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The Italian National External Quality Assessment Program in Cytogenetics: 4 years of activity (2013-2016) following the introduction of poor performance criteria

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Abstract

Background. Italian External Quality Assessment (IEQA) Program in Cytogenetics, established in 2001 by the Istituto Superiore di Sanità (ISS), covers both Constitutional and Oncohaematological diagnosis. In 2013, performance criteria were defined and adopted. In this paper, we present the data from the first 4 years of activity (2013-2016) following the introduction of performance criteria.

Methods. The enrollment is voluntary, fee-based and open to both public and private Italian laboratories. The scheme is annual and retrospective; a national panel of experts assess technical, analytical and interpretative performance.

Results. Overall, 95 distinct Italian laboratories participated in different Cytogenetics IEQA schemes over the 2013-2016 years and most of the laboratories took part in Constitutional diagnosis. General hospitals and local health centers represented 40% of the total participants and the percentage of laboratories from Northern Regions was more than 45% of total participants throughout the 4-year period. As regards the performance evaluation, on average, 11, 9 and 23% of participants were marked as poor performers in Prenatal, Postnatal and Oncohaematological schemes, respectively. With regard to criti-

Key words

- external quality assessment
- conventional cytogenetics
- quality assurance in genetic testing
- quality standards promotion

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cal errors, ISCN nomenclature in Prenatal and Postnatal schemes, and interpretation in Oncohaematological diagnosis, were identified as main issues. On the other hand, karyotype errors and inadequate analysis decreased strongly, over the 4 years, in Constitutional and Oncohaematological diagnosis, respectively.
Conclusions. Our data show that the introduction of poor performance encourages laboratories to address critical issues, and the IEQA participation helps to improve quality in cytogenetic testing.

INTRODUCTION

Genetic testing is a complex and structured process, which requires accurate and reliable procedures as well as comprehensive and exhaustive reporting of results. Elevated quality standards are fundamental since a genetic test is usually performed once in the individual's lifetime and results can often imply important choices, not only for patients, but also for their relatives. The effects of diagnostic errors may lead to far-reaching dangerous consequences, such as therapy or reproductive inappropriate decisions. Indeed, as explained in Organisation for Economic Cooperation and Development (OECD) Guidelines, all molecular genetic testing services should be provided and practiced under a quality assurance framework and the performance of laboratories offering clinical molecular genetic tests should be measured [1]. In terms of continual improvement in quality assurance and according to ISO15189, the establishment of a quality assurance framework requires the development of a quality management system that covers both management and technical aspects, such as personnel and training, document control, standard operating procedures, validation and assuring quality of examination by internal quality control and External Quality Assessment (EQA) [2, 3]. The participation in EQA programs, which are interlaboratory comparisons by means of an external and independent body, aims to verify and improve the overall quality of the diagnostic service of a genetic laboratory. EQA acts as an essential monitoring tool to evaluate the level of the accuracy of the result given to the patient and the compliance to best practice guidelines and international standards [4]. Moreover, EQA has primarily an educational role and provides a training opportunity for laboratories by comparing their own skills against a "gold standard" and through a peer assessment.

In the European scenario, the main EQA programs designed to improve the quality of molecular or cytogenetic reports are offered by three providers, the Cytogenomic External Quality Assessment Service (CEQAS), the European Molecular Quality Network (EMQN) and the Cystic Fibrosis European Network (CF Network) [5-7].

In 2001, the Italian National Centre for Rare Diseases (CNMR) of the Istituto Superiore di Sanità (ISS), in collaboration with the Italian Society of Human Genetics (SIGU), launched the first trial of EQA for genetic testing on a national scale [8]. After the successful pilot experience, the Italian EQA (IEQA) program was established and supported through specific research projects. In 2004, the governmental document "Linee guida per le attività di genetica medica" indicated the ISS as coordinator of the national EQA [9]. In 2009, the IEQA was recognized as institutional activity and was updated in 2015 by the new Official Bulletin of the Italian Republic [10, 11]. The enrollment is voluntary, fee-based and open to all Italian laboratories, both public and private, placed on the national territory.

Currently, IEQA offers nine different schemes in three distinct macro-areas: Molecular Genetics (Cystic Fibrosis, Beta Thalassemia and Fragile X Syndrome), Oncological Genetics (Adenomatous Polyposis Coli, Hereditary Breast and Ovarian Cancer and Lynch Syndrome) and Conventional Cytogenetics (Constitutional Cytogenetics – prenatal and postnatal diagnosis – and Oncohaemotological Cytogenetics).

Cytogenetic analysis is a relevant genetic testing category: chromosomal abnormalities can lead to several constitutional genetic disorders and represent a characteristic feature of different neoplasms. The IEQA program in conventional Cytogenetics is retrospective and covers both Constitutional and Oncohaematological diagnosis [12]. Assessment in Cytogenetics IEQA program takes into account technical, analytical and interpretative performance as well as reporting accuracy. On the basis of the experience gathered during the first ten years of IEQA activity, a detailed marking system was developed and in 2013 poor performance criteria were established and adopted. In agreement with the European EQA programs, the poor performance criteria were introduced to allow objective comparisons between laboratories and to better identify any critical deficiencies based on European and/or National Cytogenetics Guidelines.

The purpose of this paper is to illustrate the characteristics of genetic laboratories participating in Cytogenetics IEQA program and to present the data from the first 4 years of activity (2013-2016) following the introduction of poor performance criteria.

MATERIALS AND METHODS

Organization of the IEQA

The structural framework of IEQA has been previously described [12, 13]. IEQA is organized and coordinated by the CNMR-ISS, and it is carried out in collaboration with SIGU. The IEQA Organizer and national experts provide advice on the scientific context of the schemes and take decisions about assessment criteria and the development of the Program. The enrollment is voluntary, fee-based and open to both public and private Italian laboratories. Schemes are strictly coded, i.e. a unique Identification Number is assigned to each laboratory by the scheme organizer (ISS) – the only one knowing the identity of the participant – and laborato-

ries are requested to submit anonymous reports, i.e. remove any structure, staff and patient identifying details before the submission.

The program is annual and the format is retrospective: laboratories are asked to submit, in their own reserved area on the web utility, images (3 metaphases and 2 karyotypes) and their final reports. Following specific instructions, laboratories are required to submit: one random case and one case with structural rearrangements in Constitutional Cytogenetics, whereas two cases with an abnormal karyotype are requested in Oncohaematological diagnosis. In the early stages of IEQA, laboratories were asked to send images from only one clinical case [12]. Subsequently, it has been considerate appropriate assess two clinical cases, in order to have a comprehensive evaluation of laboratory's skills. All the data uploaded on the web utility by laboratories are evaluated by the assessors according to defined and declared to participants performance criteria. An annual workshop is organized, where laboratories, assessors and the Scheme Organizer meet in order to discuss the results and critical issues from the EQA.

Web utility

In 2008 a dedicated web utility was developed by CNMR-ISS, in order to simplify communications and facilitate data sharing among ISS, laboratories and assessors [13]. In 2015, the web utility was updated, and an assessment interface among assessors/ISS/laboratories was implemented, in order to optimize both the assessment and the final draft of assessment reports sent to laboratories. Participant laboratories receive an identification code and a password to access to their own reserved working area. Laboratories have a one month-period to complete the uploading process. Once all data have been assessed and reviewed, laboratories can download, in their own reserved area, a report with scores and comments about the analysis.

Assessment

National experts, selected from National Societies (SIGU and Italian Society of Hematology-SIE) evaluate the data of the enrolled laboratories. Assessment criteria are established by the CNMR-ISS and the panel of national experts according to current National or International Guidelines [14, 15]. Assessment takes into account technical, analytical and interpretative performance. Following assessment, participating laboratories receive a report containing: the list of parameters and information assessed in reports and images, and the performance category assigned including the score achieved and also comments or suggestions. Since 2013, only two categories of performance in any single IEQA were set out: satisfactory and poor. A general letter and a personal report are sent to each laboratory. The general letter includes the overall performance of all participants, as well as the most frequently critical errors and main issues of the EQA round.

Those participants that perform poorly in Cytogenetics IEQA in the current round, and at least once in the two previous rounds, are classified as persistent poor performers. Following the identification of a persistent poor performance, the IEQA coordinator formally notifies the laboratory's Chief advising of the recurrence of poor performance and providing evidence of critical errors made. In addition, reference guidelines and any suggestions for diagnostic genetic testing are supplied, in order to improve the quality of cases submitted by laboratory.

Performance criteria

Performance criteria were established by the CNMR-ISS and by assessors, on the basis of the SIGU Guidelines for Cytogenetics Diagnosis and European Cytogeneticists Association (ECA) Guidelines for Acquired Cytogenetics [14, 15]. All images and reports are evaluated independently by 2 groups of assessors, one for Constitutional diagnosis and the other one for the Oncohaematological scheme. In Constitutional diagnosis, the assessment group consists of 5 national experts, whereas 3 assessors are required in Oncohaematological diagnosis. In each cytogenetics scheme, the assessors evaluate laboratories twice: first on-line, independently of each other, and then through a collective face-to-face discussion about laboratories performance. If there are discrepancies, data are assessed collectively one more time and final scores are reached by simultaneous voting. The assessment covers the following parameters: banding quality of images, karyotype/Analysis, completeness and adequacy of the analysis, correct use of the International System for Human Cytogenetic Nomenclature (ISCN), written description of the result, interpretation, report content and reporting times. The scores of the marking system are reported in *Table 1*. Poor performance penalty is assigned for the following critical errors, common to both Constitutional and Oncohaematological schemes: inadequate banding quality, incorrect analysis, more than two karyotype errors, incorrect or absent written description of the result, incorrect or absent interpretation, report containing inconsistent statements and/or missing important information. Moreover, only for the Oncohaematological scheme, poor performance is assigned for the failure to achieve a threshold score, defined as total sum of the score referred to technical, analytical and interpretative performances. The presence of one critical error, in at least one case, leads the laboratory to a poor performance.

RESULTS

Laboratories participating in cytogenetics IEQA

Overall, 4 rounds have been completed after the introduction of poor performance criteria (from 2013 to 2016); 95 distinct Italian laboratories participated in different Cytogenetics IEQA schemes and 54 constantly throughout the entire period (over the 2013-2016 years). The total number of participants is 62% of the Cytogenetics laboratories, as reported in the 2012 SIGU census [16].

From the beginning of IEQA until 2009, the program was addressed only to public laboratories and, in the 2013-2016 years, the general hospitals and the local health centers represented the majority of Italian participants *(Figure 1)*. Comparing the affiliation of laboratories participating in IEQA over the 2013-2016

Table 1
General assessment criteria and marking scores for constitutional and acquired cytogenetics in Italian External Quality Assessment

EQA Cytogenetics- Assessment criteria	Constitutional cytogenetics	Oncohaematological cytogenetics
	Max score	
Banding quality of images	3	Only comment
Karyotype/analysis	4	4 or 3*
Completeness/adequacy of the analysis	2	2
Written description of the result (ISCN nomenclature and description)	2	2
Interpretation	3	3
Report content	1	1
Reporting times	0.5	0.5

*Max score of 4 for 2013 and 2014; max score of 3 for 2015 and 2016 rounds.

period, no substantial differences have been observed through the years: in addition to the public participants, a relevant part (with a minimum of 28% to a maximum of 32%) consists of commercial laboratories, followed by Research Hospitals (Istituti di Ricovero e Cura a Carattere Scientifico, IRCCS) and Universities in similar percentages *(Figure 1)*.

With regard to geographical distribution of participants, a significant decreasing North-to-South gradient is evident *(Table 2)*, according to similar distribution of the genetic services across the country [16, 17]. The percentage of laboratories localized in the Northern Regions was more than 45% of total participants throughout the 4-year period, with the highest number of laboratories placed in Lombardia Region. As regards the two main Islands (Sardinia and Sicily), almost all participants came from Sicily. Four out of 20 Italian regions never took part in Cytogenetics IEQA programs (namely Valle d'Aosta, Abruzzo, Basilicata and Molise). The Umbria region participated for the first time in 2016.

As regards the schemes distribution, most of the laboratories participated in Constitutional diagnosis. Precisely, 68, 67, 64 and 59% participated to both Prenatal and Postnatal diagnosis EQA in 2013, 2014, 2015 and 2016, respectively *(Table 2)*. In addition, the Postnatal diagnosis was the Cytogenetics scheme with the largest number of participants. The majority of laboratories had taken part in more than one scheme, and 17, 21, 15 and 15% participated in all schemes offered, in 2013, 2014, 2015 and 2016, respectively.

PERFORMANCE OF THE PARTICIPANTS IN CYTOGENETICS IEQA: SATISFACTORY, POOR AND PERSISTENT POOR PERFORMERS

Satisfactory and poor performers

In the early stages of IEQA, the assessment included comments about laboratories performance and suggestions on how to improve the analysis; no marking system was in place [12]. In 2013, only two categories of performance in any single scheme were set out: satisfac-

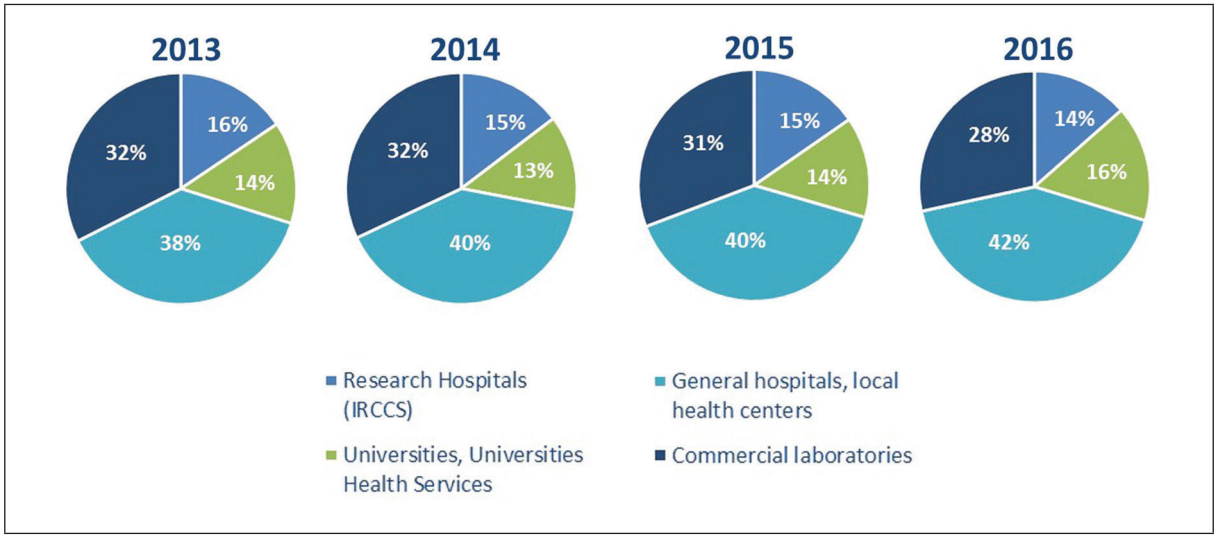

Figure 1
Distribution by affiliation of the Italian structures where genetic participating laboratories are hosted. Years of participation: 2013-2016.

Table 2
Geographical distribution and schemes distribution of Italian medical genetics laboratories participating in IEQA Cytogenetics Program

	2013	2014	2015	2016	
North	35	34	36	34	Geographical distribution
Centre	16	17	16	17	
South	14	11	13	12	
Islands	11	12	13	11	
Total	76	74	78	74	
Pre/Post/Onco	13	16	12	11	Schemes distribution
Pre/Post	39	34	38	33	
Post/Onco	6	4	7	7	
Pre	1	2	1	1	
Post	10	10	13	14	
Onco	7	8	7	8	
Total	76	74	78	74	

Pre = Prenatal scheme; Post = Postnatal scheme; Onco = Oncohaematological scheme.

tory and poor. Satisfactory performance was defined as the quality standard to be achieved by all laboratories performing diagnostic genetic testing. Satisfactory performing laboratories were evaluated through a scoring system based on a specific set of assessment criteria. As shown in *Table 1*, the highest score points are related to analytical and interpretative skills of participants. Accordingly, the poor performance is given both in Constitutional and Oncohaematological Cytogenetics when critical errors in either analytical or interpretation category are identified or the report contains inconsistent statements. Following the introduction of performance criteria, 9 participants in 2013 withdrew from the EQA program, while 4 out of 8 laboratories, joining for the first time the IEQAs in 2013, participated constantly since then.

In Constitutional Cytogenetics, from 2013 to 2016, the participants into the Prenatal scheme were 53, 52, 51 and 45, whereas 68, 64, 70 and 65 laboratories had taken part in the Postnatal diagnosis. The number of participants in Oncohaematological scheme was 26, 28, 26 and 26 in 2013, 2014, 2015 and 2016, respectively *(Figure 2A)*.

As regards the performance evaluation, *Figure 2B* shows the number of poor *versus* satisfactory performers participating in IEQA different rounds and *Table 3* summarizes the most frequently critical errors leading to poor performance, in all reports submitted. With regard to Constitutional Cytogenetics, no significant variation in number of poor performers was observed: on average, 11 and 9% of prenatal and postnatal laboratories, respectively. Concerning the critical errors, the number of karyotype errors decreased drastically over the 2013-2016 period: in 2016, no karyotype errors were identified in both Prenatal and Postnatal diagnosis. By contrast, the percentage of reports including misleading or absent ISCN nomenclature increased to 5.5 and 3% in Prenatal and Postnatal schemes, respectively. Throughout the 4-year period, the incorrect use of ISCN nomenclature was the most recurrent critical error, indicating that there is a pressing need for a more effective training on this issue.

As regards the Oncohaematological diagnosis, a consistent number of failing performers was identified: on average, 23% of participants over the 2013-2016 years. In particular, between 2013 and 2015 years, the Oncohaematological diagnosis was the scheme with the highest percentage of poor perfomers. Notably, the percentage of Oncohaematological poor performers increased, from 19% (2013) to 38% (2015). This figure fits with a major change in the interpretation assessment criteria after the publication of the ECA Guidelines [15]. In 2015, as shown in *Table 3*, 27% of all reports were insufficient because of an incorrect or absent interpretation. Noteworthy, in 2016 the percentage of critical error referred to the interpretation decreased to 4%, contributing primarily to the strong reduction of poor performers to 11%. Inadequate or unassessable analysis, because reports are missing needed information to assess the complete analytical process, was found, on average, in about 5% of all Oncohaematological cases submitted in 2013 and 2014.

Persistent poor performers

In 2015, in order to easily detect any poor performance trends, and to better find out specific training needs, the persistent poor performance condition was defined. As already mentioned, those participants that perform poorly in Cytogenetics IEQA in the current round, and at least once in the two previous rounds, are classified as persistent poor performers. The identification of persistent poor performance does not represent another performance category by itself, but rather acts as an additional educational tool to draw attention to recurrent critical deficiencies in poor performers. To date, the Oncohaematological diagnosis was the scheme with the highest number of persistent failing participants, with 3 and 2 persistent poor performers in 2015 and 2016, respectively. In Constitutional Cytogenetics, a total number of 2 and 1 persistent poor performers were identified in 2015 and 2016, respectively. Almost all the persistent poor performers failed for the same deficiencies which caused the previous poor performance, and in particular for cytogenetic incorrect analysis, more than two karyotype errors, and incorrect or absent interpretation. Interestingly, 2 out of 3 Oncohaematological persistent poor performers in 2015, achieved sufficient performance in 2016; furthermore, one failing performer in Postnatal diagnosis for three consecutive years (2013-2015), received satisfactory performance in 2016.

DISCUSSION

Cytogenetics is a field of genetics that concerns the investigation of structural and numeric chromosomal abnormalities, which can cause several genetic disorders related to growth or development defects, such as intellectual disability, developmental delay, dysmorphisms. Chromosomal alterations can also be associated to reproductive problems leading to infertility or

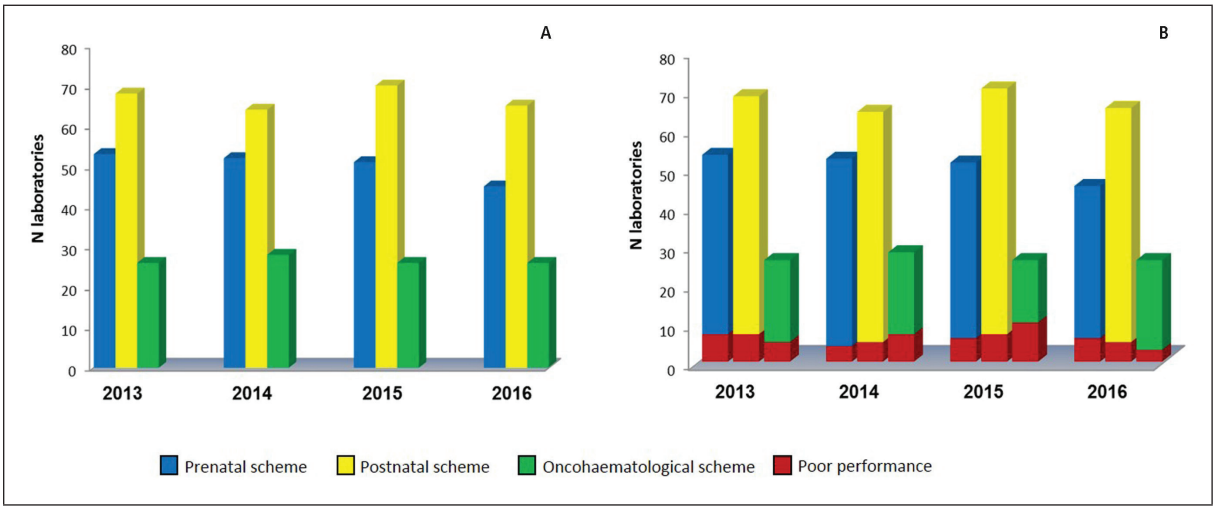

Figure 2
Participation of Italian laboratories in Cytogenetics. Program from 2013 to 2016. Total number of laboratories (A) and poor *versus* satisfactory performers (B) participating to Prenatal, Postnatal and Oncohaematological schemes, respectively.

recurrent miscarriages. It is well known that cytogenetic analyses are performed also during pregnancy (i.e. chorionic villus sampling and amniocentesis) since chromosomal aberrations are common causes of prenatal death or congenital diseases (e.g. Down syndrome). Moreover, cytogenetics in oncohaematologic disorders is a crucial tool for diagnosis, prognosis, and clinical decision-making.

Genetic laboratories can verify the reliability of data analysis and the accuracy of reporting through the participation in national or international EQA programs. In Europe, the first scheme for EQA in Cytogenetics was established in the UK in the early 1980s [12]. In 2014 was established the CEQAS, the European provider which offers schemes in constitutional diagnosis, preimplantation genetic diagnosis, haematological and oncological cytogenetics [5].

The Cytogenetics IEQA program, started by CNMR-ISS in 2001, uses a retrospective format, which implies a general difficulty in inter-laboratory comparisons due to different complexity of cases submitted, whereas has the advantage of enabling the examination of the real practices of the laboratories [18]. In particular, the retrospective format encourages the participation of laboratories which detect chromosomal anomalies in routine clinical practice and the assessment is based on the genetic report effectively given to the patient.

The enrollment is on voluntary basis, although par-

Table 3
Poor performers and critical errors of laboratories in Prenatal, Postnatal and Oncohaematological IEQA schemes in 2013-2016. Data are given as percentage. Poor performers and critical errors percentages are referred to laboratories and all cases submitted, respectively

	2013			2014			2015			2016		
	Pre	Post	Onco	Pre	Post	Onco	Pre	Post	Onco	Pre	Post	Onco
Poor performers												
	13	10	19	8	8	25	12	10	38	13	8	11
Critical errors												
Karyotype errors	5.7	1.5	0	1	0	0	2	0.7	2	0	0	0
Incorrect analysis	2	0	0	0	1.6	3.5	0	0	2	0	0.8	0
Misleading or absent ISCN nomenclature	1	1.5	0	3	2	0	3	3.5	0	5.5	3	2
Inadequate banding quality	0	1.5	0	2	0	0	0	0	0	0	0	0
Incorrect or absent written description of the result	0	1.5	4	0	0.8	3.5	2	1.4	0	2	0	0
Inadequate or unassessable analysis	0	0	6	0	0	3.5	0	0	0	0	0	0
Incorrect or absent interpretation*	0	0	0	1	0	9	0	0	27	0	0	4
The report contains inconsistent statements	0	0	0	0	0	0	1	0.7	0	1	0	4

Pre = Prenatal scheme; Post = Postnatal scheme; Onco = Oncohaematological scheme. ISCN = International System for Human Cytogenetic Nomenclature. *In Oncohaematological scheme, absence of interpretation is critical error from 2015 round.

ticipation in EQA schemes is mandatory for accreditation based on ISO15189 standard, which specifies the requirements for quality and competence in medical laboratories and focuses mainly on the patient care and management procedures [2]. Interestingly, collected data show that the largest percentage (about 40%) of participants in Cytogenetics IEQA program, over the 2013-2016 period, is represented by general hospitals or local health centers, and this highlights the constant effort of public health systems in order to promote educational training and continuous professional improvement. Another considerable ratio, about one third of all participants, performed commercial activities, in line with the growing request for genetic tests, which are becoming increasingly inexpensive and widely available tests. Moreover, it is remarkable that the majority of laboratories had taken part in more than one scheme, suggesting that the participants appraise EQA as important tool to evaluate different cytogenetic tests offered by laboratory.

The unequal distribution of participants among the Italian Regions, in particular the decreasing gradient moving from the Northern to the Southern and Islander Regions, is in agreement with the geographic distribution of genetic services across the country and may be explained by the early beginning of genetic activities in the Northern Regions, as reported in SIGU censuses [16, 17]. Regarding the participation rate in Cytogenetics IEQA schemes, most of laboratories had taken part in constitutional diagnosis, although a slight decrease in the number of participants has occurred from 2013 to 2016, in both Prenatal and Postnatal schemes. This reduction could be a consequence of a partial replacement of constitutional cytogenetics by the molecular tests, primarily due to introduction and consolidation of Non-Invasive Prenatal Testing and progressive substitution of FISH analyses by microarrays testing [16]. However, recent findings in Postnatal Cytogenetics scheme of CEQAS provided evidence for the importance of conventional Cytogenetics (karyotyping) in the detection of genomic abnormalities not correctly identifiable by array and DNA-sequencing methods [19].

The setting of the marking system and poor performance category allowed objective comparisons between participants based on assessment criteria defined to achieve high standards of genetic testing in diagnostic laboratories. Since 2013, the identification of poor performance is a key element of the IEQA assessment in order to differentiate between critical and minor errors. Overall technical performance (quality of metaphases, chromosomes and banding) in both constitutional and oncohaematological schemes, was satisfactory. Conversely, critical inaccuracies in the analysis were detected, such as karyotype errors and wrong use of standard cytogenetic nomenclature, (ISCN nomenclature) mainly for constitutional diagnosis. The ISCN is the standard accepted international nomenclature for human chromosomes and was established to answer the need for a common system of standardized terminology for human cytogenetics [20, 21]. Hence, ISCN nomenclature is critical for the interpretation of cytogenetic result, since reports should be clear, accurate and all information should be coherent with standardized and unambiguous rules.

In Oncohaematological scheme, in 2013 and 2014 IEQA rounds, inadequacy of analysis was identified as a recurrent critical error. In this regard, some of poor performers did not include in their reports the limitation of the test used. It should be pointed out that the level of analysis is dependent on the referral reason and, when the analysis is not appropriate, the interpretation of the result could be not correct and mislead the clinician in the diagnosis or prognosis or therapy. According to ECA Guidelines, published at the beginning of 2013, the reports of acquired cytogenetic abnormalities should include some interpretative information, such as the relationship of any abnormalities found to the referral reason, and association with prognosis if a robust association from multiple publications/international trials/trial protocols exists [15]. In 2015, incorrect or absent interpretation was identified in 27% of all reports, contributing for the most part to the highest number of poor performers (38%). Conversely, in 2016, critical interpretative insufficiencies were found only in 4% of all submitted reports, suggesting that Cytogenetics IEQA participation promoted internal review to address this issue according to the European Guidelines.

When a laboratory does not implement positive corrective actions to overcome any critical deficiencies, the risk of becoming a persistent poor performer is high. Persistent poor performance is a serious alarm bell concerning the diagnostic service of a genetic laboratory, indicating that persistent failing laboratories need further training to overcome their recurrent critical issues. Hence, the identification of persistent poor performance aims to strongly suggest a laboratory to undertake a root cause analysis for recurrent failing performance. Even though EQA programs are not responsible for setting the internal quality management system, participation in EQAs can have a significant influence over all aspects of genetic testing, such as the technical quality, the completeness of analysis, all the information needed to be included in the report and also the report structure itself [22]. For this reason, when a laboratory receives a persistent poor performance, the IEQA coordinator will formally advise the laboratory's Chief informing of recurrent critical errors made by laboratory and providing reference guidelines and suggestions on how to deal with specific problems. Unfortunately, following identification of a persistent poor performer, it is difficult to follow and monitor the implementation of corrective measures undertaken by laboratory, since the IEQA is not mandatory but only on voluntary basis. In this regard, a mandatory IEQA could act through a panel to plan and coordinate the best support actions aiming at the improvement of the genetic testing performed by Italian diagnostic laboratories.

Furthermore, as reported by Hastings, *et al.* [4], a minority of poor performers and persistent poor performers, choose to drop out of the EQA program, and do not register for the next round. In this point, it should be considered that the majority of poor performers, which continue to enroll in Cytogenetics IEQA schemes, reach satisfactory results one or maximum two rounds

after the failing performance (to date, on average 86 and 72% of poor performers, for Constitutional and Oncohaematological schemes, respectively).

Overall, our data suggest that IEQA enrollment should be mandatory, and the continuous IEQA participation is important to ensure an adequate quality service with reliable and accurate results of genetic testing and to promote best clinical practices for the patient care. Moreover, since the relevant value of EQAs for continuous improving is recognized at International level, it has clearly emerged the need to harmonise this activity among different Scheme Organisers in Europe. Within this context, the CNMR-ISS is involved in the activities of EuroGentest excellence network, which aims at the standardisation and harmonisation of the quality of genetic testing across Europe. In particular, the Quality Sub-Committee of the European Society of Human Genetics, as part of EuroGentest, has promoted an enlarged concerted effort to improve diagnostic performance of genetic laboratories in Europe. The CNMR has fully supported this initiative and is actively involved contributing with the Italian experience of the IEQA to the desirable establishment of an increasingly coordinated approach to quality of genetic testing.

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Conflict of interest statement

None.

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