Researchers question process for reviewing coverage of 'off label' cancer drug use

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A group of University of North Carolina Lineberger Comprehensive Cancer Center researchers is calling for an overhaul of the process that determines which cancer drugs used off-label—or beyond their approved use—are reimbursed by federally-funded health insurance in the United States.

In a paper published online by the *Journal of the American Medical Association*, the physician-researchers raised concerns that there are inconsistencies between the five reference guides, or compendia, that the Centers for Medicare and Medicaid Services uses to determine which drugs it will reimburse for off-label uses in cancer care. They also cited the "weak quality" of evidence used in some cases to green-light some off-label uses in oncology, which they argue could be leading to poor quality of patient care and high costs.

"The quality and consistency of these very important compendia resources is not what it should be, given the level of scrutiny that's appropriate for highly toxic and expensive cancer drugs," said the study's corresponding author Ethan Basch, MD, MSc, director of UNC Lineberger Comprehensive Cancer Center's Cancer Outcomes Research Program and a professor in the UNC School of Medicine Division of Hematology/Oncology. "We could be causing substantial suffering for cancer patients because of the sometimes cavalier use of off-label drugs. A new, more rigorous approach is warranted in order to protect our patients."

The researchers report that off-label use of drugs is widely practiced in oncology care. A 2013 study found that off-label uses accounted for $5 billion in cancer drug costs in 2010.

"Off-label drugs are used in many different scenarios in cancer care," said William Wood, MD, MPH, a UNC Lineberger member, an associate professor in the UNC School of Medicine Division of Hematology/Oncology and a co-author of the study. "They can be used if treatment options are limited in a certain situation, or if a clinician wants to try something unconventional, which could be a high quality decision or a poor quality decision. The concern is that people could be getting treatments that are inappropriate and that the risks may be greater than the benefits of these treatments."

Federal law specifies that the Centers for Medicare & Medicaid Services should pay for a drug not used in accordance with the U.S. Food and Drug Administration's label when one of the five reference guides states the drug's off-label use is medically appropriate. Private insurers often use the compendia recommendations to inform coverage decisions, they also report.

But the authors write that previous research has found that the quality of evidence in the reference guides used is sometimes less rigorous than standards for FDA-approved drug uses. In their own analysis of off-label uses for cancer drugs, Basch and his colleagues found limitations in the level, quantity, consistency, and timeliness of evidence cited.

The researchers offer four steps for improving the review process: develop methodological standards for evaluating evidence used to back off-label drug recommendations; combine the findings into one "single, rigorously developed resource" rather than five inconsistent reference guides; assess whether those reviewing and determining off-label drug use policies have potential financial conflicts of interest; and make the

compendia listings, which currently are only available by subscription, free to the public.

They also recommended that the FDA, or a public-private partnership, should oversee the decision-making process. "The FDA has the ability to review evidence using strict standards, and the purview of the FDA over oncology is increasing with the development of the FDA Oncology Center of Excellence," Basch said. "We are advocating for an approach that would be different from regular drug approval, but improving on the current system."

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