STOOL DNA TESTING FOR EARLY DETECTION OF COLORECTAL CANCER

Rapid assessment of other technologies using the HTA Core Model®

for Rapid Relative Effectiveness Assessment

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Introduction:

- Deoxyribonucleic acid (DNA) stool testing for the early detection of colorectal cancer (CRC) is a non-invasive technology that supplements the established stool tests [e.g. fecal immunochemical test (FIT) or guaiac (based) fecal occult blood test (gFOBT)] for CRC detection with the stool-based analysis of tumor DNA.
- Currently CE-marked stool DNA tests in Europe: ColoAlert® (PharmGenomics), Cologuard® (Exact Sciences). Only ColoAlert® sold on the European market.
- Expected benefit of DNA stool testing: having a non-invasive screening test that is superior to gFOBT and FIT in terms of test accuracy and comparable in terms of patient compliance and can replace those tests in the screening pathway.

Methods:

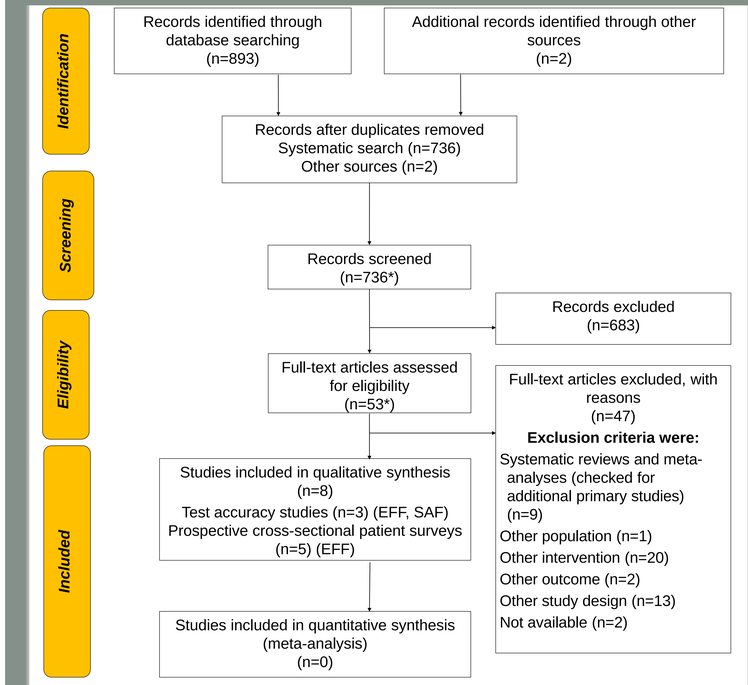
- Systematic literature search in Medline, Cochrane Library and EMBASE, complemented by a hand search as well as an internet search. Clinical trial registries assessed for registered ongoing clinical trials or observational studies.
- One of the two manufacturers completed the short version of the EUnetHTA submission template, and several device-specific questions and issues were clarified further via correspondence with the manufacturer.
- Five patient interviews.
- Markov state-transition cohort model of CRC to assess benefits, harms and/or burden, as well as benefit-harm tradeoffs of five screening strategies

Risk of Bias:

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Imperiale *et al.* 2014 (Cologuard)	☹	☺	☺	☺	☺	☺	☺
Brenner *et al.* 2017 (Cologuard)	☹	☺	☺	☺	☺	☺	☺
Dollinger *et al.* 2018 (ColoAlert®)	☹	☺	☺	☹	☹	☹	☺

Legend: ☺ low risk; ☹ high risk.

Flow Chart of study selection process:



Results:

- Stool DNA testing with Cologuard® showed higher sensitivity for the detection of CRC and advanced adenoma than FIT, but lower specificity. However, the results depended to a degree on the exact type of FIT used. The test failure rate was higher for Cologuard® than for FIT.
- Stool DNA testing with ColoAlert® (although referring to a former version of the product) had higher sensitivity for the detection of CRC and adenoma compared with gFOBT, but lower specificity. Sensitivity was comparable to M2-PK, whereas specificity was higher. The combined test failure rate of all three stool tests in this study was higher than that of FIT (as seen in the Cologuard® study). There was no direct evidence of the test accuracy for only advanced adenoma and no information on the exact proportion of test failures in the DNA assay alone compared with the other stool tests.
- Overall, the certainty of evidence is moderate to high for Cologuard® results (two studies, both referring to the same Cologuard® study population) and low to very low for ColoAlert® results (one study).
- None of the primary studies reported adverse events, no primary studies reported (or were found on) user-dependent harms of DNA stool tests, and no studies were found that directly investigat-ed the consequences of false positive or false negative test results from the viewpoint of patient safety.
- Decision-analytic modeling enabled the assessment of comparative long-term screenee-/patient-relevant benefits, harms and burden and the benefit-harm balance of stool DNA testing, FIT and colonoscopy in a screening program. Based on this decision analysis, 10-yearly colonoscopy is the most effective strategy, but also leads to the greatest burden for the screenee because of colonoscopies. Three-yearly ColoAlert® was dominated in the benefit-harm analysis. The choice between 10-yearly colonoscopy, 3-yearly Cologuard® and biannual FIT depends on how much additional burden resulting from colonoscopies one is willing to accept to gain one additional life year or to avert one additional CRC death. Results were sensitive to screening adherence rates.

Conclusions:

- Stool DNA testing showed a promising benefit-harm balance when different screening strategies were compared, but this is only currently relevant to Cologuard®. By contrast, ColoAlert® is the only stool DNA test currently sold in Europe and is available at a lower cost than Cologuard®. In addition, a high degree of uncertainty surrounds the evidence on ColoAlert®. A cross-sectional screening study including the current product version and FIT as well as gFOBT as comparators could shed light on these issues. In terms of the comparator tests, especially FIT, it would be desirable to carefully select one, or even more than one, different brand(s) as comparators and provide some rationale for those choices.

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