PERSONALIZED MEDICINE COALITION

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Submitted electronically

Re: Review Protocol titled: *Blood-based Tests for Multiple Cancer Screening: A Systematic Review*

Dear Dr. Chang,

The Personalized Medicine Coalition (PMC), a multi-stakeholder group comprising more than 200 institutions and individuals from across the health care spectrum appreciates the opportunity to comment on the Agency for Healthcare Research and Quality's (AHRQ's) Review Protocol titled: *Blood-based Tests for Multiple Cancer Screening: A Systematic Review*. PMC recognizes the transformative potential of early cancer screening tests for cancer care and prevention. Throughout PMC's 20-year history we have observed that the deployment of innovative tools like these is impeded when scientific developments outpace the evidence to inform policy changes and delivery system reforms necessary for their implementation. When this occurs, patients are most often left with limited or no access. It is premature for AHRQ to conduct this systematic review given that there are studies in progress and in development to produce data on multiple aspects of early cancer detection testing. These studies are critical for informing patients, provider and payer decision-making. PMC is concerned with the timing and scope of AHRQ's review, and we, therefore, urge AHRQ to reconsider undertaking this effort.

Personalized medicine is an evolving field in which physicians use diagnostic tests and individual details about a person and their health to determine which medical treatments will work best for each patient or use medical interventions to alter molecular mechanisms that impact health. By combining data from diagnostic tests with an individual's medical history, circumstances and values, health care providers can develop targeted treatment and prevention plans with their patients.

Personalized medicine is helping to shift patient and provider experiences away from trial-and-error treatment of late-stage diseases in favor of more streamlined approaches to disease prevention and treatment, which will lead to improved patient outcomes, a reduction in unnecessary treatment costs, and better patient and provider satisfaction. Despite growing consensus that personalized medicine approaches have

significant value, their implementation – and, consequently, patient access – across the United States is highly variable.[i]

Statement of Neutrality

Many of PMC's members will present their own responses to AHRQ's Review Protocol titled: *Blood-based Tests for Multiple Cancer Screening: A Systematic Review*. PMC's comments are designed to provide feedback so that the general concept of personalized medicine can advance and are not intended to adversely impact the ability of individual PMC members, alone or in combination, to pursue separate comments with respect to this evidence review or related issues.

Burden of Cancer

The United Staes has seen a decline in cancer mortality rates over the past three decades.[ii] In fact, annual cancer death rates in the U.S. have dropped more than 30 percent since their peak in 1991.[iii] Today, there are more than 18 million Americans who have survived cancer thanks to a record numbers of cancer treatment approvals by the U.S. Food and Drug Administration (FDA)[iv] and exciting new opportunities to prevent, diagnose, and improve the well-being of many cancer patients.

Implementation of cancer screening and early detection tests into routine practice for some highly prevalent cancers[v] have made the potential for long-term survival possible for more people, giving them more years with their loved ones and the ability to stop some cancers before they even start. Despite this progress, cancer remains the second leading cause of death in the U.S. and nearly two million new cancer cases are diagnosed each year.

Through the current phase of the Biden Administration's Cancer Moonshot, federal agencies, scientists, the medical community, the private sector, and patient advocates have mobilized to drive innovative action and life-saving progress forward in ways that can reach all Americans.[vi] The Moonshot's three main goals are decreasing overall cancer mortality rates by at least 50 percent by 2047, improving access to cancer care and control for everyone, and "ending cancer as we know it."

According to a National Cancer Institute (NCI) analysis, to attain a 50 percent reduction in cancer mortality rates, faster progress must be made against the most common cancers. "Ending cancer as we know it" requires progress against cancers that have proven the most difficult to treat and disparities that play a significant role in cancer incidence rates for specific populations must be addressed.[vii] Early cancer detection tests may be useful in helping to achieve each of the Cancer Moonshot's goals, but these goals are not reflected in AHRQ's unbalanced framework for reviewing the evidence on multi-cancer early detection tests.

Benefits of Early Detection

Cancer screening and earlier detection are pivotal to guiding interventions earlier in asymptomatic cancer patients,[viii] often resulting in improved outcomes and reduced morbidities associated with advanced cancer, as well as potential significant reductions in the cost and complexity of cancer care.[ixxxi]

The United States Preventive Services Task Force (USPSTF), which is responsible for releasing evidence-based recommendations to improve population health, recommends routine screening for breast, cervical, colorectal, and lung cancer.[xii] Proven screening tests for these cancers have led to finding and treating these types of cancer earlier.[xiii]

However, even current recommended cancer screening and early detection tests, such as colonoscopies, stool-based tests, mammograms, low-dose CT scans, and cervical cytology, face hurdles hindering equitable access in a real-world setting. Low adherence rates among eligible populations, low test sensitivity for early-stage disease, and high false positive rates are some of the barriers to screening.[xiv] Insufficient compliance with, or access to, reliable early screening technologies leads to cancer diagnoses at later stages. Such diagnoses pose greater challenges for effective treatment.[xv] [xvi]

For more than two decades, the field of personalized medicine has been anticipating the emergence of minimally invasive early detection tests that rely on an advanced understanding of molecular signals in patients' bodies to warn physicians more quickly about the development of diseases like cancer. By detecting cancer signals in the bloodstreams of seemingly healthy individuals, early cancer detection tests promise to put patients on the path to personalized cancer treatment more quickly and with less invasive intervention. Multi-cancer early detection tests are poised to redefine the current landscape by screening for multiple different cancer types at once and detecting cancers that would otherwise have been missed by traditional routinely recommended screening tests or caught too late.[xvii] [xviii]

By prioritizing key questions in its' systematic review such as the impact of multi-cancer early detection tests on reducing cancer-specific and all-cause mortality, and emphasizing perceived harms of over-screening with these tests, AHRQ fundamentally discounts the fact that nearly 4 out of 10 people in the U.S. will develop cancer during their lifetimes and two out of every three cancer cases occur in cancer indications without recommended routine screening. This leads to diagnoses in advanced stages of disease and a higher likelihood of mortality.[xix] Currently, about 70 percent of all cancer deaths come from cancers for which there are currently no proven screening tests and for some cancers no outward symptoms in early stage leading to diagnosis at an advanced stage.[xx]

When reviewing the impact of multi-cancer early detection tests, any analysis should include endpoints that evaluate the potential benefits of these tests in reducing premature cancer-related deaths, cancer-related morbidity, disability, functional decline, and other measures of clinical improvement that may be expected from earlier detection of cancer. A reduction in advanced disease burden should also be considered as a proxy for mortality when coupled with models for subsequent mortality. One improvement to the AHRQ review protocol would be to update "Figure 1. Analytic framework for blood-based tests for multiple cancer screening" to include opportunities where the benefits of multi-cancer early detection tests can be examined along with potential harms. Further, AHRQ should undertake a rigorous multi-stakeholder consultation process where the timing for any systematic review can be discussed to align with the availability of results from ongoing studies, and where patient voices can be incorporated to inform AHRQ's approach to understanding how individuals weigh the potential benefits and harms of early cancer detection.

Challenges with Timing and Scope of Review

PMC has been working to inform strategies that enable timely access to personalized medicine based on the value it provides to patients, the health care system, and society. Health systems are still developing and adopting the procedures necessary to facilitate broader utilization of personalized medicine. We believe widespread access to multi-cancer early detection tests hinges on clinical utility data showing that use of these tests can improve patient management and net health outcomes.[xxi] Studies are already underway and at different phases of development to provide this data.

The NHS-England is conducting a prospective, randomized, controlled trial to assess the performance and clinical utility of a multi-cancer early detection test for population screening in the United Kingdom when added to standard of care. The study has enrolled more than 140,000 people between the ages of 50 and 77 and was designed with three successive rounds of screening. The primary endpoint of the trial is an absolute reduction in the number of cancers diagnosed at stages 3 and 4. A key secondary endpoint is modeled cancer-specific mortality. The NHS study is expected to read out in 2026.[xxii]

In the U.S., the NCI's new Cancer Screening Research Network launched the pilot NCI Vanguard Study this year. The Vanguard Study is a study intended to evaluate whether the benefits of using multi-cancer detection tests to screen for cancer outweigh the harms, and whether these tests can detect cancer early enough to reduce deaths. The Vanguard Study is in a feasibility stage to assess participant willingness for randomization into one of three study arms; to evaluate the feasibility of protocol-defined diagnostic workflows and adherence to testing and diagnostic follow-up; to determine reliability and timeliness of blood specimen testing and return by participating companies; and to identify facilitators and barriers to recruitment/retention/compliance of diverse participant groups. The first phase of the Vanguard Study, initiated in 2024, will inform the design of a larger clinical trial involving about 225,000 people.[xxiii]

The National Academies of Science, Engineering and Medicine (NASEM) is currently examining the state of the science for the clinical use of multi-cancer early detection testing. Recognizing that the development of minimally invasive approaches to screen for multiple tumor types at once could address unmet need created by the paucity of effective screening tests for most cancers, the NASEM will convene stakeholders this fall to discuss challenges and opportunities in validating multi-cancer early detection tests and determining their clinical utility, strategies for cancer care downstream of multi-cancer early detection testing, and limitations of multi-cancer early detection testing. The NASEM is taking another step to highlight research and policy gaps for assessing multi-cancer early detection tests' impact on cancer care and health outcomes.[xxiv]

The FDA recently granted an investigational device exemption for use of a multi-cancer early detection test in the Falcon Registry. The study recruited its first patient in August and aims to recruit up to 25,000 participants. The study will assess the clinical performance, patient and provider experience, and psychological impact of multi-cancer early detection test testing over a five-year period. Patients aged 50 to 80 with no history of cancer will receive annual testing for three years, with two additional years of follow-on data collection. Data from this cohort will be compared to that collected from a comparator cohort of up to 50,000 patients who are demographically and clinically similar to study participant but who receive standard care without multi-cancer early detection testing.[xxv]

Collaborations between multi-cancer early detection test manufacturers, health systems, and payer organizations are also in place to help to generate near-term clinical utility data and accelerate knowledge generation. Point32Health, a nonprofit payer, is conducting a multi-phased pilot in which Point32Health is providing a multi-cancer early detection test to certain employees depending on their age and family history, as well as healthcare provider groups serving the plan's members. The pilot will generate real-world evidence and assess the impact of multi-cancer early detection testing on care resource utilization and other outcomes.[xxvi]

The FDA also granted an investigational device exemption for use of a multi-cancer early detection test in a prospective, multi-center study to assess the real-world clinical impact of multi-cancer early detection testing in addition to currently recommended cancer screenings. The three-year study seeks to compare up to 50,000 Medicare beneficiaries who have received usual care plus a multi-cancer early detection test with a comparator arm of beneficiaries who receive usual care without a multi-cancer early detection test, at up to 50 study sites. To measure clinical impact, the study will assess reduction in diagnosed stage IV cancers, safety associated with multi-cancer early detection test use, and health care resource utilization associated with cancer diagnostic workup in the Medicare population. Community Health Network began enrollment of a diverse range of study participants this year and costs will be covered by Medicare.[xxvii]

Public-private consortia in the U.S. and abroad are evaluating emerging data from multi-cancer early detection studies and establishing standards in multi-cancer early detection technology by developing recommendations for baseline implementation of testing, including standardized procedures for use in a clinical setting and communication of multi-cancer early detection testing results.[xxviii][xxix][xxx] The consortia are developing a public-outreach approach that identifies and mitigates potential health inequities that could arise from the use of multi-cancer early detection technology.

These and other efforts are accelerating because the field believes that they are necessary to inform approaches on incorporating early cancer detection tests into the standard of care. It is premature for AHRQ to conduct this systematic review given that there are studies in progress and in development to produce data on multiple aspects of early cancer detection testing. These studies are critical for informing patients, provider and payer decision-making. If pursued now AHRQ's review will not consider their results and at best return minimal or insufficient evidence to answer key questions impacting oncology patient.

Conclusion

Thank you for the opportunity to comment on this systematic review and your consideration. PMC would be pleased to serve as a resource for you and your staff to ensure AHRQ's Effective Healthcare Program can support the ongoing development and delivery of personalized medicine products and services for all patients. If you have any questions about the content of this letter, you can contact me at cbens@personalizedmedicinecoalition.org or David Davenport, PMC's Manager of Science and Public Policy, at ddavenport@personalizedmedicinecoalition.org.

Sincerely,

Cynthia A. Bens
Senior Vice President, Public Policy

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