CAPITOL STREET

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Multi Cancer Tests: Not One Size Fits All

Blood-Based Tests Face FDA Panel as CMS/FDA Pilot Galleri

Relevant Companies

Last week, the FDA Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee met to discuss and make recommendations on the design of multi-cancer detection (MCD) in vitro diagnostic devices (tests) here. The panel also discussed potential study designs and outcomes that could inform the benefits and risks of MCD screening tests.

Our Take & Next Up

The FDA is unsure how to address multi-cancer tests and has largely been skeptical of these screening tests in the past. Our main takeaways from the hastily convened advisory panel are found below. On coverage, CMS/FDA announced a 50,000 Medicare beneficiary pilot for Galleri while not promising long term coverage. As a reminder there is no Medicare coverage category for pan-cancer screening (here) but legislation has been introduced. The FDA has not yet approved any multi-cancer detection tests**.** The FDA discussed USPSTF and coverage/pricing, which is not the jurisdiction of the agency. The FDA has more questions than answers at this point on pan-cancer screening, and legislation for Medicare coverage is unlikely to pass any time soon, given significant costs to the government (CMS).

Key Points

CMS/FDA Pilot under investigational device exemption (IDE) here. The Galleri-Medicare study is a first-of-its-kind real-world study designed to further evaluate the clinical impact of the Galleri multi-cancer early detection (MCED) test among Medicare beneficiaries, including racial and ethnic minorities, and seniors from historically underserved communities. The Galleri-Medicare study seeks to compare up to 50,000 Medicare beneficiaries who have received usual care + an annual Galleri test with a matched comparator arm of beneficiaries who receive usual care alone. Medicare will cover the costs of Galleri (~$900 per test) and related and routine items and services for study participants.

Pricing and coverage are not under the FDA's jurisdiction, but MCD testing is expected to have a significant downstream cost burden to healthcare system and payers longer term. Widespread testing combined with the possibility of misdiagnosis from false positives opens the healthcare system up to more diagnostic procedures being required than before. We do not expect the agency to cover MCDs due to the potential cost burden, but the tests present possible utility in preventing progression of cancer in Medicare populations that are at a higher risk for cancer compared to the general population. Lawmakers are considering expanding CMS coverage for MCDs.

The *Medicare Multi-Cancer Early Detection (MCED) Screening Coverage Act* (text here) is unlikely to pass Congress near term due to its price tag. The bipartisan & bicameral bill was reintroduced in both chambers this summer and would establish a Medicare coverage pathway for MCDs following FDA approval. The bill has significant Congressional and patient support but failed to move this year, like other healthcare priorities, and is stymied by a CBO cost score.

MCD tests are currently available through a Clinical Laboratory Improvement Amendments (CLIA) waiver since the sample testing is done in a central laboratory regulated by CLIA. The agency is expected to be stringent in its first approval of multi-cancer screening tests. Developers may be asked to support further post-approval data collection to answer the agency's key questions around rate of false positives, and clinical impact to providers and patient outcomes.

The cancer advisory meeting attracted little fanfare and the FDA provided little notice prior to the panel, which hasn't met for a decade. The meeting was announced on Monday November 13 and the FDA only accepted comments until November 15. The panel has not met since 2014 and appointed non-committee members one day prior. During the session, the committee panel acknowledged gaps in panel representation for pathologist and laboratory science experts.

- **USPSTF coverage was discussed but remember that is not the jurisdiction of FDA**. Prior to the first MCD approval, the agency is expected to undertake a communication campaign to ensure that providers and patients understand the risks and guide best practices for use and follow-up (similar to gene therapies).
- **On coverage, it is unlikely that the Preventive Services Task Force would approve of MCD usage as part of the standard of care in the near term**. The Task Force is likely to hold off on multicancer tests due to the downstream cost burden of additional screenings combined with the ongoing unknown risks of a multi-cancer test.
- **Roche was the only industry representative present.** Nathan Winslow (Roche Dx) asserted that multicancer screening tests are intended to be used as complementary to standard screening methods. The non-invasive nature of tests and the potential health equity benefit was also touted as things that the FDA should consider in their review. GRAIL's (ILMN) multi-cancer early detection (MCED) test was mentioned by both public stakeholders who were supportive of access to testing and by committee members who were more skeptical about the test's utility in clinical practice. Other blood-based testing companies include Emergent Science, Exact Sciences, Myriad, Invitae, Foundation Medicine, and Guardant Health.
- **FDA had more questions than answers with Dr. Tim Stenzel (retiring in 2023, Office of In Vitro Diagnostics and Radiological Health) asking the committee for minimum numbers around ideal specificity and sensitivity.** The committee largely concluded that there is not one size fits all solution, but committee members, Dr. Mitchell Gail and Dr. Karla Ballman, wanted tests to show specificity of 99%. There was more flexibility around sensitivity. As a reminder, specificity is a test's ability to designate an individual who does not have a disease as negative. FDA and committee members were concerned about the risks related to a false positive from MCDs and the impact of patients having to undergo further diagnostic screening.
- **Conflict on the right endpoints for test validation: lowering cancer stage vs mortality.** The committee was split on an appropriate endpoint for clinical validation. Committee member Dr. Philip Castle was a strong proponent of using cancer-specific mortality as he noted reduction in late-stage cancers did not always correlate with a mortality benefit. Other committee members noted that palliative care and new therapeutics prolong life and complicate mortality. As a reminder, the FDA cannot evaluate

mortality as the agency can't legally evaluate clinical utility for devices. Any mortality data that is collected by developers would instead be evaluated by payers, including CMS.

- **Committee members cautioned against widespread cancer testing in the general population without clear procedures on data collection and follow-up.** Cancer is not common in the general population and the risks are dependent on certain demographic factors like age. Committee members referenced past history of poor implementation of widespread screening tools.

    - Dr. Daniel Swerdlow noted the chaos of implementation of low- dose CTs for lung cancer screening and how much information needed to be made available to patients, primary care providers and specialists.

    - Dr. Edward Bujold emphasized issues with PSA tests as it was not properly vetted for use other than recurrent prostate cancer before its indication was expanded to initial screening for prostate cancer. However, some members believed there is an opportunity for multi-cancer tests in cancer survivors as they have a higher rate of cancers, are more motivated to seek follow-up and are already connected with specialist care.

The meeting comes as the FDA is finalizing guidance on laboratory developed tests (LDTs), which will likely end up in court if FDA (largely) finalizes as proposed. The *VALID Act* (largely the brainchild of the Senate HELP Committee) was not passed in 2023 (our analysis here) and is unlikely to pass this year but is the preferred regulatory pathway for test developers. In September, the FDA released proposed guidance (here) on how they will regulate LDTs under the agency's medical device authorities. FDA is defining LDTs broadly, asserting that many manufacturers of high complexity tests have cloaked themselves as LDT manufacturers. FDA intends to phase out general enforcement discretion approach so that LDTs will fall under the same enforcement approach as other in vitro diagnostics. The final guidance is expected in 1H 2024. If finalized as proposed, we expect lawsuits to be filed against the agency from myriad organizations e.g., American Clinical Laboratory Association (ACLA).

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