Title
Multi-Cancer Screening Tests: Communicating About Risks Should be Prioritized

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COMMENTARY

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Multi-Cancer Screening Tests: Communicating About Risks Should be Prioritized

In June of 2021, Klein and colleagues[1] reported the results of a prospective, case-controlled, observational study on the clinical validity of a multi-cancer early detection (MCED) test developed by GRAIL, Inc. Based on a blood draw providing cell-free DNA (deoxyribonucleic acid) and its interpretation through machine learning, this test has been developed with the aim of increasing the number of detected cancers through population screening. The authors reported a specificity for cancer signal detection of 99.5% and an overall sensitivity of 51.5%. They concluded that the MCED test demonstrates high specificity and accuracy and that "these results support the feasibility of this blood-based MCED test as a complement to existing single-cancer screening tests." The study showed that the MCED test succeeded in identifying cancer effectively, but do these results merit adopting a broad cancer screening program?

Cancer screening is based on a widely adopted premise that earlier detection is better. Detecting and removing a lesion that would have not negatively affected a patient's life is of no benefit to the patient and is an example of over-diagnosis and overtreatment, respectively. The high rate of newly discovered malignant lesions in autopsy reports that did not contribute to the cause of death should make us ask: "Are these pathological lesions 'true' cancers?". Some have advocated for the use of the term "indolent lesion of epithelial origin," (abbreviated IDLE) to make a distinction between lesions that eventually threaten the duration or quality of a patient's life and those that never cause any trouble.[2] Three types of what are broadly called "cancers" can be described: 1) slowly progressive, where early detection may prevent death, 2) rapidly progressive, where early detection may have little or no benefit, 3) and indolent lesions, which when found and treated, constitute over diagnosis and overtreatment.[2] To date, there is no test—not laboratory, imaging, genomic or other test—that reliably distinguishes these 3 fates from each other.

Epidemiologic signatures of cancers show that, in some tumor types, there has been a rise in diagnosis rates over time, but rates of mortality have remained stable, a phenomenon potentially explained by overdiagnosis through early detection programs and broad cancer screening programs.[3] Melanoma is a striking example, and providers have advocated to stop systematic screening skin examinations to prevent patient harm.[4] While the simple premise of "earlier detection is better" has ensued in cancer research for decades, epidemiological studies have demonstrated otherwise.

The MCED trial reported an overall sensitivity of 51.5%, which increased with stage. Stage I cancers had a 16.8% (14.5% to 19.5%) sensitivity and stage IV had a 90.1% (87.5% to 92.2%) sensitivity. What would be the outcome if a falsely "reassuring" result would delay the detection of a true cancer? Considering the sensitivity detection rate for stage I tumors, how many of these have the potential to cause harm, and how many of these are lesions that would never have caused trouble? As there is no established tool available to make the distinction, only a randomized trial can elucidate the true benefit and harm of a MCED screening strategy.

To help aid such randomized efforts, consider this power calculation. Researchers estimate that based on data from the Surveillance, Epidemiology, and End Results Program, adults diagnosed between ages 40 to 79, assuming a stage shift with one-third of stage IV cancers with similar outcomes to stage III, one-third with similar outcomes to stage II and one-third with similar outcomes to stage I, this would lead to a 24% reduction of all cancer-related deaths.[5] From the 2006-2015 data, the absolute number of cancer deaths expected after 5 years of follow-up in this age bracket is 241 for every 100,000 persons. This is a 0.241% risk of dying from cancer during a 5-year period. A 24% reduction

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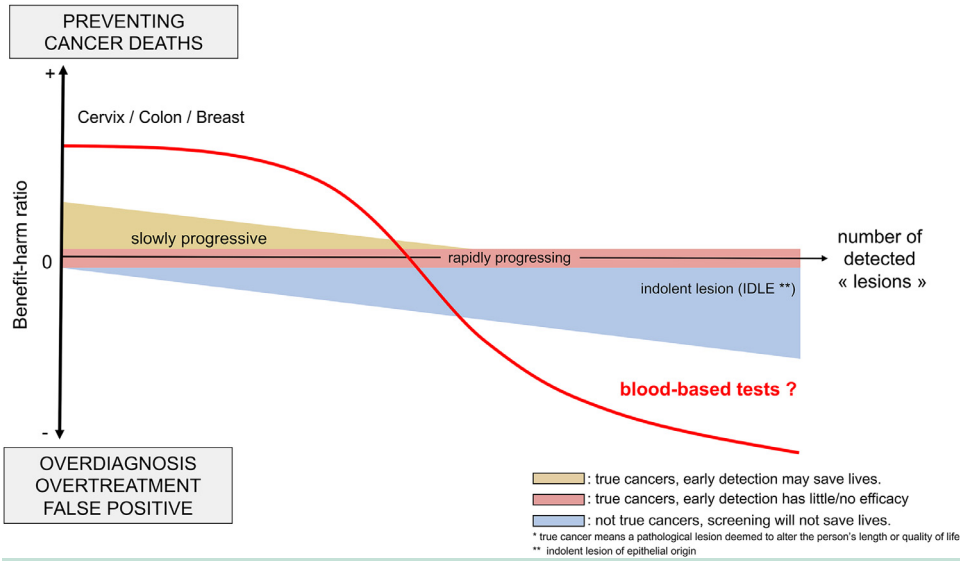

Figure Model of screening outcomes based on 3 different types of detected lesions. The more detected lesions (increase sensitivity), the more detected indolent lesions (decrease specificity for "true cancers"). IDLE = indolent lesion of epithelial origin.

would lower the risk to 0.182%, saving 59 people from dying of cancer during a 5-year period for every 100,000 people. Setting a 0.05 probability of type-I error (alpha) with an 80% power, the sample size needed to prove such a benefit would be 190,348 people (95,174 in each arm). If we assume that the 24% estimate is optimistic and estimate the sample size for a lesser reduction of the risk, such as 20%, 15%, 10% or 5% risk reduction, sample sizes of 290,000, 530,000, 1.2 million, and 5.0 million, respectively, would be needed to show benefit from detecting cancer at an earlier stage.

The MCED trial found a "low" false-positive rate of 0.5%.[1] If one considers the 200 million adults populating the United States, the test will lead to 1 million people receiving a false-positive test if applied broadly. The first consequence would be a psychological blow for people and their relatives—Being told that you may have a cancer is a devastating event. Next, a cascade of testing will ensue. How many computed tomography scans, magnetic resonance imaging scans, and removals of tumors of various localization (ovaries, prostate, thyroids, etc.) would be needed to exclude cancer diagnosis? How many complications and long-term sequelae will result from screening, which are not captured by cancer-specific mortality endpoint? And, much concerning, what happens if the blood test yields a positive result (meaning having a cancer), but the primary tumor cannot be found?

With a 24% reduction rate of all-cancer mortality, the blood test screening strategy, within the 95,174 people in the experimental arm, would prevent 59 people of dying from cancer, while giving 4,758 people a false cancer diagnosis. The risk of diagnostic strategies, with a catastrophic cascade of medical interventions that may arise after the suspicion of a cancer diagnosis, must be considered. The fact that some screening trials, such as the NELSON trial in lung cancer, did find a difference in specific-cancer mortality that did not translate in all-cause mortality, could be partly driven by this phenomenon, possibly overcoming the benefit by net harm in some situations.[6]

What if most dangerous cancers are not candidates for screening due to their biology and natural course? What if pushing screening strategies will only lead to finding fewer true cancers, and do more harm? We illustrate this hypothesis in the Figure, based on the 3 types of "cancers" already described.[2] Without a randomized trial, it is currently impossible to know which type of cancer is detected with any blood tests, and in which manner this will affect populations being screened. Beyond overdiagnosis, cancer-specific mortality endpoint may miss catastrophic consequences while suspecting a cancer diagnosis due to a false positive result.

Dr. Knock, the eponymous lead in Jules Romains' 1932 theatre play, states: "Every healthy man is a patient in disguise."[7] Soon, the town that Dr. Knock is responsible for turns into a giant living hospital. In societies accepting less and less risk, communication about risks of screening strategies should be prioritized when associated with unproven benefit. As care providers, we should avoid becoming blind disciples of Dr. Knock, in the name of the "Triumph of Medicine," turning thousands of healthy people into patients.

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References

1. Klein EA, Richards D, Cohn A, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol* 2021:1167–77.
2. Esserman LJ, Thompson IM, Reid B, et al. Addressing overdiagnosis and overtreatment in cancer: a prescription for change. *Lancet Oncol* 2014;15(6):e234–42.
3. Welch HG, Kramer BS, Black WC. Epidemiologic signatures in cancer. *N Engl J Med* 2019;381(14):1378–86.
4. Welch HG, Mazer BL, Adamson AS. The rapid rise in cutaneous melanoma diagnoses. *N Engl J Med* 2021;384(1):72–9.
5. Clarke CA, Hubbell E, Kurian AW, Colditz GA, Hartman AR, Gomez SL. Projected reductions in absolute cancer−related deaths from diagnosing cancers before metastasis, 2006−2015. *Cancer Epidemiol Biomarkers Prev* 2020;29(5):895–902.
6. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med* 2020;382(6):503–13.
7. Romain J. *Knock Ou Le Triomphe de La Médecine*. 1923.