September 9, 2024

Chiquita Brooks-LaSure, Administrator
Centers for Medicare & Medicaid Services
U.S. Department of Health and Human Services
Attention: CMS-1809-7
P.O. Box 8010
Baltimore, MD 21244–8016

Submitted via http://www.regulations.gov

Re: Medicare and Medicaid Programs; CY 2025 Payment Policies Under the Physician Fee Schedule and Other Changes to Part B Payment and Coverage Policies; Medicare Shared Savings Program Requirements; Medicare Prescription Drug Inflation Rebate Program; and Medicare Overpayments [CMS-1809-7]

Dear Administrator Brooks-LaSure:

The Alliance for Regenerative Medicine ("ARM") appreciates the opportunity to comment on the Centers for Medicare & Medicaid Services' ("CMS") proposed payment updates to the calendar year 2025 Medicare Physician Fee Schedule (the "Proposed Rule").[1]

ARM is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis. We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

As of August 2024, there were 2,919 regenerative medicine and advanced therapies developers worldwide sponsoring 1,851 clinical trials across dozens of indications, including rare monogenetic diseases, oncology, cardiovascular, central nervous system, musculoskeletal, metabolic disorders, ophthalmological disorders, and more.[2]

To the benefit of Medicare beneficiaries, for the past decade, treating hematologic malignancies has

[1] 89 Fed. Reg. 61596 (July 31, 2024).
[2] See https://alliancerm.org/wp-content/uploads/2024/08/August-2024-Sector-Snapshot_Final.pdf.

been and remains one of the main indications targeted by engineered cell therapies. Leading the charge are chimeric antigen receptor T-cell ("CAR-T") therapies, which have receptors that specifically target cancer cells. Currently, six CAR-T therapies for blood cancers are approved in the United States. However, many more cell therapies for blood cancers, including non-CAR-T approaches, are in the clinical pipeline. Of the ten most explored indications in cell therapy, nine fall within the scope of blood cancer. Also, in early December, the Food and Drug Administration (FDA) approved two gene therapies for SCD, one of which is the first approved medication that uses the gene-editing tool CRISPR. These two gene therapies use a novel technique to modify the expression of an individual's genes and result in an individual making more fetal hemoglobin, a type of oxygen-carrying blood protein present at birth. These one-time treatments have created the potential to cure this hereditary condition. Other types of cell and gene therapies also are critical to the health of Medicare beneficiaries. Recent therapy approvals for metastatic melanoma and Hemophilia A and B are providing new options to Medicare patients suffering from these diseases.

ARM thanks CMS for its efforts to promote Medicare beneficiary access to cell and gene therapies, and recognizes that many of CMS's recent proposals – both in the Proposed Rule and in other areas – are intended to foster such access. To further promote appropriate access to cell and gene therapies and to support the Medicare beneficiaries receiving these treatments, ARM urges CMS to:

- Ensure that there is separate payment for each cell collection and dose preparation activity necessary to administer CAR-Ts by amending the Healthcare Common Procedure Coding System ("HCPCS") codes for such products.

- Exempt all cell and gene therapies from the drug discard requirements, given their unique characteristics.

- Cover dental services for Medicare beneficiaries needing immunosuppressive therapies and continue to explore means for establishing dental coverage for beneficiaries with sickle cell disease or hemophilia.

- Establish reimbursement for educating Medicare beneficiaries on cell and gene therapies, including those treating hemophilia.

The remainder of our letter addresses these issues in more detail.

CMS Should Ensure That Cell Collection and Dose Preparation Activities for Cell and Gene Therapies Are Separately Payable

ARM appreciates CMS for its proposal to establish Relative Value Units ("RVUs") for the four Current Procedural Terminology (CPT®)[3] codes related to CAR-T therapies. ARM agrees with the importance of establishing such values to ensure that there is a pathway for clinicians to be properly reimbursed for the services associated with the preparation and administration of these critical therapies. As stated in the proposed rule, three newly established Category I CPT codes (effective January 1, 2025) for CAR-T cell therapy ancillary services did not receive any practice

[3] CPT® is a registered trademark of the American Medical Association.

expense valuation recommendation from the RUC.

Code	Description	Work RVU	Practice Expense
3X018	CAR-T therapy; harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR-T cells, per day	1.94	None
3X019	CAR-T therapy; preparation of blood-derived T lymphocytes for transportation (e.g., cryopreservation, storage)	0.79	None
3X020	CAR-T therapy; receipt and preparation of CAR-T cells for administration	0.80	None
3X021	CAR-T therapy; CAR-T cell administration, autologous	3.00	RUC recommendation accepted in proposed rule

However, ARM recommends that CMS take an additional step to ensure that clinicians can receive Medicare reimbursement for the services identified by these codes. In particular, CMS should modify the HCPCS product codes to indicate that they do not include specific payment for cell collection and dose preparation. Many such codes, such as Q2041 for Yescarta and Q2056 for Carvykti, currently indicate that the product code includes both leukapheresis and dose preparation procedures. As a result, Medicare historically has denied payment for claims for cell collection and dose preparation. ARM urges CMS to consider valuations proposed by relevant physician societies and adopt these valuations in the final rule. In addition, the Advisory Board on Hospital Outpatient Payment (HOP Panel) recently recommended a shift to status indicator S for CPT codes 3X018, 3X019, and 3X020. Providers and practitioners should be appropriately reimbursed when they provide services associated with therapeutic interventions; therefore, we urge CMS to recognize the physician work and related malpractice costs that are associated with providing the CAR T services.

This change to product codes is even more critical given the evolution of cell and gene therapy administration to the outpatient setting. As therapeutic approaches progress, critical elements upstream in the administration process, such as cell collection or dose preparation, have shifted to physician offices or other outpatient locations. In such a scenario, reimbursement for the cell collection activities will be made to one entity and reimbursement for the product costs will be made to a different entity. Medicare coding should not be a barrier to arrangements that enhance access to care. In other contexts, CMS has recognized the value of Medicare beneficiaries being able to access services in community settings. To maintain consistency, the Agency should take steps to foster access to cell and gene therapies in non-hospital settings, which are often less costly and more convenient for patients. Indeed, the option of administration in less acute sites of care, including the hospital outpatient department and physician office, often reflects patient preference, involves less resource intensity in treatment, and typically provides more

reimbursement certainty.[4]

CMS Should Utilize the Unique Circumstances Authority to Exempt Cell and Gene Therapies from Drug Discard Refund Requirements

ARM appreciates CMS's willingness to consider applications to increase the applicable percentage for certain products under the drug discard program, which requires manufacturers to pay refunds in certain cases where a portion of their product is discarded and not administered to the patient. However, ARM maintains its recommendation that CMS should establish a 100% applicable percentage for all cell and gene therapies, without the need for each manufacturer to submit an application justifying the exemption. There are numerous reasons why cell and gene therapies should be categorically exempt from the drug discard policy.

First, these therapies are typically one-time durable treatments representing a completely different clinical regimen than the currently listed top discarded drugs, which require frequent and regular delivery of the product to a beneficiary. The overwhelmingly one-time nature of these therapies requires that all potentially needed medication be on hand and available for all procedures, consistent with clinical trial data and FDA-approved labeling.

Second, the administration and manufacturing of these products is tailored to each patient and thus the volume of material packaged for administration is often individualized, as it is dependent upon many factors including but not limited to each patient's cell volume and weight. As such, these therapies follow a specific coding designation methodology, which describes cell therapy codes by the number of cells, a component of the overall material within the package as compared to IV administered drugs that are typically described as units of all the material within the vial or bag.

Third, the often one-time and lengthy administration process underscores the importance of having ample drug at the time of administration to minimize physician and patient burden, avoid unnecessary complications related to redosing which is not always permissible, and prevent further disease progression that could result from delayed treatment. For example, the administration of a CAR-T cell product may be terminated if the patient experiences an adverse event and as such the remainder of the product is not utilized. In these cases, the remainder of the product is not eligible to be administered to another patient, as it is a personalized medicine and the must be discarded. Physicians should not be forced to risk performing an incomplete and ineffective procedure because of a limitation on the amount of available product. This is currently the natural consequence of applying the discarded drug policy to cell and gene therapies.

Finally, while many patients currently receive cell and gene therapies in the inpatient setting, increasing provider familiarity has resulted in more administration of these therapies in less acute sites of care, which (as indicated above) is better for patients and the healthcare system. Notably, comparable overall outcomes in safety, efficacy, and quality of life between outpatient and inpatient CAR-T administration occur while reducing their economic burden by incurring costs that

[4] Myers GD, Verneris MR, Goy A, et al. Perspectives on outpatient administration of CAR-T cell therapy in aggressive B-cell lymphoma and acute lymphoblastic leukemia. Journal for Immunotherapy of Cancer 2021.

are two to four times lower.[5] An exemption of the drug discard policy can help accelerate this trend.

For these reasons, ARM strongly encourages the Agency to consider the complex and personalized nature of cell and gene therapies as a unique circumstance that greatly differentiates them from most drugs reimbursed under Medicare Part B and exempt them from the drug discard policy.

CMS Should Cover Dental Care Administered in Connection with Immunosuppressive Therapies and Continue to Explore Dental Coverage for Cell and Gene Therapies More Generally

In the Proposed Rule, CMS notes that Medicare may cover dental services "when the dental services are inextricably linked to, and substantially related and integral to the clinical success of, other covered services."[6] This coverage standard can be met when "dental services serve to mitigate the substantial risk to the success of the medical services."

As CMS suggests in its own commentary, this standard is met in the case of an immunosuppressive therapy. CMS cites to evidence from the American College of Rheumatology and other reputable sources that the use of immunosuppression therapy can lead to the spread of serious oral or dental infections. Therefore, the recommended clinical protocol is the provision of preventive dental services prior to the administration of such therapies to ensure that the patient is cleared of any infections before beginning the therapy. Undoubtedly, a dental infection that would cause a Medicare beneficiary to have to cease use of an immunosuppressive therapy would result in a "substantial risk to the success" of such therapy. For example, similar to CAR-T cell therapy, dental services should be considered a clinical prerequisite to gene therapy with myeloablative conditioning. Without diagnosing and then treating any presenting infection of the mouth prior to myeloablative conditioning, this could lead to systemic infection or sepsis, as well as other complications for the patient.[7] ARM appreciates CMS' recent partnership with the Agency for Healthcare Research and Quality (AHRQ) to conduct rapid evidence product literature reviews in both sickle cell disease (SCD) and hemophilia. CMS states that there is a lack of literature to support coverage of dental services for patients with SCD and hemophilia, however, ARM disagrees with this assessment. In AHRQs report on SCD Kawar et al (citation) clearly states that "standard of care for dental management of sickle cell disease patients" includes "prevention and early intervention…routine dental visits…collaboration between healthcare team (including hematologist) and dentist is important".[8]

ARM agrees with the need for coverage of dental services for Medicare beneficiaries who need immunosuppressive therapy. However, ARM disagrees with CMS's suggestion that such coverage should be limited to *only* individuals with autoimmune diseases. As CMS notes, immunosuppressive

[5] Hansen DK, Liu YH, Ranjan S, Bhandari H, Potluri R, McFarland L, De Braganca KC, Huo S. 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 (Basel). 2023 Dec 7;15(24):5746. doi: 10.3390/cancers15245746. PMID: 38136292; PMCID: PMC10741664.
[6] 89 Fed. Reg. 61596, 61747 (July 31, 2024).
[7] 88 Fed. Reg. at 52,377.
[8] Kawar N, Alrayyes S, Yang B, Aljewari H. Oral health management considerations for patients with sickle cell disease. Dis Mon 2018;64(6):296301.

therapies are used in other contexts, and in some cases may be administered in conjunction with cell and gene therapies.[9] ARM reiterates support from last year's response which highlight how periodic dental care reduces the risks of dental complications requiring haemostatic therapy (such as tooth extractions that may require clotting factor treatment) or oral surgeries requiring clotting factor replacement therapy. We therefore recommend that Medicare cover dental care prior to the initiation of immunosuppressive therapy even in cases where a Medicare beneficiary does not have an autoimmune disease.

ARM also implores CMS to continue to consider evidence related to coverage of dental care for Medicare beneficiaries with sickle cell disease or hemophilia. As the studies submitted to CMS indicate, these two populations need access to quality dental care. ARM appreciates that CMS is looking for opportunities to expand coverage of dental care in accordance with the Medicare statute. CMS should continue to evaluate studies and other information showing how quality dental care can improve medical outcomes for these two populations.

CMS Should Establish Payment for Educating Medicare Beneficiaries on Cell and Gene Therapies, Including Those Treating Hemophilia

ARM understands CMS' assertion that a furnishing fee should not be provided with respect to gene therapies utilized to treat hemophilia, since such therapies are clinician-administered, not self-administered.

ARM recognizes that certain services that are intended to be reimbursed by the clotting factor furnishing fee – such as costs incurred with delivery of the clotting factor to the patient – are not generally present in the case of clinician-administered CGTs. However, the clotting factor furnishing fee also includes a component for educating Medicare beneficiaries on the drug, in recognition that Medicare beneficiaries need to properly understand these complex therapies before receipt.

Patient education is particularly critical in the case of cell and gene therapies. Cell and gene therapies, including those for hemophilia, are highly complex and novel treatments. Patients often require extensive education to understand the procedure, its benefits, risks, and long-term implications. Given the life-changing and potentially curative nature of gene therapies, it is crucial that patients carry out fully informed decisions. Due to these complexities, properly educating patients about cell and gene therapies often requires significant investment from healthcare providers. This may involve multiple sessions to cover all aspects of the treatment and answer patient questions. These sessions often involve different specialists who may conduct incident to services, including geneticists, clinical pharmacists, financial coordinators, and social workers.

Therefore, if CMS concludes a furnishing fee is not appropriate for gene therapies used to treat hemophilia, ARM recommends that CMS establish a separate mechanism for reimbursing clinicians

[9] "Considering the adverse immunological events observed in some of the previous trials of AAV gene therapy, it is becoming increasingly common to include an immunosuppression regimen, usually for a limited period of time." Immune Responses and Immunosuppressive Strategies for Adeno-Associated Virus-Based Gene Therapy for Treatment of Central Nervous System Disorders: Current Knowledge and Approaches, Hum Gene Ther. December 2022; 33(23-24): 1228–1245.

for efforts spent educating Medicare beneficiaries about the unique aspects of their cell and gene therapy options. Establishing a mechanism to reimburse providers for such thorough counseling could help ensure Medicare beneficiaries receive comprehensive information about these potentially life-altering treatments so they can make an informed decision about whether these treatments are appropriate and reduce re-hospitalizations.

CMS has the statutory authority to establish such payments. CMS has previously determined that although the Medicare statute does not mandate coverage of patient education, "reimbursement may be made under Medicare for such programs furnished by providers of services (i.e., hospitals, SNFs, HHAs, and OPT providers) to the extent that the programs are appropriate, integral parts in the rendition of covered services which are reasonable and necessary for the treatment of the individual's illness or injury."[10] The Agency already reimburses for patient education as part of Chronic Care Management (CCM) services for conditions such as Hepatitis, osteoporosis and ischemic heart disease. In the proposed rule, CMS further explained that education coverage should be "closely related to the care and treatment of the patient."

When counseling the beneficiary on a CGT prior to or following administration, the Agency should allow medical professionals who are eligible to bill for Medicare for office/outpatient (O/O) evaluation and management (E/M) visits to utilize HCPCS code G2211 – [visit complexity inherent to evaluation and management associated with medical care services that serve as the continuing focal point for all needed health care services and/or with medical care services that are part of ongoing care related to a patient's single, serious condition or a complex condition].[11] While no specific diagnosis is required for HCPCS code G2211 to be billed, the Agency notes it would be appropriate to report a health condition that is a single, serious condition and/or a complex condition for which the billing practitioner is engaging the patient in a continuous and active collaborative plan of care related to an identified health condition—*the management of which requires the direction of a practitioner with specialized clinical knowledge, skill, and experience*. The novelty of cell and gene therapies not only warrants providers to engage in specialized clinical training programs to appropriately administer these treatments but also requires supplemental education for other clinicians to counsel patients on the availability, appropriateness, and other considerations regarding CGTs.[12]

G2211 should be applied for visits that include cell and gene therapy education in recognition for the additional complexity and time required.

Additionally, the 2003 Comptroller report used to evaluate the adequacy of hemophilia treatment reimbursement with a focus on factor costs was published nearly twenty years prior to the first hemophilia gene therapy approval. As noted in the 2003 Comptroller report, "clotting factor providers also incur costs associated with storing and shipping clotting factor" this statement is also

[10] CMS, National Coverage Determination, Institutional and Home Care Patient Education Programs, https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=250&ncdver=1&bc=0.
[11] CMS, Frequently Asked Questions (FAQs) About Office/Outpatient (O/O) Evaluation and Management (E/M) Visit Complexity Add-On HCPCS Code G2211, https://www.cms.gov/files/document/hcpcs-g2211-faq.pdf
[12] CHOP Research Institute, Cell and Gene Therapy Clinical Training Program, https://www.research.chop.edu/services/cell-and-gene-therapy-clinical-training-program

true for gene therapy and these costs are intended to be offset by the furnishing fee. CMS should thus reconsider the classification of gene therapies as it relates to its administration and explore coverage and reimbursement options for proper patient education.

Conclusion

The field of regenerative medicine has the potential to restore hope for patients while lowering long-term costs and improving quality outcomes. CMS should continue to take steps to ensure Medicare beneficiaries can benefit from cell and gene therapies.

We thank CMS for its consideration of our comments. Please feel free to contact Monet Stanford at mstanford@alliancerm.org with questions.

Sincerely,

Erica Cischke, MPH

Vice President, Government Affairs Alliance for Regenerative Medicine