FELOLVASÓLAP

Ajánlattevő neve: Frank Diagnosztika Kft.
Ajánlattevő székhelye: 1036 Budapest, Dereglye utca 2.

Kapcsolattartó személy:

Név:	Dr. Csajka Márta
Beosztás:	ügyvezető igazgató
Cím:	1036 Budapest, Dereglye u. 2.
Telefon:	06 1 250-1813
Fax:	06 1 368-5721
e-mail:	frankdiagn@frank-diagn.hu

Reagens neve: OC-Sensor Diana Latex, Buffer, Standard, Control, Sampling bottle

A bírálat során értékelésre kerülő adatok:

Bírálati részszempont	**Megajánlott érték**
Nettó ajánlati ár összesen	22.750.000 Ft
Kalibrációs stabilitás időtartama	28 nap
Minta stabilitás időtartama szobahőmérsékleten	29 nap
Reagens stabilitás nagysága a felbontást követően	29 nap
Mérési tartomány nagysága	50-1000 ng/ml
Nem-negatív (teszt-pozitív) leletek aránya	5,5 %
Érzékenység aránya	95 %
Fajlagosság aránya	97,8 %
Pozitív jósló érték aránya	77,9 %
Analízis sebesség	280 db/óra/készülék

FRANK Diagnosztika Kft.

Dátum Budapest, 2013. augusztus 23.

.....
Dr. Csajka Márta
ügyvezető igazgató

Tartalomjegyzék

-2-

NYILATKOZAT AZ ELEKTRONIKUS FORMÁTUMÚ AJÁNLATRÓL

Alulírott Dr. Csajka Márta, mint a Frank Diagnosztika Kft. 1036 Budapest, Dereglye u. 2. ajánlattevő cégjegyzésre jogosult képviselője az Országos Tisztifőorvosi Hivatal ajánlatkérő által indított, „Immunkémiai székletvér reagens és a szűréshez szükséges egyéb kiegészítők" tárgyú közbeszerzési eljárás során kijelentem, hogy a társaságunk által elektronikus formában is benyújtott ajánlat (jelszó nélkül olvasható, de nem módosítható file) példánya a papír alapú eredeti példánnyal megegyezik.

FRANK Diagnosztika Kft.

Dátum Budapest, 2013. augusztus 23.

.....

Dr. Csajka Márta
ügyvezető igazgató

NYILATKOZAT A KBT. 40. § VONATKOZÁSÁBAN

Alulírott Dr. Csajka Márta, mint a Frank Diagnosztika Kft. 1036 Budapest, Dereglye u. 2. ajánlattevő cégjegyzésre jogosult képviselője az Országos Tisztifőorvosi Hivatal ajánlatkérő által indított, „Immunkémiai székletvér reagens és a szűréshez szükséges egyéb kiegészítők" tárgyú közbeszerzési eljárás során nyilatkozom, hogy a **közbeszerzésnek az alábbi a része(i) teljesítéséhez veszünk igénybe alvállalkozót:**

nincs ilyen, nem kívánunk alvállalkozót igénybe venni a teljesítéshez

A előző pontban megjelölt rész(ek) tekintetében a közbeszerzés értékének 10 %-át meghaladó mértékben igénybe venni kívánt alvállalkozó(k) adatai, valamint a közbeszerzésnek az a százalékos aránya, amelynek teljesítésében a megjelölt alvállalkozók közre fognak működni:

a. Neve: .....
b. Székhelye: .....
c. Postacíme: .....
d. Telefon-, és fax száma: .....
e. Közbeszerzésért felelős személy neve: .....
f. E-mail címe: .....
g. Százalékos arány, amelynek teljesítésében az alvállalkozó(k) közre fog működni:....%
h. A közbeszerzés részei, ahol az ajánlattevő 10% feletti alvállalkozót vesz igénybe:
.....

FRANK Diagnosztika Kft.

Dátum Budapest, 2013. augusztus 23.

.....
Dr. Csajka Márta
ügyvezető igazgató

NYILATKOZAT A KBT. 60. § (3) BEKEZDÉSE VONATKOZÁSÁBAN

Dr. Csajka Márta, mint a Frank Diagnosztika Kft. 1036 Budapest, Dereglye u. 2. ajánlattevő cégjegyzésre jogosult képviselője nyilatkozom, hogy az Országos Tisztifőorvosi Hivatal által az „Immunkémiai székletvér reagens és a szűréshez szükséges egyéb kiegészítők" tárgyban meghirdetett közbeszerzési eljáráson társaságunk részt kíván venni.

Ajánlatunkat az eljárást megindító felhívás és dokumentáció szerint állítottuk össze, és az azokban foglalt feltételeket elfogadjuk.

Ajánlatunk elfogadása esetén a szerződéstervezetben foglaltakat teljes egészében elfogadjuk és a feladatot a szerződéstervezetben foglaltaknak megfelelő módon teljesítjük, a Kbt. 130. §-ban illetve a Ptk.198. § (1) bekezdésben és a szerződés teljesítésére vonatkozó rendelkezéseiben foglaltak tudomásul vétele mellett.

Elfogadjuk ajánlatkérő döntését, miszerint az „összességében legelőnyösebb ajánlat" értékelési szempont alapján választja ki a nyertes ajánlattevőt. Kijelentjük, hogy amennyiben az ajánlatkérő az ajánlatunkat elfogadja, akkor az ajánlattételi felhívásban megjelölt időpontban a szerződés aláírására készek vagyunk. Ajánlati árunkat a szerződés teljesítése során fenntartjuk.

FRANK Diagnosztika Kft.

Dátum Budapest, 2013. augusztus 23.

.....

Dr. Csajka Márta
ügyvezető igazgató

NYILATKOZAT
KKV. VONATKOZÁSÁBAN

Alulírott Dr. Csajka Márta, mint a Frank Diagnosztika Kft. 1036 Budapest, Dereglye u. 2. ajánlattevő cégjegyzésre jogosult képviselője az Országos Tisztifőorvosi Hivatal ajánlatkérő által indított, „Immunkémiai székletvér reagens és a szűréshez szükséges egyéb kiegészítők" tárgyú közbeszerzési eljárás során kijelentem, hogy társaságunk

a.) a kis- és középvállalkozásokról, fejlődésük támogatásáról szóló 2004. évi XXXIV. törvény 3. §-a szerint

mikrovállalkozásnak

kisvállalkozásnak

középvállalkozásnak minősül.

b.) nem tartozik a kis- és középvállalkozásokról, fejlődésük támogatásáról szóló 2004. évi XXXIV. törvény hatálya alá.

Dátum Budapest, 2013. augusztus 23.

FRANK Diagnosztika Kft.

.....

Dr. Csajka Márta
ügyvezető igazgató

NYILATKOZAT
AZ IDEGEN NYELVŰ DOKUMENTUMOK FORDÍTÁSÁNAK MEGFELELŐSÉGÉRŐL

Alulírott Dr. Csajka Márta, mint a Frank Diagnosztika Kft. 1036 Budapest, Dereglye u. 2. ajánlattevő cégjegyzésre jogosult képviselője az Országos Tisztifőorvosi Hivatal ajánlatkérő által indított, „Immunkémiai székletvér reagens és a szűréshez szükséges egyéb kiegészítők" tárgyú közbeszerzési eljárás során kijelentem, hogy az általunk csatolt idegen nyelvű dokumentumok magyar nyelvű fordítása az idegen nyelvű dokumentumok tartalmával megegyezik, ezért felelősséget vállalunk.

FRANK Diagnosztika Kft.

Dátum Budapest, 2013. augusztus 23.

.....

Dr. Csajka Márta
ügyvezető igazgató

ALÁÍRÁSI CÍMPÉLDÁNY

Alulírott ***DR. CSAJKA MÁRTA*** (született: Budapest, 1959. évi március hó 06. napján, anyja neve: Czakó Irén Márta) 1037 Budapest, Remetehegyi út 109. szám alatti lakos, mint a **FRANK Diagnosztika Korlátolt Felelősségű Társaság** (rövidített elnevezése: FRANK Diagnosztika Kft, székhelye: 1036 Budapest, Dereglye utca 2.) **vezető tisztségviselője**, a társaságot akként jegyzem, hogy a társaság kézzel vagy géppel előírt, előnyomott vagy nyomtatott cégneve alá a nevemet ***önállóan*** az alábbiak szerint írom:

.....
Dr. Csajka Márta

dr. Barbalics Miklós közjegyző
1036 Budapest, Árpád fejedelem útja 53/A. I./5.
Tel./Fax: 06 (1) 368-8305 email: barbalics@mokk.hu

Ügyszám: 11071/H/1625/2011.

Alulírott ***közjegyzőhelyettes*** tanúsítom, hogy ezt a fenti aláírási címpéldányt ***DR. CSAJKA MÁRTA*** (született: Budapest, 1959. évi március hó 06. napján, anyja neve: Czakó Irén Márta), 1037 Budapest, Remetehegyi út 109. szám alatti lakos, aki személyazonosságát a felmutatott 278865EA számú személyazonosító igazolványával, lakcímét a 745587 HL számú lakcímet igazoló hatósági igazolványával igazolta, a mai napon előttem sajátkezűleg írta alá.----------

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Az Ügyfél tudomásul vette a közjegyzőhelyettes tájékoztatását a közjegyzőkről szóló 1991. évi XLI. törvény 122. § (2)-(10) bekezdéseiben foglaltakról, vagyis a személyazonosság on-line ellenőrzésére vonatkozó rendelkezésekről.----------

---

Kelt Budapesten, 2011. (kettőezer-tizenegyedik) év április hónap 14. (tizennegyedik) napján. -

---

dr. Barbalics Miklós KÖZJEGYZŐ 5. BUDAPEST III.4.

dr. Graf Tamás
közjegyzőhelyettes

NYILATKOZAT
A SZÁMLÁT VEZETŐ PÉNZÜGYI INTÉZMÉNYEK VONATKOZÁSÁBAN

Alulírott Dr. Csajka Márta, mint a Frank Diagnosztika Kft. 1036 Budapest, Dereglye u. 2. ajánlattevő cégjegyzésre jogosult képviselője az Országos Tisztifőorvosi Hivatal ajánlatkérő által indított, „Immunkémiai székletvér reagens és a szűréshez szükséges egyéb kiegészítők" tárgyú közbeszerzési eljárás során kijelentem, hogy társaságunk pénzforgalmi számláit a következő pénzügyi intézmények vezetik illetve, a megnevezetteken kívül más pénzügyi intézmény nem vezet részükre pénzforgalmi számlát:

1.
Pénzintézet neve: Budapest Bank Nyrt
Bankszámla szám: 10102103-05233504-00000000

2.
Pénzintézet neve: Budapest Bank Nyrt
Bankszámla szám: 10102103-05233500-01002308

3.
Pénzintézet neve: Erste Bank Nyrt
Bankszámla szám: 11996231-06127024-10000001

Dátum Budapest, 2013. augusztus 23.

FRANK Diagnosztika Kft.

.....

Dr. Csajka Márta
ügyvezető igazgató

BUDAPEST BANK BUSINESS

A GE Capital tagja

Frank Diagnosztika Kft.
Budapest
Dereglye u. 2.
1036

cjkv. sz.: 0370/2013.
ügyintéző: Fehér Zsuzsanna

Tárgy: Bankinformáció

Az információt adja:	**Budapest Bank Zrt.**
Gazdálkodó szervezet neve:	**Frank Diagnosztika Kft.**
Számlaszám:	**10102103-05233500-01002308 EUR**
	10102103-05233504-00000000 HUF

A Frank Diagnosztika Kft. (1036 Budapest, Dereglye u. 2.) 10102103-05233500-01002308 számú EUR számláját 2008. december 10-től és 10102103-05233504-00000000 számú elszámolási számláját 1994. december 07-től vezetjük a Budapest Bank Zrt. Óbudai Fiókjában.

A Frank Diagnosztika Kft. számláin az ajánlati felhívás feladásától (2013.07.31.) visszaszámított 2 évben nem fordult elő, hogy a pénzforgalmi számlái terhére benyújtott azonnali beszedési megbízás* fedezet hiánya miatt nem volt teljesíthető.

A nyilatkozat a kiadás időpontjában Bank által ismert állapotot tükrözi és nem jelent kötelezettséget vagy felelősségvállalást a Budapest Bank Zrt. részéről.

Kelt: Budapest, 2013. év augusztus hó 07. napján

Tisztelettel:

BUDAPEST BANK Zrt.

Budapest Bank Zrt.

Klemencsics Katinka
Kiemelt Ügyfélkapcsolati Menedzser

Ipacs Bernadett
Kiemelt Ügyfélkapcsolati Menedzser

*18/2009. (VIII.6.) MNB rendelet szerinti átutalási végzés, hatósági átutalási megbízás és felhatalmazó levélen alapuló beszedési megbízás.

ERSTE BANK HUNGARY ZRT.

H-1138 Budapest, Népfürdő u. 24-26.
Cégjegyzékszám: 01-10-041054
Telefon: 06-40-222-223

Iktató szám:2436/2013

FRANK Diagnosztika Kft.
Dr Csajka Márta ügyvezető részére
1036 Budapest, Dereglye utca 2.

Tárgy: **Bankinformáció a FRANK Diagnosztika Kft.-ről**

Alulírottak, az ERSTE BANK Hungary Zrt. (H-1138 Budapest, Népfürdő u. 24-26.; cégjegyzékszám: 01-10-041054, KSH szám: 10197879-6419-114-01, adószám: 10197879-4-44, csoportazonosító szám: 17781042-5-44, csoport közösségi adószám: HU17781042) képviseletében igazoljuk, hogy Ügyfelünk, a **FRANK Diagnosztika Kft.** (székhely: 1036 Budapest, Dereglye utca 2., cégjegyzékszám: 01-09-070792) az alábbiakban részletezett pénzforgalmi bankszámlát vezeti Bankunknál:

Bankszámla száma	Bankszámla devizaneme	Számlanyitás napja
11996231-06127024-10000001	HUF	2000.06.15.

A **FRANK Diagnosztika Kft.**-vel 2000.06.15. napja óta állunk üzleti kapcsolatban.

- Számláján az ajánlati felhívás feladásától (2013.07.31) visszaszámított 2 évben, azonnali beszedési megbízás fedezet hiánya miatti visszautasítás nem fordult elő, és jelen igazolás kiadásának időpontjában sem mutatkozik.

Jelen bankinformációt, minden kötelezettségvállalás nélkül, az ügyfél kérésére 1, azaz egy eredeti példányban adtuk ki.

Budapest, 2013. augusztus 06.

Tisztelettel,

ERSTE BANK HUNGARY Zrt.
1138 Budapest, Népfürdő u. 24-26.
100.

.....

György László Károlyné
Vezető ügyfélmenedzser

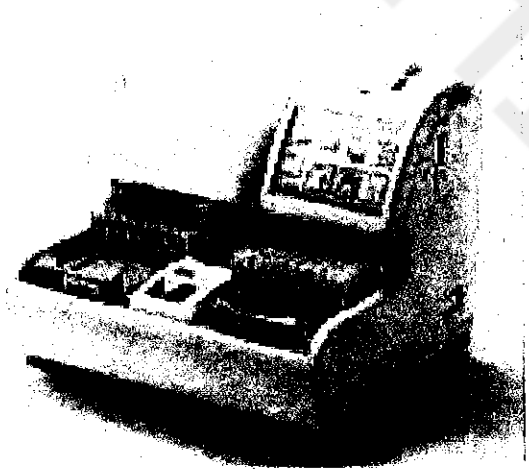
.....

Rohonyné Kovács Mónika Zsófia
Vezető ügyfélmenedzser

ERSTE BANK HUNGARY ZRT.

Technikai specifikáció

OC Sensor Diana



Technikai adatok

Kapacitás: 280 minta/óra

Működési elve: latex agglutinációs immun-turbidimetria

Mintatartó: 150 minta (10 mintatartó állvány x 15)

Reakció küvetta: többször használható, eldobható akril küvetta, tisztítása automatikusan történik

Mintavevő rendszer: automatikus

Reagens felszívás: automatikus

Hőmérséklet szabályzó rendszer: blokk melegítő 37°C

Reagens tároló: blokk melegítő 25°C

Fényforrás: LED 660 nm

Detektor: fotodióda

Adatbevitel: érintőképernyő, színes LCD

Adat kinyerés, továbbítás: Hőnyomtató, RS323C, USB

Interfész kapcsolat pl. LIMS rendszerhez

Memória: 100.000 teszt eredmény tárolására alkalmas

STAT funkció

Méret: 630mm x 560 mm x 560 mm

Súly: 60 kg

Alkalmazás: CE, IVD

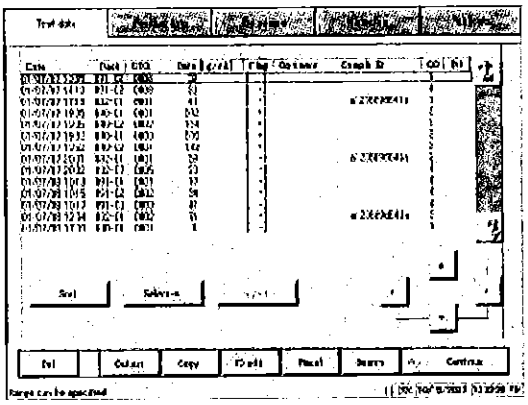
Analitikai és egyéb teljesítmény mutatók

A folyamat teljesen automatizált: A mintavevő üvegeket a készülék automatikusan feldolgozza, a nincs szükség a minta bármiféle kezelésére, hígítására. A mintavevőket a készülék tartókeretébe kell helyezni. A készülék beszkenneli a vonalkódot és elmenti a kvantitatív eredményt. (Lásd a csatolt brosúrát)

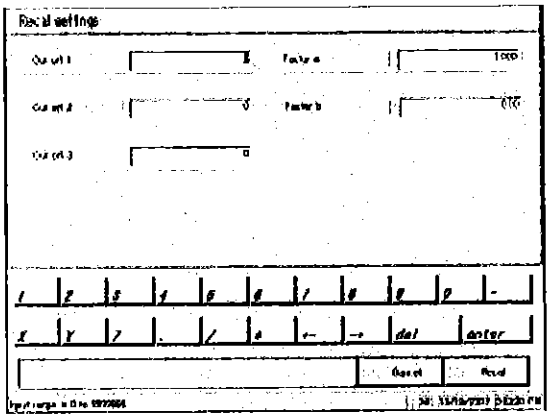
Mérési tartomány: Az OC Sensor Diana készülék 50-1000 ng/ml tartományban képes kvantitatív eredményt adni. (Lásd a csatolt gyártói nyilatkozatot) Ha a humán hemoglobin koncentráció kisebb, mint 50 ng/ml a CV érték emelkedik. 1000 ng/ml koncentráció felett a készülék a mintát továbbhígítja. (Lásd a csatolt gyártói nyilatkozatot)

Analízis sebessége: 280 minta/óra (Lásd a csatolt brosúrát)

A készülékkel végzett mérések kvantitatív eredményt adnak: a vizsgálat eredményét a készülék ng/ml-ben mutatja, illetve a téves leolvasás elkerülése érdekében (+), vagy (-) jelet tesz a kijelzett érték mellé. (Lásd a csatolt brosúrát)



Cut-off: 50 ng/ml, vagy magasabb, egyszerre 3 különböző érték beállítására van lehetőség a minta vizsgálata előtt, vagy után (Lásd a csatolt brosúrát, illetve publikációt)

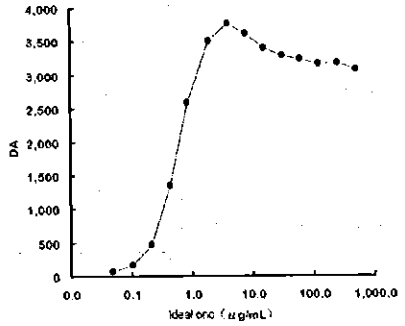


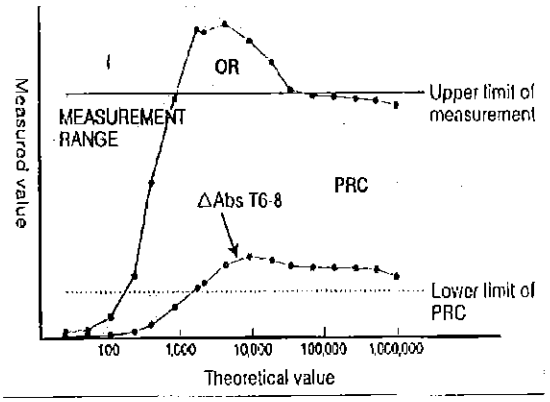
Prozon hatás: Ha a minta HbA0 koncentrációja meghaladja az 1000 ng/ml-t, a készülék jelzést küld a felhasználó számára („overread or prozone effect"), majd a mintát továbbhígítja és a tényleges eredményt mutatja. A készülék nagyon pontosan jelzi a prozon hatást, kettős ellenőrző rendszere folyamatosan vizsgálja minden egyes minta minőségét. (Lásd a csatolt brosúrát és az alábbi ábrát)

1. OR (Over Range) A készülék „OR" jelzést ad, ha a minta abszorbancia értéke nagyobb, mint a kalibrátoré (6)
2. PRC: A készülék „PRC" jelzést ad, ha a minta abszorbancia értéke nagyobb, mint a kalibrátoré és a koncentráció kisebb, mint 1000 ng/ml

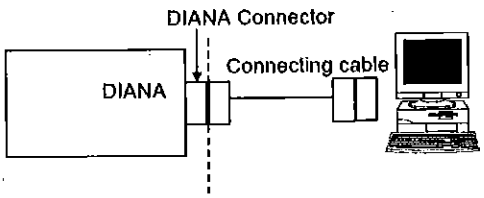
Excess antigen- Prozone

Ideal conc (ng/mL)	OS	measured (ng/mL)	PRC Flag
0	-7	0	
49	68	49	
103	170	103	
211	473	211	
442	1346	442	
831	2686	831	
1,953	3409		OR
3,906	3763		OR
7,813	3612		OR
16,625	3390		OR
31,250	3292		OR
62,500	3224		OR
125,000	3163		OR
250,000	3171		OR
500,000	3078		OR





Kórházi informatikai hálózatba köthető: Interfész kapcsolat pl. LIMS rendszerhez



Biztosított a standard laboratóriumi belső és külső minőségbiztosítási eljárás alkalmazhatósága:
Az OC Sensor platform rugalmas rendszer, mely lehetővé teszi a külső minőségbiztosítási eljárásokban való részvételt. A gyártó maga is koordinál ilyen jellegű vizsgálatsorozatokat, mely során minden felhasználó számára párhuzamosan vak mintákat küldenek, mellyel a készülék pontosságát-pontatlanságát ellenőrzik. Az OC- Sensor felhasználók számára az Eiken által szervezett programban, jelenleg több, mint 800 labor vesz részt.

Garancia, karbantartás: A szerződés időtartama alatt a készülékre teljes körű garanciát vállalunk kivéve a készülék és a reagensek nem megfelelő használatából adódó hibákat és az ebből adódó javításhoz szükséges alkatrészeket.
A készülék nem igényel szerviz által történő rendszeres karbantartást.

Diagnosztikai teljesítőképesség

A következő adatok randomizált kontrollált népességszűrési vizsgálatok eredményein alapulnak. Hollandiában 20.623 50-75 éves egyén szűrését végezték el 2006-2007-ben. Két teszt összehasonlítására került sor: gFOBT (Hemoccult-II) és iFOBT (OC Sensor), a pozitív FOBT-ket kolonoszkópiával erősítették meg.
A mérés 100 ng HB/ml cut-off értékkel történt.

Pozitív jósló érték aránya (PPV) polip és rák esetében: 77,9%
Nem-negatív (teszt-pozitív) leletek aránya: 5,5%
Fajlagosság aránya rák és előrehaladott adenóma esetében: 97,8%

Publikáció: (Csatolva)

Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population
van Rossum LG, van Rijn AF, et al.
Gastroenterology 2008; 135: 82-90
Impakt faktor: 13,44

A következő két, a rendszer teljesítőképességét igazoló indikátor a pozitív esetek vizsgálata során született publikációval támasztható alá.

Érzékenység aránya rák esetében: 95,0%
(Cut-off: 50 ng/ml, két mérés páciensenként)

Publikáció: (Csatolva)

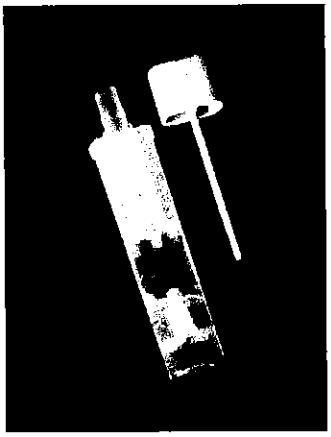
Cumulative evaluation of a quantitative immunochemical fecal occult blood test to determine its optimal clinical use.
Rozen P, Comaneshter D, et al.
Cancer 2010; 116: 2115-2125
Impakt faktor: 4,8

ROC görbe, Cut-off érték
(Páciensenként egy, kettő, vagy három vizsgálat)

Publikáció: (Csatolva)

A quantitative immunochemical fecal occult blood test for colorectal neoplasia.
Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E, Birkenfeld S,
Leshno M, Niv Y.
Annals of Internal Medicine 2007 Feb 20;146(4):244-55. 4. ábra
Impakt faktor 16,2

Mintavevő:



Könnyen kezelhető mind a páciensek, mind a laboratóriumi személyzet számára
Higiénikus, pontos mintavételt tesz lehetővé, a laboratóriumi személyzetnek nem kell érintkeznie a mintával; a minta feldolgozása automatikus
Rendelkezik magyar nyelvű használati útmutatóval (Lásd a mellékelt használati útmutatót)
Lehetővé teszi 2 minta/páciens gyűjtését
Alkalmas postai továbbításra, alakja lapos, nagy sűrűségű polipropilénből készül, mely megfelel az UN 3373 Diagnosztikai minták szállítására vonatkozó szabványnak
A mintavevő szűrőrendszere megakadályozza, hogy a készülék a minta feldolgozása során eltömődjön.
A stabilizáló puffer lehetővé teszi, hogy a minta szállítása során, szobahőmérsékleten 85%-os hemoglobin stabilitás, illetve 2-10°C-on hűtőben tárolva 97%-os hemoglobin stabilitás mellett 29 nap múlva is pontos mérési eredményt kapjunk.

Lejárati ideje: gyártástól számított 18 hónap
Státusz: CE, IVD (Lásd a csatolt Megfelelőségi nyilatkozatot)

Reagensek:

Latex reagens: felbontás után a készülékben tárolva szobahőmérsékleten 29 napig stabil
Puffer: felbontás után 2-10°C-on 8 hétig stabil
Kontrol: a készülékben tárolva 28 napig stabil
A reagensek gyártástól számított lejárati ideje 12 hónap.
Vonalkóddal ellátottak a könnyebb beazonosíthatóságért
A reagensek validáltak a készülékre.
Státusz: CE, IVD (Lásd a csatolt Megfelelőségi nyilatkozatot)

NYILATKOZAT
FOLYÓIRATOKRÓL

Alulírott Dr. Csajka Márta, mint a Frank Diagnosztika Kft., 1036 Budapest Dereglye utca 2. ajánlattevő cégjegyzésre jogosult képviselője az Országos Tisztifőorvosi Hivatal ajánlatkérő által indított, „Immunkémiai székletvér reagens és a szűréshez szükséges egyéb kiegészítők" tárgyú közbeszerzési eljárás során kijelentem, hogy társaságunk ajánlatában a következő folyóiratokat jelölte meg a bírálati résszempontok igazolására.

Érzékenység aránya vonatkozásában:
Cumulative evaluation of a quantitative immunochemical fecal occult blood test to determine its optimal clinical use.
Rozen P, Comaneshter D, et al.
Cancer 2010; 116: 2115-2125
Impakt faktor: 4,8

Nem-negatív leletek aránya, Fajlagosság aránya, Pozitív jósló érték aránya vonatkozásában:
Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population
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Gastroenterology 2008; 135: 82-90
Impakt faktor: 13,44

ROC görbe vonatkozásában:
A quantitative immunochemical fecal occult blood test for colorectal neoplasia. Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E, Birkenfeld S, Leshno M, Niv Y.
Annals of Internal Medicine 2007 Feb 20;146(4):244-55. 4. ábra
Impakt faktor 16,2

Budapest, 2013.augusztus 23.

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Dr. Csajka Márta
ügyvezető igazgató

Original Article

Cumulative Evaluation of a Quantitative Immunochemical Fecal Occult Blood Test to Determine Its Optimal Clinical Use

Paul Rozen, MB, BS[1,2]; Doron Comaneshter, MSc[3]; Zohar Levi, MD[1]; Rachel Hazazi, MSc[1]; Alex Vilkin, MD[1]; Eran Maoz, MD[4]; Shlomo Birkenfeld, MD[4]; and Yaron Niv, MD[1,2]

BACKGROUND: Quantified, human hemoglobin (Hb)-specific, immunochemical fecal occult blood test (IFOBT) measurements are now used for colorectal cancer (CRC) screening. The objective was to evaluate sensitivity and specificity for CRC and advanced adenomatous polyps (APs) by the fecal Hb threshold used to determine a positive test and the number of IFOBTs prepared per test, so as to determine the least number of colonoscopies required to detect a neoplasm. **METHODS:** Cumulative data were analyzed from a prospective cross-sectional double-blind study of 1682 consecutive, ambulatory, nonbleeding colonoscopy patients who volunteered for IFOBTs, most of above average risk, from 3 ambulatory-endoscopy centers. Fecal Hb was measured in 3 samples and analyzed by an automated instrument, and the highest result ≥50 ng Hb/mL of buffer was related to findings. **RESULTS:** Colonoscopy identified CRC in 20 patients and advanced APs in 129. Sensitivity for either was best when any of 3 tests had ≥50 ng Hb/mL of buffer; sensitivity was 61.1% (95% confidence interval [CI], 53.2-68.9), and specificity was 87.8% (95% CI, 86.2-89.4). Positive tests identified 100% of CRCs and 55% of advanced APs every 3.1 colonoscopies. Sensitivity of a single test at the commonly used 100-ng Hb/mL threshold was lower at 31.5% (95% CI, 24.1-39.0) ($P<.001$), but specificity was higher at 96.4% (95% CI, 95.5-97.3) ($P<.001$). Positive tests identified 65% of CRCs and 26.4% of advanced APs every 2.2 colonoscopies. **CONCLUSIONS:** The fecal Hb cutoff chosen by the screener and the number of samples collected per patient determine sensitivity and specificity for CRC/advanced AP; these factors determine the number of colonoscopies needed for positive tests and neoplasia yield. This information provides guidelines for IFOBT screening. Limitations are 1-time screening and most examinees not being at average risk for CRC. *Cancer* 2010;000:000-000. © *2010 American Cancer Society.*

KEYWORDS: adenoma, colorectal cancer, fecal occult blood, immunochemical fecal occult blood test, predictive values, sensitivity, specificity.

We have completed a colonoscopy evaluation of an automated-developed quantified immunochemical fecal occult blood test (IFOBT) specific for human hemoglobin (Hb). The aim was to learn its performance characteristics and suitability to replace our standard guaiac screening test (guaiac FOBT).[1]

The primary aim of screening is detection of asymptomatic colorectal cancer (CRC).[2] A secondary aim is identification and removal of advanced adenomatous polyps (APs), namely those ≥1 cm or with ≥20% villous component or any high-grade dysplasia.[2,3]

With increasing use of office-developed qualitative or quantified IFOBTs, there is no uniformity in choosing the fecal Hb threshold determining a positive test for CRC and/or advanced AP or the number of IFOBTs to prepare.[4-15] These will influence screenees' compliance, quality of test performance, need for endoscopy, and costs.[15]

Because of dissatisfaction with guaiac FOBTs, there is demand for 1-stop colonoscopy screening that is both diagnostic and, if necessary, therapeutic by removing adenomas. Therefore, an optimal noninvasive screening test should be

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sensitive for CRC and for as many advanced APs as possible, so as to maximize the yield from colonoscopy performed for positive tests and minimize unnecessary, costly examinations occasionally associated with morbidity.[16]

During our evaluation of the quantified IFOBT, we published a report of our experience on its stability and reproducibility under laboratory conditions, a clinical comparison with guaiac FOBT, sensitivity and specificity for adenomas, and an evaluation and description of advantages of Hb quantification.[1,17-20] Study completion allows for cumulative analyses of results, increasing the study population size, and providing more detailed performance details. Present aims were to: 1) confirm the stability of test samples in the clinical setting; 2) evaluate the sensitivity and specificity for CRC or advanced AP over a range of fecal Hb development thresholds to determine a positive test and the number of IFOBTs collected; 3) examine the number of follow-up colonoscopies needed for positive tests to identify CRC, CRC or advanced AP, and advanced AP; and 4) provide information to our screening program on thresholds to use and the number of IFOBTs to prepare, so as to estimate consequent demands for colonoscopy.

MATERIALS AND METHODS

A prospective, cross-sectional, double-blind study was conducted on colonoscopy patients from 3 endoscopy centers. Details have been given in full elsewhere.[20]

Patients

Subjects included consecutive asymptomatic ambulatory persons invited for elective screening or follow-up colonoscopy, patients from our high-risk family clinic, or mildly symptomatic patients who volunteered for the IFOBT study. They included the initial 1000 patients analyzed for technical evaluation of IFOBT methodology, sensitivity, and specificity for cancer and/or advanced APs.[20]

Exclusion criteria included hospitalization, visible rectal bleeding, known CRC or advanced AP, known or subsequent diagnosis of inflammatory bowel disease, hematuria, menstruation, lack of comprehension or cooperation in preparing a fecal test, and incomplete colonoscopy examination.[20]

Endoscopy and Lesions

Colonoscopy was to the cecum or obstructing carcinoma if present. Lesions were biopsied and/or removed; numbers of polyps and their sites were grouped as being in proximal (cecum to and including splenic flexure) or distal large bowel. Polyp size was estimated with open biopsy forceps of known width and described as pedunculated or sessile. Adenomas were grouped by histology and dysplasia; advanced APs <10 mm were re-examined by a single gastrointestinal pathologist to confirm the diagnosis.

Fecal Sampling and FOBT Analysis

Participants received instructions on preparing 3 consecutive IFOBTs the week before colonoscopy without diet or medication limitations other than stopping aspirin and anticoagulants before endoscopy.[21] Samples were stored at 4°C and developed within 3 weeks.[17,18]

The OC-MICRO instrument (Eiken, Tokyo, Japan) was used to process and quantify the IFOBT. Each result was automatically printed as nanograms Hb per milliliter of buffer.[17,18,20] Hb levels <50 ng/mL are regarded as negative. Technical publications translated from the Japanese are available.[17]

The ethics committee of the Rabin Medical Center approved the study in 2004.

Analyses and Statistical Methods

Patients were classified according to their most advanced disease, CRC or only advanced AP. Analysis was per patient; the highest amount of fecal Hb measured in patients' IFOBTs was related to their most advanced neoplasm.[19,20]

Fecal Hb level was analyzed as dichotomous parameters from 50 to 200 ng Hb/mL of buffer at 25-ng Hb/mL increments. Receiver operator characteristic (ROC) curves were drawn to best determine fecal Hb cutoff levels that discriminated between diagnoses. Comparison of areas under ROC curves (AUC) (first IFOBT, higher of first 2 IFOBTs, and all 3 IFOBTs) were by Mann-Whitney nonparametric test.

Diagnostic power of IFOBT measurements was evaluated by sensitivity, specificity, positive and negative predictive values, and likelihood ratios, accompanied by 95% confidence intervals. Cochran nonparametric test for repeated dichotomous variables was used to examine overall differences between IFOBTs at each threshold. Multiple comparisons of sensitivity and specificity at 25-ng Hb/mL increments between number of IFOBTs (first vs higher of first 2 vs all 3) were by the McNemar test, and the significance level was corrected for multiple testing by Sidak's method. Positive predictive values were used to determine the number of colonoscopy examinations

resulting from a positive test to identify a CRC, or CRC or advanced AP.

Statistical Package for Social Sciences (SPSS Inc., Chicago, Ill) for Windows, version 14.0, and StAR software (http://protein.bio.puc.cl/star.html) were used to compare between ROC AUCs.

RESULTS

Patients

After exclusions, 6.3% of patients scheduled for colonoscopy and fulfilling study criteria refused to participate in the IFOBT study, and a further 22.2% did not return or correctly prepare the tests; data from 1682 ambulatory examinees was analyzed. They were either asymptomatic but at increased risk for colorectal neoplasms (77%), or having symptoms investigated but without rectal bleeding. Their mean age was 63.7 ± 11.88 years, and 50.4% were men.

Colonoscopy Results

Colonoscopy identified cancer in 20 examinees; 12 (60%) were sited in the proximal colon, 10 were stage 1, 6 were stage 2, 1 was stage 4, and 3 were unknown. Adenomas occurred in 329 patients without CRC, 129 having advanced AP. Together, 149 had CRC or advanced AP.

Fecal Hb Measurements in Patients With or Without CRC or Advanced AP

ROC analyses

ROC analyses were generated for CRC, CRC or advanced AP, or only advanced AP, using results of the first IFOBT collected, the highest of the first 2, or all 3 IFOBTs, and their AUCs were compared (Table 1). The highest AUC was for CRC and the higher of 2 IFOBTs as compared with 1 test ($P = .067$); the AUC for CRC or advanced AP or only advanced AP was insignificantly higher with the highest of 3 tests.

By using ROC analysis, we determined the fecal Hb measurement of the first, first 2, or all 3 IFOBTs collected that gave the highest sensitivity and its associated specificity and likelihood ratios for CRC, CRC or advanced AP, and advanced AP (Table 2). The highest sensitivities were obtained at the lowest threshold analyzed (≥50 ng Hb/mL) and by using the highest result in any of 3 tests; however, this was associated with the lowest specificity and likelihood-positive ratios.

We also determined the fecal Hb values that provided 95% specificity and the associated sensitivity and likelihood ratios for CRC, CRC or advanced AP, and advanced AP. The fecal Hb needed was least with the first IFOBT, but was associated with the lowest sensitivity and likelihood-positive ratio. The highest sensitivity was obtained by using fecal levels of >185 (for advanced AP and CRC or advanced AP) and 350 (for CRC) ng Hb/mL buffer (Table 2).

Positivity results

At each development threshold, positivity rates of first, second, and third IFOBTs were not significantly different (Cochran test) (Table 3). At each threshold, cumulative positivity, which would lead to colonoscopy, increased as more tests were examined and decreased as the analytic thresholds for fecal Hb were raised.

Sensitivity, specificity, and likelihood ratios for CRC, CRC or advanced AP, or advanced AP

Analyses at each fecal Hb threshold and for each patient's highest IFOBT measurement are given in Table 4. Overall, sensitivity for CRC, CRC or advanced AP, or advanced AP increased significantly at each threshold as more tests were analyzed (Cochran test, $P<.001$); for CRC the increase ranged from $P<.001$ at the highest threshold to $P = .015$ at the lowest. Sensitivity of the first IFOBT was less than that of the highest of the first 2 or all 3 tests at that threshold, and at higher thresholds. Conversely, specificity was higher with the least number of

Table 1. AUCs Derived From ROC Curves for Patients Having Cancer, Cancer or Advanced Adenoma, or Only Advanced Adenoma, Using the First or the Highest of 2 or 3 IFOBTs Measured

Diagnosis	No. of Patients	AUC, First IFOBT (95% CI)	AUC, Higher of First 2 IFOBTs (95% CI)	*P* for 1 vs 2 Tests	AUC, Highest of 3 IFOBTs (95% CI)	*P* for 2 vs 3 Tests
Cancer	20	0.892 (0.809-0.974)	0.957 (0.935-0.978)	.067	0.959 (0.941-0.977)	.444
Cancer or advanced adenoma	149	0.758 (0.711-0.805)	0.781 (0.736-0.825)	.245	0.793 (0.750-0.836)	.353
Advanced adenoma	129	0.735 (0.684-0.787)	0.751 (0.702-0.800)	.329	0.765 (0.717-0.813)	.343

AUC indicates area under the curve; ROC, receiver operator characteristic; IFOBT, immunochemical fecal occult blood test; CI, confidence interval.

Table 2. Fecal Hb Measurements (Left Column) Derived From ROC Analyses for First, Highest of First 2, or All 3 IFOBTs to Obtain the Highest Sensitivity and Associated Specificity and Positive and Negative Likelihood Ratios, for Cancer, Cancer or Advanced Adenoma, or Advanced Adenoma or to Obtain 95% Specificity and Its Associated Sensitivity and Likelihood Ratios

Diagnosis/IFOBT, ng Hb/mL Buffer	First IFOBT				Higher of 2 IFOBTs				Highest of 3 IFOBTs			
	Sensitivity, %	Specificity, %	Positive LR	Negative LR	Sensitivity, %	Specificity, %	Positive LR	Negative LR	Sensitivity, %	Specificity, %	Positive LR	Negative LR
Cancer for highest sensitivity												
64.5 ng	75	92.3	9.73	0.27								
56 ng					95	88.4	8.18	0.06				
56.5 ng									100	85.7	7.01	0.00
Cancer for 95% specificity												
116 ng	60	95	12.0	0.42								
248 ng					65	95	13.02	0.37				
350 ng									70	95	14.02	0.32
AAP or CRC for highest sensitivity												
60 ng	41.6	94.1	7.08	0.62								
51.5 ng					55	90.5	5.78	0.50				
54.5 ng									61.6	88.7	5.41	0.44
AAP or CRC for 95% specificity												
68.5 ng	38.3	95	7.61	0.65								
120.5 ng					38.3	95	7.72	0.65				
189 ng									43.6	95	8.80	0.59
AAP[a] for highest sensitivity												
51 ng	36.4	93.4	5.53	0.68								
50.5 ng					48.8	90.4	5.09	0.57				
50.5 ng									55.0	88.0	4.59	0.51
AAP for 95% specificity												
68.5 ng	33.3	95	6.63	0.70								
118 ng					32.6	95	6.48	0.71				
185 ng									38.0	95	7.56	0.65

Hb indicates hemoglobin; ROC, receiver operator characteristic; IFOBT, immunochemical fecal occult blood test; LR, likelihood ratio; AAP, advanced adenomatous polyp; CRC, colorectal cancer.
[a]Values calculated from the level of ≥50 ng of fecal Hb.

Table 3. IFOBT Positivity for Each Test Prepared Over a Range of Thresholds, Analyzed Within 3 Weeks

Threshold, ng Hb/mL Buffer	First IFOBT, %	Second IFOBT, %	Third IFOBT, %	*P*
50 ng Hb/mL	9.74	9.49	8.76	.368
Cumulative positivity		13.79	16.53	
75 ng Hb/mL	7.59	7.53	7.53	.994
Cumulative positivity		10.58	13.08	
100 ng Hb/mL	6.12	6.12	6.43	.833
Cumulative positivity		8.74	10.88	
125 ng Hb/mL	5.45	5.08	5.51	.701
Cumulative positivity		7.67	9.51	
150 ng Hb/mL	4.84	4.65	5.21	.597
Cumulative positivity		7.13	8.98	
200 ng Hb/mL	4.41	4.04	4.35	.754
Cumulative positivity		6.42	8.03	

Hb indicates hemoglobin; IFOBT, immunochemical fecal occult blood test.
Cochran test for significance between tests, and cumulative positivity for first 2 and all 3 tests at each threshold are shown.

tests performed at each threshold and at higher thresholds ($P<.001$).

Cancer

Sensitivity for CRC was 100% when using the highest measurement of 3 IFOBTs examined at the lowest threshold of ≥50 ng Hb/mL of buffer (Table 5). The 95% sensitivity with 2 tests was not significantly different from 75% sensitivity with 1 test (McNemar paired test). Sensitivity for CRC progressively decreased with increasing thresholds, but at each threshold it was highest with 3 tests. However, this difference only became significant at 150 ng Hb/mL of buffer, 55% for 1 test v. 85% for the highest of 3 tests, $P = .031$.

The sensitivity of 2 tests at 50 ng Hb/mL of buffer was significantly higher than that of the commonly used single test at 100 ng Hb/mL ($P = .031$), but significantly less specific ($P<.001$) (Table 4).

Cancer or advanced adenomas, or only advanced AP

At the lowest threshold of ≥50 ng Hb/mL of buffer and using the highest measurement of 3 IFOBTs, sensitivity for CRC or advanced AP was 61.1%, which was significantly different from the 55.0% sensitivity with 2 tests ($P = .004$); for advanced AP sensitivities were, respectively 55% and 48.8% ($P = .008$) (Tables 4 and 5). Sensitivity of the higher of 2 IFOBTs for CRC or advanced AP was significantly greater than that of 1 test at 41.6% ($P<.001$); for advanced AP it was 36.4% ($P<.001$). This differentiation remained consistent at all thresholds and is mainly attributable to differences in sensitivity and specificity for advanced AP when increasing the number of IFOBTs.

Sensitivity of any test at 50 ng Hb/mL of buffer for CRC or advanced AP was significantly higher than the commonly used single test at 100 ng Hb/mL ($P<.001$), but significantly less specific ($P<.001$) (Table 4).

Predictive values for significant neoplasms and need for colonoscopy follow-up

Positive predictive values for CRC and CRC or advanced AP were highest with the first IFOBT, decreased with increasing number of tests performed at each threshold, and increased with rising fecal Hb cutoff levels (Table 6). Conversely, negative predictive values rose with increasing number of IFOBTs tested at each threshold and deceased when including both CRC or advanced AP and with rising cutoff values for fecal Hb.

By using positive predictive data for each threshold and number of IFOBTs prepared, the number of persons needing colonoscopy for positive tests to detect CRC and CRC or advanced AP was calculated (Table 5). The number depended on whether the endpoint was CRC specifically or CRC or advanced AP, threshold chosen, number of tests prepared, and sensitivity required. For example, the number of colonoscopies needed ranged from 13.9 for detecting CRC (when any of 3 IFOBTs had ≥50 ng Hb/mL of buffer) to 1.9 for CRC or advanced AP (using the first IFOBTs examined at 200 ng Hb/mL).

At the lowest threshold of 50 ng Hb/mL, to identify a CRC or advanced AP, performing either 1 or 2 IFOBTs required colonoscopy for positive tests on 2.7 to 2.8 persons to detect a neoplasm. Performing 2 tests required

Table 4. IFOBT Sensitivity, Specificity (%), and Positive and Negative Likelihood Ratios (95% CIs), for Cancer (n = 20), Cancer or Advanced Adenoma (n = 149), or Only Advanced Adenoma (n = 129) in 1682 Persons Having Both Colonoscopy and IFOBTs, Using First or Highest of 2 or 3 Fecal Hemoglobin Measurements, at Differing Thresholds (ng Hb/mL of Buffer) for Occult Blood

IFOBT Threshold/ Diagnosis	First IFOBT				Higher of 2 IFOBTs				Highest of 3 IFOBTs			
	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR	Negative LR	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR	Negative LR	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR	Negative LR
≥50 ng Hb/mL												
Cancer	75.0[a] (56.0-94.0)	91.0[b] (89.7-92.4)	8.36 (3.49-20.0)	0.27 (0.24-0.32)	95.0[c] (85.4-105)	87.2[d] (85.6-88.8)	7.41 (1.19-46.3)	0.06 (0.05-0.07)	100 (100-100)	84.5 (82.7-86.2)	6.44 (NA-NA)	0.00 (NA-NA)
CRC or AAP	41.6[e] (33.7-49.5)	93.3[f] (92.1- 94.6)	6.25 (4.73-8.25)	0.63 (0.55-0.71)	55.0[g] (47.0-63.0)	90.2 (88.7- 91.7)	5.62 (4.29-7.37)	0.50 (0.44-0.56)	61.1[h] (53.2-68.9)	87.8 (86.2-89.4)	5.01 (3.81-6.58)	0.44 (0.40-0.50)
AAP	36.4 (28.1-44.7)	93.3 (92.1-94.6)	5.47 (4.02-7.46)	0.68 (0.61-0.77)	48.8 (40.2- 57.5)	90.2 (88.7-91.7)	4.99 (3.74-6.67)	0.57 (0.51-0.63)	55.0 (46.5-63.6)	87.8 (86.2-89.4)	4.51 (3 39-6.01)	0.51 (0.46-0.57)
≥75 ng Hb/mL												
Cancer	70.0 (49.9-90.1)	93.2 (92.0-94.4)	10.29 (4.51-23.5)	0.32 (0.28-0.38)	90.0 (76.9-103)	90.4 (89.0-91.8)	9.35 (2.48-35.2)	0.11 (0.10-0.13)	95.0 (85.4-105)	87.9 (86.3-89.5)	7.86 (1.25-49.5)	0.06 (0.05-0.07)
CRC or AAP	36.2 (28.5-44.0)	95.2 (94.2-96.3)	7.61 (5.69-10.1)	0.67 (0.58-0.77)	47.7 (39.6-55.7)	93.0 (91.7-94.3)	6.83 (5.20-8.96)	0.56 (0.49-0.64)	55.7 (47.7-63.7)	91.18 (9.6-92.5)	6.23 (4.75-8.17)	0.49 (0.43-0.55)
AAP	31.0 (23.0-39.0)	95.2 (94.2-96.3)	6.51 (4.69-9.03)	0.72 (0.64-0.82)	41.1 (32.6-49.6)	93.0 (91.7-94.3)	5.89 (4.36-7.94)	0.63 (0.56-0.72)	49.6 (41.0-58.2)	91.1 (89.6-92.5)	5.55 (4.15-7.42)	0.55 (0.49-0.62)
≥100 ng Hb/mL												
Cancer	65.0[i] (44.1-85.9)	94.6[i] (93.6-95.7)	12.13 (5.5-26.7)	0.37 (0.31-0.44)	80.0 (62.5-97.5)	92.1 (90.8-93.4)	10.15 (3.86-26.7)	0.22 (0.19-0.25)	90.0 (76.9-103)	90.1 (88.6-91.5)	9.07 (2.41-34.1)	0.11 (0.10-0.13)
CRC or AAP	31.5[k] (24.1-39.0)	96.4[j] (95.5-97.3)	8.79 (6.48-11.9)	0.71 (0.61-0.82)	43.0 (35.0-50.9)	94.6 (93.5-95.7)	7.93 (6.01-10.5)	0.60 (0.52-0.69)	51.0 (43.0-59.0)	93.0 (91.7-94.3)	7.31 (5.57-9.59)	0.53 (0.46-0.60)
AAP	26.4 (18.8-34.0)	96.4 (95.5-97.3)	7.34 (5.18-10.4)	0.76 (0.67-0.88)	37.2 (28.9-45.6)	94.6 (93.5-95.7)	6.87 (5.05-9.36)	0.66 (0.58-0.76)	45.0 (36.4-53.5)	93.0 (91.7-94.3)	6.44 (4.80-8.65)	0.59 (0.52-0.67)
≥125 ng Hb/mL												
Cancer	60.0 (38.5-81.5)	95.2 (94.2- 96.3)	12.62 (5.87-27.1)	0.37 (0.31-0.44)	75.0 (56.0-94.0)	93.1 (91.9-94.4)	10.93 (4.52-26.4)	0.27 (0.23-0.31)	85.0 (69.4-101)	91.4 (90.0-92.7)	9.88 (3.30-29.6)	0.16 (0.14-0.19)
CRC or AAP	27.5 (20.3-34.7)	96.7 (95.8-97.6)	8.43 (6.12-11.6)	0.75 (0.65-0.87)	37.6 (29.8-45.4)	95.2 (94.2-96.3)	7.89 (5.93-10.5)	0.66 (0.57-0.75)	45.6 (37.6-53.6)	94.0 (92.8-95.2)	7.60 (5.78-10.0)	0.58 (0.50-0.66)
AAP	22.5 (15.3- 29.7)	96.7 (95.8-97.6)	6.89 (4.74-10.0)	0.80 (0.70-0.91)	31.8 (23.7-39.8)	95.2 (94.2-96.3)	6.67 (4.82-9.24)	0.72 (0.63-0.82)	39.5 (31.1-48.0)	94.0 (92.8-95.2)	6.59 (4.87-8.92)	0.64 (0.57-0.73)
≥150 ng Hb/mL												
Cancer	55.0 (33.2-76.8)	95.8 (94.8-96.8)	13.05 (6.15-27.7)	0.42 (0.35- 0.50)	75.0 (56.0- 94.0)	93.7 (92.5-94.9)	11.87 (4.90-28.8)	0.27 (0.23-0.32)	85.0 (69.4-101)	91.9 (90.6-93.2)	10.54 (3.51-31.7)	0.16 (0.14-0.19)
CRC or AAP	26.8 (19.7-34.0)	97.3 (96.5-98.1)	10.03 (7.26-13.9)	0.75 (0.64-0.88)	36.9 (29.2- 44.7)	95.8 (94.8- 96.8)	8.71 (6.52-11.6)	0.66 (0.57-0.76)	45.6 (37.6-53.6)	94.6 (93.5-95.7)	8.43 (6.40-11.1)	0.57 (0.50-0.66)
AAP	22.5 (15.3-29.7)	97.3 (96.5-98.1)	8.40 (5.78-12.2)	0.80 (0.69-0.92)	31.0 (23.0-39.0)	95.8 (94.8-96.8)	7.31 (5.27-10.2)	0.72 (0.63-0.83)	39.5 (31.1- 48.0)	94.6 (93.5- 95.7)	7.30 (5.39-9.89)	0.64 (0.56-0.73)
≥200 ng Hb/mL												
Cancer	55.0 (33.2-76.8)	96.3 (95.4-97.2)	14.73 (6.93- 31.3)	0.47 (0.39-0.56)	70.0 (49.9-90.1)	94.3 (93.2- 95.5)	12.38 (5.41-28.3)	0.32 (0.27-0.38)	80.0 (62.5-97.5)	92.8 (91.6-94.1)	11.17 (4.24-29.5)	0.22 (0.18- 0.25)
CRC or AAP	26.2 (19.1-33.2)	97.8 (97.0-98.5)	11.79 (8.51- 16.4)	0.76 (0.64- 0.90)	34.9 (27.2-42.6)	96.3 (95.4-97.3)	9.55 (7.12-12.8)	0.68 (0.58-0.79)	43.0 (35.0-50.9)	95.4 (94.3-96.4)	9.27 (7.02-12.3)	0.60 (0.5-0.70)
AAP	21.7 (14.6-28.8)	97.8 (97.0-98.5)	9.78 (6.69- 14.3)	0.80 (0.68-0.94)	29.5 (21.6-37.3	96.3 (95.4- 97.3)	8.06 (5.77-11.3)	0.73 (0.63-0.84)	37.2 (28.9-45.6)	95.4 (94.3- 96.4)	8.03 (5.90-10.9)	0.66 (0.57-0.76)

IFOBT indicates immunochemical fecal occult blood test; CI, confidence interval; Hb, hemoglobin; LR, likelihood ratio; CRC, colorectal cancer; AAP, advanced adenomatous polyp; NA, not applicable.

AAP includes having a single adenoma ≥10 mm or ≥20% villous or high-grade dysplasia.

For CRC: [a] vs [i], P=0.5; [b] < [i], P<.001; [c] > [i], P=.031; [d] < [i], P<.001.

For CRC or AAP: [e]<[g], P<.001; [g]<[h], P=.004; [c], [g], and [h]>[k], P<.001; [f]<[j], P<.001.

Table 5. IFOBT Sensitivity and 95% CIs (%) for Cancer, Cancer or Advanced Adenoma, or Only Advanced Adenoma in 1682 Persons Having Both Colonoscopy and IFOBTs, Using the First or Highest of 2 or 3 Fecal Hemoglobin Measurements at Differing Thresholds (ng Hb/mL of Buffer), and Significant Differences in Sensitivity by Number of Tests Performed

Diagnosis/IFOBT Threshold	No. of Patients	First IFOBT	Higher of 2 IFOBTs		Highest of 3 IFOBTs		
		Sensitivity, % (95% CI)	Sensitivity, % (95% CI)	*P*, Sensitivity 1 vs 2 Tests	Sensitivity, % (95% CI)	*P*, Sensitivity 1 vs 3 Tests	*P*, Sensitivity 2 vs 3 Tests
≥50 ng Hb/mL							
Cancer	20	75.0 (56.0-94.0)	95.0 (85.4-105)	.125	100 (100-100)	NC	NC
CRC or AAP	149	41.6 (33.7-49.5)	55.0 (47.0-63.0)	<.001	61.1 (53.2-68.9)	<.001	<.004
AAP	129	36.4 (28.1-44.7)	48.8 (40.2-57.5)	<.001	55.0 (46.5-63.6)	<.001	.008
≥75 ng Hb/mL							
Cancer	20	70.0 (49.9-90.1)	90.0 (76.9-103)	.125	95.0 (85.4-105)	.063	1.0
CRC or AAP	149	36.2 (28.5-44.0)	47.7 (39.6-55.7)	<.001	55.7 (47.7-63.7)	<.001	<.001
AAP	129	31.0 (23.0-39.0)	41.1 (32.6-49.6)	<.001	49.6 (41.0-58.2)	<.001	<.001
≥100 ng Hb/mL							
Cancer	20	65.0 (44.1-85.9)	80.0 (62.5-97.5)	.250	90.0 (76.9-103)	.063	.500
CRC or AAP	149	31.5 (24.1-39.0)	43.0 (35.0-50.9)	<.001	51.0 (43.0-59.0)	<.001	<.001
AAP	129	26.4 (18.8-34.0)	37.2 (28.9-45.6)	<.001	45.0 (36.4-53.5)	<.001	.002
≥125 ng Hb/mL							
Cancer	20	60.0 (38.5-81.5)	75.0 (56.0-94.0)	.250	85.0 (69.4-101)	.063	.500
CRC or AAP	149	27.5 (20.3-34.7)	37.6 (29.8-45.4)	<.001	45.6 (37.6-53.6)	<.001	<.001
AAP	129	22.5 (15.3-29.7)	31.8 (23.7-39.8)	<.001	39.5 (31.1-48.0)	<.001	.002
≥150 ng Hb/mL							
Cancer	20	55.0 (33.2-76.8)	75.0 (56.0-94.0)	.125	85.0 (69.4-101)	.031	.500
CRC or AAP	149	26.8 (19.7-34.0)	36.9 (29.2-44.7)	<.001	45.6 (37.6-53.6)	<.001	<.001
AAP	129	22.5 (15.3-29.7)	31.0 (23.0-39.0)	<.001	39.5 (31.1-48.0)	<.001	<.001
≥200 ng Hb/mL							
Cancer	20	55.0 (33.2-76.8)	70.0 (49.9-90.1)	.250	80.0 (62.5-97.5)	.063	.500
CRC or AAP	149	26.2 (19.1-33.2)	34.9 (27.2-42.6)	<.001	43.0 (35.0-50.9)	<.001	<.001
AAP	129	21.7 (14.6-28.8)	29.5 (21.6-37.3)	.002	37.2 (28.9-45.6)	<.001	.002

IFOBT indicates immunochemical fecal occult blood test; CI, confidence interval; Hb, hemoglobin; NC, cannot be computed; CRC, colorectal cancer; AAP, advanced adenomatous polyp.

colonoscopy on 13.8% of the population (Table 3), in contrast to 9.7% with 1 test, but with a 32.3% increased detection of CRC or advanced AP ($P<.001$). Performing 3 IFOBTs required colonoscopy on 16.5% or 3.1 persons per case of CRC or advanced AP, detecting a further 11% of neoplasms ($P=.004$).

Examining 1 test at thresholds >50 ng Hb/mL gradually decreased the number of colonoscopies needed from 2.4 to 1.9 to detect a neoplasm, but also the number of CRC cases or advanced APs identified. Examining 2 or 3 IFOBTs at thresholds >50 ng Hb/mL increased the number of neoplasms detected, but still required 2.1 to 2.7 colonoscopies per neoplasm depending on threshold used.

Neoplasms not detected

At the lowest development threshold (50 ng Hb/mL buffer) and using all 3 IFOBTs, all CRC were detected, but 58 (45%) advanced APs were not; 52% were sited in the proximal colon, 71% were ≥10 mm, 76% were sessile, and 19% had high-grade dysplasia.

DISCUSSION

This colonoscopy-controlled study allowed for detailed evaluation of quantitative immunochemical determination of fecal occult blood in a large number of persons, some bearing CRC and/or advanced AP, IFOBT sensitivity and specificity for these neoplasms over a range of fecal Hb thresholds, and the number of IFOBTs collected per patient. As anticipated, fecal Hb loss was significantly associated with CRC and less so with advanced AP. As shown by ROC analysis, IFOBT sensitivity was highest at low thresholds and as more IFOBTs were analyzed at that cutoff. Conversely, specificity was highest at high thresholds and with the fewest IFOBTs analyzed at that cutoff.

Successful immunochemical identification of neoplasms depends on identifying intact globin. Our results

Table 6. IFOBT Positive and Negative Predictive Values for Identifying Some of 149 Neoplasms (Cancer, n = 20; Advanced Adenoma, n = 129) in 1682 Persons Having Colonoscopy and IFOBTs: Number of Colonoscopies Needed to Identify a Patient With Cancer, or Cancer or Advanced Adenoma, Using the First or Highest of 2 or 3 IFOBT Measurements at Differing Fecal Hemoglobin Thresholds

IFOBT Threshold/ Diagnosis	First IFOBT				Higher of 2 IFOBTs				Highest of 3 IFOBTs			
	No.[a]	PPV, % (95% CI)	NPV, %	Colonoscopies[b]	No.[a]	PPV, % (95% CI)	NPV, % (95% CI)	Colonoscopies[b]	No.[a]	PPV, % (95% CI)	NPV, % (95% CI)	Colonoscopies[b]
≥50 ng Hb/mL												
Cancer	15	9.1 (4.7-13.6)	99.7 (99.4-100)	11	19	8.2 (4.7-11.7)	99.9 (99.8-100)	12.2	20	7.2 (4.2-10.2)	100 (100-100)	13.9
CRC or AAP	62	37.8 (30.4-45.2)	94.3 (93.1-95.4)	2.7	82	35.3 (29.2-41.5)	95.4 (94.3-96.5)	2.8	91	32.7 (27.2-38.2)	95.9 (94.8-96.9)	3.1
≥75 ng Hb/mL												
Cancer	14	11.0 (5.61-6.5)	99.6 (99.3-99.9)	9	18	10.1 (5.7-14.5)	99.9 (99.7-100)	9.9	19	8.6 (4.9-12.3)	99.9 (99.8-100)	11.6
CRC or AAP	54	42.5 (33.9-51.1)	93.9 (92.7-95.1)	2.4	71	39.9 (32.7-47.1)	94.8 (93.7-95.9)	2.5	83	37.7 (31.3-44.1)	95.5 (94.4-96.5)	2.7
≥100 ng Hb/mL												
Cancer	13	12.7 (6.3-19.2)	99.6 (99.2-99.9)	7.9	16	10.9 (5.81-5.9)	99.7 (99.5-100)	9.2	18	9.8 (5.5-14.2)	99.9 (99.7-100)	10.2
CRC or AAP	47	46.1 (36.4-55.8)	93.5 (92.3-94.8)	2.2	64	43.5 (35.5-51.6)	94.5 (93.3-95.6)	2.3	76	41.5 (34.4-48.7)	95.1 (94.0-96.2)	2.4
≥125 ng Hb/mL												
Cancer	12	13.2 (6.2-20.1)	99.5 (99.1-99.8)	7.6	15	11.6 (6.11-7.2)	99.7 (99.4-100)	8.6	17	10.6 (5.9-15.4)	99.8 (99.6-100)	9.4
CRC or AAP	41	45.1 (34.8-55.3)	93.2 (92.0-94.4)	2.2	56	43.4 (34.9-52.0)	94.0 (92.8-95.2)	2.3	68	42.5 (34.8-50.2)	94.7 (93.6-95.8)	2.4
≥150 ng Hb/mL												
Cancer	11	13.6 (6.1-21.0)	99.4 (99.1-99.8)	7.4	15	12.5 (6.61-8.4)	99.7 (99.4-100)	8	17	11.3 (6.2-16.3)	99.8 (99.6-100)	8.9
CRC or AAP	40	49.4 (38.5-60.3)	93.2 (92.0-94.4)	2.0	55	45.8 (36.9-54.7)	94.0 (92.8-95.2)	2.2	68	45.0 (37.1-53.0)	94.7 (93.6-95.8)	2.2
≥200 ng Hb/mL												
Cancer	11	15.1 (6.9-23.3)	99.4 (99.1-99.8)	6.6	14	13.0 (6.6-19.3)	99.6 (99.3-99.9)	7.7	16	11.9 (6.4-17.3)	99.7 (99.5-100)	8.4
CRC or AAP	39	53.4 (42.0-64.9)	93.2 (91.9-94.4)	1.9	52	48.1 (38.7-57.6)	93.8 (92.6-95.0)	2.1	64	47.4 (39.0-55.8)	94.5 (93.4-95.6)	2.1

IFOBT indicates immunochemical fecal occult blood test; PPV, positive predictive value; CI, confidence interval; NPV, negative predictive value; Hb, hemoglobin; CRC, colorectal cancer; AAP, advanced adenomatous polyp.

[a]Number of neoplasms detected.

[b]Number of colonoscopies needed for positive tests to identify a neoplasm.

indicate that fecal Hb stability in the colon and the collection and storage methods used were adequate to identify all cancers and over half the advanced APs with 2 or 3 tests at the lowest cutoff, although FOBT identification of advanced APs has not been the aim of screening guidelines.[2]

Size and number of adenomas also determine the amount of detectable fecal Hb, and 55% of advanced APs were detected.[19] However, as this was a high-risk population, they might have had larger and more advanced APs than an average-risk population. Hb loss from most nonadvanced APs was not significantly increased; this is an advantage, as colonoscopy screening identifies numerous nonadvanced AP-bearing persons who enter into a labor-intensive and expensive adenoma follow-up protocol with associated morbidity.[16]

Specificity for CRC or advanced AP depends on the threshold chosen to determine sensitivity.[22] This depends on screening policy, that is, whether to identify only CRC or also as many advanced APs as possible at that screening round, and whether to chose a level of specificity that reduces the number of colonoscopies needed at that time in anticipation of detecting significant lesions by future rescreening.

Average-risk screening usually aims at ≥95% specificity for CRC; this was obtained with 1 IFOBT analyzed at 100 ng Hb/mL of buffer threshold. Every second colonoscopy for positive IFOBTs identified 65% of CRCs (significantly less than 2 tests at 50 ng Hb/mL of buffer) and/or 26.4% of advanced APs. Conversely, where screening colonoscopy is considered, sensitivity for CRC and also advanced AP is paramount, so with 2 or 3 tests at the 50 ng Hb/mL threshold, every third colonoscopy identified 95% to 100% of CRCs and 48.8% to 55% of advanced APs ($P<.001$), but with specificity of 90.2% to 87.8% ($P<.001$), requiring more colonoscopies for positive tests. In our above average-risk population, higher sensitivity identified most significant neoplasms and potentially avoided performing 83.5% to 86.2% unnecessary colonoscopies at that time, thus allowing colonoscopy to be less a screening than a diagnostic and therapeutic procedure. These decisions can be addressed by providing the quantitative IFOBT result and using clinical judgment on the need for follow-up tests.[20]

Our study population is not comparable to the average-risk populations of studies using IFOBTs with fixed sensitivity for Hb (determined by manufacturers), or are quantitative but do not include colonoscopy. Published experience on the number of IFOBTs to collect and the cutoff to use for optimal sensitivity and specificity has been oriented toward identifying CRC in average-risk populations. Bleeding from colonic neoplasms is often intermittent, so based on experience with guaiac FOBTs, we collected 3 fecal tests and did find a significant advantage in identifying neoplasms, especially advanced APs, with 2 or 3 IFOBTs.[1,20] Annual 2-day IFOBT collections in the average-risk population is used in Japan and Australia, 1- or 2-day annual testing in some European countries, Uruguay, and Taiwan, and 1-day biennial testing in Italy.[4,6-10,12-14,22]

In Japanese reports with OC-MICRO, the threshold chosen was 150 ng fecal Hb/mL buffer versus the 100-ng Hb/mL cutoff used in Europe.[5,13,14] According to the OC-MICRO manufacturer, for average-risk screening in Japan, 2 tests are suggested and should be analyzed at 100 ng Hb/mL of buffer.[17] A cost-effective analysis from Taiwan, based on 1 IFOBT with 66% follow-up colonoscopy on tests having ≥30 ng Hb/mL of buffer and estimating interval CRCs from a cancer registry, concluded that optimal cutoff was 100 ng Hb/mL buffer.[11] A screening study performed in northern Italy collected 2 IFOBTs and used a ≥80-ng Hb/mL buffer threshold for performing colonoscopy with 89% compliance but no estimate of false-negative rates. The authors concluded that 2 versus 1 IFOBT examined at the 100-ng Hb/mL threshold increased identification of CRCs by 21%; using a ≥80-ng Hb/mL threshold mainly increased numbers of advanced APs detected, a finding similar to ours.[14,19] Hol et al, in Holland, offered colonoscopy to screenees having ≥50 ng Hb/mL buffer in a single IFOBT, and concluded that a 75-ng Hb cutoff provided better utilization of colonoscopy resources.[22]

Our study consisted of a single round of testing, and we expect that systematic rescreening would detect adenomas progressing in size, or fast-growing interval cancers because of genetic drive.[23,24] Also, there are patients with adenomas, including some with advanced features, or even cancers missed at colonoscopy, reinforcing the clinical utility of systematic FOBT rescreening.[24-27]

Choosing a screening test should take into consideration test characteristics, demands on screenees, and compliance for performance. Fluid fecal samples are temperature sensitive, and Hb degradation occurs if samples are not stored at 4°C.[17,18] Requesting only 1 test gives low sensitivity, but high specificity that reduces the number of colonoscopy examinations. Requesting 2 or 3 IFOBTs increase costs, possibly reduces compliance, but improves sensitivity without markedly increasing the

number of colonoscopies needed for positive tests to detect a neoplasm. In our experience, patients used to undergoing 3 guaiac FOBTs had no problem undergoing 3 IFOBTs. Availability of a highly sensitive and specific noninvasive test might also improve screening compliance. There is no advantage in quantification if tests are analyzed at a fixed threshold. The latter can be provided by dry IFOBT cards that are more temperature stable.[5,9,10]

In addition to the above issues, the clinical utility of a screening test can be evaluated by the sensitivity for significant neoplasms and the number of colonoscopies needed to detect them. In our above average-risk population, a CRC or advanced AP was found at every third colonoscopy for positive IFOBT. Lieberman et al estimated the number of colonoscopies needed to identify an adenoma $\geq$10 mm to range from 10 to 28 depending on sex and age.[28] In a colonoscopy screening study of asymptomatic volunteers, Imperiale et al found CRC or advanced AP in every 18 colonoscopies performed.[29] Truly comparative information awaits results of our average-risk study. In addition, a cost-benefit analysis, based on available information, is now needed.

This study's strengths are its large size and that all patients had colonoscopy and systematic evaluation of 3 IFOBTs over a range of fecal Hb thresholds. This provides information that the screener can use to draft policy relevant to identification of CRC and advanced AP and colonoscopic treatment of advanced APs. Clinical limitations of this study are that the volunteer population was a heterogeneous mixture of average- and above average-risk patients, and some were mildly symptomatic. Technical limitations are discussed elsewhere.[20]

In conclusion, in our above average-risk population, we found that by deciding on the number of IFOBTs to prepare and the test threshold to use, this quantified IFOBT can detect most CRCs and advanced APs. The screening policy chosen will determine test sensitivity and specificity and the number of colonoscopies needed for positive tests.

CONFLICT OF INTEREST DISCLOSURES

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Random Comparison of Guaiac and Immunochemical Fecal Occult Blood Tests for Colorectal Cancer in a Screening Population

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Background & Aims: **Despite poor performance, guaiac-based fecal occult blood tests (G-FOBT) are most frequently implemented for colorectal cancer screening. Immunochemical fecal occult blood tests (I-FOBT) are claimed to perform better, without randomized comparison in screening populations. Our aim was to randomly compare G-FOBT with I-FOBT in a screening population.** ***Methods:*** **We conducted a population-based study on a random sample of 20,623 individuals 50–75 years of age, randomized to either G-FOBT (Hemoccult-II) or I-FOBT (OC-Sensor). Tests and invitations were sent together. For I-FOBT, the standard cutoff of 100 ng/ml was used. Positive FOBTs were verified with colonoscopy. Advanced adenomas were defined as ≥10 mm, high-grade dysplasia, or ≥20% villous component.** ***Results:*** **There were 10,993 tests returned: 4836 (46.9%) G-FOBTs and 6157 (59.6%) I-FOBTs. The participation rate difference was 12.7% ($P < .01$). Of G-FOBTs, 117 (2.4%) were positive versus 339 (5.5%) of I-FOBTs. The positivity rate difference was 3.1% ($P < .01$). Cancer and advanced adenomas were found, respectively, in 11 and 48 of G-FOBTs and in 24 and 121 of I-FOBTs. Differences in positive predictive value for cancer and advanced adenomas and cancer were, respectively, 2.1% ($P = .4$) and −3.6% ($P = .5$). Differences in specificities favor G-FOBT and were, respectively, 2.3% ($P < .01$) and −1.3% ($P < .01$). Differences in intention-to-screen detection rates favor I-FOBT and were, respectively, 0.1% ($P < .05$) and 0.9% ($P < .01$).** ***Conclusions:*** **The number-to-scope to find 1 cancer was comparable between the tests. However, participation and detection rates for advanced adenomas and cancer were significantly higher for I-FOBT. G-FOBT significantly underestimates the prevalence of advanced adenomas and cancer in the screening population compared with I-FOBT.**

More than 30 years ago, guaiac-based fecal occult blood tests (G-FOBT) to screen for colorectal cancer (CRC) were introduced.[1,2] A G-FOBT is a relatively inexpensive test, easy to use that can be carried out at home. However, G-FOBTs are not specific for human blood and quality control on the evaluation of the tests is hardly possible.[3] Despite these disadvantages, the G-FOBT is still the most implemented test for CRC screening.[4–9]

A promising alternative is the immunochemical fecal occult blood test (I-FOBT). I-FOBTs are also inexpensive and noninvasive; in addition, these tests are often easier to carry out than G-FOBTs. Another advantage of I-FOBTs is that they are specific for human blood. The most prominent advantage is that many I-FOBTs make quality control possible. At least in theory, they also promise better diagnostic performance than G-FOBTs. In several studies I-FOBTs, seem to have higher specificity compared with G-FOBTs.[10–14]

To demonstrate that I-FOBTs have improved diagnostic performance, the tests should be compared with G-FOBTs in a randomized design in a general screening population. Up to now, direct comparison has only been performed in subjects at higher risk for CRC, like subjects with a positive G-FOBT, symptomatic patients, or patients already diagnosed with CRC.[15–19] Also, some studies focused on test performance parameters of both G-FOBT and I-FOBT by asking people to perform both tests at the same time, but such an approach may have negative impact on participation rates.[20–23] Another study comparing G-FOBT with I-FOBT was performed in a non-randomized design and the specific I-FOBT used (Inform) was not semiquantitative, did not allow quality control, and had to be performed on 2 days with separate bowel movements.[10] In the present study, we aimed to randomly compare the test performance parameters of the Hemoccult II G-FOBT (Beckman Coulter, Fullerton, CA) with the OC-sensor I-FOBT (Eiken Chemical Co., Tokyo, Japan) in a screening population.

Abbreviations used in this paper: 95% CI, 95% confidence interval; CRC, colorectal cancer; FOBT, fecal occult blood test; G-FOBT, guaiac-based fecal occult blood test; I-FOBT, immunochemical fecal occult blood test; Negatives, FOBT-negative patients; Positives, FOBT-positive patients; PPV, positive predictive value.

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Methods

Population

The population in this prospective study was a random selection of the general Dutch population between 50 and 75 years of age in Nijmegen, Amsterdam, and surrounding areas. Population data with respect to date of birth, gender, and postal area were provided by the civil service of the municipalities and updated every 8 weeks to keep the database up to date with respect to moving, age, and death. Institutionalized and symptomatic people were excluded. Symptomatic people were advised to contact their physician.

Randomization, Invitation, and Participation

From the municipal databases, random samples were taken according to postal address and randomized to receive a G-FOBT or an I-FOBT. If >1 individual was listed at the same address they received the same test to ensure relative blinding to the alternative test. Deviation from an equal distribution of the test allocation was prevented by an especially designed randomization program. From June 2006 to February 2007, randomized individuals received the allocated test, immediately with the invitation, an information brochure, a consent form, and a freepost envelope. The information brochure was designed in accordance with brochures used in other countries and provided concise background information for CRC screening and follow-up examination in case of a positive FOBT. Phone numbers to help desks in the 2 screening areas were given as well as links to informative websites. The only intervention to raise participation was a single written reminder 2 weeks after the initial invitation. The time for adherence—the time between invitation and returning the test—was unrestricted. Time for adherence was only restricted by closing of the study at May 1, 2007, after which time only follow-up was completed.

FOBTs

In this study 2 FOBTs were compared. The most commonly implemented G-FOBT, Hemoccult II (Beckman Coulter) was used. For the I-FOBT an automated semiquantitative I-FOBT: OC-sensor (Eiken Chemical Co.) was chosen to allow quality control. No diet instructions were given and people were instructed to prevent contact of feces with toilet bowl water and urine and not to perform the test if visible blood was present. Illustrations as well as written instructions and examples aided in fecal sampling. To ensure consistent testing quality, 2 specially trained laboratory workers analyzed all FOBTs in 1 gastroenterology research laboratory in Nijmegen.

A complete Hemoccult II test consists of 3 separate cards. With that 6 applicator sticks, a collecting envelope, and written instructions were sent. Each card should be used on a consecutive day with defecation and on each card 2 samples of different parts of the defecation should be applied with a separate applicator stick. People were instructed to put all 3 test cards in a supplied collecting envelope and to return it as freepost. The cards were not rehydrated.[24] If the test was performed incorrectly or <3 cards were returned, new test cards were sent with an letter explaining how to perform the test correctly. Incomplete tests were rare and almost always due to applying the stool on the wrong side of the card. Positivity was defined as blue discoloration of any of the 6 stool samples within 30–60 seconds after applying the developing solution. Ninety-nine percent of the tests were developed within 6 days. Tests were stored according to manufacturer instructions.

The OC-Sensor test consisted of a single sampling tube and written instructions. The sampling tube, filled with stabilizing buffer, had an integrated fecal probe. Participants were instructed to scrape different parts of the surface of their defecation with the probe. The amount of feces that can be inserted into the sample bottle is regulated to approximately 10 mg.[14] Participants were instructed to return the test as soon as possible because lasting exposition to room temperature might result in degradation of hemoglobin in the sampling solution.[13] If the test could not be returned immediately, storage in a refrigerator was advised. In the laboratory, tests were immediately developed or stored at 4°C. Of the tests, 75% were developed within 2 days and 99.6% within 6 days. Samples were processed by the OC-Micro instrument (Eiken Chemical Co.).[14] All patients with an I-FOBT ≥50 ng hemoglobin per milliliter sample solution (ng/ml) were invited for colonoscopy. Because the manufacturer recommends a cutoff of 100 ng/ml (corresponding to ±20 μg hemoglobin per gram of feces[14]) and because this cutoff value has been applied in several studies,[25–30] we decided beforehand to use the 100 ng/ml cutoff level in the analysis of this study.

Colonoscopy and Lesions

Colonoscopy was offered to all FOBT-positive patients (Positives). All colonoscopies were performed by experienced gastroenterologists using conscious sedation with midazolam. If the cecum could not be reached at the initial colonoscopy, the procedure was repeated using propofol anesthesia, and occasionally a computed tomographic colonoscopy was performed followed by a second colonoscopy if necessary. If possible, all observed neoplasias were removed, and other lesions were biopsied if necessary. Lesions were classified as pedunculated or sessile polyps, carcinoma, or other and recorded in number, size (≤5, 6–9, or ≥10 mm) and location (proximal [cecum to splenic flexure] or distal [descending colon to rectum]). Histology was evaluated by an experienced pathologist and graded as carcinoma, tubular adenoma, tubulovillous adenoma, villous adenoma, serrated adenoma, hyperplastic polyp, or miscellaneous. Polyp size was measured by the endoscopist. Advanced adenomas

were defined as adenomas ≥10 mm, with high-grade dysplasia or with a villous component ≥20%.[31] All early and late complications of colonoscopy were recorded. All colonoscopies were completed in May 2007.

Data Analysis

The participation rate was calculated as the number of persons returning a FOBT relative to the number of invitations sent. The positivity rate was calculated as the number of persons with a positive FOBT (Positives) relative to the number of persons returning a FOBT. In screening studies usually only the detection rate of true positives relative to the number of persons actually participating by returning a FOBT are presented, that is, the detection rate according to per-protocol analysis. We also present the detection rate according to the intent-to-screen analysis, or the number of true positives relative to the number of invited persons. By determining the intent-to-screen detection rate, the difference in participation and performance are combined in 1 overall rate. The number needed to screen to find 1 true positive was calculated as the number of invited persons relative to the number of true positives. The positive predictive value (PPV) was calculated as the number of true positives relative to the total number of positives followed up with colonoscopy. The number needed to scope to find 1 true positive was calculated as the number of endoscopies relative to the number of true positives.

The specificity was calculated under the rare disease assumption, as 1 minus the number of false positives relative to the total number of participants reduced by the number of true positives, disregarding the number of false FOBT-negative patients (Negatives).[32] In relatively rare diseases, the overestimation of the specificity owing to disregarding the number of false negatives, is limited to the confidence interval of the true specificity. A small decrease in specificity in mass screening can be clinically relevant because this would result in many more colonoscopies. Therefore, we only present the specificity for advanced adenomas and cancer; we discuss the precision of the estimation in the Discussion.

Rates and rate differences of participation, positivity, detection, PPV, and specificity were calculated and all percentages were reported with 95% confidence intervals (95% CI). Rate differences are statistically significant if the confidence interval does not include zero. Statistically significant differences are supplemented with *P*-values. In the tables, statistically significant differences are bolded. If >1 lesion was present, a patient was classified by the most advanced lesion. As such, were classified from more to less severe: from carcinoma, to ≥1 adenoma ≥10 mm, to ≥3 small adenomas. With adjusted logistic regression analysis, the influence of gender and age on the performance of the tests was evaluated. Statistical analysis and randomization were performed with SAS system for windows, software version 8.02 (SAS Institute Inc., Cary, NC).

Power was based on the lowest expected difference of all subgroups, namely, the difference in detection rate, for CRC between FOBTs. Based on literature data, a minimal difference of 0.3% in CRC detection was expected. With a sample size of 6083 in each group, a 2-group χ^2 test with a .05 2-sided significance level would have 80% power to detect a 0.3% difference between FOBTs, assuming detection rates of 0.2% for G-FOBT and 0.5% for I-FOBT. A sample size of 10,000 in each group was considered to be sufficient.

Ethical Approval and Consent

The study was reviewed and approved by the Dutch Health Council (2005/03WBO, The Hague, The Netherlands). All participants gave written informed consent for the FOBT and, if positive, for colonoscopy.

Results

Population

Overall 20,623 individuals were invited; 10,301 received a G-FOBT and 10,322 an I-FOBT (Figure 1). The mean age of the invited individuals was 60.7 ± 7.1 years (mean ± SD) and was not different between the FOBT groups. More women than men were randomly selected with a difference of 3.4% (95% CI, 2.5–4.4; $P < .01$). After

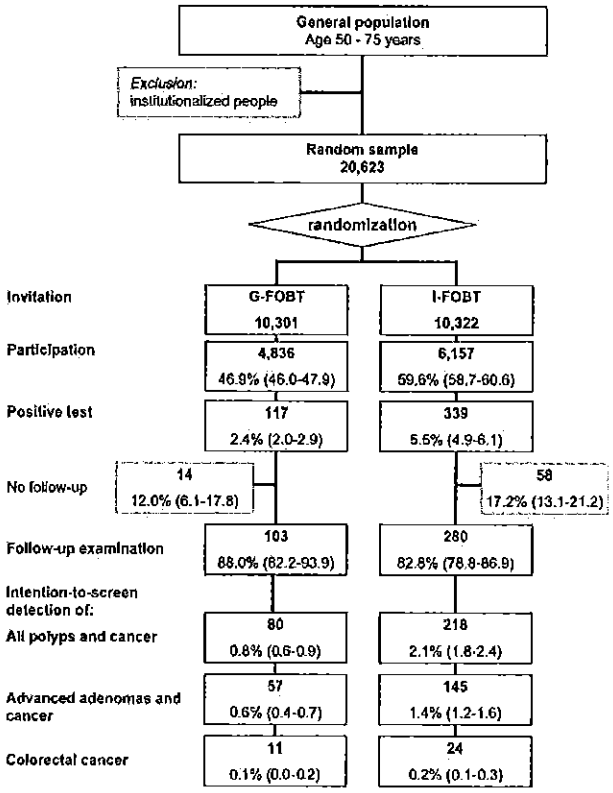

Figure 1. Flow chart from invitation to detection with numbers, percentages and 95% confidence intervals between brackets.

Table 1. Characteristics of Invited Persons and Participants According to Test With 95% Confidence Intervals

	Invited (n = 20,623)				Participants (n = 10,993)			
	G-FOBT (n = 10,301)		I-FOBT (n = 10,322)		G-FOBT (n = 4836)		I-FOBT (n = 6157)	
Characteristics	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Gender								
Male	47.8	(46.8–48.8)	48.8	(47.8–49.7)	43.2	(41.8–44.6)	45.8	(44.6–47.0)
Female	52.2	(51.2–53.2)	51.2	(50.3–52.2)	56.8	(55.4–58.2)	54.2	(53.0–55.4)
Age (y)								
<60	50.4	(49.4–51.4)	51.7	(50.7–52.7)	47.5	(46–48.9)	51.0	(49.7–52.2)
≥60	49.6	(48.6–50.6)	48.3	(47.3–49.3)	52.5	(51.1–54.0)	49.0	(47.8–50.3)

test allocation, gender differences were equal for both tests (Table 1). T1

Tests were returned by 10,993 individuals, 4836 (46.9%) in the G-FOBT group and 6157 (59.6%) in the I-FOBT group. The difference of 12.7% (95% CI, 11.3–14.1; $P <$ .01) was statistically significant. Time for adherence, after correction for 3-day testing for G-FOBT and 1-day testing for I-FOBT, was on average longer for G-FOBT (21 days) than for I-FOBT(19 days; $P <$ .01). For 75% of the participants, time for adherence was within 28 and 23 days, respectively ($P <$ .01) and for <1% of both FOBTs >100 days (P = .2).

Of the G-FOBT participants 117 (2.4%) tested positive and 339 (5.5%) of the I-FOBT participants, with a difference of 3.1% (95% CI, 2.3–3.8; $P <$ .01; Figure 1 and Table 3). Of female participants, 189 (3.1%), and of male participants, 266 (5.4%), were positive, with a difference of 2.3% (95% CI, 1.6–3.1; $P <$ .01). Of participants ≤60 years, 172 (3.2%), and of participants ≤60 years 282 (5.1%), were positive, with a difference of 1.9% (95% CI, 1.2–2.7; $P <$ .01). The age of 1 woman I-FOBT participant was unknown. Age and gender were equally distributed over both FOBTs. T3

Colonoscopy Results

To evaluate the outcome in the 456 FOBT Positives, a colonoscopy was performed in 383 (84%). The cecum was reached in 358 patients (94%). In patients in whom the cecum was not reached during the initial colonoscopy, a successful second colonoscopy was performed under propofolol anesthesia. In the 383 patients endoscoped, a total of 35 cancers and 899 polyps were found (Table 2). AQ: 2 T2

Cancer was found in 11 of the G-FOBTs and in 24 of the I-FOBTs. Advanced adenomas were found in 46 of the G-FOBTs and in 121 of the I-FOBTs. The intention-to-screen detection rates of the I-FOBT were significantly higher than the intention-to-screen detection rates of the G-FOBT (Table 3). The difference in intention-to-screen detection rates for patients with all polyps and cancer was 1.3% (95% CI, 1.0–1.7; $P <$ .01). The difference in intention-to-screen detection rates for all patients with advanced adenomas and cancer was 0.9% (95% CI, 0.6–1.1; $P <$ .01) and for all patients with cancer 0.1% (95% CI, 0.0–0.2; $P <$ .05). The number needed to screen according to intention to screen to find an advanced adenoma or carcinoma was 181 for G-FOBT and 71 for I-FOBT, and to find 1 cancer was 936 for G-FOBT and 430 for I-FOBT.

None of the differences in PPVs (Table 3) between G-FOBT and I-FOBT were statistically significant; the difference in PPV for advanced adenomas and cancer was estimated to be −3.6% (95% CI, −14.8 to 7.7; P = .5) and for cancer was estimated to be −2.1% (95% CI, −8.6 to 4.4; P = .4) lower for I-FOBT. The number needed to scope to find 1 person with an advanced adenoma or cancer was <2 for both FOBTs. The estimated specificity of the I-FOBT was statistically significantly lower, but

Table 2. Number of Colonoscopies and Number of Polyps and Cancer per Test, With Subdivisions for Kind of Polyp, Kind of Adenoma, and Size of Polyps

	G-FOBT	I-FOBT
Number of colonoscopies	103	280
Number of polyps and cancer[a]	231	703
Cancer	11	24
Polyps	220	679
Subdivision of polyps[b]	220	679
Adenomas	154	470
Hyperplastic polyps	62	163
Serrated polyps	2	31
Other polyps	2	15
Subdivision of all adenomas[c]	154	470
Tubular	93	295
Tubulovillous	42	138
Villous	12	15
Unclassified	7	22
Size of all polyps (mm)[d]	220	679
≥10	60	155
6–9	43	125
≤5	117	399

[a]The number of lesions was higher than the number of colonoscopies because >1 lesion per colonoscopy is possible.
[b]Polyps were subdivided in adenomatous, hyperplastic, serrated, or other polyps.
[c]Adenomas were subdivided in tubular, villous, tubulovillous, or unclassified adenomas.
[d]All polyps were subdivided by size in ≥10, 6–9, and ≤5 mm.

Table 3. Test Performance of G-FOBT Versus I-FOBT(≥100 ng/ml)

Test performance	G-FOBT			I-FOBT			Difference[a]	
	n	%	95% CI	*n*	%	95% CI	%	95% CI
Participation rate[b]	4.836	46.9	(46.0–47.9)	6.157	59.6	(58.7–60.6)	**12.7**	**(11.3–14.1)**
FOBT-positive patients	117	2.4	(2.0–2.9)	339	5.5	(4.9–6.1)	**3.1**	**(2.3–3.8)**
Complete follow-up of FOBT-positive patients[c]	103	88.0	(82.2–93.9)	280	82.6	(78.6–86.6)	−5.4	(−13.1 to 2.3)
Detection rate intention to screen[d]								
All polyps and cancer	80	0.8	(0.6–0.9)	218	2.1	(1.8–2.4)	**1.3**	**(1.0–1.7)**
All adenomas and cancer	72	0.7	(0.5–0.9)	201	1.9	(1.7–2.2)	**1.2**	**(0.9–1.6)**
All advanced adenomas and cancer[e]	57	0.6	(0.4–0.7)	145	1.4	(1.2–1.6)	**0.9**	**(0.6–1.1)**
Cancer	11	0.1	(0.0–0.2)	24	0.2	(0.1–0.3)	**0.1**	**(0.0–0.2)**
≥1 adenoma ≥10 mm	41	0.4	(0.3–0.5)	106	1.0	(0.8–1.2)	**0.6**	**(0.4–0.9)**
≥1 adenoma with high-grade dysplasia	3	0.0	(0.0–0.1)	4	0.0	(0.0–0.1)	**0.0**	**(0.0–0.1)**
≥1 adenoma with a villous component ≥20%	2	0.0	(0.0–0.0)	11	0.1	(0.0–0.2)	**0.1**	**(0.0–0.2)**
Detection rate per protocol[f]								
All polyps and cancer	80	1.7	(1.3–2.0)	218	3.5	(3.1–4.0)	**1.9**	**(1.3–2.5)**
All adenomas and cancer	72	1.5	(1.1–1.8)	201	3.3	(2.8–3.7)	**1.8**	**(1.2–2.4)**
All advanced adenomas and cancer[g]	57	1.2	(0.9–1.5)	145	2.4	(2.0–2.7)	**1.2**	**(0.7–1.7)**
Cancer	11	0.2	(0.1–0.4)	24	0.4	(0.2–0.5)	**0.2**	**(0.0–0.4)**
≥1 adenoma ≥10 mm	41	0.8	(0.6–1.1)	106	1.7	(1.4–2)	**0.9**	**(0.4–1.3)**
≥1 adenoma with high-grade dysplasia	3	0.1	(0.0–0.1)	4	0.1	(0.0–0.1)	0.0	(−0.1 to 0.1)
≥1 adenoma with a villous component ≥20%	2	0.0	(0.0–0.1)	11	0.2	(0.1–0.3)	**0.1%**	**(0.0–0.3)**
Positive predictive value[h]								
All polyps and cancer	80	77.7	(69.6–85.7)	218	77.9	(73.0–82.7)	0.2	(−9.2 to 9.6)
All adenomas and cancer	72	69.9	(61.0–78.8)	201	71.8	(66.5–77.1)	1.9	(−8.3 to 12.1)
All advanced adenomas and cancer[e]	57	55.3	(45.7–64.9)	145	51.8	(45.9–57.6)	−3.6	(−14.8 to 7.7)
Cancer	11	10.7	(4.7–16.6)	24	8.6	(5.3–11.9)	−2.1	(−8.6 to 4.4)
≥1 adenoma ≥10 mm	41	39.8	(30.4–49.3)	106	37.9	(32.2–43.5)	−1.9	(−12.9 to 9.0)
≥1 adenoma with high-grade dysplasia	3	2.9	(0.0–6.2)	4	1.4	(0.0–2.8)	−1.5	(−4.5 to 1.5)
≥1 adenoma with a villous component ≥20%	2	1.9	(0.0–4.6)	11	3.9	(1.7–6.2)	2.0	(−2.1 to 6.1)
Specificity[h]								
All advanced adenomas and cancer[e]	46	99.0	(98.8–99.3)	135	97.8	(97.4–98.1)	**−1.3**	**(−1.8 to −0.8)**
Cancer	92	98.1	(97.7–98.5)	256	95.8	(95.3–96.3)	**−2.3**	**(−2.9 to −1.6)**
≥1 adenoma ≥10 mm	62	98.7	(98.4–99.0)	174	97.1	(96.7–97.5)	**−1.6**	**(−2.1 to −1.0)**
≥1 adenoma with high-grade dysplasia	100	97.9	(97.5–98.3)	276	95.5	(95.0–96.0)	**−2.4**	**(−3.1 to −1.7)**
≥1 adenoma with a villous component ≥20%	101	97.9	(97.5–98.3)	269	95.6	(95.1–96.1)	**−2.3**	**(−3.0 to −1.6)**

[a]Differences with a 95% CI completely lower or higher than 0 are statistically significant **(bold)**, which means that the *P*-value does not exceed .05.
[b]Participation rate is the number of persons returning a FOBT relative to the number of invitations sent.
[c]Complete follow-up with colonoscopy of FOBT-positive patients (Positives). Rates are the number of colonoscoped patients relative to the number of Positives.
[d]Detection rate Intention to screen is the percentage of persons with lesions relative to the number of persons invited to be screened.
[e]The subgroups of advanced adenomas and cancer are ordered relative to the most advanced lesion per patient into cancer; ≥1 adenoma ≥10 mm (and no cancer) or high-grade dysplasia (and no cancer or any adenomas ≥10 mm) or ≥20% villous component (and no cancer or any adenomas ≥10 mm or high-grade dysplasia).
[f]Detection rate per protocol is the percentage of persons with lesions relative to the number of participants.
[g]Positive predictive value is the percentage of persons with lesions relative to the number of positives with follow-up with a colonoscopy.
[h]Specificity is the number of true negatives relative to the number of persons without lesions under the rare disease assumption. Numbers presented are the number of false-positives per group. Specificity is only presented for the subgroup "advanced adenoma and cancer" because the estimation might not be robust enough for the other subgroups.

only −1.3% (95% CI, −1.8 to −0.8; $P < .01$) for advanced adenomas and cancer and −2.3% (95% CI, −2.9 to −1.6; $P < .01$) for cancer.

Age and gender were randomized equally over the FOBTs, but as known risk factors for advanced adenomas and cancer we studied the differences between FOBTs for age and gender (Table 4). The detection rates for women and younger participants were lower, but the differences between FOBTs were consistent. The unadjusted, and for gender- and age-adjusted odds ratios for the intention-to-screen detection rates of advanced adenomas and cancer for FOBTs were both 0.4 (95% CI, 0.3–0.5; $P < .01$).

Discussion

In this population study, we randomly compared the performance of a G-FOBT with an I-FOBT in a previously screening naïve population.[33] Another study comparing G-FOBT (Hemoccult-II) with I-FOBT was not

Table 4. Positive Tests and Detection Rates According to Intention to Screen of G-FOBT and I-FOBT by Gender and Age

	Men			Women			Age <60			Age ≥60		
	n	%	95% CI	*n*	%	95% CI	*n*[a]	%	95% CI	*n*[a]	%	95% CI
FOBT-positive patients[b]												
G-FOBT	69	3.3	(2.5–4.1)	48	1.7	(1.3–2.2)	48	2.1	(1.5–2.7)	69	2.7	(2.1–3.4)
I-FOBT	197	7.0	(6.0–7.9)	142	4.3	(3.6–4.9)	124	4.0	(3.3–4.6)	214	7.1	(6.2–8.0)
Complete follow-up[c]												
G-FOBT	60	87.0	(79–95)	43	89.6	(81–98)	41	85.4	(75–95)	62	89.9	(83–97)
I-FOBT	163	82.7	(78–88)	117	82.4	(76–89)	107	86.3	(80–92)	172	80.4	(75–86)
Detection rate Intention-to-screen[d]												
All polyps and cancer												
G-FOBT	52	1.1	(0.8–1.3)	28	0.5	(0.3–0.7)	29	0.6	(0.4–0.8)	51	1.0	(0.7–1.3)
I-FOBT	131	2.6	(2.2–3.0)	87	1.6	(1.3–2.0)	80	1.5	(1.2–1.8)	138	2.8	(2.3–3.2)
All adenomas and cancer												
G-FOBT	46	0.9	(0.7–1.2)	26	0.5	(0.3–0.7)	24	0.5	(0.3–0.7)	48	0.9	(0.7–1.2)
I-FOBT	123	2.4	(2.0–2.9)	78	1.5	(1.2–1.8)	72	1.4	(1.0–1.7)	129	2.6	(2.2–3.0)
All advanced adenomas and cancer[e]												
G-FOBT	39	0.8	(0.5–1.0)	18	0.3	(0.2–0.5)	23	0.4	(0.3–0.6)	34	0.7	(0.4–0.9)
I-FOBT	93	1.8	(1.5–2.2)	52	1.0	(0.7–1.2)	51	1.0	(0.7–1.2)	94	1.9	(1.5–2.3)
Cancer												
G-FOBT	5	0.1	(0.0–0.2)	6	0.1	(0.0–0.2)	3	0.1	(0.0–0.1)	8	0.2	(0.0–0.3)
I-FOBT	16	0.3	(0.2–0.5)	8	0.2	(0.0–0.3)	6	0.1	(0.0–0.2)	18	0.4	(0.2–0.5)
≥1 adenoma ≥10 mm												
G-FOBT	30	0.6	(0.4–0.8)	11	0.2	(0.1–0.3)	19	0.4	(0.2–0.5)	22	0.4	(0.3–0.6)
I-FOBT	71	1.4	(1.1–1.7)	35	0.7	(0.4–0.9)	42	0.8	(0.6–1.0)	64	1.3	(1.0–1.6)
≥1 adenoma with high-grade dysplasia												
G-FOBT	2	0.0	(0.0–0.1)	1	0.0	(0.0–0.1)	0	0.0	(0.0–0.0)	3	0.1	(−0.0 to 0.1)
I-FOBT	2	0.0	(0.0–0.1)	2	0.0	(0.0–0.1)	0	0.0	(0.0–0.0)	4	0.1	(0.0–0.2)
≥1 adenoma ≥20% villous component												
G-FOBT	2	0.1	(0.0–0.2)	0	0.0	(0.0–0.0)	1	0.0	(0.0–0.1)	1	0.0	(−0.0 to 0.1)
I-FOBT	4	0.1	(0.0–0.3)	7	0.2	(0.1–0.4)	3	0.1	(−0.0 to 0.2)	8	0.3	(0.1–0.4)

[a]The age of 1 female I-FOBT participant was unknown.
[b]Positivity rates are the number of positives relative to the number of participants.
[c]Complete follow-up with colonoscopy of FOBT-positive patients (Positives). Rates are the number of colonoscoped patients relative to the number of positives.
[d]Detection rate intent to screen is the percentage of persons with lesions relative to the number of persons invited to be screened.
[e]The subgroups of advanced adenomas and cancer are ordered relative to the most advanced lesion per patient into cancer, ≥1 adenoma ≥10 mm (and no cancer) or high-grade dysplasia (and no cancer or any adenomas ≥10 mm) or ≥20% villous component (and no cancer or any adenomas ≥10 mm or high-grade dysplasia).

randomized, included far fewer persons, and used a different I-FOBT. This I-FOBT(Inform) was not quantitative, making quality control less adequate.[10] Despite these drawbacks, the results of this study were in line with ours. Other studies evaluating I-FOBTs included far less subjects and did not focus on a screening population, but investigated high-risk groups, like symptomatic patients, patients with a positive G-FOBT, or even patients with CRC.[15–19] Other studies were indeed designed for a screening population, but less subjects were included and asked to perform both the G-FOBT and the I-FOBT at the same time, which might induce selection bias in favor of highly motivated participants.[20–23]

Our study revealed several interesting results. First, direct comparison of the tests demonstrated a significantly higher participation rate for the I-FOBT. The reasons for this difference are not apparent and presently under investigation. Second, the specificity of the I-FOBT for advanced adenomas and cancer was significantly lower compared with the G-FOBT, but the detection rate for advanced adenomas and cancer of the I-FOBT was significantly higher. Consequently, 3 times as many subjects tested with the I-FOBT are referred for a negative colonoscopy. On the other hand, 3 times as many patients with advanced adenomas and >2 times more patients with cancer are left undetected in the G-FOBT group compared with the I-FOBT group, ultimately resulting in comparable PPVs for both tests.

There is ongoing debate on how to screen the population for relevant colorectal lesions. The available FOBTs have suboptimal specificity and sensitivity. The generally accepted gold standard, colonoscopy, is cumbersome, expensive, has capacity problems, and complications. In addition, sigmoidoscopy misses advanced adenomas and cancer in the right side of the colon. In previous colonoscopy-based screening studies, detection rates for ad-

vanced adenomas are between 1.8% and 10.6%, and for cancer between 0.3% and 1.0%.[26,34-37] In our study, including all participants, the detection rate of advanced adenomas and cancer was on average 1.9%, and for cancer 0.3%. However, in 56% of the participants with a positive FOBT, advanced adenomas and cancer were found and cancer alone in 8.6%.

What is the meaning of our findings for a general screening population? In 2004 a total of 410,000 endoscopies including gastroduodenoscopies, endoscopic retrograde cholangiopancreatographies, and colonoscopies were performed in Dutch endoscopy centers.[38] In our country, 4.5 million people between 50 and 75 years are potential candidates for screening. This implies that, in a G-FOBT based screening program, 42,500 additional colonoscopies have to be performed to detect almost 4,500 cancers and 20,000 advanced adenomas. In an I-FOBT–based screening program, almost 125,000 additional colonoscopies have to be performed to detect about 11,000 cancers and 55,000 advanced adenomas. If the population at risk will primarily be screened by colonoscopy, about 1.2 million colonoscopies have to be performed to detect about 9,700 cancers and 75,000 advanced adenomas presuming that, according to Segnan et al,[35] 26.5% of the population will participate in such a screening program, that 0.8% of these subjects will have cancer, and 6.3% advanced adenomas. Thus, the number to scope to find 1 cancer or 1 advanced adenoma are comparable between G-FOBT- and I-FOBT–based screening programs. Compared with FOBT-based screening programs, the number to scope to find 1 cancer in a colonoscopy based screening program is 13 times higher and the number to find 1 advanced adenoma is 7 times higher.

Another major advantage of the I-FOBT we used is that the test is semiquantitative. This allows shifting the cutoff value of the test. When resources are limited and the prevalence of CRC in the population is expected to be low, one could consider increasing the cutoff value of the test and vice versa. In addition, the I-FOBT does not have dietary restrictions, because it is specific for human blood. In contrast, extensive dietary restrictions are advised for the G-FOBT to avoid false-positive test results, although others question this.[39,40] In our study, we did not advise dietary measures for subjects receiving the G-FOBT, because this would make comparison unfairly biased in favor of the I-FOBT.

Despite written and verbal information about colonoscopy before and after performing a FOBT, 16% of subjects with a positive test refused this follow-up examination. This was comparable to other FOBT-based screening studies.[19,20,27,30] The majority of the subjects ultimately refused colonoscopy because of anxiety. Increased adherence positively influences detection rates and the precision of the confidence intervals for both tests, but the conclusions of our study will not change, because adherence was not dependent on the kind of FOBT.

Advanced adenomas and cancer were found more often in men than in women, despite the fact that more women than men participated in the study. In addition, advanced adenomas and cancer were also more often detected in older persons. This is in line with other studies.[36,41,42] Thus, the diagnostic yield increases with age. This finding may help to narrow the age range for screening in different populations, depending on resources and prevalence of advanced adenomas and cancer. Male preponderance for advanced adenomas and cancer may be attributed to sex hormones; it has been hypothesized that estrogens may have protective effects on the development of CRC, or to gender differences in exposure to environmental factors, like smoking, dietary fiber, or exercise.[43] There was no difference between FOBTs concerning the preponderance of males and older individuals having advanced adenomas or cancer.

Several previous studies dealt with the diagnostic performance of FOBTs. Most of these studies reported comparable results to our data.[4,5,10,25-28,44] Although some studies reported lower diagnostic performance for G-FOBTs, others showed somewhat better results for I-FOBTs.[4,5,25,26] Up to now, a randomized comparison between G-FOBT and I-FOBT in a screening population was lacking. There can be several reasons for the observed differences between these studies. One of the most important variables is the definition of advanced adenomas, which varies between studies. It remains unclear which lesions ultimately will develop into cancer and in what timeframe.[45,46] Therefore, we were conservative in defining advanced adenomas. We also provided subgroup analyses to make comparison between studies more feasible.

There is a small difference in specificity between G-FOBT and I-FOBT. However, even small differences in specificity result in high absolute numbers of false positives, increasing costs and work load for endoscopy units. The method we used for estimating specificity slightly overestimates the true specificity especially for more prevalent lesions and more sensitive tests.[32] In turn, the difference in specificity is slightly underestimated up to at most 0.2% for advanced adenomas and cancer, increasing the difference in favor of the G-FOBT. Overall, the conclusions about statistical significance and clinical relevance therefore do not change by the systematic error of the specificity estimation.

In conclusion, direct comparison between a G-FOBT and an I-FOBT revealed that the number to scope to find 1 CRC is not different between G-FOBT and I-FOBT. However, participation and detection rates for advanced adenomas and cancer were significantly higher in the group tested with I-FOBT. By result, 2.5 times more advanced adenomas and cancer and 2.2 times more cancers were detected with I-FOBT compared with G-FOBT. Therefore, G-FOBT significantly underestimates the preva-

lence of advanced adenomas and cancer compared with I-FOBT in a screening population.

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This trial is registered under ISRCTN57917442 at Current Controlled Trials (www.controlled-trials.com).

Annals of Internal Medicine | ARTICLE

A Quantitative Immunochemical Fecal Occult Blood Test for Colorectal Neoplasia

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Background: Guaiac-based fecal occult blood tests (FOBTs) for colorectal cancer screening are not specific for human hemoglobin and have low sensitivity. Automated-development, immunochemical FOBT is quality-controlled, is specific for human hemoglobin, and does not require diet restriction.

Objectives: To measure the sensitivity and specificity of quantitative immunochemical fecal hemoglobin measurements for detection of cancer and advanced adenoma in patients undergoing colonoscopy, to determine fecal hemoglobin thresholds that give the highest posttest probability for neoplasia, and to determine the number of immunochemical FOBTs needed.

Design: Prospective, cross-sectional study.

Setting: Ambulatory endoscopy services of the main health medical organization in Tel Aviv, Israel.

Participants: 1000 consecutive ambulatory patients—some asymptomatic but at increased risk for colorectal neoplasia and some symptomatic—who were undergoing elective colonoscopy and volunteered to prepare immunochemical FOBTs.

Intervention: The hemoglobin content of 3 bowel movements was measured, and the highest value was compared with colonoscopy findings.

Measurements: Sensitivity, specificity, predictive values, likelihood ratios, and 95% CIs of fecal hemoglobin measurements for clinically significant neoplasia, their relationship to the amount of fecal hemoglobin measured, and the number of immunochemical FOBTs performed.

Results: Colonoscopy identified clinically significant neoplasia in 91 patients (cancer in 17 patients and advanced adenomas in 74 patients). Using 3 immunochemical FOBTs and a hemoglobin threshold of 75 ng/mL of buffer, sensitivity and specificity were 94.1% (95% CI, 82.9% to 100.0%) and 87.5% (CI, 85.4% to 89.6%), respectively, for cancer and 67% (CI, 57.4% to 76.7%) and 91.4% (CI, 89.6% to 93.2%), respectively, for any clinically significant neoplasia.

Limitations: The fecal sampling method is standardized, but the sample size depends on fecal consistency. Some patients were tested while discontinuing aspirin and anticoagulant therapies. Study patients were at increased risk, and results might not apply to average-risk populations.

Conclusions: Quantitative immunochemical FOBT has good sensitivity and specificity for detection of clinically significant neoplasia. Test performance in screening average-risk populations is not known.

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A colorectal cancer screening test should identify persons with early-stage cancer that is an immediate medical threat and persons with advanced adenomas that could be a future threat. As well as having high sensitivity, the screening test should have high specificity for detecting clinically significant neoplasia, cancer, and advanced adenomas to minimize follow-up colonoscopy examinations (1).

The commonly used guaiac-based fecal occult blood tests (FOBTs) have low specificity for detecting human hemoglobin and relatively low sensitivity for identifying clinically significant colorectal neoplasia (1–8). Office-developed qualitative immunochemical FOBTs are specific for detection of human hemoglobin and have improved test specificity (1, 4–6, 9–13). However, the manufacturers designed the test to have sensitivity for measuring hemoglobin similar to that of a sensitive guaiac-based FOBT, which is a limitation. Moreover, we found that doing the actual measuring in the office was not conducive to large-scale screening while maintaining quality control (1, 2, 6). We investigated a clinical laboratory–based immunochemical test that measures the hemoglobin content of a stool sample.

Laboratory-based, automated, immunochemical measurement of fecal human hemoglobin eliminates the need for diet restrictions, is specific for human hemoglobin, and allows for quality control. In addition, clinicians can choose a fecal hemoglobin threshold level to perform colonoscopy and can adjust this threshold to take account of the patient's risk for advanced neoplasia and the availability of quality colonoscopy (1, 14–20).

The quantitative immunochemical FOBT has been evaluated in Japan and elsewhere (14–22). However, to our knowledge, no English-language publication systemat-

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Context

Although screening with a guaiac-based fecal occult blood test (FOBT) reduces colorectal cancer mortality, better tests are needed.

Contribution

In the study, 1000 patients undergoing diagnostic colonoscopy provided fecal samples that a clinical laboratory tested with a quantitative immunochemical test for hemoglobin. Hemoglobin content was highest in samples from people with significant neoplasia, for which sensitivity and specificity were 67% and 91%, respectively. Positive and negative likelihood ratios were 7.8 and 0.36, respectively.

Cautions

The authors did not compare the immunochemical FOBT with guaiac-based FOBT. The study included people with symptoms.

Implications

The quantitative immunochemical test for fecal hemoglobin is a promising test that needs evaluation in a screening population.

—The Editors

ically compares fecal immunochemical hemoglobin content with total colonoscopy findings. We aimed to measure the sensitivity and specificity of different levels of fecal hemoglobin for detecting clinically significant colorectal neoplasia versus colonoscopy, to determine the posttest probability of advanced neoplasia at different fecal hemoglobin threshold values, and to determine the optimal number of fecal samples.

Methods

Patients

We asked consecutive ambulatory persons who were referred for colonoscopy to volunteer to prepare immunochemical FOBTs for research purposes. Some patients were asymptomatic and were invited for elective colonoscopy, some patients were at high risk for colorectal cancer (these patients were from our clinic), and some patients were symptomatic and were referred by their treating physician (Table 1 and Figure 1). We have reported partial findings on the initial 500 patients (20).

Exclusions were concurrent hospitalization, visible rectal bleeding, known diagnosis of inflammatory bowel disease, hematuria, menstruation at the time of obtaining a stool specimen, and inability to prepare the immunochemical FOBT (Figure 1). We did not exclude patients with long-term use of nonsteroidal anti-inflammatory drugs or anticoagulant therapy that was stopped for colonoscopy.

Endoscopy and Lesions

We inserted the colonoscope to the cecum or an obstructing carcinoma. We excluded 49 patients with an incomplete colonoscopy. Biopsy was done on lesions or they were removed, and their sites were noted. We classified abnormal findings by number of polyps, polyp sizes, and sites grouped by location (proximal [colon cecum to and including splenic flexure] or distal colon) and by histologic characteristics. The endoscopist estimated polyp size with a calibrated open biopsy forceps. We grouped adenomas and mass lesions by diameter or size ($\leq$5 mm, 6 to 9 mm, or $\geq$10 mm) and by histologic characteristics (tubular, serrated, tubulovillous, or villous). We classified dysplasia as low grade or high grade. Pathologists were blinded to the immunochemical FOBT results. Clinically significant neoplasia includes colorectal cancer or advanced polyps (adenomas $\geq$10 mm in diameter, adenomas with $\geq$20% villous histologic characteristics, or any high-grade dysplasia regardless of size) (23). We classified patients with more than 1 lesion according to the most advanced lesion. We reexamined all advanced adenomas smaller than 10 mm to confirm their histologic diagnosis (24).

Fecal Sampling

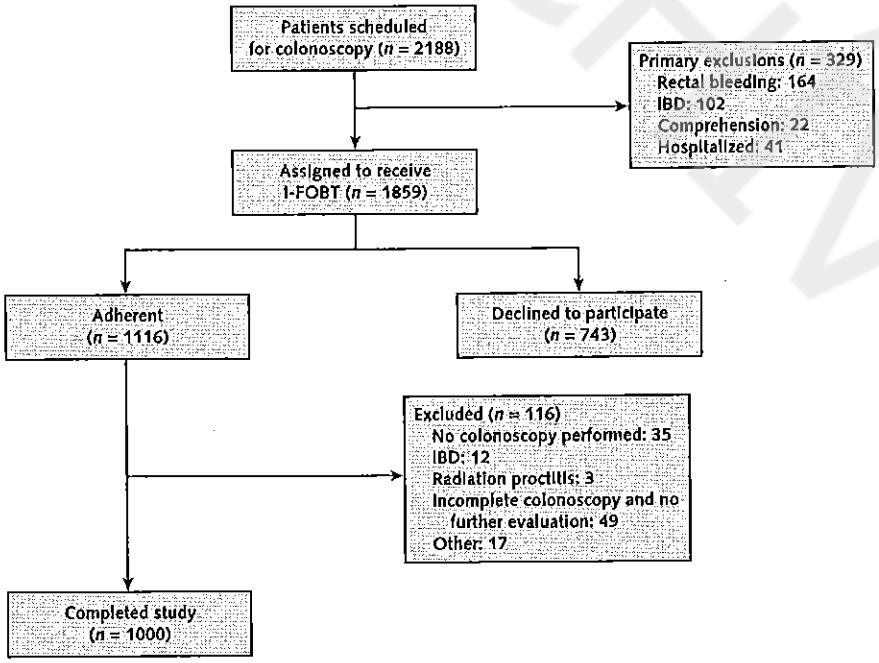
Participants received an explanation of the test and written instructions on how to prepare the fecal samples. After voiding urine and flushing the toilet before having a bowel movement, participants placed a disposable paper "float" in the toilet bowl to immobilize the stool for easy sampling (**Appendix Figure 1**, available at www.annals.org). Each fecal sample tube has a unique bar code. Before preparing the sample, the patient wrote his or her name and the date on the tube. The immunochemical FOBT sampling probe is inserted into an 8-cm × 2-cm test tube–shaped container. The patient inserts the probe into several different areas of the stool and then reinserts it firmly into the tube to seal it (**Appendix Figure 2**, available at www.annals.org). The probe tip with the fecal sample is suspended in a standard volume of hemoglobin-stabilizing

Table 1. **Baseline Characteristics***

Characteristic	Value
Total patients, *n*	1000
Men, *n* (%)	500 (50)
Mean age (SD), y	63.2 (12.1)
Reasons for colonoscopy, *n* (%)	
Positive guaiac-based FOBT result	101 (10.1)
Asymptomatic high-risk	428 (42.8)
Past colorectal neoplasia	348 (34.8)
Family history of colorectal neoplasia	80 (8)
Symptomatic	471 (47.1)
Change in bowel habits	150 (15)
Anemia	99 (9.9)
Abdominal pain, weight loss	120 (12)
Anal symptoms	54 (5.4)
Other	48 (4.8)

* FOBT = fecal occult blood test.

Figure 1. Study flow diagram.



I-FOBT = immunochemical fecal occult blood test; IBD = inflammatory bowel disease.

buffer. According to the manufacturer's manual, the amount of stool obtained by this process is semistandardized (but does depend on fecal consistency) at 10 mg (SD, 0.5). According to the manufacturer's data, the mean specimen size ranges from 9.03 mg (SD, 0.29) for diarrhea to 11.89 mg (SD, 0.76) for hard stools. Examinees prepared 3 daily or consecutive samples during the week before colonoscopy examination. They observed no dietary or medication restrictions other than stopping aspirin and anticoagulant therapy before endoscopy. Samples were stored in double ziplock bags at 4 °C until development within 2 weeks (20, 25). We processed the samples by using the OC-MICRO instrument (Eiken Chemical Co., Tokyo, Japan) as described in the Appendix (available at www.annals.org).

For pricing the immunochemical FOBT at $20, we used the local agent's price for 3 tests and added administrative costs. In comparison, the authorized pricing (from Israel's Ministry of Health) is $13 for screening with 3 guaiac-based FOBTs.

The ethics committee of the Rabin Medical Center, Tel Aviv, Israel, approved the study in 2004. All participants gave written informed consent for the immunochemical FOBT and colonoscopy examination.

Statistical Analysis

We recorded each patient's most severe pathologic finding (histologic characteristics, polyp size, and number of polyps) and the highest amount of fecal hemoglobin measured in that patient's 3 immunochemical FOBT samples. We classified persons with only small rectal hyperplastic polyps as not having neoplasia. We analyzed fecal hemoglobin measurements according to the number of adenomas (<3 adenomas or ≥3 adenomas), lesion size, site in the colon (proximal or distal), and histology. We analyzed colorectal cancer and advanced adenoma separately and together as clinically significant colorectal neoplasia.

Since the study sample was heterogeneous, we compared the sensitivity and specificity of the immunochemical FOBT in the 3 main categories of reason for referral (Appendix Table 1, available at www.annals.org) by using the chi-square test and Fisher exact test.

To classify a patient's fecal hemoglobin level as normal or abnormal, we used 2 thresholds: the published and manufacturer-suggested threshold of 100 ng/mL of buffer and a threshold of 75 ng/mL, which we thought would give a higher sensitivity for detecting clinically significant neoplasia (14, 15, 20). We also repeated these analyses at different thresholds in increments of 25 ng/mL, ranging from 50 ng/mL to 200 ng/mL.

We measured the diagnostic value of the immunochemical FOBT for detecting clinically significant neoplasia by using 5 criteria: sensitivity, specificity, likelihood ratios, and posttest probability after a negative and positive result. We compared sensitivity and specificity by using threshold values of 75 ng/mL or greater and 100 ng/mL or

greater for abnormal findings and the McNemar test for symmetry. We reported polyp sizes and fecal hemoglobin measurements as means (SDs) and by quartiles. We also reported 95% CIs for means and likelihood ratios (26).

Since the distribution of fecal hemoglobin measurements was not normally distributed, we used 1) a parametric test for $\log_2$-transformed data (since log of 0 is not defined, we coded original measurements of 0 as −5) and 2) nonparametric tests for nontransformed data. We measured the degree of association among pathology findings, number and size of polyps, histology, and the immunochemical fecal hemoglobin measurement by the Mann–Whitney test for the 2 independent groups.

We compared fecal hemoglobin measurements in independent diagnosis categories by the Kruskal–Wallis nonparametric analysis of variance (ANOVA). We made multiple comparisons between each pair of diagnosis categories by using Gabriel, Dunnet, and Games–Howell tests. In addition, we compared combinations of categories—all adenomas versus normal colonoscopies and clinically significant neoplasia versus other adenomas.

We drew receiver-operating characteristic (ROC) curves for each immunochemical FOBT prepared as aids to determine immunochemical fecal hemoglobin cutoff values and the number of tests that best discriminates between clinically significant neoplasia and other findings. We compared fecal hemoglobin measurements in 3 samples by using ANOVA with repeated measures, and we calculated interclass correlation coefficient for all 3 measures and Pearson correlation coefficients between each pair of measures.

We calculated the positive and negative likelihood ratios for clinically significant neoplasia and constructed a nomogram to relate pretest probability to posttest probability (26). The nomogram uses the likelihood form of the Bayes' theorem to estimate the effect of a diagnostic test result on the probability that a patient has the disease.

We used SPSS for Windows software, version 13.0 (SPSS Inc., Chicago, Illinois), for the analysis.

Role of the Funding Sources

Instrument and reagents were provided by the Eiken Chemical Company, Tokyo, Japan; Alfa Wasserman, Milan, Italy; and Pharmatrade, Kfar Saba, Israel. Research grants from the Eiken Chemical Company and the Katzman Family Foundation supported other costs. The funding sources had no role in the design, analysis, or interpretation of the study or in the decision to submit the manuscript for publication.

Results

Patients

Of 2188 patients who were scheduled for colonoscopy, 1859 met the study criteria and were invited to participate. Of these patients, 1116 agreed to participate. We subsequently excluded 116 patients, and 1000 patients completed the study (Figure 1). Table 1 shows their characteristics. Patients with an elevated fecal hemoglobin level but normal colonoscopy examination were followed clinically.

Colonoscopy Results

Seventy patients had incomplete colonoscopy examinations because of inadequate bowel preparation, technical problems, or patient discomfort. We repeated colonoscopy in 14 patients and included these patients in the study sample. None of the 56 remaining patients had repeated colonoscopy, and they were excluded from the study (3 patients had a normal double-contrast barium enema, 4 patients had normal computed tomography colonography, and 49 patients had no further large-bowel investigations). Appendix Table 1 (available at www.annals.org) shows immunochemical FOBT results and clinically significant neoplasia according to the reason for colonoscopy referral. Immunochemical FOBT sensitivity and specificity for neoplasia were similar in the 3 major diagnostic categories.

We found polyps in 356 patients. One hundred twelve patients had a hyperplastic polyp smaller than 10 mm, 13.1% of patients had single adenomas, and 11.3% of patients had several adenomas. Thirteen adenomas had high-grade dysplasia, and 2 adenomas were smaller than 10 mm (Table 2).

We defined clinically significant neoplasia (found in 91 patients) as cancer ($n = 17$) or at least 1 advanced adenoma ($n = 74$) (Table 2).

Fecal Hemoglobin Measurements

We measured the hemoglobin content of each of 3 consecutive fecal samples but considered them to represent 1 test, to which we assigned the highest of the 3 immunochemical FOBT results.

Hyperplastic Polyps

Fecal hemoglobin measurements in 739 patients with only hyperplastic polyps smaller than 10 mm did not differ from those of patients with normal colonoscopy (fecal hemoglobin level, 35 ng/mL [SD, 150] [95% CI, 23 to 47 ng/mL] vs. 35 ng/mL [SD, 143] [CI, 25 to 45 ng/mL]).

Adenomas or Advanced Adenomas

Table 2 displays the characteristics of the adenomatous polyps and the patients' fecal hemoglobin measurements. Patients with adenomas of 6 to 9 mm or 10 mm or greater in diameter, as well as patients with 3 or more adenomas, had significantly elevated but differing fecal hemoglobin levels compared with patients with normal examinations ($P < 0.001$). Patients with villous or serrated adenomas or high-grade dysplasia had higher fecal hemoglobin levels than those with tubular adenomas and low-grade dysplasia or no neoplasia ($P < 0.001$). In patients with an advanced adenoma, fecal hemoglobin measure-

Table 2. Characteristics of Lesions Found at Colonoscopy and Highest Measurements of 3 Fecal Hemoglobin Tests*

Characteristic	Patients, *n* (%)	Mean Lesion Size (SD) [95% CI], *mm*	Mean I-FOBT Result (SD) [95% CI], *ng/mL*	Fecal Hemoglobin Level, *ng/mL*				
				Minimum	Maximum	25th Percentile	Median	75th Percentile
Normal	739 (73.9)		35 (143) [25–45]	0	1641	0	6	16
Adenomas	244 (24.4)	6.9 (5.4) [6.2–7.6]	202 (490) [140–263]	0	3050	2	17	107
Histology								
LGD: tubular	198 (81.1)	5.6 (3.8) [5.1–6.2]	137 (384) [84–191]	0	2864	1	12	61
LGD: tubulovillous or villous	31 (12.7)	11.7 (6.9) [9.2–14.1]	484 (775) [211–757]	0	3050	14	107	606
LGD: serrated	2 (0.9)	24.0 (8.5) [12.2–35.8]	1628 (1120) [76–3180]	836	2420	–	–	–
HGD (any adenoma)	13 (5.3)	12.1 (8.2) [7.2–16.5]	298 (464) [45–550]	3	1695	20	113	424
Size in diameter								
≤5 mm	132 (54.1)	3.6 (1.0) [3.4–3.7]	78 (247) [36–120]	0	1774	0	10	26
6–9 mm	54 (22.1)	7.0 (1.3) [6.7–7.4]	142 (337) [52–232]	0	1695	7	20	70
≥10 mm	58 (23.8)	14.3 (6.1) [12.8–15.9]	538 (789) [335–741]	0	3050	22	171	628
Number								
<3 adenomas	159 (65.2)	6.8 (5.9) [5.9–7.8]	131 (298) [84–177]	0	2069	1	16	99
≥3 adenomas	85 (34.8)	7.0 (4.3) [6.1–7.9]	336 (707) [185–486]	0	3050	5	17	172
All nonadvanced adenomas	170 (17.0)	4.4 (1.80) [4.1–4.7]	79 (236) [44–115]	0	1774	1	11	32
Advanced adenoma†	74 (7.4)	12.6 (6.4) [11.2–14.1]	485 (744) [315–654]	0	3050	19	113	570
Colon site								
Proximal‡	31 (12.7)	12.4 (6.8) [10.1–14.7]	499 (774) [227–772]	0	2864	14	107	510
Distal	42 (17.2)	12.9 (6.2) [11.0–14.7]	501 (737) [279–724]	0	3050	22	132	628
Cancer	17 (1.7)	32.9 (11.0) [27.7–38.1]	1087 (821) [697–1477]	57	2425	322	1047	1749
Stages								
Dukes stages A and B	15 (88.2)	30.7 (9.3) [26.0–35.4]	1045 (777) [652–1439]	57	2385	271	1047	1746
Dukes stage C or higher	2 (11.8)	50.0 (7.10) [40.2–59.8]	1399 (1452) [614–3411]	372	2425	–	–	–
Colon site								
Proximal‡	10 (58.8)	33.8 (10.30) [27.4–40.2]	701 (672) [285–1118]	57	1752	106	450	1436
Distal	7 (41.2)	31.7 (12.5) [22.4–41.0]	1637 (720) [1104–2171]	737	2425	1047	1436	2385
Cancer and advanced adenoma†	91 (9.1)	17 (11.8) [14.6–19.5]	597 (790) [435–759]	2	55	26	15	836

* HGD = high-grade dysplasia; I-FOBT = immunochemical fecal occult blood test; LGD = low-grade dysplasia.
† Includes single adenomas >10 mm in size or ≥20% villous in histology or any HGD.
‡ Proximal: Colon from cecum to and including splenic flexure.

ments were similar whether the location was the proximal or distal colon ($P = 0.510$).

Cancer

The fecal hemoglobin measurements of patients with cancer were significantly elevated compared with those of patients with no neoplasia ($P < 0.001$), regardless of cancer stage or site (Table 2). Fecal hemoglobin level was significantly higher with distal colorectal cancer than with proximal colorectal cancer ($P = 0.025$).

All Clinically Significant Neoplasia

The 91 patients with clinically significant neoplasia include 17 patients with cancer and 74 patients with at least 1 advanced adenoma. Their mean fecal hemoglobin measurements were significantly elevated compared with those of patients with non–clinically significant neoplasia or normal colonoscopy ($P < 0.001$) (Table 2).

Range of Fecal Hemoglobin Measurements

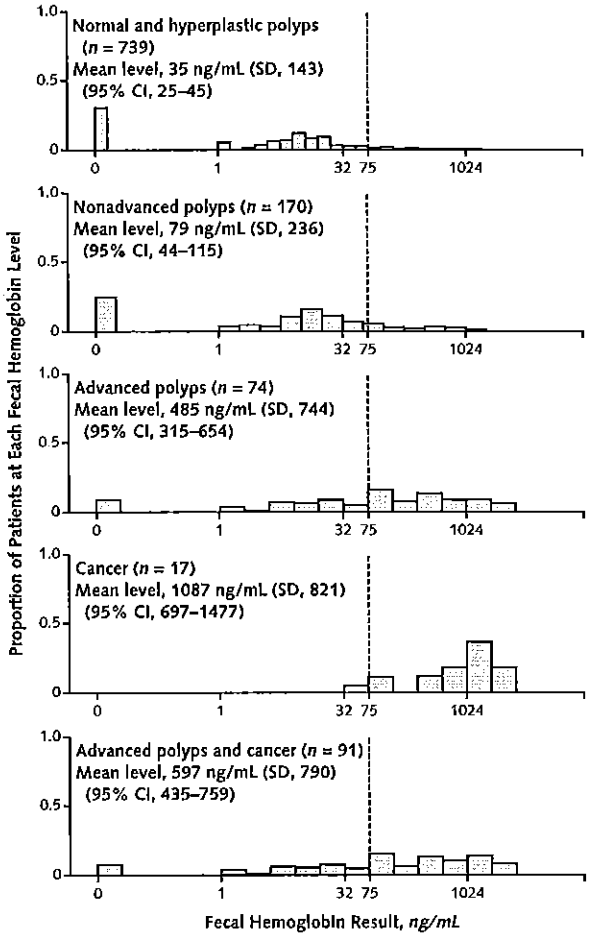
Figure 2 shows the distribution of fecal hemoglobin levels in patients whose most clinically significant lesion was a nonadvanced adenoma, an advanced adenoma, cancer, or any clinically significant neoplasia. No fecal hemoglobin level perfectly distinguishes patients with advanced neoplasia from other patients.

Sensitivity, Specificity, and Likelihood Ratio for Clinically Significant Neoplasia

We measured the sensitivity and specificity of the immunochemical FOBT result (by using the highest level in 3 samples) at various hemoglobin thresholds (Table 3). At the 75-ng/mL fecal hemoglobin threshold, the sensitivity and specificity for detecting all clinically significant neoplasia were 67.0% (CI, 57.4% to 76.7%) and 91.4% (CI, 89.6% to 93.2%), respectively. The corresponding positive and negative likelihood ratios were 7.81 and 0.36, respectively. At the 100-ng/mL fecal hemoglobin threshold, sensitivity and specificity were 61.5% (CI, 51.5% to 71.5%) and 93.4% (CI, 91.8% to 95.0%), respectively, and posi-

9

Figure 2. Histograms of fecal hemoglobin density.



Using a $\log_2$ scale, the analysis demonstrates statistically significantly different values for advanced polyps, cancer, or clinically significant neoplasia compared with normal and hyperplastic polyps or nonadvanced polyps, with little overlap of the latter 2 conditions. The mean fecal hemoglobin value (SD) and 95% CI are indicated for each category. The 75-ng/mL hemoglobin threshold for calling a test result positive or negative is indicated in each category (*dashed lines*). The vertical bars represent the proportion that has the specified immunochemical fecal hemoglobin level.

tive and negative likelihood ratios were 9.32 and 0.41, respectively. The 75-ng/mL fecal hemoglobin threshold increased sensitivity but reduced specificity. The sensitivity for detecting cancer was considerably higher than that for detecting all clinically significant neoplasia, but specificity was lower (Table 3).

Within-Patient Variation in Immunochemical FOBT Results

Figure 3 demonstrates the within-patient variation of the first 2 immunochemical FOBT measurements from each patient. It also shows the relative proportions of patients with clinically significant neoplasia (cancer or advanced adenomas) versus other results for each of the 4 possible combinations of first and second immunochemical FOBT results (above or below the 75-ng/mL fecal hemoglobin threshold).

The interclass correlation coefficient between the $\log_2$ transformations of all 3 immunochemical FOBT samples was 0.583 (data not shown). The correlation coefficients of the first and second immunochemical FOBT samples, first and third, and second and third were 0.597, 0.553, and 0.599, respectively. These moderate correlations presumably reflect daily variations in blood loss. Appendix Table 2 (available at www.annals.org) shows that using the highest of all 3 tests gave the highest sensitivity but gave somewhat lower specificity.

The Number of Immunochemical FOBTs Needed to Identify Clinically Significant Neoplasia

Figure 4 displays ROC curves obtained with the first, the initial 2, and all 3 immunochemical FOBT measurements for each participant. The area under the curve (an overall measure of test discrimination) for cancer or all clinically significant neoplasia was the same when using the highest measurement of all 3 tests or just of the first 2 tests, indicating that using either 2 or 3 tests provided the best discrimination for cancer. Appendix Table 2 (available at www.annals.org) shows that sensitivity increases and specificity decreases as the number of samples increases at both the 75-ng/mL and 100-ng/mL thresholds.

Posttest Probability Corresponding to Immunochemical FOBT Results

Figure 5 illustrates the posttest probability of advanced neoplasia for selected pretest probabilities of disease across increasing fecal hemoglobin thresholds. The posttest probability after a positive test result (equal to positive predictive value) varies little as the immunochemical FOBT threshold increases. Figure 6 is a nomogram for estimating the posttest probability at different fecal hemoglobin levels. Appendix Table 3 (available at www.annals.org) contains the likelihood ratios for specific fecal hemoglobin levels.

False-Negative Immunochemical FOBT Results

Two cases of cancer were not identified at the 100-ng/mL hemoglobin threshold: a proximal, 1.5-cm, Dukes stage A malignant lesion (fecal hemoglobin level, 57 ng/mL) and a proximal, 3-cm, Dukes stage C malignant lesion (fecal hemoglobin level, 85 ng/mL). At the 75-ng/mL threshold, only the former was not detected. The remaining cases not identified were advanced adenomas, that were 45% of which were smaller than 10 mm in diameter.

False-Positive Immunochemical FOBT Results

Sixty screened patients without clinically significant colorectal neoplasia had a fecal hemoglobin measurement greater than 100 ng/mL, and 78 screened patients with a measurement greater than 75 ng/mL were followed clinically for a mean of 16.4 months (SD, 4.2). One patient, who had both a family history of colorectal cancer and a

Table 3. Sensitivity, Specificity, and Likelihood Ratios by Fecal Hemoglobin Level, Using the Highest of 3 Test Results*

Variable	Patients with True-Positive Test Result, *n*	Patients with False-Negative Test Result, *n*	Patients with True-Negative Test Result, *n*	Patients with False-Positive Test Result, *n*	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive LR (95% CI)	Negative LR (95% CI)
Cancer								
Fecal hemoglobin threshold								
≥50 ng/mL	17	0	830	153	100 (100–100)	84.4 (82.2–86.7)	6.42 (NA)	0 (NA)
≥75 ng/mL	16	1	865	118	94.1 (82.9–100)	87.5 (85.4–89.6)	7.52 (1.2–47.23)	0.07 (0.06–0.08)
≥100 ng/mL	15	2	882	101	88.2 (72.9–100)	89.7 (87.8–91.6)	8.59 (2.28–32.28)	0.13 (0.11–0.16)
≥125 ng/mL	14	3	899	84	82.4 (64.2–100)	91.5 (89.7–93.2)	9.64 (3.19–29.08)	0.19 (0.16–0.23)
≥150 ng/mL	14	3	903	80	82.4 (64.2–100)	91.9 (90.2–93.6)	10.12 (3.35–30.60)	0.19 (0.16–0.23)
All clinically significant neoplasia (cancer and advanced polyps)								
Fecal hemoglobin threshold								
≥50 ng/mL	66	25	805	104	72.5 (63.4–81.7)	88.6 (86.5–90.6)	6.34 (4.29–9.36)	0.31 (0.26–0.37)
≥75 ng/mL	61	30	836	73	67 (57.4–76.7)	91.4 (89.6–93.2)	7.81 (5.39–11.32)	0.36 (0.3–0.43)
≥100 ng/mL	56	35	849	60	61.5 (51.5–71.5)	93.4 (91.8–95.0)	9.32 (6.51–13.35)	0.41 (0.34–0.5)
≥125 ng/mL	49	42	860	49	53.8 (43.6–64.1)	94.6 (93.1–96.1)	9.99 (7.04–14.18)	0.49 (0.4–0.6)
≥150 ng/mL	49	42	864	45	53.8 (43.6–64.1)	95 (93.6–96.5)	10.88 (7.66–15.45)	0.49 (0.39–0.6)

* LR = likelihood ratio; NA = not applicable.

personal history of adenomas, was found to have a 1-cm colorectal adenoma with low-grade dysplasia at the hepatic flexure after 2 years.

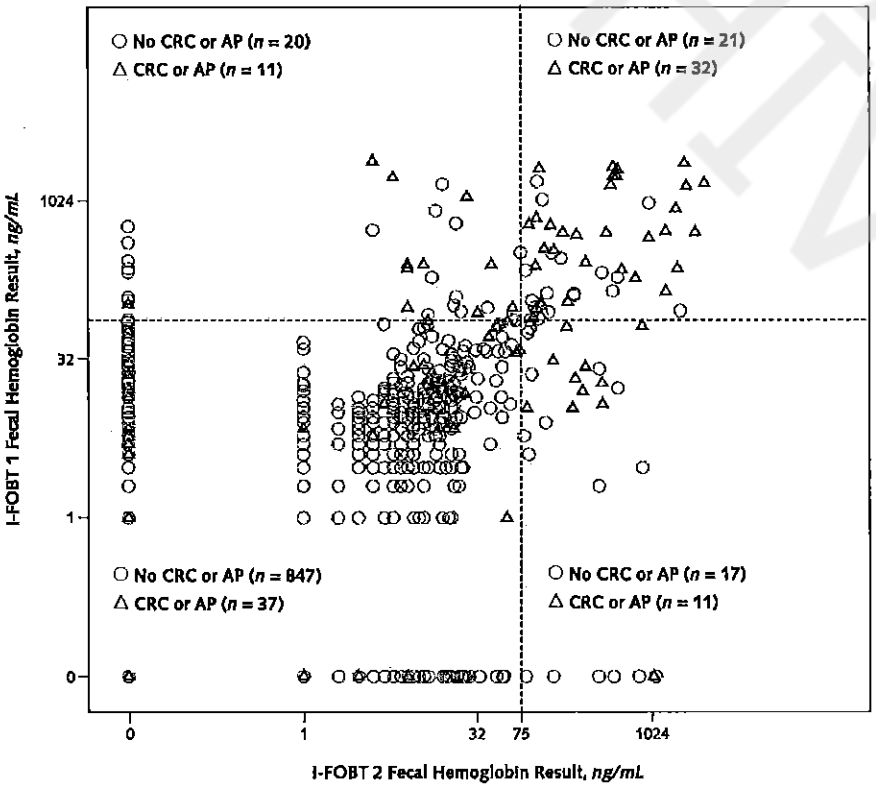
Discussion

We performed a detailed evaluation of an immunochemical method to measure the amount of occult blood in fecal samples. When using the hemoglobin threshold of 75 ng/mL or greater to define an abnormal result, the test's sensitivity was 94.1% for detecting colorectal cancer and 67.0% for detecting all clinically significant neoplasia with corresponding specificities of 87.5% and 91.4%, respectively. The amount of fecal hemoglobin in most nonadvanced adenomas was less than 75 ng/mL. This is an advantage, because colonoscopy screening has been criticized for identifying many persons with adenoma who are then entered into a labor-intensive and expensive adenoma follow-up protocol (27). In our heterogeneous study sample, the positive predictive value of 43.9% meant that almost every second colonoscopy performed for a positive immunochemical FOBT result diagnosed a clinically significant neoplasm.

In previous publications (20, 25), we examined the reproducibility of hemoglobin quantification, the stability of the immunochemical FOBT in clinical practice, intrapatient daily variation in fecal hemoglobin loss, and a preliminary comparison of fecal hemoglobin levels with colonoscopy results in 500 patients. Our present analysis adds an additional 500 examinees and many additional analyses that will help physicians to choose the optimal fecal hemoglobin threshold level that triggers a follow-up colonoscopy. To validate this premise, and in contrast to most other retrospective evaluations, we performed a prospective study of patients undergoing colonoscopy (18, 22, 28). We confirmed that the immunochemical FOBT hemoglobin threshold of 100 ng/mL provided acceptable specificity but found, in our larger study sample, a lower sensitivity than with a 75-ng/mL hemoglobin threshold (20). In fact, the quantification of fecal hemoglobin levels allows the clinician to choose the immunochemical FOBT threshold that best suits the clinical situation. For example, the threshold for screening an average-risk population might differ from that for a higher-risk population.

Deciding whether our findings apply to an average-risk screening population is difficult. One issue is whether immunochemical FOBT is more sensitive and specific in a relatively high-risk population, such as that of our study sample, than in lower-risk populations. Bampton and colleagues (19) studied high-risk patients undergoing colonoscopy surveillance. They used the Inform (Insure, Enterix, North Ryde, New South Wales, Australia) immunochemical FOBT between periodic colonoscopy examinations. A positive test result identified all cases of interval cancer and some advanced adenomas (19). We had similar findings (29). In contrast, in a large colonoscopy study of asymptomatic, average-risk screened patients (30), testing a single stool sample with the MagStream (Fujirebio Inc., Tokyo, Japan) automated immunochemical FOBT detected 65.8% of cases of cancer but only 27.1% of all cases of advanced neoplasia. The sensitivity for detecting cancer was similar to the 64.7% sensitivity that we obtained by

Figure 3. Scatterplot illustrating the joint distribution of the first 2 immunochemical fecal occult blood test (*I-FOBT*) measurements on a $\log_2$-transformation scale.



The internal lines are at a 75-ng/mL hemoglobin threshold for calling a test result positive or negative, and numbers in each section show classifications of patients based on this cutoff. Each symbol represents a pair of first and second fecal hemoglobin measurements for one patient. A total of 847 patients without colorectal cancer (*CRC*) or advanced adenomatous polyps (*APs*) (*open circles*) were classified below the 75-ng/mL value as having negative test results for both measurements, while 37 patients with CRC or AP (*open triangles*) also had negative test results. Twenty-one patients without CRC or AP were classified above the threshold as having positive test results both times, as were 32 patients with CRC or AP. Seventeen and 20 patients without CRC or AP were below the cutoff value for 1 measurement but were above the cutoff value for the other measurement. This also occurred for 11 patients with CRC or AP. The correlation coefficient for the first and second I-FOBT (I-FOBT 1 and I-FOBT 2, respectively) samples was 0.597.

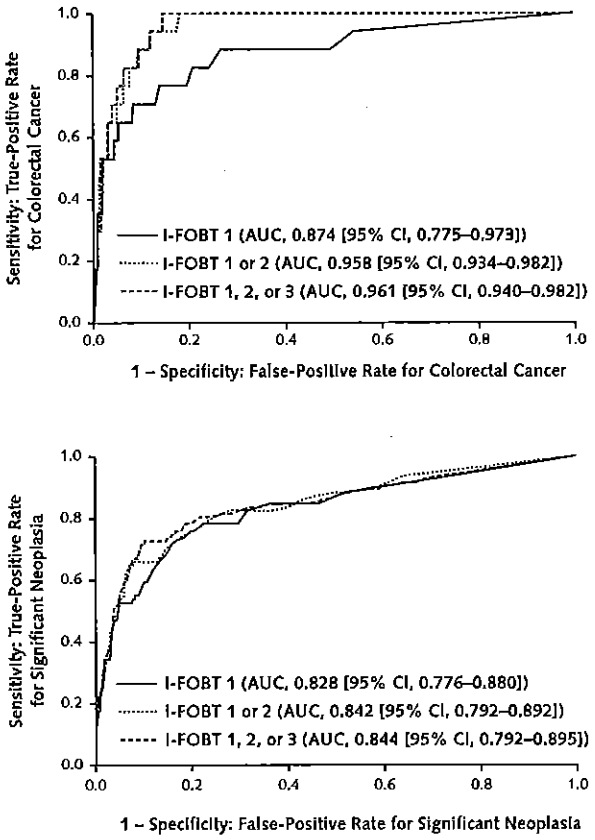
using only the first fecal sample and a 75-ng/mL hemoglobin threshold. That study's sensitivity for detecting advanced adenomas was lower than ours, but the study did not specify the immunochemical FOBT threshold used. We also had compared our results by using a 100-ng/mL hemoglobin threshold with those obtained in the same average-risk screening population with a sensitive guaiac-based FOBT (Hemoccult SENSA, Beckman Coulter, Fullerton, California) who were undergoing colonoscopy. The sensitivity of the 2 FOBTs for detecting clinically significant neoplasia was equal, but the specificity of the immunochemical FOBT test was much higher, which would reduce the number of follow-up colonoscopy examinations needed to identify a patient with a clinically significant neoplasm (21).

We cannot specify the fecal hemoglobin threshold that is most suitable for the average-risk screening population. The objective of the threshold for an average-risk population should be to increase specificity and reduce the proportion of false-positive results. To set the cutoff value for the immunochemical FOBT, we should use the threshold approach to clinical decision making, which involves the pretest probability and the benefits and harms of detection and is a task beyond the scope of our article (31, 32). This approach is illustrated by our nomogram evaluation (Figure 6).

Deciding how many fecal samples and choosing the optimal fecal hemoglobin threshold for screening an average-risk population will also involve evaluating costs and access to colonoscopy (1, 33, 34) (Appendix, available at www.annals.org).

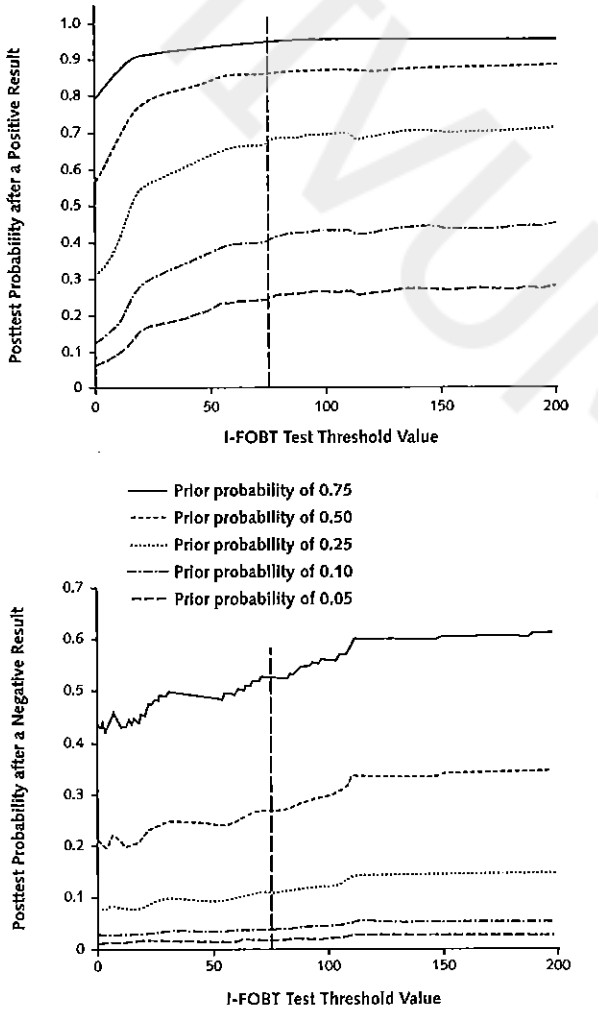
Our study has several limitations. First, the study sample was a heterogeneous mixture of patients who were referred for colonoscopy for clinical indications. Some patients were symptomatic or were taking nonsteroidal anti-inflammatory drugs or anticoagulants, and we are evaluating how these factors affect immunochemical FOBT levels (35). Relative to an asymptomatic screening population,

Figure 4. Receiver-operating characteristic curves for sensitivity and specificity for colorectal cancer (*top*) and clinically significant neoplasia (cancer and advanced polyps) (*bottom*).



Each line represents the highest fecal immunochemical hemoglobin measurement from the specified sequence of fecal samples collected and their added value to provide maximum sensitivity and specificity. I-FOBT 1 = first immunochemical fecal occult blood test collected; I-FOBT 2 = first 2 I-FOBTs collected; I-FOBT 3 = all 3 I-FOBTs collected. Overall, there was no difference between collecting 2 or 3 I-FOBTs. However, the highest sensitivity was obtained when the fecal hemoglobin measurements of all 3 I-FOBTs were used at a 75-ng/mL threshold for calling a test result positive or negative (Appendix Table 2, available at www.annals.org). AUC = area under the curve.

Figure 5. The posttest probability after a positive test result (*top*) and negative test result (*bottom*) for clinically significant neoplasia (colorectal cancer or advanced adenomatous polyps).



The values are presented as a function of the immunochemical fecal occult blood test (*I-FOBT*) threshold for calling a test result positive or negative, with alternate pretest probabilities of colorectal cancer or advanced adenomatous polyps of 0.05, 0.10, 0.25, 0.50, and 0.75. For every I-FOBT threshold value, the sensitivity and specificity (also presented on the receiver-operating characteristic curve) were calculated, as well as positive and negative likelihood ratios. Posttest probabilities for a positive I-FOBT result (*top*) and for a negative I-FOBT result (*bottom*) were calculated.

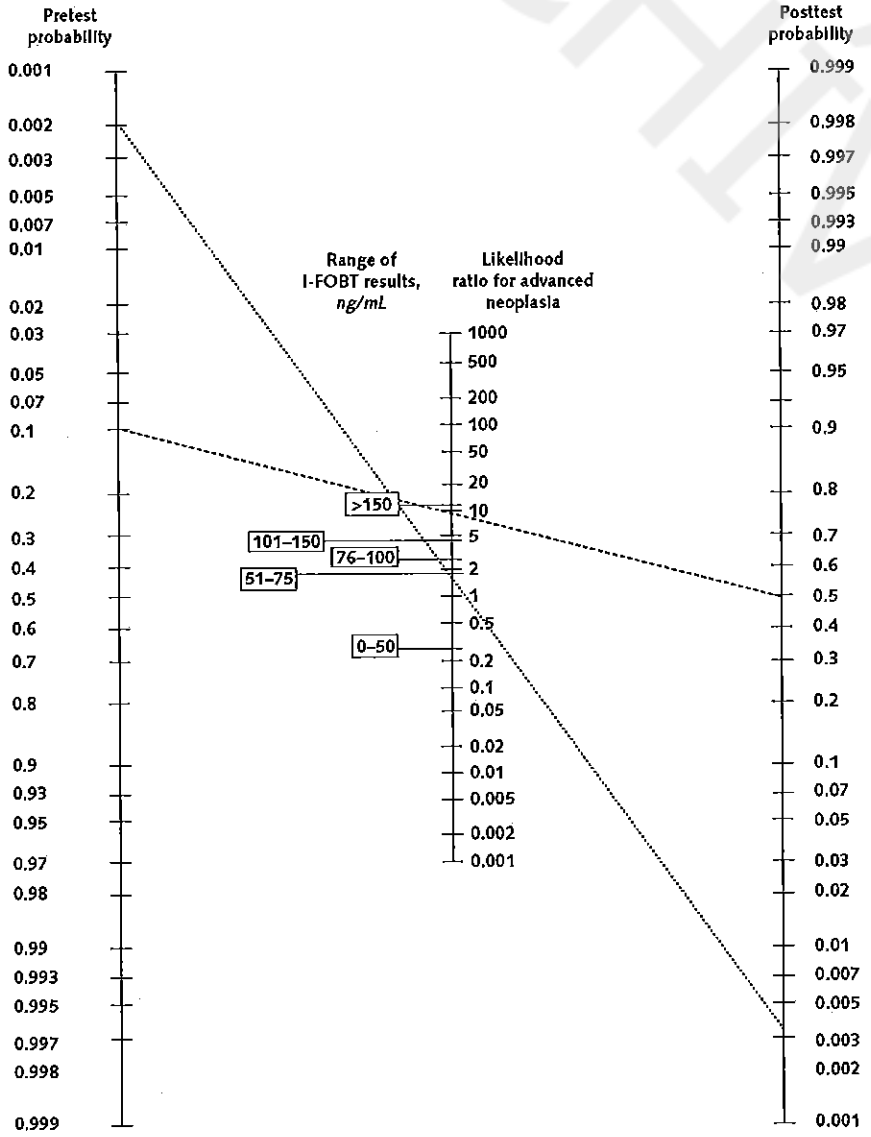
symptomatic patients were more likely to have several large neoplasms that were prone to bleed and were detectable by immunochemical FOBT. Despite this heterogeneity, immunochemical FOBT sensitivity or specificity did not significantly differ among major categories of reasons for referral. We have no direct evidence to extrapolate our findings to the performance of immunochemical FOBT in the target population for screening: average-risk patients 50 years of age or older.

Second, the amount of feces sampled depends on fecal consistency, and therefore, the concentration of hemoglobin in a standard amount of buffer may vary independently of the amount of fecal blood. Also, the amount of bleeding from neoplasia is not consistent or uniform, as shown by the moderate correlations among the 3 immunochemical FOBTs collected. This source of measurement error is common to all methods for detecting fecal blood and is a further reason for using several fecal samples.

Third, the small proximal malignant lesions and small advanced adenomas had low levels of fecal hemoglobin (24, 36).

Fourth, we used colonoscopy as our gold standard. We

Figure 6. Fagan nomogram.



The nomogram provides a graphical tool for estimating how much the result of a test changes the probability that a patient has the disease. To use the nomogram, one should first estimate the probability of the disease before testing, which is often the disease prevalence, although it may be increased or decreased on the basis of clinical findings in the patient population or in a particular patient. The next step is to determine the likelihood ratio corresponding to the diagnostic test result. A line is drawn connecting the pretest probability and the point on the middle vertical line corresponding to the likelihood ratio for the test result (represented by a range of test results [*boxes*]). This line is extended to intersect with the right-hand vertical line, which gives the posttest probability. This point is the new estimate of probability that the patient has the disease. For example, in this heterogeneous-risk, symptomatic study sample, clinically significant neoplasia was found in 91 of 1000 patients (prior probability, 0.091). For a patient with an immunochemical fecal occult blood test (*I-FOBT*) result greater than 150 ng/mL, the sensitivity and specificity of the test were 54% and 95%, respectively, providing a likelihood ratio of 10.881 (0.54/[1 − 0.95]), and posttest probability was 52% (*dashed line*). However, a patient with a pretest probability of 0.002, which is similar to that in a low-risk screening population, and an I-FOBT result between 51 and 75 ng/mL, for which the likelihood ratio is 1.92, would have a posttest probability of advanced neoplasia of 0.38% (*dotted line*). These demonstrate and emphasize how the level of I-FOBT influences the posttest probability of clinically significant neoplasia. The clinical observations behind the likelihood ratios in the nomogram are available in Appendix Table 3, available at www.annals.org.

did not supplement colonoscopy by routine computed tomography colonography, which could have identified more adenomas (37). Other authors have found patients with clinically significant neoplasia who had negative results on initial colonoscopy. This reinforces the value of periodically repeating immunochemical FOBT screening (19, 38).

Despite concern about varying fecal consistency and its effect on sampling, fecal hemoglobin content varied sys-

tematically by site, pathology, and lesion size. Since the immunochemical test for blood requires antigenically intact globin, we expected the lower level of immunochemical fecal hemoglobin associated with cancer in the proximal colon and expected the same with advanced adenomas (30). We were surprised to find that fecal hemoglobin measurements from advanced adenomas did not vary by site. Nonadvanced adenomas that increased in size and number were associated with more detectable fecal occult blood.

In conclusion, we found that the automated process immunochemical FOBT provided a quantified hemoglobin result similar to other laboratory tests. In contrast to the office-developed guaiac-based and immunochemical FOBTs, which have a threshold for positivity determined by the manufacturer, our test allows the physician to chose the level of fecal hemoglobin at which colonoscopy should be recommended. From our experience, the 75-ng/mL hemoglobin threshold provides a sensitive test for detecting clinically significant colorectal neoplasia with an acceptable specificity. By obtaining 3 immunochemical FOBT samples, we improved the sensitivity for detecting cancer and advanced adenomas. The recommendations on the number of immunochemical FOBT samples needed and the hemoglobin threshold to be used will be clearer after completing prospective studies in the average-risk and high-risk follow-up patient populations.

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Note: These results were presented, in part, at Digestive Diseases Week, Los Angeles, California, 20–25 May 2006.

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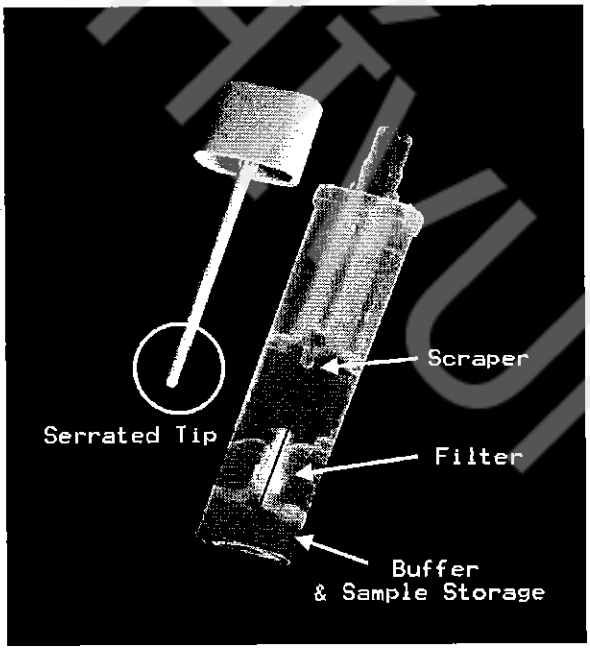
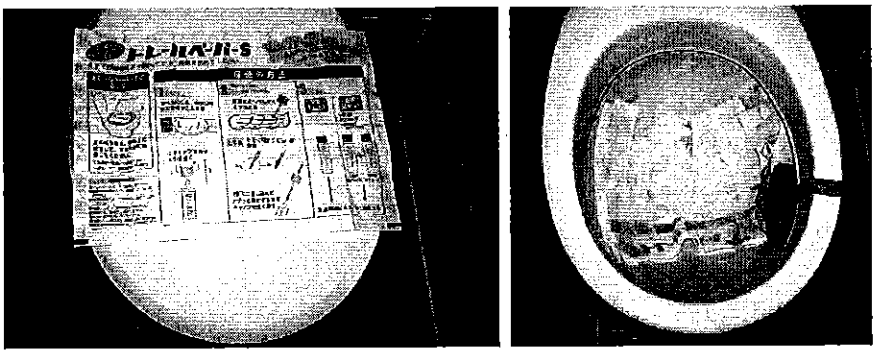
Administrative, technical, or logistic support: R. Hazazi, A. Vilkin, Z. Levi, A. Waked, Y. Niv.
Collection and assembly of data: Z. Levi, R. Hazazi, A. Vilkin, A. Waked.

Appendix Figure 2. Stool probe and fecal sample storage tube.



The patient removes the fecal probe that has a serrated tip that accumulates the fecal sample. The probe is then reinserted deeper into the tube past a scraper and through a membrane that removes excess feces. The bottom compartment of the tube contains a 2-mL buffer solution for stabilizing the fecal specimen in the tip serrations.

Appendix Figure 1. Folded paper "float" opened (*left*) and placed in toilet bowl (*right*).



After defecation and fecal sampling, the participant flushes the float into the toilet.

Appendix

Instrument for Immunochemical FOBT Analysis

The desktop instrument is self-contained and requires standard power supply (Appendix Figure 3). Ten patient-prepared fecal sample tubes are loaded into the sample rack and, in parallel, another rack has disposable reaction cells. The instrument automatically samples and mixes 25 μL from the 2-mL fecal buffer solution in each sample tube with the latex antihuman hemoglobin antibody reagent. The turbidity is read as an optical change and is compared with a standard calibration curve. Calibration is prepared for each day's analysis by using the provided known high and low value control test fluids (range of hemoglobin measurements, 20 to 2000 ng/mL). Results for each tube are automatically printed. Further technical details, in Japanese-language publications translated into English, are available (25).

Considerations in Establishing a Threshold Level of Fecal Hemoglobin

In considering the clinical importance of high sensitivity for detecting clinically significant neoplasia in our colonoscopy-oriented screening practice, we decided to accept a slightly lower specificity and to use the 75-ng/mL hemoglobin threshold for advising colonoscopy in our pilot, average-risk population screening study. Because of intrapatient variation of daily fecal hemoglobin loss, we will continue collecting 3 consecutive fecal tests annually because we obtained a statistically significantly higher sensitivity than that found with fewer samples. This is in contrast to the annual 2-day immunochemical FOBT collection that is routinely used for the average-risk populations with a 150-ng/mL fecal hemoglobin threshold in Japan, the United States, and Australia; 1-day testing with a 100-ng/mL threshold in Uruguay; and 1-day biennial testing with a 100-ng/mL threshold in Italy (15, 17–19, 22, 28, 33). These issues might also explain the reported low performance of an immunochemical FOBT compared with colonoscopy screening (30).

Appendix Figure 3. The desktop OC-MICRO instrument.

The instrument is 32 cm wide, 53 cm deep, and 42 cm high. The top left bottle contains diluting solution, the center bottle contains cleaning fluid, and the right bottle contains distilled water. Two trays are loaded into the instrument. One tray holds 10 patient-prepared immunochemical fecal occult blood test tubes, and the other tray is for tubes where the immunochemical fecal occult blood test–antibody reaction occurs. The hemoglobin value is automatically calculated from the resulting turbidity. (The OC-MICRO is manufactured by Eiken Chemical Co., Tokyo, Japan.)

Appendix Table 1. Immunochemical Fecal Occult Blood Test and Endoscopy Results for Cancer or Clinically Significant Neoplasia, by Reasons for Colonoscopy*

Reason for Colonoscopy	Patients, *n*	Patients with True-Positive Test Results, *n*	Patients with False-Negative Test Results, *n*	Patients with True-Negative Test Results, *n*	Patients with False-Positive Test Results, *n*	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive LR (95% CI)	Negative LR (95% CI)
Finding: Colorectal cancer									
Asymptomatic†									
Positive guaiac-based FOBT result	101	2	0	90	9	100 (100 to 100)	90.9 (85.2 to 96.6)	11 (NA)	0 (NA)
Asymptomatic high-risk†									
Past colorectal neoplasia	348	6	0	302	40	100 (100 to 100)	88.3 (84.9 to 91.7)	8.55 (NA)	0 (NA)
Family history of colorectal neoplasia	80	2	1	64	13	66.7 (13.3 to 120)	83.1 (74.7 to 91.5)	3.95 (0.56 to 27.97)	0.4 (0.25 to 0.63)
Symptomatic†									
Changed bowel habits	150	0	0	139	11	–	92.7 (88.5 to 96.8)	–	–
Anemia	99	5	0	72	22	100 (100 to 100)	76.6 (68 to 85.2)	4.27 (NA)	0 (NA)
Abdominal pain, weight loss	120	0	0	108	12	–	90 (84.6 to 95.4)	–	–
Other symptoms	102	1	0	85	16	100 (100 to 100)	84.2 (77 to 91.3)	6.31 (NA)	0 (NA)
Finding: Clinically significant neoplasia: cancer and advanced polyps									
Asymptomatic†									
Positive guaiac-based FOBT result	101	3	0	90	8	100 (100 to 100)	91.8 (86.4 to 97.3)	12.25 (NA)	0 (NA)
Asymptomatic high-risk†									
Past colorectal neoplasia	348	19	6	296	27	76 (59.3 to 92.7)	91.6 (88.6 to 94.7)	9.09 (4.1 to 20.17)	0.26 (0.19 to 0.36)
Family history of colorectal neoplasia	80	10	8	57	5	55.6 (32.6 to 78.5)	91.9 (85.2 to 98.7)	6.89 (3.15 to 15.06)	0.48 (0.25 to 0.93)
Symptomatic†									
Changed bowel habits	150	7	6	133	4	53.8 (26.7 to 80.9)	97.1 (94.3 to 99.9)	18.44 (7.24 to 46.99)	0.48 (0.23 to 0.98)
Anemia	99	13	0	72	14	100 (100 to 100)	83.7 (75.9 to 91.5)	6.14 (NA)	0 (NA)
Abdominal pain, weight loss	120	1	1	107	11	50 (−19.3 to 119)	90.7 (85.4 to 95.9)	5.36 (0.52 to 54.84)	0.55 (0.36 to 0.84)
Other symptoms	102	8	9	76	9	47.1 (23.3 to 70.8)	89.4 (82.9 to 96)	4.44 (2.0 to 9.87)	0.59 (0.38 to 0.93)

* FOBT = fecal occult blood test; LR = likelihood ratio; NA = not applicable.
† Fecal occult blood test sensitivity and specificity did not significantly differ among these groups.

Appendix Table 2. Sensitivities, Specificities, and 95% CIs for Colorectal Cancer and All Clinically Significant Neoplasia according to Fecal Hemoglobin Thresholds*

Variable	Sensitivity (95% CI), %		Specificity (95% CI), %	
	≥75-ng/mL Fecal Hemoglobin Threshold	≥100-ng/mL Fecal Hemoglobin Threshold	≥75-ng/mL Fecal Hemoglobin Threshold	≥100-ng/mL Fecal Hemoglobin Threshold
Colorectal cancer				
I-FOBT 1	64.7 (42–87.4)	64.7 (42–87.4)	92.6 (90.9–94.2)	94.3 (92.9–95.8)
I-FOBT 1 or 2	88.2 (72.9–100)	82.4 (64.2–100)	90 (88.2–91.9)	91.9 (90.2–93.6)
I-FOBT 1, 2, or 3	94.1 (82.9–100)	88.2 (72.9–100)	87.5 (85.4–89.6)	89.7 (87.8–91.6)
Clinically significant neoplasia: cancer and advanced polyps				
I-FOBT 1	47.3 (37–57.5)	40.7 (30.6–50.8)	95.5 (94.1–96.8)	96.7 (95.5–97.9)
I-FOBT 1 or 2	59.3 (49.2–69.4)†	53.8 (43.6–64.1)	93.5 (91.9–95.1)‡	95.0 (93.6–96.5)
I-FOBT 1, 2, or 3	67.0 (57.4–76.7)§	61.5 (51.5–71.5)	91.4 (89.6–93.2)‖	93.4 (91.8–95.0)

* I-FOBT = immunochemical fecal occult blood test.
† 59.3 <67.0 (P <0.001).
‡ 93.5 >91.4 (P <0.001).
§ 67.0 >61.5 (P = 0.063).
‖ 91.4 <93.4 (P <0.001).

Appendix Table 3. Likelihood Ratios for Specific Fecal Hemoglobin Levels*

Range of Fecal Hemoglobin Values	Patients with Clinically Significant Neoplasia, *n*	Sensitivity	Patients without Clinically Significant Neoplasia, *n*	Specificity	Likelihood Ratio
0–50 ng/mL	25	0.275	806	0.113	0.31
51–75 ng/mL	5	0.055	26	0.971	1.92
76–100 ng/mL	5	0.055	17	0.981	2.94
101–150 ng/mL	7	0.077	15	0.983	4.66
>150 ng/mL	49	0.538	45	0.950	10.88
All values	91	1.0	909		

* Values in the table are the basis for the likelihood ratios for Figure 6. Clinically significant neoplasia includes cancer and advanced polyps.

Egy beteg vizsgálatára lebontott költségek bemutatása

Alulírott Dr. Csajka Márta, mint a Frank Diagnosztika Kft., 1036 Budapest Dereglye utca 2. ajánlattevő cégjegyzésre jogosult képviselője az Országos Tisztifőorvosi Hivatal ajánlatkérő által indított, „Immunkémiai székletvér reagens és a szűréshez szükséges egyéb kiegészítők" tárgyú közbeszerzési eljárás során kijelentem, hogy a szerződés időtartama alatt az alábbiakban részlezetett reagensek, kalibrátorok és kontrollok a mérések gyakoriságától (heti, vagy napi mérések), valamint a beérkező minták esetleges egyenetlen eloszlása esetén is elegendőek 13 000 személy szűrését biztosító 26 000 vizsgálat elvégzésére.

1. Önköltségi ár betegenként / vizsgálatonként:

nettó egységár:	875 HUF,
ÁFA (5 %):	43,75 HUF,
bruttó egységár:	918,75 HUF.

2. Ár 26.000 darabra:

Teljes nettó ár:	22.750.000 HUF,
ÁFA (5%):	1.137.500 HUF,
teljes bruttó ár:	23.887.500 HUF,

3. Költségek részletesen:

Megnevezés	Mennyiség	Nettó egységár	Nettó összár
OC-Sensor Diana-Latex (5 x 15 mL)	23 doboz	322.000	7.406.000
OC-Sensor Diana-Buffer (500 mL)	33 doboz	38.000	1.254.000
OC-AUTO SAMPLING BOTTLE (100db)	260 doboz	50.400	13.104.000
OC-Liquid Standard (1 x 3 mL)	3 doboz	38.000	114.000
OC-Control LV1 liquid (2 x 5 mL)	5 doboz	83.200	416.000
OC-Control LV2 liquid (2 x 5 mL)	5 doboz	83.200	416.000
OC-Sensor sample cup (1000/box)	1 doboz	40.000	40.000

Budapest, 2013. év augusztus hó 23. nap

FRANK Diagnosztika Kft.

.....

Dr. Csajka Márta
gyógyszerész, ügyvezető