Systematic Review of Participation, Positivity, and Yield Over Time in Fecal Immunochemical Test-Based Organized Colorectal Cancer Screening Programs

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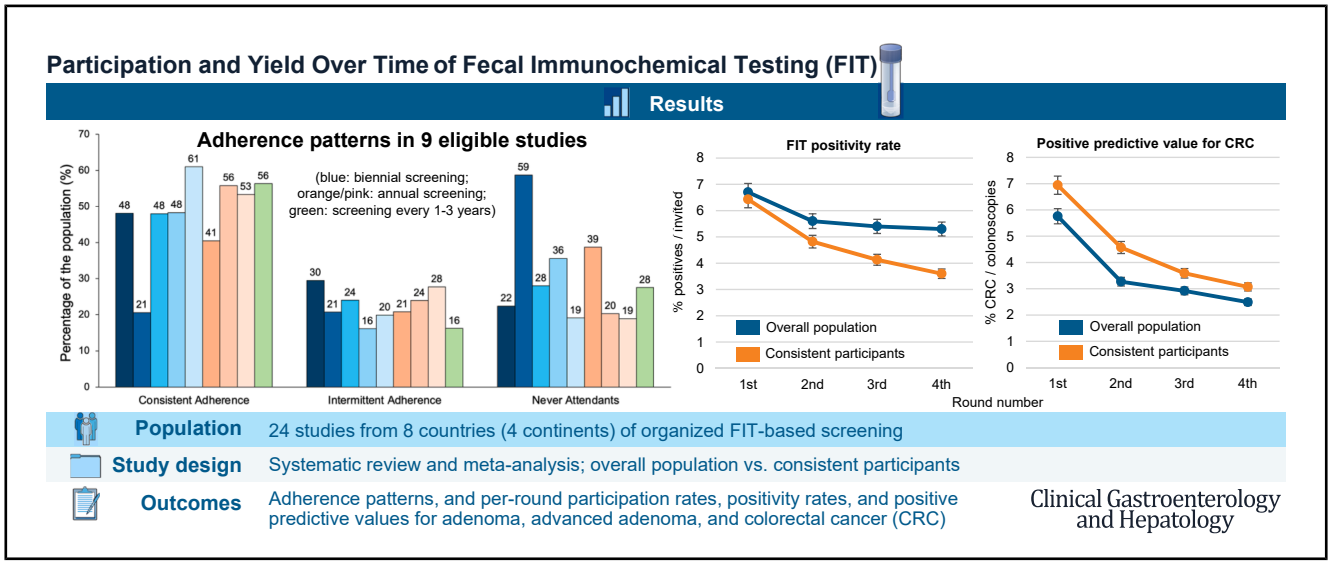

BACKGROUND & AIMS: **Fecal immunochemical testing (FIT), the most common colorectal cancer (CRC) screening modality worldwide, requires programmatic participation over decades. We performed a systematic review and meta-analysis to ascertain overall adherence patterns, per-round participation, FIT positivity, and neoplasia detection rates in organized FIT-based screening programs, contrasting initial vs subsequent screening rounds.**

METHODS: **We systematically searched the PubMed, Embase, and Cochrane databases. Adherence patterns were defined as consistent screeners (all rounds), intermittent screeners, and never attendants. Per-round participation, FIT positivity, and positive predictive values (PPVs) for CRC, advanced adenoma (AA), and adenoma were determined overall and for consistent screeners. Subgroup analyses were performed by screening periodicity and FIT positivity cutoff.**

***Authors share co-first authorship.**

Abbreviations used in this paper: **AA, advanced adenoma; AXIS, Appraisal of Cross-Sectional Studies; CI, confidence interval; CRC, colorectal cancer; DR, detection rate; FIT, fecal immunochemical testing; gFOBT, guaiac fecal occult blood testing; Hb, hemoglobin; PICO, patient, intervention, comparison, and outcome; PPV, positive predictive value; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SD, standard deviation.**

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2026.02.009

RESULTS: **Of 4414 candidate studies, 24 were included. Adherence patterns were: 47.1% (standard deviation [SD], 11.6%) consistent screeners, 22.7% (SD, 4.7%) intermittent screeners, and 30.3% (SD, 12.2%) never attendants. Overall pooled results from the first through fourth rounds showed per-round participation of 51.3% (95% confidence interval [CI], 37.4%–65.3%); 56.7% (95% CI, 41.3%–72.2%), 56.9% (95% CI, 38.7%–75.3%), and 56.5% (95% CI, 44%–68.6%); FIT positivity of 6.6% (95% CI, 5.9%–7.3%), 5.6% (95% CI, 4.6%–6.6%), 5.3% (95% CI, 4.0%–6.6%), and 5.3% (3.7%–6.9%); CRC PPV of 5.8% (95% CI, 4.1%–7.4%), 3.3% (95% CI, 2.3%–4.3%), 2.9% (95% CI, 2.2%–3.7%), and 2.5% (95% CI, 1.4%–3.5%); AA PPV of 32.8% (95% CI, 23.5%–42.0%), 28.3% (95% CI, 21.8%–34.7%), 22.7% (95% CI, 16.5%–28.9%), and 23% (95% CI, 10.1%–35.9%); and adenoma PPV of 48.6% (95% CI, 45.8%–51.4%), 46.2% (95% CI, 42.4%–50.1%), 48.7% (95% CI, 43.9%–53.6%), and 44.6% (95% CI, 38.2%–51.0%), respectively. Similar trends were observed for consistent screeners and for biennial FIT with 20 μg Hb/g feces positivity cutoff.**

CONCLUSIONS: **Organized FIT-based CRC screening programs achieve consistent participation in nearly one-half of persons and no participation in approximately one-third. FIT-positivity and yields for CRC, AA, and adenoma are highest in the first round and may stabilize at clinically relevant steady states at the third to fourth rounds.**

Keywords: Adherence; Colorectal Cancer; Fecal Immunochemical Test; Participation; Screening; Uptake.

Colorectal cancer (CRC) is the third most common cancer in the world.[1] Screening for CRC precursors including advanced adenomas (AAs) and for early-stage CRCs has proven effective in decreasing CRC incidence and CRC-related deaths.[2] CRC screening around the world commonly spans ages 50 to 74 years,[3] with a few countries including the United States recently lowering the screening initiation age to 45 years. Various CRC screening modalities exist, including stool-based tests and colonoscopy, each with its own set of barriers, invasiveness, and diagnostic accuracy.[4]

The fecal immunochemical test (FIT) is the preferred nonendoscopic test in programmatic screening worldwide. As with any test, participation rates are a key determinant of screening effectiveness, but it is especially relevant for FIT, in which the impact of screening is achieved over multiple rounds. Randomized controlled trials of guaiac fecal occult blood testing (gFOBT) demonstrated the effectiveness of gFOBT vs no screening.[5–8] In practice, FIT has overtaken gFOBT as the preferred stool-based CRC screening test, but we are unlikely to generate evidence for FIT vs no screening from randomized controlled trials with long-term follow-up.[9,10] As multiple FIT-based organized screening programs around the world mature, the possibility to analyze observational data through multiple screening rounds is now arising.

Most studies assessing FIT effectiveness have focused on short-term metrics, including one-time interventions.[11] Multiple ways to describe longitudinal adherence in FOBT programs have been developed, as summarized in a recent literature review by Doria-Rose et al.[12] These include adherence patterns such as consistent screeners vs inconsistent screeners vs never attendants, number of cycles attended, and detailed reporting of the possible permutations in the heterogeneous group of inconsistent screeners. There is no consensus on how to capture longitudinal adherence, and there has been no comprehensive assessment of participation, FIT positivity, and yield over time across multiple screening programs around the world.

Our aims were to characterize adherence patterns, and to evaluate FIT participation rates, positivity rates, and neoplasia detection yield over time in organized (non-opportunistic) multi-round FIT-based screening programs across the world. We performed a systematic review and meta-analysis of published studies. Our goal was to ascertain if there are generalizable conclusions regarding adherence patterns across different organized screening programs, and to explore how FIT positivity and neoplasia detection yield vary from initial through subsequent screening rounds, accounting for FIT interval and positivity threshold.

Methods

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1).[13] The protocol was registered prospectively at PROSPERO (CRD42023448999).

Search Strategy

We developed patient, intervention, comparison, and outcome (PICO) questions to capture our research questions (Supplementary Table 2). In consultation with a certified medical librarian (CS-A), a comprehensive search of the available electronic literature was performed to find studies describing overall adherence patterns, and per-round participation rates, FIT

positivity rates, and CRC, AA, or adenoma detection yield in FIT-based organized screening programs through multiple screening rounds.

We searched PubMed, EMBASE, and Cochrane databases from January 1, 2012, through July 31, 2023. The search strategy is shown in Supplementary Appendix 1. Language was restricted to English or Spanish. No publication status restrictions were imposed. References cited in related articles and meta-analyses were searched for additional eligible studies, referred to as cross-references. Before drafting of the final manuscript, an updated search through December 12, 2024, was performed.

Study Selection and Data Extraction

Two reviewers (SB-M and MP) independently screened all titles and abstracts, reviewed full-text manuscripts, and, after selection of articles fulfilling the eligibility criteria, carried out data extraction. A standardized template was developed to extract data from eligible studies. Extracted data comprised first author, year of publication, study design, study location, screening years, participants' age range, screening periodicity (annual, biennial, or triennial), FIT cutoff (in μg of Hb per g of feces), number of FIT samples, number of screening rounds, number of participants, positive FITs, follow-up colonoscopies, and the number of subjects identified as having CRC, AA, or adenoma. Data on CRC stage were extracted when available. Such data were scarce, and we therefore elected to report in the Supplementary Material. Disagreement among reviewers was resolved through discussion among all authors.

Study Type

We included cohort studies and clinical trials describing participation rates and patterns, and FIT results over time in FIT-based organized screening programs for average-risk populations.[14–37] Studies were excluded if they reported on opportunistic screening or screening targeting special groups, screening performed with methods other than FIT (eg, gFOBT, sigmoidoscopy, direct colonoscopy), screening programs offering participants the choice among different screening tests, screening programs in which FIT was used for triage after a positive primary screening test (eg, FIT following gFOBT), subjects with any high-risk condition for CRC (inflammatory bowel disease, hereditary CRC syndromes, personal history of CRC), or if data from only one round of screening were reported. Studies or trials with multiple arms comparing different screening methods were also excluded. When identical populations in overlapped study periods were included in several studies reporting the same outcomes, only the most comprehensive study was selected.

What You Need to Know

Background

Fecal immunochemical testing (FIT) is the preferred screening modality in organized colorectal cancer screening programs globally. Although FIT effectiveness relies on repeated participation over time, most studies have focused on single-round performance. There has been no comprehensive synthesis of evidence on longitudinal adherence patterns and yield across multiple FIT screening rounds.

Findings

This systematic review and meta-analysis, which identified 24 relevant studies, shows that only about one-half of individuals consistently participate in organized FIT screening, whereas one-third never participate. FIT positivity and positive predictive values for colorectal cancer and advanced neoplasia are highest at the first round and appear to stabilize at lower, but still clinically significant, levels by the third or fourth round. These trends are more marked in consistent screeners and closed cohorts.

Implications for patient care

At the level of screening programs, standardized reporting of individual longitudinal adherence trajectories and outcomes could optimize program evaluation and comparisons. At the level of individuals, screening trajectories and results could support personalized screening strategies, including extended intervals or early cessation in low-risk consistent screeners, which could improve programmatic cost-effectiveness and resource allocation.

Definitions and Outcomes

Subjects were classified into 3 overall adherence patterns across all rounds offered: consistent screeners who attended all rounds for which they were invited, intermittent screeners who attended some but not all rounds for which they were invited, and never attendants who did not attend any round for which they were invited. Intermittent screeners were further allocated to 2 subcategories when relevant data were available: drop out (participation in initial rounds followed by subsequent non-participation), and delayed entry (initial non-participation followed by participation in later rounds).[14]

The population of each study was defined as an open cohort when, in every screening round, new subjects with no prior screening round offers could be offered screening, and as a closed cohort when only patients invited at an initial round were followed through subsequent rounds.

For each screening round, participation rates, FIT positivity rates, follow-up colonoscopy completion rates, and positive predictive values (PPV) and detection rates

(DRs) for CRC, AA, and adenoma were calculated. Participation rate was calculated as the number of participants (individuals who returned a completed FIT kit) relative to all invitees, FIT positivity rate as the number of positive FIT relative to all participants, follow-up colonoscopy completion rate as the number of follow-up colonoscopies relative to all positive FIT, PPV as the number of persons with lesions detected relative to all persons undergoing colonoscopies following a positive FIT, all expressed as a percentage, and DR as the number of persons with lesions detected relative to all participants, all expressed as a percentage.

All study outcomes were ascertained for each program's screening round among the overall screening population in each study. The study outcomes were also ascertained for consistent screeners across all screening rounds offered when such data were reported.

Among the 11 included studies describing the yield of FIT for AA across rounds, 8 studies defined AA as those adenomas $\geq$10 mm, with villous component or high-grade dysplasia,[15,20,22,24,28,29,35,36] 2 studies defined AA as either an adenoma $\geq$10 mm, with villous component or high-grade dysplasia or 3 or more adenomas,[23,25] and finally, 1 study defined AA as those with villous histology without referring to the size or the presence of dysplasia.[21]

Risk of Bias Assessment

We assessed the quality of the included articles using the Appraisal of Cross-Sectional Studies (AXIS) tool, which consists of 20 items rated as "yes," "no," or "don't know" to evaluate the risk of bias (Supplementary Table 3). Because our review focused solely on programs utilizing FIT and colonoscopy after positive FIT (screening tools known for their high diagnostic accuracy), we excluded items 8 and 9, which address the validity and reliability of measurements.

Subgroup Analyses

In an attempt to minimize heterogeneity among studies, subgroup analyses were performed for different screening periodicities (ie, annual or biennial), for different FIT positivity cutoff values (ie, 20 or 10 μg Hb/g of feces), and for open and closed cohorts.

Statistical Analysis

For adherence patterns, means and standard deviations (SDs) were calculated across studies. For per-round participation rates, FIT positivity rates, PPVs, and DRs, studies were combined in separate meta-analyses to obtain pooled mean estimates and 95% confidence intervals (CIs). Due to the scarcity of studies reporting on 5 or more rounds, per-round pooled estimates were provided for the first through fourth rounds only. Random-effects meta-analyses using the generic inverse variance weighting method were performed. To mitigate potential bias arising from low-event data, studies reporting zero cases of the outcome of interest were excluded from the meta-analysis. Statistical heterogeneity among studies was assessed using the I^2 statistic, with an I^2 <25%, 25% to 50%, and >50% indicating low, medium, and high heterogeneity, respectively. The possibility of publication bias was assessed by inspection of funnel plots. The meta-analyses were performed using Review Manager 5.3 (The Nordic-Cochrane Center, The Cochrane Collaboration).

Results

Literature Search, Included Studies, Risk of Bias, and Publication Bias Assessment

The initial literature search yielded 7772 citations, of which 4414 remained after removal of duplicates. After applying the selection criteria, addition of cross-references, and a first screening of titles and abstracts, 119 studies were selected and reviewed in detail (Supplementary Appendix 2), leading to selection of 24 studies for inclusion in the final analysis (Figure 1).[14–23,25–27,28–37] These studies consist of 8 studies from the Netherlands, 5 from Italy, 3 from the United States, 3 from Australia, 2 from Spain, 1 from Sweden, 1 from Slovenia, and 1 from South Korea. Most of these studies provided real-world data, although some of them had an experimental setting. Also, most of the studies reported the initial rounds of the screening program, but there are some exceptions reporting on already stablished programs[17] or programs transitioning from gFOBT.[27,31] The age of participants ranged from 50 to 74 years. Most of the studies reported on 2 to 4 annual or biennial rounds, with 4 reporting on 5 to 7 rounds. Most studies (63%) reported on biennial programs. The most common FIT positivity cutoff values were 20 (38%), and 10 (38%) μg Hb/g feces. Table 1 provides an overview of the individual studies with their demographic data.

Supplementary Figure 1 shows the results of the risk of bias assessment. Supplementary Figure 2 shows funnel plots, which are quite symmetrical around the x-axis, suggesting the absence of publication bias.

Overall Adherence Patterns Across All Rounds Offered

Nine studies reported data on overall adherence patterns, allowing classification of participants as consistent screeners, intermittent screeners, and never attendants (Figure 2).[17–19,27,30,31,34,24,28] Across these 9 studies, the fraction of the population behaving as consistent screeners was on average 47.9% (SD, 11.6%; range, 20.6%–61.0%). The fraction of the population behaving as intermittent screeners was on average 22.1% (SD, 4.5%; range,

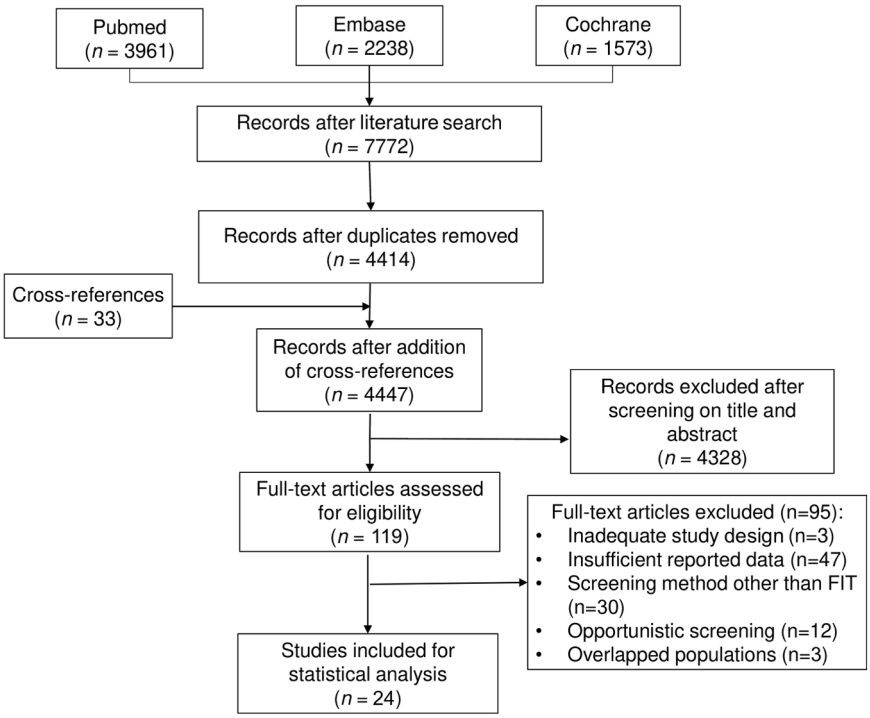

Figure 1. Flow diagram of study selection.

16.1%–29.5%). The fraction of the population behaving as never attendants was on average 29.9% (SD, 12.6%; range, 18.9%–58.7%). In studies that reported intermittent participation with some granularity,[14,27,30–32,34] the fractions of the population displaying late entry (on average, 9.9%; SD, 2.8%) or drop-out (on average, 9.5%; SD, 2.6%) appeared comparable.

Participation Rates per Round Over Time

Thirteen studies reported per-round participation rates across multiple screening rounds.[15,18,20–23,26,31,33,28,29,37] The pooled participation rates from the first through fourth rounds irrespective of FIT interval were 51.3%, 56.7%, 56.9%, and 56.5%, respectively (Figure 3, Supplementary Figures 3–5). Similar results for per-round participation rates were observed in annual (5 studies) vs biennial (8 studies) screening programs (Table 2, Figure 3, Supplementary Figures 3–5). In closed cohorts, per-round participation rates (61.4%–72.0%) were higher than in open cohorts (35.9%–43.9%) (Supplementary Figures 6 and 7).

Colonoscopy Follow-Up

Follow-up colonoscopy completion rate remained stable and over 87% through all rounds (Supplementary Figure 8).

FIT Positivity Rates per Round Over Time

Fourteen studies reported on FIT positivity rates across multiple screening rounds.[15,16,18,20–23,25,26,35,36,24,28,29] For the overall population, FIT positivity rates were highest at the first round and then decreased: 6.6%, 5.6%, 5.3%, and 5.3%, from the first through fourth rounds, respectively (Table 2, Figure 4, Supplementary Figures 9 and 10). In a subgroup analysis including only 4 studies reporting on biennial programs with a FIT positivity cutoff of 20 μg Hb/g feces, a similar pattern was observed but with lower positivity rates: 5.9%, 5.4%, 4.7%, and 4.1% from the first through fourth rounds, respectively (Supplementary Figure 11). For consistent screeners, FIT positivity across 5 studies from the first through fourth rounds was 6.4%, 4.8%, 4.1%, and 3.6%, respectively (Table 2, Supplementary Figures 9 and 12). In closed cohorts, the difference between first vs subsequent round results for FIT positivity was more marked compared with open cohorts (Supplementary Figures 13 and 14).

PPVs for CRC, AA, and Adenoma per Round Over Time

Twelve studies reported on detection yields across multiple screening rounds.[15,16,20–23,25,35,36,24,28,29] For the overall population (Table 2, Figure 4, Supplementary Figure 9), PPVs from the first through fourth rounds were: CRC 5.8%, 3.3%, 2.9%, and 2.5%, respectively (Supplementary Figure 15); AA 32.8%, 28.3%, 22.7%, and 23.0%, respectively (Supplementary Figure 16); and adenoma 48.6%, 46.2%, 48.7%, and 44.6%, respectively (Supplementary Figure 17).

In a subgroup analysis including only biennial programs with a FIT positivity cutoff of 20 μg Hb/g feces

Table 1. Characteristics of the Included Studies

Author, year of publication	Design; setting	Country	Patient inclusion	Periodicity	FIT cutoff, *μg Hb/g*	No. rounds	Age range, *y*	Type of cohort[a]	Population[b]	Analyses to be included in
Crotta, 2012	Cohort; real-world; program initiation	Italy	2001–2008	Biennial	20	4	50–74	Closed	Overall	Adherence patterns, participation rate, positivity rate, yields
Parente, 2013	Cohort; real-world; program initiation	Italy	2005–2009	Biennial	20	2	50–69	Open	Overall	Participation rate, positivity rate, yields
Portillo, 2018	Cohort; real-world; program initiation	Spain	2009–2014	Biennial	20	3	50–69	Closed	Consistent	Participation rate, positivity rate, yields
Zorzi, 2018	Cohort; real-world: program initiation	Italy	2002–2014	Biennial	20	6	50–69	Closed	Consistent	Participation rate, positivity rate, yields
Benito, 2019	Cohort; real-world; transition from gFOBT	Spain	2000–2017	Biennial	20	4	50–69	Open	Overall	Adherence patterns, participation rate
Baldacchini, 2020	Cohort; real-world; program initiation	Italy	2005–2016	Biennial	20	5	50–69	Open	Overall and consistent	Participation rate, positivity rates, yields
Tepes, 2020	Registry; real-world; program initiation	Slovenia	2008–2013	Biennial	20	3	50–69	Open	Overall	Participation rate, positivity rate, yields
Baldacchini, 2022	Cohort; real-world; program initiation	Italy	2005–2016	Biennial	20	7	50–69	Open	Overall	Adherence patterns
Denters, 2012	Cohort; real-world; program initiation	Netherlands	2006–2009	Biennial	10	2	50–74	Closed	Consistent	Participation rate, positivity rate, yields
Denters, 2013	Cohort; real-world; program initiation	Netherlands	2006–2009	Biennial	10	2	50–74	Open	Overall	Adherence patterns, participation rate
Stegeman, 2015	Cohort; experimental; program initiation	Netherlands	2007–2012	Biennial	10	3	50–75	Open	Overall	Participation rate, positivity rate, yields
Van der Vlugt, 2017	Cohort; experimental; program initiation	Netherlands	2006–2014	Biennial	10	4	50–74	Open	Overall	Adherence patterns
Schreuders, 2019	Cohort; real-world; program initiation	Netherlands	2006–2014	Biennial	10	3	50–74	Closed	Overall	Participation rate, positivity rate, yields
Heyman, 2024	Cohort; real-world; transition from gFOBT	Sweden	2015–2020	Biennial	40	3	60–70	Closed	Overall	Adherence patterns

Table 1. Continued

Author, year of publication	Design; setting	Country	Patient inclusion	Periodicity	FIT cutoff, *μg Hb/g*	No. rounds	Age range, *y*	Type of cohort[a]	Population[b]	Analyses to be included in
Breekveldt, 2022	Cohort; real-world; program initiation	Netherlands	2014–2017	Biennial	47	2	55–75	Closed	Consistent	Positivity rate, yields
Van Roon, 2013	RCT; experimental; program initiation	Netherlands	2006–2012	1–3 y	10	2	50–74	Close	Overall	Participation rate, positivity rate, yields
Kapidzic, 2014	Cohort; real-world; program initiation	Netherlands	2006–2016	1–3 y	10	3	50–74	Closed	Overall	Participation rate, positivity rate, yields
Jensen, 2016	Cohort; real-world: program initiation[c]	United States	2007–2010	Annual	20	4	50–70	Closed	Overall	Participation rate, positivity rate, yields
Choi, 2012	Cohort; real-world; program initiation	South Korea	2004–2008	Annual	NA[d]	5	>50	Open	Overall	Participation rate, positivity rate
Duncan, 2014	Cohort; experimental: program initiation[c]	Australia	2008–2010	Annual	NA[d]	3	50–75	Closed	Overall	Adherence patterns
Cole, 2013	Cohort; real-world; program initiation[c]	Australia	2003–2009	Annual	10	2	55–74	Closed	Overall	Adherence patterns
Baker, 2015	RCT; experimental; program initiation[c]	United States	2011–2012	Annual	10	2	51–75	Closed	Overall and consistent	Participation rate
Gordon, 2015	Cohort; real-world; established program	United States	2010–2012	Annual	NA[d]	3	50–75	Closed	Overall	Adherence patterns
Osborne, 2017	Cohort; experimental; program initiation[c]	Australia	2008–2011	Annual	NA[d]	4	50–74	Closed	Overall	Adherence patterns, participation rate positivity rate

FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; Hb, hemoglobin; NA, not available; RCT, randomized control trial.

[a]Open cohort: in every screening round new population with no prior rounds can come in. Closed cohort: only patients invited from the first round are invited across subsequent rounds (subsequent screening rounds not replenished with screening-naive individuals.)

[b]Overall population: all the invited population. Consistent population: only population who has participated in the screening every time they have been eligible.

[c]High opportunistic background.

[d]NA: not stated in publication and unable to verify via personal communication.

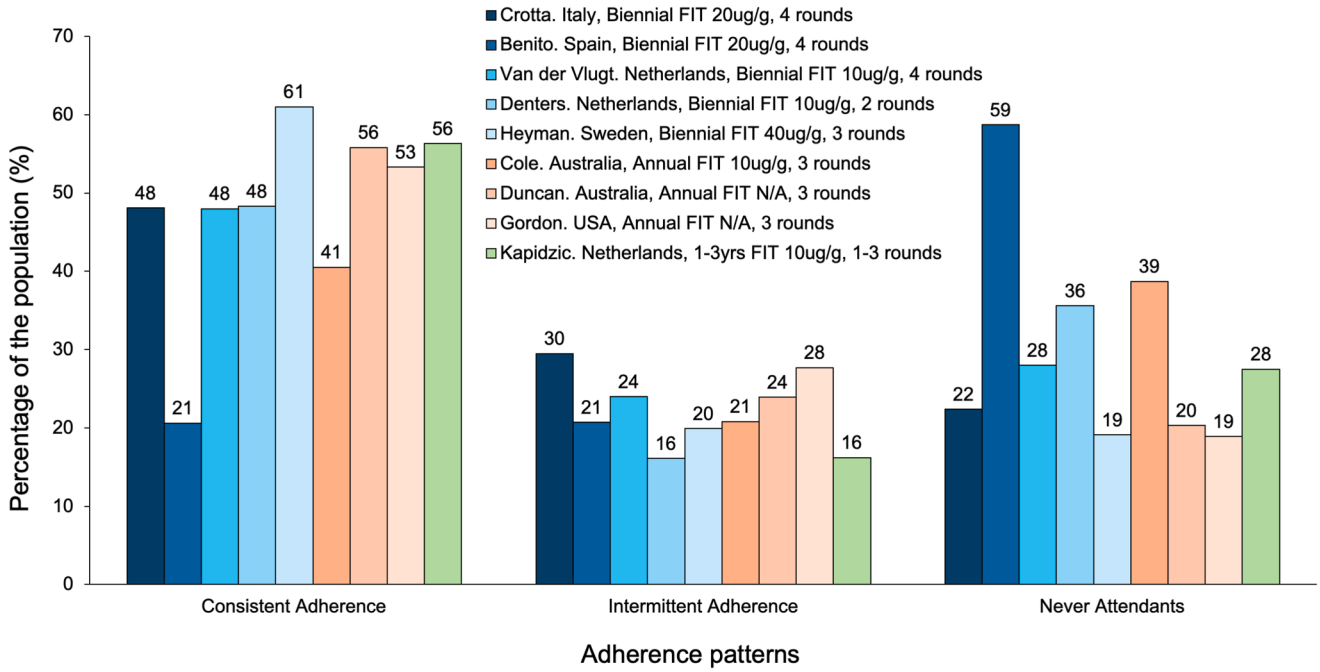

Figure 2. Adherence patterns allowing classification of participants as consistent screeners, intermittent screeners, and never attendants. Bars in shades of *blue* reflect biennial screening, bars in shades of *orange/pink* reflect annual screening, and the bar in *green* reflects screening every 1 to 3 years.

(Supplementary Figure 18), PPVs from the first through third rounds were: CRC 6.1%, 3.6%, and 3.4%, respectively (Supplementary Figure 19); AA 33.3%, 29.8%, and 27.3%, respectively (Supplementary Figure 20); and adenoma 46.1%, 45%, and 47.8%, respectively (Supplementary Figure 21).

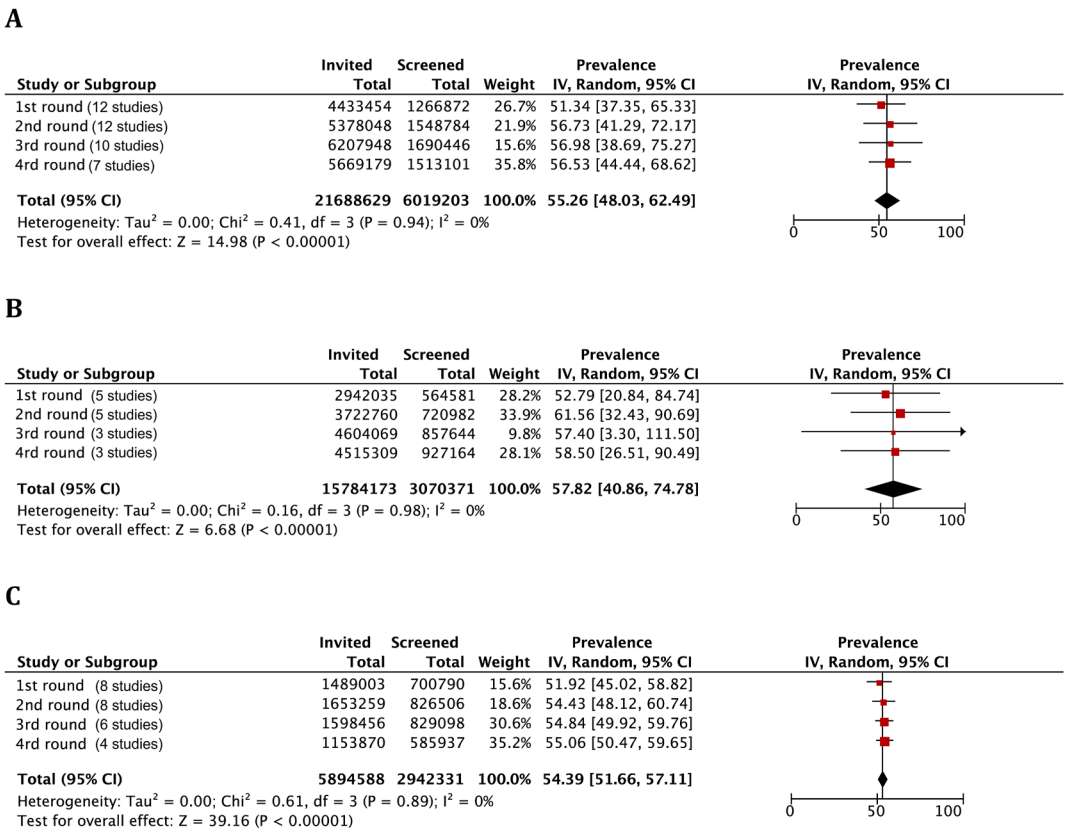

Figure 3. Participation rates across multiple screening rounds in FIT-based CRC organized screening programs for all programs (*A*), annual programs (*B*), and biennial programs (*C*). IV, inverse variance.

Table 2. Pooled Participation Rates, Positivity Rates, PPVs, and DRs for CRC, AA, and Adenoma, Over 4 Rounds of FIT Screening, Stratified by Program Interval and Adherence Pattern

	Round 1, % (95% CI)	Round 2, % (95% CI)	Round 3, % (95% CI)	Round 4, % (95% CI)
Participation				
Annual	52.8 (20.8–84.7)	61.6 (32.4–90.7)	57.4 (3.3–111.5)	58.5 (26.5–90.5)
Biennial	51.9 (45.0–58.8)	54.4 (48.1–60.8)	54.8 (49.9–59.8)	55.1 (50.5–59.7)
Positivity				
Overall	6.6 (5.9–7.3)	5.6 (4.6–6.7)	5.3 (4.0–6.6)	5.3 (3.7–6.9)
Consistent	6.4 (6.0–6.9)	4.8 (4.3–5.3)	4.1 (3.1–5.1)	3.6 (3.0–4.2)
PPV - CRC				
Overall	5.8 (4.1–7.4)	3.3 (2.3–4.3)	2.9 (2.2–3.7)	2.5 (1.5–3.6)
Consistent	6.9 (6.0–7.9)	4.6 (3.5–5.6)	3.6 (3.1–4.1)	3.1 (2.7–3.5)
PPV - AA				
Overall	32.8 (23.5–42.0)	28.3 (21.8–34.7)	22.7 (16.5–28.9)	23.0 (10.2–35.8)
Consistent	38.7 (32.9–44.6)	30.6 (24.2–37.0)	28.2 (20.7–35.8)	24.9 (21.2–28.6)
PPV - Adenoma				
Overall	48.6 (45.8–51.4)	46.2 (42.4–50.1)	48.7 (43.9–53.6)	44.6 (38.2–51.0)
Consistent	53.4 (47.5–59.4)	46.7 (42.1–51.3)	42.6 (37.6–47.6)	42.4 (39.0–45.9)
DR - CRC				
Overall	0.3 (0.2–0.4)	0.2 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.1)
Consistent	0.4 (0.3–0.5)	0.2 (0.1–0.3)	0.1 (0.1–0.2)	0.1 (0.1–0.1)
DR - AA				
Overall	1.9 (1.2–2.7)	1.4 (0.9–2.0)	1.0 (0.5–1.5)	1.0 (0.5–1.5)
Consistent	2.3 (1.7–2.9)	1.4 (1.0–1.9)	1.1 (0.7–1.6)	0.8 (0.8–0.9)
DR - Adenoma				
Overall	2.5 (1.7–3.3)	2.1 (1.3–2.9)	2.0 (1.1–2.8)	1.1 (0.8–1.5)
Consistent	2.6 (2.3–2.9)	1.8 (1.5–2.1)	1.3 (1.3–1.4)	1.4 (1.4–1.5)

AA, advanced adenoma; CI, confidence interval; CRC, colorectal cancer; DR, detection rate; PPV, positive predictive value.

For consistent screeners (Table 2, Supplementary Figures 9 and 22), PPVs from the first through fourth rounds were: CRC 6.9%, 4.6%, 3.6%, and 3.1%, respectively (Supplementary Figure 23); AA 38.7%, 30.6%, 28.2%, and 24.9%, respectively (Supplementary Figure 24); and adenoma 53.4%, 46.7%, 42.6%, and 42.4%, respectively (Supplementary Figure 25).

In closed cohorts, the difference between first vs subsequent round results for CRC PPV appeared more marked compared with open cohorts (Supplementary Figures 26–31).

Data on DRs for CRC, AA, and adenoma for the overall population and the consistent screeners is described in Table 2 and Supplementary Figures 32–39.

CRC Stage per Round Over Time

Six studies provided information regarding CRC stage at diagnosis in organized screening programs. From those, we could extract information regarding CRC stage for the overall screening population from 5 studies,[20,22,23,25,29] and for the consistent screeners from 2 studies.[29,35] In the overall screening population, CRC stages I to II constituted 72.7%, 73.6%, and 71.3% of CRC's in the first through third rounds, respectively. In the consistent screeners, CRC stages I to II comprised 76.5%, 70.3% and 73.9% of CRCs in the first through third rounds, respectively. The available data on CRC stage are shown in Supplementary Table 4.

Discussion

Our synthesis of programmatic FIT-based screening data from around the world provides valuable insights on overall adherence patterns across multiple screening rounds, and on per-round participation rates, FIT positivity rates, and yields for neoplasia from the initial round through subsequent screening rounds. Overall, approximately 48% (range, 21%–61%) of screen-eligible individuals in organized programs consistently participate in screening, approximately 30% (range, 19%–59%) do not participate at all, and the remainder participate intermittently. Per-round participation rates remain relatively stable from the first through fourth screening rounds and are comparable between annual and biennial programs. Per-round FIT positivity rates and the PPV for CRC decline from the first through fourth rounds, with a more pronounced drop between the first and second rounds and an apparent later stabilization. In contrast, the per-round PPVs for AA and

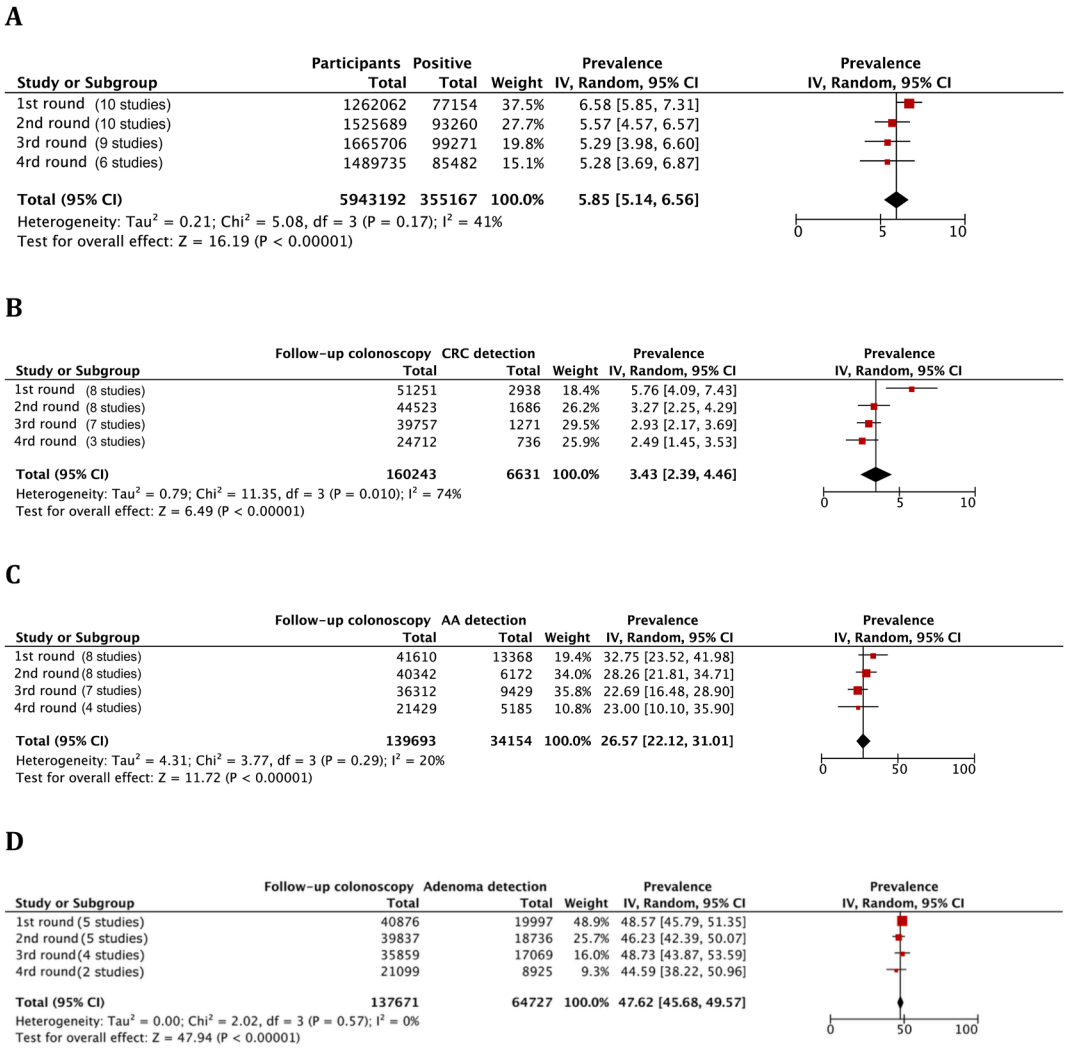

Figure 4. Positivity rate (*A*) and PPV for CRC (*B*), AA (*C*), and adenoma (*D*) of FIT per round in the overall screening population participating in FIT-based organized screening programs. IV, inverse variance.

adenomas decrease more gradually from the first through subsequent rounds. Among consistent screeners, the declines in FIT positivity rates seem to occur more rapidly than in the overall screening-eligible population. Although more subtle, this trend is also suggested for the PPVs.

Multiple clinical trials demonstrate that screening decreases CRC incidence and mortality.[5,6,10,38,39] Currently, the most widely adopted population-based screening strategies are colonoscopy every 10 years or FIT every 1 or 2 years, followed by colonoscopy if the result is positive. In a recent randomized controlled trial, invitation to biennial FIT screening was not inferior to invitation to a 1-time colonoscopy in reducing 10-year CRC incidence and CRC-related mortality.[10] Biennial FIT screening was better accepted by the population than colonoscopy, which enhanced the overall effectiveness of the FIT strategy.[40] Our results highlight the challenges and opportunities related to participation in organized FIT-based CRC screening programs: it is not clear how one might achieve participation at least once among those who remain unscreened after multiple screening round offers, or how one might sustain screening adherence over time among those who adhere only intermittently. A modeling study by Heisser et al[41] suggests that sporadic screening adherence among a large portion of the population prevents substantially more CRC cases and deaths than perfect, selective adherence within a small, highly compliant group, even at identical overall adherence levels. Public health interventions should prioritize maximizing the reach of screening to engage 'never-attendants,' rather than focusing resources on ensuring perfect repeat adherence among those already participating.

A major limitation of many reports of CRC screening programs' outcomes is that key metrics are reported according to the calendar year (ie, program's round).[21,24,28,29] This reporting approach fails to account for the individual screening round each participant is undergoing, or their screening behavior in previous rounds. Understanding longitudinal adherence within different subpopulations is essential. Evaluations of

closed cohorts and cohorts of consistent screenees provide the best assessment of changes in per-round results from initial to subsequent rounds, reflecting the balance between ongoing removal of neoplasia from the population and age-dependent development of new neoplasia. Such evaluations can define the maximum benefit that specific screening methods can offer and can identify when per-round results stabilize even as screenees age.

Several methods have been proposed to describe longitudinal adherence in CRC screening programs.[12] These include stratified single-round attendance (number attending among eligible per round); all possible adherence permutations; attendance stratified into consistent, inconsistent, and never; number of times attended; number of times attended with respect to offered rounds; overall program adherence; and proportion of time covered.[42,43] Each of these metrics has limitations, and no consensus has been reached on a standard method for reporting adherence across rounds. In our review, most studies only reported per-round stratified attendance; only 9 studies described participation in enough detail to allow for the extraction of overall adherence patterns at the level of individuals. In aggregate, total population per-round participation rates in the included studies were approximately in the 50% to 60% range and seemed to remain stable over multiple rounds, in contrast with reports of decline in uptake over subsequent rounds.[43] These participation rates exceed those of the landmark COLONPREV trial,[10] likely reflecting the difference between "real-world" established programs and an experimental randomized controlled trial, in which the investigational nature may have influenced uptake. European guidelines define a minimum screening uptake rate of 45% and a desirable rate of at least 65%, but do not currently provide recommendations for longitudinal adherence across multiple rounds.[44] Current outreach efforts appear sufficient for the subgroup of the population that is inclined to screen consistently. It remains to be determined if and how the approximately 30% who consistently do not screen at all could be encouraged to participate. Among intermittent screeners, we observed similar rates for dropouts and late adopters. These patterns probably reflect different underlying individual and system-level factors. The outlier results in the study by Benito et al[31] are likely attributable to a 'carry-over' effect from the program's initial rounds using gFOBT, a test known to have lower acceptability than FIT.

Our results highlight how FIT positivity rate and PPVs (specially for CRC) show a gradual decrease from the first through the fourth round, with the steepest drops between the first round ("prevalence round") and the second round. Robust data through further rounds might confirm a tendency towards stabilization at a steady state in per-round results. The few available studies reporting on fifth and sixth rounds show how adenoma and AA DRs seem to reach a steady state between the third and fifth rounds, whereas CRC detection maintains slight decreases through the fifth and sixth rounds.[36,29] Our results suggest that, in consistent screenees (vs the overall population) or closed (vs open) cohorts, FIT-positivity and neoplasia yield may reach a steady state within fewer rounds. These groups have minimal or no late-entry/intermittent screening at a wide range of age-related rates of prevalent neoplasia.

We are not aware of any previous systematic review and metanalysis that explores comprehensively the per-round participation and performance of population-based CRC screening programs using FIT. Previous systematic reviews focused on overall (no round-specific) performance of organized FIT-based programs,[45] repeat FIT or gFOBT prevalence in diverse settings,[46] gender differences in FIT uptake,[47] or FIT performance outside an organized setting.[48,49]

Our results reinforce the evidence that programmatic FIT screening identifies and removes a substantial cumulative number of CRCs and advanced precursor lesions from round to round. This could support the development of risk-based, personalized screening strategies based on an individual's screening history and results. Such individualized approaches could alleviate pressure on screening programs and endoscopy services. It remains to be determined, for instance, whether individuals who participate consistently in screening and have multiple consecutive negative results could be candidates for extended screening intervals, an increase in the FIT positivity cutoff value, or even early cessation of screening.

Our study has limitations. First, we observed substantial heterogeneity across all analyses, likely due to differences among studies in FIT cutoff thresholds, screening intervals, countries, recruitment periods, age ranges, underlying cancer prevalences, study design (experimental vs real world), and setting (initial, established, or gFOBT-transitioning programs; variable opportunistic background screening). Second, the number of individuals undergoing FIT decreased between the first and fourth rounds, with few studies reporting 5 or more rounds.[26,32,36,29] Third, a sex-based analysis was not feasible. Fourth, in some studies, FIT-based screening programs were preceded by gFOBT-based screening, potentially influencing early round positivity.[31] Fifth, it was beyond this study's scope to synthesize data on opportunistic screening, given that the absence of a dynamic list of screen-eligible persons in the opportunistic setting makes it challenging to determine screening results as a function of individual screening history. Adherence with fecal-based screening is superior in organized vs opportunistic screening.[50–52] Sixth, 1 study did not report colonoscopy completion rate, requiring the use of FIT positivity as the denominator to calculate PPVs.[16] Finally, a potential bias may arise from the reinvitation of individuals with a previous positive FIT and a negative colonoscopy, who may dilute positivity and detection rates in subsequent rounds.

Conclusion

In conclusion, our systematic review and meta-analysis provide a comprehensive overview of longitudinal adherence patterns, FIT positivity rates, and detection yields across successive rounds of organized FIT-based CRC screening programs worldwide. Per-round participation rates remain stable across rounds, with nearly one-half of the eligible population screening consistently, but a substantial proportion persistently not participating at all. Positivity rates and PPVs decline across rounds, more markedly among consistent participants. Our results underscore the need for standardized reporting of longitudinal participation, emphasizing individual-level per-round participation and results. This approach could enhance program evaluation, facilitate cross-country comparisons, promote research on personalized screening based on screening history, and ultimately optimize the effectiveness and cost-effectiveness of CRC screening and surveillance programs.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2026.02.009.

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Acknowledgments
The authors would like to thank and acknowledge Pablo Guijarro for his assistance with the design and editing of the figures.

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Conflicts of interest
These authors disclose the following: Rodrigo Jover has received research grants from MSD; and has participated as an advisor to MSD, Norgine, Alfa-Sigma, and GISupply. Uri Ladabaum has participated in the advisory board for UniversalDx, Lean Medical, Vivante, and Kohler Ventures; and as consultant for Medtronic, Clinical Genomics, Guardant Health, Freenome, and ChekCap.

Antoni Castells has participated in the advisory board for UniversalDx, Goodgut, and ProAlt; and received research grants from Eiken. The remaining authors disclose no conflicts.

Funding
This work was supported by the Gorrindo Family Research Grant, Instituto de Salud Carlos III (PI20/01527, PI23/01974), and Instituto de Investigación Sanitaria y Biomédica de Alicante Foundation (UGP-24-095). The Funding sources had no role in the study design, analysis, interpretation of data, writing, or submission of the manuscript.

Data Availability
Data, analytic methods, and study materials will be made available to other researchers from the corresponding author upon reasonable request.