Clinical pathology selected abstracts

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Cost-effectiveness of liquid biopsy for colorectal cancer screening

March 2024—Despite research into colorectal cancer screening and clinical experience, screening uptake remains low. Colorectal cancer (CRC) screening involves noninvasive tests, such as a fecal immunochemical test (FIT) and stool-based DNA tests, as well as invasive tests, such as colonoscopy. The latter has the best performance characteristics for early cancer and adenoma detection. The average adherence to CRC screening is 60.6 percent for U.S. patients aged 50 to 75 years, which is well below the 80 percent goal for adherence set by the National Colorectal Cancer Roundtable and American Cancer Society. Offering stool-based tests to patients who refuse colonoscopy results in only a modest increase in adherence, to 67 percent. Of interest, CRC that develops in unscreened patients is estimated to account for 28 to 44 percent of CRC deaths. No blood test is yet recommended for CRC screening. Blood tests and liquid biopsies using circulating tumor DNA-based markers are being developed for single-cancer and multicancer early detection (MCED), including for CRC. Although investment in liquid biopsy for its potential to detect early cancer has been increasing, it is unclear whether it will be a cost-effective CRC strategy in the United States. The authors conducted a study to estimate the cost-effectiveness of liquid biopsy as a first- or second-line CRC screening strategy in the United States compared to no screening and screening with three approved methods, including colonoscopy, FIT, and stool DNA. They hypothesized that liquid biopsy would improve CRC detection and decrease the number of deaths from the disease. The authors performed an economic evaluation using a Markov model to compare no screening to colonoscopy, liquid biopsy, liquid biopsy following nonadherence to colonoscopy, stool DNA, and FIT. Adherence to first-line screening with colonoscopy, stool DNA, or FIT was assumed to be 60.6 percent, and adherence to liquid biopsy was assumed to be 100 percent. Patients who did not adhere to colonoscopy, stool DNA, or FIT were not offered other CRC screening methods. Among the colonoscopy-liquid biopsy hybrid study participants, liquid biopsy was the second-line screening for those who deferred colonoscopy. Additional scenario analyses were performed to include the possibility of liquid biopsy detecting polyps. The model outcomes included life expectancy, total cost, and incremental cost-effectiveness ratios. A strategy was considered cost-effective if it had an incremental cost-effectiveness ratio of less than the U.S. willingness-to-pay threshold of $100,000 per life-year gained. The results showed that in a simulated cohort of patients aged 45 years who had an average risk of developing CRC, colonoscopy was the most cost-effective strategy, with an incremental cost-effectiveness ratio of $28,071 per life-year gained. The colonoscopy-liquid biopsy hybrid had the greatest gain in life-years but had an incremental cost-effectiveness ratio of $377,538. The colonoscopy-liquid biopsy hybrid model had an even greater gain in life-years if liquid biopsy could detect polyps but overall remained too costly. The authors concluded that colonoscopy is a cost-effective strategy for colorectal cancer screening in the general population. With many liquid biopsy tests coming to market, this analysis sets threshold targets for liquid biopsy performance and cost to guide future medical policy decision-making.

Aziz Z, Wagner S, Agyekum A, et al. Cost-effectiveness of liquid biopsy for colorectal cancer screening in patients who are unscreened. *JAMA Network Open*. 2023;6(11). doi:10.1001/jamanetworkopen.2023.43392

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Efforts to reduce simultaneous ordering of ESR and CRP testing

C-reactive protein and erythrocyte sedimentation rate are commonly ordered together to assess inflammation, although the latter is a nonspecific inflammatory marker. Erythrocyte sedimentation rate (ESR) may remain elevated several days after an inciting inflammatory event and can fluctuate with other factors, including age, gender, and comorbidities. C-reactive protein (CRP) is more specific and sensitive for monitoring acute inflammation and can rise and fall at a rate similar to that of inflammatory response. Consequently, the American

Society for Clinical Pathology (ASCP) developed a Choosing Wisely recommendation that discourages the routine use of ESR for patients who have undiagnosed conditions. Yet even with the recommendation, clinicians often co-order ESR and CRP. Of interest, studies have shown that false-negative ESR testing is common and that active inflammation is almost always present when ESR is normal and CRP is elevated. While interventions to reduce this pattern of co-ordering have been conducted in some health care settings, studies in resource-limited settings are lacking. The authors conducted a study in which they described a quality improvement project that used clinical decision-support tools to reduce unnecessary ESR testing across NYC Health + Hospitals, the largest safety net health care system in the United States. Their first intervention involved incorporating an informational nudge into the ESR order. This statement read, "H + H High Value Care Council does not recommend ordering both ESR and CRP when ordering inflammatory markers. Instead, use CRP alone." The investigators added a detailed explanation of the potential harm of false-negative and false-positive results in the process instructions of the orders and a link to the ASCP Choosing Wisely recommendation. Their second intervention integrated a best practice advisory that triggered when the clinician ordered CRP and ESR simultaneously. This advisory read, "ESR and CRP are both being ordered. ESR is less sensitive and specific for acute inflammation. Click Accept to remove ESR order and continue ordering CRP." The advisory defaulted to remove the ESR order. However, this advisory could be dismissed and the clinician could proceed with the order. The authors then analyzed ESR order rates per 1,000 patient days in the inpatient setting and per 1,000 patient encounters in the outpatient setting, as well as ESR/CRP co-ordering rates. The results showed that inpatient ESR orders decreased from 12.02 preintervention to 5.61 postintervention per 1,000 patient days (-53.3 percent; $P<.001$). Outpatient ESR orders decreased from 6.09 preintervention to 4.07 postintervention per 1,000 patient encounters (-33.2 percent; $P<.001$). Co-ordering rates showed a 50 percent relative reduction. Of interest, the CRP orders increased slightly through this intervention (eight percent inpatient without time trend and one percent outpatient with time trend). The authors noted that the smaller reduction in ESR use in the ambulatory setting may be attributable to patients likely being more stable than in an acute care setting, so ESR may be a better predictor of acute inflammation among this group. The authors concluded that using a nonintrusive normative nudge and a best practice advisory embedded in the EHR can help reduce inappropriate co-ordering of ESR and CRP. This is one of the first studies of a low-cost intervention for ESR and CRP co-ordering to change ordering practices in a cost-constrained large safety net health system. These efforts support the ASCP Choosing Wisely initiative of reducing unnecessary laboratory testing.

Cho HJ, Talledo J, Alaiev D, et al. Choosing Wisely and reducing the simultaneous ordering of erythrocyte sedimentation rate and C-reactive protein testing in a large safety net system. *Am J Clin Pathol*. 2023;160:585–592.

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