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The Cancer Institute of HCA Healthcare

The CAR-T Cell Therapy Tsunami: Emerging Therapies and Barriers to Access

C .Fred LeMaistre MD

CAR T is a breakthrough in cellular therapy that utilizes genetically-modified versions of a patient's own T cells to kill tumor cells and offer unprecedented outcomes

The Basics of CAR T Therapy

CAR T is a breakthrough Cellular Therapy

Chemistry → Biologics → Cellular Therapy

CAR Ts are a next-generation evolution in drug development toward true personalized medicine in oncology

- Next frontier of Oncology innovation; true "n=1" personalized medicine
- **Two CAR T products currently approved in** in ALL and NHL
- **400+ cellular therapy trials** on-going
- The FDA has **>800 active** cell-based or directly administered gene therapy **INDs** currently on file
- The FDA expects to **approve 10 to 20 cell** / gene therapy products per year by 2025
- **CAR-T will cause significant erosion of HCT**

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Sources: Clinicaltrials.gov; FDA

OBJECTIVES

What are CAR-T Cells?	• How are they made? • How do they work? • Are there similarities to HCT?
What Is Required For Delivery?	• Programmatic Infrastructure • REMS training • FACT Requirements
Barriers to Access	• Approved centers • Reimbursement

WHAT IS IMMUNE EFFECTOR CELL THERAPY (IECT)?

- IECT **modulate an immune response for therapeutic intent**. This includes genetically engineered **chimeric antigen receptor T cells (CAR-T cells)** and therapeutic vaccines.


T cells


B cells


NK cells


Dendritic cells

Mesenchymal Stromal cells

- These **genetically modified cells** recognize **specific antigens on tumor cells** resulting in their activation and proliferation resulting in destruction of malignant cells.
- IECT are considered **"a living drug"** since they tend to persist for long periods of time.
- IECT are generally created from the **patient's blood cells** although this technology is evolving to develop **"off the shelf"** immune effector cells.

Car t-cell therapy introduction

Following the same basic steps as an autologous bone marrow treatment, CAR T is a natural extension of HCT programs assets and expertise

Evolving from BMT to CAR T

	1 Cell Collection	2 Cell Processing	3 Cryo-Preservation	4 Chemo-therapy	5 Reinfusion	6 Short-Term Monitoring
BMT[1]	Collect patient's **stem cells**	**Purify and concentrate** the extracted cells	**Freeze cells** to preserve for later reinfusion	**High-dose chemo** to prep for infusion	Reinfuse the patient's **BMT cells**	Monitor the patient: **in-patient or out-patient**
vs.	↓	↓	↓	↓	↓	↓
CAR T	Collect patient's **T-cells**	Modify cells with biotech / pharma **viral vector technology**	**Freeze cells** to preserve for later reinfusion	**Low-dose chemo** to prep for infusion	Reinfuse the **CAR T cells**	Monitor the patient: **in-patient and out-patient**

Expertise

- Practiced in individualized and **specialized administration of patient therapy**
- Command over **autologous process** (e.g., patient flow, supply chain, logistics)
- Understanding of **cell viability standards**

Assets

- Equipment and capabilities to support **cell collection and cryopreservation**
- **Brand equity** and leadership in the bone marrow transplant space

Process Management Infrastructure

- **Track-and-trace** and **secure chain of custody** capabilities
- CAR T **eligibility criteria integrated** into EMR system and apheresis machine

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1) Process detailed above is for an autologous BMT

CAR T Therapy: Toxicity

- **No significant acute infusional toxicity**
- **Tumor lysis syndrome**
  - Rarely occurs; effector cell expansion requires time negating massive tumor lysis
- **Cytokine release syndrome (CRS)**
  - Life-threatening if not managed by expert multidisciplinary team
  - May include cardiac events, hepatotoxicity, or renal toxicity
- **Neurologic toxicity**
  - 3 subtypes: acute, delayed, idiosyncratic
- **Cytopenias**
  - Macrophage activation syndrome (MAS) or HLH is a very rare and severe form
  - B-cell aplasia and hypogammaglobulinemia

IMPROVING MORE LIVES IN MORE WAYS: CAR T-CELL THERAPY SUCCESS

Raising the Bar for Cellular Therapy

The NEW ENGLAND JOURNAL of MEDICINE

Study published May 2019

Full Author List:
N Raje, MD, **J Berdeja, MD**, Y Lin, MD, PhD,D Siegel, MD, PhD., S Jagannath, MD, D Madduri, MD, M Liedtke, MD, J Rosenblatt, MD, MV Maus, MD, PhD, A Turka, L-P Lam, PharmD., RA Morgan, PhD, K Friedman, PhD, M Massaro, MPH, J Wang, PharmD, PhD, G Russotti, PhD, Z Yang, PhD, T Campbell, MD, PhD,K Hege, MD, F Petrocca, MD, MT Quigley, MS, N Munshi, MD, JN Kochenderfer, MD

"I fought this cancer so fiercely for six years and then suddenly, CAR T-Cell Therapy began to fight the cancer FOR me. I am now retired and I am truly blessed to be given a second chance at life…"

- Brenda,
60 year old
multiple myeloma
survivor

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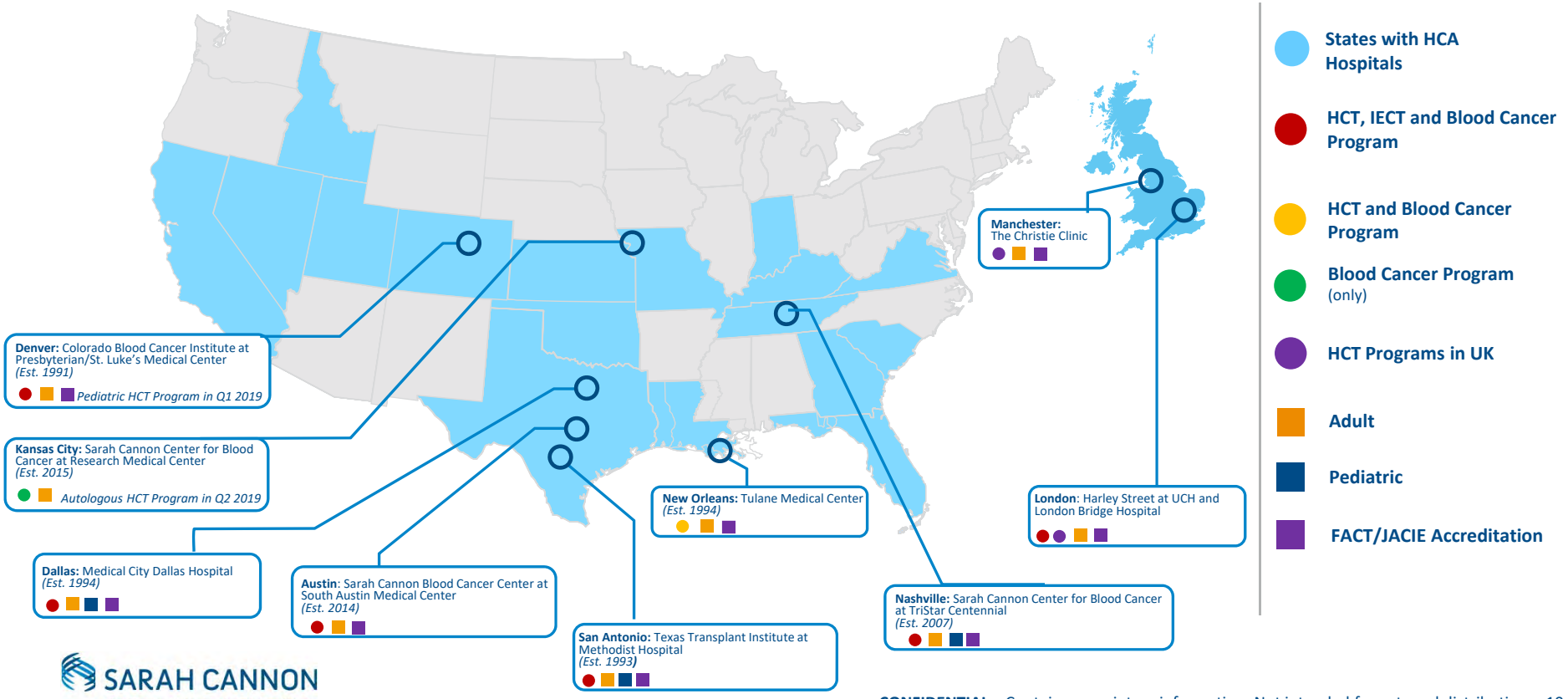
What Is Required For Delivery?

SARAH CANNON BLOOD CANCER NETWORK PROGRAMS



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SARAH CANNON IMMUNE EFFECTOR CELL THERAPY EXPERIENCE

Studies open in:

- Multiple Myeloma
- Diffuse Large B-Cell Lymphoma
- Mantle Cell Lymphoma
- Indolent Non-Hodgkin Lymphoma
- B-Cell Non-Hodgkin Lymphoma
- ALL
- CLL/SLL
- AML/MDS
- Multi Indication Solid Tumor
  - Sarcoma
  - Melanoma
- Non Small Cell Lung Cancer
- CRISPR CD34+gene therapy Sickle Cell Disease
- Biomarker Driven basket trial

> 30

Immune Effector Cell Therapy studies opened since Dec 2015

> 140

patients enrolled since April 2016

- Multiple Myeloma
- Lymphoma
- NSCLC
- Leukemia (AML, ALL, CLL)
- Sarcoma
- Melanoma
- Sickle Cell Disease

Immune Cell Therapy Committees

- Coordination and standardization of research processes across centers for both blood cancer and solid tumor indications
- Local committees comprised of site transplant, nursing, research staff and physicians meet monthly at each center
- Local committees report to Sarah Cannon Immune Effector Cell Therapy leadership monthly

Commercial CAR T-Cell Therapy

- 5 Programs in U.S. certified by Novartis
- 5 Programs in U.S. certified by Kite
- 1 Program in UK in process of Gilead certification

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UPDATED: 05AUG2019

STANDARDIZATION ACROSS SARAH CANNON BLOOD CANCER NETWORK

- **1 QM plan and metrics**
- Quarterly Network QM Committee meetings
- **Clinical Pathways**
- **Patient Eligibility Criteria**
- Mock FACT Survey Process

- **Physician, APP privileging criteria and competencies**
- **Competencies for Nursing** and Advanced Practice Clinicians

- **SOPs standardized**
- Ongoing SOP Review process in place

- **Standardized Payer Contract Template and Language**
- **Network-level Vendor Contracting**
- Implemented Revenue Optimization strategies
- Expense management committees

- **Integrated Clinical Care and Research**
- Abstracts/Presentations at ASH & Tandem
- **Pipeline development and operations support**

- **StafaCT: Developed BMT information solution for Cellular Therapy, Apheresis and Clinical operations**
- Meet requirements from FACT, FDA, HRSA and Payers
- **Developed Hematology Navigation software**

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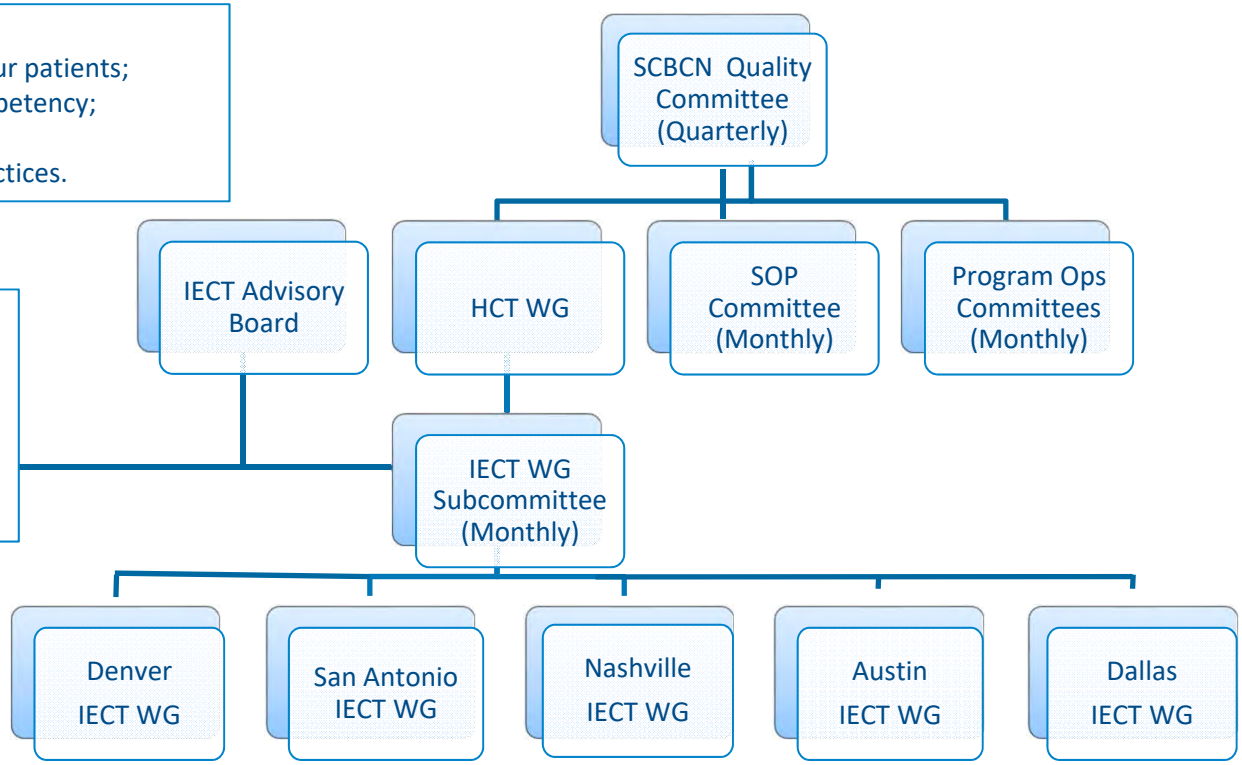
IECT COMMITTEE STRUCTURE

Committee Goals
- Ensure safety, consistency and quality for our patients;
- Demonstrate Network capabilities and competency;
- Improve patient outcomes;
- Share lessons learned and develop best practices.

IECT Subcommittee Members
- Carlos Bachier, MD
- Peter McSweeney, MD
- Aravind Ramakrishnan, MD
- Paul Shaughnessy, MD
- Vikas Bhushan, MD
- Program Administrators
- SC Support Team



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IECT OPERATIONS TOOLKIT DEVELOPED BY SARAH CANNON

Competencies & Privileges

- RN
- Apheresis
- CTL Tech
- Research RN
- Clinical Pharmacist
- APP
- Physician privileges

SOPs & Resource Documents

- All FACT-required SOPs
- Prep for vendor-required SOP management
- Pre-site selection checklist
- CRS Grading Tool
- Patient Consent form
- CAR T-Cell Readiness checklist
- CARTOX 10 documentation tool

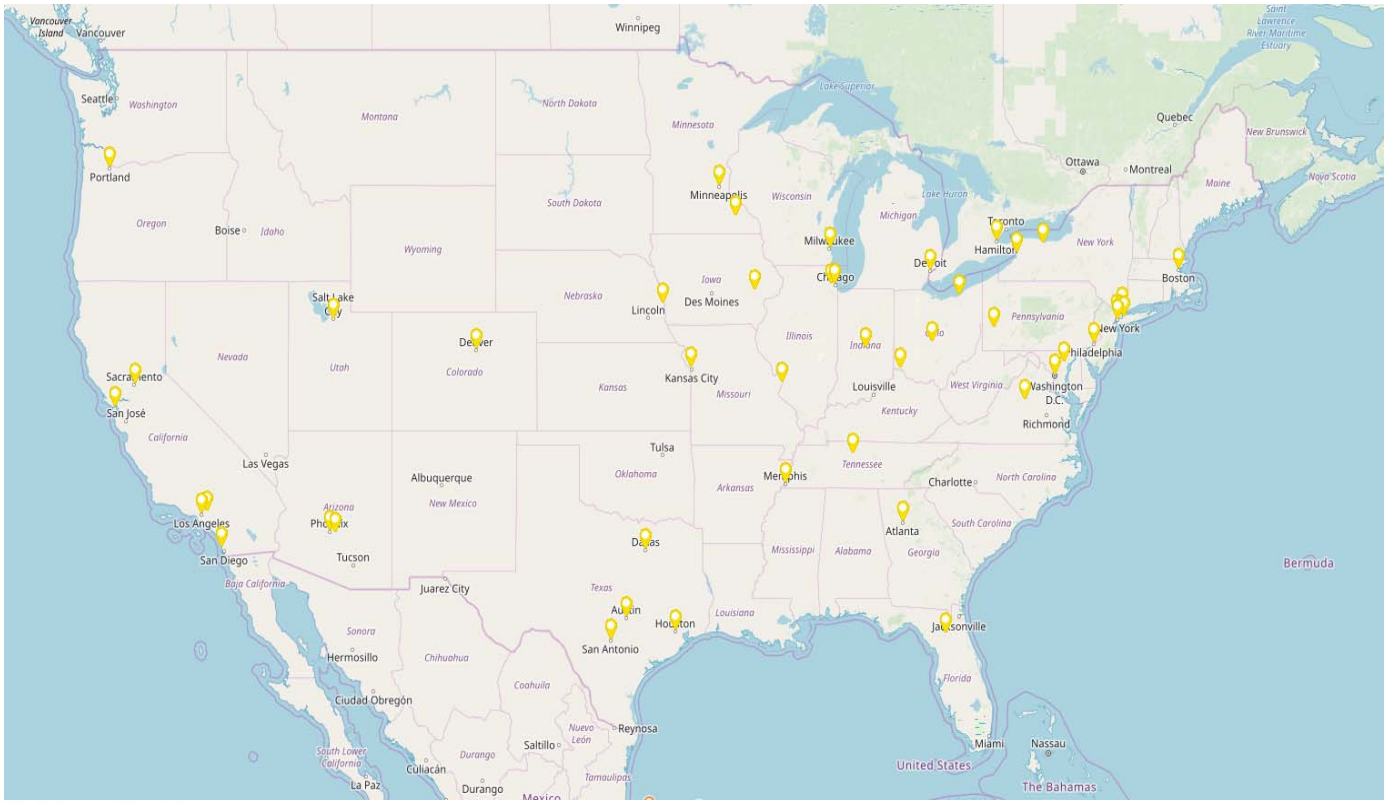
Education & Training

- HealthStream IECT Education module
- Consulting Physician Training slide deck
- Data Coordinator Training
- Patient Education & Wallet Cards
- Nurse neuro assessment training
- Mock collection & Infusion case study

Finance & Contracting

- Vendor Qualifications
- Payer/Vendor contracting
- Coding & Billing Updates

Geographic Distribution of FACT-IEC accredited programs



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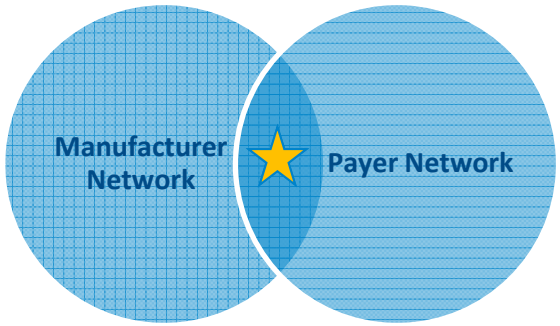
What are Risk Evaluation and Mitigation Strategies (REMS)?

- U.S. Food and Drug Administration (FDA) safety program for medications with serious safety concerns
  - Both drugs and biologics can have REMS
  - Used to ensure that the benefits outweigh the risks
- Designed to reinforce safe medication use
  - Labeling (including package inserts) is usually sufficient, but REMS is required for products with greater risks
- Applies to *commercial, licensed* products
  - Research products do not have REMS

BARRIERS TO ACCESS

CREDENTIALS MATTER FOR PROVIDING IECT



Manufacturer

- Demonstrated expertise
- FACT Accreditation
- Contract to provide care in specific manner
- Clinical and administrative training for all involved staff (REMS)

Payer

- Demonstrated expertise
- In-network facility with specific contract; Center of Excellence Network
- FACT Accreditation
- For some payers – use of manufacturer standards as proxy for specialized designation

Source: Presentation by Stephanie Farnia at the 2018 ASBMT BMT Administrator Meeting

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ARE FDA APPROVED CAR-T PRODUCTS COVERED?

TWO FDA APPROVED CAR T PRODUCTS

CAR T-cell therapy is only FDA approved for two indications:

- ≤ 25 years with **acute lymphoblastic leukemia** that is refractory or in 2nd or later relapse.
  *Currently, fewer than 1 in 3 of these patients survive 5 years** **$475,000**
- ≥ 18 years and older with **aggressive B-cell lymphoma** that is refractory or in 2nd or later relapse.
  *Palliative care is currently the only option for these patients** **$373,000**

- Commercial:
  - **Most** commercially insured patients have coverage for Yescarta® (*axicabtigene ciloleucel*) and/or Kymriah® (*tisagenlecleucel*)
  - May be limitations for specific plans and/or employer-sponsored groups
- Medicare:
  - In IPPS, it is a drug used in a part of a covered episode of care, i.e. MS DRG 16**
  - Q codes and payment for the OPPS setting

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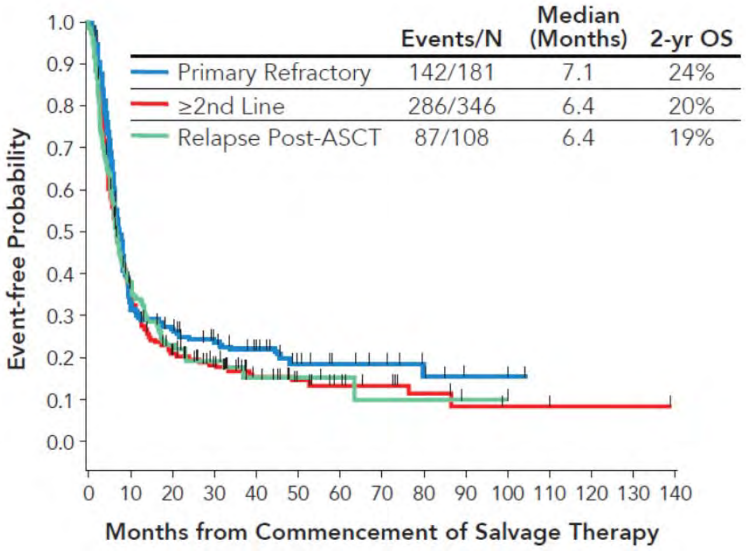
*INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW " *Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value"*
***PPS exempt hospitals have a different payment mechanism*

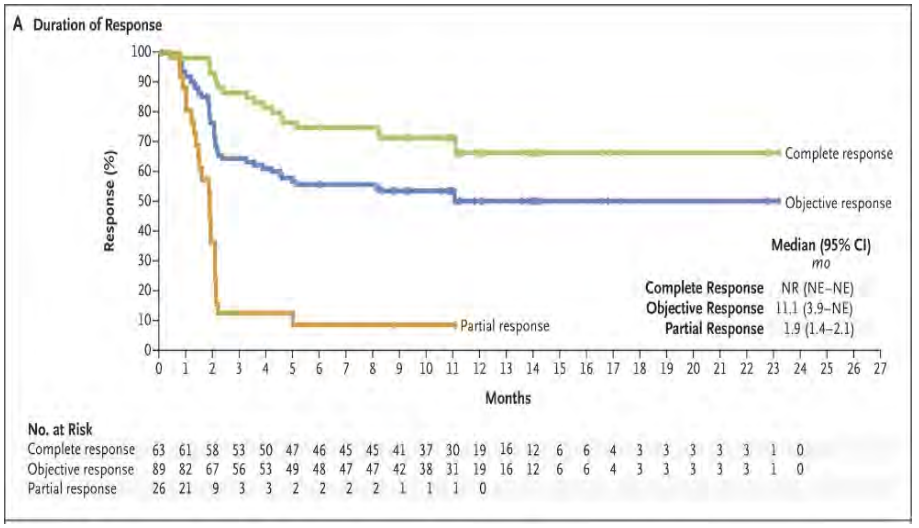
Prior to Car-T cell Refractory DLBCL Patients had Poor Outcomes

- Complete Response (CR) 8%



Crump M, et al. Blood. 2017 Aug 3. pii: blood-2017-03-769620.

- Complete Response (CR) 51%



Neelapu, et al. NEJM 2017; 377:253

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NATIONAL COVERAGE DETERMINIATION FOR CAR T-CELL THERAPY

- **CMS announced on August 7th that they cover CAR T-cell therapy for cancer** with T-cells expressing at least one CAR when administered at healthcare facilities enrolled in the **FDA REMS**. Must use an FDA-approved product for an approved indication.
- The policy **continues coverage for routine costs in clinical trials** that use CAR T-cell therapy as an investigational agent.
- Coverage with Evidence Development **(CED) is not required.**
- **No additional reporting to a registry** is required.
- **No Patient-Reported Outcomes required.**
- **Medicare will pay for CAR T-cell therapy in 2019 and 2020 for beneficiaries enrolled in MA plans** as coverage criteria in the NCD met criteria as a **significant cost**.
- **2 FDA approvals in MM** and 1 in NHL anticipated for 2020.

How are FDA approved CAR-T products reimbursed?

PAYMENT LANDSCAPE STARTING OCTOBER 1, 2020

	Inpatient	Outpatient hospital-based	Outpatient physician office
Commercial payers	• Case rate or **SCA** with % of billed • **Drug cost as pass-through**	• Case rate or **SCA** with % of billed • **Drug cost as pass-through**	• Not at this time - Biopharma & payers requiring FACT accreditation
Government	• In 2020 IPPS, it will remain in **MS-DRG 16 ($43,127)** • No additional drug payment except for **NTAP**, will cover up to 65% of drug cost. NTAP goes away in Nov 2020. • Depending on hospital charges the hospital may have the opportunity for outlier payment (chargemaster optics)	• Q code-based reimbursement – ASP +6% Drug cost covered • **Q code includes drug, leukapheresis and dose preparation procedures per infusion** • Potential risk of admissions within 72 hours	• Not at this time - Biopharma requiring FACT accreditation

Based on Novartis and Kite's estimates of the average cost for an administered dose for FY 2019, CMS currently estimates that the NTAP will increase overall in FY 2020 payments by $93,585,700 (Maximum add-on payment of $242,450 * 386 patient)

TWO FDA APPROVED CAR T PRODUCTS

CAR T-cell therapy is only FDA approved for two indications:

- ≤ 25 years with acute lymphoblastic leukemia that is refractory or in 2nd or later relapse.
  *Currently, fewer than 1 in 3 of these patients survive 5 years** $475,000
- **≥ 18 years and older with aggressive B-cell lymphoma that is refractory or in 2nd or later relapse.**
  Palliative care is currently the only option for these patients* **$373,000**

- Inpatient CAR-T cases are grouped to MS-DRG 016 based on the presence of one of two CAR-T ICD-10-PCS codes (XW033C3 and XW043C3)

MS-DRG O16 Title	National Unadjusted PPS Payment*
Autologous Bone Marrow Transplant with CC/MCC or T-cell Immunotherapy	**$43,127**

- The national unadjusted PPS payment represents the payment amount before hospital specific adjustments are applied which will impact overall payment

- INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW " *Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value"*
- *PPS exempt hospitals have a different payment mechanism*

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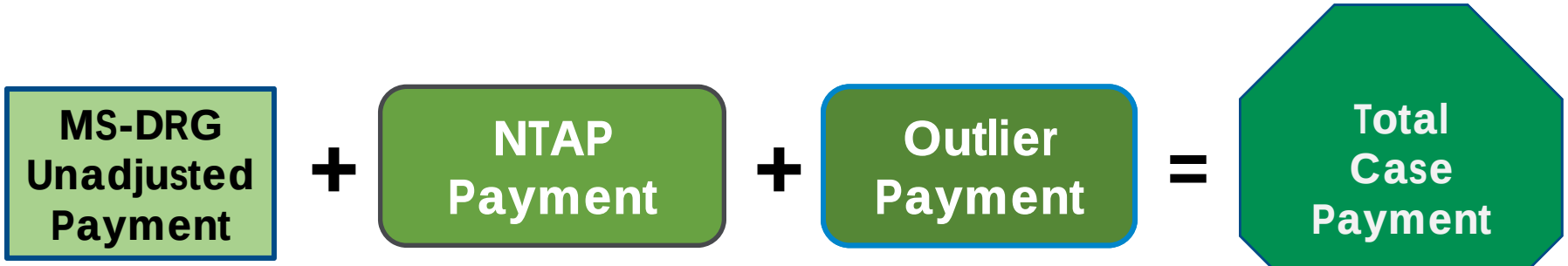
IPPS PAYMENT OVERVIEW



*Both the **NTAP and the outlier are <u>dependent</u> on the total billed charges** for the case and the hospital's overall operating cost to charge ratio (CCR) which comes from each hospital's Medicare cost report*

The final MS-DRG payment is typically adjusted by one or more hospital specific factors such as the wage index, Indirect Medical Education (IME), and/or Disproportionate Share (DSH) as applicable

Source: Presentation by Jugna Shaw at the 2018 ASBMT BMT Administrator Meeting

Hospital Case Example to Evaluate Payment Impact for FY 2020 Based on CMS' Finalized Changes

Hospital and Patient Characteristics

Both hospitals A and B:

- Pay the manufacturer $373,000
- Have a wage-index of 1.0 and no other adjustments
- Have an overall operating cost-to-charge ratio of 0.25
- Have the exact same patient care charges

The only difference between Hospital A and B is the CAR-T product charge billed on the claim. Hospital B's charges is reflective of its operating CCR of .25, but Hospital A's is not.

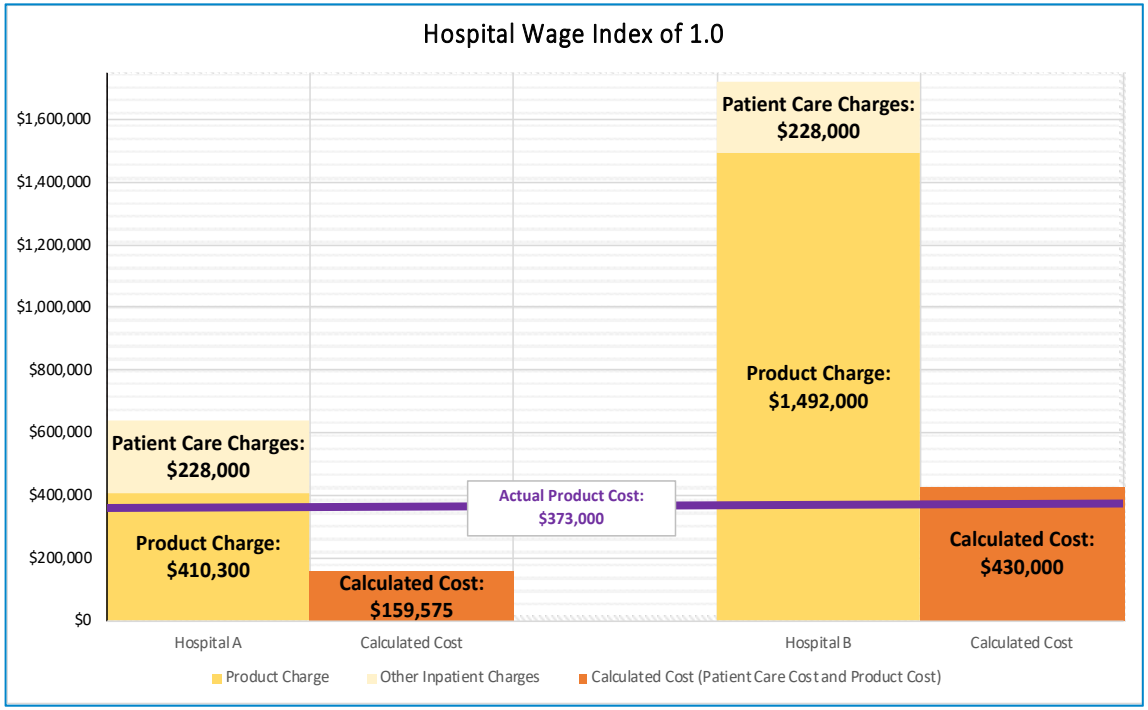
Hospital A Example Inpatient Hospital Claim			Hospital B Example Inpatient Hospital Claim		
Description	Units	Total Charges	Description	Units	Total Charges
Room & Board	14	$63,000	Room & Board	14	$63,000
Pharmacy	100	$45,000	Pharmacy	100	$45,000
Supplies	20	$13,000	Supplies	20	$13,000
Laboratory	520	$32,000	Laboratory	520	$32,000
All other	50	$75,000	All other	50	$75,000
CAR-T Drug*	1	$410,300	CAR-T Drug*	1	$1,492,000
Total Charges		$638,300	Total Charges		$1,720,000

** In the claims examples shown, the CAR-T product charge is split out from other pharmacy charges for illustrative purposes to demonstrate how reporting of the CAR-T product can occur. This would require explicit instructions from CMS.*

ASTCT

Charge and Cost Variations for Two Different PPS Hospitals Providing CAR-T

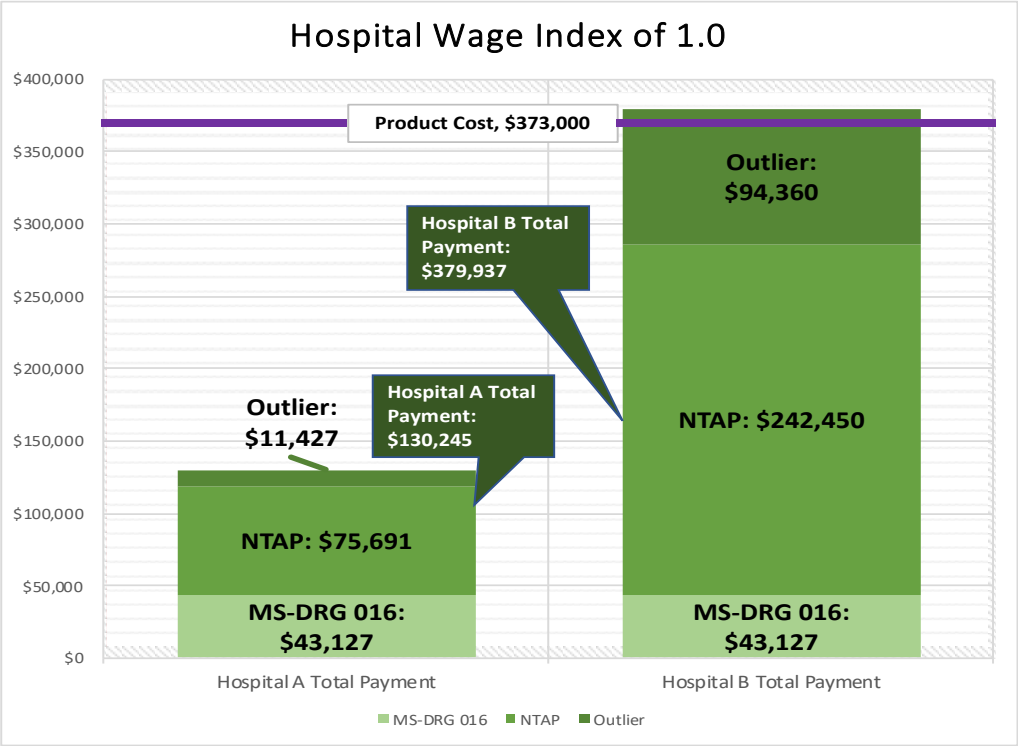
- Hospital A and B have different total charges
- CMS determines the "calculated cost" by multiplying the total billed charges by the hospital's overall CCR which in our example is 0.25 for both hospitals
- Because of the difference in total charges between Hospital A and B, CMS' calculated cost for each hospital is very different



Note: *"calculated cost" does not equal "actual cost"; yet this is the information used in determining Medicare payment*

Calculated Cost for Each Hospital Impacts NTAP and Outlier Payment Amounts Received

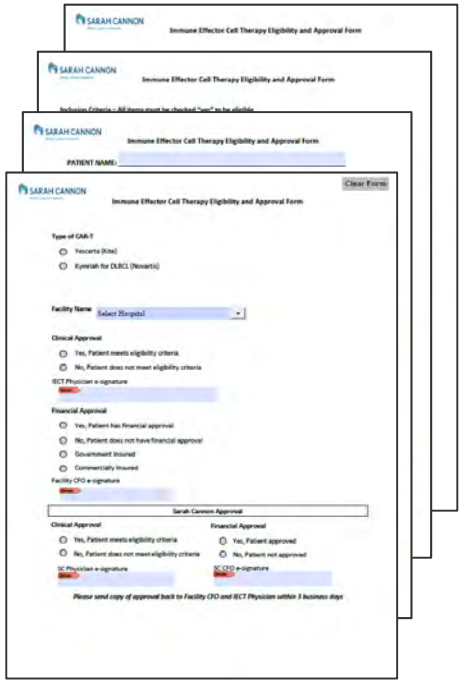
- Calculated cost (patient care + product cost)
  - Hospital A = $159,575
  - Hospital B = $430,000
- Payment components
  - MS-DRG 016 payment is the same for Hospital A and B since we haven't applied any adjustments in our example
  - NTAP payment varies because total charges and calculated costs vary
  - Outlier payment varies because total charges and calculated costs vary



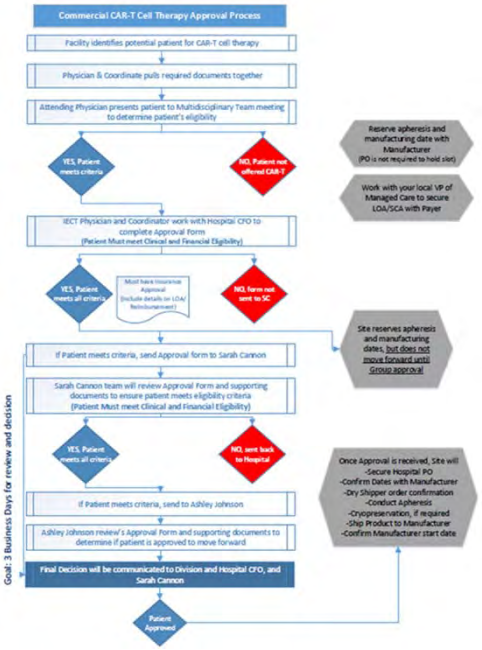
SARAH CANNON'S FORMAL PROCESS TO PROVIDE OVERSIGHT

- **Standardized Patient Eligibility Form** to be completed for each patient
- Each patient's eligibility reviewed at the **program's multidisciplinary team** meeting and at **the Corporate level**, to ensure patient meets our clinical and financial eligibility criteria
- The current **IECT Committee will review each patient** to ensure patient meets our clinical eligibility criteria, and review the expenses and payer mix of each patient

Patient Eligibility Form



Patient Approval Process



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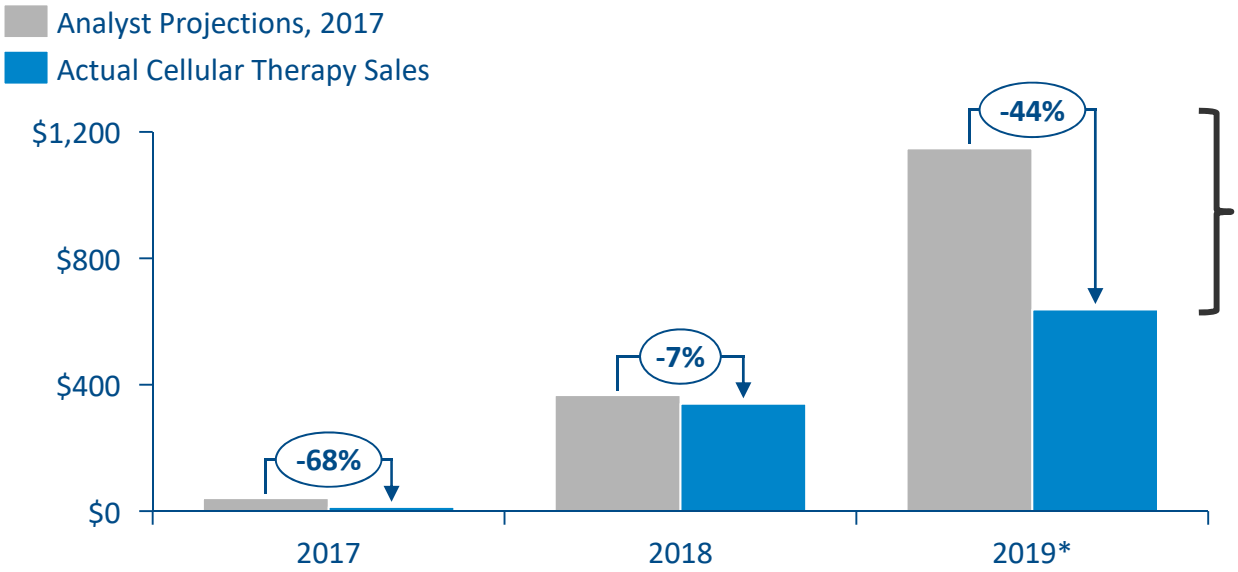
Blood Cancer Network

Following that excitement, how did sales actually perform?

Actual vs. 2017 Projections of CAR T Sales, USD, $M



WHAT'S DRIVING THE GAP?

Hint: It's more than just high pricing

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Source: GlobalData, Maxim Group, Novartis Quarterly Financial Results, Gilead Quarterly Earnings
** 2019 Actual Cellular Therapy Sales is a projection of 2019 Q1 and S2 sales applied across the full year*

UNSOLVED CELLULAR THERAPY COMMERCIALIZATION CHALLENGES TIE BACK TO THE PROVIDER

1

Healthcare Delivery Infrastructure

- Care delivery network setup one site at a time: apheresis → infusion
- Long-term patient monitoring / follow up

Resource-intensive process →

2

Individualized Patient Approvals

- Individualized authorization process
- C-level approval often required by the provider

Elongated approval →

3

Therapy Delivery Economics

- Government reimbursement
- In-patient procedure billed at a fixed case rate

Unprofitable care delivery →

4

Supply Chain Orchestration

- Coordination of manufacturing and patient treatment timelines
- Lengthy production cycle time

Delayed care delivery →

5

Access to Care

- Academic centers have limited reach
- Minimal sites available in the community setting

Unintended access barriers

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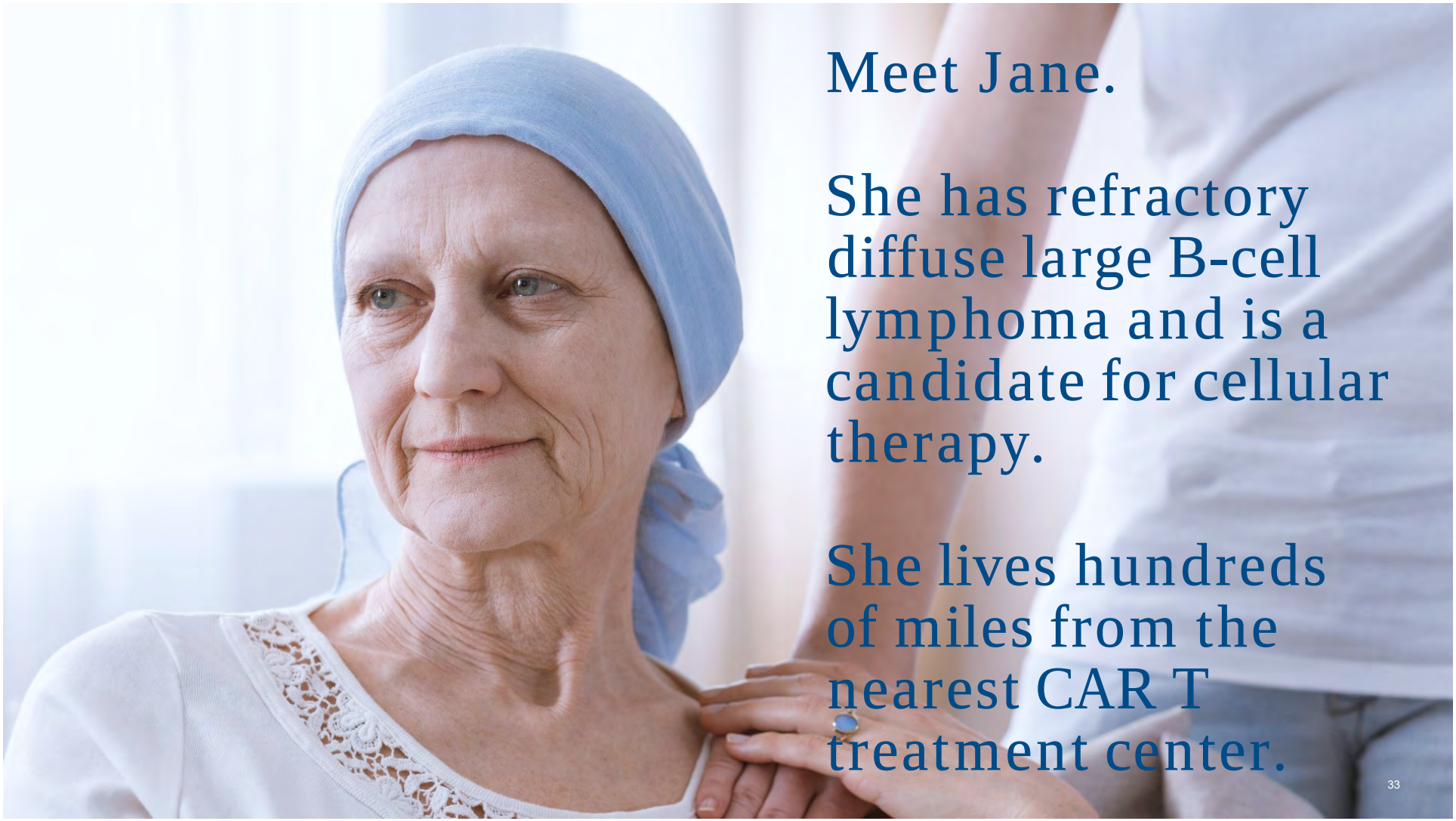

Meet Jane.
She has refractory diffuse large B-cell lymphoma and is a candidate for cellular therapy.
She lives hundreds of miles from the nearest CAR T treatment center.

Jane waits for her health insurer to approve the treatment.

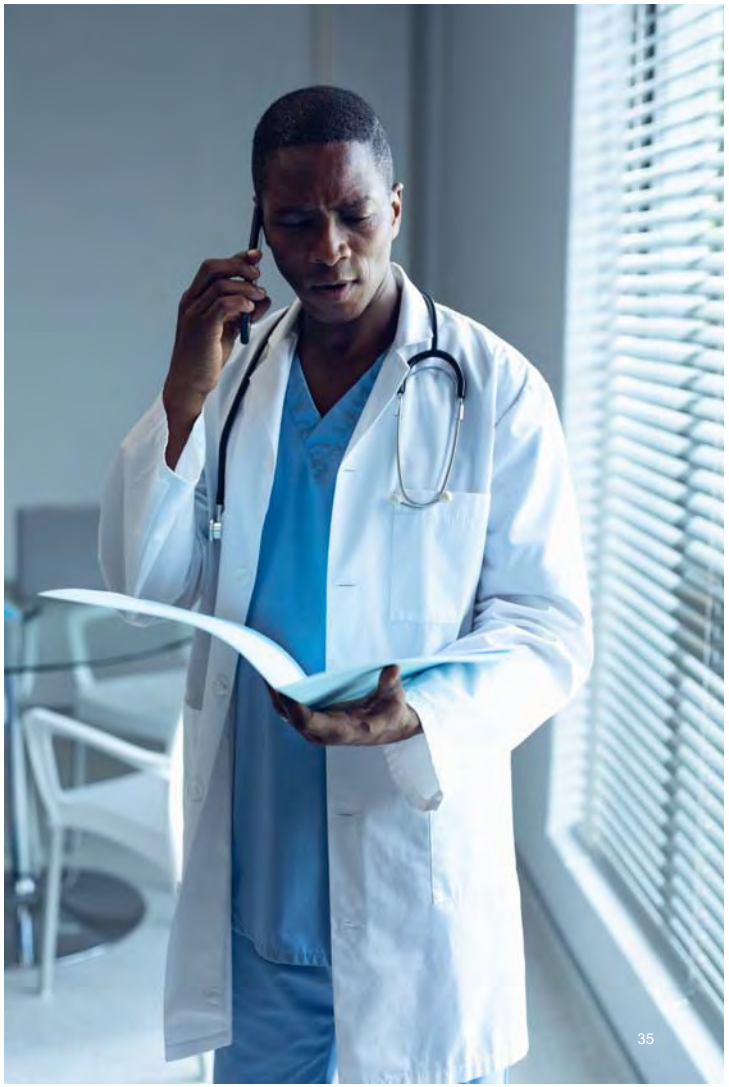
Jane:

“What is taking so long? My doctor prescribed this treatment weeks ago…”

Jane's doctor struggles to get her treatment approved by hospital administration.

Jane's Doctor:

"This is ridiculous – it's bad enough having to fight with insurance... and now the hospital CFO?"



The costs of CAR T treatments are staggering for patients like Jane.

Jane:

“Can I even afford this treatment?”

Similarly, her institution considers the financial implications of Jane's treatment.

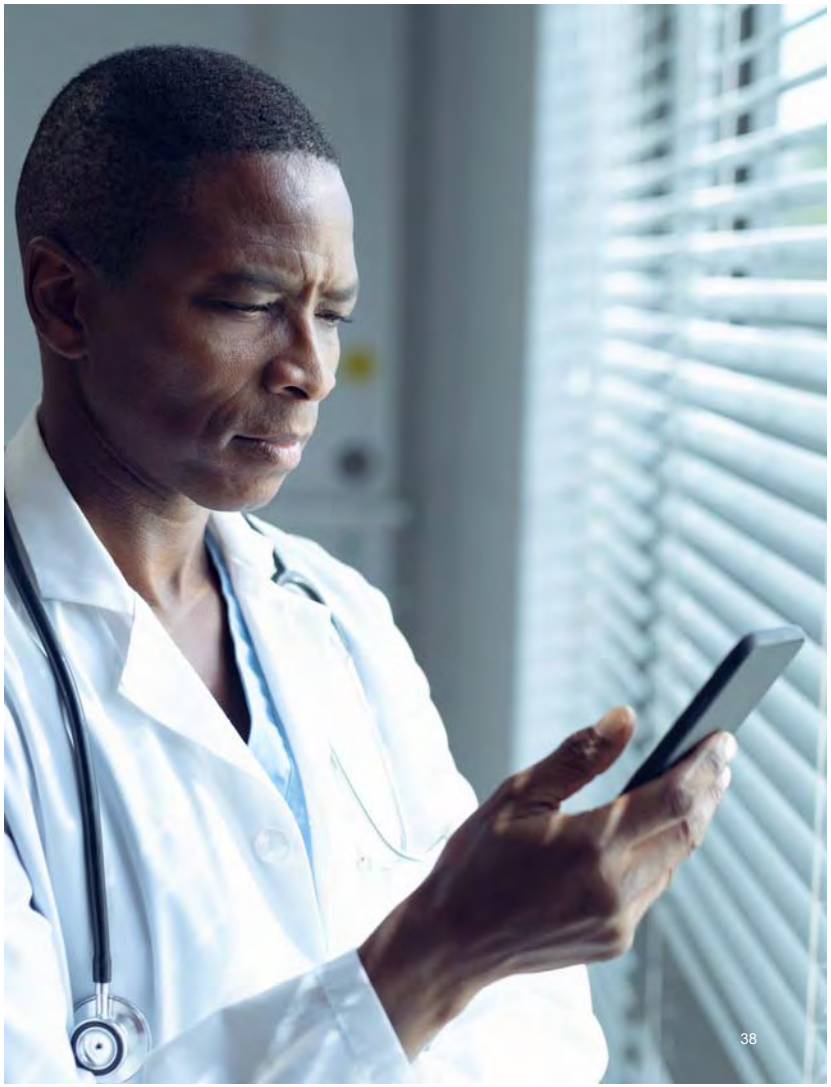
Hospital CFO:

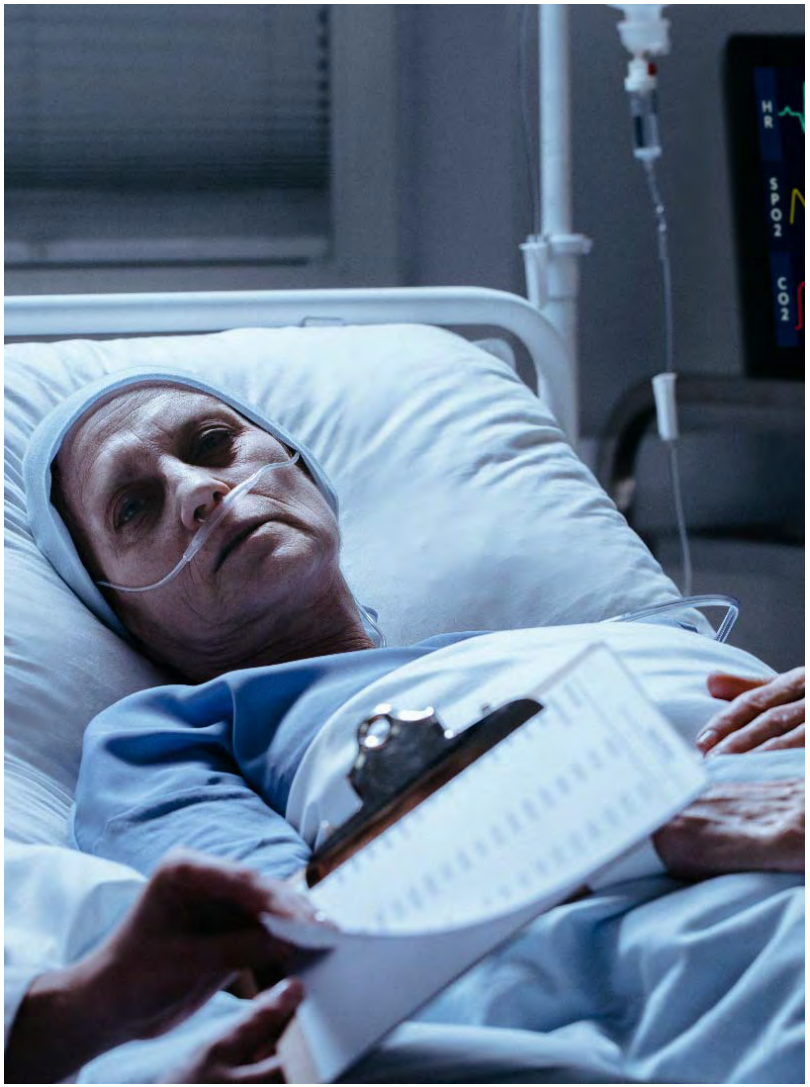
"Another Medicare patient. I want her to get the treatment, but how much will it set us back?"

Jane's treatment is further delayed due to supply chain issues.

Jane's Doctor:

"Another delay from the manufacturer? We've already delayed Jane's infusion and can't wait much longer…"





Jane's condition worsens as she continues to wait for her CAR T therapy.

Jane:

"I'm feeling worse by the day. Is there another treatment I can get instead?"

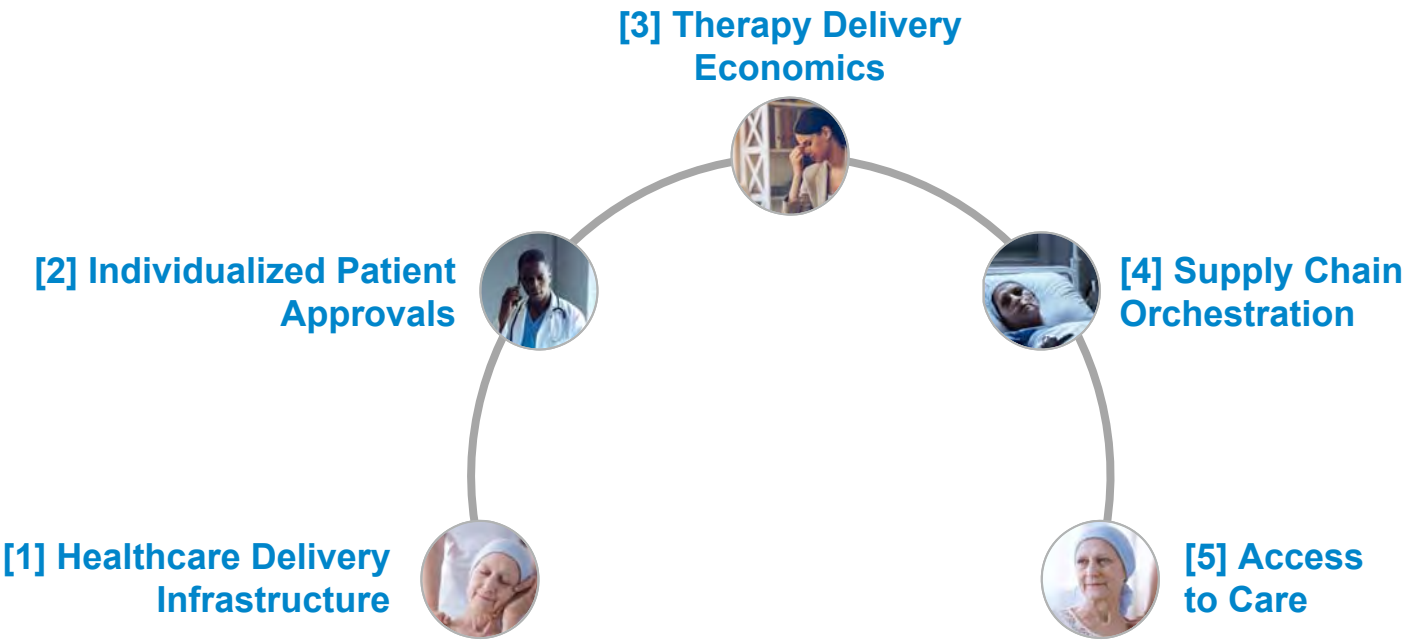
Jane's condition worsens as she continues to wait for her CAR T therapy.

Will Jane ultimately receive CAR T treatment?

Jane:

"I'm feeling worse by the day. Is there another treatment I can get instead?"

Partnering with a provider could be the answer



The cellular therapy market may never take off if these issues aren't solved.

THANK YOU