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ORIGINAL ARTICLE

Colorectal cancer screening in patients with inherited bleeding disorders: high cancer detection rate in hemophilia patients

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Abstract

Background: The population-based colorectal cancer (CRC) screening program in individuals aged 55 to 75 years in the Netherlands uses fecal immunochemical testing

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(FIT), to detect hemoglobin in feces, followed by colonoscopy in individuals with a positive FIT.

Objectives: The objectives of this study are to assess the false-positive rate, detection rate, and positive predictive value of FIT for CRC and advanced adenoma (AA) in patients with Von Willebrand disease (VWD) or hemophilia.

Methods: We performed a multicenter, nationwide cross-sectional study embedded in 2 nationwide studies on VWD and hemophilia in the Netherlands.

Results: In total, 493 patients with hemophilia (n = 329) or VWD (n = 164) were included, of whom 351 patients participated in the CRC screening program (71.2%). FIT positivity and false-positive rate in patients with hemophilia and VWD were significantly higher than those in the general population (14.8% vs. 4.3%, p < .001 and 10.3% vs. 2.3%, p <.001, respectively). In patients with hemophilia, the detection rate of CRC/AA was significantly higher than that in the general male population (4.5% vs. 1.8%, p = .02), and the positive predictive value of FIT for CRC/AA was comparable (32.3% vs. 39.7%, n.s.). In patients with VWD, the detection rate was similar to that of the general population (0.8% vs. 1.4%, n.s.), whereas the positive predictive value was significantly lower than that in the general population (6.3% vs. 36.8%, p = .02).

Conclusion: This study indicates that despite a high false-positive rate of FIT in patients with inherited bleeding disorders, the detection rate of CRC and/or AA in hemophilia patients is high. FIT performs different in patients with hemophilia or VWD compared with the general population.

KEYWORDS
colorectal neoplasms, hemophilia A, hemophilia B, mass screening, occult blood, Von Willebrand diseases

1 | INTRODUCTION

Colorectal cancer (CRC) is a major contributor to cancer-related mortality worldwide [1]. In the Netherlands, a population-based CRC screening program was launched in 2014 [2]. This screening program aims to reduce the CRC-related mortality by detecting CRC at earlier stages and reducing the CRC incidence [3]. Individuals aged 55 to 75 years receive an invitation to participate in the screening program once every 2 years by sending in a stool sample [3]. The participation rate is approximately 72% [4]. The screening program uses fecal immunochemical testing (FIT) to detect human hemoglobin in feces [3]. Individuals with a positive FIT are referred for colonoscopy, provided that they are considered eligible for the procedure during an intake interview [3,5]. A colonoscopy is performed in approximately 86% of individuals with a positive FIT result [4]. Relevant outcomes of the screening program are advanced adenoma (AA) and CRC [2,3,5].

The screening program is expected to reduce the CRC-related mortality on the long term [3]. A significant decrease in the incidence of advanced-stage CRC was observed at the population level after implementation of the screening program: from 117 per 100 000 population in 2013 to 94.7 per 100 000 population in 2018 [3].

Essentials

- We studied the fecal immunochemical test (FIT) performance in inherited bleeding disorders.
- The false-positive rate of FIT in patients with inherited bleeding disorders is high.
- Colorectal cancer detection rate in hemophilia patients was higher than that in the general population.
- The positive predictive value of FIT was low in patients with Von Willebrand disease.

Moreover, several observational studies showed lower CRC-related mortality in screened populations compared with unscreened populations [6–8].

So far, no studies have been conducted on the performance of the CRC screening program in a selected cohort of patients with inherited bleeding disorders, such as Von Willebrand disease (VWD) and hemophilia, whereas the outcome of screening in these patients may substantially differ from that of the general population.

VWD is the most common inherited bleeding disorder with an estimated prevalence of 1% [9,10]. It is divided into the following 3 types: type 1 is characterized by a partial quantitative deficiency of Von Willebrand factor (VWF, 70%-80% of cases); type 2, by qualitative VWF defects (20% of cases); and type 3, by a complete deficiency of VWF (<5% of cases) [11,12]. Patients with VWD mainly experience mucocutaneous bleedings [13]. VWF mediates platelet adhesion and aggregation at sites of vascular injury and serves as a carrier protein for coagulation factor VIII (FVIII) [14]. Apart from its important role in primary hemostasis, VWF also acts as an inhibitor of angiogenesis [15,16]. It is well known that patients with VWD may experience gastrointestinal bleeding because of the presence of angiodysplasia [13,17,18]. The self-reported prevalence of gastrointestinal bleeding in patients with moderate to severe VWD is approximately 15% [13].

Hemophilia is a rare X-linked inherited bleeding disorder caused by the deficiency of FVIII (hemophilia A) or coagulation factor IX (FIX) (hemophilia B). Disease severity is based on the residual FVIII or FIX activity: severe (<0.01 IU/mL), moderate (0.01-0.05 IU/mL), and mild (>0.05-0.40 IU/mL) [19]. Patients with severe hemophilia can experience spontaneous muscle and joint bleedings [20]. In moderate and mild hemophilia, bleedings mostly occur after surgery, trauma, or injury [20]. Gastrointestinal bleeding may also occur in these patients [21].

False-positive FIT results may occur because of bleeding from other sources than CRC and/or AA [22]. Consequently, given the fact that bleeding occurs more easily in patients with bleeding disorders, we hypothesized that the false-positive rate of FIT is higher in patients with inherited bleeding disorders than that in the general population. In addition, we hypothesized that the detection rate, ie the proportion of participants in whom CRC and/or AA is detected, is higher in patients with inherited bleeding disorders than that in the general population because (pre-)malignant lesions in the colon may have a higher tendency to bleed. Therefore, our study aims to assess the false-positive rate, detection rate, and positive predictive value of FIT for CRC and AA in patients with VWD and hemophilia and to compare these results with the general population in the Netherlands. In addition, we aim to assess the prevalence of abnormal results and bleeding complications of colonoscopy.

2 | METHODS

2.1 | Study design

We performed a multicenter, nationwide cross-sectional study embedded in 2 nationwide studies in the Dutch Hemophilia Treatment Centers on VWD and hemophilia, the Willebrand in the Netherlands-Prospective study (WiN-Pro), and the Hemophilia in the Netherlands 6 study (HiN6), respectively. The WiN-Pro study is an ongoing nationwide, multicenter, prospective cohort study in patients with VWD (ClinicalTrials.gov: NCT03521583), which started recruitment in July 2019. The inclusion criteria were historically lowest VWF antigen and/or VWF activity and/or VWF collagen binding ≤0.30 IU/mL and/or FVIII:C ≤0.40 IU/mL and treatment at a Hemophilia Treatment Center in the Netherlands. Patients

with concomitant bleeding disorders or acquired VWD were excluded. Participants of the WiN-Pro study were recruited from the Erasmus University Medical Center, Rotterdam; Leiden University Medical Center; Haga Hospital, The Hague; Amsterdam University Medical Center, Amsterdam; and University Medical Center Groningen. The HiN6 study is the 6th nationwide, multicenter, cross-sectional study among patients with hemophilia in the Netherlands and was performed between May 2018 and August 2019 [23]. The recruitment methods have been described previously [24]. All male patients with severe, moderate, or mild hemophilia A or B, who were treated at a Hemophilia Treatment Center in the Netherlands, were eligible for inclusion in this study [23].

For the current study, participants aged ≥55 years at study inclusion and who answered the questions concerning the CRC screening program were selected. Since the screening program in the Netherlands was launched in 2014 and runs until the age of 75, the oldest eligible participants were born in 1938 [2].

Participants of both studies completed an extensive questionnaire that included questions about participation in the CRC screening program and FIT and colonoscopy results, if performed. The HiN6 study specifically asked about first-time participation in the CRC screening program, the WiN-Pro study about any participation. In both studies, patients self-reported data on medication use at study inclusion. As part of the WiN-Pro study, historically lowest VWF and FVIII levels were provided by the patient's Hemophilia Treatment Center. Historically lowest levels below the lower limit of detection were noted as 0.01 IU/mL below that level, and values <0.01 were noted as zero. In addition, the International Society for Thrombosis and Hemostasis Bleeding Assessment Tool (ISTH-BAT) [25] was assessed by the investigator at study inclusion. Only the WiN-Pro study collected data on periprocedural prophylactic treatment and bleeding complications of colonoscopy. More details on the HiN6 study questionnaire have been previously described [23]. To improve reliability, a standardized electronic case report form was used in the HiN6 study to collect data on clinical characteristics, FIT, and colonoscopy results from electronic patient files [23,26]. When data in the case report form were missing, self-reported data from the questionnaire were used, if available [26]. In the case of discordant results, data from electronic patient files were used [26]. Concerning participation in the screening program self-reported data were used. If self-reported data were missing or if the case report form indicated that the patient participated in the screening program, data from the case report form were used.

The HiN6 study was approved by the Medical Ethical Committee of the Leiden University Medical Center (NL59114.058.17), the WiN-Pro study was approved by the Erasmus University Medical Center, Rotterdam (NL62238.078.18). Informed consent was obtained from all participants.

2.2 | Data on the general population in the Netherlands

Data on performance of the CRC screening program in the general population in the Netherlands were provided by the National Institute for Public Health and the Environment (RIVM). For this study, we used

the results of the annual national monitoring of the CRC screening program from 2019. For the comparison with patients with hemophilia, the results from the general male population were used. For the comparison with patients with VWD, the results from the general population (men/women) were used.

2.3 | Definitions and outcomes

We used the same definitions and outcomes as the national monitoring of the CRC screening program in the Netherlands [4]. The FIT participation rate was defined as the number of patients who reported to have participated in the CRC screening program divided by the number of patients invited based on their age. The positivity rate was defined as the number of participants with a positive FIT result divided by the total number of participants [4]. The positive predictive value was defined as

the proportion of participants with CRC and/or AA of the total number of participants who underwent a colonoscopy [4]. The false-positive rate was defined as the number of patients without CRC or AA detected during colonoscopy divided by the number of patients who reported to have participated in the screening program [2]. The detection rate was defined as the proportion of participants in whom CRC and/or AA was detected of all participants in the screening program.

2.4 | Statistical analysis

Continuous data were described as median with interquartile ranges (IQR), and categorical data, as numbers and percentages. Exact confidence intervals (CI) for proportions were calculated based on the binomial distribution. Comparisons with the general population were

TABLE 1 Characteristics of patients with hemophilia.

	Severe (N = 103)	Moderate (N = 43)	Mild (N = 183)	Total (N = 329)
Age (y) *median [IQR]*	63 [58-68]	64 [61-71]	64 [59-70]	63 [59-69]
Hemophilia type (%)	A = 92 (89.3) B = 11 (10.7)	A = 39 (90.7) B = 4 (9.3)	A = 169 (92.3) B = 13 (7.1) NA: 1	A = 300 (91.2) B = 28 (8.5) NA: 1
BMI (kg/m^2) *median [IQR]*	25.5 [23.3-27.8] NA: 13	25.7 [23.7-27.2] NA: 3	25.9 [24.0-28.7] NA: 17	25.7 [23.8-28.4] NA: 33
Prophylaxis use (%)	85 (82.5)	5 (11.6) NA: 1	1 (0.5) NA: 1	91 (27.7) NA: 2
Inhibitors ever (%)	10 (9.7)	5 (11.6) NA: 2	16 (8.7) NA: 14	31 (9.4) NA: 16
Blood group (%)	O: 36 (35.0) Non O: 55 (53.4) NA: 12 (11.7)	O: 15 (34.9) Non O: 12 (27.9) NA: 16 (37.2)	O: 51 (27.9) Non O: 51 (27.9) NA: 81 (44.3)	O: 102 (31.0) Non O: 118 (35.9) NA: 109 (33.1)
Lowest baseline FVIII/ FIX activity[a] (IU/mL) *median [IQR]*	0.00 [0.00-0.00] NA: 6	0.02 [0.02-0.04] NA: 7	0.13 [0.08-0.23] NA: 41	0.06 [0.00-0.15] NA: 54
HIV infection (%)	11 (10.7)	0 (0.0) NA: 1	0 (0.0) NA: 3	11 (3.3) NA: 4
HCV ever (%)	91 (88.3) NA: 5	21 (48.8) NA: 7	35 (19.1) NA: 29	147 (44.7) NA: 41
Comorbidity[b] (%)	74 (71.8) NA: 6	27 (62.8) NA: 1	118 (64.5) NA: 11	219 (66.6) NA: 18
NSAID, antiplatelet and anticoagulant drugs (%)	PAI = 4 (3.9) NA: 29	PAI = 1 (2.3) NA: 9	PAI = 16 (8.7) NSAID = 3 (1.6) VKA = 1 (0.5) NA: 40	PAI = 21 (6.4) NSAID = 3 (0.9) VKA = 1 (0.3) NA: 78
Concomitant bleeding disorder	NA: 7	VWD: 1 NA: 7	VWD: 1 Platelet disorder: 1 Other clotting factor deficiency: 1 NA: 42	VWD: 2 Platelet disorder: 1 Other clotting factor deficiency: 1 NA: 56

BMI, body mass index; FIX, factor IX; FVIII, factor VIII; HCV, hepatitis C virus; NA, indicates for each variable the number of participants with missing data for that variable; NSAID, nonsteroidal anti-inflammatory drug; PAI, platelet aggregation inhibitor; VKA, vitamin K antagonist.
[a] Lowest baseline factor VIII/IX activity was measured by the one-stage clotting assay.
[b] Comorbidity indicates the presence of ≥1 comorbidity.

made with two-sided binomial tests. *P* values were adjusted for multiple testing with the methods of Benjamini and Hochberg [27]. We computed the age-standardized morbidity ratio (SMR) for the comparison of the detection rate with the general population. The SMR is the ratio of the observed number of CRC and AA and the expected number of CRC and AA, if the age-specific detection rates from the general population would apply in the study population [28]. This measure accounts for differences in age distribution between populations [29]. The 95% CI of the SMR was approximated with the method of VandenBrouke [28]. Statistical analyses were performed in R version 4.0.3 (2020-10-10), with the packages openxlsx (version 4.2.3), foreign (version 0.8-80), and binom (version 1.1-1.1) [30–33].

2.5 | Sensitivity analysis

Only the HiN6 study collected data on the year of participation in the CRC screening program. We performed a sensitivity analysis in patients with hemophilia excluding subjects who participated in the screening program in 2014, because the national CRC screening program used a cutoff level for FIT positivity of 15 μg hemoglobin/g feces when it was first implemented in 2014 [2]. To optimize program performance, the cutoff level for a positive FIT was increased to 47 μg hemoglobin/g feces in July 2014 [2].

3 | RESULTS

3.1 | Patient characteristics

We included 493 patients with hemophilia (*n* = 329) and VWD (*n* = 164), with median ages of 63 (IQR [59-69]) and 65 (IQR [61-72]) years, respectively. Fifty-eight patients with hemophilia and 3 patients with VWD were excluded because of missing data for questions concerning the CRC screening program. In total, 67% of patients with hemophilia patients and 73% of VWD patients reported to have at least one comorbidity. Of all hemophilia patients, 300 had hemophilia A (91%) and most had mild hemophilia (56%). Most severe hemophilia patients used long-term prophylaxis with coagulation factor concentrates (83%). Hypertension (36%), hypercholesterolemia (17%), and cardiovascular disease (12%), including ischemic heart disease, stroke, heart failure, valve disease, and arrhythmias, were the most commonly reported comorbidities by patients with hemophilia. In total, 7.6% of patients with hemophilia used platelet aggregation inhibitors (*N* = 21), nonsteroidal anti-inflammatory drugs (NSAIDs) (*N* = 3), or vitamin K antagonists (*N* = 1). Of the patients with VWD, 58% had type 1, 40% had type 2, and 2% had type 3 VWD. Most patients with VWD were women (69%) and had blood group O (53%). Hypertension (35%), cardiovascular disease (18%), and malignancies (13%) were the most commonly reported comorbidities by patients with VWD. In total, 15% of patients with VWD used platelet aggregation inhibitors (*N* = 14), NSAIDs (*N* = 1), vitamin K antagonists (*N* = 4), or direct oral anticoagulants (*N* = 5). The characteristics of patients with hemophilia and VWD are displayed in Tables 1 and 2, respectively.

TABLE 2 Characteristics of patients with Von Willebrand disease.

	VWD patients (*N* = 164)
VWD type (%)	Type 1: 95 (57.9) Type 2: 65 (39.6) Type 3: 4 (2.4)
Age (y) *median [IQR]*	65 [61-72]
Female sex (%)	113 (68.9)
BMI (kg/m^2) *median [IQR]*	26.3 [23.1-29.7]
Blood group (%)	O: 87 (53.0) Non O: 54 (32.9) NA: 23 (14.0)
Historically lowest VWF:Ag (IU/mL) *median [IQR]*	0.31 [0.22-0.44]
Historically lowest VWF:Act (IU/mL) *median [IQR]*	0.19 [0.09-0.26]
Historically lowest FVIII:C (IU/mL) *median [IQR]*	0.46 [0.33-0.59]
Comorbidity[a] (%)	119 (72.6)
NSAID, antiplatelet and anticoagulant drugs (%)	PAI = 14 (8.5) NSAID = 1 (0.6) VKA = 4 (2.4) DOAC = 5 (3.0)
ISTH-BAT score *median [IQR]*	13 [8–18]

BMI, body mass index; DOAC, direct oral anticoagulant; FVIII:C, factor VIII activity; ISTH-BAT, International Society for Thrombosis and Hemostasis Bleeding Assessment Tool; NA, indicates the number of participants with missing data for that variable; NSAID, nonsteroidal anti-inflammatory drug; PAI, platelet aggregation inhibitor; VKA, vitamin K antagonist; VWD, Von Willebrand disease; VWF:Act, Von Willebrand factor activity; VWF:Ag, Von Willebrand factor antigen.
[a] Comorbidity indicates the presence of ≥1 comorbidity.

3.2 | Performance of CRC screening program in patients with hemophilia or VWD

Figure 1 shows the flowchart of the screening process in patients with hemophilia and VWD. In total, 351 patients participated in the CRC screening program, of whom 52 (14.8%) had a positive FIT result. A colonoscopy was performed in 47 of these patients. One of these 47 patients underwent a computed tomography colonography (CTC) instead of a colonoscopy after the positive FIT result. This patient had type 3 VWD and could not be prophylactically treated with coagulation factor concentrates because of a history of anaphylaxis. Moreover, 3 patients with VWD did not have a colonoscopy after a positive FIT result for unknown reasons. One hemophilia patient refused to have a colonoscopy because of hemophilia. The other hemophilia patient had not undergone the colonoscopy yet at the time of the HiN6 survey. Of the 47 patients who had a colonoscopy, CRC was detected in 2 patients and AA in 9 patients.

In comparison to the general population in the Netherlands, the FIT participation rate in our study population, the hemophilia and VWD patients combined, was similar (71.2% vs. 71.8%, respectively,
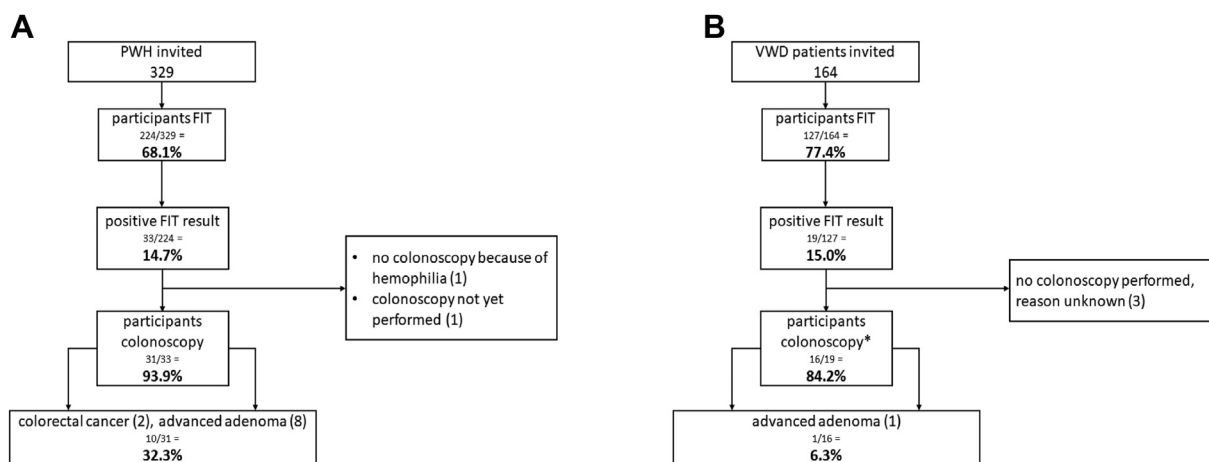
A

B

FIGURE 1 Flowchart of screening process. (A) Hemophilia patients and (B) Von Willebrand disease patients. FIT, fecal immunochemical test; PWH, patients with hemophilia; VWD, Von Willebrand disease. * One VWD patient could not be prophylactically treated with coagulation factor concentrates because of a history of anaphylaxis; therefore, a computed tomography colonography instead of a colonoscopy was performed after the positive FIT result.

p = .82) (Table 3). Patients with hemophilia or VWD had a significantly higher FIT positivity rate compared with the general population (14.8% vs. 4.3%, respectively, p< .001). The false-positive rate was also significantly higher in patients with hemophilia or VWD compared with the general population (10.3% vs. 2.3%, respectively, p < .001). The positive predictive value of FIT for CRC and/or AA in our study population was lower than that in the general population, although not statistically significant (23.4% vs. 36.8%, respectively, p = .10). However, the detection rate of CRC and/or AA was significantly higher in patients with hemophilia or VWD than that in the general population (3.1% vs. 1.4%, respectively, p = .03). The age-standardized detection rate in our study population was 2.2 times higher compared with the general population (SMR 2.2, 95% CI [1.1-3.7]).

3.3 | Performance of CRC screening program in patients with hemophilia

In patients with hemophilia, the FIT participation rate was comparable to the general male population (68.1% vs. 69.1%, respectively, p = .78) (Table 3 and Supplementary Table S1). The positivity rate and false-positive FIT rate were both significantly higher in patients with hemophilia than those in the general male population (14.7% vs. 5.2%, p < .001 and 9.4% vs. 2.7%, p < .001, respectively). However, the positive predictive value of FIT for CRC and/or AA in these patients was comparable to the general male population (32.3% vs. 39.7%, respectively, p = .58). The detection rate of CRC and/or AA was significantly higher in patients with hemophilia than that in the general

TABLE 3 Performance of screening program compared with the general population.

	All patients[a] [95% CI] (N = 493)		Hemophilia patients [95% CI] (N = 329)		VWD patients [95% CI] (N = 164)		GP	GP male
FIT participation rate (N/N)[b]	71.2% [67.0-75.2] (351/493)	p = .82	68.1% [62.7-73.1] (224/329)	p = .78	77.4% [70.3-83.6] (127/164)	p = .16	71.8%	69.1%
Positivity rate (N/N)[b]	14.8% [11.3-19.0] (52/351)	p < .001	14.7% [10.4-20.1] (33/224)	p < .001	15.0% [9.3-22.4] (19/127)	p < .001	4.3%	5.2%
False-positive rate (N/N)[b]	10.3% [7.3-13.9] (36/351)	p < .001	9.4% [5.9-14.0] (21/224)	p < .001	11.8% [6.8-18.7] (15/127)	p < .001	2.3%	2.7%
PPV CRC and/or AA (N/N)[b]	23.4% [12.3-38.0] (11/47)	p = .10	32.3% [16.7-51.4] (10/31)	p = .58	6.3% [0.2-30.2] (1/16)	p = .02	36.8%	39.7%
Detection rate CRC and/ or AA (N/N)[b]	3.1% [1.6-5.5] (11/351)	p = .03	4.5% [2.2-8.1] (10/224)	p = .02	0.8% [0.0-4.3] (1/127)	p = 1	1.4%	1.8%

p values from two-sided binomial tests for the comparison with the general population. Hemophilia patients were compared with the general male population in the Netherlands.

AA, advanced adenoma; CRC, colorectal cancer; FIT, fecal immunochemical test; GP, general population; PPV, positive predictive value.
[a] All patients include both hemophilia and Von Willebrand disease patients.
[b] Numerator and denominator given for the given parameter.

TABLE 4 Performance of screening program in moderate-severe versus mild hemophilia patients and in hemophilia patients excluding participants from 2014.

	Moderate and severe [95% CI] (N = 146)	Mild [95% CI] (N = 183)	Hemophilia patients[a] [95% CI] (N = 300)
FIT participation rate	60.3% [51.9-68.3]	74.3% [67.4-80.5]	65.0% [59.3-70.4]
Positivity rate	11.4% [5.6-19.9]	16.9% [11.0-24.3]	14.4% [9.8-20.1]
False-positive rate	8.0% [3.3-15.7]	10.3% [5.7-16.7]	9.7% [6.0-14.8]
PPV CRC and/or AA	33.3% [7.5-70.1]	31.8% [13.9-54.9]	26.9% [11.6-47.8]
Detection rate CRC and/or AA	3.4% [0.7-9.6]	5.1% [2.1-10.3]	3.6% [1.5-7.3]

AA, advanced adenoma; CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; PPV, positive predictive value;.

[a] Performance of screening program in patients with hemophilia, excluding participants from 2014.

male population (4.5% vs. 1.8%, respectively, *p* = .02). The age-standardized detection rate was 2.5 times higher in patients with hemophilia compared with the general male population (SMR 2.5, 95% CI [1.2-4.3]).

Table 4 shows the performance of the screening program in moderate to severe hemophilia patients compared to patients with mild hemophilia. Since most patients with severe hemophilia used prophylaxis, we grouped patients with severe and moderate hemophilia together. No relevant differences were observed between these groups.

3.4 | Performance of CRC screening program in patients with VWD

In patients with VWD, the FIT participation rate was slightly higher than that in the general population; however, this difference was not statistically significant (77.4% vs. 71.8%, respectively, *p* = .16) (Table 3 and Supplementary Table S1). The positivity and false-positive FIT rates were both significantly higher in VWD patients than those in the general population (15.0% vs. 4.3%, *p* < .001 and 11.8% vs. 2.3%, *p* < .001, respectively). Moreover, the positive predictive value of FIT for CRC and/or AA in these patients was significantly lower than that in the general population (6.3% vs. 36.8%, respectively, *p* = .02). However, the detection rate in patients with VWD was similar to the general population (0.8% vs. 1.4%, respectively, *p* = 1). In patients with VWD, the SMR could not be calculated because the expected number of AA and CRC was zero.

3.5 | Colonoscopy findings

Abnormalities were found in 29 of 47 patients with a positive FIT result who had a colonoscopy (61.7%, 95% CI [46.4-75.5]). In 31 hemophilia patients, 2 CRC, 8 AA, and 13 nonadvanced adenomas or polyps were found (74.2%, 95% CI [55.4-88.1]), and in 16 patients with VWD, no CRC, 1 AA, and 5 nonadvanced adenomas or polyps were found (37.5%, 95% CI [15.2-64.6]). The percentage of patients with VWD in whom abnormalities during colonoscopy were found was significantly lower than that in the general population (37.5% vs. 72.3%, respectively, *p* = .008), and no difference was found between

patients with hemophilia and the general male population (74.2% vs. 76.4%, respectively, *p* = .83).

3.6 | Use of prophylactic hemostatic treatment and bleeding complications in patients with VWD

The diagnosis of VWD was already established at the time of colonoscopy in all patients with VWD who had a colonoscopy after a positive FIT result. Detailed information of patients with VWD who had a colonoscopy is displayed in Table 5. Four of 16 patients with VWD who had a colonoscopy after a positive FIT result reported a bleeding episode during or after the colonoscopy, of whom one patient had not received periprocedural prophylactic treatment. VWF concentrates were administered in 3 bleeding patients (in one patient combined with TXA), and 2 patients had to be hospitalized (12.5%). In comparison, the bleeding complication rate in the general population, defined as bleeding requiring hospitalization, colonoscopy, or blood transfusion, was 0.39% [34]. Of the patients who experienced a bleeding complication, AA was detected during colonoscopy in one patient, and in 2 patients, nonadvanced adenomas were found. These patients had type 1 (*n* = 1) and type 2 (*n* = 3) VWD.

3.7 | Sensitivity analysis

In total, 29 patients with hemophilia participated in the CRC screening program in 2014. After excluding these patients, we found similar results (Table 4).

4 | DISCUSSION

This first nationwide study on the performance of the CRC screening program in patients with inherited bleeding disorders showed that the FIT positivity and false-positive rates were significantly higher in patients with inherited bleeding disorders compared with the general population. In hemophilia patients, the detection rate of CRC and/or AA was also significantly higher than that in the general male population, and the positive predictive value of FIT for CRC and/or AA was not affected. However, in patients with VWD, the positive predictive value

TABLE 5 Patients with VWD who had a colonoscopy after a positive FIT result.

Age[a]	VWD type	Prophylaxis	Bleeding	Treatment bleeding	Colonoscopy findings
57	1 Vicenza	TXA + CFC	-	n.a.	Nonadvanced adenoma/polyp
57	1	TXA + DDAVP	-	n.a.	-
62	1	-	Yes	Hospitalization	Nonadvanced adenoma/polyp
63	1	TXA + DDAVP	-	n.a.	-
66	2A	CFC	Yes	Hospitalization + CFC	Nonadvanced adenoma/polyp
67	2M	DDAVP	-	n.a.	-
67	1	CFC	-	n.a.	-
68[b]	3	-	-	n.a.	-
70	2B	CFC	-	n.a.	-
70	2A	TXA + CFC	Yes	TXA + CFC	-
73	1	CFC	-	n.a.	-
74	1	-	-	n.a.	Nonadvanced adenoma/polyp
76	2M	CFC	-	n.a.	Nonadvanced adenoma/polyp
77	1	TXA	-	n.a.	-
79	1	CFC	-	n.a.	-
80	2B	CFC	Yes	CFC	Advanced adenoma

CFC, coagulation factor concentrates; DDAVP, 1-deamino-8-D-arginine vasopressin; n.a., not applicable; TXA, tranexamic acid, VWD, Von Willebrand disease.

[a] Age at study inclusion.

[b] This patient could not be prophylactically treated with coagulation factor concentrates because of a history of anaphylaxis; therefore, a computed tomography colonography instead of a colonoscopy was performed after the positive FIT result.

of FIT for CRC and/or AA was significantly lower than that in the general population. Our findings are relevant to a large population of patients with inherited bleeding disorders because most CRC screening programs worldwide are based on FIT [35].

Apart from the bleeding disorder, the use of NSAIDs and anticoagulant therapy in our study population (7.6% and 15% of patients with hemophilia and VWD, respectively) may have contributed to the higher FIT positivity and false-positive rate we found in comparison to the general population. Moreover, although only a minority of our study population was affected by chronic complications related to hepatitis C, such as liver cirrhosis and bleeding from esophageal varices or gastric lesions, these might also have contributed to the higher false-positive rate in patients with hemophilia.

There are several possible contributing factors to the higher detection rate we found in patients with hemophilia. First, a higher bleeding tendency of (pre-)malignant lesions in the colon. Second, hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections have been previously shown to be associated with an increased risk of CRC [36]. In our study, 45% and 3% of patients with hemophilia have been previously infected with HCV and HIV, respectively. However, only 5 patients had an active HCV infection at the time of HiN6 study inclusion. Third, men show a higher detection rate in the general population compared with women [34]. Because all included patients with hemophilia are men, we selected only men in the comparative cohort. The detection rate was still significantly higher in patients with hemophilia than that in the general male population.

Bleeding from gastrointestinal angiodysplasia rather than (pre-)malignant lesions in the colon could explain the lower positive predictive value of FIT observed in patients with VWD. Gastrointestinal angiodysplasia is a vascular abnormality that is frequently observed in patients with VWD and which is associated with gastrointestinal bleeding [15,37]. Bleeding from gastrointestinal angiodysplasia mainly occurs in VWD types that are characterized by loss of high-molecular-weight VWF multimers, such as type 2A, 2B, and 3 VWD [15,17,38,39]. No angiodysplastic lesions were reported by patients with VWD in our study, but earlier studies have shown that these are frequently not found upon colonoscopy [40,41]. Video capsule endoscopy in addition to conventional endoscopy has been shown to be superior in detecting gastrointestinal angiodysplasia than endoscopy alone [41].

Implementation of any national screening program is based on an extensive evaluation of benefits and harms. On one hand, the higher detection rate found in patients with hemophilia could be beneficial because detection and removal of premalignant lesions can reduce mortality and morbidity, with the opportunity for less invasive treatment and lower treatment costs [35]. However, the detection rate among patients with VWD did not differ from the general population. On the other hand, the higher false-positive rate may predispose patients with inherited bleeding disorders to additional harms of the screening program. First, unnecessary colonoscopies are performed in these patients with associated bleeding risks and need for prophylactic treatment. Second, false-positive FIT results are associated with

adverse psychological effects up to 6 weeks after colonoscopy [42]. Since in patients with VWD the positive predictive value was lower than that in the general population, the benefit-to-harm ratio of the CRC screening program seems less favorable in patients with VWD. Moreover, our results indicate that bleeding from other sources may be more prominent in VWD than in hemophilia, and therefore, the balance between a higher bleeding tendency of (pre-) malignant lesions versus bleeding from other sources is less favorable in patients with VWD than that in patients with hemophilia. Future research should focus on whether a higher cutoff value for FIT positivity should be used to optimize the program performance in patients with bleeding disorders, in particular in patients with VWD.

The reported bleeding complication rate was 25% in patients with VWD who had undergone a colonoscopy after a positive FIT result. Bleeding complications in the general population are only reported if they require hospitalization, colonoscopy, or blood transfusion. According to this definition, the bleeding complication rate in VWD patients was 12.5%, which was still higher than observed in the general population. However, the bleeding complication rate in patients with VWD was based on only a small number of observations. Unfortunately, no data on peri- and postprocedural bleeding complications were collected in patients with hemophilia. One retrospective study in 48 patients with an inherited bleeding disorder (of whom 50% had hemophilia and 38% VWD) reported a bleeding rate of 2% and 4.8% postcolonoscopy and postcolonoscopy with polypectomy, respectively [43]. These rates were comparable to the general population. Another retrospective cohort study in patients with bleeding disorders who had undergone a colonoscopy reported a bleeding complication rate of 7.8%, which included both minor and major bleeding complications [44]. Of the included patients, 45% had VWD and 34% had hemophilia. Patients who experienced a bleeding complication either had a severe bleeding disorder, defined as severe hemophilia, type 3 VWD, acquired VWD, dysfibrinogenemia, and platelet function disorders, or had undergone a high risk intervention (excision of moderate-to-large-sized polyps) [44]. However, these 2 studies were not restricted to a CRC screening setting. A meta-analysis of population-based studies found that the post-colonoscopy bleeding rate was significantly higher after colonoscopy with polypectomy than without polypectomy (9.8/1000 colonoscopies vs. 0.6/1000 colonoscopies, respectively) [45]. In our study, 3 of the 4 patients experienced a bleeding complication after the detection of AA or nonadvanced adenoma during colonoscopy. In those cases, the usual treatment is immediate polypectomy [46], which could have contributed to the high bleeding complication rate we observed.

As previously suggested in the literature, CTC after a positive FIT result could be considered as an alternative to colonoscopy in patients with inherited bleeding disorders, since the sensitivity of CTC is comparable to colonoscopy [47,48]. This minimally invasive procedure is less burdensome to patients, does not predispose patients to bleeding complications, and could save the use of expensive coagulation factor concentrates [47]. However, CTC is associated with radiation risk [49]. Colon capsule endoscopy (CCE) is another noninvasive screening modality, which uses a swallowable capsule with a camera [35]. CCE can be used as an alternative to colonoscopy in CRC screening programs [50]. Sensitivity and specificity of CCE for polyps >6 mm range from 79% to 96% and 66% to 97%, respectively [50]. However, a disadvantage of these techniques is that subsequent colonoscopy is needed in case polypectomy is necessary [51]. Further research is needed to evaluate the use of these techniques in a screening setting, in particular for patients with inherited bleeding disorders.

Our findings in patients with hemophilia are similar to studies on the effect of oral anticoagulants and NSAIDs on FIT performance [22]. This meta-analysis showed that the positive predictive value of FIT for CRC and/or AA was not affected [22]. The positivity rate of FIT was only calculated for 2 included studies, which was higher among oral anticoagulants users and patients undergoing dual antiplatelet therapy compared with nonusers [52,53]. In addition, the detection rate was also higher in dual antiplatelet therapy users than that in nonusers [52]. However, no false-positive rates were reported in this meta-analysis.

A limitation of this study is the low overall response rate of patients with hemophilia or VWD to participate in the HiN6 study and WiN-Pro study of 46% and 50%, respectively [23]. Nonparticipants may have a different FIT participation rate compared with participants of these studies, and therefore, a possibility of selection bias cannot be ruled out. However, it is unlikely that participation is related to outcomes of the CRC screening program. In addition, most of the WiN-Pro study data were self-reported by patients, which could lead to information bias. Although some patients may have misunderstood questions about the screening program and therefore might be misclassified, this is likely to be nondifferential. Moreover, patients with a negative FIT had not undergone verification by means of colonoscopy nor did we collect data on interval cancers. Therefore, we were not able to calculate the sensitivity, specificity, and negative predictive value of FIT for CRC and/or AA.

In conclusion, despite higher positivity and false-positive rates of FIT in patients with inherited bleeding disorders compared with the general population, the detection rate of CRC and/or AA in patients with hemophilia is high. In patients with hemophilia, the positive predictive value of FIT for CRC and/or AA is not affected, whereas in patients with VWD, the positive predictive value is lower than that in the general population. Additional studies are needed to evaluate possible adjustment of the CRC screening program for patients with hemophilia and VWD.

AUTHOR CONTRIBUTIONS

This manuscript has been read and approved for submission by all authors. E.K. Kempers collected data, performed statistical analysis, interpreted data, and wrote the manuscript. C.B. van Kwawegen collected data, interpreted data, and critically revised the manuscript. J. de Meris, M.C.W. Spaander., and F.C.J.I. Heubel-Moenen critically revised the manuscript. S.E.M. Schols, P. F. Ypma, L.F.D. van Vulpen, M. Coppens, K. Fijnvandraat, K. Meijer, and J. Eikenboom collected data and critically revised the manuscript. S.C. Gouw and J.G. van der Bom designed the study and critically revised the manuscript. F.W.G. Lee-beek designed the study, interpreted data, and critically revised the manuscript. M.J.H.A. Kruip conceived of and designed the study, interpreted data, and critically revised the manuscript.

DECLARATION OF COMPETING INTERESTS

M.C.W.S. received research support from Sysmex, Sentinel, Norgine, and Medtronics. M.C. received grants or research support from Bayer, CSL Behring, Daiichi Sankyo, Novo Nordisk, Roche, and UniQure. He received consulting or lecturing fees from Alexion, Bayer, CSL Behring, Daiichi Sankyo, Novo Nordisk, Sobi, and Viatris. J.G.v.d.B. received an unrestricted research grant from Novo Nordisk and teaching fees from Bayer, all paid to the institution. K.F. received consultancy fees from Sobi, Sanofi, NovoNordisk, and Roche and research funding from CSL Behring, Novo Nordisk, and Sobi. She is a member on an entity's Board of Directors or advisory committee for EAHAD. K.M. reports speaker fees from Alexion, Bayer, and CSL Behring; participation in trial steering committee for Bayer; consulting fees from UniQure; and participation in data monitoring and endpoint adjudication committee for Octapharma. J.E. received research support from CSL Behring. S.C.G. received an unrestricted research grant from Sobi. F.W.G.L. received research support from CSL Behring, Shire/Takeda, Sobi, and UniQure and is consultant for UniQure, CSL, Biomarin, and Shire/Takeda, of which the fees go to the institution. He was a DSMB member for a study by Roche. M.J.H.A.K. received funding for research outside this project from Sobi, a speakers fee from Roche, Sobi, and BMS, all payments were made to the institute. E.K.K., C.B.v.K, J.d.M., S.E.M.S., P.F.Y., F.C.J.I. H.-M., and L.F.D.v.V have no conflict of interest to declare.

REFERENCES

[1] International Agency for Research on Cancer. Global Cancer Observatory. http://gco.iarc.fr/; 2022. [accessed February 21, 2022].

[2] Toes-Zoutendijk E, van Leerdam ME, Dekker E, van Hees F, Penning C, Nagtegaal I, van der Meulen MP, van Vuuren AJ, Kuipers EJ, Bonfrer JMG, Biermann K, Thomeer MGJ, van Veldhuizen H, Kroep S, van Ballegooijen M, Meijer GA, de Koning HJ, Spaander MCW, Lansdorp-Vogelaar I. Dutch National Colorectal Cancer Screening Working Group. Real-time monitoring of results during first year of Dutch colorectal cancer screening program and optimization by altering fecal immunochemical test cut-off levels. Gastroenterology. 2017;152:767–775.e2.

[3] Breekveldt ECH, Lansdorp-Vogelaar I, Toes-Zoutendijk E, Spaander MCW, van Vuuren AJ, van Kemenade FJ, Ramakers CRB, Dekker E, Nagtegaal ID, Krul MF, Kok NFM, Kuhlmann KFD, Vink GR, van Leerdam ME, Elferink MAG. Dutch National Colorectal Cancer Screening Working Group. Colorectal cancer incidence, mortality, tumour characteristics, and treatment before and after introduction of the faecal immunochemical testing-based screening programme in the Netherlands: a population-based study. Lancet Gastroenterol Hepatol. 2022;7:60–8.

[4] The Netherlands Comprehensive Cancer Organisation. National monitoring of the colorectal cancer screening programme in the Netherlands. http://www.rivm.nl/en/national-monitoring-of-colorectal-cancer-screening-programme; 2020. [accessed February 21, 2022].

[5] Kooyker AI, Toes-Zoutendijk E, Opstal-van Winden AWJ, Spaander MCW, Buskermolen M, van Vuuren HJ, Kuipers EJ, van Kemenade FJ, Ramakers C, Thomeer MGJ, Dekker E, Nagtegaal ID, de Koning HJ, van Leerdam ME, Lansdorp-Vogelaar I. The second round of the Dutch colorectal cancer screening program: impact of an increased fecal immunochemical test cut-off level on yield of screening. Int J Cancer. 2020;147:1098–106.

[6] Chiu HM, Chen SL, Yen AM, Chiu SY, Fann JC, Lee YC, Pan SL, Wu MS, Liao CS, Chen HH, Koong SL, Chiou ST. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. Cancer. 2015;121:3221–9.

[7] Giorgi Rossi P, Vicentini M, Sacchettini C, Di Felice E, Caroli S, Ferrari F, Mangone L, Pezzarossi A, Roncaglia F, Campari C, Sassatelli R, Sacchero R, Sereni G, Paterlini L, Zappa M. Impact of screening program on incidence of colorectal cancer: a cohort study in Italy. Am J Gastroenterol. 2015;110:1359–66.

[8] Zorzi M, Fedeli U, Schievano E, Bovo E, Guzzinati S, Baracco S, Fedato C, Saugo M, Dei Tos AP. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. Gut. 2015;64:784–90.

[9] Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood. 1987;69:454–9.

[10] Werner EJ, Broxson EH, Tucker EL, Giroux DS, Shults J, Abshire TC. Prevalence of von Willebrand disease in children: a multiethnic study. J Pediatr. 1993;123:893–8.

[11] Sadler JE, Budde U, Eikenboom JC, Favaloro EJ, Hill FG, Holmberg L, Ingerslev J, Lee CA, Lillicrap D, Mannucci PM, Mazurier C, Meyer D, Nichols WL, Nishino M, Peake IR, Rodeghiero F, Schneppenheim R, Ruggeri ZM, Srivastava A, Montgomery RR, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost. 2006;4:2103–14.

[12] Leebeek FW, Eikenboom JC. Von Willebrand's disease. N Engl J Med. 2016;375:2067–80.

[13] de Wee EM, Sanders YV, Mauser-Bunschoten EP, van der Bom JG, Degenaar-Dujardin ME, Eikenboom J, de Goede-Bolder A, Laros-van Gorkom BA, Meijer K, Hamulyák K, Nijziel MR, Fijnvandraat K, Leebeek FW. WiN study group. Determinants of bleeding phenotype in adult patients with moderate or severe von Willebrand disease. Thromb Haemost. 2012;108:683–92.

[14] Ruggeri ZM. Structure of von Willebrand factor and its function in platelet adhesion and thrombus formation. Best Pract Res Clin Haematol. 2001;14:257–79.

[15] Randi AM, Smith KE, Castaman G. von Willebrand factor regulation of blood vessel formation. Blood. 2018;132:132–40.

[16] Starke RD, Ferraro F, Paschalaki KE, Dryden NH, McKinnon TA, Sutton RE, Payne EM, Haskard DO, Hughes AD, Cutler DF, Laffan MA, Randi AM. Endothelial von Willebrand factor regulates angiogenesis. Blood. 2011;117:1071–80.

[17] Makris M. Gastrointestinal bleeding in von Willebrand disease. Thromb Res. 2006;118(Suppl 1):S13–7.

[18] Castaman G, Federici AB, Tosetto A, La Marca S, Stufano F, Mannucci PM, Rodeghiero F. Different bleeding risk in type 2A and

2M von Willebrand disease: a 2-year prospective study in 107 patients. *J Thromb Haemost*. 2012;10:632–8.

[19] Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12:1935–9. https://doi.org/10.1111/jth.12672

[20] Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. *Lancet*. 2016;388: 187–97.

[21] Mittal R, Spero JA, Lewis JH, Taylor F, Ragni MV, Bontempo FA, Van Thiel DH. Patterns of gastrointestinal hemorrhage in hemophilia. *Gastroenterology*. 1985;88:515–22.

[22] Nieuwenburg SAV, Vuik FER, Kruip MJHA, Kuipers EJ, Spaander MCW. Effect of anticoagulants and NSAIDs on accuracy of faecal immunochemical tests (FITs) in colorectal cancer screening: a systematic review and meta-analysis. *Gut*. 2019;68:866–72.

[23] Versloot O, van Balen EC, Hassan S, Schols SEM, Leebeek FWG, Eikenboom J, Coppens M, van Vulpen LFD, Smit C, Driessens MHE, van der Net J, Gouw SC, Fischer K. Haemophilia in the Netherlands 6 steering committee. Similar sports participation as the general population in Dutch persons with haemophilia; results from a nationwide study. *Haemophilia*. 2021;27:876–85.

[24] Hoefnagels JW, Schrijvers LH, Leebeek FWG, Eikenboom J, Schols SEM, Smit C, Schutgens REG, Gouw SC, Fischer K. Haemophilia in the Netherlands 6 steering committee. Adherence to prophylaxis and its association with activation of self-management and treatment satisfaction. *Haemophilia*. 2021;27:581–90.

[25] Rodeghiero F, Tosetto A, Abshire T, Arnold DM, Coller B, James P, Neunert C, Lillicrap D. ISTH/SSC joint VWF and Perinatal/Pediatric Hemostasis Subcommittees Working Group. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. *J Thromb Haemost*. 2010;8:2063–5.

[26] Hassan S, van Balen EC, Smit C, Mauser-Bunschoten EP, van Vulpen LFD, Eikenboom J, Beckers EAM, Hooimeijer L, Ypma PF, Nieuwenhuizen L, Coppens M, Schols SEM, Leebeek FWG, Driessens MH, Rosendaal FR, van der Bom JG, Gouw SC. Health and treatment outcomes of patients with hemophilia in the Netherlands, 1972–2019. *J Thromb Haemost*. 2021;19:2394–406.

[27] Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B (Methodol)*. 1995;57:289–300.

[28] Vandenbroucke JP. A shortcut method for calculating the 95 per cent confidence interval of the standardized mortality ratio. *Am J Epidemiol*. 1982;115:303–4.

[29] Hassan S, Monahan RC, Mauser-Bunschoten EP, van Vulpen LFD, Eikenboom J, Beckers EAM, Hooimeijer L, Ypma PF, Nieuwenhuizen L, Coppens M, Schols SEM, Leebeek FWG, Smit C, Driessens MH, le Cessie S, van Balen EC, Rosendaal FR, van der Bom JG, Gouw SC. Mortality, life expectancy, and causes of death of persons with hemophilia in the Netherlands 2001–2018. *J Thromb Haemost*. 2021;19:645–53.

[30] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. https://www.R-project.org/; 2020. [accessed April 5, 2022].

[31] Schauberger P., Walker A. (2020). openxlsx: Read, Write and Edit xlsx Files. R package version 4.2.3. https://CRAN.R-project.org/package=openxlsx; [accessed May 23, 2022].

[32] R Core Team. foreign: Read Data Stored by 'Minitab', 'S', 'SAS', 'SPSS', 'Stata', 'Systat', 'Weka', 'dBase', ... R package version 0.8-80. https://CRAN.R-project.org/package=foreign; 2020. [accessed May 23, 2022].

[33] Dorai-Raj S. binom: Binomial Confidence Intervals for Several Parameterizations. R package version 1.1-1.1. https://CRAN.R-project.org/package=binom; 2022. [accessed May 23, 2022].

[34] The Netherlands Comprehensive Cancer Organisation. National monitoring of the colorectal cancer screening programme in the Netherlands. http://www.rivm.nl/en/national-monitoring-of-colorectal-cancer-screening-programme; 2019. [accessed February 21, 2022].

[35] Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, Kuipers EJ. Colorectal cancer screening: a global overview of existing programmes. *Gut*. 2015;64:1637–49.

[36] Darvishian M, Butt ZA, Wong S, Yoshida EM, Khinda J, Otterstatter M, Yu A, Binka M, Rossi C, McKee G, Pearce M, Alvarez M, Wong J, Cook D, Grennan T, Buxton J, Tyndall M, Woods R, Krajden M, Bhatti P, Janjua NZ. Elevated risk of colorectal, liver, and pancreatic cancers among HCV, HBV and/or HIV (co) infected individuals in a population based cohort in Canada. *Ther Adv Med Oncol*. 2021;13:1758835921992987.

[37] Tsagianni A, Comer DM, Yabes JG, Ragni MV. Von Willebrand disease and gastrointestinal bleeding: a national inpatient sample study. *Thromb Res*. 2019;178:119–23.

[38] Fressinaud E, Meyer D. International survey of patients with von Willebrand disease and angiodysplasia. *Thromb Haemost*. 1993;70:546.

[39] Satoh Y, Kita H, Kihira K, Mutoh H, Osawa H, Satoh K, Ido K, Sakata Y, Sugano K. Gastrointestinal angiodysplasia in a patient with type 2 von Willebrand's disease and analysis of exon 28 of the von Willebrand factor gene. *Am J Gastroenterol*. 2004;99:2495–8.

[40] Makris M, Federici AB, Mannucci PM, Bolton-Maggs PHB, Yee TT, Abshire T, Berntorp E. The natural history of occult or angiodysplastic gastrointestinal bleeding in von Willebrand disease. *Haemophilia*. 2015;21:338–42.

[41] Rauch A, Paris C, Repesse Y, Branche J, D'Oiron R, Harroche A, Ternisien C, Castet SM, Lebreton A, Pan-Petesch B, Volot F, Claeyssens S, Chamouni P, Gay V, Berger C, Desprez D, Falaise C, Biron Andreani C, Marichez C, Pradines B, et al. Gastrointestinal bleeding from angiodysplasia in von Willebrand disease: improved diagnosis and outcome prediction using videocapsule on top of conventional endoscopy. *J Thromb Haemost*. 2021;19:380–6.

[42] Denters MJ, Deutekom M, Essink-Bot ML, Bossuyt PM, Fockens P, Dekker E. FIT false-positives in colorectal cancer screening experience psychological distress up to 6 weeks after colonoscopy. *Support Care Cancer*. 2013;21:2809–15.

[43] Tomaszewski M, Bienz M, Kherad O, Restellini S, Laflèche T, Barkun A, Warner M, Bessissow T. Low endoscopy bleeding risk in patients with congenital bleeding disorders. *Haemophilia*. 2019;25:289–95.

[44] Azer SM, Eckerman AL, Rodriguez V, Nichols WL Jr, Ashrani AA, Hook CC, Marshall AL, Pruthi RK. Hemostatic prophylaxis and colonoscopy outcomes for patients with bleeding disorders: a retrospective cohort study and review of the literature. *Haemophilia*. 2020;26:257–68.

[45] Reumkens A, Rondagh EJ, Bakker CM, Winkens B, Masclee AA, Sanduleanu S. Post-colonoscopy complications: a systematic review, time trends, and meta-analysis of population-based studies. *Am J Gastroenterol*. 2016;111:1092–101.

[46] Dekker E, Van Leerdam ME, Hazewinkel Y, Sanduleanu S, Vasen HF, Lansdorp-Vogelaar I, et al. Nederlandse richtlijn coloscopie surveillance. https://www.mdl.nl/files/richlijnen/Richtlijn_Coloscopie_Surveillance_definitief_2013.pdf; [accessed May 26, 2022].

[47] Astermark J, Makris M, Mauser-Bunschoten E, Nemes L, D'Oiron R, Oldenburg J, Ingerslev J. Malignancy in Haemophilia Workshop Group. Malignant disease in the haemophilic population: moving towards a management consensus? *Haemophilia*. 2012;18:664–71.

[48] Pickhardt PJ, Choi JR, Hwang I, Butler JA, Puckett ML, Hildebrandt HA, Wong RK, Nugent PA, Mysliwiec PA, Schindler WR. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med*. 2003;349:2191–200.

[49] Berrington de Gonzalez A, Kim KP, Yee J. CT colonography: perforation rates and potential radiation risks. *Gastrointest Endosc Clin N Am.* 2010;20:279–91.

[50] Vuik FER, Nieuwenburg SAV, Moen S, Spada C, Senore C, Hassan C, Pennazio M, Rondonotti E, Pecere S, Kuipers EJ, Spaander MCW. Colon capsule endoscopy in colorectal cancer screening: a systematic review. *Endoscopy.* 2021;53:815–24.

[51] Spada C, Hassan C, Bellini D, Burling D, Cappello G, Carretero C, Dekker E, Eliakim R, de Haan M, Kaminski MF, Koulaouzidis A, Laghi A, Lefere P, Mang T, Milluzzo SM, Morrin M, McNamara D, Neri E, Pecere S, Pioche M, Plumb A, Rondonotti E, Spaander MC, Taylor S, Fernandez-Urien I, van Hooft JE, Stoker J, Regge D. Imaging alternatives to colonoscopy: CT colonography and colon capsule. European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline—Update 2020. *Endoscopy.* 2020;52:1127–41.

[52] Bujanda L, Lanas Á, Quintero E, Castells A, Sarasqueta C, Cubiella J, Hernandez V, Morillas JD, Perez-Fernández T, Salas D, Andreu M, Carballo F, Bessa X, Cosme A, Jover R, COLONPREV Study Investigators. Effect of aspirin and antiplatelet drugs on the outcome of the fecal immunochemical test. *Mayo Clin Proc.* 2013;88:683–9.

[53] Bujanda L, Sarasqueta C, Lanas Á, Quintero E, Cubiella J, Hernandez V, Morillas JD, Perez-Fernández T, Salas D, Andreu M, Carballo F, Bessa X, Portillo I, Jover R, Balaguer F, Cosme A, Castells A. COLONPREV study investigators. Effect of oral anticoagulants on the outcome of faecal immunochemical test. *Br J Cancer.* 2014;110:1334–7.

SUPPLEMENTARY MATERIAL