



June 15, 2018

Tamara Syrek Jensen, J.D.
Director, Coverage & Analysis Group
Centers for Medicare & Medicaid Services
Mailstop S3-02-01
7500 Security Blvd.
Baltimore, MD 21244

Sent electronically

RE: Medicare National Coverage Analysis for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancer (CAG-00451N)

Dear Ms. Syrek Jensen:

The Personalized Medicine Coalition (PMC), a multi-stakeholder group comprising more than 230 institutions across the health care spectrum, appreciates the opportunity to submit comments regarding the Centers for Medicare & Medicaid Services (CMS)' National Coverage Analysis (NCA) for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancer.¹ While we recognize that a national coverage policy could provide some uniformity in the path to coverage for FDA-approved CAR T-cell therapies, the timing of this NCA may be premature and could complicate beneficiary access.

Personalized medicine is an evolving field that uses diagnostic tools to identify specific biological markers, often genetic, to help determine which medical treatments and procedures will be best for each patient. By combining this information with an individual's medical history, circumstances, and values, personalized medicine allows doctors and patients to develop targeted prevention and treatment plans.

Personalized medicine is helping to shift the patient and provider experience away from trial-and-error and toward a more streamlined process for making clinical decisions, which will lead to improved patient outcomes, a reduction in unnecessary treatment costs, and better patient and provider satisfaction. As noted above, PMC's members are leading the way in personalized medicine and recommend that patients who may benefit from this approach undergo appropriate testing and tailored treatment as soon as possible during their clinical experiences.

PMC recently released "*Personalized Medicine at FDA: 2017 Progress Report.*" The report documents a record number of new personalized medicines approvals by the

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U.S. Food and Drug Administration (FDA). This marks the fourth consecutive year that personalized medicines accounted for more than 20 percent of all new drug approvals.ⁱⁱ Two of the 19 personalized medicines approved in 2017 were CAR T-cell therapies, an adoptive cell transfer (ACT) class of immunotherapies where a patients' immune cells are collected and genetically changed to treat his/her cancer. Because of its potential to further transform cancer care for patients with incurable blood cancers, the American Society of Clinical Oncology named ACT using CAR T-cells their 2018 "Advance of the Year."ⁱⁱⁱ

CAR T-cell therapy is the result of decades of research in biology, genetics and immunology supported by the National Institutes of Health and the biopharmaceutical industry. A study conducted by the Massachusetts Institute of Technology NEWDIGS FoCUS Project predicts that by the end of 2022 there will be about 40 gene therapy products approved by the FDA, with 45 percent of these for products targeting cancer.^{iv} In light of this entirely new approach to treatment the FDA has developed new structures for evaluating cell and gene therapies and has demonstrated remarkable speed in bringing CAR T-cell therapies to market. Like FDA, CMS has signaled a belief that CAR T-cell therapies represent a significant advancement in cancer care and we appreciate the opportunity to provide feedback on how CMS can ensure continued beneficiary access to CAR T-cell therapies.

Statement of Neutrality

Many of PMC's members will present their own responses to CMS and will actively advocate for those positions. PMC's comments are designed to provide feedback so that the general concept of personalized medicine can advance, and are not intended to impact adversely the ability of individual PMC members, alone or in combination, to pursue separate comments with respect to the NCA on CAR T-cell therapies for cancer.

Burden of Disease and Treatment with CAR T-cell Therapies

The two CAR T-cell therapies approved by the FDA in 2017 are intended to treat children and young adults with acute lymphoblastic leukemia (ALL) and adults with diffuse large B-cell lymphoma (DLBCL). ALL and DLBCL are cancers with a very poor prognosis.

The expected survival for adults with relapsed ALL is less than six months. Among children with cancer, relapsed ALL is a leading cause of cancer-related death.^v Treatment with CAR T-cell therapy for ALL resulted in complete remissions in up to 90 percent of adults and children with this disease. In contrast, other available treatments for relapsed ALL have a response rate of 30 percent to 43 percent, depending on the type of treatment. In some patients, remissions have lasted up to two years. Such durable remissions offered many patients the chance to undergo bone marrow transplants, a procedure that can be curative.^{vi}

DLBCL is the most common type of non-Hodgkin lymphoma. In a multicenter clinical trial of patients with DLBCL that worsened after at least two prior therapies, the cancer responded to a CAR T-cell therapy called tisagenlecleucel in 59 percent of 51 patients and the cancer went into remission in 43 percent of patients. At 6 months, 79 percent of patients had not had a recurrence of lymphoma. In a different clinical trial, patients with relapsed or refractory DLBCL, refractory primary mediastinal B-cell lymphoma, or transformed follicular lymphoma, received another CAR T-cell therapy, axicabtagene

ciloleucel. Among the first 92 patients who were treated, the response rate was 82 percent, with complete remissions occurring in 54 percent of patients.^{vii}

CAR T-cell therapies have made a profound impact in extending the lives of some people with ALL and DLBCL, however this course of treatment can have serious side effects that are still under investigation. Side effects include high fever, chills, flu-like symptoms, neurological changes, infection, low blood cell counts, and a weakened immune system. Oncologists who administer CAR T-cell treatments often use the immune-suppressing drug tocilizumab, which was approved by the FDA to manage adverse reactions like these, but it does not always reverse complications. Researchers are actively working to understand the causes of adverse reactions like these and exploring methods to further mitigate them. One study is examining the use of anakinra, prior to administration of CAR T-cells to target neurotoxicity.^{viii}

Researchers are also pursuing CAR T-cell therapies in other types of cancer. There have been promising results, especially in multiple myeloma. An early clinical trial of patients with relapsed, treatment resistant multiple myeloma reported that 33 out of 35 (94 percent) patients demonstrated clinical remission upon receiving a CAR T-cell therapy targeting B-cell maturation protein. In this study most patients had only mild side effects.^{ix}

Considerations for CMS in Exploring National Coverage

Tremendous advancement in CAR T-cell therapy should be supported by a thoughtful reimbursement structure. Unfortunately, the complexity of CAR T-cell treatment has created a daunting reimbursement landscape for patients and providers to navigate.

Medicare currently limits settings where beneficiaries can receive CAR T-cell treatment due to the acute nature of treatment side effects, Medicare coding and claims procedures do not sufficiently cover the upfront cost to hospitals that provide care for patients with these novel therapies, and some providers are excluded from administering CAR T-cell therapy altogether. We recognize that CMS recently proposed improvements that would address some of these access concerns in its Medicare Hospital Prospective Payment System Proposed Rule for 2019. PMC will be submitting comments separately on the proposed changes.

Manufacturers of the FDA-approved CAR-T therapies have responded to the current patchwork of coverage by developing programs that provide financial assistance to patients and their caregivers. These programs help cover co-pays and transportation costs so that patients can receive care in facilities that administer CAR T-cell therapy. Solutions like these are making CAR T-cell therapies available to some patients, as all stakeholders work to ensure that these therapies are accessible to all patients who may benefit from them.

Despite its complexity we believe this reimbursement landscape can be best shaped through ongoing, robust stakeholder dialogue that is already occurring outside of the NCD process. CMS should continue efforts to educate providers and others in the healthcare community on these innovative products and instruct its Medicare Administrative Contractors and providers on how to cover and process claims. If CMS advances a proposed national coverage policy for CAR T-cell therapies we respectfully ask you to consider the following:

- FDA Commissioner Scott Gottlieb has stated that the field is at a turning point and the FDA may have to accept more uncertainty for pre-market approval of cell-based therapies like CAR T.^x In instances like these, CMS should work with biopharmaceutical companies to begin conversations about data collection as early as possible in product development process to establish what evidence will be necessary for coverage upon FDA approval. Data collection and reporting requirements should not create unnecessary burdens for patients and providers.
- Coverage policies are often based on treatment criteria and clinical guidelines. This approach may not be feasible for CAR T-cell therapies given their personalized nature. The lack of treatment criteria and clinical guidelines has been problematic for some commercial payers in determining coverage for CAR T-cell therapies. CAR T-cell therapies are transformative and address the individual needs of patients who are often without other options. A Medicare national coverage policy should not create the same barrier for patients and providers in the commercial market when the biological rationale for treatment exists but treatment criteria are still evolving.
- CAR T-cell therapies may have certain attributes at the time of FDA approval but there are specialized considerations for delivery of each therapy. A national coverage policy would need to be flexible enough to keep pace with new research that produces results to reduce treatment complications or yield other improvements in patient response to CAR T-cell treatment.

Conclusion

Thank you for considering our comments. If CMS moves forward with developing a proposed decision memo on CAR T-cell therapy for cancer, PMC welcomes the opportunity to serve as a resource for you. We hope any additional activity by the CMS on this issue can achieve the goal PMC shares with the agency of delivering appropriate, efficient, and accessible health care to every patients. If you have any questions about the content of this letter, please contact me at 202-589-1769 or cbens@personalizedmedicinecoalition.org.

Sincerely,



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- ⁱ Centers for Medicare & Medicaid Services. *National Coverage Analysis for Chimeric Antigen Receptor (CAR) T cell Therapy for Cancer*. May 16, 2018 <https://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=291>
- ⁱⁱ Personalized Medicine Coalition. *Personalized Medicine at FDA 2017 Progress Report*. January 30, 2018 http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM_at_FDA_2017_Progress_Report.pdf
- ⁱⁱⁱ American Society of Clinical Oncology. *Clinical Cancer Advances of 2018*. January 30, 2018 <https://www.asco.org/sites/new-www.asco.org/files/content-files/research-and-progress/documents/CCA-2018-Report.pdf>
- ^{iv} Massachusetts Institute of Technology NEWDIGS FoCUS Project. *Existing Gene Therapy Pipeline Likely to Yield Dozens of Approved Products Within Five Years; Research Brief*. November 13, 2017. http://newdigs.mit.edu/sites/default/files/FoCUS_Research_Brief_2017F211v011.pdf
- ^v American Society of Clinical Oncology. *At the Leading Edge of Precision Medicine: Souped-up Immune Cell*. April 5, 2017. <https://www.asco.org/about-asco/press-center/cancer-perspectives/leading-edge-precision-medicine-souped-immune-cells>
- ^{vi} American Society of Clinical Oncology. *At the Leading Edge of Precision Medicine: Souped-up Immune Cell*. April 5, 2017. <https://www.asco.org/about-asco/press-center/cancer-perspectives/leading-edge-precision-medicine-souped-immune-cells>
- ^{vii} American Society of Clinical Oncology. *Clinical Cancer Advances of 2018*. January 30, 2018 <https://www.asco.org/sites/new-www.asco.org/files/content-files/research-and-progress/documents/CCA-2018-Report.pdf>
- ^{viii} Margherita Norelli; Barbara Camisa; Giulia Barbiera; Laura Falcone; Ayurzana Purevdorj; Marco Genua; Francesca Sanvito; Maurilio Ponzoni; Claudio Doglioni; Patrizia Cristofori; Catia Traversari; Claudio Bordignon; Fabio Ciceri; Renato Ostuni; Chiara Bonini; Monica Casucci; Attilio Bondanza. *Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells*. June 2018. <https://www.ncbi.nlm.nih.gov/pubmed/29808007>
- ^{ix} Frank (Xiaohu) Fan, Wanhong Zhao, Jie Liu, Aili He, Yinxia Chen, Xingmei Cao, Nan Yang, Baiyan Wang, Pengyu Zhang, Yilin Zhang, Fangxia Wang, Bo Lei, Liufang Gu, Xugeng Wang, Qiuchuan Zhuang, Wanggang Zhang; Nanjing Legend Biotech, Nanjing, China; Hematology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China. *Durable Remissions with BCMA Specific Chimeric Antigen Receptor (CAR)-modified T Cells in Patients with Refractory/Relapsed Multiple Myeloma*. June 5, 2017. <https://meetinglibrary.asco.org/record/153928/abstract>
- ^x U.S. Food and Drug Administration. *Remarks by Commissioner Gottlieb to the Alliance for Regenerative Medicine's Annual Board Meeting*. May 22, 2018. <https://www.fda.gov/NewsEvents/Speeches/ucm608445.htm>