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GUIDANCE FOR FAECAL OCCULT BLOOD TESTING: QUANTITATIVE IMMUNOCHEMICAL METHOD (FIT-HB) IN COLORECTAL CANCER SCREENING PROGRAMMES

GISCoR First Level Working Group

EDITED BY:
Tiziana Rubeca (Firenze)
Stefano Rapi (Firenze)
Silvia Deandrea (Varese)

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SUPPLEMENTO

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Editors

Tiziana Rubeca
Project coordinator
Regional Cancer Prevention Laboratory, Cancer Prevention and Research Institute - ISPO, Florence

Stefano Rapi
Careggi University Hospital (AOU-Careggi), Florence. Project Manager - Italian Society of Clinical Biochemistry and Clinical Molecular Biology - SIBioC, SIBioC - GISCoR, Harmonisation of pre-analytical phase of faecal testing; Editor for the pre-analytical and analytical testing phases

Silvia Deandrea, European Commission, Directorate-General Joint Research Centre, Directorate F - Health, Consumers, and Reference Materials; Editor for Key Performance Indicators (KPIs)

First level working group members

Morena Malaspina, Central Screening Laboratory, Umbria Region, Perugia
Basilio Ubaldo Passamonti, Central Screening Laboratory, Umbria Region, Perugia
Elena Grassi, Public Health Laboratory - Local Health Authority, Brescia
Anna Maria Cioccarelli, Public Health Laboratory - Local Health Authority, Sondrio
Enrico Marchetti, Central Screening Laboratory, Umbria Region, Perugia
Michela Boni, University Hospital of Ferrara, Sant'Anna, Cona (Ferrara)
Filippo Cellai, Regional Cancer Prevention Laboratory, Cancer Prevention and Research Institute - ISPO, Florence

External reviewers

Marco Pradella, Coordinator, National Committee on Quality and Accreditation, Italian Society of Clinical Pathology and Laboratory Medicine - SIPMeL

Franco Gattafoni, Inspector, Certification, Inspection and Laboratories Department - ACCREDIA; Project Manager, European Accreditation (EA) Working Group, European Commission Initiative on Breast Cancer - ECIBC/ European Commission Directorate-General, Joint Research Centre, Varese

Sabrina Rotolo, Inspector, Certification, Inspection and Laboratories Department - ACCREDIA

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Abstract

Background: in Italy, colorectal cancer screening is included as part of the Italian National Health Service - SSN (Servizio Sanitario Nazionale) Essential Levels of Care - LEA (Livelli Essenziali Assistenziali) and the European Guidelines, which specify quantitative FIT-Hb testing as the best strategy for organised screening programmes. To ensure consistent operating standards in Member States, European regulations require the implementation of certification and accreditation requirements for diagnostic and care-related processes. The requirement, based on ISO 17021 accreditation standards, includes ISO 9001 certification for systems and ISO 15189:2012 accreditation for laboratories.

Methodology: various phases of the analytical process (pre-test, test, post-test) were evaluated in detail and provided operational guidelines for adjusting analytical and managerial procedures using: (a) feedback from members of GISCoR screening labs; (b) performance data obtained via a systematic review of the literature and the Osservatorio Nazionale Screening (ONS) Survey; (c) recommendations for laboratory practice issued by the World Endoscopy Organization "FIT for Screening" Working Group; (d) selected guidelines from the National Guidelines Clearinghouse database; and (e) Canadian, Australian and European screening programme websites. With respect to ISO 15189:2012 standards for accreditation of medical laboratories, GISCoR's guidance has been re-evaluated and revised by auditors from the Italian certification body (ACCREDIA) to assess its compliance and completeness with the aim of finalising operating procedures.

Conclusions: the implementation and maintenance of operational standards required by complex systems (e.g. screening programmes) involving constant interaction between facilities and the supporting organisational structure are not easy to achieve. The guide aims to provide laboratories with the necessary guidance for proper process management.

Keywords: colorectal cancer screening; faecal occult blood testing; indicators; ISO 15189

Foreword

An overview of various screening programmes confirms that laboratory-based screening tests (e.g. HR-HPV or faecal occult blood tests using a quantitative approach) provide more reproducible results than using other types of tests (e.g. Pap test, mammography). This increased reproducibility is certainly an advantage in implementing screening programmes, ensuring – on the one hand – good comparability between geographic areas or different time periods, while the "learning curve" (i.e. the time needed for a screening technician to reach an adequate level of quality) of the technician is significantly shorter.

However, despite these advantages, laboratory testing itself can pose quality-related issues as well. In fact, the expansion of screening programmes facilitates market access and increases the production of FIT test kits from various manufacturers, which can make comparing results problematic. Consequently, the screening community has reacted proactively. For example, in the case of colorectal screening, a study of the effects of temperature on fit positivity rate prompted manufacturers of diagnostic kits to improve their products. Thus, making the *Guidance for faecal occult blood testing: quantitative immunochemical method (FIT-Hb) in colorectal cancer screening programmes* (hereafter referred to as the "guide") quite timely.

Coordinated by Tiziana Rubeca, Stefano Rapi and Silvia Deandrea, in collaboration with the European Commission's Joint Research Centre, the guide represents the collaboration between practitioners who are active in the field of research and those who manage laboratory-based screening programmes in support of faecal occult blood testing research.*

The guide examines all stages of the FIT testing process comparing, whenever possible, data from the most frequently used tests in Italy. For each stage of the process, suggestions for monitoring the quality of the diagnostic report are provided, when possible. Furthermore, as the screening test relies on samples which have been collected by the kit user, an indicator of non-compliance is of particular interest, as it can impact costs as well as test adherence.

The guidance provided in this document will undoubtedly contribute to the development and/or improvement in the quality of colorectal screening within our country – particularly during this significant period of programme implementation in central and southern Italy. Likewise, as with other procedural manuals, an English version of the guide would be beneficial to screening programmes throughout Europe.

In conclusion, with respect to organised screening programmes and current clinical practice, this guide is further confirmation that quality remains the primary focus. The commitment of the ONS, GISCoR, as well as other key partners, will continue to assure citizens that adopted quality standards will remain high – even in the wake of increasing participation rates – to ensure cost-effectiveness of the care pathway.

Emanuela Anghinoni
President, Gruppo Italiano Screening Colorettale (GISCoR)

Marco Zappa
Director, Osservatorio Nazionale Screening (ONS)

* As a measure of quality control, the group submitted their recommendations to an external panel of experts for further review.

Introduction

The GISCoR First Level Working Group's previous work regarding the use of faecal occult blood testing in colorectal cancer screening[1] was to provide operational guidance regarding the primary test used in screening programmes. Following the EU Council Recommendation of 2 December 2003,[2,3] the Italian Ministry of Health issued *Recommendations for planning and implementation of population-based screening for the prevention of breast, cervical and colorectal cancers* (*Raccomandazioni per la pianificazione e l'esecuzione degli screening di popolazione per la prevenzione del cancro della mammella, del cancro della cervice uterina e del cancro del colon retto*),[4] which indicated the initiation of colorectal screening (now part of the LEA) – with the implementation of programmes throughout most of the country.

The launch of new programmes, at national and European level, has piqued the interest of diagnostic companies, resulting in the introduction of new analytical methods. However, these methods differ significantly in terms of analytical strategies and overall performance. This proliferation of analytical methods has led the scientific community to place greater focus on the various components of the analytical process, and to pay closer attention regarding the implications of alignment, harmonisation and, in general, the analytical quality and correct use of methods with respect to the epidemiological parameters of the population.

In recent years, an increase in information and data has resulted in the re-evaluation of the appropriateness of previous issued guidance. EU Regulation 765/2008 recommends the adoption of harmonised standards with regard to accreditation and certification processes for all organisations that intend to manufacture products and deliver services. Thus, ensuring maximum quality assurance through the application of harmonised standards. For organisations delivering services related to the screening and diagnosis process, this involves the certification of processes and services in accordance with ISO 17021 certification (under ISO 9001 or EN 15224), or alternatively, according to ISO 17065 standards. Clinical laboratories function in compliance with ISO 15189.[5] For laboratories conducting faecal occult blood testing, this recommendation is consistent with European guidelines for colorectal screening,[6] which recommend that laboratories conducting this test (within a screening context) be associated with an ISO 15189-accredited laboratory (recommendation 4.12).

Finally, given the specifics of faecal matrix testing and ISO 15189 standards, it is important to initiate a review of operating procedures, which involve the entire laboratory process. This document addresses the various technical and managerial aspects of laboratory proficiency, from the sampling phase and configuration of the analytical set-up to the interpretation and dissemination of the results, as well as management of critical findings.

The latest addition to the guide attempts to simplify subsequent changes to facility certification and accreditation by addressing the key aspects of the analytical process to be included in tender specifications and specific operating procedures and/or standard operating procedures (SOPs).

Aspects of the laboratory testing process

PRE-ANALYTICAL PHASE

Due to the lack of binding protocols from regulating authorities and/or guidelines from scientific organisations and societies, the pre-testing phase of faecal immunochemical tests for haemoglobin (FIT-Hb) is the most problematic and least harmonised aspect of the entire diagnostic pathway. Findings from the World Endoscopy Organization's "FIT for Screening" Working Group[7] facilitated reconsideration of this phase – taking a systematic approach to the problem. However, clear and detailed guidelines are still needed for a definitive solution.[8]

The FIT-Hb test is based on self-sampling of biological material by the user with the help of specific devices for sample collection. However, because intermittent bleeding (even in the presence of advanced lesions) and non-homogeneous dispersion of haemoglobin in faecal matter can influence test results, the pre-analytical phase is vulnerable to problems related to the individual characteristics of the sample. Consequently, in terms of the overall test result, this issue of "uncertainty" with respect to the sample is significant.

Furthermore, considerable variations in the specific weight and consistency of the source material often result in different amounts of collected faecal matter – leading to erroneous test outcomes. Some experimental tests[8,9] have confirmed the lack of correlation between the expected quantity of material (stated by the manufacturers) and the actual quantity collected in the devices during the pre-analytical phase (table 1).

A further source of pre-analytical variability is the composition and volume of the specimen collection device (SCD) used to render the Hb soluble and stable. Due to patent protections, the exact composition of the buffers used in various SCDs is unknown. However, buffer composition has been linked to the pH and the ionic strength of the reaction buffer, and therefore the structure and reactivity of the molecule; all of which affects haemoglobin stability and, in certain circumstances, the specificity of the test result.[11,12] Finally, difficulties in characterising and comparing performance of various quantitative FIT-Hb methods[9] are the direct result of

Table 1. Evaluation of the sampling accuracy of commercial sampling devices used in faecal immunochemical tests for haemoglobin (FIT-Hb).

DEVICE	Theroretical[a]	GMEC[b]	Halloran[c]	Mean recovery (%)[d]		
	(mg)	(mg)	(mg)	test 1	test 2	test 3
OC Sensor Diana	10	15	11.2	76	97	78
HM Jack arc	2	4	2.2	112	121	116
FOBGOLD	10	16	10	72	87	92
NS Plus	10	14	9.5	56	79	77

[a] quantity of faeces collected according to the manufacturer's statements
[b] evaluation by the Guildford Medical Device Evaluation Centre (GMEC)[9]
[c] values provided for reference 10
[d] tests with otherwise-structured faecal matter (Bristol scale types 4 and 5). The values report the mean percentage of recovery compared to the value stated by the manufacturer of a sequence of 8 samples from the same material (table modified from ref. 8).

the close relationship between the SCD, the analytical system used, and the results provided by the individual test.
The pre-analytical phase is a crucial step in the laboratory process. However, pending the issuance of European-specific recommendations by a recognised authority regarding the production of SCD, it is essential that laboratories are involved in the initial evaluation of these devices. Specifically, it has been suggested that benchmarking is included in the drafting phase of tender specifications assigning qualitative scores to the following information:

1. buffer capacity to stabilise Hb;
2. convenience of the SCD;
3. quality (completeness, simplicity) of self-sampling instructions;
4. provided performance features of the SCDs;
5. volume of the SCD;
6. buffer volume used;
7. "Risk phrases" related to the material contained in the SCD (as defined in Annex III of European Union Directive 67/548/EEC: Nature of special risks attributed to dangerous substances and preparations.

The buffer capacity to stabilise Hb (point 1) under various storage conditions is recognised as a crucial factor in preventing the degradation of the material before the analytical run.
Convenience of the device (point 2) is directly associated with the repeatability of self-sampling.
The volume of the SCD (point 5) provides pertinent information on the expected ratio between the faecal matter and the buffer used (µL faeces/mL buffer) and allows immediate comparison of epidemiological performance of different methods in the event that there is a change of testing method.[13]
The buffer volume used (point 6) and the associated risk phrases (point 7) are significant, in terms of the disposed material and the safety of patients and technicians.

ANALYTICAL PHASE

REFERENCE METHODOLOGY AND LABORATORY REQUIREMENTS

To ensure systematic control of the entire analytical process, faecal occult blood testing within screening programmes must be conducted in laboratories accredited by the Italian National Health Service (SSN). According to guidelines evaluated by the GISCoR working group[6,14-16] and scientific findings,[17,18] in order to optimise screening efficiency and cost-effectiveness, the following is recommended:

- use of quantitative immunochemical methods (FIT-Hb);
- faecal Hb testing on a single sample;
- use of specific cut-offs for the method used and the programme's operational capabilities.

Since cut-offs lower than those recommended by the manufacturer inevitably result in an increased positivity rate (irrespective of identified neoplasms[18] and low-risk lesions), it is recommended that the cut-off is defined according to the operational capacity of the facilities providing the assessment (colonoscopy units); as the lack of personnel or resources could impact waiting times.[19-22]
In order to make the results easy to interpret, the use of qualitative (positive or negative) categories with the addition of guidance for any subsequent assessment provided by the programme is recommended.[14] The cut-off value provided by the investigation should be stored and shared with the screening programme's epidemiology subdivision in order to study, verify and optimise the process.[23]

Instrumentation for FIT-Hb testing should be subject to all normal procedures and checks as required by good laboratory practice for immunometric tests.

We recommend that individual SOPs specify:

1. systematic use of at least two levels of internal quality control (IQC) material;
2. use of IQC with control material, preferably manufactured by a third-party and not by the company providing the instrumentation;
3. methods for the creation, verification, and preservation of instrument control cards and analytical results;[24]
4. scheduling and recording of preventive, regular, and emergency maintenance of instruments
5. for each analytical run: record and monitor control materials used, responses provided, technicians' approval, traceability and single sample procedures, including documentation regarding revision of results before release (ISO 15189 5.7.1 Review of results, ISO 15189 5.9.1 Release of results);[5]
6. a broader use of computer resources for managing the analytical process, i.e. CQi, technician approval, transfer and storage of analytical results, including the traceability of the entire process in the time required by relevant legislation;
7. a detailed description of the methods used for presentation of the results, the decoding used in the conversion of quantitative results (provided by the instrument) as well as the qualitative results that are sent to the user;[13]
8. membership in at least one external quality assessment (EQA) programme in Italy; when this is not possible, it is recommended that IQC activities be integrated with inter-laboratory comparisons;
9. taking into account the critical issues related to proper management of the pre-analytical phase, we recommend maximum laboratory involvement in drafting and verifying protocols and SOPs for sampling, storage, and dispatch of biological material; particular attention should be paid to communicating with the user regarding the proper methods for management of the sample and delivery to the laboratory (ISO/TS 20658 4.3, ISO 15189 5.4.4.2, ISO 151895.4.4.3). [5]

We also recommend a sufficient coordination with the Screening Centre, which should provide the user with comprehensive information on:

1. methods for collecting biological material (specific for test kit used); the optimal sampling methods are related to the shape of the sampling stick, and thus differ according to the test kit used; therefore, a specific intervention to reduce non-conformity related to "non-testable" samples due to excess or deficient material would be useful;
2. biodegradation temperature (for methods currently in use, conservation at 4° C is advisable); if the sampling device cannot be immediately sent to the collection centre, the patient should be informed how to avoid degradation of Hb in the sample;[11]
3. use refrigerators and refrigerated containers at collection centres and for transportation of the material; this recommendation is necessary to prevent the degradation of Hb contained in the SCD. According to GISCoR, only 19.7% of screening centres transported material to the laboratory under controlled temperatures while 23.7% of the transport was done at room temperature, and 56.6% had mixed temperatures; [25]
4. Recording the sample collection date;[14] it is advisable to establish a protocol for timing, temperature monitoring, and shipping to be implemented by the user at the time of collection. Recent data from GISCoR[25] show that the sampling date is not reported for 77.5% of samples.

SOPs should explicitly state the measures for failing to comply with analytical and technical quality parameters, such as:

1. modality, registration and management of non-conformities, especially during the pre-analytical phase;
2. significant deviation from values obtained for IQC (ISO 15189 4.9);[5]
3. significant deviation from EQA programmes (ISO 15189 4.10); [5]
4. errors and delays related to the timeliness of the exam and delivery of the result;
5. case studies and methods for requesting repeated collection;
6. management of borderline results (grey zone); given the performance characteristics of the methods, analytical imprecision (approximately 10%), the high variability of the pre-analytical phase, the intermittency of bleeding (even in the presence of neoplastic lesions), and Health Technology Assessments (HTA) aimed at optimising the cost/benefit ratio upstream of the programme, it is strongly advised to not request new samples in the event of borderline values, regardless of the method used;
7. warehouse management: timeliness of material arrival, internal and supplier non-conformity; it is recommended that a new sample should only be requested in the event of significant errors in the pre-analytical phase: storage temperature, material dispatch time and unsuitable material.

In the event of an out-of-specification analytical set, it is recommended to repeat the test run using the sample already at the laboratory. Positive results above the linearity limit of the method (LS) should be recorded as ">LS".

PERFORMANCE CHARACTERISTICS OF METHODS, CONTROL MATERIALS, AND ANALYTICAL QUALITY

To provide an overall assessment of the current status of FIT-Hb methods used in Italy, information provided on performance is recorded during normal laboratory operations and EQA cycles.

INTERNAL QUALITY CONTROL (IQC)

The inability to interchange available methods and control materials remains one of the unresolved analytical issues in FIT-Hb testing. The responses of the control materials are therefore method-dependent. Available test methods use control material supplied by the manufacturer (rather than a third party) or are "self-validating", i.e. method-specific and not satisfactory in terms of regulatory and metrological requirements. The use of third-party control materials (even in the absence of certified values) is very important in order to highlight any systematic discrepancies in the analytical response, which are otherwise compensated for by the affinity between calibrators and controls produced by the same manufacturer.

When using material with no assigned value, it is necessary to obtain an estimate of the expected value, which must be kept with industry documentation. Furthermore, the laboratory shall operate in accordance with procedures described in internationally recognised guidelines.[23]

The use of IT systems dedicated to quality control management is strongly advised.

Given the differences in analytical results between available methods and control materials, it is appropriate to report the experimental values obtained by the various methods to allow laboratories to conduct a preliminary assessment of the methods' performance characteristics.

The **table 2** shows the performance of laboratories with respect to available IQC materials and according to specific tender specifications. For all methods, these controls were supplied by the manufacturer and could not be changed according to manufacturer declarations.

Table 2. IQC operating ranges on quantitative analytical systems used by screening laboratories in Italy. The following data are included: duration of verification, number of batches used and analytical ranges. In detail ranges of targets set by manufacturers, bias and coefficients of variation (CV).

	No. OF MONTHS	No. OF BATCHES	No. OF SESSIONS	TARGET	BIAS (%)	CV
OC Sensor Diana						
low	12	6	8÷38	127÷137	-1.5÷3.4	1.6÷4.4
high	12	6	8÷38	432÷453	-3.1÷7.5	0.89÷2.3
HM Jack arc						
low	6	1	108	24	-2.1÷3.1	2.8÷5.9
high	6	1	108	95	-0.5÷7.4	2.3÷4.9
FOBGOLD						
low	12	5	15÷71	78÷90	-10.4÷8.9	5.6÷11.5
high	12	5	15÷71	309÷318	-10.7÷ 5.6	1.7÷7.8
NS Plus						
low	12	3	42÷198	96÷101	-3.8÷9.9	2.9÷7.8
high	12	3	42÷198	246÷264	-5.3÷8.0	2.4÷6.1

Table 3. Experimental results obtained with the various instruments, using third-party control materials. The following data are included: duration of the investigation, number of values included, mean and standard deviation values (ng/mL), and the range of bias (%) obtained.

	OC Sensor Diana				HM Jack arc				FOBGOLD				NS Plus			
batches	**days**	**No.**	**mean±sd**	**bias (%)**	**days**	**No.**	**mean±sd**	**bias (%)**	**days**	**No.**	**mean±sd**	**bias (%)**	**days**	**No.**	**mean±sd**	**bias (%)**
Poly1*	9	24	67±1.9	-2.4÷3.6	7	22	38±1.9	-5.6÷9	6	16	33±5.0	-7.6÷6.6	nv	nv	nv	nv
Poly2*	9	24	378±23.4	-3.6÷4.2	7	22	199±6	-7÷1.8	8	26	376±22.0	-10÷2.1	9	26	63±6.9	-11.1÷14.8
Care1**	9	26	129±1.1	-1.6÷0.7	8	24	130±2.3	-4.2÷1.9	9	26	578±5.4	-1.8÷0.6	8	24	166±23.1	-23.2÷9.9
Care2**	9	26	793±8.0	-1.4÷0.9	8	24	794±6.6	0.1÷0.9	9	26	1.660±22	-2.6÷0.2	8	24	10.6±244.1	-37.2÷25.6
Lyo1***	9	28	198±15.1	-9÷-1.7	7	22	219±7.1	0÷7.7	9	26	170±8.4	-4.7÷4.7	8	14	44±6.0	-21.6÷18.9
Lyo2***	9	28	130±3.8	-3.4÷5.4	7	22	141±3.9	-3.5÷5.5	9	26	77±7.8	12.3÷8.5	nv	nv	nv	nv
Lyo3***	9	28	179±7.3	-5.8÷5.3	7	22	190±11.4	-7.5÷2.5	9	26	152±9.5	-4.7÷7.4	nv	nv	nv	nv

nv: not evaluable
* ready-to-use Polymed controls (Polymed Srl, Florence - Italy)
** ready-to-use Care controls (Care Srl, Genoa - Italy)
*** freeze-dried Polymed controls (Polymed Srl, Florence - Italy)

Table 3 shows the "experimental" results obtained from an investigation of certain third-party control materials found in Italy. The information collected confirms the lack of a standard reference for different analytical methods and the difficulties related to the procurement of usable third-party material. The data provided in Table 3 is intended to provide the preliminary guidance for selecting adequate materials and setting analytical targets for different methods.

The experiment was conducted over eight days with material stored at 4°C. The freeze-dried controls were reconstituted with the buffer used by the analytical system (as indicated by the manufacturer). The results obtained confirmed the inability to interchange control materials and the absence of a standard reference for analytical methods – particularly when they are based on different analytical strategies.

It is therefore desirable to develop new control materials to address the current shortcomings.

EXTERNAL QUALITY ASSESSMENT (EQA)

Laboratories are required to participate in EQA programmes for all manner of testing (ISO 15189 5.6.3.1 Participation).[5] Apart from the financial proposal and specific regional guidelines, the criteria for selecting EQA programmes (which can be assessed during the tender specifications phase) are:

- the number of laboratories participating in the analytical laboratory system. In order to obtain statistically useful information, at least 8 facilities are required;
- dispersion (i.e. type deviation and variation coefficient %) of the data provided by participating laboratories. Dispersion is an indirect index of the quality of the material used by the vendor and it can be deduced through comparison of reports;
- number of cycles offered and how to send the material via the EQA manager during the year;
- experience of the EQA programme manager;
- type of report (timeliness, completeness, clarity, readability).

Clearly, the selection must include independent and accredited providers, or those able to demonstrate that they operate in accordance with standard ISO 17043, following an audit by the client.

The choice will obviously have to be considered with respect to independent and accredited "providers", or that it can demonstrate that they operate in accordance with ISO 17043, subject to client audit.

Currently, there are no EQA cycles available to assess faecal matter during the pre-analytical phase; Italian programmes focus on verifying the analytical phase.[26,27] However, in the UK, the Weqas programme[28] is developing quality control measures to assess the performance of the pre-analytical phase.

The periodic revisions of the data provided by the laboratories participating in the EQA cycles represent significant evidence regarding the state of the art of methods and are the easiest strategy to highlight metrological differences between available methods.

POST-TESTING PROCESS / POST-ANALYTICAL PHASE

The international guidelines require that results be expressed according to a qualitative, binary "POSITIVE/NEGATIVE" format,[14] with a requirement to undergo a colonoscopy in the event of a positive result or repetition of the test in two years for negative results.
In the event of a positive result, a personalised response with details regarding the result and follow-up is preferable.[6]
Although there is no consensus regarding the way in which quantitative results are expressed, it is strongly recommended that µg Hb/gr stools be used as the unit of measure for reporting quantitative data. However, the growing use of µg Hb/ml of sample material[13] appears to be the preferred unit of measure in the future, as the material is not weighed but obtained via self-sampling by filling a specific region of the device. Furthermore, it provides information regarding the characteristics of the devices to the manufacturer.[29] Therefore, it is strongly recommended to not use the ng Hb/mL buffer as it is extremely difficult to compare values between different methods. The table 4 shows the numeric coefficients needed to convert ng/ml to µg/g according to the method used[9]. It is suggested that the cut-off is assessed every six months if the indicators are not met.

Table 4. Conversion factors of results expressed as ng/mL to µg/g for quantitative immunochemical methods used in Italy.*

	FAECAL MASS (mg)	BUFFER VOLUME (ml)	CONVERSION FACTOR
OC Sensor Diana	10	2.0	0.20
HM Jack arc	2	2.0	1.00
FOBGOLD	10	1.7	0.17
NS Plus	10	1.9	0.19

Formula: µg Hb/g faeces = $\frac{\text{(ng Hb/ml x ml buffer)}}{\text{faecal mass in mg of faeces}}$

* Table adapted from Carroll MRR, Piggott C, Pearson S, Seaman HE, Halloran SP. Evaluation of quantitative faecal immunochemical tests for haemoglobin. Guildford Medical Device Evaluation Centre (GMEC), Guildford, UK, 2013.

Hopefully, the generation of detailed guidance on methods for collecting faecal matter by standardisation bodies and scientific societies will be required in the future.

Key performance indicators – KPIs

KPIs OF THE ANALYTICAL PROCESS

In order to assess and monitor the characteristics of the process, and to obtain useful information for improving the process itself, it is suggested that indicators be used to analyse the most critical organisational, instrumental, and procedural factors within various phases of the analytical process. Monitoring of "non-conformity", defined as "non-fulfilment of a requirement", where the "requirement or expectation is generally implied or binding" (ISO 9000: 2005)*, is an essential tool for building indicators which monitor the analytical process. Based on data collected by laboratories currently active in reading faecal immunologic blood tests in population-based programmes,[30] various types of non-conformity distinguished:

Non-conformity in the pre-analytical phase

For all situations where the sample is not suitable for performing the test:

- unsuitable container (improper test/biological/material spillage/rupture or breakage);
- expired test tube;
- sample date inconsistent with stability indications provided by the manufacturer;
- illegible bar code (reprinted/rejected);
- incorrect or incomplete request (user not eligible for screening/no informed consent/incomplete or incorrect personal details);
- incorrect sampling (insufficient or excess material).

Non-conformity in the analytical phase

For all situations where the scheduled analytical process has been suspended:

- failure to read the sample identification code;
- failed or partial aspiration of the sample (device too full/empty/instrument unable to pick-up sample material from the device);
- broken sampling device/accidental stoppage of instrument;
- computer operating system crash.

Non-conformity in the post-analytical phase

For all situations where the data transfer is not handled properly:

- failure in transfer to the laboratory computer system;
- delays in reporting results from the analytical tool (or in the production of digital documents with results);
- unsuitable reports due to printing errors;
- reports sent to the wrong person due to a computer error.

Non-conformity can be further classified into:

- minor non-conformity (non-conformity can be solved during the process);
- major non-conformity (non-conformity cannot be resolved and requires another sample from the user).

* Non-conformity may be classified according to its severity and impact (critical/major, non-critical/minor) it may have on processes. The former may cast doubt over the organisation's ability to fulfil its role; the latter may cast doubt over the ability to manage a single process or a single activity (non-critical).

The working group proposes monitoring indicators in all three phases (pre-analytical, analytical and post-analytical) for major non-conformity.

Types of major non-conformity

- unsuitable container;
- incorrect test tube;
- biological contamination;
- material misalignment/rupture;
- expired test tube;
- sample date inconsistent with stability indications supplied by the manufacturer;
- incorrect sampling (insufficient / excessive material);
- incorrect specimen identification;
- lack of informed consent.

The following minor non-conformity is not subject to the indicator:

- illegible barcode (reprinted/rejected;)
- bad request (the user is ineligible for the test);
- missing sample identification code;
- failed or partial suction of the material (over-full/empty device / instrumentation fails to pierce the device);
- sampling device broken or damaged;
- stoppage or breakage of instrumentation;
- computer operating system crashes;
- data transfer is missing;
- report printing delayed;
- unsuitable reports (print errors/reports delivered without signature);
- referrals not delivered in accordance with modalities and "timeliness".

In the case of major non-conformity, the laboratory will confirm the percentage of negative events and then take corrective measures as defined in **box 1**.

As guideline recommendations[6] on acceptable and desirable values for inadequate tests are based on performance data from the guaiac test, the working group has revised the data collected from participating laboratories in order to propose more meaningful evaluation criteria for existing screening laboratories. The proposed criteria are more restrictive than those given in the guidelines (<3% acceptable and <1% desirable) and are consistent with the GISCoR indicator already in use (<1% acceptable).[31] However, it must be taken into account that the indicator measuring "inadequate tests" for the screening programme as a whole and the indicator for measuring "major non-conformity" from a laboratory point of view may measure phenomena that do not fully overlap.
It is recommended that non-conformity be recorded for each analytical run and revised on a quarterly basis.

Box 1. Percentage of major non-conformity in the total tests received by the laboratory during the testing period.

Desirable % of non-conformities:	<0.1
Good % of non-conformities:	0.1 ≤n ≤0.5
Acceptable % of non-conformities:	0.5 ≤n ≤1

VERIFICATION OF LABORATORY PERFORMANCE USING EQA CYCLES

The EQA programme has the task of verifying and certifying the reliability of independent third-party laboratories and to report any deviation of performance from expected values. The laboratory must define the appropriate corrective measures in the event of significant deviations from the expected results in terms of z-scores or per cent difference, and analyse and document the evaluation of individual reports by investigating any possible causes of non-acceptability. It is in the interest of the laboratory to evaluate the method in use based on the overall responses from the participants in the EQA cycles according to its method/system, and to use periodic reports in the qualitative scoring phase of the tender specifications, in order to purchase new equipment.

PERIODIC MONITORING OF EPIDEMIOLOGICAL INDICATORS

Table 5 presents general epidemiological indicators of FIT-Hb performance, as recommended by GISCoR.[31] These indicators are usually monitored at programme level, on the basis of data collected by the laboratory, endoscopy centres, pathology services, etc. Therefore, these parameters provide an overall assessment of the programme's performance and can be influenced by several stakeholders. However, from the test selection stage, the quality of the FIT-Hb test plays a key role in achieving the expected objectives. Conversely, evaluation of programme results using epidemiological indicators may provide indications regarding the quality and suitability of FIT-Hb analytical procedures.

For the sake of completeness, the table also includes the "standards" related to the rate of compliance with participation in colonoscopy, which does not fall under the parameters of laboratory competence.

An evaluation of the results from the GISCoR survey,[20] shows that the overall data on compliance for the period 2011-2012 reported an average positive rate within both the acceptable and desirable standards. The data were homogeneous, with "outliers" almost exclusively in small or recently activated programmes. The average detection rate for cancer lay between the acceptable and desirable levels, and above the desirable level for advanced adenoma, in both the first and subsequent examinations. Finally, with regard to the positive predictive value, the Italian screening programmes results were well above the desirable standard set for both types of lesions (in both initial and subsequent exams).

Considering the effect of variability in the pre-analytical phase, the lack of commutability of the examination as well as the social and economic impact of the use of methods with inadequate epidemiological indicators, it is essential to refer to epidemiological indicators when choosing the FIT-Hb to use in a screening programme. The GISCoR survey data suggest that the tests and cut-offs used in most programmes examined can ensure adequate performance at the primary screening level, notwithstanding all the other factors not measured by the GISCoR surveys, resulting in an inability to make inferences from observational data found in the survey.

Regarding the level of influence different types of tests have on programme performance indicators, please refer to the results of the meta-analysis conducted by GISCoR Working Groups on Laboratory and Organisation Level (2016 GISCoR National Congress, Florence),[32] which conducted a literature review of studies carried out in screening programmes that allowed the evaluation of quantitative FIT-Hb methods.[33-35]

RECOMMENDATIONS ON TEST PERFORMANCE INDICATORS

It is recommended:

- quarterly monitoring of non-conformity rate;
- testing laboratory performance using EQA cycles;

Table 5. Epidemiological indicators of the occult blood test.

	STANDARD	
	Acceptable standard	**Desirable standard**
FIT + test 1	<6%	<5%
FIT + subsequent tests	<4.5%	<3.5%
Participation to assessment	>85%	>90%
Positive predictive value for advanced adenoma or carcinoma	first test >25% subsequent tests >15%	>30% >20%
Carcinoma detection rate	first test >2‰ subsequent tests >1‰	>2.5‰ >1.5‰
Advanced adenoma detection rate	first test >7.5‰ subsequent tests >5‰	>10‰ >7.5‰

- when choosing the FIT-Hb method, it is recommended to use pilot studies,[6] integrated between user laboratories and epidemiology services, to define performance in detail and optimise decision-making values (cut off).[33-35] During the economic evaluation of the methods and at the time of the selection of the analytical methods, it is highly recommended that the whole process be evaluated in terms of cost-benefit ratio, with a detailed evaluation of the expected epidemiological parameters;
- sharing indicator values is recommended, in particular data on non-conformity and results of internal and external quality assessments, with the team responsible for screening quality assurance, including the medical, technical, nursing and auxiliary staff involved throughout the whole process.[6]

APPENDIX I

METHODS FOR DEVELOPING THE GUIDE

The GISCoR First Level Working Group on faecal occult blood testing developed these recommendations based on the document published in 2009,[1] using a "review by consensus" process and the following sources of information:

- feedback received from technicians who applied the 2009 recommendations (obtained through regular meetings of the GISCoR Working Group level I at national conferences);
- the performance data of occult blood tests, as reported by the National Screening Observatory Survey;[36]
- a systematic review conducted by the GISCoR Working Group Levels I and II on the performance of different types of immunochemistry (PROSPERO record: CRD42015017128);
- chapter 4 of the European Guidelines: Fecal Occult Blood Testing;[6]
- recommendations issued by the World Endoscopy Organization "FIT for Screening" Working Group;[7]
- recommendations in guidelines relevant for laboratory practice, selected through the National Guidelines Clearinghouse database and Canadian, Australian, and European screening programmes websites;[14-16]
- the contents of ISO 15189: 2012 *Standard for Medical Laboratory Accreditation*.[5]

For specific aspects related to ISO 15189 accreditation and ISO 9001 or EN 15224 certification, consult the following international/European/Italian documents:

- ILAC G18:04/2010 Guideline for the Formulation of Scopes of Accreditation for Laboratories;
- ILAC G26:07/2012 Guidance for the Implementation of a Medical Laboratory Accreditation System;
- ILAC P9:06/2014 ILAC Policy for Participation in Proficiency Testing Activities;
- ILAC P10:01/2013 ILAC Policy on Traceability of Measurement Results;
- ILAC P14:01/2013 ILAC Policy for Uncertainty in Calibration;
- EA-2/15 M (July 2008) EA requirements for the accreditation of flexible scopes;
- ACCREDIA RT-26 rev. 05 - Guidelines for accreditation with flexible scope field of accreditation;
- ACCREDIA RT-04 rev. 03 - Guidelines for accreditation of evaluation and certification bodies for quality management systems in sector EA 38 "Healthcare and other social services";
- ACCREDIA RT-35 rev. 00 - Guidelines for accreditation of medical laboratories;
- ACCREDIA RT-24 rev. 02 - Validation testing.

The working group met three times to discuss the collected material. The first draft of the new guide, submitted by the coordinator, was further discussed during two additional meetings and via e-mail. A specific training day took place at ACCREDIA, with healthcare specialists in the field of accreditation and certification standards participating in the process. Finally, the first public version of the guide was approved at the 2016 GISCoR Congress in Florence. The guide was peer-reviewed for aspects related to the analytical processes by Prof. Marco Pradella, Franco Gattafoni, Sabrina Rotolo, ACCREDIA inspectors, specialists in healthcare facilities, and experts in healthcare accreditation and certification.
The final version of the guide was submitted on 23 January 2017.

Silvia Deandrea's time on this project and English translation of the Guidance were funded under Administrative Arrangements *17.030600/12//S12.635313* and *17.030100/16//S12.746515* between the European Commission Directorate-General Health and Food Safety and the Directorate-General Joint Research Centre.

APPENDIX II

CERTIFICATION OF THE SCREENING PROCESS

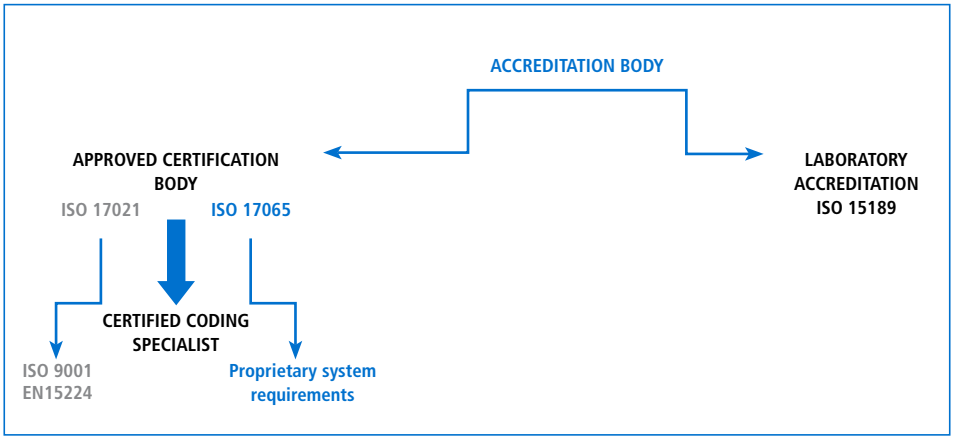
The screening and diagnosis process consists of two sub-processes:

- services related to the start and completion of the process;
- services related to Laboratory Medicine.

Since both are closely related, for the purpose of the overall quality of the macro-process, both should be subject to independent third-party evaluation. Furthermore, as there are no accreditation standards for the evaluation of the first sub-process, a "general" certification (i.e. general requirements already established by ISO* 9001 or EN 15224 specific for the healthcare sector - under ISO 17021 accreditation) or, more specifically, a "process"/"service" certification, accredited to ISO 17065, with requirements directly set by the "scheme owner".
The second sub-process falls under the ISO 15189 accreditation standard, where the same "scheme owner" can set specific requirements for the processes/disciplines subject to accreditation.

* ISO: International Organization for Standardization.

Figure 1. Independent third party recognition scheme.



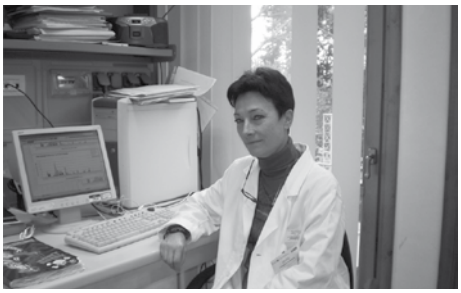
Epidemiol Prev 2017; 41 (5-6) Suppl1: 1-32. doi: 10.19191/EP17.5-6S1.P001.101

BIBLIOGRAPHY

1. GISCoR Laboratory Working Group, Raccomandazioni per la determinazione del sangue occulto fecale (SOF) nei programme di screening per il carcinoma colorettale - Metodo immunologico (Recommendations for faecal occult blood (FOB) testing in colorectal carcinoma screening programmes - Immunoassay method). Epidemiol Prev. 2009; 33 (4-5) suppl 3:1-16.
2. Council of the European Union (2003/878/EC), Council Recommendation of 2 December 2003 on cancer screening. OJ L 327, 16.12.2003, p. 34.
3. Arbyn, M., Van Oyen, H., Lynge, E., Micksche, M., Faivre, J., Jordan, J., European Commission's proposal for a Council recommendation on cancer screening. BMJ 2003, Aug 2; 327(7409):289-90.
4. Working Groups appointed by the Decrees of the Minister of Health (3/11/2004 and 18/10/2005), pursuant to Law 138/2004 (Art. 2-bis), General Department of Prevention, Ministry of Health, November 2006. Raccomandazioni per la pianificazione e l'esecuzione degli screening di popolazione per la prevenzione del cancro della mammella, del cancro della cervice uterina e del cancro del colon retto (Recommendations for the planning and implementation of population-based screening for the prevention of breast, cervical and colorectal cancers).
5. UNI EN ISO 15189: 2013 Medical laboratories - Requirements for quality and competence.
6. Von Karsa L, Patnick J, Segnan N. European guidelines for quality assurance in colorectal cancer screening and diagnosis. 1st edition, 2010. Luxemburg: Publication Office of the European Union.
7. Fraser, C.G., Allison, J.E., Halloran, S.P., Young, G.P., Expert Working Group on Fecal Immunochemical Tests for Hemoglobin, Colorectal Cancer Screening Committee, World Endoscopy Organization. A proposal to standardize reporting units for fecal immunochemical tests for hemoglobin. J Natl Cancer Inst. 2012; 104: 810-4.
8. Rapi, S., Fraser, C.G., Cellai, F., Berardi, M., Rubeca, T., Valutazioni preliminari per La proposta di un unico dispositivo di campionamento per la ricerca dell'emoglobina su materiale fecale (Preliminary assessments for a standard sampling device for fecal hemoglobin detection), Biochimica Clinica 2015; 30(6) 559-562.
9. Carroll, M.R.R., Piggott, C., Pearson, S., Seaman, H.E., Halloran, S.P., Evaluation of quantitative faecal immunochemical tests for haemoglobin. Guildford Medical Device Evaluation Centre (GMEC), Guildford, UK, 2013.
10. http://194.97.148.137/assets/downloads/pdf/resources/ccsc/2012/02_Stephen Halloran_FITforSceening.pdf
11. Grazzini, G., Ventura, L., Rubeca, T., Rapi, S., Cellai, F., Di Dia, P.P., Mallardi, B., Mantellini, P., Zappa, M., Castiglione, G., Impact of a new sampling buffer on faecal haemoglobin stability in a colorectal cancer screening programme by faecal immunochemical test (FIT). Eur J Cancer Prev. 2016 Jun.
12. Grazzini, G., Ventura, L., Zappa, M., Ciatto, S., Confortini, M., Rapi, S., Rubeca, T., Visioli, C.B., Halloran, S.P., Influence of seasonal variations in ambient temperatures on performance of immunochemical faecal occult blood test for colorectal cancer screening: observational study from the Florence district. Gut. 2010; 59(11):1511-5.
13. Fraser, C.G., Rapi, S., Rubeca T., A proposal to Standardize Reporting Units for Fecal Immunochemical Tests for Hemoglobin. J Natl Cancer Inst. 2015; 108(1).
14. Alberta Colorectal Cancer Screening Program. Standards and Guidelines, Version 4.0.
15. Rabeneck, L., Rumble, R.B., Thompson, F., Mills, M., Oleschuk, C., Whibley, A.H., Messersmith, H., Lewis N., The FIT Guidelines Expert Panel Fecal Immunochemical Tests Compared with Guaiac Fecal Occult Blood. Tests for Population-Based Colorectal Cancer Screening, Evidence-Based Series 15-8: Section 1. Report date: 8 November 2011.
16. Publication of the Superior Health Council No. 8901. Immunochemical Faecal Occult Blood Tests for Colorectal Cancer Screening, 8 May 2013.
17. Fraser, C., Halloran, S.P., Allison, J.E., Young, G.P., Making colorectal cancer screening FITTER for purpose with quantitative faecal immunochemical tests for haemoglobin (FIT). Clinical Chemistry and Laboratory Medicine, 2013; 51 (11): 2065-7.
18. Grazzini, G., Visioli, C.B., Zorzi, M., Ciatto, S., Banovich, F., Bonanomi, A.G., Bortoli, A., Castiglione, G., Cazzola, L., Confortini, M., Mantellini, P., Rubeca, T., Zappa, M., Immunochemical faecal occult blood test: number of samples and positivity cutoff. What is the best strategy for colorectal cancer? British Journal of Cancer, 2009; 100, 259-65.
19. ISPO I Programmi di screening della Regione Toscana (Tuscany Region Screening Programmes). 15° Rapporto - I risultati 2013 (Tuscany Region Screening Programmes, 15th Report - 2013 Results), Editing Scientific Press.
20. Zorzi, M., Da Re, F., Mantellini, P., Naldoni, C., Sassoli de' Bianchi, P., et al. Screening for colorectal cancer in Italy: 2011-2012 survey. Epidemiol Prev. 2015; (39)3 Suppl: 93-106.
21. I programmi di screening della regione Emilia Romagna (Emilia-Romagna Screening Programmes). Report 2013 - ISSN 2464-9252 no. 90-2016.
22. https://www.ats-brescia.it/media/documenti/comunicazione/convegni%202016/farmacisti/CERE DA.pdf
23. Allison, J.E., Fraser, C.G., Halloran, S.P., Young, G.P., Chapter 4: Quality Indicators and Benchmarks for Guideline-Recommended Fecal Occult Blood Tests. Colorectal Cancer Screening Quality and Benchmarks, Editors: A. Shaukat and J. Allen (2015).
24. Clinical and Laboratory Standards Institute (CLSI). C24-Ed4 Statistical Quality. Control for Quantitative Measurement Procedures: Principles and Definitions, 4th Edition, Wayne, Pennsylvania, 2016.
25. http://www.giscor.it/convegni/giscor2014/20141114/sessione-2/corradini-giscor-20141114.pdf

26. www.aou-careggi.toscana.it/crrveq
27. www.centroricercabiomedica.net/
28. http://www.weqas.com/services/eqa/fob-fit/
29. Rapi, S., Berardi, M., Cellai, F., Ciattini, S., Chelazzi, L., Ognibene, A., Rubeca, T., Effects of faecal sampling on pre-analytical and analytical phases in quantitative faecal immunological tests for haemoglobin (FIT-Hb). IJBM 2017. DOI: 10.5301/ijbm.5000265.
30. Deandrea, S., Tidone, E., Bellini, A., Bisanti, L., Leonardo, N., Silvestri, A.R., Consonni, D., Implementation of failure mode and effects analysis to the specimens' flow in a population-based colorectal cancer screening programme using immunochemical faecal occult blood tests. A quality improvement project from Milano colorectal cancer screening programme, submitted.
31. Zorzi, M., de' Bianchi, P.S., Grazzini, G., Senore, C., Gruppo di lavoro sugli indicatori del GISCoR. [Quality indicators for the evaluation of colorectal cancer screening programmes]. Epidemiol Prev. 2007 Nov-Dec; 31(6 Suppl 1):6-56.
32. http://www.giscor.it/convegni/giscor-2016/20161111/deandrea_giscor_20161111.pdf
33. Passamonti, B., Malaspina, M., Fraser, C.G., Tintori, B., Carlani, A., D'Angelo, V., Galeazzi, P., Di Dato, E., Mariotti, L., Bulletti, S., D'Amico, M.R., Gustinucci, D., Martinelli, N., Spita, N., Cesarini, E., Rubeca, T., Giaimo, M., Segnan, N., Senore, C., A comparative effectiveness trial of two faecal immunochemical tests for haemoglobin (FIT). Assessment of test performance and adherence in a single round of a population-based screening programme for colorectal cancer. Gut. 2016 Dec 14.
34. Rubeca, T., Rapi, S., Confortini, M., Brogioni, M., Grazzini, G., Zappa, M., Puliti, D., Castiglione, G., Ciatto, S., Evaluation of diagnostic accuracy of screening by fecal occult blood testing (FOBT). Comparison of FOB Gold and OC Sensor assays in a consecutive prospective screening series. Int J Biol Markers. 2006 Jul-Sep; 21(3):157-61. Erratum in: Int J Biol Markers, 2007 Jan-Mar; 22(1):86.
35. Rubeca, T., Peruzzi, B., Confortini, M., Rapi, S., Overall evaluation of an immunological latex agglutination system for fecal occult blood testing in the colorectal cancer screening program of Florence. Int J Biol Markers, 2012 Oct 8; 27(3):e195-202.
36. http://www.osservatorionazionalescreening.it/

Working group member biographies



Tiziana Rubeca, born in Florence on 14 April 1956.

In 1980, she graduated from the University of Florence with a degree in biology and has been the Director of Biology at the Regional Cancer Prevention Laboratory, Cancer Research and Prevention Institute (ISPO) in Florence since 1991 – where she manages biochemical investigations. She also oversees quantitative faecal haemoglobin testing: FIT-Hb (Level 1) for colorectal screening at the Local Health Authority in Florence (former ASL 10).
In 1995, started working on the use of faecal occult blood testing as a level 1 test in population-based screening, originally focussing on the guaiac test, then moving on to immunological methods. As part of her work, she has built upon the experience she has gained by becoming involved in training and consultancy at Italian organisations that intend to set up a colorectal cancer prevention programme. Furthermore, as one of the founding members of the Italian Colorectal Screening Group (GISCoR), she has held various positions, including vice-chair, Level 1 coordinator, and treasurer.
Since 2006, as part of the working group, she has worked to raise awareness of EQA programme providers in the launch of FIT-Hb specific programmes; as a result, all the Italian screening laboratories are involved in EQA programmes.
Throughout her career, she has published numerous studies on the clinical performance and technical analytical characteristics of tests in screening programmes – contributing to the definition of performance indicators to monitor the quality of provided services.
Since October 2012, she has been an active member of the Tumour Markers Research Group at the Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC) and in 2014, she was a member of the Tuscany region working group for responsible for drafting Cancer Prevention Guidelines: Organisational and Diagnostic Pathways (Linee guida di prevenzione oncologica. Percorsi organizzativi e diagnostici). Starting that same year, she has been a member of the SIBIoC-GISCoR inter-facility working group on the Standardisation of faecal material sampling devices (Standardizzazione dei dispositivi di prelievo del materiale fecale).
Ms Rubeca has no institutional or financial ties that could have had an influence on the preparation of the *Guidance for faecal occult blood testing: quantitative immunochemical method (FIT-Hb) in colorectal cancer screening programmes*.

Stefano Rapi, born in Florence, 5 November 1956.

Mr. Rapi, has a degree in chemistry from the University of Florence with a postgradu-

ate specialisation in clinical biochemistry and completion of a postgraduate specialisation course in preparation and use of radiopharmaceuticals from the University of Bologna.
Since 1991, he has been the Level I Chemical Director at the General Laboratory, Careggi University Hospital, Florence. During his career, he has focussed on the evaluation of measuring equipment and analytical methods. He has also worked on national and international research projects as manager of analytical instruments.
In 2006, he started documenting various methods of quantitative faecal haemoglobin testing, working in collaboration with ISPO Florence to evaluate the analytical and epidemiological performance of a FIT-Hb test being introduced in Italy. Following this initial involvement, he continued to focus on the analytical anomalies resulting from investigations of faecal material, while working on various studies of FIT-Hb performance.
From 2008-2009, he was a member of the GISCoR working group responsible for drafting the Recommendations for faecal occult blood (FOB) testing in screening programmes (Raccomandazioni per la determinazione del sangue occulto fecale (SOF) nei programmi di screening).
In 2014, as part of the work on the harmonisation of the pre-analytical phase at Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBIoC), he was awarded a grant for a study aimed at reducing pre-analytical errors in faecal testing (Standardisation of faecal material sampling devices / Standardizzazione dei dispositivi di prelievo del materiale fecale). The study was co-financed by GISCoR in 2015. During this period, he was a member of the Tuscany Region working group responsible for the drafting of Cancer Prevention Guidelines: Organisational and Diagnostic Pathways (Linee guida di prevenzione oncologica. percorsi organizzativi e diagnostici).
He has given numerous presentations on FIT-Hb testing and the pre-analytical aspects of the tests during training courses, as well as national and international scientific conferences. Furthermore, on behalf of his organisation, he has participated in the drafting and evaluation of tender specifications for the Tuscany Region for the purchase of FIT-Hb instrumentation. Since October 2012, he has been an active member of the Tumour Markers Research Group at SIBioC, and has worked on the Clinical handbook for circulating markers (Guida all'uso clinico dei marcatori circolanti).
Mr Rapi has no institutional or financial ties that could have had an influence on the preparation of the *Guidance for faecal occult blood testing: quantitative immunochemical method (FIT-Hb) in colorectal cancer screening programmes*.

Silvia Deandrea, born in Pavia, 13 April 1978.

Ms Deandrea, has a degree in medicine and surgery with a postgraduate specialisation in hygiene and preventive medicine from the University of Pavia as well as a PhD in biomedical statistics from the University of Milan.
Ms Deandrea started working on quality-related issues as a junior consultant at the Joint Commission International (JCI). As a medical officer working for the Milan Local Health Authority (ASL Milano), she was responsible for epidemiological monitoring and quality management of breast and colorectal cancer screening programmes. In particular, while working in the field of colorectal screening, she lead a working group conducting a Failure Mode Effect Analysis (FMEA) on the test-tube pathway from pharmacy delivery to the

laboratory processing, and worked on FIT-Hb performance analyses using the colloidal gold method.
Since 2012, she has worked at the European Commission, Joint Research Centre (JRC) on the European Commission's Initiative on Breast Cancer – focussing on the development of a European diagnostic and treatment scheme for breast cancer services. While at the JRC, Ms Deandrea participates in the GISCoR Laboratory Working Group and is planning a meta-analysis comparing the performance of various types of FIT-Hb in population-based programmes.
Ms Deandrea has no institutional or financial ties that could have had an influence on the preparation of the *Guidance for faecal occult blood testing: quantitative immunochemical method (FIT-Hb) in colorectal cancer screening programmes*.

Basilio "Ubaldo" Passamonti, born in Rieti, 11 June 1953.

In 1977, Mr Passamonti received a degree in biological sciences from the University of Perugia and went on complete a postgraduate specialisation in biochemistry and microbiology from the University of Camerino in 1985.
Since 1979, he has worked as healthcare officer for Umbria Local Health Authority (USL Umbria 1) and in 2005, he has acted as Corporate Responsible for colon cancer screening and Director of the Laboratory Diagnostics Unit and Regional Screening Laboratory. As part of the regional screening, he is a member of the Regional Panel for Comprehensive Screening (Tavolo Regionale di Coordinamento degli Screening), and carries out research on the design and organisation of HTA studies (Passamonti et al. A comparative effectiveness trial of two faecal immunochemical tests for haemoglobin (FIT). Assessment of test performance and adherence in a single round of a population-based screening programme for colorectal cancer. Gut, in press (2016).
Since 2005, Mr Passamonti has provided training courses for general practitioners, district technicians and USL Umbria 1 and Umbria 2 laboratories. That same year, he became a member of GISCoR – where he has participated in the laboratory group and multicentre studies, and has contributed to the drafting of the Handbook of Indicators (Manuale degli indicatori) for colorectal cancer screening, published in Epidemiologia & Prevenzione, 2007 (Epidemiology & Prevention, 2007).
Since 2013, Mr Passamonti has participated in the Multicentre FL-DNA Study organised by the Romagna Scientific Institute for the Research and Treatment of Cancer (Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori), aimed at evaluating amplification of the DNA derived from exfoliated tumour cells in positive faecal occult blood samples. In addition, he collaborates with the Umbria Cancer Register (Registro Tumori Umbro) on the evaluation of colorectal screening results, and participates in national research to improve laboratory practices (e.g. impact study, HTA studies in colorectal screening). He is a member of the Regional Group on Participatory Design (Gruppo Regionale Progettazione partecipata) that reviews diagnostic and therapeutic colorectal cancer screening pathways, together with various professionals at different screening levels.
Mr Passamonti has no institutional or financial ties that could have had an influence on the preparation of the *Guidance for faecal occult blood testing: quantitative immunochemical method (FIT-Hb) in colorectal cancer screening programmes*.

Enrico Marchetti, born in Terni, 6 November 1947.

Mr Marchetti graduated from the University of Perugia with a degree in biology in 1977. Since 2000, he has been Director of Biology (Managing Biologist) at the Clinical Medicine 2 Laboratory, AOU Perugia Hospital (Azienda Ospedaliera di Perugia). From 2002, he has been Managing Biologist for the Cytology Centre Laboratory in Terni 4 Local Health Authority (Terni formerly ASL 4 di Terni) (under the Cancer Research and Prevention Service / Servizio per lo Studio e la Prevenzione Oncologica).
Since 2009, Mr Marchetti has been head of the biochemical investigations sector at his facility and head of Level 1 testing (quantitative faecal haemoglobin testing (FIT-Hb)) in colorectal cancer screening at ASL 4 di Terni. During his career, he has published on the topic of colorectal cancer screening. Previously, he was a member of the GISCoR Working Group for responsible for drafting the Interval Cancers Detection Handbook (Manuale sulla rilevazione dei cancri di intervallo) (2013).
Mr Marchetti has no institutional or financial ties that could have had an influence on the preparation of the *Guidance for faecal occult blood testing: quantitative immunochemical method (FIT-Hb) in colorectal cancer screening programmes*.

Morena Malaspina, born in Terni, 23 May 1961.

Ms Malaspina earned her degree in biological sciences from the University of Perugia in 1990 and her postgraduate specialisation in biochemistry and chemistry from the University of Camerino in 1998. Since 2007, she has been employed by the Umbria 1 Local Health Authority (AUSL Umbria 1) as Consulting Medical Director of the Regional Laboratory for Colorectal Cancer. She is responsible for management and development of the colorectal screening laboratory, and as part of regional screening, she manages the laboratory routine in terms of organisation of work and evaluation of results, internal and external quality controls, and carries out research on the design and organisation of HTA studies (Passamonti et al. A comparative effectiveness trial of two faecal immunochemical tests for haemoglobin (FIT). Assessment of test performance and adherence in a single round of a population-based screening programme for colorectal cancer. Gut, in press (2016).
In 2005, she ran training courses for all laboratory technicians at USL Umbria 1, entitled Colorectal cancer screening: Organisation, Laboratory and Results (Screening carcinoma del colon retto: Organizzazione, Laboratorio e Risultati).
From 2006 to 2012, Ms Malaspina became a member of GISCoR – where she has participated in the laboratory group and multicentre studies, and contributed to the drafting of the Handbook of Indicators (Manuale degli indicatori) for colorectal cancer screening, published in Epidemiologia & Preven-

zione, 2007 (Epidemiology & Prevention, 2007). Since 2013, she has participated in the Multicentre FL-DNA Study organised by the Romagna Scientific Institute for the Research and Treatment of Cancer (Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori), aimed at evaluating amplification of the DNA derived from exfoliated tumour cells in positive faecal occult blood samples. She collaborates with the Umbria Cancer Register (Registro Tumori Umbro) on the evaluation of colorectal screening results, and participates in national research to improve laboratory practices (e.g. impact study, HTA studies in colorectal screening). Ms Malaspina is a member of the Regional Group on Participatory Design (Gruppo Regionale Progettazione partecipata) that reviews diagnostic and therapeutic colorectal cancer screening pathways, together with various professionals at different screening levels.
Ms Malaspina has no institutional or financial ties that could have had an influence on the preparation of the *Guidance for faecal occult blood testing: quantitative immunochemical method (FIT-Hb) in colorectal cancer screening programmes*.

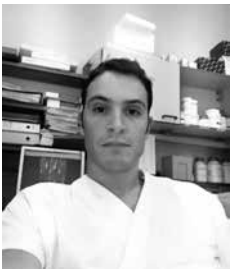
Elena Grassi, born in Brescia, 28 June 1960.

Ms Grassi received her degree in medicine and surgery from the University of Brescia in 1986 with a postgraduate specialisation in clinical biochemistry in 1990 and has been a full-time medical director at the Public Health Laboratory, ATS di Brescia (Brescia Health Protection Agency) (formerly ASL Brescia [Brescia Local Health Authority]) since 1993.
Since 2005, she has focussed on Level 1 testing (faecal occult blood testing) as part of the colorectal cancer screening programme in the Province of Brescia. Ms Grassi has presented at SIBIoC and GISCoR national congresses, is a published author and invited speaker/moderator at various conferences, and since 2015, she has been an active member of the GISCoR Laboratory Working Group.
Ms Grassi has no institutional or financial ties that could have had an influence on the preparation of the *Guidance for faecal occult blood testing: quantitative immunochemical method (FIT-Hb) in colorectal cancer screening programmes*.

Anna Maria Cioccarelli, born in Sondrio, 12 July 1959.

Ms Cioccarelli received her degree in medicine and surgery from the University of Milan in 1986. Her postgraduate specialisation is in pathology laboratory diagnostics from the University of Pavia. Since 1989, she was appointed permanent Medical Director by the Health Protection Agency in Sondrio (ATS della Montagna, Sondrio), and is head of the ATS della Montagna Prevention Laboratory. In 2005, she started work on the use of faecal occult blood testing as a first level test in screening for colorectal cancer.
Since 2005, she has participated in meetings and working groups at the Lombardy Region Directorate General of Health (Regione Lombardia Direzione Generale Sanità) draft-

ing protocols and guidelines on the management of colorectal cancer screening.
Ms Cioccarelli has no institutional or financial ties that could have had an influence on the preparation of the *Guidance for faecal occult blood testing: quantitative immunochemical method (FIT-Hb) in colorectal cancer screening programmes*.



Filippo Cellai, born in Livorno, 14 June 1985.

Mr Cellai received his degree in biological sciences with a postgraduate specialisation in clinical pathology from the University of Pisa.
Mr Cellai works as an associate biologist at Cancer Research and Prevention Institute - ISPO. Since graduating, he has gained experience in applied research in cancer screening, and participates in various projects on colorectal screening and faecal occult blood testing at the Regional Cancer Prevention Laboratory (Laboratorio Regionale di Prevenzione Oncologica). In particular, he has worked on studies assessing the analytical evaluation of new analytical systems for faecal occult blood testing using the immunochemical method, comparison of analytical methods, standardisation of faecal matrix sampling devices, and harmonisation of the pre-analytical phase of the FIT-Hb tests.
Mr Cellai has contributed to the drafting of scientific material, reports, and presentations given at national and international conferences. Since 2013, he has been a member of SIBioC – Laboratory Medicine in collaboration with GISCoR on the Standardisation of faecal material sampling devices (Standardizzazione dei dispositivi di prelievo di materiale fecale). In addition, he is currently working as an associate at the Oncogenic Risk Factors (Fattori di Rischio Oncogeno) Laboratory at ISPO, where he is involve in the study of genomic biomarkers damage and oncogenic risk factors.
Mr Cellai has no institutional or financial ties that could have had an influence on the preparation of the *Guidance for faecal occult blood testing: quantitative immunochemical method (FIT-Hb) in colorectal cancer screening programmes.*

Michela Boni, born in Ferrara on 11 May 1975.

Ms Boni received her degree in biological sciences in 2000 with a postgraduate specialisation in clinical pathology, at the University of Ferrara.
Since 2006, Ms Boni has held various positions and received numerous scholarships at the Central Provincial Analysis Laboratory (LUP), Ferrara (Analysis Laboratory, Delta Hospital (Ospedale del Delta), Lagosanto, and Chemical-Clinical Analysis Laboratory, Arcispedale Sant'Anna, Cona). She has been appointed as permanent Biology Director at LUP, Ferrara (Cona site). In September 2016, she was assigned to the Department of Specialisation and Computerisation. In recent years, she has mainly been involved with autoimmunity, allergology and molecular biology and has participated in an inter-facility project between the Ferrara Local

Health Authority (AUSL Ferrara) and Ferrara University Hospital (AOU Ferrara) to develop a decision support system aimed at the correct repetition of laboratory tests.
Since 2009, Ms Boni has also had an interest in laboratory work related to the Level I test (FIT-Hb) as part of colorectal cancer prevention screening, for which she serves as the laboratory contact, supervises the analytical pathway and monitors quality indicators and non-compliance. Since 2010, as a member of the Working Group for the Laboratory Department of the Emilia-Romagna Region for the colorectal screening programme, she has participated in occasional accredited professional training and discussion meetings.
As a member of the Regional Working Group, she has also participated in the revision of the chapter on level I of the Diagnostics and therapeutic screening protocol for the early diagnosis of colorectal cancer in the Emilia-Romagna Region (Protocollo Diagnostico-Terapeutico dello Screening per la diagnosi precoce del tumore del colon-retto nella Regione Emilia-Romagna) (2nd edition, 2012).
Ms Boni has co-authored presentations at national conferences, and spoken at regional meetings where she shared her experience in cooperation and comparison between laboratory networks in the Emilia-Romagna region involved in colorectal cancer screening, in order to achieve a set of common quality standards. She has also spoken at internal training courses on Level I screening activity at her agency, and is an active member of the GISCoR Laboratory Working Group.
Ms Boni has no institutional or financial ties that could have had an influence on the preparation of the *Guidance for faecal occult blood testing: quantitative immunochemical method (FIT-Hb) in colorectal cancer screening programmes*.

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