

Longitudinal adherence to Immunochemical fecal occult blood testing vs guaiac-based FOBT in an organized colorectal cancer screening program

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27 **ABSTRACT**

28 Longitudinal adherence is a critical component of the efficacy of stool-based screening programs
29 because they should be repeated every 1-2 years. Few data have been published on the uptake in
30 multiple rounds of fecal occult blood test-based (FOBT) colorectal cancer (CRC) screening.

31 We calculated two measures of longitudinal adherence to biennial FOBT (guaiac fecal occult blood
32 test:gFOBT or fecal immunochemical test:FIT) to better understand its impact on the programmatic
33 effectiveness of a population-based CRC screening program (2000-2017).

34 Ongoing population-based CRC program of men and women aged 50-69 years (n=131,862).
35 *Variables:* Age at first CRC screening invitation, sex, number of screening invitations, number of
36 screens, deprivation score, and uptake rate. Logistic regression models were used to assess the
37 independent effect of sex, age at first invitation, deprivation and the type of screening test offered
38 on adherence.

39 The uptake rate for gFOBT was 23.9% and for the FIT 37.4%. The overall rate of consistently
40 screened invitees after seven rounds of screening was 14.2%, being 20.6% for those individuals
41 who used FIT and 14.3% for those who used gFOBT. Factors associated with continued
42 participation (consistent vs inconsistent screenees) showed that longitudinal adherence was
43 associated with age, screening test used, and number of invitations. Continued participation was
44 lower in individuals who were screened using FIT than among those screened using gFOBT (OR:
45 0.68;95%CI:0.57-0.81).

46 The overall rate of consistently screened invitees for CRC screening was higher with FIT than
47 gFOBT. Studying the rate of individuals being current for screening may help to anticipate potential
48 benefits before long-term outcome data are available.

49 INTRODUCTION

50 Colorectal cancer (CRC) screening is a simple and effective public health intervention that prevents
51 and minimizes the impact of CRC on the community. There is convincing evidence supporting the
52 fecal occult blood test (FOBT), sigmoidoscopy and colonoscopy as screening tools (1-9).

53 Uptake is a key indicator of the potential effectiveness of any screening intervention because it
54 reflects the degree to which a population is exposed to the intervention. Bulliard et al. (10)
55 published a review of cancer screening uptake definitions and measures, focusing primarily on
56 uptake in a single round of screening and noted that measures of uptake across multiple rounds of
57 screening are complex. Several indicators measure adherence; the choice of the indicator depends
58 on the objective. Determining who is eligible to be studied depends on the question of interest, and
59 there are three possibilities: the entire population (studies focused on the proportion of the
60 population in need of screening), people meeting eligibility criteria for screening (relevant
61 considerations for screening eligibility include those related to the risk level; invitation to screen;
62 prior cancer, symptoms, or tests; and screening ascertainment), and people who have been
63 previously screened (measure of the time to rescreening) (10, 11).

64 Longitudinal adherence is a critical component of stool-based screening programs for screening
65 efficacy because screens should be repeated every 1-2 years, and the attrition rate has important
66 implications for the long-term effectiveness of the screening program (12, 13). The effectiveness of
67 an FOBT screening program is highly dependent on uptake in multiple rounds (14). Ideally, eligible
68 invitees accept the invitation to be screened in every screening round (12, 15). The best indicator to
69 study the effectiveness is to calculate the percentage of consistently screened individuals among all
70 invitees.

71 Few data have been published on the uptake in multiple rounds of FOBT-based CRC screenings in
72 a large population-based open cohort. To compare the published data, the measure used to
73 calculate longitudinal adherence, especially the screening eligibility criteria and the length of the
74 study period, needs to be considered. The longitudinal adherence of individuals eligible for
75 colorectal cancer screenings using the guaiac fecal occult blood test (gFOBT) ranges from 38.1% to
76 47.2% (4, 6, 16, 17). Between 14.3% and 44.4% of invitees were consistently screened for CRC
77 using the gFOBT (12,15,18-20). Screening programs using the fecal immunochemical test (FIT)
78 reported 38.3%-53.6% rates of consistently screened invitees (21-24). In all these studies, the
79 number of rounds studied was at most three or four.

80 European guidelines for quality assurance in colorectal cancer screening and diagnosis have
81 defined a standard for uptake; however, the desirable target would be to achieve an uptake rate of

82 65% (25). These guidelines recommend minimal uptake, but there is no recommendation for
83 longitudinal adherence.

84 In the context of an intervention or program, studying longitudinal adherence may help to anticipate
85 the potential benefits before long-term outcome data are available. Measuring longitudinal
86 adherence may also help identify opportunities to develop interventions and programs that reduce
87 disparities.

88 In 2000, Catalonia was the first region to launch a population-based CRC screening program using
89 FOBT in Hospitalet de Llobregat (26). The first two screening rounds were part of the pilot study.
90 Over time, the screening program was strategically modified to attain quality indicators and to make
91 it more accessible to the population (26,27). Nowadays, several regions of Spain have active CRC
92 screening programs (28,29).

93 We calculated two measures of longitudinal adherence to biennial FOBT (gFOBT or FIT) to better
94 understand its impact on the programmatic effectiveness of a population-based CRC screening
95 program from 2000 to 2017.

96 **METHODS**

97 Seven rounds of the Catalan CRC biennial screening program were performed from February 2000
98 to June 2017 (first round from 2000 to 2002; second round from 2003 to 2005; third round from
99 2006 to 2008; fourth round from 2008 to 2010; fifth round from 2010 to 2012; sixth round from 2012
100 to 2014; and seventh round from 2014 to 2017).

101 **Study Population:** The target population included 131,862 men and women aged 50–69 years
102 who were residents in the screening area, Hospitalet de Llobregat, a municipality to the immediate
103 southwest of Barcelona. The analysis evaluating screening adherence was restricted to subjects
104 invited to participate at least twice between 2000 and 2017 (n=103,122).

105 To analyze the effect of the type of screening test used on longitudinal adherence, we compared
106 subjects who were invited at least twice for gFOBT-based screenings irrespective of further
107 invitations for FIT-based screenings with subjects who were invited at least twice for FIT-based
108 screenings and had never been invited for gFOBT-based screenings (n=93,107).

109 **Screening Procedure:** This study was performed within our ongoing, population-based CRC
110 screening program. The study design has been previously described (26, 27, 30). Briefly, a biennial
111 population-based screening program for CCR using the FOBT was launched in Hospitalet de
112 Llobregat, an industrial city of 260,288 inhabitants. Participants with positive screening results were
113 referred for a colonoscopy. Participants with no lesions found during the colonoscopy were invited

114 for another screening after 10 years if eligible. The program was free to the public and included
115 men and women aged 50 to 69 years.

116 **Exclusion Criteria:** Subjects were excluded if they had any of the following: a personal history of
117 CRC or adenomas, familial CRC cancer, inflammatory bowel disease, a colonoscopy in the
118 previous 5 years or FOBT in the previous 2 years, or a terminal disease or a severe disabling
119 condition. Subjects with an invalid mailing address and removals from the screening area registry
120 were also excluded because they could not be invited to a screening.

121 **Screening Test:** The gFOBT was the only test used in the first three screening rounds (Hema-
122 screen™; Immunostics, Inc New Jersey, USA). In the fourth round, the FIT (OC Sensorµ, Palex)
123 was partially introduced and offered to 12,727 individuals to assess its feasibility and acceptability
124 (eligible population assigned to two Basic Health Areas randomly selected). The gFOBT was
125 offered to the remaining target population (n=50,199) (eligible population assigned to 10 Basic
126 Health Areas).

127 Based on the favorable results obtained with the FIT, the Catalan Cancer Strategy decided that the
128 FIT would be used throughout Catalonia. Thus, in the fifth, sixth, and seventh rounds of CRC
129 screenings, the FIT was the only test used.

130 **Variables:** Data on age at first invitation, sex, number of screening invitations and number of
131 screens were retrieved from the program database. Since no individual information on
132 socioeconomic status (SES) was available, a deprivation score, elaborated by the Catalan Agency
133 for Quality and Health Technology Assessment and calculated for basic healthcare areas of the
134 Catalan territory, was used (31). This score combined several pieces of contextual data, such as
135 income deprivation, employment deprivation, health deprivation and average education, into a
136 single deprivation score for a basic healthcare area [score: 0-100]. Higher scores on this index
137 represent greater socioeconomic deprivation.

138 The uptake rate was calculated as the number of participants (persons with a FOBT performed
139 properly) relative to all eligible invitees. Uptake rates were calculated for each screening round.

140 We have used two measures to calculate the longitudinal adherence. The first measure is the
141 continued participation, which answers the research question: what is the prevalence of receiving
142 regular screening? This measure gives information about long-term satisfaction with the screening
143 program (10). Participants are studied and analyzed if they continue over time with screening. The
144 denominator of this indicator is the number of individuals who have participated.

145 The second measure is the percentage of invited individuals with a consistent screening behavior,
146 which answers the research question: who could potentially benefit most from cancer screening?

147 What proportion of invitees participates in all screening rounds? In this case, the denominator is the
148 individuals invited to the cancer screening program and the numerator the individuals that have
149 been tested as many time as invited. The measure gives information about the percentage of
150 eligible population that can benefit from the program, the effectiveness of the screening program.
151 Thus, this could be an intermediate indicator of mortality, which is a very expensive indicator and
152 requires a lot of time to calculate it. Nevertheless, this measure depends on the individuals who
153 enhance uptake in screening and those who continued being screened over time.

154 To classify individuals according to their screening behavior we considered three categories: never
155 screened individuals (no uptake in any round of the screening), inconsistent screenees (attending at
156 least one round of screening but less than the total eligible number of screenings), and consistent
157 screenees (attending all rounds of screenings when eligible). We have examined the proportion of
158 individuals who participated in the screening after two or more invitations (late adopters) and those
159 who discontinued screening (quitters) in the next round.

160 **Statistical Analyses:** A descriptive analysis was performed to identify invitees with a consistent
161 screening behavior over seven screening rounds and by type of test. The Joinpoint Regression
162 Program (Version 4.5.0.1, Statistical Methodology and Applications Branch, Surveillance Research
163 Program, National Cancer Institute, Bethesda, MD, USA) was used to analyze uptake trends for the
164 whole population and to detect where a significant change in the trend occurred.

165 Multivariate logistic regression models were used to assess the independent effects of sex, age at
166 first invitation (5-year category), deprivation (10-point category) and type of screening test offered,
167 on screening adherence. All the models were further adjusted for the number of invitations and
168 average uptake after the first screening invitation. These models provided odds ratios (ORs) and
169 95% confidence intervals (CIs) that allowed us to compare: 1: consistent vs inconsistent screenees,
170 2: inconsistent screenees vs never screened individuals and 3: screenees (both consistent and
171 inconsistent screenees) vs never screened individuals.

172 **Ethics:** Our CRC screening program, similar to all Spanish population-based screening programs,
173 followed public health laws and the Organic Law on Data Protection. The study protocol was
174 approved by the ethics committee of the University Hospital of Bellvitge (PR261/17).

175 **RESULTS**

176 **Uptake:** Over the seven screening rounds, the uptake rates increased significantly from 17.2% to
177 38.0%. Of the 131,862 individuals eligible for the seven screening rounds, 62.8% were 'never
178 participants', and 37.2% participated at least once (Table 1, Supplementary figure 1).

179 **Consistently screened invitees:** The number of times that invitees participated during the seven
180 screening rounds displayed for the number of times that invitees were eligible is summarized in
181 Table 2. The overall screening rate after seven rounds of screening was 14.2% (18,681/131,862).
182 According to the number of invitations it ranged from 16.03% to 12.51% (Table 2).The overall
183 screening rate according to the type of test is shown in table 3, 14.3 for Guaiac test and 20.6 in FIT
184 (Table 3).

185 **Inconsistent screenees:** Inconsistent screenees can be classified in two main groups: those who
186 changed screening behavior over time (late adopters and quitters) and those with an erratic
187 behavior regarding screening. Table 4 shows the proportion of individuals who participated in the
188 screening after two or more invitations (late adopters) and those who stopped being screened
189 (quitters) (Table 4).

190 **Late Adopters:** Individuals who enhanced uptake after being invited one time in the previous round
191 and not having participated was 11.2% for the gFOBT and 12.6% for the FIT (Supplementary tables
192 2 and 4).

193 **Quitters:** The proportion of quitters for both tests was approximately 25% after their first screen.
194 The percentage of participants who withdrew after two rounds of screenings and after three rounds
195 of screenings was greater for the FIT than for the gFOBT and for three rounds (FIT:13.8% and 8.7%
196 and gFOBT: 7.1% and 5.4%, respectively; Supplementary tables 2 and 4).

197 **Continued participation:** Table 5 provides the results of the multivariate logistic regression
198 analysis examining predictors of longitudinal adherence in CRC screenings. Model 1, that analysed
199 factors associated with continued participation (consistent vs inconsistent screenees), longitudinal
200 adherence was associated with age, screening test used (gFOBT or FIT), and number of invitations.
201 Continued participation was lower among individuals who used the FIT than among those who used
202 the gFOBT (OR: 0.68; 95% CI: 0.57-0.81).

203 No differences in sex or deprivation index were observed. The age at first invitation (5-year change)
204 was associated with adherence to CRC screenings. Elderly individuals were more likely to be
205 adherent than were their younger counterparts.

206 The model that compared inconsistent screenees versus never screened individuals (Model 2)
207 revealed that screening uptake was associated with sex, deprivation index and test type. The ORs
208 showed that women participated more than men, especially those with a lower deprivation index
209 and those who were invited to participate in screenings using the FIT. Similar findings were found
210 with the model that compared those never screened with screenees (both consistent and
211 inconsistent screenees) (Model 3); women, those with a lower deprivation index and who used FIT
212 were more likely to have been screened at least once (Table 5).

213 **DISCUSSION**

214 This population-based study calculated two longitudinal adherence indicators to CRC screening
215 with FOBT. The results showed a longitudinal decrease in adherence over 7 screening rounds. In
216 addition, it was observed that the overall rate of consistently screened invitees for CRC screening
217 was higher with FIT than guaiac test despite lower continued participation. Factors associated with
218 initial uptake were quite different from those relating to adherence in subsequent rounds of
219 screenings. Continued participation was associated with age, screening test used (gFOBT or FIT),
220 and number of invitations.

221 Monitoring longitudinal screening adherence is important (22, 24, 32), especially for FOBT, because
222 individuals are more likely to adhere to screening options that require fewer screenings over time
223 (33). There is little information on uptake patterns in any screening program that is predicated on
224 repeated invitations at regular intervals (15, 18, 19, 21-24) (Supplementary table 3). To the best of
225 our knowledge, no study has compared the longitudinal adherence (neither continued participation
226 among screenees nor proportion of consistently screened invitees) of both tests (gFOBT and FIT)

227 Given the scarcity of information on the impact of repeated FIT or gFOBT screenings, such data are
228 of major importance for countries considering or planning the implementation of population-based
229 FIT or gFOBT screening programs. The replacement of the gFOBT with quantitative FIT screenings
230 should increase uptake. When comparing the FIT and the Guaiac, in terms of continued
231 participation, in our screening program is lower in the FIT, but instead, the number of people who
232 join the screening program was greater in FIT than in the Guaiac and therefore, the percentage of
233 consistently screened invitees was still greater with the FIT. The latter measure gives information
234 about how many individuals could potentially benefit most from cancer screening (some individuals
235 who have been screened sporadically may also get some benefit from being screened) (14).

236 The longitudinal decrease in adherence may be partially explained by screening fatigue. Invitees
237 lose the motivation to participate because of a false perception of decreased CRC risk after several
238 negative test outcomes (34). Screening fatigue considerably reduces screening effectiveness and is
239 a potential threat for FOBT screening programs because repeated testing is important to achieve
240 reasonable sensitivity for detecting advanced neoplasia. Furthermore, CRC risk increases with age,
241 stressing the importance of uptake among older individuals (35).

242 Late adopters (individuals who participate in CRC screenings after several invitations) contributed to
243 overall uptake. Here, previous non-attenders were re-invited every 2 years, irrespective of whether
244 they had previously responded, because this practice improves uptake (36). Increased awareness
245 of CRC screening and sufficient information on CRC and FIT screenings may enhance the uptake
246 in successive rounds because the target population is screening-naïve when first approached (36).
247 It is important to keep inviting to the previous nonparticipants because, in our study, up to 8.4% of

248 the population participated after three invitations, regardless of the type of test (gFOBT or FIT). In
249 cancer screening programs where uptake is less than 45%, any intervention is important to increase
250 uptake, especially when the intervention mainly involves sending an invitation letter and a reminder.

251 In addition, it is important to consider the percentage of quitters, especially when uptake is <45%.
252 Almost 25% of the participants do not participate again in the next round. Primary care
253 professionals should be closely involved in interventions designed to improve longitudinal
254 adherence. The general practitioner role is pivotal not only to increase uptake in FOBT screenings
255 but also to ensure adherence with repeat testing for people with negative FOBT results (18).
256 General practitioners could increase their involvement in CRC screening if they had more
257 involvement with patient information at different stages of the screening process. Their privileged
258 mode of communication remains face-to-face consultation with the patient (37).

259 The strengths of our study include access to a large cohort of an average-risk population composed
260 of participants of the age ranges that are typically invited for CRC screening programs worldwide.
261 Our study also had several limitations. First, SES could only be assigned by postal code, as a proxy
262 for individual level SES. Second, 17 years have passed since the screening program was
263 implemented, and many organizational changes have occurred. These changes may have
264 contributed to uptake modification and longitudinal adherence; however, these changes have not
265 been monitored and therefore cannot be identified as confounding factors. Third, the first two
266 rounds of screenings were pilot rounds with uptake values of 17.2% and 22.3%, respectively, which
267 conditioned full adherence. When we excluded these two rounds, the full adherence over five
268 rounds of screenings improved by six percentage points (from 14.2% to 20.6%).

269 To improve the comparability of longitudinal adherence indicators in cancer screening interventions,
270 the definitions and associated terminology need to be explicit, standard terms should be favored
271 and the use of the same term for different meanings needs to be avoided (10).

272 In summary, there are differences in the longitudinal adherence of FIT and gFOBT screening; the
273 FIT increased overall uptake but decreased continued participation. In programs with an overall
274 uptake of less than 45%, it is considered appropriate to focus on interventions that improve initial
275 uptake. When the uptake is 45% or higher, then it is important to design specific interventions
276 focused on maintaining adherence. Identifying the proportion of consistently screened individuals is
277 important in order to anticipate the population benefits of screening before having mortality data
278 available.

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385 **Table 1. Colorectal cancer screening uptake per rounds.**

Screening round number	Screening test	Number of BHA involved	Target population	Uptake [†]		Rescreening [‡]
				n	%	%
1 (Pilot)	Guaiaac	11	63,872	11,005	17.2	
2 (Pilot)	Guaiaac	12	66,519	14,816	22.3	73.2
3	Guaiaac	12	65,142	17,742	27.2	87.0
4	Guaiaac	10	50,199	15,135	30.2	87.3
	FIT	2	12,727	4,625	36.3	
5	FIT	12	63,824	22,981	36.0	89.7
6	FIT	12	60,906	23,325	38.3	88.7
7	FIT	12	61,428	23,366	38.0	81.2
Overall	FIT or Guaiaac	12	131,862	48,974	37.2	83.7

386 BHA: Basic Healthcare Area (There are 12 BHA in L'Hospitalet); FIT: fecal immunochemical testing [†]Uptake: total number of people who have
 387 used and returned a screening test irrespective of result. This includes individuals with inadequate/incomplete results. [‡] Rescreening (Refers to two
 388 consecutive rounds): total number of people invited for screening in Round n and Round n -1 who participated in both rounds.

389 Uptake trend: The percentage change per screening round from 2000 to 2012 was 20.10 and from 2012 to 2017 was 0.98 (derived from Jointpoint
 390 regression analysis)

391 **Table 2.** Number of times invitees participated in the CRC screening program displayed for the number of times they were eligible.

		Number of Invitation							
		1	2	3	4	5	6	7	Total
Number of Participations	0	24,820	18,546	12,257	9,683	7,678	6,004	3,900	82,888
	1	3,920	3,472	2,334	1,797	1,781	1,441	938	15,683
	2		4,205	2,009	1,562	1,340	1,308	774	11,198
	3			2,680	1,748	1,358	1,222	692	7,700
	4				2,356	1,483	1,136	715	5,690
	5					2,200	1,446	769	4,415
	6						2,067	968	3,035
	7							1,253	1,253
Total		28,740	26,223	19,280	17,146	15,840	14,624	10,009	131,862
Consistently screened invitees*			16.0%	13.9%	13.7%	13.8%	14.1%	12.5%	14.2%**

392 *Consistently screened invitees: being tested as many times as getting invited.

393 ** When excluding Pilot Screening Rounds (Round 1 and Round 2), the overall percentage of consistently screened invitees is 20.9%

394 (Supplementary table 1)

395 **Table 3 Individuals invited to a CRC screening program by test used and number of invitations**

Screening test*	Number of invitations	Individuals invited to screening program					
		Never screened		Inconsistent Screenees		Consistent Screenees	
		N	%	n	%	n	%
Guaiac*	2	19740	72.1	3556	13.0	4082	14.9
	3	15690	63.5	5495	22.2	3541	14.3
	4	13106	58.3	6327	28.2	3031	13.5
	All	48536	65.1	15378	20.6	10654	14.3
FIT**	2	5892	63.6	1309	14.1	2059	22.2
	3	4514	54.7	2208	26.8	1532	18.6
	4	470	45.9	325	31.7	230	22.4
	All	10876	58.7	3842	20.7	3821	20.6

396 FIT: faecal immunochemical testing

397 *Individuals who were offered guaiac were included in the analysis, irrespective of further invitation for FIT-based screened (n=74,568).

398 ** Individuals who were offered FIT as the only screening test of choice (n=18,539)

399 **Table 4. Participation and withdrawal according to the number of previous participations.**

Number of previous invitations	Number of previous participations	Participation to the current round				All
		No		Yes		
		N	%	N	%	
		Never screened		Late adopters		
1	0	18546	92.4	1525	7.6	20071
2	0	12257	93.2	901	6.8	13158
3	0	9683	92.7	761	7.3	10444
4	0	7678	90.8	782	9.2	8460
5	0	6004	90.8	609	9.2	6613
6	0	3900	91.5	362	8.5	4262
		Quitters		Consistent Screenees		
1	1	1947	31.6	4205	68.4*	6152
2	2	503	15.8	2680	84.2	3183
3	3	279	10.6	2356	89.4	2635
4	4	185	7.8	2200	92.2	2385
5	5	174	7.8	2067	92.2	2241
6	6	78	5.9	1253	94.1	1331

400 Late adopters: individuals who enhance participation after ≥ 2 invitations; Quitters; individuals who discontinued screening for the next round;

401 Consistent screenees; individuals who participate every time they get a screening invitation.

402 * When excluding Pilot Screening Rounds (Round 1 and Round 2), the percentage of consistent screenees after two invitations is 80.0%.

403 **Table 5.** Factors associated with continued participation and uptake in a population-based screening program for CRC.

Independent variables	Continued participation		Uptake			
	Model 1. Consistent vs. Inconsistent screenees		Model 2. Inconsistent screenees vs. Never screened		Model 3. Screenees [†] vs. Never screened	
	OR	95% CI	OR	95% CI	OR	95% CI
Sex (ref men)	1.00		1.00		1.00	
Women	1.01	[0.97-1.06]	1.20	[1.16-1.24]	1.21	[1.17-1.24]
Age at first invitation (5-year change)	1.04	[1.01-1.07]	0.98	[0.96-1.00]	1.00	[0.99-1.02]
Deprivation index (10-point change)	0.98	[0.96-1.01]	0.88	[0.87-0.90]	0.87	[0.86-0.88]
Invitations number (ref 2)	1.00		1.00		1.00	
3 invitations	0.58	[0.54-0.61]	1.96	[1.87-2.05]	1.51	[1.46-1.57]
4 invitations	0.48	[0.45-0.52]	2.52	[2.38-2.67]	1.84	[1.76-1.93]
Type of test (ref Guaiac)	1.00		1.00		1.00	
FIT	0.68	[0.57-0.81]	1.68	[1.47-1.91]	1.38	[1.25-1.53]
Average participation at first invitation (1-percent change)	1.04	[1.03-1.05]	0.99	[0.98-1.00]	1.01	[1.00-1.01]

404 FIT: fecal immunochemical testing; OR: Odds Ratio; CI: Confidence interval. † Screenees includes both consistent and inconsistent screenees.

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