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ORIGINAL ARTICLE

Evaluating New Non-invasive Screening Tests for Colorectal Cancer: An In-Depth International Perspective—Introduction to a Special Issue of *Digestive Diseases and Sciences*

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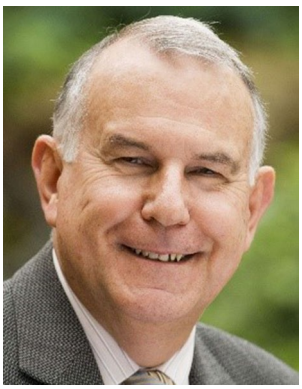

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Abstract

Colorectal cancer (CRC) is a global disease accounting for nearly one in 10 cancer cases and deaths which can be reduced through CRC screening. In 2023 the World Endoscopy Organization (WEO) set forth twelve newly stated principles whereby new non-invasive CRC screening tests could be efficiently evaluated by a rigorous phased comparative approach. The complexities of evaluating new and evolving CRC screening tests and the necessity for a "one size does not fit all" approach was stressed. This special issue of *Digestive Diseases and Sciences* expands on this document and provides in-depth discussions of several of the issues raised during its development from a global perspective.

Keywords Colorectal cancer screening · Cancer prevention · Colonoscopy

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Colorectal cancer (CRC) is a global disease, with an estimated greater than 1.9 million new cases and 904,000 deaths occurring annually world-wide, accounting for nearly one in 10 overall cancer cases and deaths [1, 2]. CRC incidence rates are rising steadily tracking with increasing socioeconomic development in previously low GDP countries. Colonoscopy, while a dominant CRC screening modality in the United States, is not the primary initial screening modality in many countries. Programmatic population-based screening most often employees a first-step non-invasive test, fecal immunochemical testing (FIT) in most cases at the moment,

Table 1 World Endoscopy Organization guiding principles for evaluating new non-invasive tests for colorectal cancer: topics addressed

• Desired outcome of CRC screening
• Screening is a multi-step process
• A screening test identifies individuals with an increased likelihood of CRC and/or advanced precursor lesions
• Nature of precursor lesions most important to detect
• New biomarkers might detect lesions with a different natural history
• Outcomes to be estimated in a screening population
• Expectations of a new non-invasive test
• An adjustable test positivity threshold accommodates different program goals
• Predicting value by paired comparison with a proven non-invasive screening test
• Evaluation proceeds through increasingly complex phases
• Accuracy required for evaluation in a screening population
• Analytical specifications, standards and performance

These topics were discussed in Bresalier et al. [3] and expanded upon in the articles in this special issue of *Digestive Diseases and Sciences*

to determine who is most likely to benefit from subsequent colonoscopy. Colonoscopy as a first-step screening tool is generally not considered feasible as the primary screening test in economically developing countries where resources are limited. It is also an impractical approach for many underserved populations, or in considering screening for young-onset colorectal cancer, where the event rate is small and the denominator large.

In 2023, members of the World Endoscopy Organization (WEO) Colorectal Cancer Screening New Test Evaluation Expert Working Group set forth twelve newly stated principles whereby new non-invasive tests could be efficiently evaluated by a rigorous phased comparative approach, "generating data from unbiased populations that inform predictions of health impact" (Table 1) [3]. This formal consensus approach acknowledged the complexities of validating new non-invasive tests and set forth a stepwise strategy for evaluating these tests and bringing them to clinical practice with a rigorous yet flexible design, accounting for the global variation in CRC screening practice. During this consensus process, which included 47 expert gastroenterologists, endoscopists, GI surgeons, public health physicians, epidemiologists, clinical biochemists and tumor biologists, the complexities of evaluating new and evolving CRC screening tests and the importance of a tailored approach became clear. It was also realized that a single document could not adequately address these issues. This special issue of *Digestive Diseases and Sciences* expands on the aforementioned document, providing in-depth discussions of several of the issues raised during its development from a global perspective.

The first questions addressed are: What is the current role of colonoscopy in colon cancer screening? What are the potential advantages and disadvantages of colonoscopy? and What is its impact on colorectal incidence and mortality? Importantly, is it a practical first-line screening approach? These questions are addressed in back-to-back articles as a point-counterpoint discussions by Douglas Rex ("Colonoscopy remains an important option for screening for colorectal cancer") [4] and Drs. Mark Pi-Chun Chuang and Han-Mo Chiu ("Does colonoscopy as a first screening test still make sense?") [5]. Dr. Chiu and Dr. Takahisa Matsuda follow this with an overview "Adopting non-invasive approaches into precision colorectal cancer screening" [6] which reviews current CRC screening strategies, the advantages of non-invasive methods, and how these methods can be used to tailor screening intervals and risk-stratification. These authors discuss the emerging importance of using real-world data and how advanced technologies can enhance CRC screening accuracy and effectiveness. Many of these themes are echoed in subsequent articles.

The most common first-step in the multistep CRC screening pathway characteristic of organized screening programs is the fecal immunochemical test (FIT) that has become the default comparator for validation of new non-invasive screening tests. Carlo Senore et al. [7] provide an overview of the evidence and rationale for using FIT as a comparator for evaluating new non-invasive screening tests, including in single and multiple rounds of screening. Both qualitative and quantitative FIT tests are available; FIT positivity thresholds vary across major screening programs. Graeme Young and colleagues provide a survey that documents the wide range of FIT positivity thresholds that are in current use [8], and argue that one size does not fit all, proposing that adjustable thresholds ("cut-offs") for the positivity of FIT and other new tests enables the matching of diagnostic sensitivity, specificity and test positivity rate with the desired goals of individual screening programs [9].

Colorectal cancer screening of average-risk individuals can reduce colorectal cancer incidence and mortality due to early-stage cancer detection, detection and removal of

important CRC precursor lesions, and stratification of enrollment in surveillance for high-risk individuals. Non-invasive tests for CRC often perform well in detecting cancers, but less well in detecting adenomas and sessile serrated lesions [10, 11]. Adenomas differ in their potential for progressing to CRC, and even so-called advanced adenomas have varying risk [12]. What should the target lesion then be, and "how good is good enough?" Is it sufficient to target advanced precursor lesions and early-stage cancers? These questions are addressed by David Lieberman, who stresses informed decision making with knowledge of the goals and limitations of each screening program [13].

Intended use is also discussed by Patrick Bossuyt [14] who emphasizes that evaluations of clinical performance should be guided by intended use of testing and discusses the importance of statistical considerations. Study designs differ for tests that could replace an existing test, for triage tests performed before an existing screening test, and add-on tests used after existing screening tests. He stresses the importance of explicit pre-defined and minimally acceptable performance criteria for the new test and rigorous statistical hypothesis testing.

Josh Melson discusses how well development of new commercially available non-invasive tests have adhered to the guiding principles set forth by the WEO Colorectal Cancer Screening New Test Evaluation Expert Working Group [15]; Meike de Wit et al. [16] discuss an example of how one group was able to validate a new CRC screening.

The importance of defining the target population and clinical setting for the intended use of a given test and its outcome of interest is well-known. Ensuring adequate generalizability of data derived from a given population is also important. Again, one size may not fit all. Recently there has been a reported rise in CRC incidence and mortality in high-income countries in individuals under 50 years, so-called early-onset colorectal cancer (EOCRC) [17]. This increase in EOCRC may be driven by a cohort effect, with the 1990 birth cohort having 3 times the risk of CRC of that of the 1940 cohort [18], prompting both the American Cancer Society and the US Preventive Services Taskforce to make qualified recommendations to begin screening at age 45 instead of 50 in the general population [19]. It is not a given, however, that a new non-invasive test will have the same performance in the setting of EOCRC as in an older screening cohort. While CRC incidence in those under 50 has risen sharply, CRC is still much more common in older individuals. Since resource utilization is important, colonoscopy as a screening test in younger individuals may not be cost-effective. When colorectal cancer screening should begin and the impact of early-onset colorectal cancer (and the reality of an unscreened older population) is discussed by Iris Landsdorp-Vogelaar and Linda Rabineck [20].

The future role of non-invasive multi-cancer early detection tests is discussed by William Grady [21]. These tests use artificial intelligence-generated algorithms to combine markers to detect multiple cancers and tissue of origin. Unresolved issues include cost effectiveness, overdiagnosis, potential harms of evaluating false positive tests, and lack demonstrated impact on cancer-related mortality.

The process of evaluating new non-invasive screening tests for CRC and bringing them to clinical use is long and tedious. Test performance must be validated in a step-wise fashion, must be approved by regulatory agencies, and must be paid for by public health dollars or third-party payors. Randomized controlled trials require large numbers of subjects given the low event rate for CRC in a screening population [22]; furthermore, the impact on mortality cannot be determined in short-term studies. Whether modeling and the use of surrogate endpoints is a valid approach is discussed by Uri Ladabaum et al. [23], and the regulatory challenges in bringing new tests to market by Gerard Davis [24].

This series of papers then expands on themes set forward by the WEO with respect to strategies for evaluating new non-invasive tests for colorectal cancer screening and the guiding principles involved [3]. Importantly, the perspectives presented have wide-ranging implications, taking into consideration that colorectal cancer is a global disease that may manifest differently among populations of different ages, race, gender, and socioeconomic status.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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