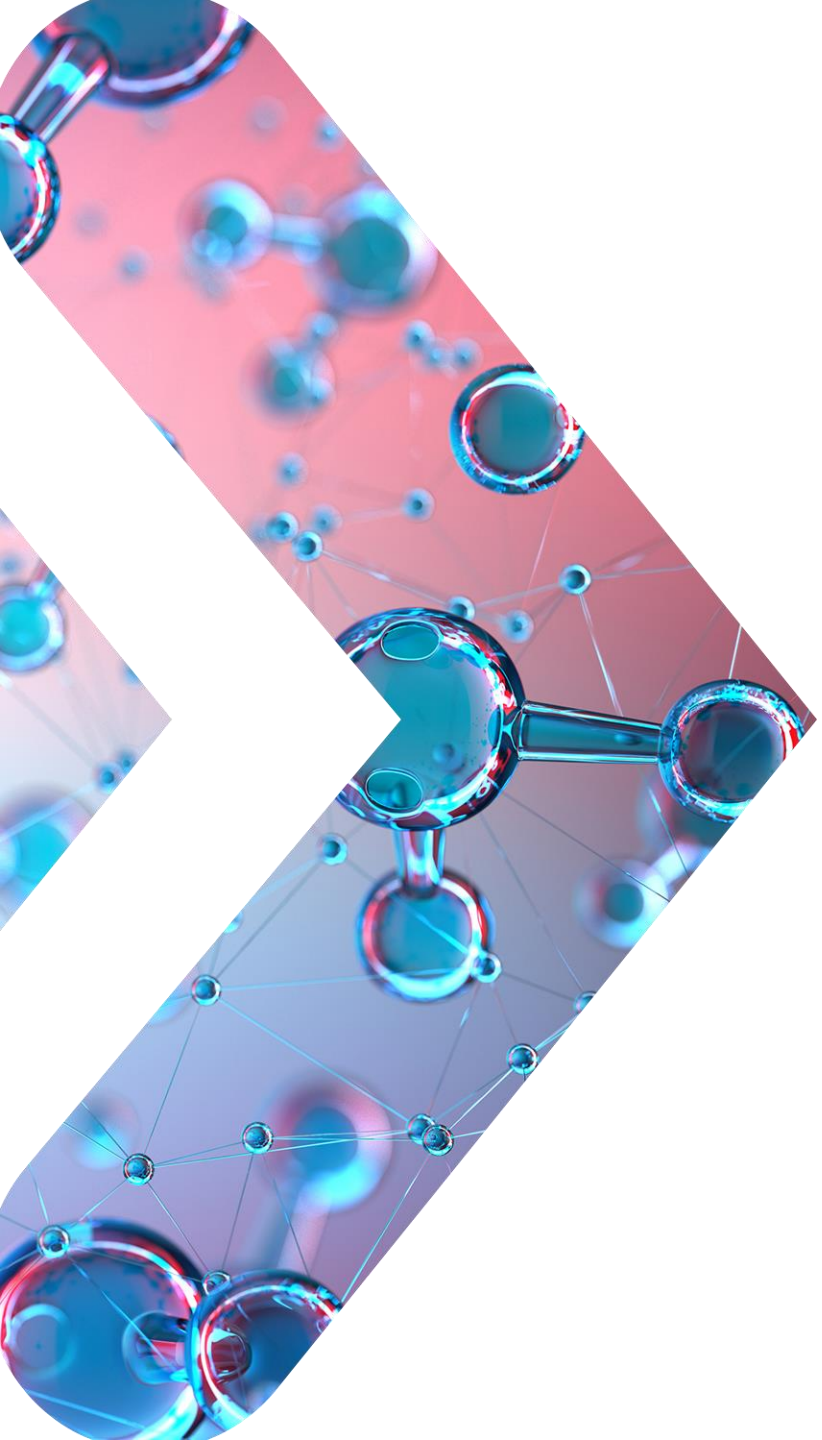

Delivering on Autoimmune Excitement Will Require Significant Changes in Cell Therapy Delivery

Health Advances and Parexel

Presented to

International Society ISCT Cell & Gene Therapy®

May 30, 2024

Speaker Introductions

Jamie Pierson
Senior Project Leader, Parexel

- Cell and Gene Therapy Program Lead
- Expertise leading cross-functional teams globally to deliver high-quality and patient-focused clinical trials and help bring life-changing treatments to market faster
- Experience across multiple therapeutic areas with specific interest in pediatric rare disease, neurology, and oncology

Ned Wydysh, PhD
Vice President, Health Advances

- Co-Leader of the Health Advances Biopharma, Cell and Gene Therapy, and Oncology Practice
- Expertise in portfolio planning, development, and commercialization strategy across therapeutic areas, with specific interest in oncology, orphan/genetic diseases, CNS, and autoimmune diseases
- Decision Resources, Analyst in Autoimmune and Inflammatory Disease Group
- Johns Hopkins University, PhD, Chemistry
- Williams College, BA, Chemistry

Cell therapy development has expanded beyond oncology in recent years as sponsors have set sights on autoimmune indications.

More Mature

Less Mature

Indication	US Prevalence	Select Manufacturers Developing Cell Therapies
SLE & Lupus Nephritis	~250,000	Bristol Myers Squibb, Cartesian Therapeutics, GRACELL, CRISPR Therapeutics, Autolus, Fate Therapeutics, IMPACT BIO, kyverna, Sana Biotechnology, artiva, nkarta Therapeutics, CARIBOU BIOSCIENCES, NOVARTIS, Cabaletta Bio
Myasthenia Gravis	~50,000	Cabaletta Bio, kyverna, Cartesian Therapeutics, BAUDAX BIO
Multiple Sclerosis	~900,000	Bristol Myers Squibb, kyverna, abata Therapeutics, Sangamo Therapeutics, iCell Gene Therapeutics
Crohn's Disease	~1MM	Bristol Myers Squibb, AstraZeneca, TRX BIO, SONOMA BIOTHERAPEUTICS, TRACT THERAPEUTICS
Type-1 Diabetes	~2MM	AstraZeneca, VERTEX, gentibio, QuellTX, abata Therapeutics
Rheumatoid Arthritis	~1.3MM	mesoblast, RheumaGen, SONOMA BIOTHERAPEUTICS, hope BIOSCIENCES

Note: Not all cell therapies in development for autoimmune indications are CAR-Ts, but also include Tregs, MSCs, and other cell types.
Source: Health Advances analysis, Izmirly 2021 Arthritis Rheumatol, Wallin 2019 Neuro, Myasthenia.org, Xu 2018 J Clin Med, Lewis 2023 Gastro, CDC.

If these programs are successful, the number of patients eligible to receive cell therapies could grow from tens of thousands to millions in the near future.

Approved **CAR-Ts** for **oncology** indications

~50,000

addressable US patients

Autoimmune disorders with **CAR-Ts** in development

~1MM

estimated US prevalence

Autoimmune disorders with **any cell therapy** in development*

~5MM

estimated US prevalence

* Includes Type 1 Diabetes

Source: Health Advances analysis, Datamonitor, FDA, company websites.

Delivering on the promise of gene-edited cell therapies for autoimmune disease will require significant changes in how cell therapy is delivered.

Addressing Millions More Autoimmune Patients will Require…

New Manufacturing and Delivery Models

Manufacturing and administration must scale for larger populations

Improved Risk-Benefit Profiles

Cell therapies must meet a safety standard for chronic, non-fatal conditions

Widespread Market Access

Today's CAR-T prices are a barrier to use in a far broader population

Today, manufacturing and infrastructure bottlenecks limit the uptake of cell therapies, challenges which will be magnified as indications for these treatments expand.

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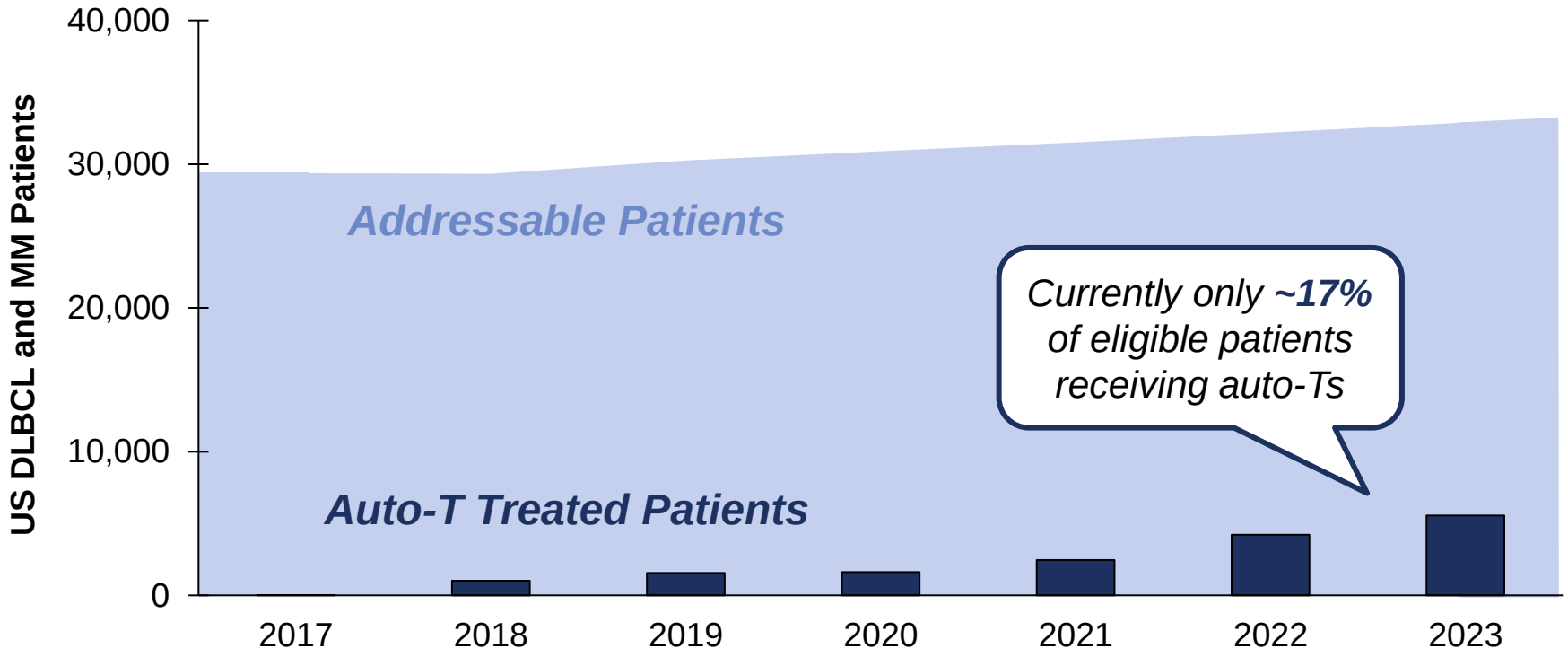
Only a small fraction of eligible patients receive CAR-Ts today, due in part to manufacturing capacity limitations for autologous cell therapies.

Addressable versus Treated Auto-T Patients

US, 2017-2023

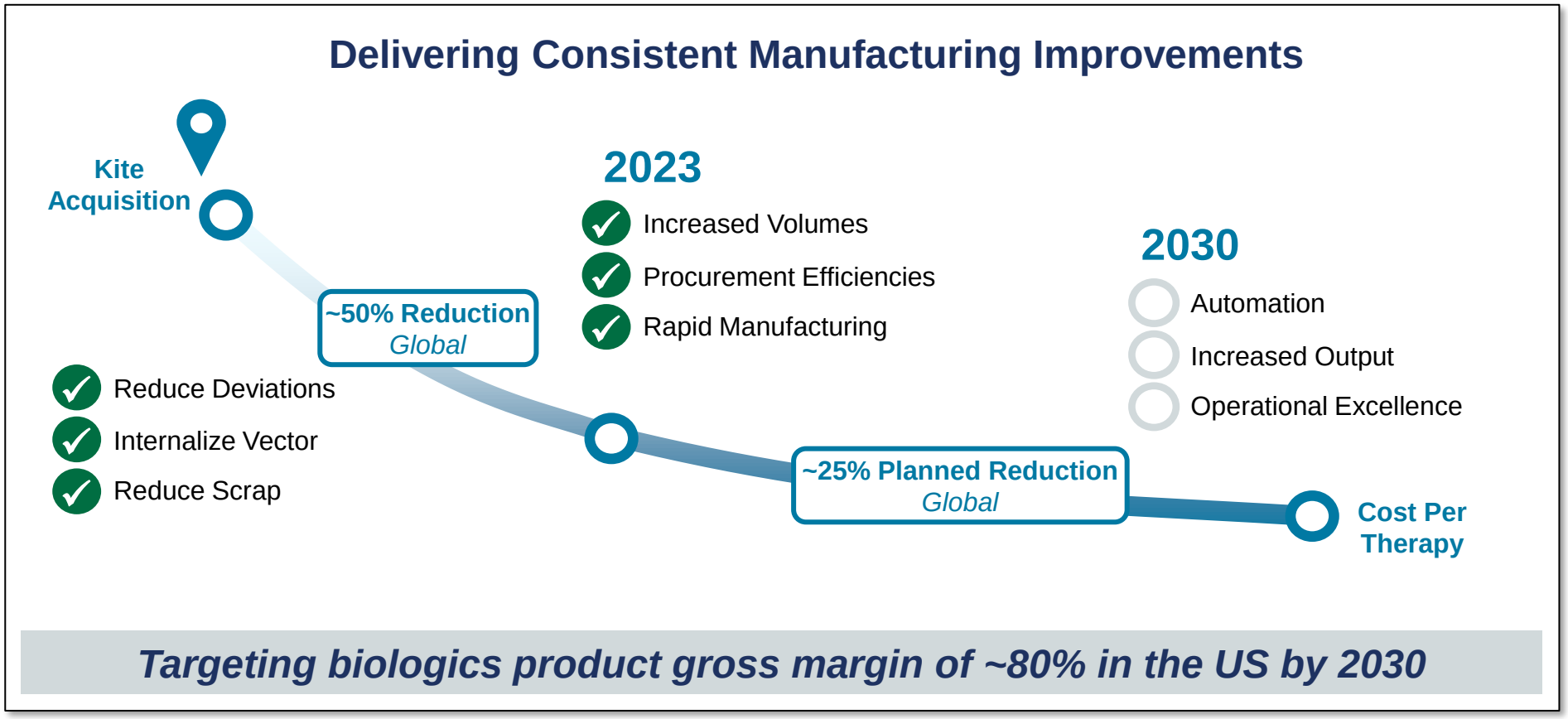


*"We have a backlog of myeloma patients who don't have access. **We have only 4 manufacturing slots but ~50-60 eligible patients**."*
– Dr. Nina Shah, UCSF

Note: Addressable patients defined as drug-treated 2L+ DLBCL or 3L+ MM patients.
Source: Health Advances interviews and analysis, Datamonitor, GlobalData, Oribiotech, Medscape.

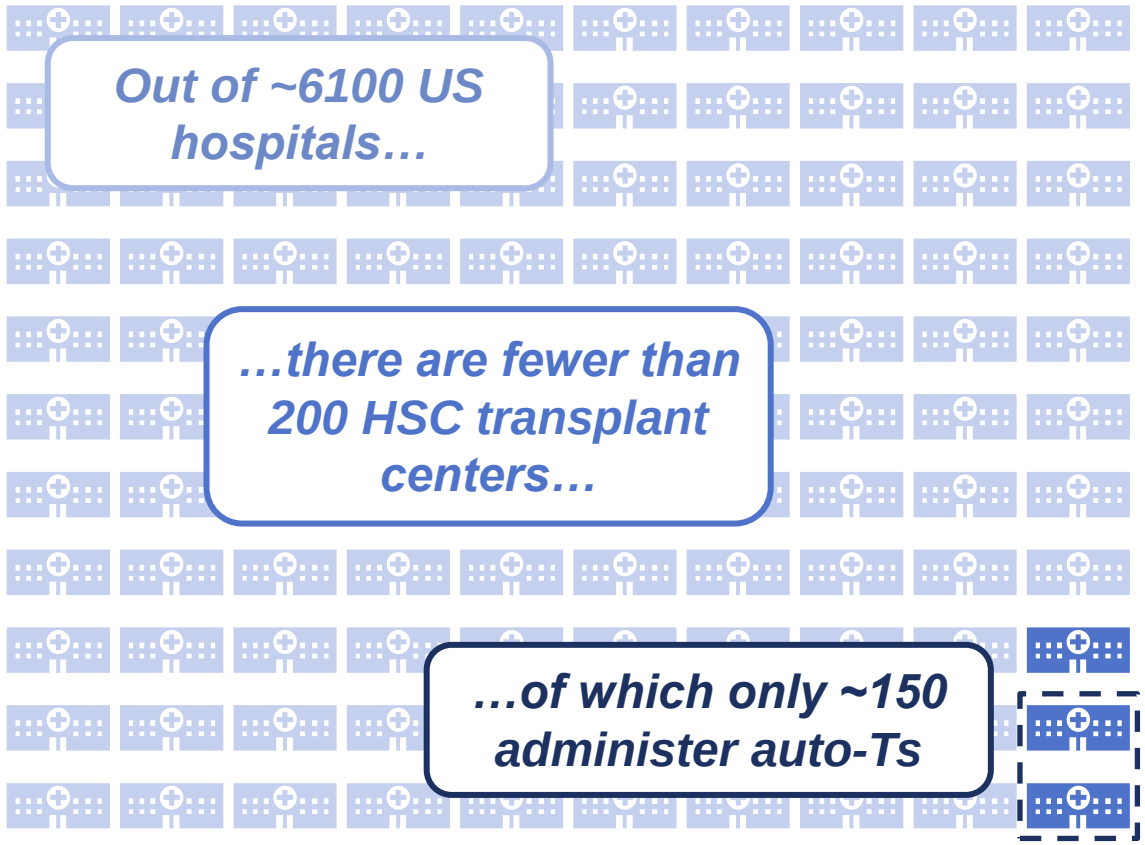
While developers are investing in increased manufacturing capacity and efficiency, incremental progress will still lag demand as CAR-Ts move to earlier lines.

GILEAD | Kite *Presentation to Investors, March 2024*



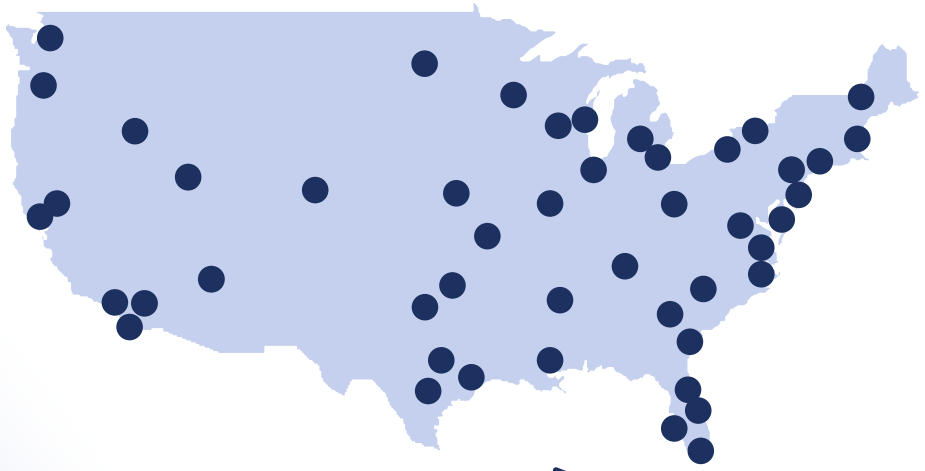
Source: Health Advances analysis, Gliead company website.

Autologous cell therapy administration occurs at specialized transplant centers, which are concentrated in urban centers and have limited capacity.



Major US Auto-T Transplant Centers

Illustrative



*"We foresee a shift to an **infrastructure-limited market**... with a gap between supply and demand of **2,000 doses per quarter** by 2030." – Leerink 2023*

Source: Health Advances interviews and analysis, Leerink, HRSA, AHA.

The successful expansion of cell therapies into autoimmune disease will require establishment of an appropriately balanced risk-benefit profile.

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Both auto- and allo-CAR-Ts in oncology carry the risk of serious complications such as CRS, which is generally acceptable in this treatment setting.

Clinical Profile in Oncology

Illustrative

Auto CAR-Ts

- ✘ Moderate CRS risk
- ✘ Class-level black box warning (T-cell malignancies)

Safety

- ✓ 90+% durable response rates

Efficacy

Allo CAR-Ts

- ✘ Moderate CRS risk
- ✘ Low GvHD risk
- ✘ Elevated risk of chrom. abnormalities

Safety

- ▪ 70+% response rates
- ▪ Relatively limited durability to date

Efficacy

*"**Risks from CAR-T therapies should be contextualized against other standard treatment modalities** such as chemotherapy and radiotherapy. These therapies have significantly higher rates of subsequent malignancies." – Dr. Bruce Levine, ISCT Past President*

Source: Health Advances analysis, BiopharmaDive, ISCT.

While the safety risks of CAR-Ts may be acceptable in oncology, that will not be the case in autoimmune disease.

	Oncology	Autoimmune Disease
Disease Severity	Fatal	Non-Fatal
Treatment Duration	Acute	Chronic
Risk of Alternative Treatments	Higher	Lower
Specialist Familiarity w/ Managing Toxicities	Higher	Lower
Acceptability of Lymphodepletion	Higher	Lower
Amenable to Current CAR-T Clinical Profile	✓	✗

"The risk tolerance in oncology is better because patients have limited time, and they're willing to take these therapies. ***For autoimmune patients, that might not necessarily be the case****." – Tiffany Chen, VP Discovery @ GentiBio*

Source: Health Advances analysis, HCPLive, Shahzad 2021 Blood, Chan 2022 Biomedicines, McCallion 2023 Clin Exp Immuno.

Finally, the broader addressable patient populations in autoimmune diseases could lead to large budget impacts and increased market access restrictions.

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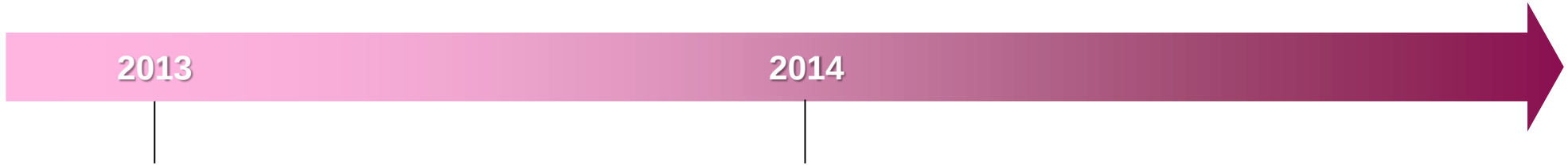
In the US, high-priced transformative drugs can struggle to achieve broad market access due to substantial budget impact on payers.

Case Study: Curative Treatments for Hepatitis C



SOVALDI™ SOFOSBUVIR 400 mg TABLETS

Sovaldi approved in US

- Improved efficacy, safety over SOC (90+% cured)
- Favorable ICER evaluation, even at annual list price of $84,000

$6.5B USD

Total US Sovaldi budget impact in 2014, incl. $4.5B by Medicare

$310B USD

Theoretical cost to treat all 3.7MM HCV patients

$361B USD

Actual spend on all drugs in 2014 by US payers

Significant Access Restrictions Due to Budget Impact

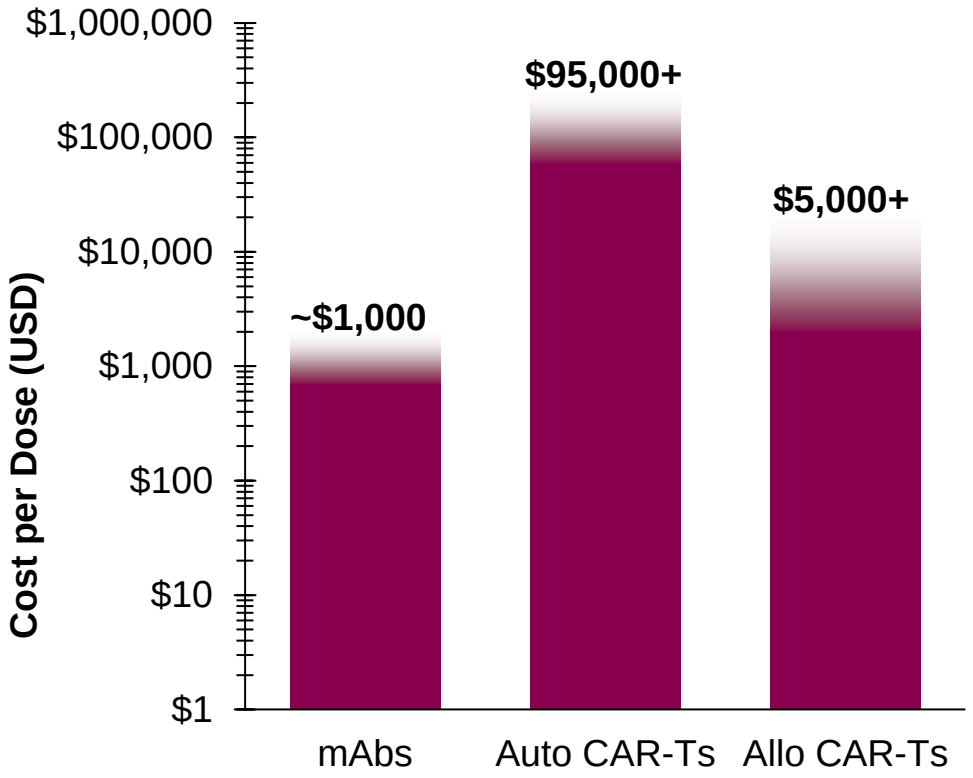
- Outright coverage denial
- Aggressive prior authorization
- Specialist prescribers only
- Restricted use to liver fibrosis population

Source: Health Advances interviews and analysis, Henry 2018 J Health Biomed Law, Linas et al 2015 Ann Intern Med.

The current price tag for auto-CAR-Ts – partly driven by high COGS – would be unsustainable if used in large patient populations. Allo-CAR-Ts will face this same challenge.

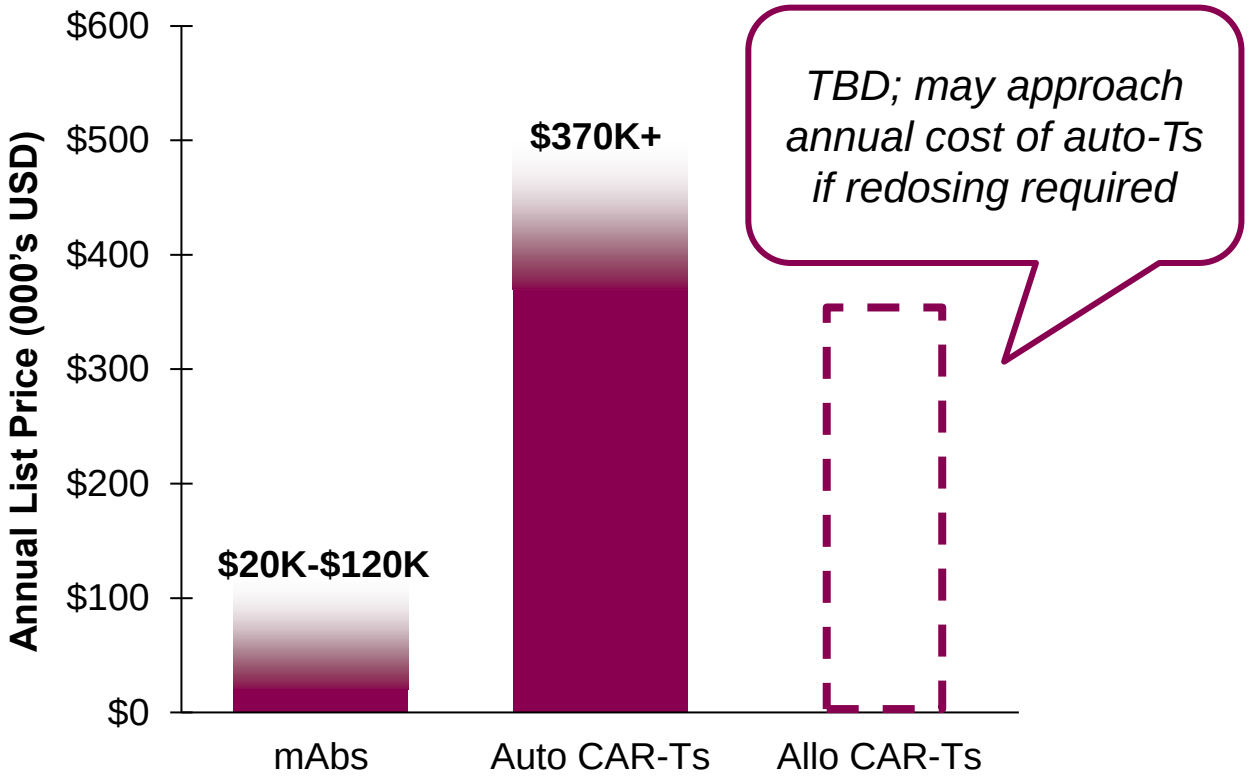
Cost of Manufacturing Per Dose

Across biologic modalities



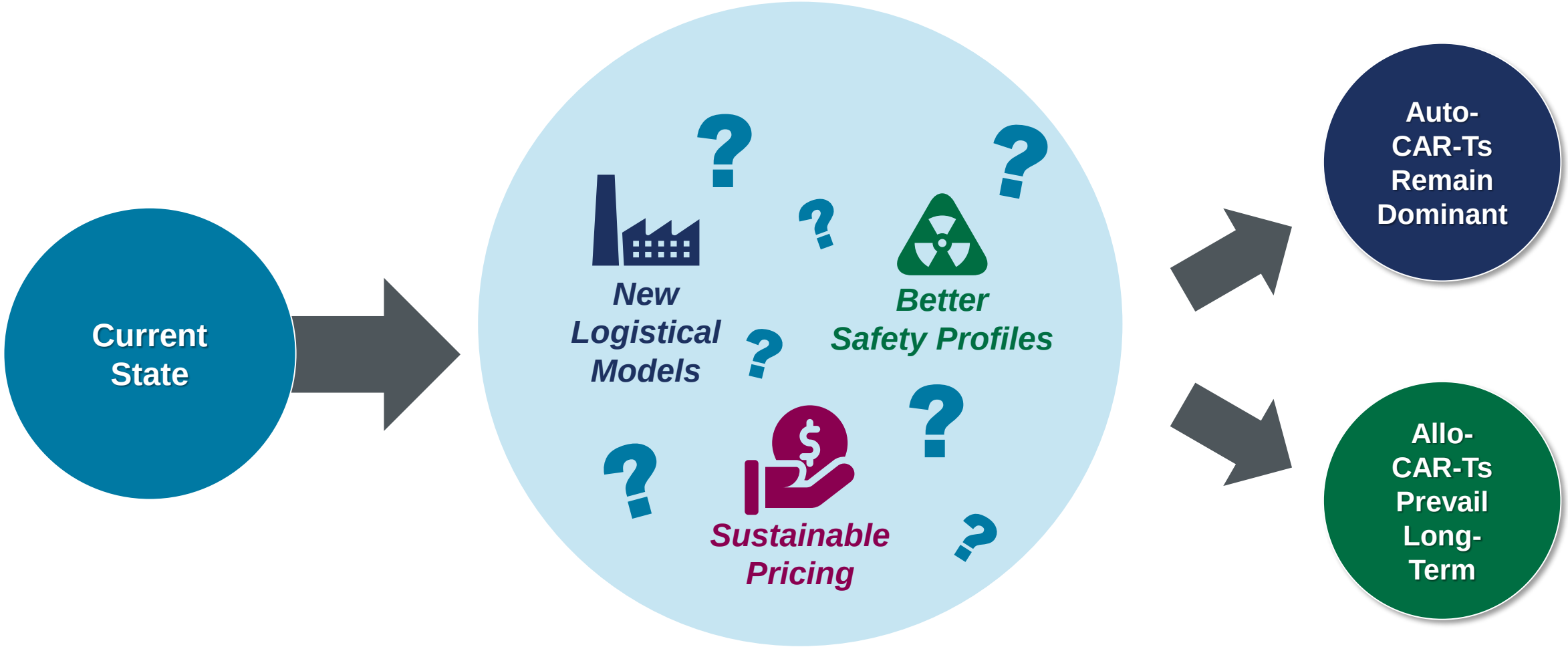
Annual List Price per Patient

Across biologic modalities



Source: Health Advances interviews and analysis, Farid 2020 MABS, GEN News, Harrison 2019 Cytotherapy, Hernandez 2018 AJMC, Choe 2022 JAMA Network Open, Jenkins 2018 Biochem Eng J, company materials.

Change will be required for either autologous or allogeneic products to become widely used in autoimmune disease. Which of these changes occur – and to what extent – will determine the dominant modality.



A future state where auto-Ts remain dominant will need new infrastructure and access models, while allo-Ts must have improved duration of efficacy to prevail.

Evolution required for…

Auto-Ts to be Dominant Cell Therapy Modality for Autoimmune

Investment in treatment infrastructure, via expansion of existing CAR-T sites and/or establishment of dedicated outpatient centers

Risk sharing between sponsors and payers (e.g., outcomes-based agreements) to reduce budget impact

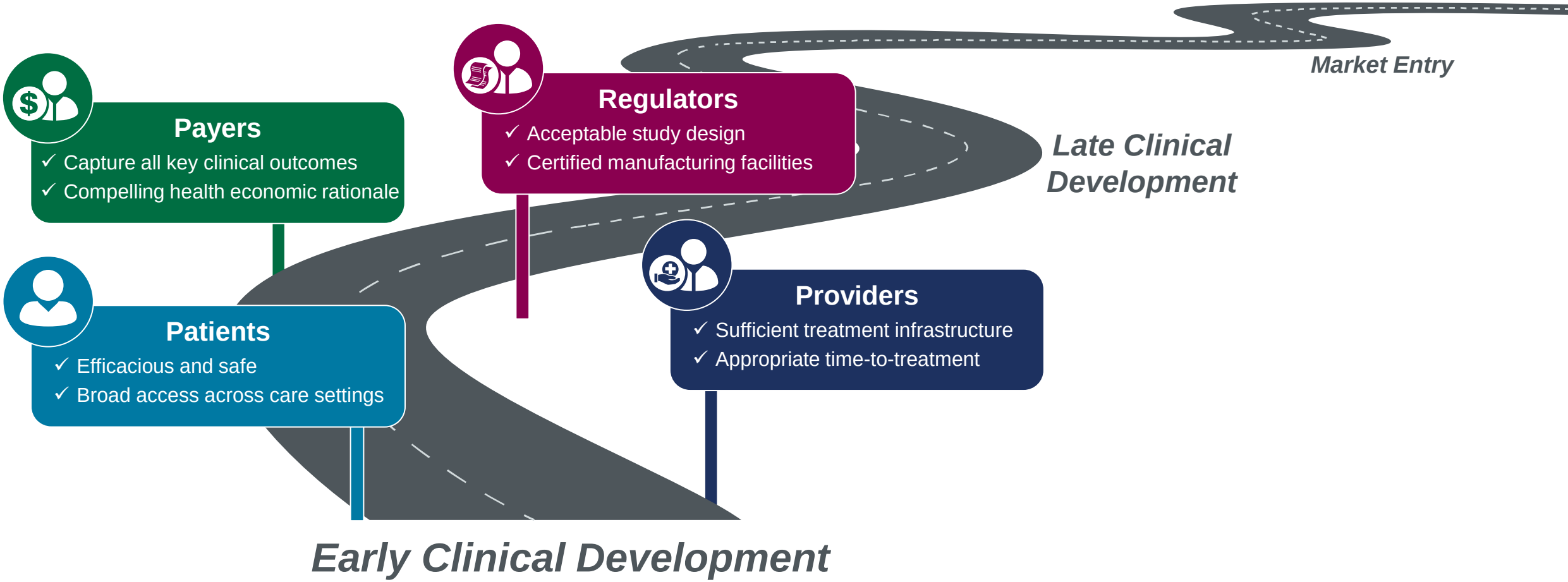
Allo-Ts to Prevail over Auto-Ts in Long-Term

More durable efficacy, highly favorable safety profile to overcome the current shortcomings of allo-Ts in hematologic malignancies

For both classes: Improved manufacturing efficiency to limit the budget impact for payers and improve access for patients

Cell therapy sponsors must start early to ensure their development, manufacturing, access, and regulatory plans align with the different stakeholder needs for autoimmune therapies.

Keys to Success for Autoimmune Cell Therapy Sponsors



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