Superior Health Council

PUBLICATION OF THE SUPERIOR HEALTH COUNCIL No. 8901

Immunochemical Faecal Occult Blood Tests for Colorectal Cancer Screening

In this scientific policy advisory report, the Superior Health Council provides recommendations for the use of immunochemical faecal occult blood tests in colorectal cancer screening programs

8 may 2013

1. INTRODUCTION AND ISSUES

The Superior Health Council (SHC) received a request for an advisory report from the Minister of Health from the "*Federation Wallonie-Bruxelles*", Mrs Fadila Laanan, concerning the use of immunological tests in colorectal cancer (CRC) screening programs.

According to the European guidelines, CRC is estimated to have a worldwide incidence of 1.2 million cases and 0.6 million deaths each year. In the EU member states, CRC ranks first in incidence and second in mortality with approximately 212 000 deaths annually. CRC is therefore an important health problem across the EU and screening can be effective in cancer control (Von Karsa et al. 2013). The EU recommends population-based screening for breast, cervical and CRC cancer using evidence-based tests with quality assurance of the entire screening process including diagnosis and management of patients with screen- detected lesions (Council recommendation of December 2nd 2003 on cancer screening (Off J Eur Union 2003: 34-38).

Currently, in most European countries, CRC screening programs are performed using an immunochemical faecal occult blood test (iFOBT) instead of the guaiac-based faecal occult blood test (gFOBT). gFOBT detects blood in stool through pseudoperoxidase activity of haeme or haemoglobin whereas iFOBT detects human globin via an immunochemical reaction. iFOBT gives a quantitative measurement of haemoglobin in stool and iFOBT has improved characteristics compared with gFOBT. Its measurement can be automated and cut-off levels can be adjusted to achieve an optimal balance between test performance and the available colonoscopy capacity in a given country (Hol et al. 2009; Van Rossum et al. 2009).

To implement a CRC program in "*Federation Wallonie-Bruxelles*", with an iFOBT, comparisons with the gFOBT and between the currently existing iFOBTs on the EU market are needed to choose the most appropriate test. Indeed, it has been shown that the different iFOBTs differ in their clinical validity (Hundt et al, 2009).

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In this report the purchase costs of an iFOBT are not considered; they may vary in accordance with the number of tests ordered and over time. This may impact indicators of cost-effectiveness.

The following questions are discussed:

1. What is the expected performance of a test in the context of a screening program for colorectal cancer?
2. What are the minimum requirements expected of an iFOBT: choosing a cut-off level, choice of threshold sensitivity and specificity which determines the positivity rate corresponding to the best sensitivity/specificity as expected under an organized screening program?
3. What are the arguments for the choice of one or two samples (compared to the expected cut-off level)
4. What are the performances of the different iFOBTs currently available on the market?
5. What are the indicators of quality of an iFOBT?
6. What are the expected cut-off levels via the settings of the reading devices of an iFOBT?
7. What are the realistic and acceptable ranges of increase in cancers and advanced adenomas?
8. What are the acceptable numbers of colonoscopies (anxiety, side effects, cost/effectiveness, ..) absorbable by the health care sector?

The SHC appointed an ad hoc work group to address these specific questions.

2. CONCLUSIONS

Using the iFOBT test results in a better participation of the target population and in the detection of many more lesions, compared to the more classic gFOBT. The detection of lesions is of course one of the main reasons to perform a screening test.

There are two immunochemical tests on the EU market which can be considered for a screening program: OC-Sensor and FOB-GOLD. For the detection of advanced adenomas (lesions that can evolve into colorectal cancer), the positive predictive value was significantly higher with the iFOBT than with the gFOBT test. This means that when someone has a positive test, the chance of actually having the disease, is significantly higher with the immunochemical than with the guaiac test.

The OC-Sensor test has been widely tested and used; comparisons between the OC-Sensor and the FOB-GOLD tests are limited; results from these studies are in favor of the OC-Sensor test because of a better sensitivity and a better test-stability. The sensitivity means the capacity to detect lesions. In this case, OC-Sensor will detect more lesions in the same population than FOB-GOLD. Test-stability means that the results of the test are not susceptible to external influences, for instance high temperature.

The optimal positivity rate of an immunochemical test for the detection of advanced adenomas and colorectal cancer in Belgium is between 3–5 %. This means that of every 100 persons who perform the test, 3 to 5 will have a positive test. This can be achieved with a one sample strategy with a cut-off value around 100 ng/mL for the OC-Sensor test. When the cut-off value (the value above which we consider someone to be ‘positive’) is too low, too many people will have a positive test, among which many without having adenomas or colorectal cancer. Moreover, when too many people have a positive test, they all have to perform the follow-up test to confirm the test result. This could be a problem, because of a lack of capacity to perform these follow-up tests. When the cut-off value is too high, too many people with lesions will not be detected by the test.

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Results from the literature show that screening for colorectal cancer with an iFOBT is more cost-effective than with the gFOBT.

KEYWORDS AND MESH TERMS[1]

MeSH terms	Keywords	Sleutelwoorden	Mots clés	Stichwörter
Mass screening	Screening Program	Bevolkingsonderzoek		
Colorectal neoplasms	Colorectal neoplasms	Dikkedarmkanker	Cancer colorectal	
Occult blood	Immunochemical faecal occult blood tests	Occult bloed		
Humans				
Aged				
Immunohistochemistry				

[1] MeSH (Medical Subject Headings) is the NLM (National Library of Medicine) controlled vocabulary thesaurus used for indexing articles for PubMed (http://www.ncbi.nlm.nih.gov/mesh). MeSH terminology is used to describe the contents of the report in a standardized way.

3. FURTHER DETAILS AND ARGUMENTATION

List of abbreviations

CRC	Colorectal Cancer
EU	European Union
FOB-GOLD	FOB-GOLD® (Sentinel, Milan, Italy)
gFOBT	Guaiac Faecal Occult Blood Test
GP	General Practitioner
iFOBT	Immunochemical Faecal Occult Blood Test
LYG	Life Years Gained
OC-SENSOR	OC-SENSOR ® (Eiken, Tokyo, Japan)
PPV	Positive Predictive Value
QALY	Quality Adjusted Life Year
SHC	Superior Health Council

3.1. Methodology

The advisory report is based on scientific and grey literature research and expert opinion.

3.2. Elaboration

3.2.1. What is the expected performance of a test in the context of a screening program for colorectal cancer?

The performance of a screening program depends on various parameters among which the participation rate of the target population and the sensitivity and specificity of the screening test as most important; other criteria that should be considered have been summarized by JM Wilson and YG Jungner (Wilson JM et al., 1968).

3.2.1.1. Participation rate

Assuming that the detection of the risk for developing a disease or of an existing subclinical disease qualify for screening according to the criteria of JM Wilson & YG Jungner, the success of a screening program is strongly dependent of the participation of the target population.

Regarding the difference in participation rates in CRC screening programs, the large majority of studies finds a higher participation rate when the iFOBT is used compared to the gFOBT. Rabeneck et al. conclude that the performance of the iFOBT is superior to the standard gFOBT in terms of screening participation rates (Rabeneck et al., 2012). On the contrary Levi et al. found a lower participation rate with iFOBT (25.9 %) compared to gFOBT (28.8 %) in Tel Aviv but the performance of the iFOBT for the detection of advanced adenomas and CRC was significantly better (Levi et al., 2011).

Van Rossum et al. showed in a Randomized Controlled Trial a statistically significant higher participation rate for the iFOBT compared to the gFOBT, respectively 60 % vs. 47 % (Van Rossum et al. 2009).

An evaluation of the randomized pilot trials in the regions of Nijmegen, Amsterdam and Rotterdam, predicted a participation rate of 60 % for the iFOBT.

Hassan et al. found that iFOBT was superior to gFOBT with regard to participation (RR: 1.16, 95 % CI 1.03-1.30) (Hassan et al. 2012).

Within a range of 1-3 years, the total number of advanced neoplasia found at repeat iFOBT screening is not influenced by the interval length (van Roon et al.,2013). Moreover, these authors found a stable and acceptably high participation in the second screening round, implying that screening intervals can be tailored to local resources.

Inviting people for CRC screening by means of a direct-mail invitation, and including a faecal sampling set (iFOBT), resulted in a higher participation rate than inviting people for a similar screening test through the general practitioner (GP) (Van Roosbroeck et al., 2012).

An interesting feature, which might be important regarding the cost of organizing a CRC screening program, is that Denters et al. did not find increased participation rates in iFOBT based colorectal cancer screening when using faeces collection paper (Denters et al., 2012).

In summary: in general, screening with the iFOBT resulted in a higher participation rate compared to the gFOBT. Direct-mail invitation results in a higher participation rate compared to invitation by the GP.

3.2.1.2. Sensitivity

Crotta et al. concluded that screening with iFOBT could have a better detection rate of CRC than with the gFOBT (Crotta et al., 2012). Hassan et al. found that iFOBT was superior to gFOBT with regard to detection of advanced neoplasia (RR: 2.28, 95 % CI: 1.68 – 3.10) and cancer (RR: 1.96, 95 % CI: 1.2 – 3.2) (Hassan et al., 2012). In a meta-analysis, Rabeneck et al. found that iFOBT was superior to the standard gFOBT in terms of detection of CRC and advanced adenoma (Rabeneck et al., 2012).

In a study of Faivre et al. it was found that three different iFOBTs were superior to the gFOBT for the detection of invasive and non-invasive colorectal cancer, for the detection of advanced adenomas and of other adenomas (Faivre et al., in press Eur J Cancer). In an Italian study the OC-Sensor test had a better sensitivity compared to the FOB-GOLD test (Rubecca et al., 2006).

Studies reported a potential instability of faecal haemoglobin at high ambient temperatures and recommended to respect a short exposure time of samples to high ambient temperature (i.e. rapid return system) (Cha et al., 2012; van Rossum et al., 2009). In a direct comparison of the OC-Sensor test with the FOD-GOLD the stability was better in the OC-Sensor (Guittet et al., 2011) However, it seems that the stability of faecal haemoglobin in the iFOBTs has strongly

improved lately because of modification of the buffer by the companies (Faivre J., personal communication).

In summary: the iFOBT is superior to the gFOBT as far as sensitivity is concerned. However, this sensitivity can be reduced when there is a delay in sample return.

3.2.1.3. Specificity

The specificity of the gFOBT is higher than the specificity of the iFOBT. Van Rossum showed that for all advanced adenomas and cancer, the specificity of the gFOBT was 99 % compared to 97.8 % for the iFOBT (≥ 100 ng/ml). For cancer, the respective specificity was 98.1 % for gFOBT and 95.8 % for iFOBT (≥ 100 ng/ml) (van Rossum et al., 2008).

In summary: the gFOBT is superior to the iFOBT as far as specificity is concerned.

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3.2.2. What are the minimum requirements expected of an iFOBT: choosing a cut-off level, choice of threshold sensitivity and specificity which determines the positivity rate corresponding to the best sensitivity / specificity as expected under an organized screening program?

In a recent study by Faivre et al., a comparison was made between three iFOBTs (Faivre et al., 2012a). The detection rate and the positive predictive value was not different between the 3 iFOBTs.

A manageable overall screening positive rate in France was considered to be in the range of 3-5 %, given the number of available endoscopists to perform colonoscopies in France. According to the expert opinion of the SHC working group, Belgium has a comparable capacity as in France to perform colonoscopies. Therefore a screening test resulting in a positivity rate between 3-5 % could be recommended for a national CRC screening program. Cut-off levels can be chosen to be compatible with such an acceptable positivity rate; if necessary, cut-off levels can be re-evaluated periodically to obtain optimal and manageable screening outcomes (Faivre et al., 2013).

Table 1 gives an overview of 2 randomized studies comparing Hemoccult (gFOBT) and OC-Sensor (1 sample, cut-off value 100 ng/mL). The positivity rate of OC-Sensor at this cut-off was in the acceptable range of positivity rate with consequences that are manageable by the health sector. Detection rates for CRC and advanced adenoma by OC-Sensor (cut off = 100 ng/mL) were 2 times higher compared to the gFOBT (Hemoccult) (Van Rossum et al., 2008; Hol et al. 2010).

	Van Rossum et al. 2008		**Hol et al. 2010**	
	Hemoccult n = 103010	**OC-Sensor n = 10322**	**Hemoccult n = 5007**	**OC-Sensor n = 5003**
Positivity rate (%)	2.4	5.5	2.8	4.8
Detection rate				
CRC (‰)	2.3	3.9	2.6	4.7
Ratio	1.7		1.8	
Advanced adenoma (‰)	9.5	19.7	9.5	19.8
Ratio	2.1		2.1	
PPV (Positive Predictive Value)				
CRC (%)	10.7	8.6	10	10
Advanced (%) adenoma	44.6	43.2	35	43

Table1: 2 randomized studies comparing Hemoccult and OC-Sensor. PPV= Positive Predictive Value

Terhaar et al. tested the specificity of OC-Sensor for the detection of CRC and advanced adenomas at different cut-off levels (50 ng/mL – 200 ng/mL) in 2145 patients. From a cut-off level of 125 ng/mL upward, no further increase in sensitivity was found (Terhaar Sive Droste et al., 2011).

In a study from the Czech Republic, the optimum cut-off value of OC-Sensor was determined as 75 ng/mL using one test (Kovarova et al., 2012a). In the Netherlands a cut-off value of 75 ng/mL was also used in their pilot project (van Rossum et al., 2009a).

Table 2 gives an overview of different studies with specificity and sensitivity data for the detection of advanced adenomas and CRC for different iFOBT at several cut-off levels.

Test IFOBT	number of samples (1 or 2)	Cut-off value (ng/mL)	Sensitivity (%)		Specificity (%)		Total N participants	Positivity (%)
			Advanced neoplasia	CRC	Advanced neoplasia	CRC		
OC-sensor(Kovarova et al. 2012)	1	50	76.2	88.6	87.4	87.2	815	
OC-sensor(Kovarova et al. 2012)	1	75 (*)	73.0	85.7	90.1	90.1	815	
OC-sensor(Kovarova et al. 2012)	1	100	71.4	85.7	91.0	91.0	815	
OC-sensor(Kovarova et al. 2012)	1	125	68.3	80.0	92.7	93.0	815	
OC-sensor(Kovarova et al. 2012)	1	150	63.5	80.0	93.5	93.5	815	
OC-sensor(Kovarova et al. 2012)	2 (highest value)	50	77.8	88.6	81.4	81.4	815	
OC-sensor(Kovarova et al. 2012)	2 (highest value)	75	74.6	85.7	84.7	84.7	815	
OC-sensor(Kovarova et al. 2012)	2 (highest value)	100	74.6	85.7	86.9	86.9	815	
OC-sensor(Kovarova et al. 2012)	2 (highest value)	125	73.0	85.7	89.1	89.1	815	
OC-sensor(Kovarova et al. 2012)	2 (highest value)	150	69.8	85.7	89.6	90.1	815	
OC-sensor(Terhaar Sive Droste et al. 2011)	1	50	54.0	92.4	89.9	86.4	2145	16.5
OC-sensor(Terhaar Sive Droste et al. 2011)	1	75	52.4	91.1	92.2	88.6	2145	14.3
OC-sensor(Terhaar Sive Droste et al. 2011)	1	100	50.5	89.9	93.5	90.0	2145	13.0
OC-sensor(Terhaar Sive Droste et al. 2011)	1	125 (*)	48.3	84.8	94.3	90.9	2145	12.1
OC-sensor(Terhaar Sive Droste et al. 2011)	1	150	46.0	82.3	95.1	81.8	2145	11.1
OC-sensor(Terhaar Sive Droste et al. 2011)	1	200	43.2	81.0	95.8	92.8	2145	10.2
OC-sensor(Hol et al. 2009)	1	50			95.5	92.9	2975	8.1
OC-sensor(Hol et al. 2009)	1	75			97.2	95.0	2975	5.7
OC-sensor(Hol et al. 2009)	1	100			97.8	95.8	2975	4.8
OC-sensor(Hol et al. 2009)	1	125			98.2	96.3	2975	4.1
OC-sensor(Hol et al. 2009)	1	150			98.4	96.6	2975	4.0
OC-sensor(Hol et al. 2009)	1	175			98.7	97.0	2975	3.6
OC-sensor(Hol et al. 2009)	1	200			98.8	97.1	2975	3.5
MagStream(Wong et al. 2012)	2	10	47.8		87.6		1075	14.6
MagStream (Wong et al. 2012)	2	20	37.7		93.2		1075	8.7
MagStream(Wong et al. 2012)	2	36	31.8		95.4		1075	6.3
FOB-GOLD(Faivre et al. 2012)	2	176					32215	5.2
MagStream(Faivre et al. 2012)	2	20					19244	4.6
OC-Sensor(Faivre et al. 2012)	2	150					33690	3.7

Table2: overview of different studies with specificity and sensitivity data for the detection of advanced adenomas and CRC for different iFOBT at several cut-off levels (* according to the paper the best cut-off level).

In summary: the optimal positivity rate for an iFOBT for the detection of advanced adenoma and CRC in Belgium is considered to be between 3-5 %. According to the literature, a cut-off level of approximately 100 ng/mL (75-125 ng/mL) with OC-sensor gives the best specificity and sensitivity for the detection of CRC and advanced adenomas.

Studies with the FOB-GOLD test are limited. In a recent advice of the Dutch Health Council on the choice between the two iFOBTs it was concluded that the FOB-GOLD was insufficiently validated and that more research is needed on the direct comparison between the OC-Sensor test and the FOB-GOLD. The Health Council concluded that there was no scientific evidence to prefer the FOB-GOLD test above the OC-Sensor (Gezondheidsraad, Briefadvies 10 april 2013; publication° 2013/06).

3.2.3. What are the arguments for the choice of one or two samples (compared to the expected cut-off level)

In Italy and in the Netherlands, the one sample biennial testing is used (OC-Sensor, cut-off 100 ng/mL and OC-Sensor, 75 ng/mL respectively)(Castiglione et al., 2002;Castiglione et al., 2007; van Rossum et al., 2008;Hol et al., 2010).

In Japan and in France, a strategy of 2 day biennial testing with OC-Sensor and a cut-off of 150 ng/mL is used because bleeding from CRC and adenomas is often intermittent and this strategy was more cost-effective (Nakama et al., 2001). However, results from a recent study suggest that by decreasing the cut-off value, a similar performance can be achieved with one day sampling (personal communication, J Faivre).

Goede et al. performed a simulation model to compare one-sample iFOBT screening, two-sample iFOBT screening (one positive), two-sample iFOBT screening (2 positive) or two-sample iFOBT screening (mean positive) for different cut-off levels between 50-200 ng Hb/mL. The analysis showed that two sample-iFOBT strategies with the mean of both tests being positive or one positive (of the 2) provides more life years gained (LYG) at acceptable costs compared to one-sample iFOBT. However, increasing the screening interval of one-sample iFOBT is more cost-effective than two iFOBT within one screening round (Goede et al., 2012).

The study from Kovarova et al. found the best results using the one sample iFOBT at the cut-off level of 75 ng/mL, this gave the best sensitivity/specificity ratio (Kovarova et al., 2012b).

The most important argument in favour of a one sample strategy is the cost. The main question is which positivity rate can be accommodated by the National Health System, while keeping at the same time a good sensitivity/specificity ratio (Faivre J et al., 2013).

In summary: the one sample strategy is most favorable in a CRC screening program compared to the two sample strategy according to the current data in the literature and the expert opinion of the SHC working group.

3.2.4. What are the performances of the different iFOBTs currently available on the market?

For this question, we refer to question 2.2.

3.2.5. What are the indicators of quality of an iFOBT?

The parameters which can be used to evaluate and monitor the implementation of CRC screening are summarized below. These indicators are based on the European Guidelines (S Moss et al. 2012):

- *Coverage of the target population through invitation*. It is recommended to obtain a high coverage (at least 95 %) to maximize the impact of a screening program.

- *Coverage of target population by examination.* This is the extent to which screening has been delivered to the target population. Screened here is defined as people tested at least once, including self-referrals but not self-registrations.

- *Level of Participation (%).* This is the proportion of invited subjects vs. the subjects who were screened. A level between 45-65 % is recommended.

- *Technical inadequate iFOBT.* It is recommended to have a rate of inadequate technical iFOBT lower than 3 %. This percentage reflects the communication to the target population. If that level is high, the communication was not good and the people did not understand how they needed to use the test.

- *Positivity rate.* The positivity ratio should be presented in a table divided into age groups (5 year) and divided into female vs. male group. The proportion of positive tests will differ by gender (higher for male) and age (higher in older age groups). The positivity rate for iFOBT will vary according to the cut-off levels.

- *Referral to follow-up colonoscopy after iFOBT.* The rate of referral for follow-up colonoscopy after a positive iFOBT is defined as the proportion of people screened with a positive test and referred to colonoscopy. High rates of referral to follow-up should be achieved for people with a positive iFOBT: 90 % is acceptable, more than 95 % is desirable.

- *Completion of follow-up colonoscopy after iFOBT.* A completion rate of follow-up colonoscopy should be above 90 % and desirable above 95 %.

- *Results follow-up colonoscopy.* The stage distribution of screen-detected cancers should be reported by screening round, age and gender. It is recommended to present the data in a table: negative, presence of adenomas of any size, presence of non-advanced adenomas, presence of advanced adenomas and presence of cancers.

- *Completion of follow-up colonoscopy after iFOBT.* The proportion of incomplete colonoscopies should be recorded. A high completion rate for follow-up colonoscopy should be achieved. 90 % is acceptable more than 95 % is desirable.

- *Detection rates.* A distinction is made for the following detection rates: lesion detection rate, adenoma detection rate, advanced adenoma detection rate and cancer detection

rate. For cancer detection rates the stage distribution is reported by screening round, age and gender.

- *Positive predictive value (PPV).* The PPV is calculated based on whether or not follow-up colonoscopy was actually performed after a positive iFOBT: PPV for detection of lesions, PPV for detection of adenomas, PPV for detection of advanced adenomas, PPV for detection of cancer.

- *Endoscopic complications.* The rate of adverse effects should be monitored carefully.

- *Time interval between completion of the test and receipt of results.* The time interval between the completion of a test and receipt of results by the subject should be as short as possible. An acceptable standard is at least 90 % within 15 days.

- *Time interval between a positive test and follow-up colonoscopy.* Follow-up colonoscopy after positive screening should be scheduled within 31 days of referral. An acceptable standard is more than 90 %, more than 95 % is desirable.

- *Long-term impact indicators.* It is preferable to collect data directly up to the introduction of a screening program to allow trends to be analyzed for example interval cancers. Evaluation of interval cancers rates requires careful linkage of cancer registration with screening history to allow cancers to be classified. This linkage should be established with the cancer registry.

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3.2.6. What are the expected cut-off levels via the settings of the reading devices of an iFOBT?

An overview of the two available iFOBT systems is presented in the table below (Halloran et al., 2012):

	OC-Sensor	FOB-Gold
Manufactured by	Eiken Chemical Co, Tokyo, Japan	Sentinel Diagnostics SpA, Milan, Italy
Principle of measurement	Latex agglutination using polystyrene latex particles coated with polyclonal anti haemoglobin Ao antibodies	Antigen-antibody agglutination reaction between human haemoglobin and polyclonal anti-human haemoglobin antibodies coated on polystyrene particles. Such an agglutination is measured as an increase in absorbance at 570 nm and is proportional to the quantity of human haemoglobin contained in the sample.
Recommended number of separate samples used for assessment	1 sample	/
Method of sample collection	Serrated stick in buffer held within the device	Screw-cap with a purposely shaped stick for faeces collection
Means of reading	OC Sensor Diana & OC Sensor Micro are both automated instruments and are both CE marked. The Diana has more memory capacity for 100 000 test results	The FOB Gold reagents can be used on any suitable immunoassay analyzer although the manufacturer provides the SENTiFOB analyzer
Speed of analysis	280 tests/hour	75 tests/hour (SENTiFOB)
Quantity collected by sampling device	10 mg of faeces	10 mg of faeces
Volume of buffer in collection device	2 mL	1.7 mL
Analyzer sample volume	35 µL	10 µL
Quality control	Standard laboratory QC procedures	Standard laboratory QC procedures
Cut-off level	CE marked for a user-defined cut-off.	CE marked for a user-defined cut-off
Limit of detection	20 ng/mL buffer	14 ng/mL buffer

3.2.7. What are the realistic and acceptable ranges of increase in cancers and advanced adenomas?

In a study by Faivre et al. iFOBTs were superior to gFOBT in detecting both invasive and non-invasive CRC and adenomas. Compared with gFOBT, the detection ratios for CRC were 1.6 for FOB-GOLD and 2.1 for OC-Sensor. The corresponding ratios for non-invasive CRC were 2.5 (FOB-GOLD) and 4.0 (OC-Sensor) and for advanced adenoma 3.6 (FOB-GOLD) and 4.0 (OC-Sensor). The detection rates for iFOBT were significant higher than with the gFOBT. For CRC (invasive and non-invasive) the PPV of gFOBT and iFOBT were not significantly different. For advanced adenomas, the PPV was significantly higher with iFOBT than with gFOBT, the PPV was higher for the OC-Sensor test compared to FOB-GOLD (Faivre et al. 2012).

3.2.8. What are the acceptable numbers of colonoscopies (anxiety, side effects, cost/effectiveness, ..) absorbable by the health care sector?

When the screening test is positive, a follow-up examination has to be performed. In the case of CRC, the follow-up examination is a colonoscopy. The specialist will examine the inside of the large bowel with a long, flexible tube. By performing a colonoscopy, it will be possible to make a diagnosis and often it will also be possible to immediately resect the polyps which are there. After a colonoscopy where nothing was found or where the polyps are resected, a next examination is only due at least five years later. The downside of a colonoscopy is that before it can be performed, the bowel has to be empty and clean. This means that one has to drink a lot and that laxatives have to be used. This is rather uncomfortable for the people involved. Also important to notice, is that performing a colonoscopy is not without danger. In one out of 1.000 colonoscopies, a perforation of the wall of the intestine will occur and in one out of 10.000 colonoscopies, the person involved will die. For this reason, it is very important that the screening test used for CRC screening, has a high specificity, so that not too many people without lesions are referred for colonoscopy after a positive test.

Because of the lower sensitivity of the gFOBT, population based screening based on iFOBT requires significantly more colonoscopy resources and results in more individuals experiencing adverse effects. Weighing these advantages and disadvantages presents a considerable challenge to policy makers (Sharp et al., 2012).

The number needed to invite to find one CRC or advanced adenoma, is 1/80 for gFOBT, 1/50 for colonoscopy and 1/40 for iFOBT (van Rossum et al., 2009). The number needed to scope is 1/15 for colonoscopy as a screening test and ½ for both gFOBT and iFOBT (van Rossum et al., 2009).

In the Flemish pilot trial, it was calculated that the implementation of a colorectal cancer screening program with iFOBT would not lead to a lack of capacity of colonoscopies (Hoeck et al., 2010).

According to data of The Netherlands, once performing an iFOBT is more cost-effective than once performing a gFOBT or than no screening at all. Compared to performing once a gFOBT, performing once an iFOBT can save 113.290.731 euros and over 12.000 life years. Compared to no screening, once performing an iFOBT can even save over 400.000.000 euros and almost 21.000 life years (van Rossum et al., 2009).

Sharp et al. found out that all scenarios would be considered highly cost-effective compared with no screening. The lowest incremental cost-effectiveness ratio was found for flexible sigmoidoscopy (€589 per quality-adjusted life year gained), followed by iFOBT (€1,696) and gFOBT (€4,428). Compared with flexible sigmoidoscopy, iFOBT was associated with greater gains in QALY's and reductions in lifetime cancer incidence and mortality, but was more costly, required considerably more colonoscopies and resulted in more complications (Sharp et al., 2012).

Based on the analyses from a microsimulation model, biennial screening for CRC with iFOBT and an uptake rate of 60 % could prevent 1.400 deaths from CRC per annum, at a cost of 2.200 euros per year of life saved (van Veen et al. 2009).

Within an exemplary screening strategy, biennial iFOBT from the age of 55 to 75, one-sample iFOBT provided 76.0 – 97.0 life years gained per 1.000 individuals, at a cost of €259,000 – 264,000 (range reflects different iFOBT cut-off levels) (Goede et al. 2013).

In summary: colonoscopies are not without danger and should not be performed when not necessary. Therefore, a test with a high specificity has to be used as a screening test.

The iFOBT has a slightly lower specificity than the gFOBT. For all advanced adenomas and cancer, the specificity of the gFOBT was 99 % compared to 97.8 % for the iFOBT (≥ 100 ng/ml), for cancer, the respective specificity was 98.1 % for gFOBT and 95.8 % for iFOBT (≥ 100 ng/ml) (van Rossum et al., 2008).

Screening for CRC is cost-effective. Screening for colorectal cancer with the iFOBT is more cost-effective than screening for CRC with the gFOBT.

4. GENERAL CONCLUSION

When organizing a colorectal cancer screening program, the iFOBT is to be preferred above the gFOBT, not only because of a better participation of the target population but also because of a better performance and because it is more cost-effective.

When choosing between the available iFOBTs, OC-Sensor and FOB-GOLD, the OC-Sensor has the advantage that it has been widely tested and used and that is has a better sensitivity and test-stability.

To achieve the optimal positivity rate in Belgium (between 3-5%), a one sample strategy with a cut-off value around 100 ng/ml for the OC-Sensor test is recommended.

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6. COMPOSITION OF THE WORKING GROUP

All experts joined the working group ***in a private capacity.*** The names of the members and experts of the Superior Health Council are indicated with an asterisk*.

The following experts were involved in drawing up the advice :

Name	Expertise	Affiliation
ARBYN Marc	Epidemiology	WIV
DE BACKER Guy *	Epidemiology, Public Health	UGent
POLUS Marc	Gastroenterology	ULg
VAN CUTSEM Eric	Digestive oncology	Leuven cancer institute, UZLeuven
VAN HAL Guido	Epidemiology and Social Medicine	University of Antwerp
VAN OYEN Herman*	Epidemiology	WIV
VAN ROOSBROECK	Centre for cancer prevention	University of Antwerp

The following external expert was heard :

FAIVRE Jean	Gastroenterology	Université de Bourgogne, Dijon, France

The working group was chaired by Guy DE BACKER, the scientific secretary was Veerle MERTENS.

About the Superior Health Council (SHC)

The Superior Health Council is a federal body that is part of the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC takes no decisions on the policies to follow, nor does it implement them. It does, however, aim at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, members of scientific institutions), 200 of whom are appointed experts of the Council. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a referring committee) and 4) the final endorsement of the advisory reports by the Board (ultimate decision-making body). This coherent set of procedures aims at allowing the SHC to issue advisory reports based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

The advisory reports drawn up by the working groups are submitted to the Board. Once they have been endorsed, they are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.css-hgr.be), except as regards confidential advisory reports. Some of them are also communicated to the press and to target groups among healthcare professionals.

The SHC is also an active partner in developing the EuSANH network (European Science Advisory Network for Health), which aims at drawing up advisory reports at the European level.

In order to receive notification about the activities and publications of the SHC, you can send a mail to info.hgr-css@health.belgium.be .

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