Guidelines and Recommendations

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Australasian guideline for the performance of sweat chloride testing 3rd edition: to support cystic fibrosis screening, diagnosis and monitoring

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Abstract: The sweat test is used as a biological marker of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction, but there is growing recognition that sweat chloride concentrations of people with cystic fibrosis (CF) can overlap with those without CF. There are also people without CF whose symptoms are caused by abnormalities of CFTR. To support clinical decisions, the sweat chloride test conducted appropriately should provide consistent results between laboratories and common decision limits should be used. International consensus guidelines now recommend a standard set of clinical decision limits for sweat chloride, with values between 30 and 59 mmol/L, as the intermediate result for all ages. It is therefore timely to update the Australasian guideline decision limits to align with international consensus guidelines and peak body recommendations. At the same time, the technical aspects for performance of the sweat chloride test should be reviewed. This paper updates (and replaces) the guideline for the performance of the sweat chloride test that were last published by the AACB in 2017. This freely available guideline was developed to support Australasian laboratories, and laboratories from other regions, with the accurate performance of sweat chloride testing. The guideline provides 16 recommendations for the performance of the sweat chloride test encompassing the total testing process. Previous recommendations related to sweat conductivity testing have been removed from this guideline. The sweat chloride decision limits of ≥30 mmol/L support a review by a CF physician for all age groups. Sweat chloride concentrations of ≥60 mmol/L are supportive of a diagnosis of CF.

Keywords: sweat chloride; CFTR; harmonisation; decision limits

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Introduction

The sweat chloride test remains an important part of the diagnosis of cystic fibrosis (CF, OMIM #219700), with sweat chloride concentration representing biological activity of the key protein involved in CF, the cystic fibrosis transmembrane conductance regulator (CFTR). However, the sweat chloride test is an imperfect measure of CFTR function and there is overlap between the concentrations from healthy, non-carrier people and those with clinical CF [usually pancreatic-sufficient patients] and many with CFTR related conditions; for example, congenital absent vas deferens, recurrent pancreatitis and sinusitis Table 1. Furthermore, sweat chloride values are known to increase with age, so that setting clear diagnostic clinical decision limits is difficult [1].

The US Cystic Fibrosis Foundation (USCFF) and the European Cystic Fibrosis Society (ECFS) consensus guidelines now offer a single set of clinical decision limits for sweat chloride across all ages, essentially classifying a sweat chloride concentration between 30 and 59 mmol/L as 'intermediate' [4, 5]. In the last iteration of the Australasian sweat test guideline, developed in conjunction with the Australasian Association for Clinical Biochemistry and Laboratory Medicine (AACB) and the Royal College of Pathologists of Australasia (RCPA) Quality Assurance Programs (QAP) [6], there were two, age-related clinical decision limits for sweat chloride based on what was known from the limited evidence of "normal" concentrations; infants less than 6 months 30–60 mmol/L were intermediate and from 6 months 40–60 mmol/L were intermediate [6]. The two clinical decision limits were also considered a way to limit 'over diagnosis' of CF. However, this has created some confusion between laboratories across Australasia, with some, guided by their CF clinicians, using a single clinical decision limit of 30–59 mmol/L as intermediate for all ages.

While there is no new data about "normal" values for sweat chloride, in particular no data at all from 6 weeks to 5 years of age and no longitudinal data at all, it seems prescient to re-consider the sweat chloride clinical decision limits recommended by the AACB-RCPAQAP as this is highly relevant for laboratories reporting sweat chloride tests, the RCPAQAP and clinicians. At the same time, it is sensible to re-look at the technical aspects for performance of the sweat chloride test considering any new information and published guidelines since 2017 [6].

The aim of this paper was to update (and replace) the guidelines for the performance of the sweat test and decision limits that were last published in 2017 [6, 7].

Table 1: Clinical features consistent with a diagnosis of CF, adapted from [2].

1. Chronic sinopulmonary disease, manifested by:	a. Persistent colonization/infection with typical CF pathogens, including *Staphylococcus aureus*, non-typeable *Haemophilus influenzae*, mucoid and nonmucoid *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacian*
	b. Chronic cough and sputum production
	c. Persistent chest radiograph abnormalities (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
	d. Airway obstruction, manifested by wheezing and air-trapping
	e. Nasal polyps; radiographic or CT abnormalities of the paranasal sinuses
	f. Digital clubbing
2. Gastrointestinal and nutritional abnormalities, including:	a. Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
	b. Pancreatic: pancreatic insufficiency, recurrent acute pancreatitis, chronic pancreatitis, pancreatic abnormalities on imaging
	c. Hepatic: prolonged neonatal jaundice, chronic hepatic disease manifested by clinical or histological evidence of focal biliary cirrhosis or multilobular cirrhosis
	d. Nutritional: failure to thrive (protein-calorie malnutrition), hypoproteinemia and oedema, complications secondary to fat-soluble vitamin deficiencies
3. Salt loss syndromes: acute salt depletion, chronic metabolic alkalosis	
4. Genital abnormalities in males, resulting in obstructive azoospermia	

[a]Note the latest CLSI guideline includes laboratory results (NBS and genomic) as part of clinical indications for a sweat chloride test [3].

Methods

Guideline development group

The AACB-RCPAQAP Inborn Errors Advisory Committee (IEAC) (previously known as the Sweat Test Working Party) developed guidelines for sweat testing; originally in 2006 and most recently in 2017 [6, 8]. In 2024 this Committee

consisted of all authors listed in this publication, with representation of paediatric clinical scientists (LG, RG, AM), pathologists (NH, EL, CS), RCPAQAP scientists (NR, PG) and a specialist in respiratory medicine (JM).

The AACB-RCPAQAP IEAC (via JM) and the Cystic Fibrosis Special Interest group (Dr. Simone Visser and Dr. Geshani Jayasuriya) of the Thoracic Society of Australia and New Zealand (TSANZ) have worked closely together to reconsider the clinical decision limits for sweat chloride.

Process for guideline update

In 2024 the IEAC decided there were sufficient changes to practice warranting the introduction of a revision of the guideline that was fit for purpose to support Australasian (and other regions) laboratories and clinicians.

The process for review is provided in Figure 1 and consisted of:

1) Meeting of CF special interest group of TSANZ to discuss the evidence and clinical practice for sweat chloride clinical decision limits (March 2024). This included both adult and paediatric CF physicians. There was consensus of this group that the USCFF and ECFS recommendations were routinely followed by CF clinicians and should be adopted in Australia.
2) Tabulation of other recent English language guidelines (Supplementary Table 1) [3–6, 8–13].
3) Reviewing the 2nd edition guideline [6], performing a gap analysis, mapping proposed changes and using a traffic light system for the IEAC members to highlight if full agreement was reached. This process continued until all recommendations were fully endorsed.
4) Following an initial presentation of the draft recommendations at the AACB-RCPA Harmonisation Workshop (25 July 2024, Sydney Australia), an open online invitation to laboratory professionals was provided via the AACB website, and direct announcement to the RCPAQAP IEM program participants and the IFCC Committee-Emerging Technologies in Paediatric Laboratory Medicine (C-ETPLM) requesting feedback of the guideline table (Table 2) in the fourth quarter of 2024.
5) A post feedback review was conducted in February 2025 by IEAC.

Rationale for change of clinical decision limits

The change to a single intermediate clinical decision limit of 30–59 mmol/L was discussed by the IEAC, with the following points raised:

1) CF is not defined by a laboratory testing definition, but by a clinical definition that incorporates the sweat chloride test as one critical component in the decisional calculus;
2) For sweat chloride interpretation, we have moved away from laboratory-based reference intervals and re-cast them as clinical decision limits that have been adopted by clinical professional societies such as ECFS and US CFF [4, 5];
3) The change to a single intermediate decision limit for all patients simplifies the interpretation and decision pathway for clinical management;
4) All laboratories adopting the same set of decision limits provides harmonisation and is best practice for patient care; and
5) CF clinicians under the auspices of the CF Special Interest Group of the TSANZ support the 30–59 mmol/L intermediate decision limit.

Recommendations

The review of the sweat chloride recommendations has produced a simpler set of 16 recommendations that are

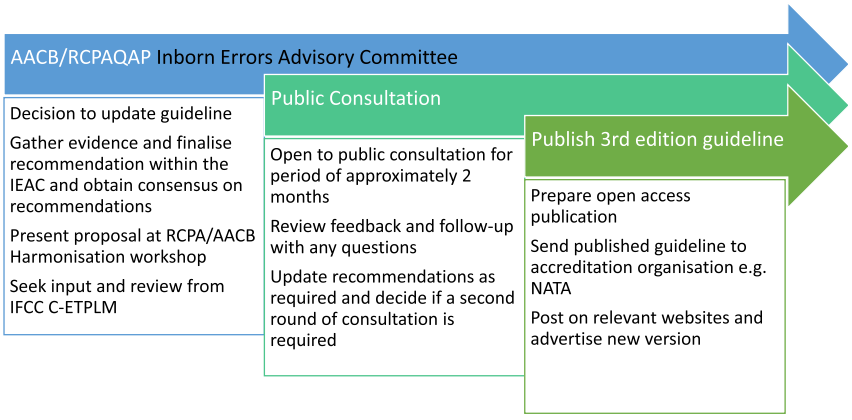


Figure 1: Overview of sweat test guideline review process. The formal consultation period opened on 7th October 2024 for feedback and closed on Friday 20th December 2024. AACB, Australasian Association for Clinical Biochemistry and Laboratory Medicine; RCPAQAP, Royal College of Pathologists of Australasia Quality Assurance Programs; NATA, National Association of Testing Authorities; IEAC, Inborn Errors Advisory Committee; IFCC C-ETPLM, International Federation of Clinical Chemistry and Laboratory Medicine Committee-Emerging Technologies in Pediatric Laboratory Medicine.

subdivided across the total testing process; that is pre-analytical, analytical and post-analytical recommendations (Table 2).

At the end of the consultation period, four responses were received and subsequently reviewed by the IEAC. The responses were: 1) provide more information on the evidence for the equivocal results range for sweat chloride concentrations of 30–59 mmol/L [12, 13]; 2) the recommendations are reasonable and it's a very good idea to have a standardised guideline for the Asia-Pacific region; 3) support the new draft as written; and 4) the videos are a beautiful useful tool to support all hospital/labs to make the

Table 2: 3rd Edition sweat chloride testing recommendations.

Number	Recommendation
Pre-analytical	
Recommendation 1	Following an abnormal newborn screening result (i.e. screen positive for CF), babies should have a sweat chloride test.
Recommendation 2	Patients presenting with clinical signs of CF should have a sweat chloride test. The list of clinical signs is provided in Table 1 [2].
Recommendation 3	To increase the likelihood of adequate sweat collection, it is recommended to perform the sweat chloride test when the subject is greater than two weeks corrected age and weighs more than 2 kg. Earlier collections may be considered if required for clinical management.
Recommendation 4	Sweat testing should be delayed if the patient is acutely unwell, dehydrated, oedematous, malnourished or does not have a suitable skin site free of eczema.
Recommendation 5	It is a sound practice to prepare a sweat test information for patients and families. An example information sheet can be found at URL TestManual (tst-mater-pams-rel5.azurewebsites.net). Families may wish to see a video of the sweat test collection https://player.vimeo.com/video/837751686?h=4b12813bf2 [14].
Recommendation 6	For effective sweat collection, stimulate the flexor surface of the forearm at 1.5–4 mA for 5 min, then place the sweat collector on the arm for up to 30 min. A minimum sweat secretion rate of $\geq$1 g/m^2/min is required, equivalent to 15 µL in 25 min. Providers should follow standardised sweat stimulation and collection procedures as covered by consistent statements in the UK (2014) and US (2024) guidelines [3, 9]. The UK guideline is freely available and can be found at https://labmed.org.uk/resource/guidelines-for-the-performance-of-the-sweat-test-for-the-investigation-of-cystic-fibrosis.html [9]. A sweat test collection video is available for health professionals continuing professional development – https://player.vimeo.com/video/824919425?h=a9225797ab [15].
Recommendation 7	Each person trained to carry out sweat collection should perform at least 10 sweat collections annually, and detailed training records must be maintained. AND An annual target of <10 % of quantity not sufficient collections across all ages.
Analytical	
Recommendation 8	Measurement of sweat sodium, osmolality and conductivity are no longer recommended tests.
Recommendation 9	Insufficient volume/weight from individual sweat collections should not be pooled for analysis. i.e. specimens from separate sites or collection times should not be pooled for analysis.
Recommendation 10	Transport and storage times and conditions should be validated by each laboratory to ensure the integrity of the sample [16, 17].
Recommendation 11	In addition to chloridimetery, inductively coupled plasma mass spectrometry (ICP-MS) and ion chromatography/high performance liquid chromatography (IC-HPLC) are appropriate for sweat chloride analysis and ICP-MS is the Joint Committee for Traceability in Laboratory Medicine (JCTLM) listed reference measurement procedure [18, 19].
Recommendation 12	Where practicable, sweat samples should be analysed and reported on the same day as the sample is collected.
Recommendation 13	The laboratory must monitor analytical performance of chloride measurement in a recognised external quality assurance program.
Post-analytical	
Recommendation 14	In relation to the sweat test, chloride should be the only analyte reported for the investigation of CF.
Recommendation 15	We advocate the following decision limits: – Sweat chloride ≥**60 mmol/L** supports the diagnosis of CF; – A patient is unlikely to have CF when the sweat chloride is ≤**29 mmol/L**; and – Patients with an intermediate sweat chloride result of **30 – 59 mmol/L** may have CF and should be referred to a physician experienced in the diagnosis of CF for clinical evaluation.
Recommendation 16	Local accreditation authorities should ensure assessors with expertise in sweat chloride testing are included in the assessor panel.

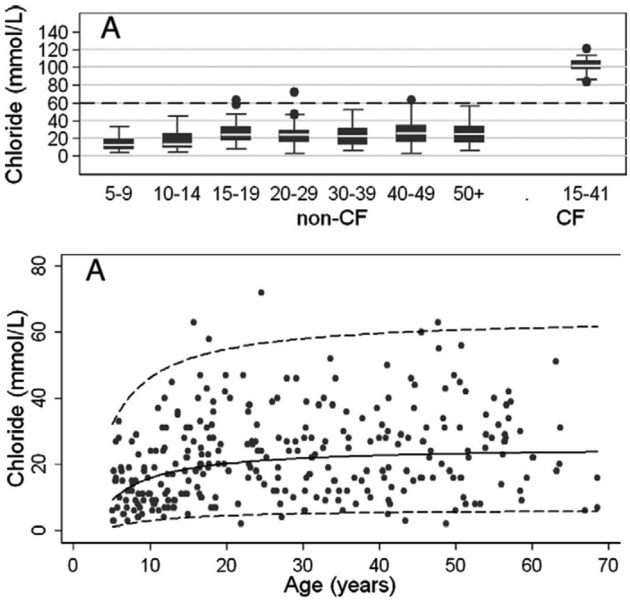


Figure 2: Sweat chloride values from healthy people. From Mishra et al. 2008; reproduced with permission from Elsevier [1].

sweat test as comfortable as possible and suggested some frequently asked questions. No changes were required to the recommendations themselves.

Regarding the feedback requesting evidence for the 30–59 mmol/L intermediate clinical decision limit, the IEAC recognises that more evidence may be ideal. However, there is little rationale from the IEAC's current perspective not to support the single intermediate decision limit provided by the clinical societies. Hence the recommendations were not substantially changed based on this feedback item. We do, however, recommend awareness be raised as to the change of sweat chloride concentrations that naturally occurs with age Figure 2 [1].

Discussion of recommendations

In this report we have successfully developed a simplified set of 16 recommendations to ensure standardisation and current best practice of sweat chloride testing to support the process for the diagnosis of CF. Since the first guideline on sweat testing produced in 1994 [20] various organisations have developed and continued to review their own guidelines to ensure currency and overall best practice to support patient care [2, 3, 6, 8–10, 20–24]. Our new and simplified recommendations have been developed by an Australasian group, but they are applicable globally (see comparison of sweat test recommendations in Supplementary Table 1; [3–6, 8–13]). In addition, the links to the patient and professional videos have been developed by members of this IEAC group to support training locally, regionally and globally [14, 15].

Below is expanded commentary to discuss pertinent aspects of the recommendations, across the total testing process for sweat chloride testing that together are aimed at harmonisation and error reduction [25].

Pre analytical

The pre-analytical component incorporates seven key recommendations focused on patients and professionals.

Commonly a sweat chloride test will be requested for symptomatic patients or where there is a family history. In addition, in regions where newborn bloodspot screening (NBS) for CF occurs (including all of Australia and New Zealand), a sweat chloride test will routinely be ordered following a positive screening result as part of the diagnostic workup. Within the recommendations there are links to an example patient information sheet and a patient orientated video of the sweat testing process [14]. These documents help provide assurance for parents with a child about to undergo the sweat test.

Ongoing competency of sweat test collection team members is a key consideration in these recommendations. Sweat collection requires a standardised series of steps, starting with cleaning of the skin on the flexor surface of either forearm, placing a pilocarpine gel (or soaked pad) attached to electrodes on the arm, stimulation at 1.5–4 mA for 5 min, removal of the device and placement of the sweat collector on the arm for up to 30 min [9, 10]. At the end of this time the sweat sample is removed, and the minimum volume (or weight) checked. The minimum sweat volume for analysis is based on the rate of sweat secretion greater than 1 g/m^2/min which equates to 18 µL of sweat collected in 30 min (or 15 µL in 25 min) [9, 10]. This process is well documented, and whilst many laboratories have moved to the coil tubing method, the principle is consistent with that developed by Gibson and Cooke in 1959 [26] and a multimedia training resource is freely available for health professionals [15].

Analytical

The analytical component incorporates six key recommendations focused on the laboratory processes.

The timeliness and sample handling post sweat collection are considered under analytical, because this is an area

that the sweat testing laboratory has direct responsibility for validating the processes. From a patient and clinical perspective, the timeliness of analysis and reporting is important to reduce the anxiety associated with an undetermined diagnosis of CF. Ideally, the sweat test analysis should be undertaken on the same day of analysis, however, in some centres, there are logistic issues that will mean that this is not always feasible. Considering a patient-focused approach, the total testing process should minimise turnaround time as much as practicable.

Sweat collection usually occurs outside of the analytic laboratory site. The distance between collection and analysis can range from being in the same building as the laboratory to remote collection at sites hundreds of kilometres away. In considering transport, and storage, an important consideration is maintaining the integrity of the sweat sample immediately following collection to the start of analysis. There is some evidence that outlines appropriate transport and storage for sweat test samples collected remotely [16]. However, these processes should be evaluated by each laboratory to account for local circumstances.

There continues to be an evolving appreciation of the role of the sweat chloride test in the diagnosis and management of CF. This evolution is seen in successive guideline revisions, such as the removal of sodium from recommendations and the inclusion of considerations for remote sample collection [6]. Most recently, the RCPAQAP for sweat testing has removed conductivity analysis from its program because of a decline (to zero) in participating Australasian laboratories offering this test [27]. This reflects a change in practice, and a likely improvement in workflow with redirection directly to sweat chloride testing.

Inductively coupled plasma mass spectrometry (ICP-MS) is the reference measurement procedure (RMP) for sweat chloride testing listed in the Joint Committee for Traceability in Laboratory Medicine (JCTLM) database [18, 19]. However, ICP-MS is not recognised in some other guidelines. For reference, in 2025 the RCPAQAP participation demonstrates that four out of the 26 participating laboratories use ICP-MS technology as their routine methodology, while the remaining laboratories employ other techniques such as Coulometry, IC-HPLC (ion chromatography-high-performance liquid chromatography) and colourimetry.

Irrespective of the method of chloride measurement, individual sweat chloride samples must NOT be pooled for analysis and samples <15 µL SHOULD NOT be analysed and MUST NOT be reported. It is the opinion of the IEAC that reporting the collection volume on the final report is useful as it provides a level of certainty that the laboratory has not deviated from this criterial sweat collection rate volume requirement.

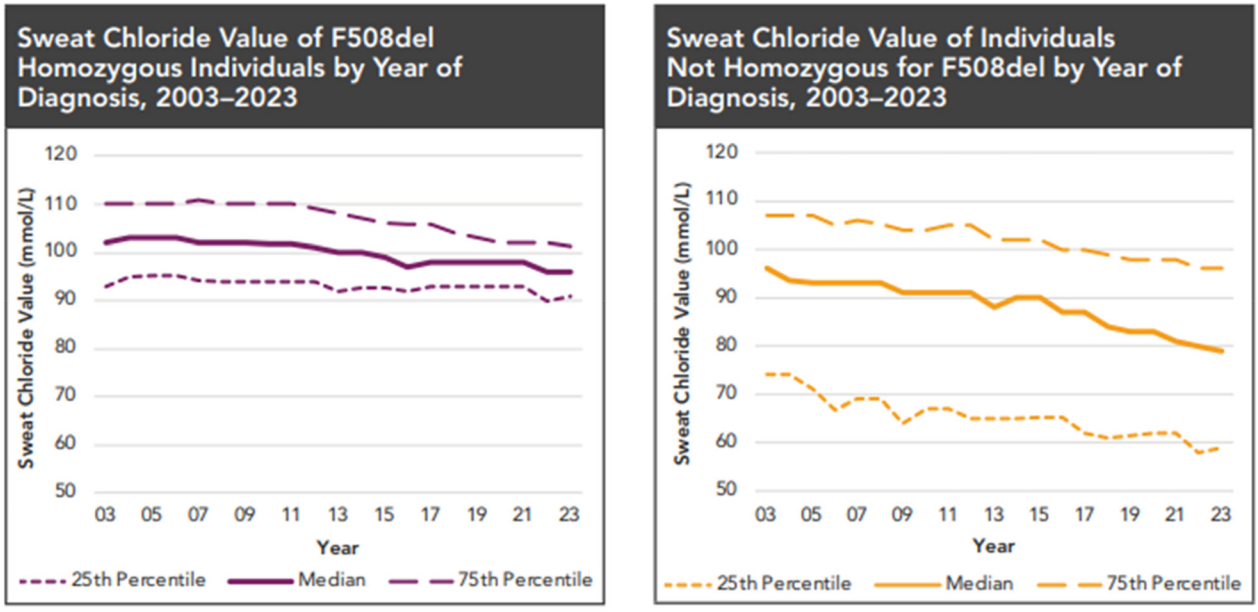
Post-analytical

The post-analytical component of sweat testing incorporates three key recommendations focused on the reporting of the sweat chloride results and overall auditing of the total testing process.

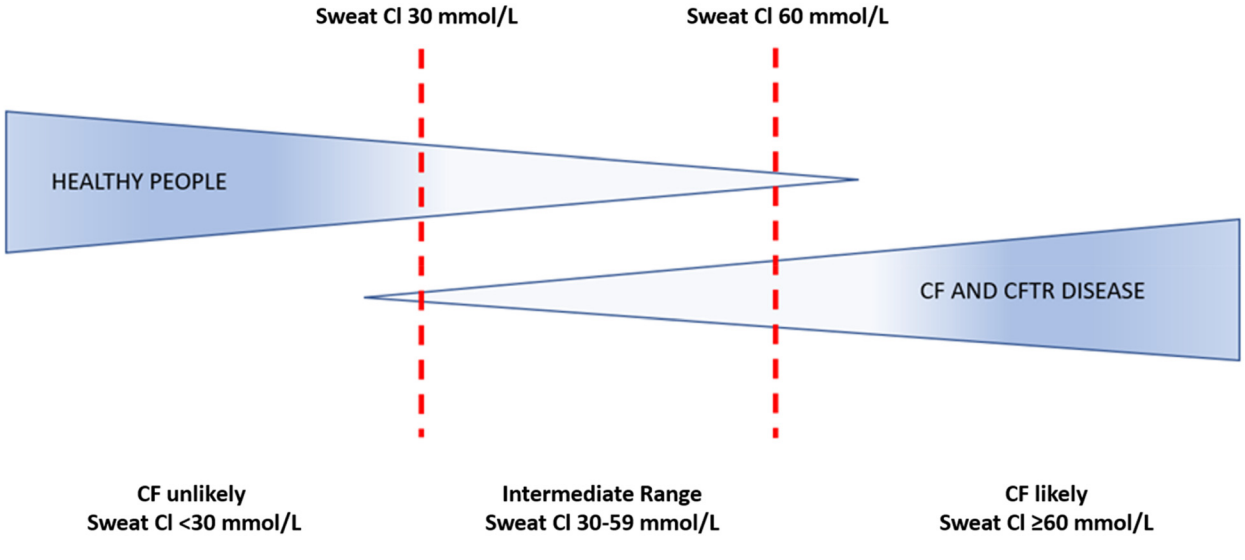
Since the publication of the last guideline, it has become apparent that there is an increasing number of people with CF or CFTR related disease who have sweat chloride values between 30 and 39 mmol/L (as distinct from the previous lower limit of ≤40 mmol/L for the intermediate lower level); Figure 3. This is because of greater recognition by clinicians of the wide phenotype of CF and information generated by increasingly available *CFTR* gene analysis by next-generation sequencing, Multiplex Ligation-dependent Probe Amplification (MLPA) for deletions, and expansion to test for deep intronic variants that may be associated with CF or CFTR related diseases. Furthermore, the availability of highly effective CFTR modulators, such as the combination elexacaftror-tezacaftor-ivacaftor (ETI, marketed as Trikafta®, in Australia and New Zealand, Vertex Pharmaceuticals) has meant that there are therapeutic options for people with troublesome disease mediated by CFTR.

Since it is clear that CF is understood as a spectrum of conditions relating to CFTR dysfunction, a traditional reference interval approach to the diagnosis of CF no longer has legitimacy. As such, the IEAC now refers to clinical decision-limits rather than reference intervals [29]. The clinical decision-limit still does not resolve the problem of the considerable overlap between the concentrations of sweat chloride for healthy (non-carrier) people and those with CFTR mediated disease, but this is best dealt with by a recommendation that sweat testing laboratories report intermediate results with a clear recommendation to consult a CF physician; Figure 4 [1]. In the face of an intermediate result, the CF physician will consider all the information needed to make a diagnosis of CF, synthesising a detailed CF phenotype with *CFTR* genetic information *and* the sweat chloride concentration.

Finally, clinicians should be aware of the variation of the sweat chloride measurement which is partly clinical and partly due to measurement. There is no way of assessing the clinical variation, except for ensuring



A)



B)

Figure 3: Relationship between sweat chloride concentrations and CF. (A) Information from the 2023 Cystic Fibrosis Foundation annual report, report median sweat chloride values for patient homozygous F508del have remained consistent over time, whereas for patients heterozygous for F508del, the median sweat chloride has decreased. This is likely a reflection of more patients with residual chloride function mutations being diagnosed with CF [28]. Reproduced with permission from the Cystic Fibrosis Foundation patient registry, 2023 annual data report. Bethesda, Maryland. ©2024 Cystic Fibrosis Foundation [28]. Reproduced with permission from the Cystic Fibrosis Foundation patient registry, 2023 annual data report. Bethesda, Maryland. ©2024 Cystic Fibrosis Foundation. (B) Relationship of sweat chloride between healthy adults and those with CF and CFTR disease.

patients are well hydrated before the test and the test is collected in a standard way according to guidelines. However, CF is a clinical diagnosis and therefore the laboratory's responsibility is to provide an appropriate report that recommends follow-up by a physician experienced in the diagnosis of CF for clinical evaluation.

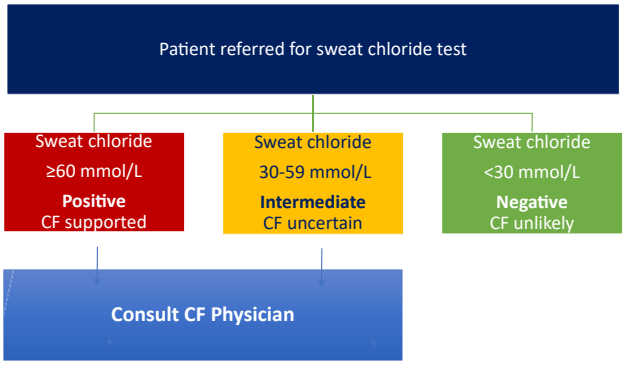


Figure 4: Interpretation of sweat chloride test results with one set of decision limits applied across all ages.

Conclusions

This freely available guideline has been developed to support Australasian laboratories, and laboratories from other regions, with the accurate performance of sweat chloride testing for the diagnosis of cystic fibrosis. This guideline provides 16 recommendations for the performance of the sweat chloride test that encompasses the total testing process. Previous recommendations related to sweat conductivity testing have been removed from this guideline as it is no longer a supported pathway. Whilst CF is a clinical diagnosis, the sweat chloride decision limits of ≥30 mmol/L support review by a CF physician for all age groups. Sweat chloride values of ≥60 mmol/L are supportive of a diagnosis of CF.

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