PHARMACY VISION 2020

CSHP SEMINAR 20 • OCTOBER 21-25

Disneyland RESORT

Successful Strategies in the Use of Gene Therapies in an Integrated Health System

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DISCLOSURE

The faculty/speakers declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria

LEARNING OBJECTIVES

- Understand the complexities of novel research approaches for gene therapies
- Decode evolving clinical considerations of gene therapies
- Recognize the key operational challenges and apply practical solutions in a rapidly changing landscape

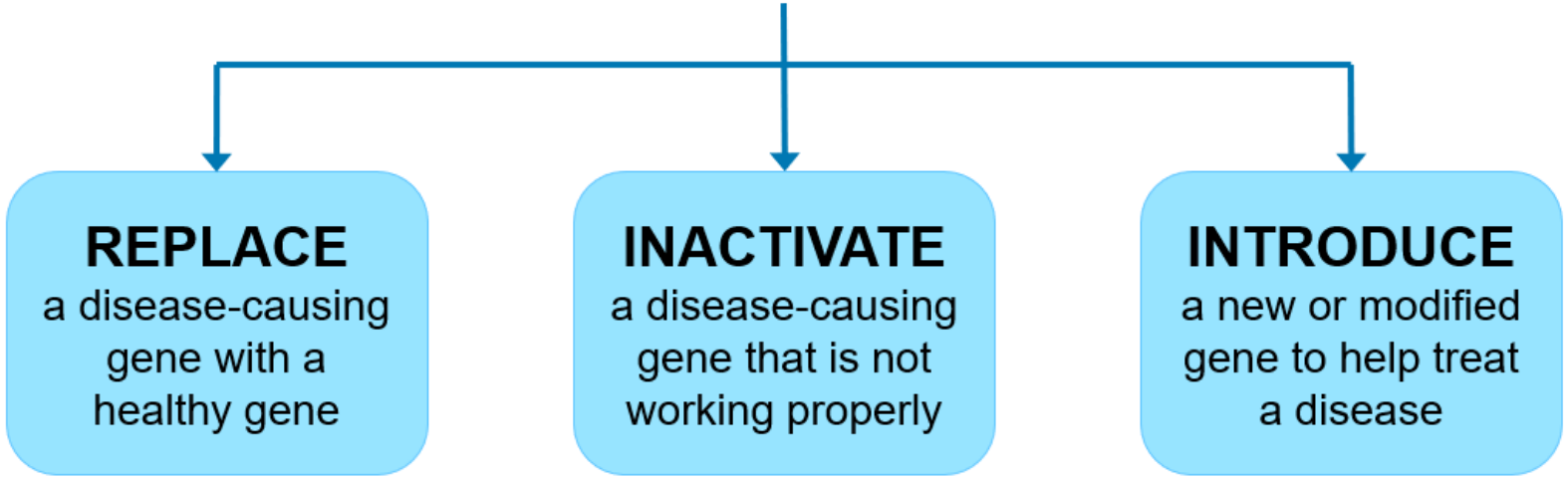
Surge in Cell & Gene Therapy Product Development

INDs = investigational new drug applications

FDA. New Policies for Cell and Gene Therapies. 2019.

FDA Definitions

Gene therapies involve the modification of genetic information in living cells to treat or cure disease via several mechanisms:



Gene therapies are biological products regulated by the FDA

Variety of gene therapy product types (i.e., viral vectors, gene editing technology)

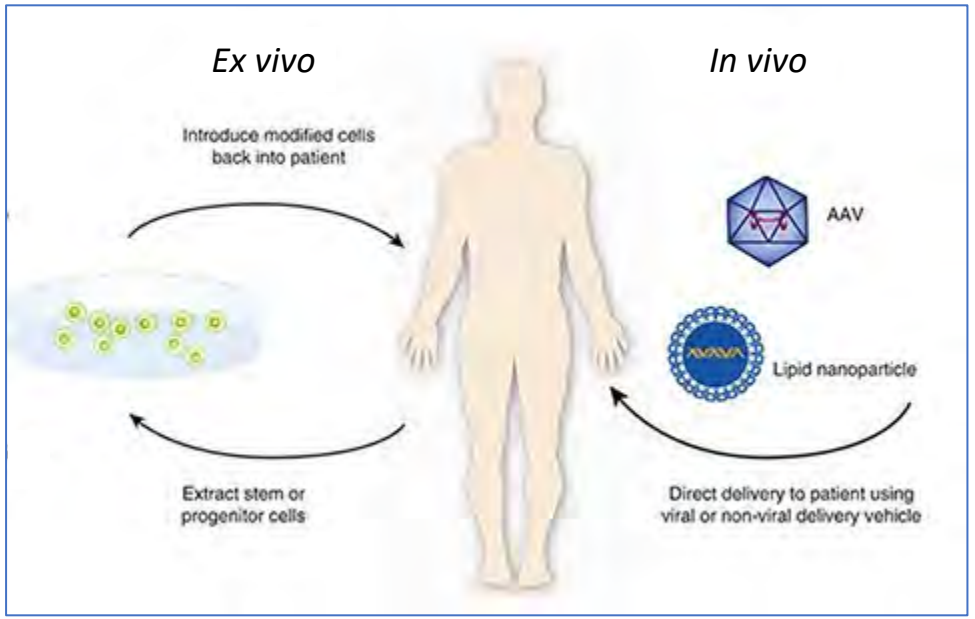
FDA. What is Gene Therapy? 2019.

Background

Gene therapy delivery can be either *in vivo* or *ex vivo*:

Ex vivo (cell-based gene therapy): gene modifications are made to cells extracted from patient and then introduced back into patient

Example: Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel), chimeric antigen receptor T-cell (CAR-T) therapies

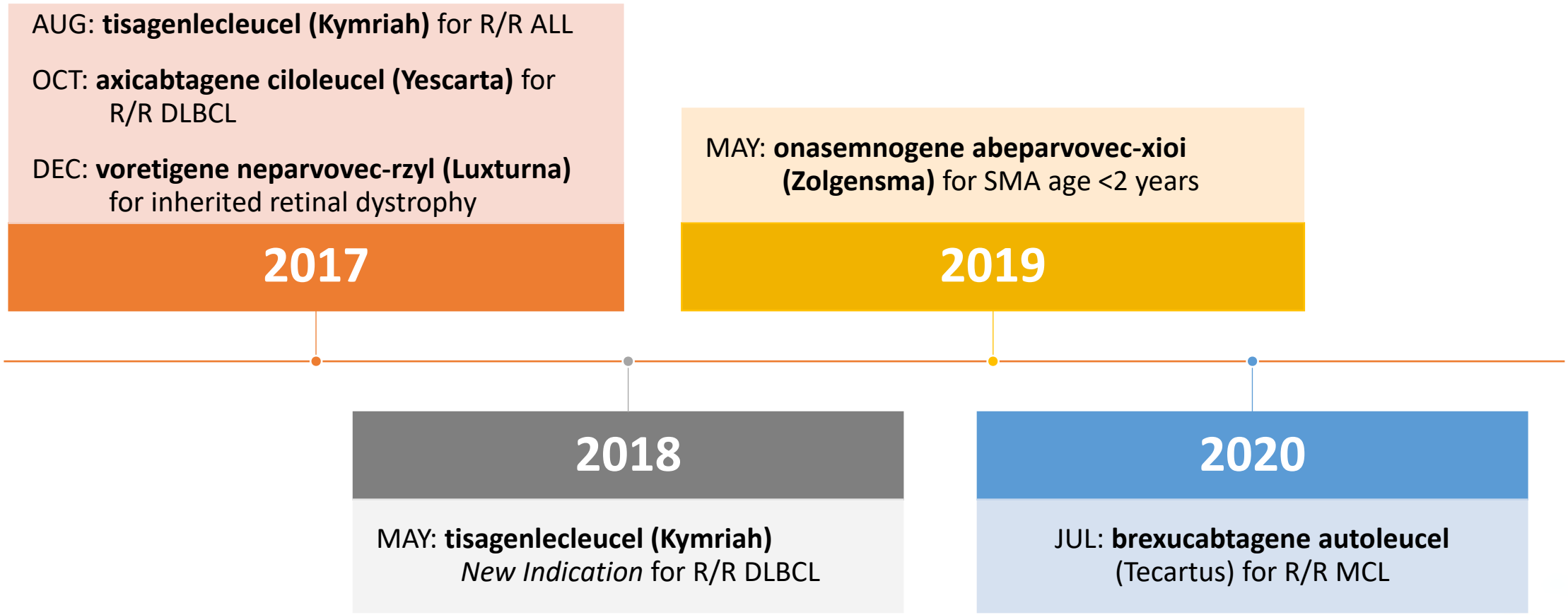


In vivo (gene therapy): gene modifications are delivered directly to cells inside patient

Example: Luxturna (voretigene neparvovec-rzyl), an adeno-associated viral (AAV) vector-based gene therapy

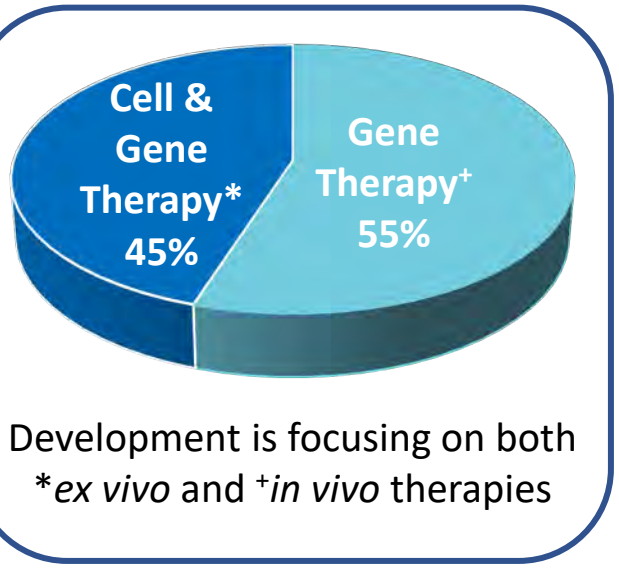
FDA. What is Gene Therapy? 2019.

Gene Therapy: Recent FDA Approvals



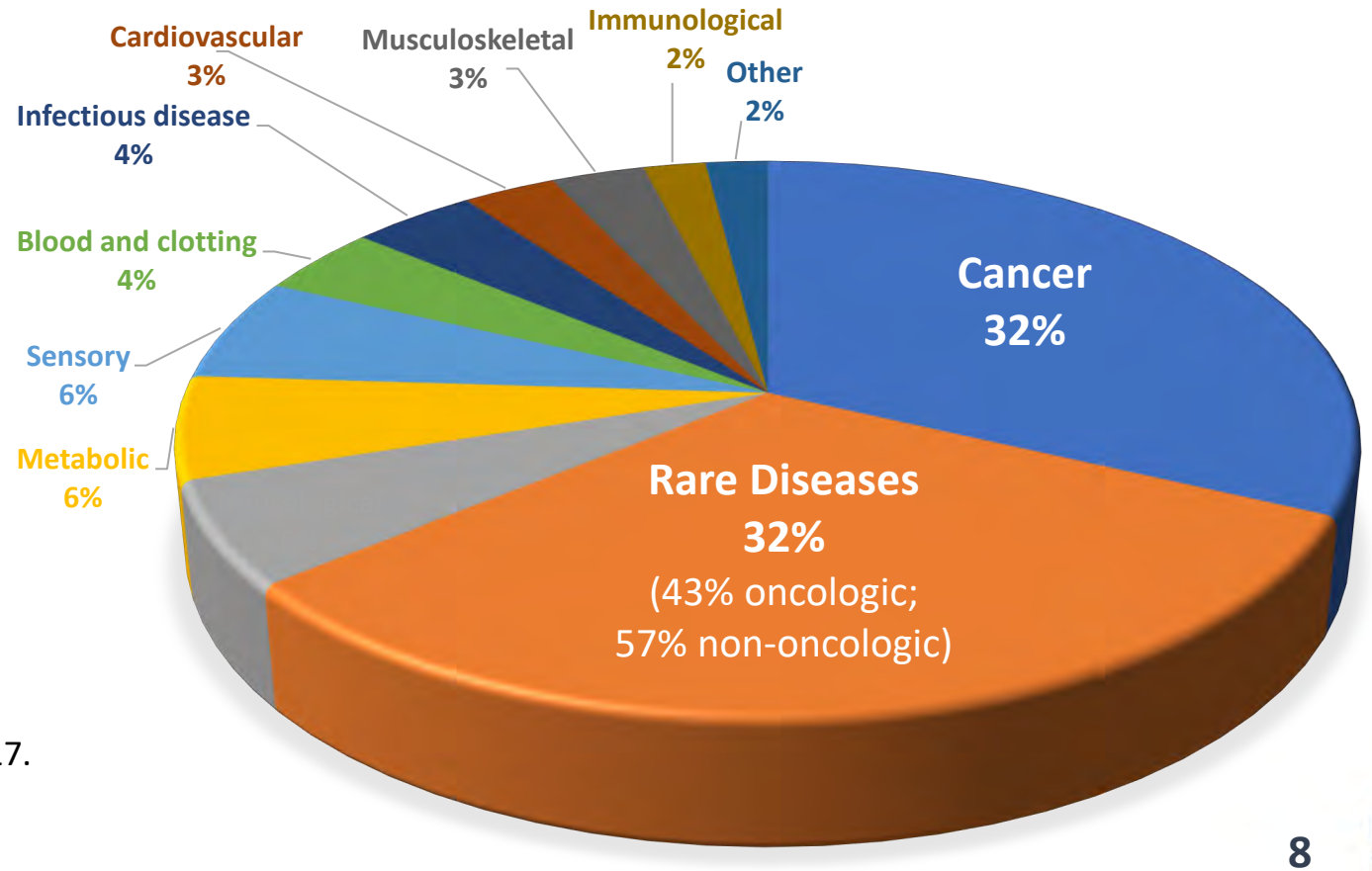
KEY: ALL = Pediatric and young adult relapsed or refractory acute lymphoblastic leukemia; DLBCL = Adult relapsed or refractory diffuse large B-cell lymphoma; R/R MCL = relapsed or refractory mantle cell lymphoma; R/R MCL = relapsed or refractory mantle cell lymphoma; SMA = spinal muscular atrophy with bi-allelic mutations in SMN1 gene

Gene Therapy Pipeline



Development is focusing on both **ex vivo* and *+in vivo* therapies

Therapy Areas Dominated by Cancer and Rare Diseases



Datamonitor Healthcare. Gene Therapy Pipeline. 2017.
Pharma Intelligence. Gene Therapy. 2018.

Late-Stage Gene Therapy Pipeline

Product	Indication	FDA status
valoctocogene roxaparvovec	hemophilia A	BLA filed (CRL Aug 2020)
lisocabtagene maraleucel	Non-Hodgkin's lymphoma	BLA filed / PDUFA Nov 2020
nadofaragene firadenovec (Instiladrin)	bladder cancer, mesothelioma	BLA filed (CRL May 2020)
idecabtagene vicleucel (bb2121)	refractory multiple myeloma	BLA filed / PDUFA 2021
eladocagene exuparvovec (GT-AADC)	AADC deficiency	Phase 2 / BLA 2H-2020
betibeglogene autotemcel (LentiGlobin)	transfusion-dependent beta-thalassemia sickle cell anemia	Rolling BLA mid-2021 Phase 3 / BLA 2H-2021
elivaldogene autotemcel (Lenti-D)	X-linked cerebral adrenoleukodystrophy	Phase 3 / BLA mid-2021
timrepigene emparvovec (BIIB111)	choroideremia	Phase 3
etranacogene dezaparvovec (AMT-061)	hemophilia B	Phase 3 / BLA 2021
fidanacogene elaparvovec (SPK 9001)	hemophilia B	Phase 3 / BLA 2021
SPK 8011	hemophilia A	Phase 3
giroctocogene fitelparvovec (SB-525)	hemophilia A	Phase 3

AADC = aromatic L-amino acid decarboxylase, BLA = biologics license application, PDUFA = prescription drug user fee act

Biomedtracker [subscription] 2020.

valoctocogene roxaparvovec

Overview

Other names:	Roctavian, Valrox
MOA:	FVIII gene replacement
Indication(s):	hemophilia A

FDA Details

Status:	CRL issued Aug 2020; delayed to 2022?
Designations:	Priority review Orphan drug Breakthrough therapy

- Delivery: *In vivo*
- Vector: adeno-associated virus (AAV5)
- Administration: IV infusion; outpatient setting
- Clinical trial(s):
  - Adults with severe hemophilia A without history of FVIII inhibitors
- Adverse events:
  - Transient ALT elevations, transient infusion reactions (headache, arthralgia)

NCT02576795. ClinicalTrials.gov. 2015; NCT03370913. ClinicalTrials.gov. 2017;
BioMarin Pharmaceuticals. Press Release. 28 May 2019; BioMarin Pharmaceuticals. Press Release. 17 June 2020.

Clinical Trial Summary

valoctocogene roxaparvovec

Data suggested treatment is associated with increased FVIII levels, decreased ABRs, decreased FVIII utilization, and target joint resolution

Phase 1/2, 5-year open-label study **4-Year Data for 6e13 vg/kg cohort** **n=7**	**Phase 3, 52-week open-label study** **26-week interim analysis** **n=22**
Based on n=6: • 95% reduction in mean ABR vs. baseline • 96% reduction in FVIII utilization vs. baseline Based on n=7: • 86% bleed-free through 4 years • All remain off FVIII prophylaxis	Based on n=16: • 50% reached/exceeded pre-specified FVIII levels of 40 IU/dL (mean: 36 IU/dL) • 85% reduction in mean ABR vs. baseline • 94% reduction in FVIII utilization vs. baseline

BioMarin Pharmaceuticals. Press Release. 28 May 2019.
BioMarin Pharmaceuticals. Press Release. 17 June 2020.

Durability Questions Remain

valoctocogene roxaparvovec

Data from participants receiving 6e13 vg/kg dose (n=7)

	Mean FVIII level Chromogenic Assay (median, IU/dL)	Mean FVIII level One-Stage Assay (median, IU/dL)	Mean annualized bleed rate (ABR)	Mean FVIII infusions per year	Mean % reduction in FVIII use
Year 1, n=7	64 IU/dL (60)	104 IU/dL (89)	0.9	2.1	98%
Year 2, n=7	36 IU/dL (26)	59 IU/dL (46)	0.2	8.8	94%
Year 3, n=7	33 IU/dL (20)	52 IU/dL (30)	0.7	5.5	96%
Year 4, n=6	24 IU/dL (16)	35 IU/dL (23)	1.3	4.6	97%

BioMarin Pharmaceuticals. Press Release. 28 May 2018.; BioMarin Pharmaceuticals. Press Release. 17 June 2020.; Pasi, et al. *N Engl J Med* . 2020.; BioMarin Pharmaceuticals. Press Release. 28 May 2019.

betibeglogene autotemcel

autologous CD34+ cells encoding βA-T87Q-globin gene

Overview

Other names:	LentiGlobin, Zyntelgo
MOA:	gene replacement
Indication(s):	transfusion-dependent β-thalassemia (TDT); sickle cell disease

FDA Details

Status:	Rolling BLA for TDT; Phase 3 SCD
Designations:	Orphan drug Breakthrough therapy Fast track

(EU conditional approval 2019)

- Delivery: *Ex vivo*
- Vector: lentiglobin viral vector BB305
- Administration: IV infusion; likely certified healthcare facilities
- Clinical trial(s):
  - TDT: Northstar-2 Phase 3 study
    - 89% (17/19) were transfusion independent for median f/u 19.4 months
  - SCD: Phase1/2 (n=14)
    - 99.5% mean reduction in annualized rate of VOCs and ACS

Biomedtracker [subscription] 2020; Bluebird bio Press Release. 12 June 2020; Bluebird bio Press Release. 12 June 2020.

Issues, Challenges, Concerns – Overview

- Long-term benefit may not be known
  - Post-market clinical trials needed

- Manufacturing and quality
  - Safe, reliable, and cost-effective

- Environmental risk
  - Shedding and transmission assessment studies

- Value assessment and cost
  - Benefit design
  - Financing and payment strategies

- Operational logistics for institutions
  - Procurement, storage, and handling
  - Preparation, administration, disposal
  - Case coordination for patient (labs, concomitant therapy, appointments, travel, etc.)
  - Care and monitoring post gene therapy

Clinical Considerations

Challenges

- Short-term follow-up in clinical trials
  - Unknown long-term side effects
  - Unsure of claim as a one-time dose
- Study population limitations (e.g., age)
- Differences in individual patient responses

Potential solution(s)

- Prioritize patients and/or therapies based on:
  - High unmet need
  - Lack of other alternative therapies
  - Availability of established supportive care
  - Disease has established treatment pathway
  - Indications w/ high incidence and low prevalence
- Explore clinical trial opportunities
- Utilization management tools

Value Assessment and Cost

Challenges

Many gene therapies are projected to cost $2M per patient!

- One-time treatment purported to provide long-term benefits and cost-savings
  - Budget impact in the short-term
  - Potential cost-savings vs increases over the long-term
  - Opportunity to treat many rare diseases with gene therapy may lead to unsustainable long-term costs
  - Additional non-drug costs need to be considered (e.g., hospitalizations, follow-up care, concomitant treatments, surgeries and procedures)
- Need a financial model for different settings (outpatient, inpatient and clinic)

Value Assessment and Cost

Potential solution(s) Consider novel approached to manage financial risks

Annuity	Payments are spread out and made over a defined period of time, from months to years
Consumer mortgage	A loan taken out directly by the patient
Direct payment/distribution	Payer purchases the gene therapy directly from the manufacturer
Discounts/revenue caps	Therapy price is reduced by a percentage if total revenue exceeds a certain target
Expanded risk pools	Dedicated fund where several stakeholders allocate a proportion of their premiums or budget toward an expanded group of patients who are eligible for gene therapy
Patient assistance/subsidy	Financial aid for patients for their expenses related to gene therapy
Pay for performance/outcomes	Innovator companies are paid for their gene therapies based on mutually agreed upon timed measures and achievements of clinical performance or outcomes in the real world
Re-insurance	Catastrophic insurance coverage purchased for gene therapy
Supplier credit	Purchased by a third-party financial entity that negotiates payment with payer

Pharma Intelligence. Gene Therapy. 2018.

Operational Logistics for Institutions

Challenges

- **Pharmacy operations**
  - Procurement
  - Storage, and biosafety/handling
  - Preparation, administration, disposal
  - Chain of control of the drug
- **Budget allocations**
- **Determining Center(s) of Excellence**
- **Healthcare settings**
  - Private room for gene therapy administration
  - Possible hospital admission
  - Training
- **Case coordination for patient**
  - Labs, concomitant therapy, appointments, travel, etc.
- **Post-gene therapy care and monitoring**

Potential solution(s)

- Develop Gene Therapy Taskforce with key stakeholders
- Develop Gene Therapy Program Management

Approaches to Benefit Design

Challenges

- Market Dynamics
  - Patient movement from one health plan to another
  - Adverse selection
- Existing benefit design may not align with gene therapy products

Potential solution(s)

- Design benefits for gene therapy
  - Co-pay/co-share
  - Deductibles
  - Mobility payments for when patients move to other health plan
  - Patient-plan contract to mitigate movement to other health plan
  - Pooled risk insurance program
- Use Medical Financial Assistance Program
- Use Manufacturer's Patient Assistance Program

Gene Therapy Ethics

Challenges

- Societal questions
  - Declining gene therapy based on religious grounds (playing God)
  - Will the high costs of gene therapy make it available only to the wealthy?
  - Could the widespread use of gene therapy make society less accepting of people who are different?
  - Should gene therapy be used to enhance basic human traits?
  - Allocation of treatment based on available evidence vs. FDA-approved indications

Potential solution(s)

- Involve medical ethicist

Legal and Regulatory Issues

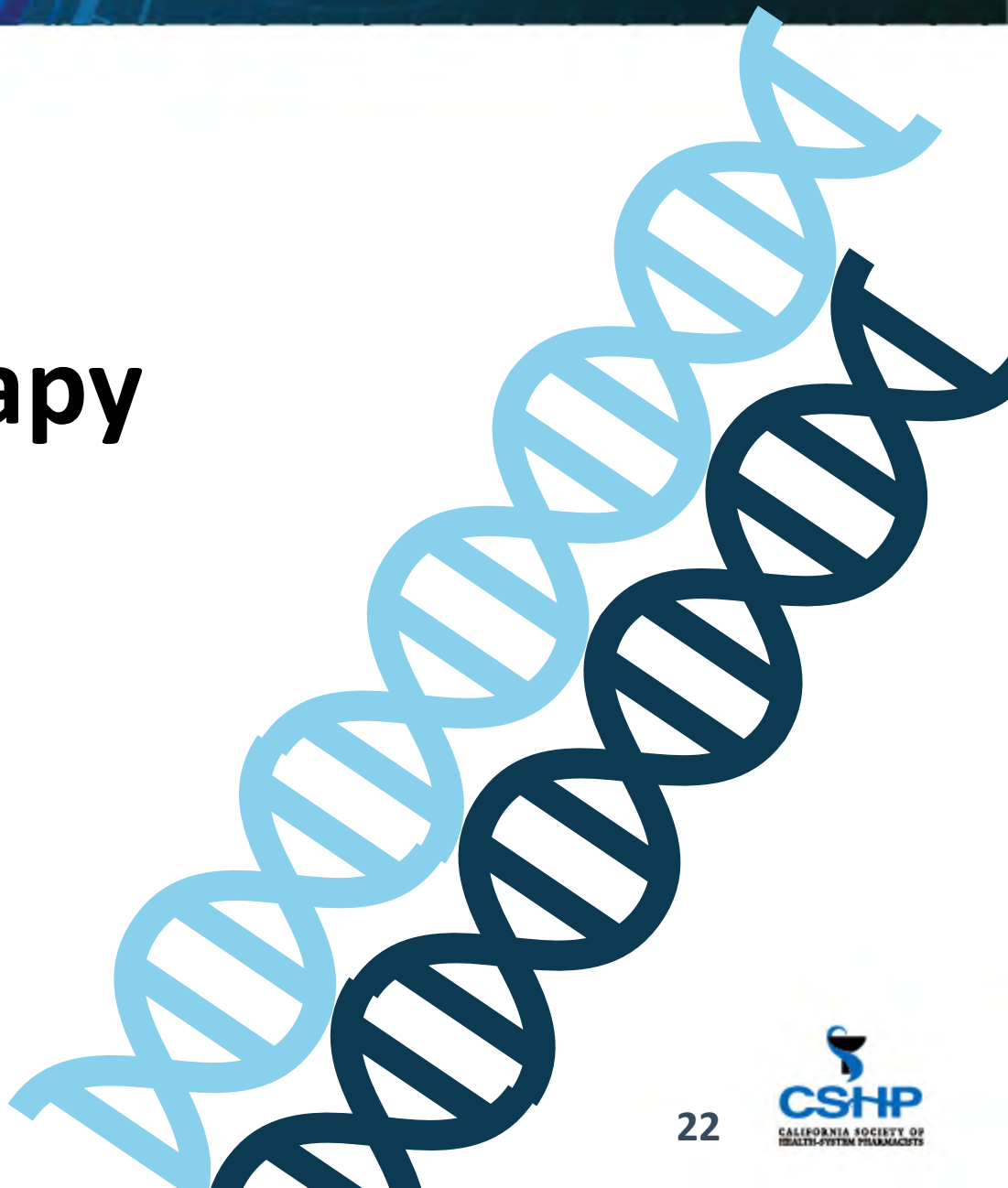
Challenges

- Medicaid drug price reporting and rebate need to be adapting to multi-year performance structures
- Anti-Kickback Statute to define explicit safe harbor for performance rebates
- FDA communication guidelines to enable appropriate performance metrics: Clinical trial endpoints often not practical for clinicians or present in data systems

Potential solution(s)

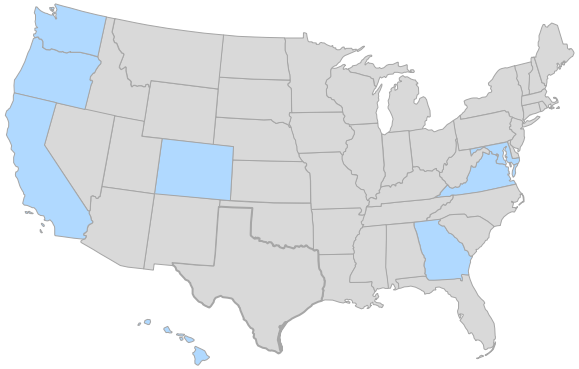
- Regulatory reform around payment models

Approach to Gene Therapy at Kaiser Permanente



Kaiser Permanente's Integrated Model

Physician-Pharmacist Partnership



- Physicians: 22,000 nationally
- National Pharmacy Services
  - Outpatient, Inpatient, and Clinic Administered Medication Services
  - Drug Intelligence & Strategy: internal support for clinicians in all care delivery sites
- Maintain goal of evidence-based treatment focusing on quality & safety

Strength of integrated medical and pharmaceutical services

- High level of collaboration
- Leverage physician expertise nationally
- Fully integrated electronic medical record
- Allows processes to review/monitor patients

Pharmaceutical Evidence Landscape

Evidence				
Understanding				
Informed prescribing				

Clinical Readiness: Challenges to Assessing Value

- Type and amount of evidence available
  - Accelerated approvals and surrogate endpoints
  - Limited or unpublished data (e.g., Phase 1/2 data, interim analyses)
  - Unknowns (e.g., optimal dosing or duration)
  - FDA integrated review document
- FDA approval of indications broader than studied
- Delayed/incomplete post-market confirmatory studies
- Long-term efficacy and safety

Onasemnogene abeparvovec-xioi (Zolgensma)

- **First gene therapy for spinal muscular atrophy (SMA)**
  - FDA Approved May 2019
- **Indication**: patients <2 years of age with SMA with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene
- **Mechanism**: gene replacement therapy using non-replicating adeno-associated virus serotype 9 (AAV9) capsid to deliver a functioning copy of the *SMN1* gene
- **Administration**: one-time intravenous infusion
- **Cost**: $2.125M per patient

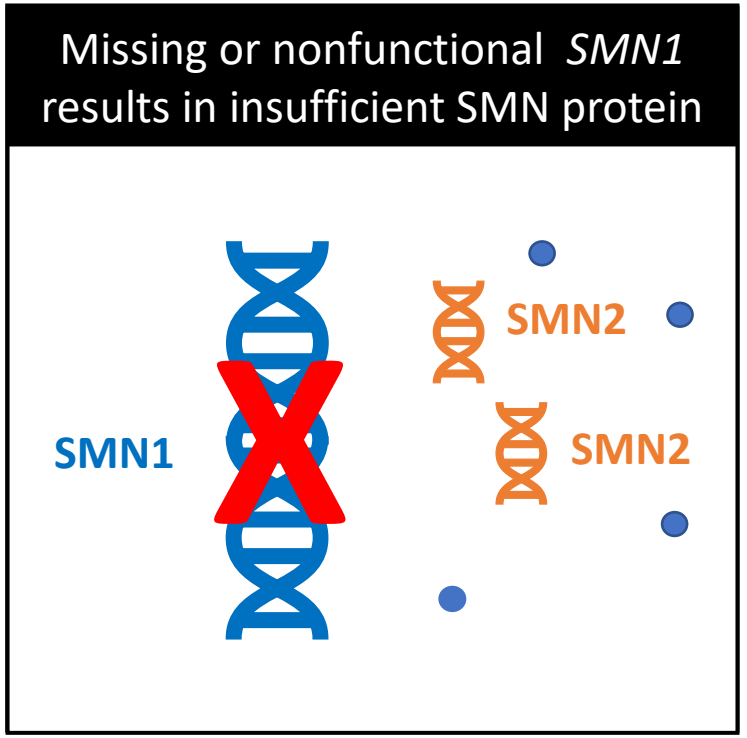
Zolgensma [package insert]. AveXis, 2019.

SMA Background

- **Rare genetic disorder caused by mutations in *SMN1* gene**
  - *SMN1:* primary gene – 100% functional SMN protein
  - *SMN2:* backup gene –10% functional SMN protein

- Low levels of SMN protein causes loss of motor neurons
  - Leads to progressive muscle weakness and atrophy

- Incidence: ~1 in 10,000 live births



Verhaart , et al. Orphanet J Rare Dis. 2017.

Four Primary Types of SMA

	Type 1	Type 2	Type 3	Type 4
Onset	Birth to ~6 months of age	6 to 18 months of age	18 months to 3 years, sometimes teens	Adulthood usually >30 years
Incidence per SMA live births	~60%	~27%	~13%	Very rare
Developmental milestones	• Muscle weakness • Difficulty breathing and swallowing • Poor head control • Cannot sit independently • Cannot crawl or walk	• Can sit without help but unable to walk	• Initially walk without support but then increase in limited mobility	• Mild motor impairment
Survival	• 50% at 10.5 months • 8% at 20 months	68% survival at age 25 years	Normal	Normal

Cure SMA. Types of SMA. https://www.curesma.org/types-of-sma/. Accessed August 3, 2020.

Onasemnogene abeparvovec-xioi (Zolgensma)

Efficacy Data at time of FDA approval

Two-year, open-label, dose-escalation Phase 1 trial (START), n=15

- Infants with SMA type 1, two copies of *SMN2* gene, symptomatic by age 6 months
- **100% of high-dose cohort (n=12) met event-free survival (no death or permanent ventilation) at age 24 months**
  - **Mean age 3.4 months** (range 0.9 to 7.9 months) at the time of treatment
  - Most able to meet some motor milestones: roll over, sit unassisted for ≥30 seconds, and feeding orally. Two able to walk independently.

Zolgensma [package insert]. AveXis, 2019.
Mendell, et al. *N Engl J Med* 2017.

Onasemnogene abeparvovec-xioi (Zolgensma)

Safety Data at time of FDA approval

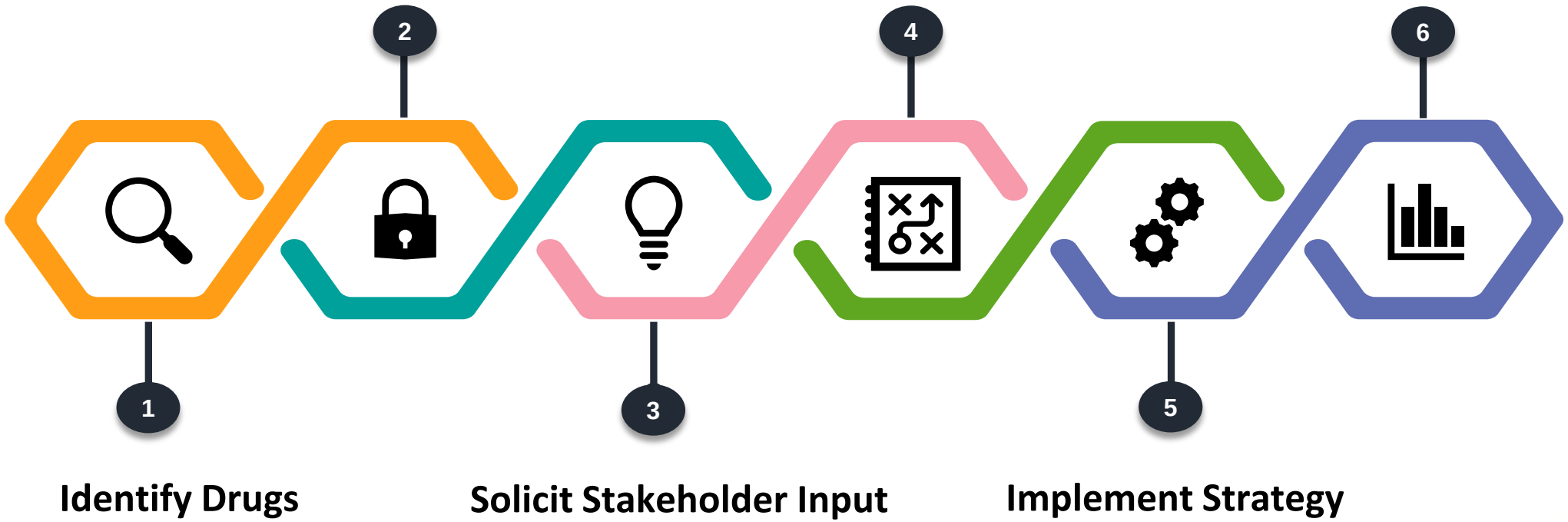
Boxed Warning: Risk for acute liver injury and elevated aminotransferases

- Most common adverse reactions: elevated aminotransferases, vomiting
- Monitoring in product labeling:
  - Liver function
  - Thrombocytopenia and elevated troponin-I (observed in ongoing studies)
- Two infant deaths reported in ongoing Phase 3 studies for SMA type 1
  - 1 respiratory failure deemed unrelated to treatment
  - 1 under investigation

Zolgensma [package insert]. AveXis, 2019.
Terry M. "A 2nd Patient Death Reported in Novartis' Gene Therapy Trial". April 22, 2019. BioSpace.

Emerging Therapeutics Strategy Program

Pipeline Surveillance & Proactive Strategy Development



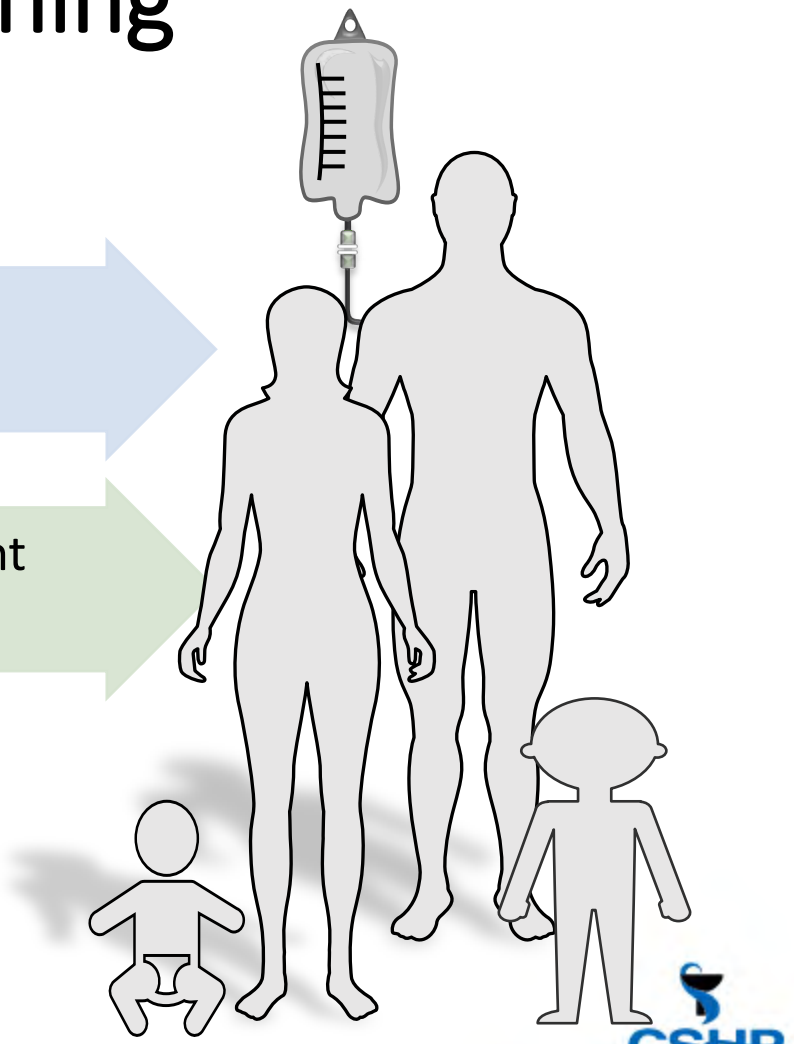
Workstreams for Gene Therapy Planning

CLINICAL

- Evidence-based analysis
- Practice recommendations

OPERATIONAL

- Multi-stakeholder engagement
- Practical application



KP Strategies

Practice Recommendations

- Criteria for Use
- Monitoring safety & efficacy
- Criteria for discontinuation (if applicable)

Needs Assessment

- Patient Population
- Benefits (Member Cost)
- Contracting
- Procurement

Tools

- EMR messaging/templates
- SharePoint
- Drug FAQs – Clinicians
- Drug FAQs – Members

Operational Readiness

Operational Readiness: onasemnogene abeparvovec-xioi (Zolgensma)

	KP Planning
Designate center of excellence	• One site each for Southern CA and Northern CA
Procurement	• Identify funds disbursement approver • Process to order, receive, and confirm delivery of customized kit
Storage and handling **Preparation and disposal**	• Biosafety level 1 (BSL1) for adeno-associated viral vector • Refrigerate upon receipt; use within 14 days • Thaw in refrigerator for 12 hours (or 4 hours at RT) • Use within 8 hours of drawing into syringe

Operational Readiness: onasemnogene abeparvovec-xioi (Zolgensma)

	KP Planning
Care Coordination Pre-infusion labs Pre-medication Patient travel Follow-up	• Order & receive anti-AAV9 antibody test from external lab • Patient to initiate prednisolone day prior to infusion • Consider patient hotel stay if traveling far • Counsel family on treatment plan; KP Financial Assistance
Administration and Monitoring	• Confirm patient arrives w/o fever; labs & premeds completed • Insert two peripheral lines (one for back-up) • Syringe pump • Consider isolated patient room • Monitor vitals during and for 2 hours post-infusion

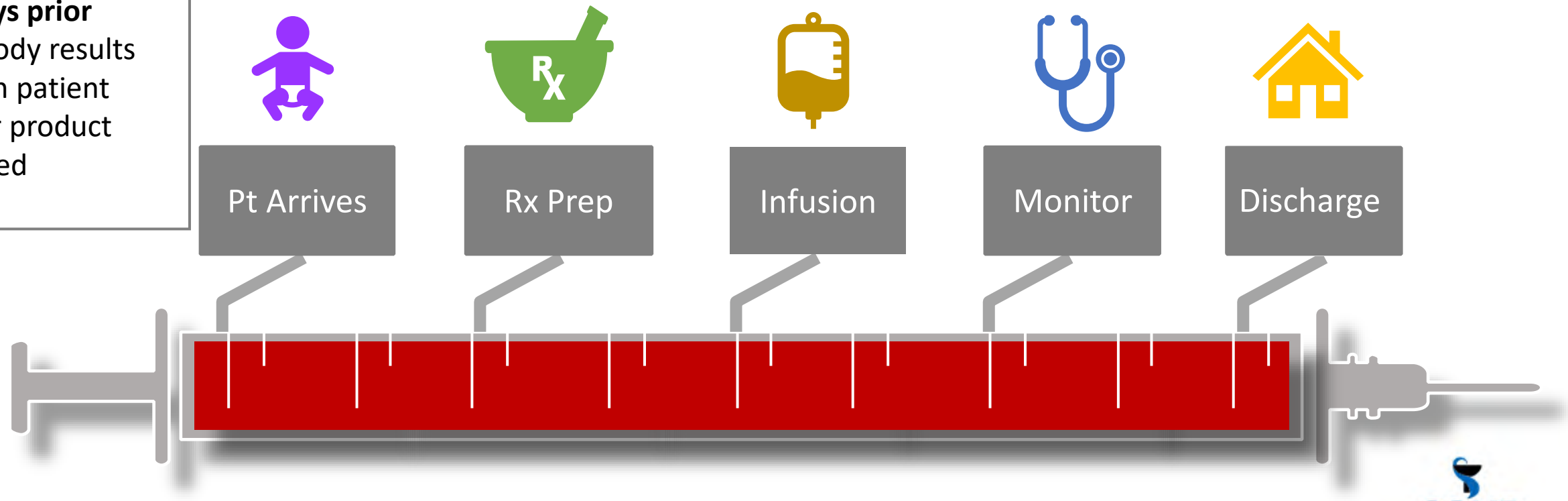
Operational Readiness: onasemnogene abeparvovec-xioi (Zolgensma)

	KP Planning
Post gene therapy care and monitoring	• Discharge w/gloves for diaper changes (stool: vector shedding primarily through body waste) • Corticosteroid treatment protocol • LFTs, CBC, Troponin-I for at least 3 months • Periodic motor function and pulmonary assessments
EMR content build	• Create order set for infusion administration • Create clinician documentation templates for initial and follow-up assessments

onasemnogene abeparvovec-xioi (Zolgensma)
KP Administration Day Timeline

2 weeks prior
- AAV9 antibody test

5-7 days prior
- antibody results
- Weigh patient
- Order product
- Premed
- Labs



Zolgensma [package insert]. AveXis, 2019.

onasemnogene abeparvovec-xioi (Zolgensma)

KP Post-infusion Monitoring

Corticosteroids

Complete at least 30 days plus taper of systemic corticosteroids to manage LFT elevations

Laboratory Monitoring for Safety

Liver function, platelets, and Troponin-I monitoring for ≥3 months post-infusion

Motor Function Assessments

Age-appropriate assessments periodically to monitor long-term effectiveness

Respiratory Assessments

Periodic pulmonology function assessments to monitor long-term effectiveness

Zolgensma [package insert]. AveXis, 2019.

Test Question #1

Chimeric antigen receptor T-cell (CAR-T) therapies are examples of ex vivo gene therapies. TRUE or FALSE?

a. True

b. False

Test Question #1 - Answer

Chimeric antigen receptor T-cell (CAR-T) therapies are examples of ex vivo gene therapies. TRUE or FALSE?

a. True

b. False

Test Question #2

All of the following are evolving clinical considerations of gene therapies EXCEPT:

a. Unknown durability of effect and long-term safety due to short-term clinical trials
b. Study population limitations (e.g., sample size, age)
c. Differences in individual patient responses
d. Benefit design for gene therapies

Test Question #2 - Answer

All of the following are evolving clinical considerations of gene therapies EXCEPT:

a. Unknown durability of effect and long-term safety due to short-term clinical trials

b. Study population limitations (e.g., sample size, age)

c. Differences in individual patient responses

d. Benefit design for gene therapies

Test Question #3

Which of the following operational challenges should be considered when implementing a process for gene therapy administration in your institution?

a. Biosafety level and environmental risk of the gene therapy
b. Antibody testing requirement for administration of the product
c. Funds disbursement for ordering the gene therapy
d. Monitoring requirements during and after gene therapy administration
e. All of the above

Test Question #3 - Answer

Which of the following operational challenges should be considered when implementing a process for gene therapy administration in your institution?

a. Biosafety level and environmental risk of the gene therapy
b. Antibody testing requirement for administration of the product
c. Funds disbursement for ordering the gene therapy
d. Monitoring requirements during and after gene therapy administration
e. All of the above

Reference List

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Session Code: