative Therapies

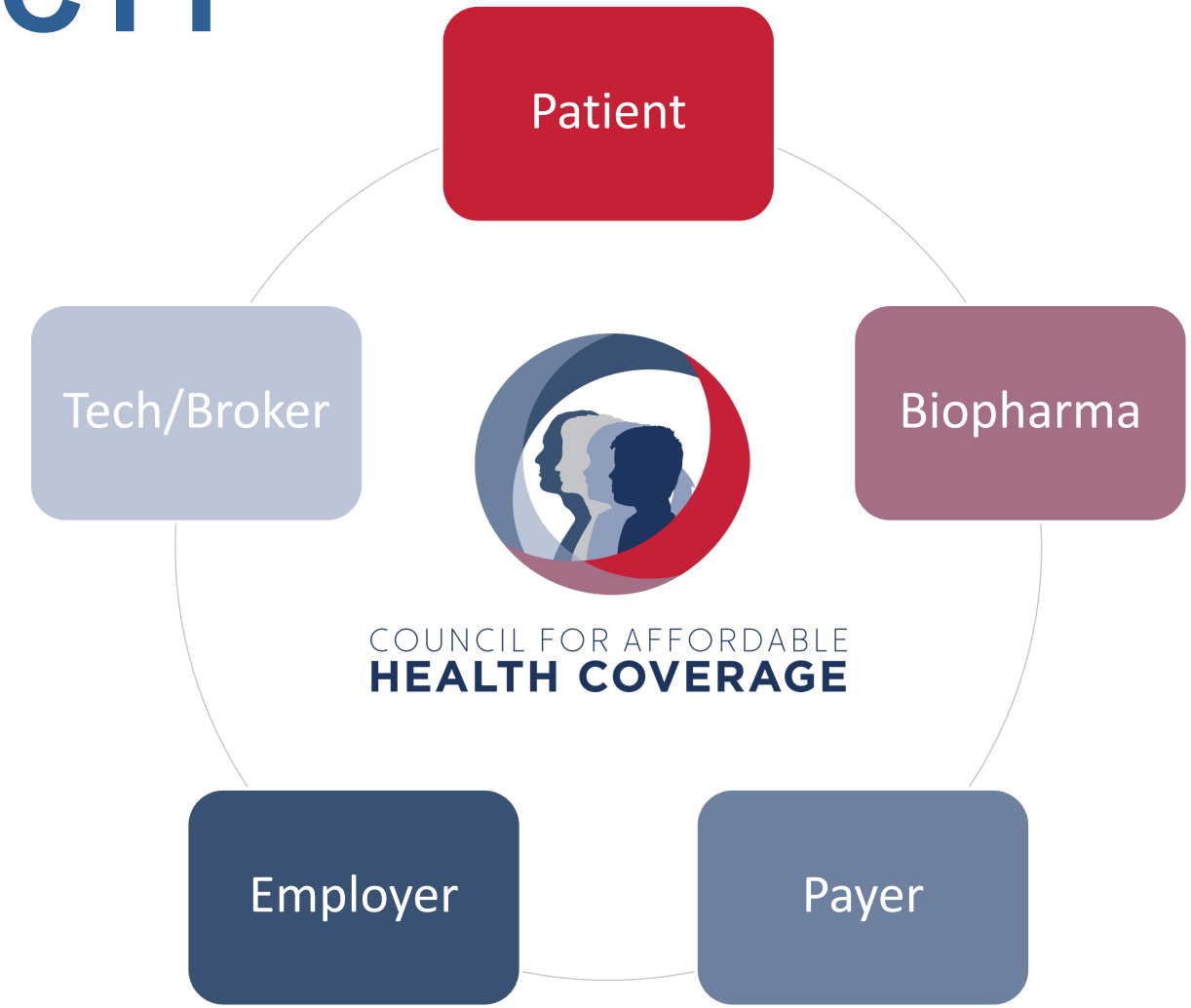
A CAMPAIGN FOR

Transformative Therapies

About CAHC and CTT

- The Council for Affordable Health Coverage (CAHC) members believe that the cost of health coverage is too high and growing too fast. CAHC promotes policies that lower health costs through increased competition, informed consumers, and more choices to help promote access to affordable coverage.

- CAHC launched the Campaign for Transformative Therapies (CTT) to unite payers, manufacturers, and patients around policies that improve access to and lowers the cost of gene therapies.



Value-Based Payment Arrangements 101

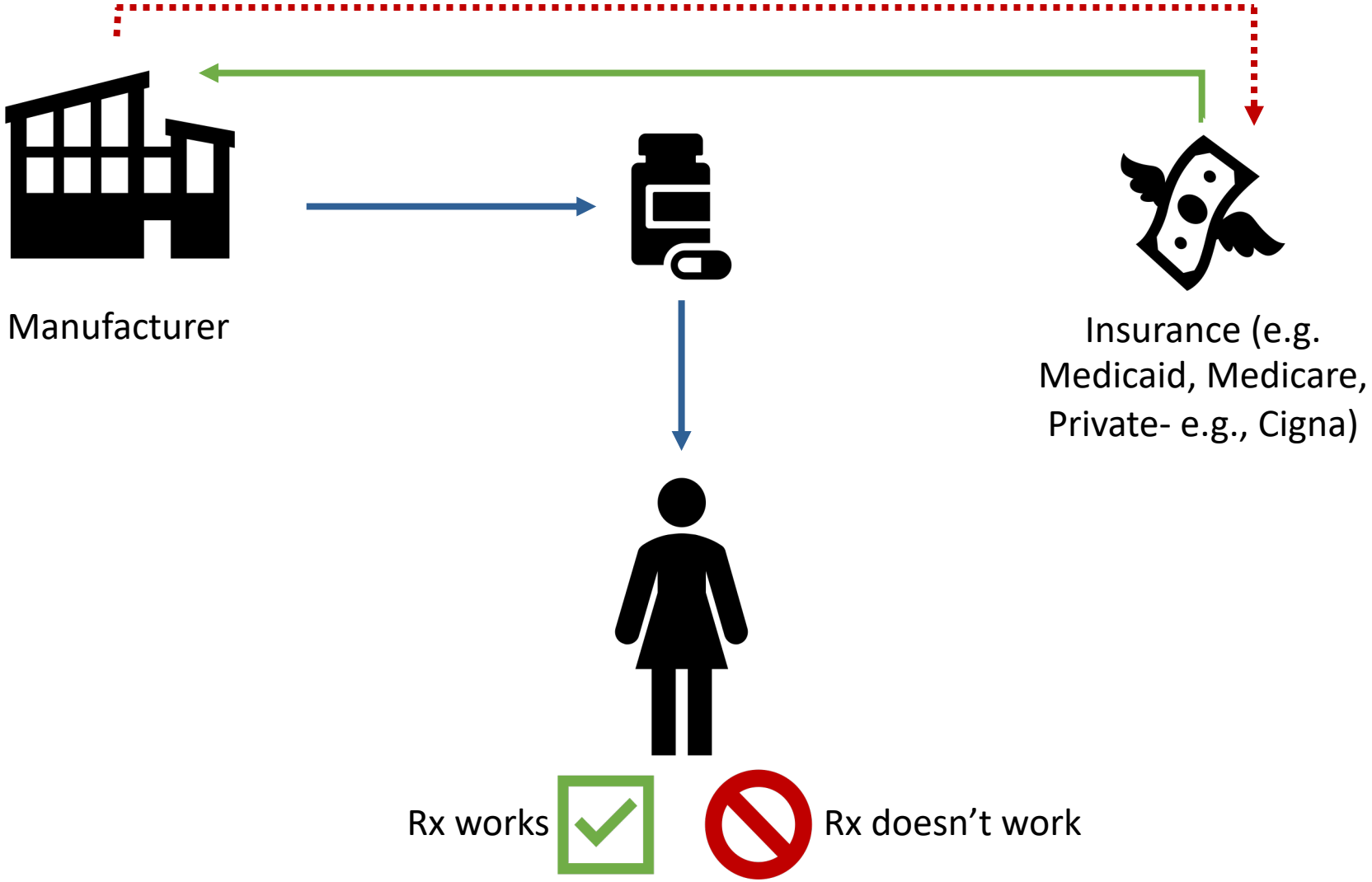
- VBPs tie reimbursement to outcomes (i.e., did the drug do what it was supposed to?)
- VBPs can base outcomes on: clinical circumstances, patient outcomes, or other measures
- The reimbursement structure can vary:
  - Rebates/refunds, paying directly for a service, etc.

Also Known As (AKA):

- Outcomes-based
- Pay-for-performance
- Innovative payment arrangements
- Alternative payment arrangements

Contract: Clear definition of terms and setting goals for patient populations → Reporting: Establish how the data will be collected → Data Analysis: Calculations based on reported data to provide accurate reimbursement → Payment: Reimbursement based on outcomes

The Basics: How VBPs Work



Improving Access and Reducing Costs

VBPs reduce wasteful spending by targeting the right drug to the right patient and refocusing spending on drugs that actually work

VBPs increase patient access by mitigating risk and costs borne by payers

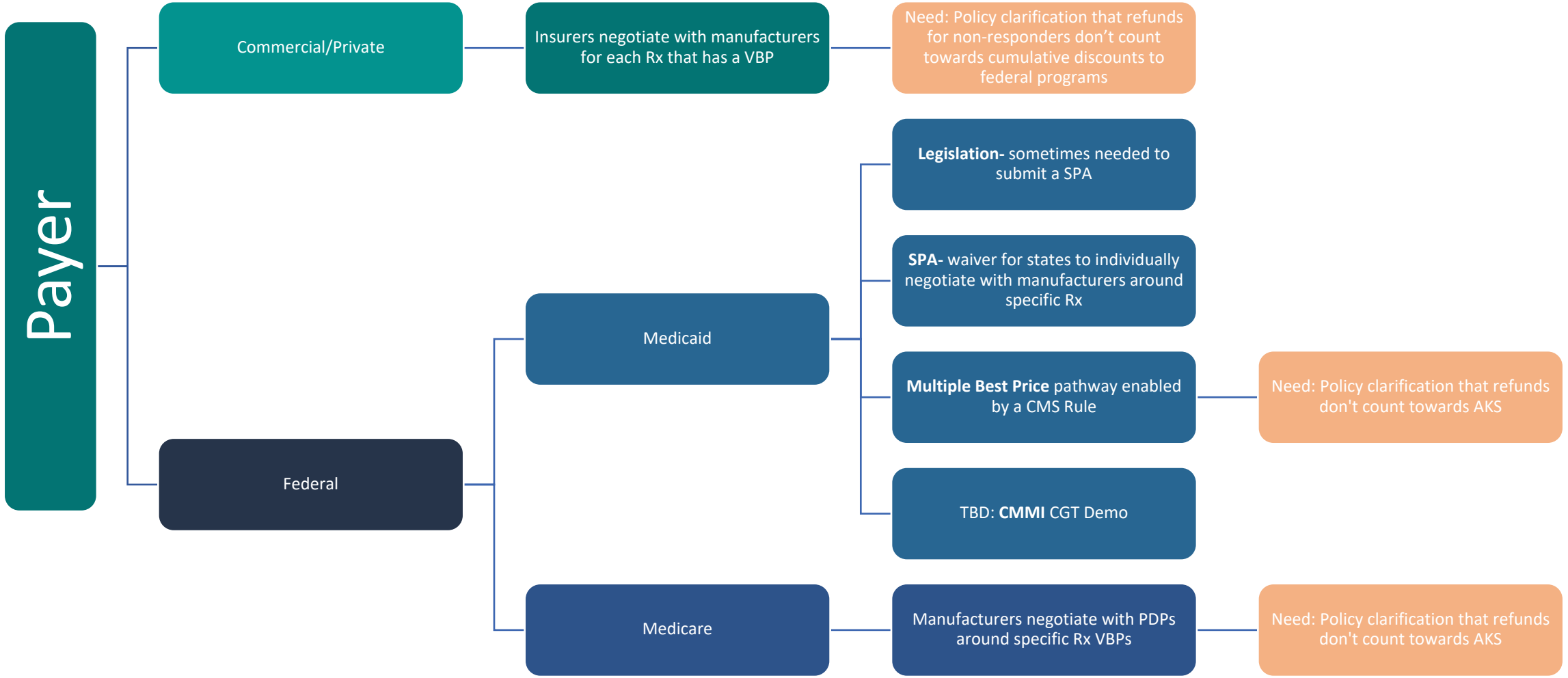
Value-Based Payments have challenges

- Administration
  - Each VBP requires a separate agreement
  - Medicaid staff needs to administer
- Objective Outcome Measurement
  - Set of patient measures need to be agreed to
  - Data availability can be an issue
- Third Party Evaluation – Requires agreement and trust
- Operational – MCO & Medical Providers
- Federal ambiguity over best price
  - *The Anti-Kickback Statute & Stark*: Under current statute, some "pay for results" discounts negotiated under a value-based contract might be construed as an unlawful inducement to use a manufacturer's drug.

… And Opportunity

- Access
  - Contracts broaden access to patients
- Risk sharing
  - Insurer receives rebates when the treatment is not as effective as promised
  - Rebates often apply on a per patient basis
- Cost Management
  - Many agreements provide more effective financing arrangements
  - Only paying when it works as promised
- Outcome and Data Analytics
  - Insurers tracks the effectiveness of the treatment ensuring effectiveness over time

VBPs: A SUSTAINABLE FINANCING MODEL FOR TRANSFORMATIVE THERAPIES



Federal Activity Update

MVP Act- H.R. 2666

Supplements a CMS Rule to facilitate VBPs to public and private payers by adding clarifications

CMMI Demo- CGT Access Model

2025- Medicaid-focused model that would establish a centralized process to facilitate VBPs for sickle cell disease gene therapies

H.R. 2666 MVP Act

Medicaid VBPs for Patients (MVP) Act

Sponsors: Reps. Guthrie (R-KS) and Eshoo (D-CA)

Summary

1. Codifies Multiple Best Price & VBP Definition
2. Clarifies that discounts from VBPs (when Rx doesn't work) don't count towards average pricing rules set in statute (ASP, AMP)
3. Adds VBP discounts as a safe harbor from AKS
4. GAO study/report on VBPs effectiveness

Questions?

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Campaign for Transformative Therapies
cahc.net | @C4AHC

STATE ADVOCACY

Kari Lato
Sr. Director, Policy & Advocacy
Rx4good

Several Pathways to OBA's

If a state wants to contract with a drug manufacturer using an outcomes-based (OBA) or value-based arrangement (VBA) in their Medicaid program, they have several different pathways to accommodate that type of contract.

State Plan Amendment

The "preferred" route based on feedback from states – does not require legislation unless state statute stipulates the need for legislation to submit/ operationalize a SPA.

Legislation

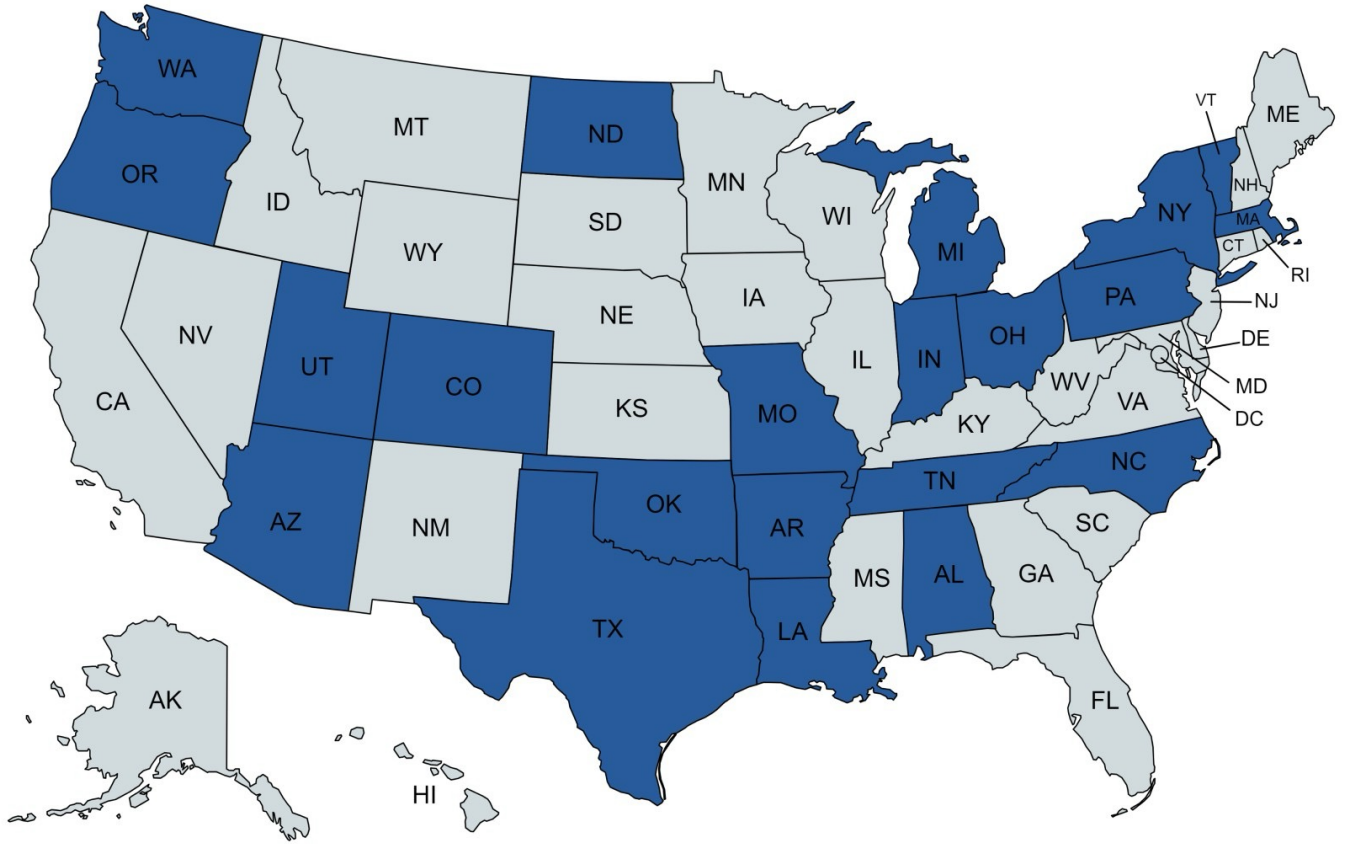
Several states have required legislation to authorize the use of OBA's in their Medicaid programs [NY, TX, MN, OH]. This is required at times for many different reasons: statutory impediments to this type of contract, requirements of SPA submission or sentiment of Medicaid (not required but Medicaid felt like they need legislative approval [NY and TX]).

Multiple Best Price Rule

Centers for Medicare and Medicaid Services (CMS) announced a rule to allow states/manufacturers to work together through a reporting system that allows manufacturers to submit multiple best prices – states have not utilized this avenue so far (they feel it is complex and lacks details to operationalize effectively).

State Plan Amendments

21 states have State Plan Amendments (SPA) authorizing them to enter into OBA's with manufacturers for Medicaid drugs



- Wisconsin OBA legislation being transmitted to the Governor's desk – passed out of the legislature at the end of January.
- Minnesota passed OBA legislation last year as part of their health omnibus legislation – awaiting state plan amendment submission.

Effective Advocacy When Legislation is Introduced

- Once legislation is introduced, it is referred to committee for a hearing.
- Testify in person or submit written comments in favor of the legislation.
- Meet with decision-makers to share why OBAs are important to the rare disease community.
- Use social media to educate and bring awareness to the issue – make sure to tag legislators and include relevant hashtags.

Rare Disease Week (Feb 25-28) and Rare Disease Day (Feb 29)

- Meet with your state legislator or your federal legislator in their district offices or Capitol.

- Share why OBAs are needed for innovative therapies. Leave the OBA fact sheet.

- Follow-up with an email or phone call.
- Take pictures of your visit, post on social media and tag your legislator.

WISCONSIN ADVOCATE

Katie Moureau

Rare Disease Mom

Other Ways You Can Help

Join the Coalition

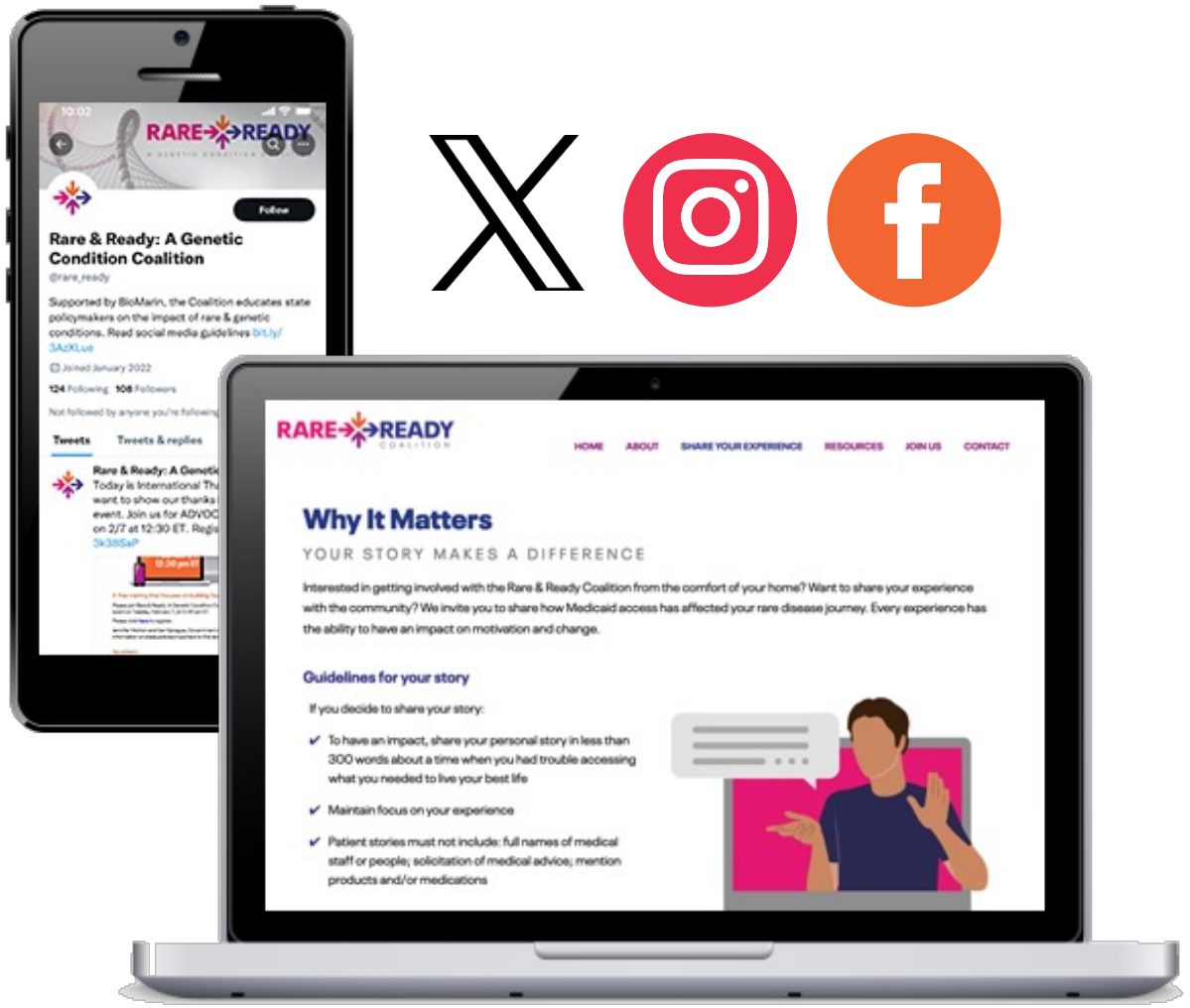
- Contact kari.lato@rx4good.com to join
- Ask others to join

Share Your Experience

- Share your story on www.rareandready.org
- Meet with decision-makers

Use Social Media

- Follow @rare_ready
- Repost on your social media channels



Evaluation Questions

- Has your understanding of the science behind gene therapy improved?
- Do you have a better understanding of federal and state policy related to outcomes-based arrangements?
- Do you feel knowledgeable enough to talk about outcomes-based arrangements to policy makers?
- After today's webinar, do you plan to talk to your federal or state legislator about outcomes-based arrangements?

THANK YOU

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