Allogeneic Chimeric Antigen Receptor T-cell (CAR-T) Therapy Administration

On behalf of the American Society of Transplantation and Cellular Therapy

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Background on Chimeric Antigen Receptor T-cell (CAR-T) Therapy

- Chimeric Antigen Receptor T-cell therapy is a type of Immune Effector Cell immunotherapy; CAR-T therapy attaches Chimeric Antigen Receptors (CARs) to T-cells
    - The CARs allow the modified cells to home in on and destroy the tumor cells expressing the target of the transferred receptor
- Currently, there are two autologous CAR-T products approved, Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel)
    - These products treat two different blood malignancies: relapsed or refractory pediatric Acute Lymphocytic Leukemia (ALL) and Diffuse Large B-cell Lymphoma (DLBCL)
    - The administration of both products is described by two ICD-10-PCS codes for autologous CAR-T administration: XW033C3 (peripheral vein) and XW043C3 (central vein)
- Within the next few months, two additional autologous products are expected to be approved by the FDA and as a result CMS has released two additional (product-specific) CAR-T ICD-10-PCS administration codes for implementation October 1, 2020
    - All four ICD-10-PCS codes are specifically for autologous CAR-T products which raises the question of how an allogeneic CAR-T product in a clinical trial should be reported

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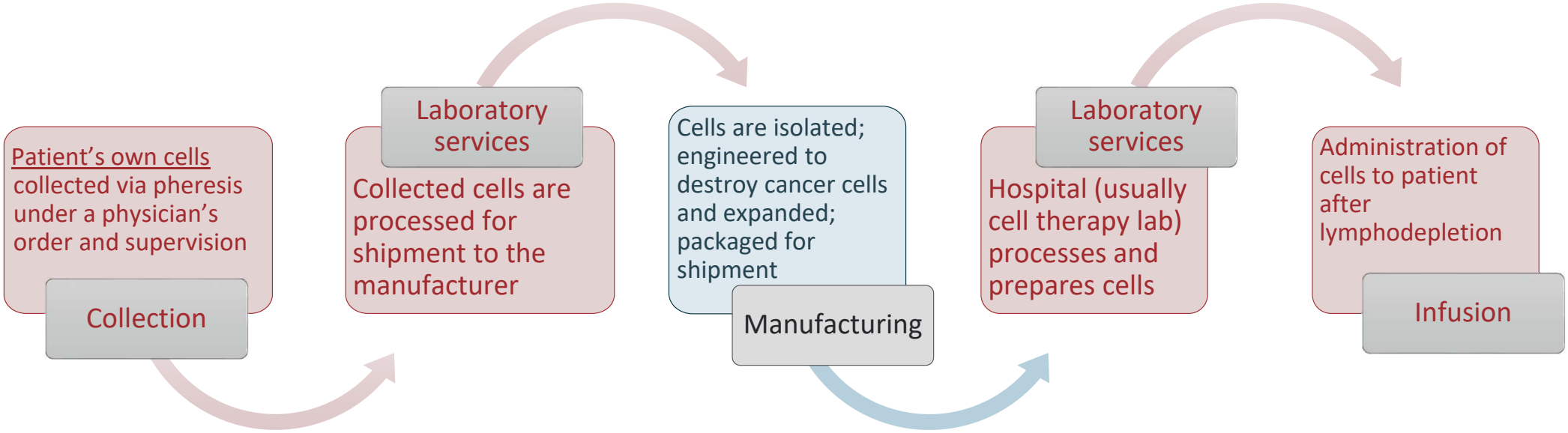
Summary of Autologous CAR-T Therapy Process



ICD-10-PCS codes already exist for reporting the administration of autologous CAR-T therapies

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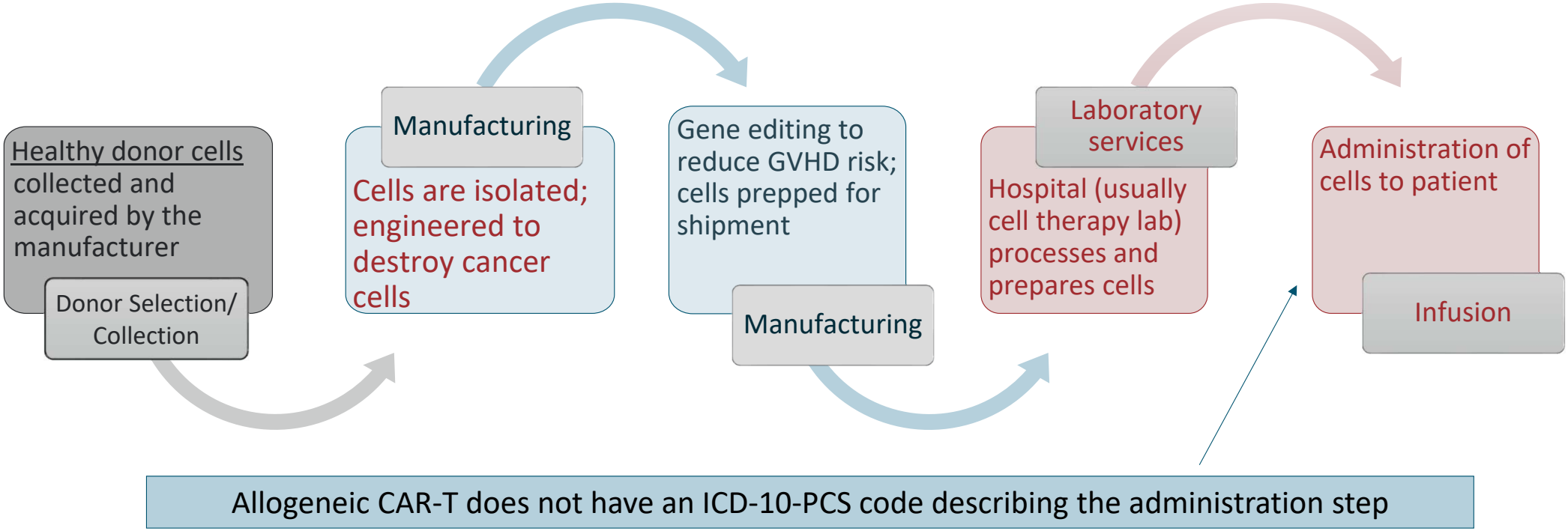
Summary of Allogeneic CAR-T Therapy Process



Allogeneic CAR-T does not have an ICD-10-PCS code describing the administration step

Differences Between Allogeneic CAR-T Therapy and Autologous CAR-T Therapy

- The difference between allogeneic and autologous CAR-T therapy is in the source of the T-cells
  - Autologous products are engineered from the patient's own T-cells, and are unique to that particular patient
    - Patient's needing CAR-T therapy must wait for their product to go through the manufacturing process
    - Prospective patients are very sick (they receive CAR-T after failing two or more lines of therapy), and sometimes do not have the T-cell supply needed to be good candidates for the autologous products
  - In contrast, allogeneic CAR-T products are created from healthy donor T-cells
    - Products will not be manufactured for each individual patient; rather the products will be available "off-the-shelf" to those who need them thereby reducing the time a patient has to wait for their therapy

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Settings of Care and Diagnoses Associated with Allogeneic CAR-T Therapy

- There are currently no approved allogeneic therapies, but there are numerous pre-clinical and clinical trials underway
  - Therapies current in clinical trials are primarily focused on b-cell malignancies, such as DLBCL, Multiple Myeloma, and others (see the table in the following slide)
- Solid tumor targets and autoimmune disease are potential indications for future allogeneic products

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Examples of Current Allogeneic CAR-T Product Clinical Trials

Sponsor	Therapy name	Therapy target	Development stage	Clinical Trial ID	Disease	Trial start date
Servier Allogene Therapeutics	UCART19	CD19	Phase 1	NCT02808442 (PALL)	Pediatric R/R ALL	6/3/16
Servier/Allogene Therapeutics	UCART19	CD19	Phase 1	NCT02746952 (CALM)	R/R ALL	8/1/16
Cellectis	UCART123	CD123	Phase 1	NCT03190278 (AMELI-01)	R/R AML	6/19/17
Cellectis	UCART123	CD123	Phase 1a	NCT03203369 (ABC123)	BPDCN	6/28/17
Poseida	P-BCMA-101	BCMA	Phase 1	NCT03288493	Multiple Myeloma	9/20/17
Celyad	CYAD-101	NKG2D Ligands	Phase 1	NCT03692429 (alloSHRINK)	CRC	11/28/18
Precision Biosciences	PBCAR0191	CD19	Phase 1/2	NCT03666000	R/R B-ALL and R/R NHL	3/11/19
Allogene Therapeutics	ALLO-501	CD19	Phase 1/2	NCT03939026 (ALPHA)	R/R DLBCL and R/R FL	5/1/19
CRISPR Therapeutics	CTX110	CD19	Phase 1	NCT04035434	NHL	7/22/19
Allogene Therapeutics	ALLO-715	BCMA	Phase 1	NCT04093596 (UNIVERSAL)	Multiple myeloma	9/23/19
Cellectis	UCART123	CD123	Phase 1	NCT04106076	High risk AML	7/11/19
Cellectis	UCART22	CD22	Phase 1	NCT04150497 (BALLI-01)	R/R B-ALL and R/R NHL	10/17/19
Cellectis	UCARTCS1	CS1	Phase 1	NCT04142619 (MELANI-01)	Multiple Myeloma	11/21/19
CRISPR Therapeutics	CTX120	BCMA	Phase 1	NCT04244656	Multiple myeloma	1/28/20

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Source: Aftab, B. T., Sasu, B., Krishnamurthy, J., Gschweng, E., Alcazer, V., & Depil, S. Toward “off-the-shelf” allogeneic CAR T cells. Advances in Cell and Gene Therapy, e86.

Routes of Administration and Dosage of Allogeneic CAR-T Therapy Products

- Since there are no currently approved products, and the dosages used in trials vary by product (and may change by the time the product is approved), it is not possible to give a specific dosage here
- Allogeneic products would be administered using the same routes as autologous products: the products would be infused, through either a percutaneous or central vein

Complications of Allogeneic CAR-T Therapy

- Like autologous CAR-T therapy products, allogeneic products could potentially cause complications such as Cytokine Release Syndrome and Immune Effector Cell Associated Neurotoxicity Syndrome
  - CRS is “a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells”
  - ICANS is “a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.”

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Source: Lee, D. W., Santomasso, B. D., Locke, F. L., Ghobadi, A., Turtle, C. J., Brudno, J. N., ... & Go, W. Y. (2019). ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biology of Blood and Marrow Transplantation, 25(4), 625-638.

Complications of Allogeneic CAR-T Therapy (cont.)

- However, allogeneic products also carry the risk of causing a type of complication that autologous products do not: Graft Vs Host Disease (GVHD)
  - Like with allogeneic hematopoietic cell transplants, the donor immune cells could view the host's body as foreign, and the donated cells attack the body
  - This is a concern whenever allogeneic cells are introduced; and is a factor that is being addressed through different strategies by allogeneic product manufacturers
  - For example, some manufacturers are using gene-editing tools (like TALEN or CRISPR/Cas9) to remove the native T-cell receptor (TCR) from donor cells (some companies are also removing major histocompatibility complex (MHC) I as well)

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Source: Poh, A. (2018). The Quest for Off-the-Shelf CAR T Cells. CANCER DISCOVERY, 8(7), 787-788.

New ICD-10-PCS Codes are Needed to Identify Allogeneic CAR-T Therapy Administration

- The four currently approved ICD-10-PCS codes for CAR-T therapy are for autologous products only, and cannot be used to accurately describe the administration of an allogeneic CAR-T product
- Though there are no currently approved allogeneic products, there are numerous ongoing trials, and it is important to be able to differentiate these new CAR-T products from the administration of autologous products or other forms of immunotherapy

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Impact of New Code for Allogeneic CAR-T Administration

- A new code would mean that coding professionals can report the inpatient administration of an allogeneic CAR-T product as such rather than being forced to report “other therapeutic substance” or some other non-specific code that would not allow any visibility into the allogeneic products under trial
- A new code would mean that researchers and others can identify the inpatient administration of an allogeneic CAR-T product
- This means that all true CAR-T cases (rather than just autologous CAR-T cases) can be identified and tracks on claims
- This would lower inaccuracies and confusion about the right ICD-10 code to use in the absence of an allogeneic code

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