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Revolutionizing Care: Adopting Emerging Therapies for Patients with Cancer

A presentation for HealthTrust Members
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Samantha Randlett, PharmD

PGY-2 Corporate Pharmacy Administration & Leadership Resident

HealthTrust Performance Group/University of Tennessee College of Pharmacy

Preceptor(s):
Laura Crow, PharmD - Director Clinical Pharmacy Member Support, HealthTrust Performance Group
Jason J Braithwaite, PharmD, MS, BCPS - Senior AVP, Clinical Pharmacy Operations & Business Development, HealthTrust Performance Group

Disclosure

- Neither the presenter nor her preceptor have conflicts of interests related to this presentation.

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Learning Objectives

Pharmacists, Nurses & Radiologists

- Recognize obstacles to the adoption of emerging therapies in cancer treatment
- Identify differences in reimbursement based on treatment setting for emerging therapies in cancer treatment
- Recall regulatory processes related to the approval of emerging therapies in cancer treatment

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Background

Market Access for New Drugs

- As technology and science improves, crucial new drugs are entering the market, but are struggling to reach the patient due to accessibility and affordability.
- Understanding these key components to market access will help prevent delays in care.

Regulatory Affairs

Reimbursement

Patient Access

- In order to understand how to navigate these challenges, HealthTrust collaborates with pharmaceutical companies to create strategic partnerships to enhance our understanding on regulatory and reimbursement landscape, potential barriers and strategies to provide benefits to patients.

Emerging Therapies

Biosimilars

A biological product this is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product

Cell Therapies

The transfer of autologous or allogenic cellular material into a patient for medical purposes

Theranostics

The combination of the words “therapy” and “diagnostics” using radioisotopes to first image a patient’s tumor for diagnostics and then therapeutically treat that tumor

- Biological product definitions. U.S. Food and Drug Administration. Accessed February 18, 2025. https://www.fda.gov/files/drugs/published/Biological-Product-Definitions.pdf
- El-Kadiry AE, Rafei M, Shammaa R. Cell therapy: types, regulation, and clinical benefits. *Front Med (Lausanne)*. 2021;8:756029. doi:10.3389/fmed.2021.756029
- What is theranostics? MD Anderson Cancer Center. October 21, 2024. Accessed February 15, 2025. https://www.mdanderson.org/cancerwise/what-is-theranostics.h00-159701490.html

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Biosimilar Landscape

Biosimilar Overview

Reference Product versus Biosimilar Product versus Generic Product

Reference Product: a single biological product, already approved by the FDA

Biosimilar Product: a biological product that is highly similar (slight differences with inactive components are acceptable) to and has no clinically meaningful differences from an existing FDA-approved reference product

Generic Product: an exact version of a brand name drug that has the same active ingredient(s)

Common indications:

- Chronic Skin Diseases
- Chronic Bowel Diseases
- Macular Degeneration
- Arthritis
- Multiple Sclerosis
- Some Cancers
- Osteoporosis

- Biological product definitions. U.S. Food and Drug Administration (FDA). Accessed February 18, 2025. https://www.fda.gov/files/drugs/published/Biological-Product-Definitions.pdf
- Biosimilars basics for patients. U.S. Food and Drug Administration (FDA). Updated August 1, 2024. Accessed February 18, 2025. https://www.fda.gov/drugs/biosimilars/biosimilars-basics-patients

Development & Regulatory Approval Process

Development for Biologics

- **Development Costs = $100M to $300M**
- Primary cost drivers:
  - Molecule complexity
  - Patent / Legal costs
  - Patient assistance programs
  - Marketing and sales

- **Development Time = 7- 8 years**
- Average time from FDA approval to launch is >2 years (2 months to 7 years):
  - Litigation
  - Pay to delay

Applications for Biologics

351(a) BLA

Contains all information and data necessary to demonstrate that the proposed biological product is safe, pure and potent

BLA = BIOLOGIC LICENSE APPLICATION

351(k) aBLA

To demonstrate biosimilarity (or interchangeability) to a reference product based on comparative assessments

ABLA = ABBREVIATED BLA

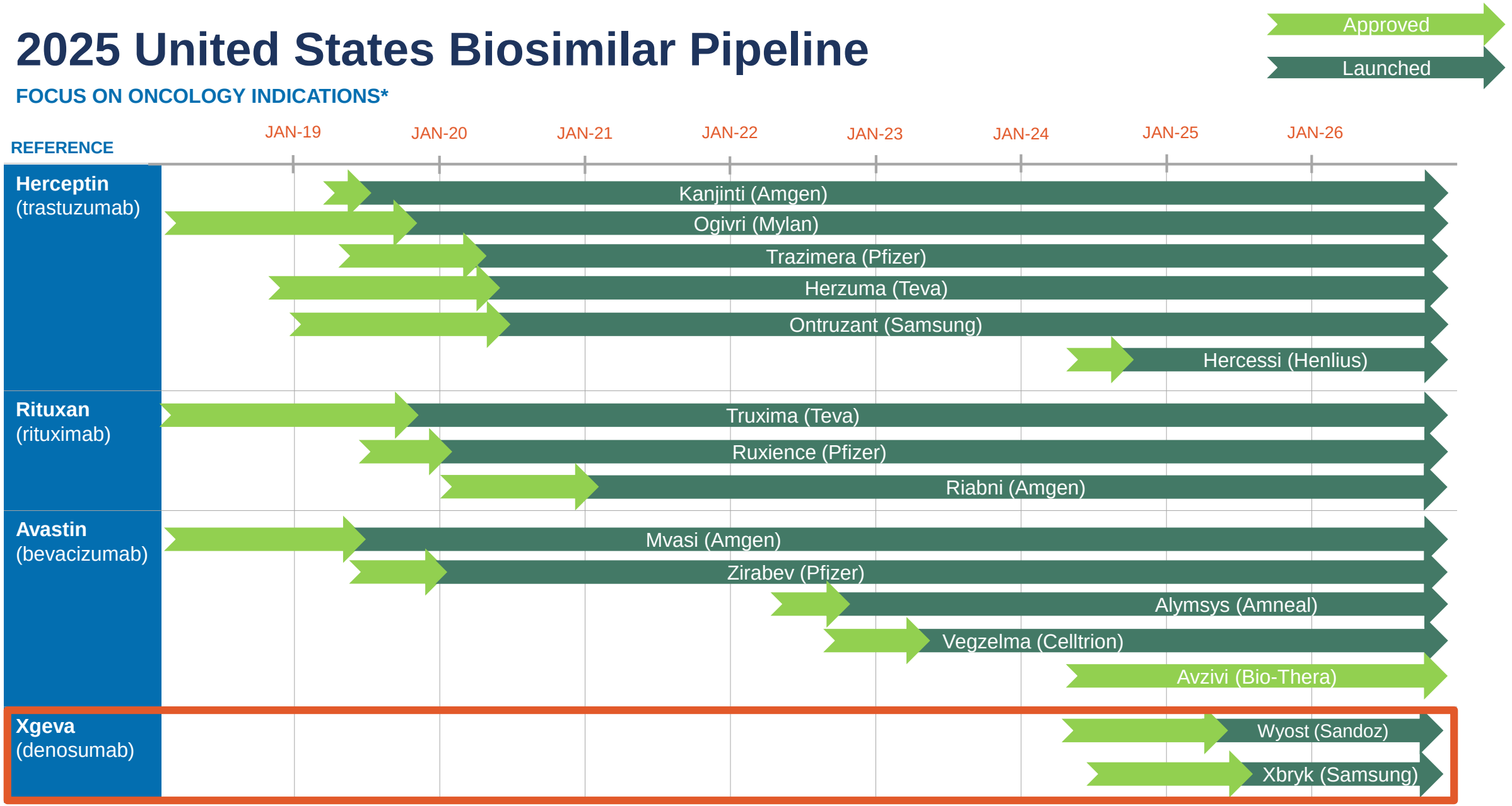
Regulatory Board

Center for Biologics Evaluation and Research (CBER) is the center within the Food and Drug Administration (FDA) that regulates biosimilars

- The U.S. generic & biosimilar medicines savings report. Association for Accessible Medicines. September 2024. Accessed February 18, 2025. https://accessiblemeds.org/sites/default/files/2024-09/AAM-2024-Generic-Biosimilar-Medicines-Savings-Report.pdf
- Biosimilars. U.S. Food and Drug Administration (FDA). Updated March 1, 2023. Accessed February 18, 2025. https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars

2025 United States Biosimilar Pipeline

FOCUS ON ONCOLOGY INDICATIONS*



*NOT ALL-INCLUSIVE LIST

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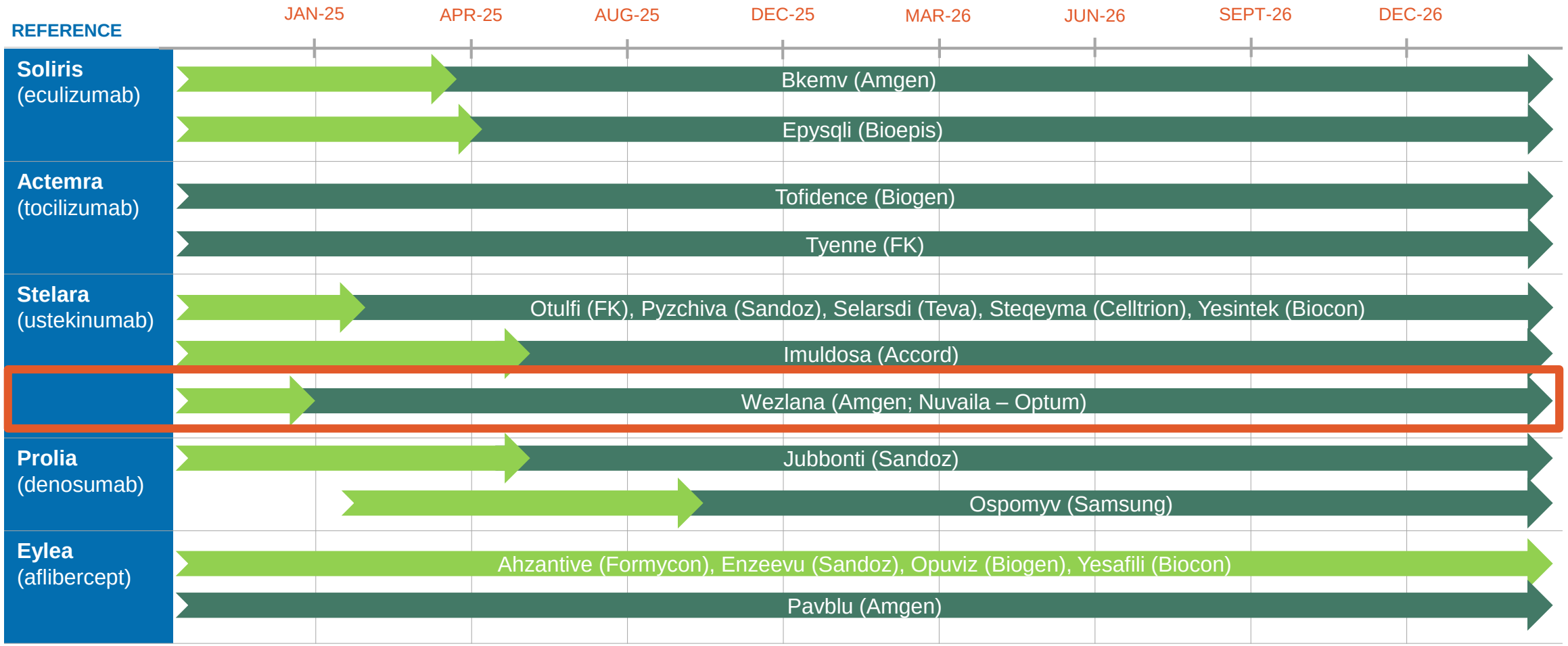
Biosimilar product information. U.S. Food and Drug Administration (FDA). Updated periodically. Accessed February 14, 2025. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information

2025 United States Biosimilar Pipeline

Approved

Launched

FOCUS ON IMPORTANT UPDATES FOR THIS YEAR*



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Biosimilar product information. U.S. Food and Drug Administration (FDA). Updated periodically. Accessed February 14, 2025. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information

Impacts to Adoption

Prescribing Habits

- Provider Hesitancy
  - Unwilling to prescribe as provider may lack familiarity with product
- Patient Comfort
- Safety and Efficacy
  - Clinical studies will continue to prove biosimilars and reference products equivalency

Barriers to Launch

- Patent litigation battles
- “Pay to delay” by brand-name pharma companies
- Interchangeability studies
- “Rebate traps” by reference product manufacturers
- Slow uptakes by PBMs
  - “White-labeling” – payers create a restricted formulary

Category Competition

- Highly variable
- Enhanced competition will most likely lowers prices
  - However, savings may not be as significant as originally projected
  - Some may not be vertically integrated
- Patient access to treatment increases with competition

Sustainability

- Payers versus Providers
  - Some manufacturers focus on payers, and some on providers
- “Average Sales Price (ASP) Game”
  - Payer-focused
  - Provider-focused
  - High WAC / Low WAC Trend

- Steinzor P. Overcoming barriers to biosimilar adoption. The American Journal of Managed Care. October 16, 2024. Accessed February 14, 2025. https://www.ajmc.com/view/overcoming-barriers-to-biosimilar-adoption
- Ferruggia K, Canavan J. Expert: overcoming barriers to wider biosimilar adoption. Pharmacy Times. February 24, 2025. Accessed February 26, 2025. https://www.pharmacytimes.com/view/expert-overcoming-barriers-to-wider-biosimilar-adoption

Audience Participation #1

Which of the following is a risk to biosimilar adoption?

A. Provider comfort in new molecule
B. Patent complexities
C. ASP Game
D. All the above

Audience Participation #1, Correct Response

Which of the following is a risk to biosimilar adoption?

A. Provider comfort in new molecule
B. Patent complexities
C. ASP Game
D. All the above

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Cell Therapy Landscape

Cell Therapy Overview

Stem Cell Based	Non-Stem Cell Based	Multicellular Therapies
• Pluripotent stem cells (PSCs) • Adult stem cells (ASCs) • Cancer stem cells (CSCs)	• Somatic cell-based therapy generally in vivo source of enzymes, cytokines, and growth factors • Example(s): chimeric antigen receptor (CAR) T-cell therapy	• Containing at least two stem cell and/or non-stem cell types • Example(s): scaffold-based or –free cellular products, stromal vascular fraction (SVF), bone marrow aspirate (BMA)-derived therapies

El-Kadiry AE, Rafei M, Shammaa R. Cell therapy: types, regulation, and clinical benefits. *Front Med (Lausanne)*. 2021;8:756029. doi:10.3389/fmed.2021.756029

Patient Case - AB

- Subjective/Objective: 50 year old male with confirmed refractory diffuse large B cell lymphoma with signs of continued progression after multiple rounds of treatment. Limited comorbidities with resolved history of hypertension. Asymptomatic. ECOG is 0. Excellent caregiver.

- Assessment:
  - Previous treatment with:
    - R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) x 6
    - GDP salvage therapy (platinum-based gemcitabine, dexamethasone, and cisplatin) x 2

- Plan:
  - CAR T-cell therapy

For the purpose of the basic understanding of this patient case, no mutations or translocations will be discussed.

Foley R, Kuruvilla J. Identification of a patient suitable for CAR-T cell therapy in the outpatient setting: a vodcast and case example. *Oncol Ther*. 2024;12(2):239-245. doi:10.1007/s40487-024-00272-9

CAR T-Cell Overview

- Chimeric Antigen Receptor (CAR) T-cell therapy is a type of treatment called immune effector cell therapy. It works by engineering a patient's own (autologous) immune cells to connect genetically modified CAR T-cells to help them better identify and attack cancer cells.
- CAR T-cell therapy is currently used as a therapy option for certain cancers when other treatments aren't effective. There has been a recent shift to study these therapies in additional disease states.

Examples of Oncology Indications*:

- B-cell acute lymphoblastic leukemia
- Diffuse large B-cell lymphoma
- Follicular lymphoma
- High-grade B-cell lymphoma
- Mantle cell lymphoma
- Multiple myeloma

*NOT ALL-INCLUSIVE LIST

El-Kadiry AE, Rafei M, Shammaa R. Cell therapy: types, regulation, and clinical benefits. *Front Med (Lausanne)*. 2021;8:756029. doi:10.3389/fmed.2021.756029

Development & Regulatory Approval Process

Development of CAR T-cell Therapy

- **Initial publications to first FDA approval = 30 years**
- **Development Costs = $400,000 to $1 million per patient**
- Primary cost drivers:
  - Multistep process to genetically engineer cells (viral vectors)
- **Development Time = 2 to 6 weeks**

Application for CAR T-cell Therapy

351(a) BLA

Contains all information and data necessary to demonstrate that the proposed biological product is safe, pure and potent

BLA = BIOLOGIC LICENSE APPLICATION

Regulatory Board

Within the Food and Drug Administrations (FDA) department of Center for Biologics Evaluations and Research (CBER), the Office of Tissues and Advanced Therapies (OTAT)

- Braendstrup P, Levine BL, Ruella M. The long road to the first FDA-approved gene therapy: chimeric antigen receptor T cells targeting CD19. *Cytotherapy*. 2020;22(2):57-69. doi:10.1016/j.jcyt.2019.12.004
- Mona Elmacken, Upendra Mahat, Nicole Verdun, Lola Fashoyin-Aje. Regulatory considerations for approval of chimeric antigen receptor T cell therapies for treatment of hematological malignancies. *Blood.* 2024;144(Supplement 1):7765. doi: 10.1182/blood-2024-210267
- Cliff ERS, Kelkar AH, Russler-Germain DA, et al. High cost of chimeric antigen receptor T-cells: challenges and solutions. *Am Soc Clin Oncol Educ Book*. 2023;43:e397912. doi:10.1200/EDBK_397912

Current Therapy Process

Release for Infusion (RFI) Certificate will accompany product for actual cell counts and volumes to be infused

- CAR T-cell therapy is customized for each individual patient

Collecting the T-cells

- White blood cells (WBCs) are removed from the patient's blood using a procedure called leukapheresis
- As the blood is removed, WBCs are separated out and red blood cells are infused back into the body

2 TO 3 HOURS

Making the CAR T-cells

- T-cells are separated from WBCs and sent to the lab
- Lab alters the cells by adding a gene specific for CAR, making them CAR T-cells
- These specific cells are grown and multiplied in the lab based on required dose

2 TO 3 WEEKS

Receiving the CAR T-cell Infusion

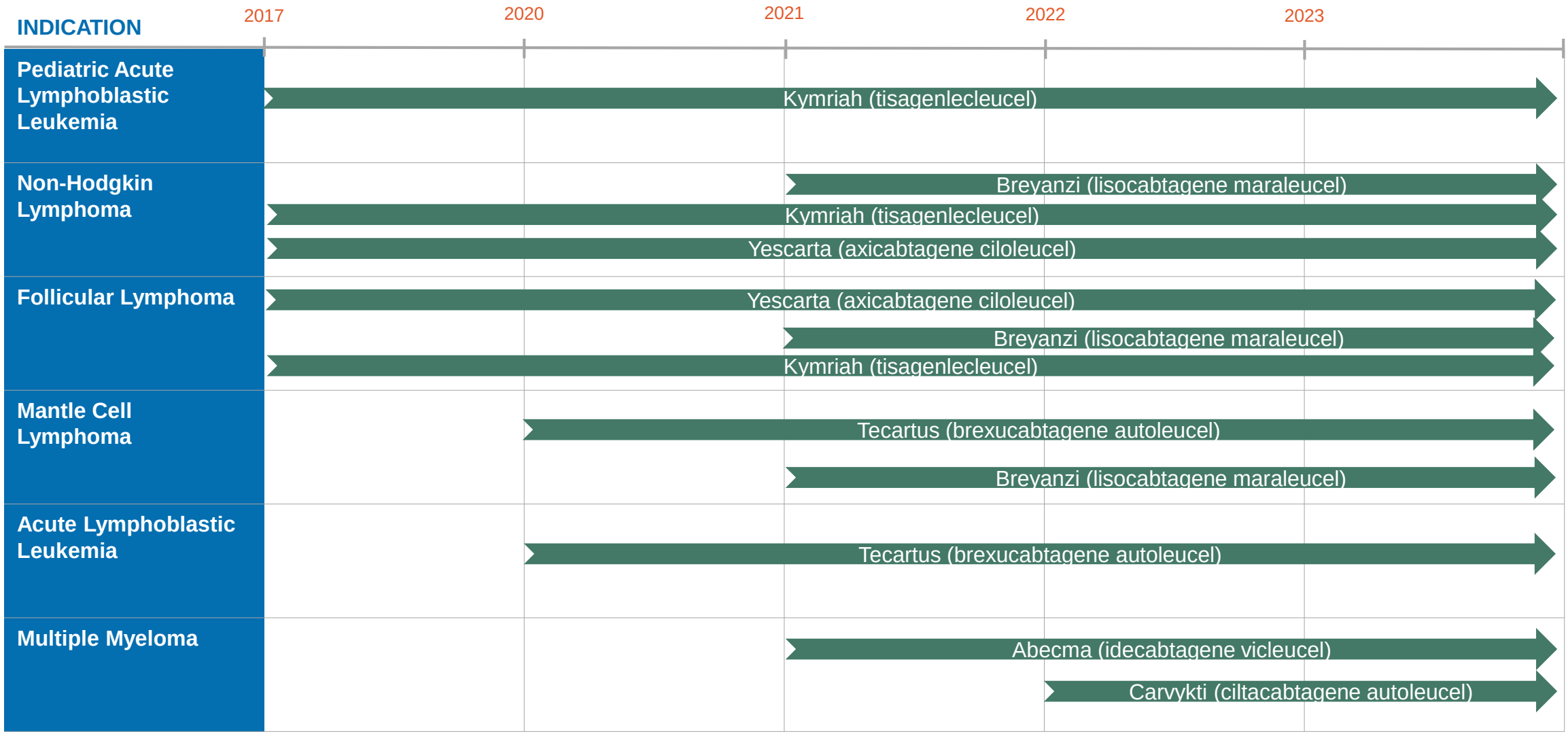
- A few days before the CAR T-cell infusion, the patient may receive chemotherapy
- CARs recognize and bind to specific proteins, or antigens on the surface of the cancer cells

30 MINUTES

Markman M. CAR T cell therapy. City of Hope. January 12, 2023. Accessed February 18, 2025. https://www.cancercenter.com/treatment-options/precision-medicine/immunotherapy/car-t-cell-therapy

United States CAR T-Cell Pipeline/Market Landscape

CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY FOR ONCOLOGY*



*NOT ALL-INCLUSIVE LIST; ONLY LISTED FOR FDA-APPROVED INDICATIONS

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Approved cellular and gene therapy products. U.S. Food and Drug Administration (FDA). Updated periodically. Accessed February 14, 2025. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

Patient Case - AB

- Diagnosis: refractory diffuse large B-cell lymphoma (DLBCL)

- Options of Therapy:

	Abecma	Breyanzi	Carvykti	Kymriah	Tecartus	Yescarta
ALL, B-cell precursor, relapsed or refractory				X*	X	
Non-Hodgkin Lymphoma (Large B-cell lymphoma, relapsed or refractory)		X		X		X
Follicular lymphoma, relapsed or refractory		X		X		X
MCL, relapsed or refractory		X			X	
Multiple myeloma, relapsed or refractory	X		X			

*up to 25 years old

Foley R, Kuruvilla J. Identification of a patient suitable for CAR-T cell therapy in the outpatient setting: a vodcast and case example. *Oncol Ther*. 2024;12(2):239-245. doi:10.1007/s40487-024-00272-9

Pivotal Clinical Trials - NHL

Clinical Trial Name	Year	Intervention	Outcomes			Results
			Overall Response Rate, %	OS at month 12, %	OS at month 24, %	
JULIET[1,5] (Kymriah)	2018	Tisagenlecleucel as single IV treatment, target dose $3x10^8$ CAR T-cells (n=115) along with SOC	52% overall response rate with a 40% complete response rate	48.2%	40.0%	"In this international study of CAR T-cell therapy in relapsed or refractory diffuse large B-cell lymphoma in adults, high rates of durable responses were produced with the use of tisagenlecleucel."
ZUMA-1[2,3,5] (Yescarta)	2019	Axi-cel as single IV treatment, target dose $2x10^6$ CAR T-cells per kg (n=101) along with SOC	74% overall response rate with a 54% complete response rate	59%	50.5%	"These 2-year follow-up data from ZUMA-1 suggest that axi-cel can induce durable responses and a median overall survival of greater than 2 years"
TRANSCEND NHL 001[4,5] (Breyanzi)	2021	Liso-cel as one of three target dose levels administered as a sequential infusion of two components at equal target doses (n=256) along with SOC	73% overall response rate with a 53% complete response rate	57.9%	44.9%	"Liso-cel resulted in a high objective response rate, with a low incidence of grade 3 or worse cytokine release syndrome and neurological events in patients with relapsed or refractory large B-cell lymphomas."

Axi-cel = axicabtagene ciloleucel; CAR = chimeric antigen receptor; IV = intravenous; Liso-cel = lisocabtagene maraleucel; OS = overall survival; SOC = standard of care

1. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380(1):45-56. doi:10.1056/NEJMoa1804980
2. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*. 2019;20(1):31-42. doi:10.1016/S1470-2045(18)30864-7
3. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544. doi:10.1056/NEJMoa1707447
4. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396(10254):839-852. doi:10.1016/S0140-6736(20)31366-0
5. Westin JR, Kersten MJ, Salles G, et al. Efficacy and safety of CD19-directed CAR-T cell therapies in patients with relapsed/refractory aggressive B-cell lymphomas: observations from the JULIET, ZUMA-1, and TRANSCEND trials. *Am J Hematol*. 2021;96(10):1295-1312. doi:10.1002/ajh.26301

REMS Programs

"A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweighs its risks."

	Abecma	Breyanzi	Carvykti	Kymriah	Tecartus	Yescarta
REMS	Yes; for cytokine release syndrome (CRS) and neurologic toxicity					
CRS Occurrence Rate	89%	54%	84%	74%	91%	90%

- CAR T-cell therapy may only be dispensed and administered at a healthcare facility that is enrolled and complies with REMS requirements.
- Immediate access to two doses of tocilizumab per patient within two hours of infusion must be available if patient needs treatment for CRS.

Approved Risk Evaluation and Mitigation Strategies (REMS). U.S. Food & Drug Administration (FDA). Updated periodically. Accessed February 2025. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

*this does not include all cost components, such as the actual drug itself

Site of Care

A report predicts CAR T-cell therapy **administration** ranging from $100,000-$600,000 per patient*

Based on 21 studies conducted between 2018-2023, **55%** of CAR T-cell administration were given outpatient

Inpatient

- Medicare Severity Diagnosis-Related Group (MS-DRG)
- New Technology Add-on Payments (NTAP)
- High-Cost Outlier Payments

Outpatient

- Outpatient Prospective Payment System (OPPS)
- Separately paid at Average Sales Price (ASP) plus 6%

Comparable response rates

72-80%

80-82%

Considerations for Outpatient Site of Care

- Strategic patient selection
- Safety monitoring education for both patient and caregiver
- Caregiver requirements
- Telemedicine tools
- Highly skilled and specialized multidisciplinary team
- Metrics for program success

- CGT payment changes proposed in FY 2025 IPPS proposed rule. Avalere Health, LLC. April 2024. Accessed February 15, 2025. https://avalere.com/insights/cgt-payment-changes-proposed-in-fy-2025-ipps-proposed-rule
- Lyman GH, Nguyen A, Snyder S, Gitlin M, Chung KC. Economic evaluation of chimeric antigen receptor T-cell therapy by site of care among patients with relapsed or refractory large B-cell lymphoma. *JAMA Netw Open*. 2020;3(4):e202072. doi:10.1001/jamanetworkopen.2020.2072
- Hansen DK, Liu Y-H, Ranjan S, et al. The impact of outpatient versus inpatient administration of CAR-T therapies on clinical, economic, and humanistic outcomes in patients with hematological cancer: a systematic literature review. *Cancers*. 2023;15(24):5746. doi:10.3390/cancers15245746

Pivotal Clinical Trials - NHL

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Outpatient administration showed:

- Lower rates of CRS
- If patient was admitted following outpatient administration, there was an association with a decrease in hospital length of stay compared to inpatient administration

1. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380(1):45-56. doi:10.1056/NEJMoa1804980
2. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*. 2019;20(1):31-42. doi:10.1016/S1470-2045(18)30864-7
3. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544. doi:10.1056/NEJMoa1707447
4. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396(10254):839-852. doi:10.1016/S0140-6736(20)31366-0
5. Westin JR, Kersten MJ, Salles G, et al. Efficacy and safety of CD19-directed CAR-T cell therapies in patients with relapsed/refractory aggressive B-cell lymphomas: observations from the JULIET, ZUMA-1, and TRANSCEND trials. *Am J Hematol*. 2021;96(10):1295-1312. doi:10.1002/ajh.26301

Patient Case - AB

- Subjective/Objective: 50 year old male with confirmed refractory diffuse large B cell lymphoma with signs of continued progression after multiple rounds of treatment. Limited comorbidities with resolved history of hypertension. Asymptomatic. ECOG is 0. Excellent caregiver.

- Plan: Kymriah (tisagenlecleucel)® administer 0.6 to 6.0 x 10^8 CAR-positive viable T cells
  - Step 1: Lymphodepleting chemotherapy (fludarabine and cyclophosphamide x3 days)
  - Step 2: Premedicate with acetaminophen and diphenhydramine ~30 - 60 minutes prior
  - Step 3: Infuse Kymriah 2 - 11 days after completion of lymphodepleting chemotherapy

- Cost Considerations
  - Site of treatment
  - Treatment process such as apheresis, bridging therapy (if needed), conditioning therapy, and administration
  - Post-infusion monitoring

Outpatient Site of Care for AB

- Clinical eligibility
  - Disease burden and comorbidities
  - Performance status and cognitive ability
  - Age and history
- Social eligibility
  - Health literacy and availability of reliable caregiver

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Patient Support Programs

	Abecma	Breyanzi	Carvykti	Kymriah	Tecartus	Yescarta
Manufacturer	Bristol Myers Squibb	Bristol Myers Squibb	Johnson & Johnson	Novartis	Kite	Kite
Patient Support Program?	Yes					
Program Name	Cell Therapy 360	Cell Therapy 360	MyCARVYKTI	Kymriah Cares	Kite Konnect	Kite Konnect

- **Goals of program(s):** to assist patients with
  - Finding a treatment center
  - Logistics support (transportation, lodging, and meal assistance)
  - Reimbursement support
  - Patient enrollment

Market Dynamics & Impact

Continued rise in cancer cases is driving industry research and growth

Driving Growth:

- New CAR therapies, CAR Natural Killer cells and CAR Macrophages, have shown promise for the development of off-the-shelf CAR products
- Rising need for targeted treatment with growing number of cancer cases

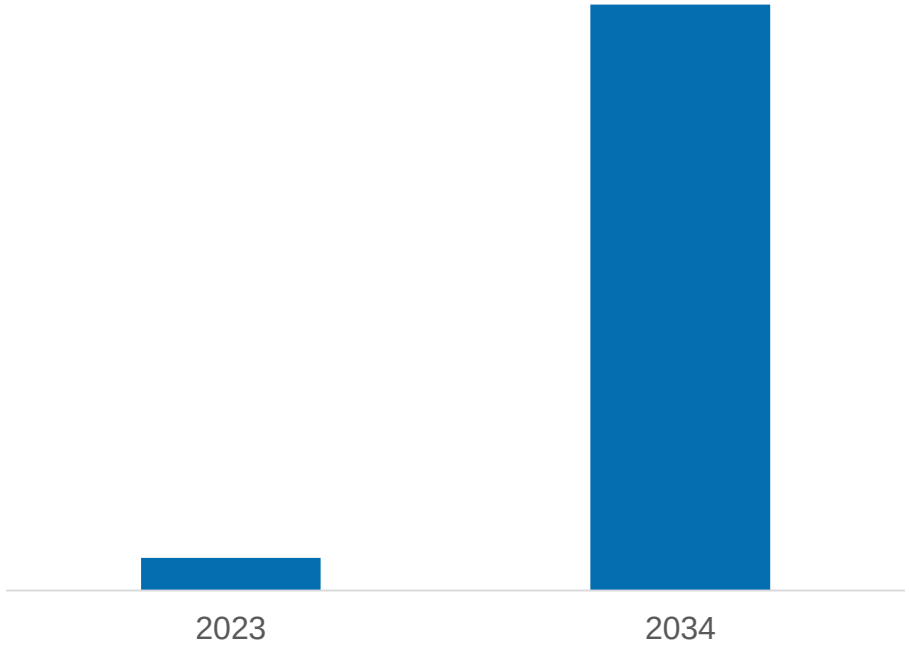
Current Challenges:

- High cost and time-consuming manufacturing process
- Relapse rates and adverse effects

Examples of Non-Oncology Indications:

- Multiple sclerosis
- Myasthenia gravis
- Cytomegalovirus infection
- Progressive multiple sclerosis
- BK virus
- Graft versus host disease

U.S. CAR T-cell projected to grow from $1.4B in 2023 to $25B in 2034



- Marei, H.E., Bedair, K., Hasan, A. *et al.* Current status and innovative developments of CAR-T-cell therapy for the treatment of breast cancer. *Cancer Cell Int.* 2025;25(1):3. doi:10.1186/s12935-024-03615-8
- CAR T cell therapy market global forecast 2025-2034. Global Market Insights. January 2025. Accessed February 15, 2025. https://www.gminsights.com/industry-analysis/car-t-cell-therapy-market
- Chen YJ, Abila B, Mostafa Kamel Y. CAR-T: what is next? *Cancers (Basel)*. 2023;15(3):663. doi:10.3390/cancers15030663

Audience Participation #2

With site-of-care shifts, what is the typical Medicare reimbursement in an outpatient setting?

A. ASP + 8 %
B. ASP + 6%
C. AWP + 8%
D. WAC + 6%

Audience Participation #2, Correct Answer

With site-of-care shifts, what is the typical Medicare reimbursement in an outpatient setting?

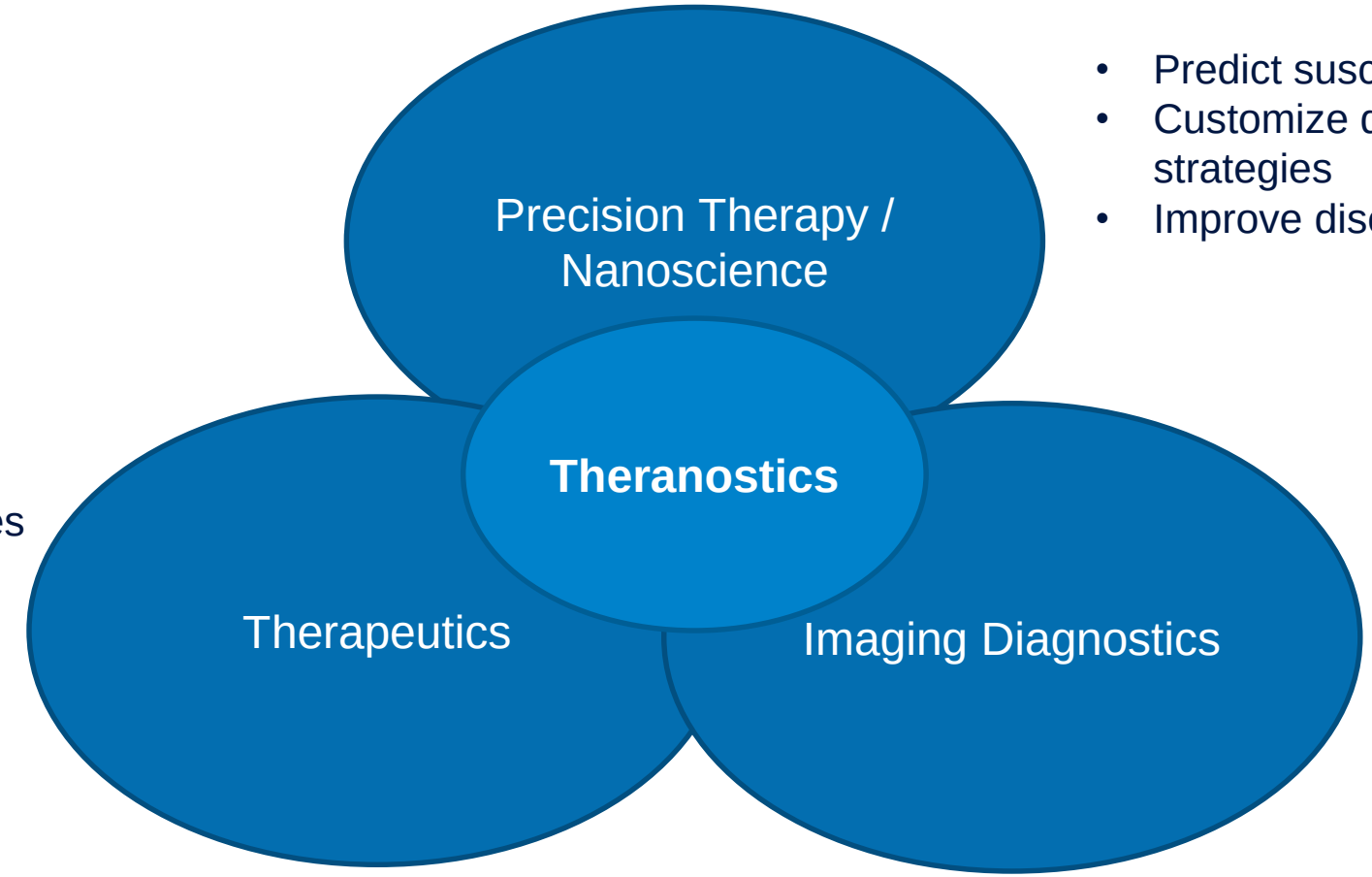
A. ASP + 8 %
B. ASP + 6%
C. AWP + 8%
D. WAC + 6%

HEALTHTRUST Performance Group®

Theranostics Landscape

Theranostics Overview

Use of diagnostic and therapeutic agents that have precision health modality



- Predict susceptibility to disease
- Customize disease-prevention strategies
- Improve disease detection

- Radionuclide
- Small molecules
- Proteins
- Peptide
- Antibody

- Positron emission tomography (PET)
- Single photon emission computed tomography (SPECT)
- Both combined with CT scan

Burkett BJ, Bartlett DJ, McGarrah PW, et al. A review of theranostics: perspectives on emerging approaches and clinical advancements. *Radiol Imaging Cancer*. 2023;5(4):e220157. doi:10.1148/rycan.220157

Patient Case - CD

- Subjective/Objective: 60 year old male with confirmed metastatic castrate-resistant prostate cancer to the bone, hilar and paratracheal lymphadenopathy. He has radiating chest & pelvic pain, breathlessness on walking upstairs, decrease in appetite, and weight loss. PSA levels are greater than 1000 ng/mL.

- Assessment:
  - Previous treatment with:
    - Palliative docetaxel, Provenge, Zytiga, Olaparib, Cabazitaxel, and palliative RT to Thoracic spine

- Plan: extensive metastatic disease and poor outcomes pivoting to a radiopharmaceutical product

Lutetium (177Lu DKFZ-PSMA-617) therapy (Pluvicto) in metastatic prostate adenocarcinoma. Nuclear Medicine Therapy. March 2023. Accessed February 15, 2025. https://nuclearmedicinetherapy.in/upload/pdf/Case-Study-Lutetium-Therapy-Pluvicto.pdf

Radiopharmaceuticals Overview

- Radiopharmaceuticals (RPs) are radioactive drugs that are intended for diagnosing a disease and treating a disease. They contain a radioactive substance that is designed to minimize exposure of healthy tissues to the radioactive substances by precisely targeting where treatment is needed.
- RPs are currently used to help diagnose or stage a disease as well as a therapy option for certain cancers. There has been a recent shift to study these therapies in additional disease states.

Examples of Indications*:

- Prostate Cancer
- Neuroendocrine Tumors
- Neuroblastoma
- Follicular Lymphoma
- Thyroid Cancer

*NOT ALL-INCLUSIVE LIST

The regulatory landscape of radiopharmaceuticals: ensuring safety and effectiveness. Regulink Ltd. February 16, 2024. Accessed February 15, 2025. https://regulink.com/media-centre/the-regulatory-landscape-of-radiopharmaceuticals-ensuring-safety-and-effectiveness/

Development & Regulatory Approval Process

Development of Radiopharmaceuticals

- **Initial publications to first FDA approval = 10 to 15 years**
- **Development Costs = $Billion(s)**
- Primary cost drivers:
  - Specificity of target population
  - Requirements of physicians

Application for Radiopharmaceuticals

NDA

Contains all information regarding preclinical and clinical testing, as well as manufacturing and quality control inspections

NDA = NEW DRUG APPLICATION

Regulatory Board

U.S. Nuclear Regulatory Commission (NRC)

- The regulatory landscape of radiopharmaceuticals: ensuring safety and effectiveness. Regulink Ltd. February 16, 2024. Accessed February 15, 2025. https://regulink.com/media-centre/the-regulatory-landscape-of-radiopharmaceuticals-ensuring-safety-and-effectiveness/
- The United States Pharmacopeial Convention. FAQs: <825> Radiopharmaceuticals. Accessed February 20, 2025. https://www.usp.org/frequently-asked-questions/radiopharmaceuticals
- Perera M and Morris M. From concept to regulatory drug approval: lessons for theranostics. *J Nucl Med*. 2022;63(12):1793-1801. doi:10.2967/jnumed.121.263301

Provider Requirements

Radioactive Materials (RAM) License

- A specific RAM license for medical use is required for human patient or human research administration of radiopharmaceuticals
  - Limited scope: for small private groups or medical institutions with limited use
  - Broad scope: for larger medical institutions for broader use
- RAM licenses for medical use follow the NRC Regulations Title 10, Code of Federal Regulations, Part 35 with RLT following Subpart E

Authorized User (AU) Training

- Typically a nuclear medicine physician, radiation oncologist, or radiologist
- Training: includes 700 hours of training, including 200 hours of classroom and laboratory instruction plus supervised work experience in handling radioactive materials
  - Specific board certifications assist in the AU certification process
    - American Board of Nuclear Medicine
    - American Board of Radiology
    - American Osteopathic Board of Radiology

Minimum Requirements to Operate Radiopharm Program

HEALTHTRUST Performance Group™

- Novartis RLT Institute. Novartis. Updated periodically. Accessed February 15, 2025. https://www.rltinstitute.novartis.com/licensing-and-safety/key-individuals/authorized-users/#chapter
- Consolidated guidance about material licenses. United States Nuclear Regulatory Commission (NRC). Published September 2019. Accessed February 15, 2025. https://www.nrc.gov/docs/ML1925/ML19256C219.pdf

Types of Emission with Application

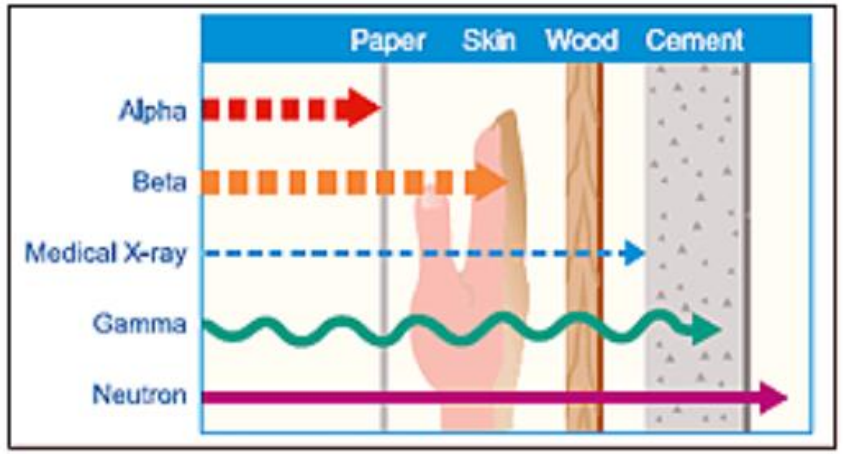
PROPERTIES OF SELECT RADIONUCLIDES

Emitter	Mechanism of Cell Death	Diagnostic	Therapeutic
α radiation	Double-strand DNA breaks		✓
β radiation	Single-strand DNA breaks		✓
γ radiation	Single-strand DNA breaks	✓	

α = alpha; β = beta; γ = gamma

Radionuclide	Therapeutic Emission	Approximate Emission Range in Tissue (mm)	Radionuclide Half-Life
Yttrium-90	β	5.3	64.1 hours
Iodine-131	β	0.8	8.0 days
Lutetrium-177	β	0.62	6.6 days
Radium-223	α	0.05-0.08	11.4 days

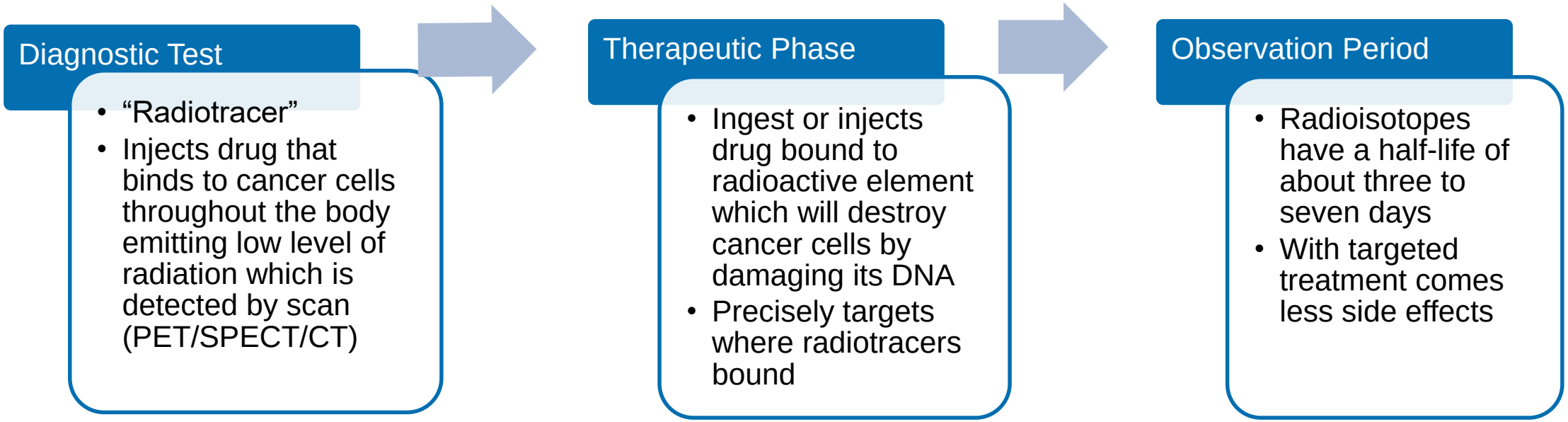
α = alpha; β = beta



- Complex therapeutics and technologies: radiopharmaceuticals. IPD Analytics. Updated periodically. Accessed February 15, 2025. https://www.ipdanalytics.com/
- Radiation basics. United States Nuclear Regulatory Commission (NRC). Accessed February 15, 2025. https://www.nrc.gov/about-nrc/radiation/health-effects/radiation-basics.html

Current Therapy Process

- Radiopharmaceutical therapy is a targeted therapy containing a radioactive particle



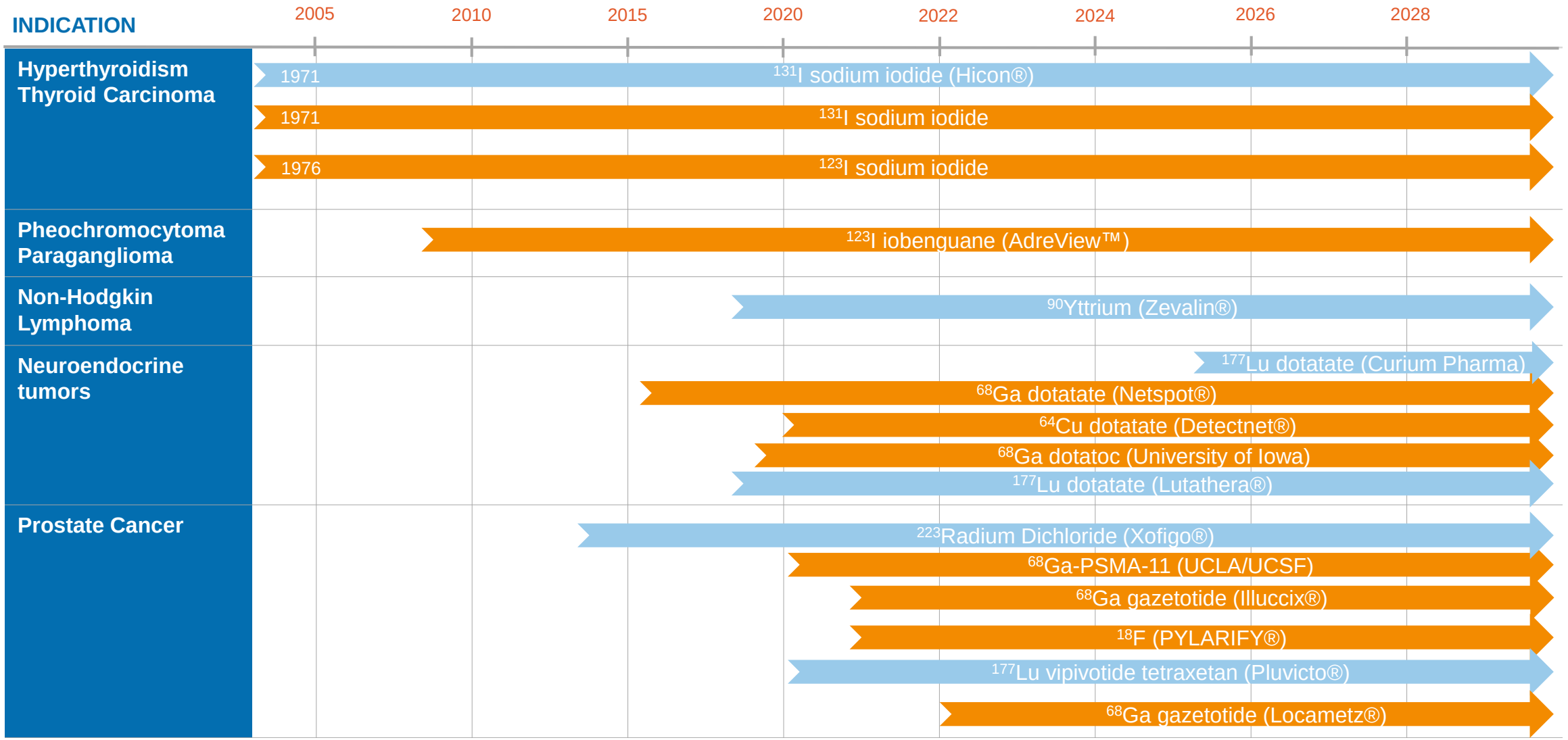
- Complex therapeutics and technologies: radiopharmaceuticals. IPD Analytics. Updated periodically. Accessed February 15, 2025. https://www.ipdanalytics.com/
- Radiation basics. United States Nuclear Regulatory Commission (NRC). Accessed February 15, 2025. https://www.nrc.gov/about-nrc/radiation/health-effects/radiation-basics.html

United States Radiopharmaceutical Pipeline

Diagnostic Agent

Therapeutic Agent

FDA-APPROVED PRODUCTS*



CU = COPPER; FDA = FOOD AND DRUG ADMINISTRATION; F = FLUORINE; GA = GALLIUM; I = IODINE; LU = LUTETIUM; *NOT ALL-INCLUSIVE LIST; CONSULT EACH RADIOPHARMACEUTICAL'S PRESCRIBING INFORMATION FOR A FULL LIST OF FDA-APPROVED INDICATIONS

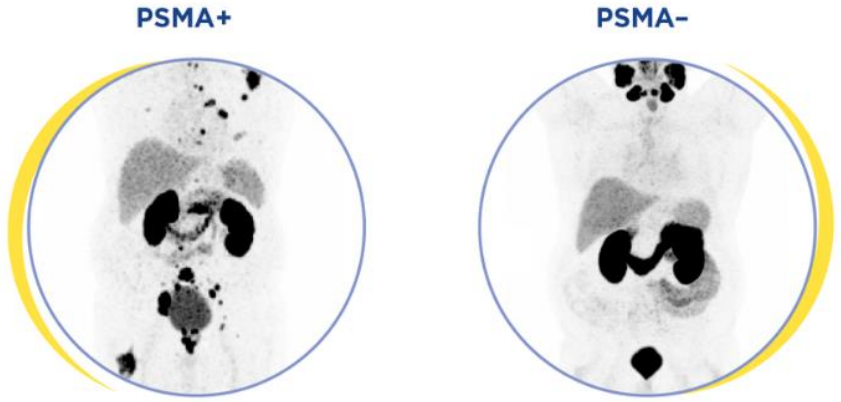
Complex therapeutics and technologies: radiopharmaceuticals. IPD Analytics. Updated periodically. Accessed February 15, 2025. https://www.ipdanalytics.com/

Patient Case - CD

- Diagnosis: confirmed metastatic castrate-resistant prostate cancer

- Confirmation of prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer utilizing Locametz®
  - Recommended radioactivity of 3 mCi - 8 mCi as a slow intravenous injection
  - PET whole body images acquired 50 - 100 minutes after administration

- PSMA+ Image Interpretation:



- Lutetium (177Lu DKFZ-PSMA-617) therapy (Pluvicto) in metastatic prostate adenocarcinoma. Nuclear Medicine Therapy. March 2023. Accessed February 15, 2025. https://nuclearmedicinetherapy.in/upload/pdf/Case-Study-Lutetium-Therapy-Pluvicto.pdf
- LOCAMETZ® (kit for the preparation of gallium Ga 68 gozetotide injection) for intravenous use. Package insert. Novartis; June 2023.
- Using LOCAMETZ® (kit for the preparation of gallium Ga 68 gozetotide injection). Novartis. Accessed February 15, 2025. https://www.locametz-hcp.com/

Patient Safety

ALARA Principle

- The core principle of radiation safety is **A**s **L**ow **A**s **R**easonably **A**chievable (ALARA)
- This minimizes radiation exposure for both staff and patients by following 3 key practices:

Radiation Exposure Limits

- Radiation Workers: 5,000 millirem (mrem) per year
- Public: 100 mrem per year (in addition to natural background radiation)
  - A yearly dose of 620 mrem has not been shown to cause harm

Time

Quick and efficient

Distance

Strategic facility layout, guidelines for patient and staff, and controlled access

Shielding

Walls tailored to facility with thickness and composition

- Complex therapeutics and technologies: radiopharmaceuticals. IPD Analytics. Updated periodically. Accessed February 15, 2025. https://www.ipdanalytics.com/
- Radiation basics. United States Nuclear Regulatory Commission (NRC). Accessed February 15, 2025. https://www.nrc.gov/about-nrc/radiation/health-effects/radiation-basics.html
- Guidelines for ALARA – As Low As Reasonably Achievable. US Centers for Disease Control and Prevention (CDC). Accessed February 27, 2025. www.cdc.gov/radiation-health/safety/alara.html

HEALTHTRUST Performance Group

Patient Case - CD

- Diagnosis: confirmed PSMA-positive mCRPC who has trial and failure of an androgen-receptor pathway inhibitor and taxane-based regimens

- Options of Therapy:*

	^{131}I sodium iodide (Hicon®)	^{90}Yttrium ibritumomab tiuxetan (Zevalin®)	^{177}Lu dotatate (Lutethera®)	^{223}Radium Dichloride (Xofigo®)	^{177}Lu vipivotide tetraxetan (Pluvicto®)
Hyperthyroidism Thyroid Carcinoma	X				
Non-Hodgkin Lymphoma		X			
Neuroendocrine tumors			X		
Prostate Cancer				X	X

*only therapy radiopharmaceuticals are listed in this table

Lutetium (177Lu DKFZ-PSMA-617) therapy (Pluvicto) in metastatic prostate adenocarcinoma. Nuclear Medicine Therapy. March 2023. Accessed February 15, 2025. https://nuclearmedicinetherapy.in/upload/pdf/Case-Study-Lutetium-Therapy-Pluvicto.pdf

Pivotal Clinical Trials – Prostate Cancer

Clinical Trial Name	Year	Intervention	Outcomes		Results
			Overall Survival	Time to first symptomatic skeletal event (SSE)	
ALSYMPCA[1,2] (Xofigo)	2013	Radium-223 at a dose of 50 kBq per kilogram intravenously every 4 weeks receiving 6 injections versus standard of care alone; all patients continued androgen deprivation therapy (n=921)	• 14.9 months versus 11.3 months • Hazard ratio 0.70 • P<0.001	• 15.6 months versus 9.8 months • Hazard ratio 0.66 • P<0.001	Survival results supported a delay in time to first SSE favoring Xofigo
VISION[3,4] (Pluvicto)	2021	177Lu-PSMA-617 at a dose of 7.4 GBq every 6 weeks for four to six cycles versus standard care alone; all patients continued protocol-permitted standard care (n=831)	• 15.3 months versus 11.3 months • Hazard ratio 0.62 • P<0.001	• N=581 • 11.5 months versus 6.8 months • Hazard ratio 0.50 • P<0.001	Prolonged overall survival when added to standard care in patients with PSMA-expressing castration-resistant prostate cancer

PSMA = prostate-specific membrane antigen; SSE = symptomatic skeletal event

1. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223. doi:10.1056/NEJMoa1213755
2. Xofigo (radium Ra 223 dichloride). Package insert. Bayer HealthCare Pharmaceuticals Inc; December 2019.
3. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2021;385(12):1091-1103. doi:10.1056/NEJMoa2107322
4. Pluvicto (lutetium Lu 177 vipivotide tetraxetan). Package insert. Novartis; September 2024.

Site of Care

Radiopharmaceuticals are typically administered in the **outpatient** setting at radiation oncology or nuclear medicine clinics

	^{131}I sodium iodide (Hicon®)	^{90}Yttrium ibritumomab tiuxetan (Zevalin®)	^{177}Lu dotatate (Lutathera®)	^{223}Radium Dichloride (Xofigo®)	^{177}Lu vipivotide tetraxetan (Pluvicto®)
Administration Route	Oral Ingestion	IV (10 min)	IV (30-40 min) with amino acid	IV (1 min)	IV (1-10 min slow injection or 30 min infusion)

Outpatient

- Diagnostic Radiopharmaceuticals = separately reimbursed for a per day cost greater than $630, all other will be policy packaged
- Pass-Through Status = payment rate of Average Sales Price (ASP) plus 6%
- Therapeutic Radiopharmaceuticals = Outpatient Prospective Payment System (OPPS) and separate Ambulatory Payment Classification (APC) groups

- Medicare and Medicaid programs. Federal Register: The daily journal of the United States Government. November 27, 2024. Accessed February 27, 2025. https://www.federalregister.gov/d/2024-25521
- CY 2025 medicare hospital outpatient prospective payment system and ambulatory surgical center payment system final rule (CMS 1809-FC). Centers of Medicare and Medicaid. November 1, 2024. Accessed February 27, 2025. https://www.cms.gov/newsroom/fact-sheets/cy-2025-medicare-hospital-outpatient-prospective-payment-system-and-ambulatory-surgical-center-0

CMS Separately Reimbursed List

Diagnostic Radiopharmaceuticals

TABLE 8: Proposed Qualifying Diagnostic Radiopharmaceuticals with Per Day Costs Exceeding $630

HCPCS Code	Short Descriptor	Proposed CY 2025 Status Indicator Assignment
A9515	Choline c-11	K
A9521	Tc99m exametazime	K
A9542	In111 ibritumomab, dx	K
A9547	In111 oxyquinoline	K
A9548	In111 pentetate	K
A9557	Tc99m bicisate	K
A9568	Technetium tc99m arcitumomab	K
A9569	Technetium tc-99m auto wbc	K
A9570	Indium in-111 auto wbc	K
A9572	Indium in-111 pentetreotide	K
A9582	Iodine i-123 iobenguane	K
A9584	Iodine i-123 ioflupane	K
A9586	Florbetapir f18	K
A9587	Gallium ga-68	K
A9588	Fluciclovine f-18	K
A9591	Fluoroestradiol f 18	K
A9592	Copper cu 64 dotatate diag	K
A9593	Gallium ga-68 psma-11 ucsf	K
A9594	Gallium ga-68 psma-11, ucla	K
A9595	Piflu f-18, dia 1 millicurie	K
A9596	Gallium illuccix 1 millicure	K
A9602	Fluorodopa f-18 diag per mci	K
A9800	Gallium locametz 1 millicuri	K
C9067	Gallium ga-68 dotatoc	K
Q9982	Flutemetamol f18 diagnostic	K
Q9983	Florbetaben f18 diagnostic	K

K = separately payable drugs

Pass-Through Status*

HCPCS Code	Descriptor	Ambulatory Payment Classification (APC)	Pass-Through Effective Date	Pass-Through End Date
A9596	Gallium ga-68 gozetotide, diagnostic, (illuccix), 1 millicurie	9443	07/01/2022	06/30/2025
A9800	Gallium ga-68 gozetotide, diagnostic, (locametz), 1 millicurie	9055	10/01/2022	09/30/2025
A9607	Lutetium lu 177 vipivotide tetraxetan, therapeutic, 1 millicurie (Pluvicto)	9054	10/01/2022	09/30/2025

*NOT ALL-INCLUSIVE LIST

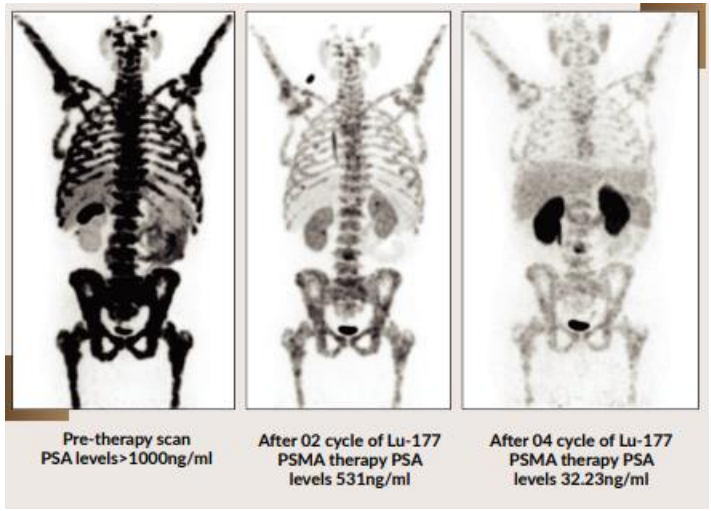
- Medicare and Medicaid programs. Federal Register: The Daily Journal of the United States Government. November 27, 2024. Accessed February 27, 2025. https://www.federalregister.gov/d/2024-25521
- CY 2025 medicare hospital outpatient prospective payment system and ambulatory surgical center payment system final rule (CMS 1809-FC). Centers of Medicare and Medicaid. November 1, 2024. Accessed February 27, 2025. https://www.cms.gov/newsroom/fact-sheets/cy-2025-medicare-hospital-outpatient-prospective-payment-system-and-ambulatory-surgical-center-0
- Pass-through payment status and new technology ambulatory payment classification (APC). Centers of Medicare and Medicaid. Updated September 10, 2024. Accessed February 27, 2025. https://www.cms.gov/medicare/payment/prospective-payment-systems/hospital-outpatient/pass-through-payment-status-new-technology-ambulatory-payment-classification-apc

Patient Case - CD

- Subjective/Objective: 60 year old male with confirmed metastatic castrate-resistant prostate cancer to the bone, hilar and paratracheal lymphadenopathy. He has radiating chest & pelvic pain, breathlessness on walking upstairs, decrease in appetite, and weight loss. PSA levels are greater than 1000 ng/mL.

- Plan: Pluvicto 7.4 GBq (200 mCi) intravenously every 6 weeks for up to 6 doses
  - Patient received 4 doses by slow intravenous infusion using renal protection protocol (hydration with intravenous normal saline) along with Enzalutamide daily (standard of care)

- Cost Considerations
  - Site of treatment
  - Treatment process
  - Post-infusion monitoring



- Lutetium (177Lu DKFZ-PSMA-617) therapy (Pluvicto) in metastatic prostate adenocarcinoma. Nuclear Medicine Therapy. March 2023. Accessed February 15, 2025. https://nuclearmedicinetherapy.in/upload/pdf/Case-Study-Lutetium-Therapy-Pluvicto.pdf
- Pluvicto (lutetium Lu 177 vipivotide tetraxetan). Package insert. Novartis; September 2024.

Patient Support Programs

	^{131}I sodium iodide (Hicon®)	^{90}Yttrium ibritumomab tiuxetan (Zevalin®)	^{177}Lu dotatate (Lutathera®)	^{223}Radium Dichloride (Xofigo®)	^{177}Lu vipivotide tetraxetan (Pluvicto®)
Manufacturer	Jubilant	Spectrum Pharmaceuticals	Novartis	Bayer Healthcare	Novartis
Patient Support Program?	No Information	No Information	Yes		
Program Name	N/A	N/A	Novartis Patient Support	Xofigo Assistance	Novartis Patient Support

- **Goals of program(s):** to assist patients with
  - Navigating the insurance process
  - Getting financial support
  - Answer questions across the treatment journey such as post treatment requirements
    - Hydration
    - Monitoring for side effects
    - Minimizing radiation exposure to family members

Market Dynamics & Impact

Continued innovation, advancements in radiochemistry and an increase in chronic conditions are contributing to industry growth

Driving Growth:

- Increasing of chronic conditions with growing population
- Focus on precision medicine
- Advancements in technology

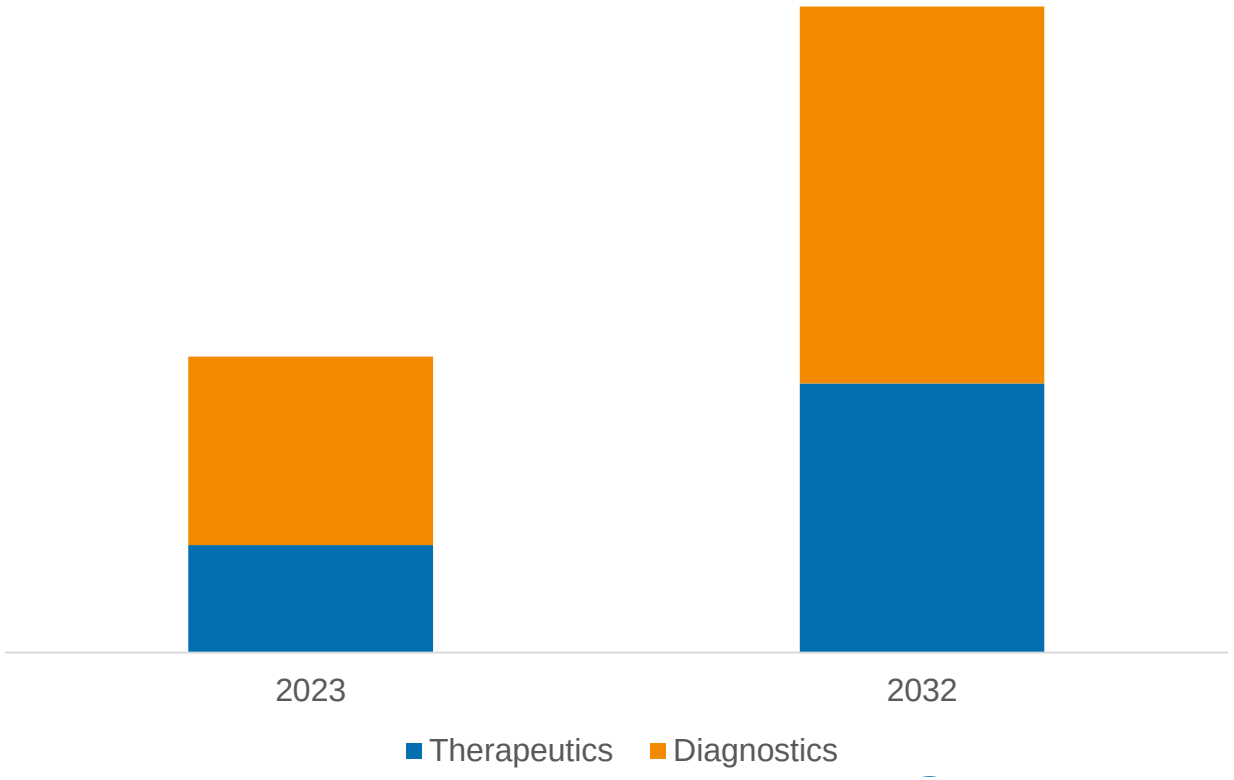
Challenges:

- High cost with limited reimbursement understanding
- Extensive training required for healthcare professionals to administer

Examples of Non-Oncology Emerging Applications:

- Diagnosing of Epilepsy
- Diagnosing of Dementia (in early stages)
- Infectious Disease

Radiopharmaceuticals projected to grow from $6.7B in 2023 to $15.4B in 2032



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- Dunleavy K. 2025 forecast: as companies rush to radiopharmaceuticals for oncology, what's next? January 10, 2025. Accessed February 15, 2025. https://www.fiercepharma.com/pharma/2025-forecast-companies-rush-radiopharmaceuticals-oncology-whats-next

Audience Participation #3

Who regulates radiopharmaceuticals?

A. U.S. Nuclear Regulatory Commission (NRC)
B. National Institute for Occupational Safety and Health (NIOSH)
C. Centers for Medicare & Medicaid Services (CMS)
D. American Pharmacist Association (APhA)

Audience Participation #3, Correct Answer

Who regulates radiopharmaceuticals?

A. U.S. Nuclear Regulatory Commission (NRC)
B. National Institute for Occupational Safety and Health (NIOSH)
C. Centers for Medicare & Medicaid Services (CMS)
D. American Pharmacist Association (APhA)

Key Takeaways of Emerging Therapies

Biosimilars

2025 is a year of many biosimilar launches, however, keep in mind the many challenges that impact adoption of biosimilars.

Cell Therapies

While CAR T cell therapy has shown promise, continued research and growth is bringing us a whole new era of CAR cell therapy expanding into more than just oncology indications.

Theranostics

The radiopharmaceutical industry is rapidly growing, while we may experience some uncertainties in the coming years, this targeting treatment option will provide clinical benefit.

References – Biosimilars

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2. Braendstrup P, Levine BL, Ruella M. The long road to the first FDA-approved gene therapy: chimeric antigen receptor T cells targeting CD19. *Cytotherapy*. 2020;22(2):57-69. doi:10.1016/j.jcyt.2019.12.004
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10. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396(10254):839-852. doi:10.1016/S0140-6736(20)31366-0
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Contact:

Samantha Randlett

P: 248.884.3914

E: Samantha.Randlett@Healthtrustpg.com

Thank you!

HEALTHTRUST
Performance Group®

1100 Dr. Martin L. King Jr. Boulevard, Suite 1100
Nashville, TN 37203