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The Reply

We thank Klein et al for replying to our work highlighting the risks and harms of multicancer early detection tests.[1] To recap: although many companies are developing a blood-based screening test for various cancers, not a single company has shown in randomized trials that healthy people are better off as a result. This alone must be the bar for widespread adoption, for reasons we note.

Klein et al doubt our estimate that perhaps 200 million Americans may someday be screened, and the implication that we will see a tsunami of false positive cases (1 million) if a multicancer test were applied to all of them. They argue that screening is confined to people aged 50-79 years.

This is false for 5 reasons. 1) The US Preventive Services Task Force recently broadened colorectal cancer screening to 45 years old.[2] 2) Cervical cancer screening starts for women aged 21 years old. 3) Mammography for women aged 40-50 remains common, despite changes to guidelines in recent years. 4) Their own test, Galleri, is undergoing a clinical trial including women above the age of 18 years (not restricted to 50 and above).[3] The test is already permitted in the United States, and can be performed in eligible people over 21 years old.[4] Lastly, 5) the authors are not considering demographic shifts in the US population pyramid over time. For these reasons, 200 million is a very reasonable estimate of the future burden of screening, and shows the massive potential if we debut their unproven test.

Klein et al note that the PATHFINDER study did not demonstrate clinical adverse events with evaluation of false positives.[5] This is a bizarre claim. The study had just 22 patients with false positive findings and was simply too small to exclude harms. If you do 22 colonoscopies, you almost surely won't see a perforation, yet 3.1 perforations and 14.6 major bleedings occur per 10,000 procedures.[6] We thank Klein et al for noting a small error. We had already corrected this prior to their letter.[7]

Without all-cause mortality as the primary endpoint, the net effect of being screened vs not screened, with potential downsides resulting from false positive detection and other risks, cannot be ascertained. Harm is guaranteed with screening, while benefits remain to be proven in the case of multicancer early detection tests: communication about risks and transparency regarding endpoints signification must be prioritized while awaiting results for randomized trials.

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