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The Italian external quality assessment program for Cystic Fibrosis sweat chloride test: CFTR modulators and the impact of a new sweat test report form

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ABSTRACT

Background: The advent of CFTR modulators highlighted that the sweat test (ST) for CF can be used also as an outcome measure for the basic defect of CFTR. Despite the technological advances, ST still remains operator-dependent and its execution should be strongly paired with guidelines. In 2022, due to the advent of CFTR modulators, the Italian CF Society introduced a specific ST report. The aim of the present paper is to discuss the impact of this new report in the 2022-23 round of the Italian External Quality Assessment program for ST (I-EQA-SCT).

Methods: The scheme of the I-EQA-SCT is prospective, enrolment is voluntary, the payment of a fee is required and results are shared through a web-facility. Assessment covers analysis, interpretation, and reporting of results. In the 2022-23 round, 2 out of the 3 mock clinical information referred to patients who started modulators.

Results: Fourteen laboratories completed the 2022-23 I-EQA-SCT round. Three of them failed in the interpretation of results from these two mock cases and/or used a wrong report not consistent with the more recent Italian Sweat Test Recommendations.

Conclusions: The overall results obtained from the laboratories involved in the I-EQA-SCT program clearly showed that the laboratories' qualitative and quantitative performance improved significantly. Results emerged from this round highlighted an issue in the report form used for monitoring patients on CFTR modulator therapy thus stressing the importance of these programs in improving both the performance of lab services and ameliorating the sweat test recommendations.

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1. Introduction

Cystic fibrosis (CF) is a progressive, inherited, rare disease in which CF transmembrane conductance regulator (CFTR) gene mutations produce abnormal CFTR proteins that negatively affect sodium and chloride transport across cellular epithelial membranes [1].

Abbreviations

ST	sweat test
I-EQA-SCT	Italian External Quality Assessment program for ST
CFTR	CF transmembrane conductance regulator
CF	cystic fibrosis
CFSPID	cystic fibrosis screening positive, inconclusive diagnosis
CRMS	CFTR related metabolic syndrome
GP	general practitioner
ECFS DNWG	European Cystic Fibrosis Society, Diagnostic Network Working Group
HEMT	highly effective modulators therapy
ICFS STWG	Italian Cystic Fibrosis Society, Sweat Test Working Group
ISS	Istituto Superiore di Sanità
ID	identification number
I-EQA-SLS	Italian external quality assessment sweat-like sample

This results in the accumulation of thick, sticky mucus, which causes progressive dysfunction in multiple organ systems.

CF rate incidence in the United States is similar to that in Canada, in UK and in Europe and is about one in every 2000 to 3000 babies at birth. According to published data, many countries demonstrate evidence of decreasing incidence of CF due to the implementation of newborn and carrier screening programs [2,3].

Prevalence varies from country to country, with a presumed underdiagnosis in African and Asian countries.

With advancing medical technology, treatments and care, individuals with CF are living longer: for individuals born between 2018 and 2022, the median predicted survival age is 56.6 years [4]. Patients with CF in developing countries have lower survival rates, with many dying in their teens.

The sweat test (ST) validated in the late '50s remains the gold standard for CF diagnosis even in the genomic era [5]. The approach to this test is essential for a correct CF diagnostic pathway in fact CF diagnosis is still challenging in screening positive newborns with inconclusive ST, labelled as CFSPID/CRMS [6] and in older subjects with a high suspicion of CF without diagnostic criteria for CF fulfilled [7]. Moreover, despite the technological advances, the ST still remains operator-dependent and its execution should be strongly paired with specific and dedicated guidelines [8], most of which have been published at national and international levels since 1998 and are aimed to standardize and improve the performance of laboratory services. In particular, the recognition of the importance of this test in CF, prompted and motivated the Italian CF Society to establish a dedicated working group that published the first Italian ST Recommendations in 2007 that were regularly updated as a consequence of technical innovations, new evidences and recently the advent of CFTR modulators.

Restoration of CFTR function with modulator treatment can be efficiently measured with sweat chloride. In this regard, the information provided in the ST report should appropriately address the clinical question.

Sweat test results are a typical example of a laboratory test composed of two parts: quantitative measure of the analyte (chloride, sodium, NaCl equivalents) and interpretation of results in ordinal scale (pathological, borderline, and normal) [8].

Interpretation should be compliant with specific clinical question and with the most recent and updated CF patient status.

Some proficiency testing and external quality assessment schemes showed that the quality of the interpretation of analytical results were inappropriate or misleading when assessed by peer review. Considering that comments on laboratory reports may affect clinical management of patients, these comments should reflect accepted practice and current guidelines [9]. Moreover, this evidence highlighted the need of a better communication between laboratory specialists and clinicians in order to avoid inappropriate tests that can cause harm to the patient [10].

Commenting laboratory results in a report should reflect a good skill both on *how* and *what* to comment and external quality assessment schemes/proficiency testing should take into consideration interpretative comments on biochemical reports [11]. The ideal comment of a laboratory result, including those referred to a sweat test, should cover the following items [12]:

- To assure about the quality of the sample, in terms of its adequacy (sample with sufficient quantity/volume) for the analysis;
- To interpret the analytical result, including the clinical implications (e.g., for diagnosis, for treatment);
- To explain the reason why no result was eventually available/performed;
- To provide information for follow-up (e.g. further testing, specialist referral);
- To provide information for re-testing in case of inadequate sample or non-physiological results.

The ST should clearly meet the minimal/optimal requirements defined in the standard of care by the ECFS DNWG [8] including

those regarding the processing of results. A unique ST report template is actually proposed, that is adequate for CF diagnosis and not appropriate for monitoring patients on highly effective modulators therapy (HEMT).

Therefore, the ICFS STWG tried to address this unmet need in 2022 introducing for the first time a specific ST report for CF patients on treatment with CFTR modulators including specific information regarding the therapy, the features of the sweat test (analyte, analytical method, reference ranges, interpretation of results).

The aim of the present paper is to discuss the impact of this new ST report format in mock cases, simulating CF patients undergoing CFTR modulators therapy by laboratories participating to the 2022-23 round of the Italian External Quality Assessment program for sweat chloride test (I-EQA-SCT) [13]. Results related to the analysis and reporting on these cases will be fully described highlighting major issues.

2. Materials and methods

The I-EQA-SCT was established in 2014 at the Italian National Center for Rare Diseases of the Istituto Superiore di Sanità (ISS, Rome) and is fully described elsewhere [13,14].

In brief, an Identification Number (ID) is assigned to each laboratory by the scheme organizers and all data are managed through a dedicated web-facility). Three sweat-like-samples (I-EQA-SLS1, I-EQA-SLS2 and I-EQA-SLS3) are commercially prepared (LTA s.r.l., Milano, Italy) and dispatched to participating laboratories with mock clinical information and technical data. The laboratories receive information about samples storage, analysis, and schedule to return results centrally after their acceptance of assessment criteria at the beginning of the round.

Two out of the three mock clinical information used for 2022-23 I-EQA-SCT round (namely, I-EQA-SLS-1 and I-EQA-SLS-2) referred to patients who started Elexacaftor/Tezacaftor/Ivacaftor therapy (Table 1).

2.1. Scoring

Results and scoring are based on technical adequacy, clinical sensitivity, and evaluation of the report.

The total maximum score is fixed at 100 and is composed of the following items:

- technical adequacy in performing a sweat chloride test (including the stimulation method, sweat collection, and analytical method) is evaluated (score range: 0,0–3,3/each parameter)
- chloride concentration results are evaluated as difference from the target value (score range: 0,0–10,0/each sample)
- clinical sensitivity evaluates the consistency of the sweat chloride results with a correct range and clinical interpretations of the results (score range: 0,0–10,0/each sample)
- evaluation of reports that is detailed in § 2.2 (score range: 0,0–10,0/each sample).

The omission of key point results in a demerit from the total score for the EQA. The same error is scored once and, if necessary, that score is associated with a dedicated comment [15].

“Poor performance” was assigned to: laboratories (i) exceeding more than 50 % of the chloride target values; (ii) obtaining incorrect concentration values due to an unintentional sample exchange and/or clerical or transcription errors; (iii) submitting a report where the interpretation is missing or wrong (reporting of reference ranges instead of commenting the results is not considered sufficient), and/or (iv) submitting reports where fundamental information is missing and/or using the wrong ST report format.

2.2. Report assessment

The assessment of the ST reports consisted in the evaluation of the correctness and completeness of the following criteria:

Table 1
Characteristics of the three sweat-like-samples (SLS) dispatched in 2022-23 I-EQA-SCT round. I-EQA-SLS-1 and I-EQA-SLS-2 refer to samples resembling patients undergoing Elexacaftor/Tezacaftor/Ivacaftor.

	I-EQA-SLS-1	I-EQA-SLS-2	I-EQA-SLS-3
Gender (mock)	female	female	male
Date of birth (mock)	03 May 1988	05 Jul 2005	25 Jul 2021
Indication for sweat test (mock)	CF patient, F508del/F508del, Kaftrio/Kalydeco started on 02 May 2019	CF patient, F508del/F508del, Orkambi started on 27 Aug 2018; Kaftrio/Kalydeco started on 25 Aug 2021	first IRT = 86.3 ng/ml; second IRT = 62.5 ng/ml, no CFTR variants detected, Asian origin
Target value	55.6 mmol/L	88.9 mmol/L	77.3 mmol/L
Sweat weight	106 mg or 150 µl	138 mg or 110 µl	115 mg or 113 µl
Expected sweat test report form	monitoring of patients on HEMT	monitoring of patients on HEMT	CF diagnosis
Expected interpretation of results	Adequate sample, sweat chloride in the borderline range	Adequate sample, sweat chloride in the pathological range	Adequate sample, sweat chloride in the pathological range that is suggestive of CF, confirm with a second test or with population specific CFTR analysis

Table 2

	Technical adequacy			I-EQA-SLS-1			I-EQA-SLS-2			I-EQA-SLS-3			TOTAL SCORE	
	Stimulation	sweat collection	analytical method	reporting results	chloride concentration	clinical sensitivity	reporting results	chloride concentration	clinical sensitivity	reporting results	chloride concentration	clinical sensitivity		
Max score	3,33	3,33	3,33	10	10	10	10	10	10	10	10	10	100,00	poor performance
Laboratory A	**3,3**	**3,3**	**3,3**	**10,0**	**5,3**	**10,0**	**10,0**	**9,0**	**10,0**	**10,0**	**5,2**	**10,0**	**89,5**	
Laboratory B	**3,3**	**3,3**	**3,3**	**10,0**	**0,0**	**5,0**	**10,0**	**0,0**	**5,0**	**10,0**	**0,0**	**10,0**	**60,0**	***
Laboratory C	**3,3**	**3,3**	**3,3**	**8,5**	**6,4**	**0,0**	**8,5**	**10,0**	**0,0**	**10,0**	**6,2**	**10,0**	**69,7**	***
Laboratory D	**3,3**	**3,3**	**3,3**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**100,0**	
Laboratory E	**3,3**	**3,3**	**3,3**	**10,0**	**3,0**	**10,0**	**10,0**	**4,1**	**10,0**	**9,0**	**5,2**	**10,0**	**81,3**	
Laboratory F	**3,3**	**3,3**	**3,3**	**10,0**	**6,4**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**6,2**	**10,0**	**92,7**	
Laboratory G	**3,3**	**3,3**	**3,3**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**100,0**	
Laboratory H	**3,3**	**3,3**	**3,3**	**10,0**	**8,8**	**10,0**	**10,0**	**8,0**	**10,0**	**9,0**	**9,3**	**10,0**	**95,0**	
Laboratory I	**3,3**	**3,3**	**3,3**	**10,0**	**10,0**	**10,0**	**10,0**	**4,2**	**10,0**	**10,0**	**9,6**	**10,0**	**93,9**	
Laboratory J	**3,3**	**3,3**	**3,3**	**10,0**	**6,4**	**10,0**	**10,0**	**9,0**	**10,0**	**10,0**	**8,3**	**10,0**	**93,7**	
Laboratory K	**3,3**	**3,3**	**3,3**	**10,0**	**6,4**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**96,4**	
Laboratory L	**3,3**	**3,3**	**3,3**	**10,0**	**8,8**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**10,0**	**98,8**	
Laboratory M	**3,3**	**3,3**	**3,3**	**10,0**	**4,1**	**10,0**	**10,0**	**0,0**	**10,0**	**10,0**	**8,3**	**10,0**	**82,4**	***
Laboratory N	**3,3**	**3,3**	**3,3**	**5,0**	**0,0**	**5,0**	**5,0**	**0,0**	**5,0**	**2,5**	**0,0**	**5,0**	**37,5**	***
min SCORE	3,3	3,3	3,3	8,5	0,0	0,0	8,5	0,0	0,0	9,0	0,0	10,0	60,0	
max SCORE	3,3	3,3	3,3	10,0	10,0	10,0	10,0	10,0	10,0	10,0	10,0	10,0	100,0	
median SCORE	3,3	3,3	3,3	9,9	6,6	8,8	9,9	7,3	8,8	9,8	7,6	10,0	88,7	

a) ST report for CF diagnosis: patient identification data; date of test; date of sample collection; date of report; weight and volume of sweat collected; indication of insufficient collection (<75 mg); stimulation method; analyte(s); analytical method; chloride reference intervals (normal if ≤ 39 mmol/L; ≤29 mmol/L in subjects less than 6 months of age; intermediate if 40–59 mmol/L, 30–59 mmol/L in subjects less than 6 months of age, abnormal if ≥ 60 mmol/L); interpretation of results; presence of signature; report readability.
b) ST report for monitoring patients on CFTR modulators: (in addition to report a)) the indication for the ST should be "monitoring of CFTR modulators"; type and starting date of CFTR modulator; type of measured analyte (only chloride is allowed); analytical method (only quantitative and validated methods for sweat chloride determination are allowed); reference intervals (≤39 mmol/L; 40–59 mmol/L; ≥60 mmol/L; interpretation of results (comment only the analytical result and the patient's condition that suggests the test repetition).

3. Results

Fourteen laboratories (indicated with letters from *A* to *N* in the present paper) completed the 2022-23 I-EQA-SCT round. Ten laboratories (namely, labs *A* to *J*) participated constantly to all rounds since 2014.

All participating laboratories belong to Italian Referral Care Centers for Cystic Fibrosis and some newborn screening laboratories. The number of laboratories performing ST in Italy is estimated to be 26, therefore 53.8 % of Italian CF laboratories is currently participating in the I-EQA-SCT.

Table 2, below, illustrates 2022-23 I-EQA-SCT general results.

Technical adequacy: all 14 laboratories reached a maximum score in the evaluation of this item including stimulation method, sweat collection, and analytical method.

Chloride concentration: median scores ranged from 6.6 to 7.6. In particular, Laboratory *B* and Laboratory *N* failed to determine all 3 samples. Laboratory M failed to determine I-EQA-SLS-2 sample.

Clinical sensitivity: median scores were generally high, ranking from 8.8/10 to 10/10. Almost all laboratories, but one (namely laboratory *C*), reported a correct interpretation on results for all 3 samples. Laboratory *C* failed twice in the interpretation of results (I-EQA-SLS-1 and I-EQA-SLS-2 samples): in both cases, mock indications were referred to patients in follow up for therapeutic monitoring. The interpretation provided by the laboratory was not consistent as they seemed to be referred to a ST for diagnosis; also, the reporting model used was not adequate for the clinical indication.

Two additional laboratories (namely, laboratory *B* and laboratory *N*) reached a score of 5 in clinical sensitivity for I-EQA-SLS-1 and I-EQA-SLS-2 samples. Laboratory *B* reported a non-appropriate interpretation of results for both samples by using *"negative"* instead of *"normal"* in describing chloride concentration value (29 mmol/L or less). Laboratory *N* made a mistake in the report form for patients in follow up for therapeutic monitoring, as indicated by the Italian ST Recommendations (www.sifc.it).

Reporting results: The ST reporting results were satisfactory, even though some laboratories still miss to include some fundamental information in their reports and/or the readability of the reports was not optimal. Most frequently missing information were: "reference intervals", "weight and volume of sweat collected", "analytical method" and "interpretation of results".

Poor performance: Four laboratories (namely, laboratories *B, C, M* and *N*) received a poor performance evaluation. In particular, laboratories *B, M* and *N* obtained suboptimal chloride titration results while, laboratory *C* made an incorrect interpretation of results in samples I-EQA-SLS-1 and 2.

4. Discussion

The ISO15189 standard for medical laboratory quality [16] defines the post-analytical phase as the processes following the examination of the biological sample, which include the formatting, releasing, reporting and retention of the examination results for future access. Recently, due to the IVDR (In Vitro Diagnostic Medical Device Regulation) implementation within European countries, there will be some new instances of standardization in delivery laboratory assays, starting with the need to guarantee the competence and traceability [17].

Studies on errors in laboratory medicine showed that most of the errors occur in the pre- and the post-analytical phases and, for this reason, quality indicators designed to monitor these sensitive phases are needed [18]. As reported in literature, the post-analytical phase is of particular importance because, the analytical results, expressed in numbers, are interpreted and converted into information for patients/clinicians [19].

Furthermore, as described by Forsman in 1996, although laboratory services account for less than 5 % of a hospital's budget, 60–70 % of the most important clinical decisions on admissions, discharges, and medications are based on laboratory test results [20]. A review by Smith et al. identified seven areas of quality improvement to reduce errors between primary care services and laboratory medicine that include also communication gaps, errors in judgement and cognition [21]. There are some specific areas where laboratory interpretation has been of particular concern: therapeutic drug monitoring [22] and genetic testing [23] need to be interpreted to provide an appropriate answer to clinicians. The lack of standardized methods to assess the quality of interpretation and audits often not focused on post-analytical reports equally contribute to generate a grey area of responsibility between clinical and laboratory services [24]. Sikaris highlighted that lab reports should facilitate the critical phases after analysis, which consist in interpretation of results and clinical action such as further testing, or repeat sampling [25]. In the last decade accreditation bodies started to include specific requirements for post and also extra-analytical phase due to the implications of the information emerging from lab reports for patient's safety [26]. Since its beginning, the Italian EQA-SCT program included the evaluation of the ST report among the quality

indicators [14].

Results from the 2022-23 I-EQA-SCT round confirm the importance of a constant and regular participation in EQA programs by laboratories; this may be due to the fact that after having received the EQA results, each laboratory has the opportunity to review its performance, address any inconsistencies and implement corrective actions [15]. In the 2022-23 I-EQA-SCT round laboratories reached a general high-quality level, although some methodological, equipment, or technical problems still may occur. In particular, three laboratories (namely, laboratory *M, B* and *N*) made an incorrect chloride concentration of 7 I-EQA-SLS samples. In this respect, the scheme organizers strongly encouraged poorly performing laboratories to review their internal processes and, in case, to contact the ICFS STWG. The final aim of such programs is to educate participants and a single occurrence of poor performance, which may be possible and isolated incidents, must be assessed and used as an opportunity to review all internal processes.

Interestingly, during the annual meeting to evaluate the results of the 2022-23 EQA-SCT round, the expert panel also discussed results from mocked CF patient undergoing CFTR modulators treatment and the impact of the new proposed reporting format to be used for this purpose.

In this respect, one laboratory out of 14 (namely, laboratory *C*) failed twice in the interpretation of results from the two mock cases referred to patients in follow up for therapeutic monitoring and laboratories *B* and *N* used an unsatisfactory reporting model and reported the result as "*negative*" instead of the "*normal*" as suggested in the Italian Sweat Test Recommendations (www.sifc.it). It seemed that these laboratories were not aware of the new ST recommendations. Nonetheless the experts realized that the new ST report resulted not satisfactory to respond to the clinical question. In particular, the panel of experts highlighted the importance to review the reference intervals ($\leq$39 mmol/L; 40–59 mmol/L; $\geq$60 mmol/L) and the interpretation of results, in relation to a clinical question which focused on determining whether the modulator therapy is effective and/or if the drug is assumed in the right way. In fact, several factors can affect the absorption and availability of the active ingredient of the drug, such as: the fat quantity in the meal or snack assumed before the drug, the right dosage of pancreatic enzymes for those who are pancreatic insufficient, other factors (food, drinks, concomitant drugs and medicinal products) and other exposure conditions (tobacco smoke) [27].

5. Conclusions

The overall results obtained from the fourteen laboratories involved in the Italian 2022-23 EQA-SCT program clearly showed that the laboratories' qualitative and quantitative performance improved significantly during time. In a previously published paper from our group [15] we stated that an important improvement was achieved in the average chloride concentration score among the laboratories that constantly participated in the Italian EQA-SCT: indeed, the average score increased 2,3-fold from the 2015–2016 scheme (median score = 12,0/30,0) to the 2018–2019 scheme (median score = 27,3/30,0). The same positive improvement was achieved for EQA-SCT clinical sensitivity assessment: in that case, the average score increased by 1.4-fold from 2015 to 2018 in the laboratories that actively and constantly participated in all Italian schemes. Of particular interest and for the first time to our knowledge a new ST report format was tested in a national quality assurance program. Results emerged from this round highlighted an issue in the report format used for monitoring patients on CFTR modulator therapy. This result was shared with the ICFS STWG who met and discussed the content of the ST report format for CF patients treated with CFTR modulators and finally they agreed to change this format. In particular, the dose of modulator was added, the reference ranges were deleted. The interpretation of the result were modified to be more focused on the specific clinical request; it is recommended to compare the sweat chloride result with the baseline value and/or the previous sweat test results during treatment taking into account the threshold of 60 mmol/L which is indicative of CF disease and to comment on the need for a further sweat test based on patient's conditions. The new ST report format for monitoring patients on CFTR modulator therapy was published in a new edition of the ICFS ST recommendations for Sweat Testing in July 2023 (www.sifc.it). The huge work made by the expert panel of assessors in the EQA SCT scheme and the efficient collaboration with the ICFS STWG led to a revision of the ST report format for monitoring patients on CFTR modulator therapy. The work made by the EQA scheme team is helpful not only to improve the performance of lab services but also to enhance the national recommendations. We consider the new proposed ST report format for monitoring patients on CFTR modulator therapy as a work in progress because new evidences could emerge from post-marketing studies and CF registry data.

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CRediT authorship contribution statement

Natalia Cirilli: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Giovanna Floridia:** Writing – review & editing, Validation, Investigation. **Annalisa Amato:** Writing – review & editing, Validation, Investigation. **Rita Padoan:** Writing – review & editing, Validation, Investigation. **Federica Censi:** Writing – review & editing, Validation, Investigation. **Gianluca Ferrari:** Writing – review & editing, Validation, Software, Investigation. **Valeria Raia:** Writing – review & editing, Validation, Investigation. **Giuseppe Castaldo:** Writing – review & editing, Validation, Investigation. **Ettore Capoluongo:** Writing – review & editing, Validation, Investigation. **Domenica Taruscio:** Writing – review & editing, Validation, Investigation. **Marco Salvatore:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Data availability

Data will be made available on request.

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