SWEAT TESTING: CONFIRMING THE DIAGNOSIS OF CYSTIC FIBROSIS - SCH

PROCEDURE

DOCUMENT SUMMARY/KEY POINTS

- Sweat testing is a diagnostic test used to diagnose Cystic Fibrosis.
- Prior to the procedure the parent(s)/carer(s) should have the procedure described to them and be given a Sweat Test Fact Sheet
- Facilities should be available to treat anaphylaxis
- A minimum of 15microlitres (µL) of sweat is required
- The procedure should only be performed by appropriately trained and experienced nurses working within the Sydney Children's Hospital, Outpatient Department. New nursing staff must be trained prior to performing sweat tests.

CHANGE SUMMARY

- Updated Recommendations for Successful Sweat Collection - Section 7
- Updated Reference Intervals, Interpretation & Reporting Guidelines- Section 11
- Updated Appendix B: SOP
- Updated Appendix C: Sweat Chloride Interpretation Flow Chart

Approved by:	SCHN Policy, Procedure and Guideline Committee	
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Team Leader:	Staff Specialist	**Area/Dept**: Respiratory SCH

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READ ACKNOWLEDGEMENT

- Nursing Staff in the Sydney Children's Hospital Outpatients Department (COPD) who perform sweat testing procedures must read and understand this document and then notify local Nurse Unit Manager (NUM) for recording by local processes.
- Each OPD Nurse trained to carry out sweat testing should perform at least 10 sweat tests annually and detailed training records must be fully documented.
- Training should be documented by the COPD NUM / COPD Educator and made available to the CF CNC (Sweat Test Training Log, confidential electronic copy).
- Auditing of sweat testing should be performed at least annually by the SEALS laboratory
- Training is based on knowledge and performance of sweat testing as illustrated by the Sweat Testing SOP (Appendix B).

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1 Introduction

Accurate measurement of sweat chloride concentration is used to diagnose cystic fibrosis (CF). A sweat test should be performed as soon as possible following a positive Newborn Screen result where practical if the baby is greater than 2 weeks corrected age and weighs more than 3 kg. The authorised sweat chloride result should be reported the same day and notified to the requestor.

Sweat chloride is the only analyte considered for diagnosis of CF. Measurement of sweat sodium, osmolality and conductivity are not acceptable tests for the diagnosis of CF.

This document provides practical information on the indications, performance and interpretation of sweat chloride concentration levels and is based on the *Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK* (Version 2)[1], *Sweat Testing: Sample Collection and Quantitative Chloride Analysis; Approved Guideline-Third Edition C34-A3 Clinical and Laboratory Standards Institute*[2], *Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation (2017)*[3] , *Australasian Guideline (2nd Edition): an Annex to the CLSI and UK Guidelines for the Performance of the Sweat Test for the Diagnosis of Cystic Fibrosis*[4] and *ECFS Standards of care guidance for sweat testing*[5]

2 Indications for Sweat Testing

There are many respiratory, gastrointestinal and metabolic indications for sweat testing. Infants and young children may present with the following:

- Positive newborn screening test for CF (elevated immunoreactive trypsinogen (IRT) followed by detection of one or two CFTR gene variants.
- *In utero* echogenic bowel or neonatal intestinal obstruction.
- Prolonged neonatal jaundice.
- A family history of CF or CF carrier status.
- Recurrent respiratory tract infections.
- Bronchiectasis
- Chronic cough
- Chronic wheezing
- Failure to thrive
- Steatorrhoea
- Nasal polyps
- Rectal prolapse
- Sputum culture positive for CF related pathogens.
- Recurrent acute pancreatitis or chronic pancreatitis.
- Monitoring and prior to initiation of therapy with CFTR modulators

The two tiered NBS assay (IRT measurement and CFTR genetic screening) is insufficient to make a diagnosis of CF.

Diagnostic genetic testing in a NATA accredited molecular genetics laboratory is recommended.

The Cystic Fibrosis Foundation (CFF) guidelines recommend sweat testing to confirm the diagnosis of CF even if two CF-causing mutations (defined by CFTR2) have been identified[6].

Additionally, there are a wide variety of symptoms where it is important to consider a diagnosis of CF/CFTR related disorder (may need a reference to define this?) in the absence of a positive NBS. (see Appendix A: Indications for Sweat Testing).

3 Summary of the Sweat Test Procedure

- **Sweat stimulation:** Approximately 5 minutes.
- **Sweat collection:** No longer than 30 minutes.
- **Quantitative sweat chloride measurement:** Result available the same day.

4 Who Should Perform Sweat Testing?

Appropriately trained and experienced nurses working within the Sydney Children's Hospital, Outpatient Department, (see Training Requirements, Section 12).

5 Parent/ Carer Information

The procedure should be described to parents/carers and a Sweat Test Fact Sheet provided. Information provided should include why the test is being performed, what the test involves, possible risks associated with the test such as a mild skin burn or the potential for repeat testing if the amount of sweat obtained is insufficient or the results are intermediate. Information should also be provided about when and who will communicate the results of the test to the family.

Newborns identified with a positive NBS result, should be offered the opportunity to consult with the genetic counsellor (ext 25607, 25608, 25609) at the commencement of the sweat collection to provide genetic counselling to the parent/family. If the CF genetic counsellor is unavailable, the on-call genetic counsellor will attend the sweat test appointment.

6 Contraindications

- Neonates less than 48 hours of age: As high electrolyte concentrations can be found in the sweat during the first few days of life.
- Known hypersensitivity to Pilocarpine.
- Do not perform sweat test on subjects receiving oxygen by an open delivery system. This does not apply to infants in a headbox or on nasal prong oxygen.

7 Recommendations for Successful Sweat Collection

- At SCH sweat is collected using the Wescor Macroduct System and a minimum of 15microlitres (µL) of sweat is required.
- To increase the likelihood of collecting an adequate sweat specimen, it is recommended that sweat testing in infants be performed when the infant is **at least 2 weeks of age** and ideally **weighs more than 3 kg**. Only if absolutely clinically indicated is sweat testing performed in younger, smaller infants (minimum 2 kg) as sweat volumes are likely to be insufficient and the risk of complications is greater. Please involve the genetic counsellor in this scenario to discuss alternative options.
- The patient should be well hydrated and free of acute illness. Delay testing if patient is oedematous or receiving corticosteroids. Avoid sites affected by eczema.
- Sweat can be collected from the flexor surface of either forearm, upper arm or thigh. **Note the density of sweat glands is less in the thigh making it a less optimal collection site**. Sweat should **not** be collected from the head including forehead (possible burns), trunk, (current crossing the heart) or any area of inflammation (eczema / rash). Avoid local anaesthetic gel or chloride containing antiseptic solutions.
- **It is sufficient to routinely carry out only one sweat collection. However, when there have been issues with previous collections or if there does not appear to be sufficient volume being collected during the process, nursing staff may consider adding a second macroduct to the other arm (see flowsheet). In general, duplicate procedures increase the time taken and the discomfort for patients without increasing the diagnostic rate.**
- **Sweat should be collected over 20-30 minutes**, i.e. not less than 20 minutes unless the Macroduct® tubing is full and not more than 30minutes
- If insufficient volume of sweat is collected and confirmed by the lab, only one repeat collection on the same day may be performed using an alternate site. Rarely there may be exceptions to this if the family live a considerable distance from the hospital.

  Do not re-stimulate the same area. If the sweat volume remains insufficient reschedule the test for another date. *Do not attempt to pool insufficient volumes of sweat from different sites*.

  Where sweat volumes appear borderline or insufficient, the lab staff will draw up and measure the volume collected to confirm sample is quantity insufficient. The sample should still be taken to the lab for confirmation of volume collected.

8 Precautions

There is a small risk of complications when performing sweat testing.

- Only use a battery powered iontophoresis system (with safety cut-out). Medical Engineering must check electrical safety of all power supplies for voltage leak and current control annually
- Infrequent but minor complications may include reddening of skin, blistering or burns but these may be minimised by a careful technique.
- An allergic reaction to pilocarpine is extremely rare. However, if skin inflammation and urticaria develop, immediately discontinue procedure and seek appropriate medical attention. Facilities should be available in the Outpatients Department to treat anaphylaxis.

  All patient specimens are potentially infectious and should be handled according to "Standard Precautions". It is recommended that collecting and laboratory personnel wear powder free gloves during sweat collection and analysis.

9 Sweat Stimulation

The child needs to be closely supervised during iontophoresis

- See the STANDARD OPERATING PROCEDURE (SOP) FOR SWEAT TESTING IN CHILDREN USING THE WESCOR MACRODUCT SYSTEM (Appendix B)
- Localised sweating is stimulated by the iontophoresis (the movement of ions through biological material under the influence of an electric current) of the cholinergic drug pilocarpine nitrate into an area of skin
- Positively charged pilocarpine ions move away from the positive electrode and into the skin where they stimulate sweat production. A negative electrode with a dilute electrolyte solution is applied to the same limb.

10 Sweat Collection: Time and Medium

- Duplicate sweat testing is NOT routinely required currently at SCH
- Sweat should be collected onto the Wescor Macroduct disc. Sweat should be collected for not less than 20 minutes and **not more than 30 minutes**.
- Collection start and finish time and the duration of sweat collection must be recorded on the laboratory request form. For example Start time: 0930 Finish time: 1000 hours, (30 minutes).
- Sweat samples should be transported to the laboratory in person for analysis as soon as possible to prevent evaporation. Macroduct should be placed in a labelled specimen

jar, then into a plastic specimen bag and physically taken to SEALS by the collecting nursing staff.

- A minimum sample of 15 microlitres (µL) should be collected into the Macroduct disc over 30 minutes
- Insufficient sweat collections should not be pooled. The full sweat test should be repeated.
- The proportion of Quality Not Sufficient (QNS) samples should be less than 5%. If lab annual audits identify >5% insufficient samples review of methodology, staff training and instrument function is warranted.

11 Reference Intervals, Interpretation & Reporting

Interpretation of Sweat Test results are as follows (see Appendix C)

- **ABNORMAL:** A sweat chloride concentration greater than or equal to 60mmol/L is diagnostic of CF. (Very rarely other conditions may cause an elevated sweat chloride concentration). Referral to the CF CNC and CF Consultant on-call should be made as soon as the result is available.
- **INTERMEDIATE:** A sweat chloride concentration between 30 - 59mmol/L is an intermediate result which requires further assessment of CF. The CF CNC and CF genetic counsellor should be informed by the Outpatient Staff on the same day. Repeat sweat testing will be booked and extended CF mutation analysis, genotyping and / or other tests may be indicated following the repeat test and will be arranged by the CF team.
- Individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range (30-59mmol/L) on two separate occasions may have CF. They should be considered for extended CFTR gene analysis and/or CFTR functional analysis.
- **NORMAL:** A sweat chloride concentration less than 30mmol/L is considered within the normal range and indicates that CF is unlikely.
- Sweat chloride is the only analyte utilised for the diagnosis of CF. Sweat conductivity measurement alone is NOT an adequate diagnostic test for the investigation of CF and is only considered a screening test for CF. Conductivity will only be measured upon request by respiratory paediatrician. It is not appropriate to undertake a conductivity test following a positive NBS.
- Elevated sweat chloride levels can occur in other conditions, (see Appendix D: Conditions (non-CF) with an elevated Sweat Electrolyte Concentration)

12 Training Requirements and Quality Control

Sweat Collecting Staff Training and Annual Assessment of Competence

- Annual training and assessment is required for all nursing staff involved in performing sweat tests.
- Each person trained to carry out sweat testing should perform at least 10 sweat tests annually and detailed training records must be documented.
- Assessment and training can be facilitated by the CF CNC/ COPD NUM/COPD Educator (page 44903)
- Training and annual assessments should be documented by the COPD NUM / COPD Educator and provided to the CF CNC (Sweat Test Training Log, confidential electronic copy).
- Training is based on knowledge and performance of sweat testing as illustrated by the Sweat Testing SOP (See: Appendix B)
- New nursing staff must be trained prior to performing sweat tests.
- Facilities should be available to treat anaphylaxis (Refer to: Anaphylaxis Guidelines).

Recording of Quality Control Data

The following parameters will be recorded on a Sweat Testing Database by the laboratory staff and emailed to the CF CNC so that results can be reported to the Respiratory Departmental Team Meeting:

1. Number of test performed by each approved sweat collector (ideally > 10/year).
2. Number of insufficient samples (ideally under 20% for infants less than 6 months and <5% for older infants/children).
3. Number of patients seen by Genetic Counsellor.
4. Number of insufficient (QNS) samples per individual collector.
5. Number of failed sweat tests due to lab technical issues.
6. Percentage of positive, negative and intermediate results.
7. Whether “Intermediate” results were discussed with CF Consultant on-call and documentation of action taken. Correlation of repeat test when initial test was intermediate
8. Correlation of result with patient clinical features and genotype.

13 References

1. Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK (Version 2) An Evidence based Guideline, 2014
2. LeGrys VA, Gibson LE, Hammond RB et al. Sweat Testing: Sample Collection and Quantitative Chloride Analysis; Approved Guideline-Third Edition C34-A3. Clinical and Laboratory Standards Institute
3. Farrell PM, White TB, Ren CL et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr 2017;181S:S4-15.
4. Massie J, Greaves R, Metz M et al. Australasian Guideline (2nd Edition): an Annex to the CLSI and UK Guidelines for the Performance of the Sweat Test for the Diagnosis of Cystic Fibrosis. Clin Biochem Rev 2017;38:115-130
5. Cirilli N, Southern KW, Barben J et al. Standards of care guidance for sweat testing:phase two of the ECFS quality improvement programme. J Cust.Fibros.2022;21:434-441.
6. Philip M. Farrell, Terry B. et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation, The Journal of Pediatrics, Volume 181, Supplement, 2017, Pages S4-S15.e1,ISSN 0022-3476.

Appendix A: Indications for Sweat Testing

1. Pulmonary and Upper Respiratory Tract Indications

- Chronic cough
- Recurrent or chronic pneumonia
- Wheezing*
- Hyperinflation*
- Tachypnoea*
- Retractions or increased work of breathing*
- Atelectasis
- Evaluation and prior to initiation of CFTR modulator therapy

2. Gastrointestinal Indications

- *In-utero* echogenic bowel
- Meconium ileus
- Meconium plug syndrome
- Prolonged neonatal jaundice
- Failure to thrive
- Steatorrhea
- Rectal prolapse
- Mucoid impacted appendix
- Distal intestinal obstruction syndrome
- Recurrent intussusception
- Cirrhosis
- Portal hypertension
- Recurrent acute and chronic pancreatitis

3. Metabolic and Other Indications

- Positive family history
- Positive newborn screening test result
- Presence of two CF-causing mutations
- Salty taste to skin
- Salt crystals on skin
- Salt-depletion syndrome
- Pseudo Bartter Syndrome
- Metabolic alkalosis
- Hypoprothrombinemia
- Vitamin A deficiency (bulging fontanelle is a key sign)
- Azoospermia
- Absent vas deferens
- Scrotal calcification
- Hypoproteinemia
- Oedema

* *If persistent or refractory to usual therapy.*

Appendix B: Standard Operating Procedure (SOP)

SOP for Sweat Testing in Children using the WESCOR MACRODUCT SYSTEM ® *

**Based on Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK: An Evidence Based Guideline*

Introduction:

Cystic fibrosis is the most common life threatening genetic disease.. The primary defect affects chloride ion and water transport across epithelial cell membranes, resulting in excessively dry and viscous secretions. The major clinical presentations are recurrent respiratory infections, pancreatic insufficiency and failure to thrive. The elevated concentration of chloride ions in sweat is the basis of the diagnostic "Sweat Test" for cystic fibrosis.

Principle:

Pilocarpine is delivered to a small area of skin, rich in sweat glands, by iontophoresis. Sweat stimulated by this process is collected directly into a Macroduct disc and sent for chloride analysis.

Precautions:

Pilocarpine **(TOXIC)**, Sweat **(BIOHAZARD)**, Electrode contact **(BURNS)**

Wash hands before and after procedure. Avoid chloride containing antiseptic solutions. If Pilocarpine comes into contact with eyes, mouth or large areas of skin, flush the area with large amounts of water.

Check electrodes before each test and replace any if they show signs of pitting or buckling. Do not use Pilogel discs that are cracked, show any signs of deterioration or have expired (check expiry date). Never leave the patient/child alone at any time during iontophoresis and investigate any complaints of "stinging" or "burning" immediately. At the end of the test the stimulated area should appear red. If there is any evidence of blistering or burning seek urgent medical assistance.

Patient and Specimen Requirements:

Reliable Sweat Test results are most likely to be achieved if an experienced operator performs the test. ONLY staff that have been trained in the use of the Wescor system should perform this test. (Need to perform a minimum of 10 tests per year and undergo annual assessment). The sweat test should be deferred in babies < 7 days old and/or < 2kg in weight, subjects who are dehydrated, systemically unwell or who have marked eczema or oedema. Sweat tests should not be performed in subjects who are on oxygen by an open delivery system (this does not apply to headbox or nasal prong oxygen).

Instrumentation and Apparatus:

1. Wescor sweat collection system (Model 3600, 3700 etc). Check the following components
   - (a) Power supply box (also charging stand and transformer if using model 3600)
   - (b) 2 iontophoresis electrodes (red and black) each with Velcro strap
   - (c) Velcro straps in different sizes, to fit Macroduct

2. Sealable tubes or cups for sweat transport and storage. E.g. Specimen yellow top container, Autoanalyser cups and caps, 100µL Haematocrit capillary tubes and Plasticine Miniseal block.
3. Mediswabs
4. Kleenex medical wipes or cotton wool balls
5. Adhesive patient medical record labels for sample identification.

Reagents

1. Macroduct Test Kit. Chemlab Cat no WE55032 consisting of 12 Pilogel discs and 6 collectors. Must be stored in a Temperature Monitored Refrigerator

   Distilled or deionised water in wash bottle.

Procedure

1. Visually check condition of power pack, connections and electrodes. Carry out any routine maintenance described in the instrument manual.
2. Explain the procedure to the patient/parents. Provide a Sydney Children's Hospital Sweat Test Fact Sheet to the parents. (Parents may have received a leaflet with their appointment).
3. Pour distilled or deionised water into clean container and soak the gauze.
4. Ask parent/guardian to remove child's clothes to expose arm or alternative collection site.
5. Select sites for iontophoresis. The inner surface of the forearm is almost always the most satisfactory site. Either arm can be used. The skin should be hairless and wrinkle free and should not be broken or irritated. In very small babies, with insufficient area on the forearm, the upper arm or outside of the thigh may be used as collection sites.
6. Swab the area selected with a Mediswab, and then with a gauze soaked in distilled or deionised water. Dry with a clean gauze.
7. Moisten the skin with a fresh gauze dampened with distilled or deionised water to ensure good current flow.
8. Place a Pilocarpine gel disc on top of each electrode and rotate the disc to ensure good contact.
9. Strap both electrodes in position. Sweat collection will take place at the red (positive) electrode site. Select this site to give the best possible contact for the Macroduct, i.e. farthest from wrist, on the area with best subcutaneous tissue. Ensure the electrodes are at least 2 cm apart to prevent any bridging of current on the skin surface between them. If necessary the negative electrode may be placed on the outer surface on the forearm, or on the upper arm.
10. Follow the manufacturer's instructions for performing the iontophoresis. Although the principle is the same for all versions of the Wescor power supply, the details may vary

slightly. The instructions below are an example and may not apply to your particular unit. Example for the 3600 SYSTEM:

(a) Plug 3600 unit into charger unit in case. Connect transformer to unit and to power supply. Wait for status light to change to green.

(b) Remove 3600 unit from charger. Plug electrodes into 3600 unit and press start button. "In Process" should light immediately and current flow light come on dimly at first.

(c) If "chirrup" alarm sounds either:

i. There is a break in the circuit or

ii. The power supply is inadequately charged.

Action is the same in both cases.

Recharge power supply (chirrup will stop when power supply is returned to charger).

Check electrode attachments.

(d) After iontophoresis is complete "chirrup" will sound briefly and "In Process" light will go out.

11. Remove electrodes from arm. Usually the stimulated area is visibly pink or red. Swab area under red (positive) electrode thoroughly using gauze soaked in distilled or deionised water. Do this at least three times and then dry the area with gauze.

12. Open packet containing Macroduct. Keeping surface covered with polythene, thread Velcro strap through (NB furry side faces OUT).

13. Immediately strap Macroduct firmly into position on patient's arm over stimulated area. Be careful not to nip skin when tightening. For small babies or other subjects who may disturb the collection, strap Macroduct into position with elastic bandage.

14. Roll down child's sleeve and leave Macroduct in position for 20 min. It may be left longer if insufficient sweat (less than 2 turns = approximately 15microlitres (µL)) has collected after 20min but **should never be left longer than 30 minutes.** Extending the collection time beyond 30 minutes **does not** increase the weight of sweat collected by a significant amount.

15. Label specimen container with patient name and medical record number, or place patient identification label sticker on specimen container. Record collection time and the length of collection on the laboratory request form.

16. Carefully remove the Macroduct from the patient, removing the Velcro/Coban straps. Place the Macroduct in the labelled specimen container and transport to pathology for immediate analysis. Do NOT squeeze the dispenser tubing as this may cause loss of sweat.

17. The minimum acceptable volume of sweat, corresponding to 1g/m^2/min is approximately 15-18 µL for a 30 minute collection. This may be assessed approximately using the insert from the Macroduct packs. Assess sweat samples for adequacy immediately after collection. **Collections of less than 15µL will not be analysed.** Insufficient

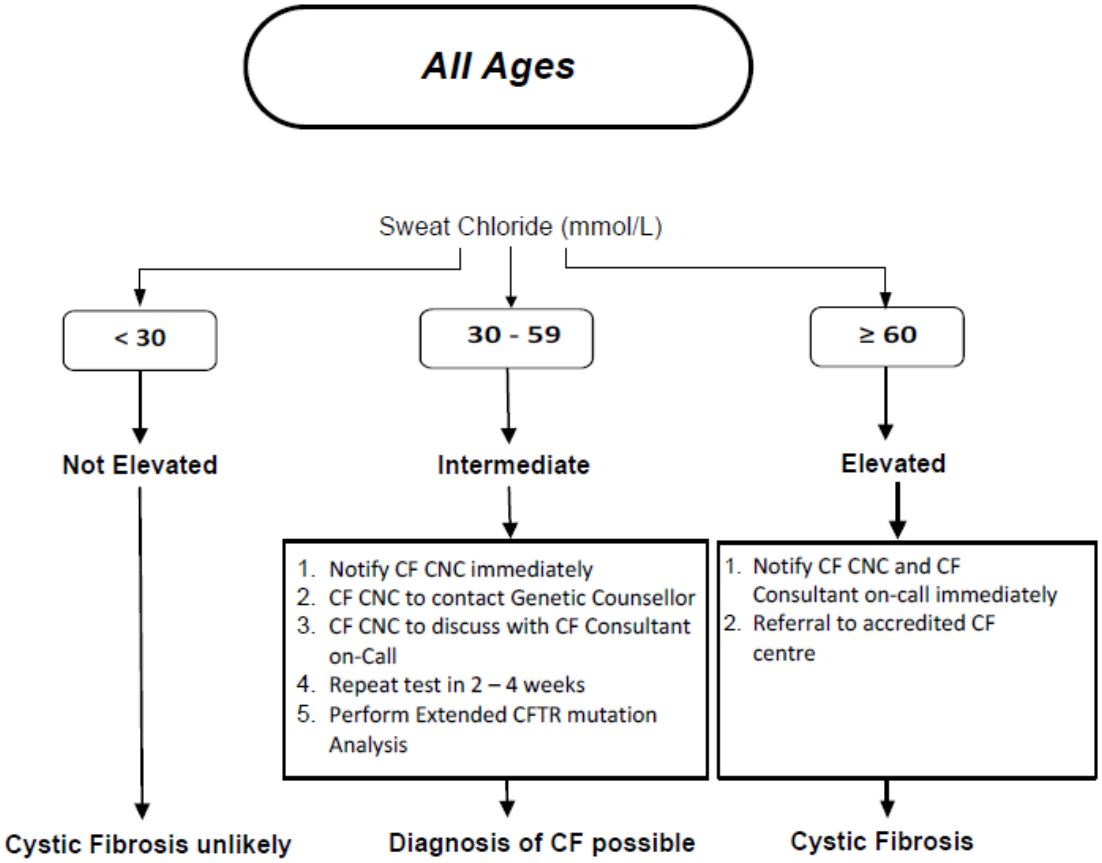
sweat collections should not be pooled to provide sufficient volume for analysis. The full sweat test should be repeated.

18. Lab will assess approximate volume of sweat and analyse accordingly.

- Volumes less than 15µL will be reported as insufficient.

19. Analysis should be carried out immediately and the result authorised and available on the same day.

Appendix C: Sweat Chloride Interpretation



- Sweat Chloride concentration of ≥ 60 mmol/L is indicative of CF
- Chloride Concentration of 30-59 mmol/L i is an intermediate result, requiring repeat sweat testing and further genetic testing
- Sweat Chloride of < 30 mmol/L makes CF unlikely but may require genetic counselling of carrier status.

Appendix D: Conditions (non-CF) with elevated Sweat Electrolyte Concentration

Reported Diseases or Conditions other than CF associated with an elevated Sweat Electrolyte Concentration (from US National Committee of Clinical and Laboratory Standards).

- Adrenal insufficiency.
- Anorexia nervosa.
- Atopic dermatitis.
- Autonomic dysfunction.
- Coeliac disease.
- Familial cholestasis.
- Fucosidosis type 1.
- Glycogen storage disease type 1.
- Hypogammaglobulinaemia.
- Hypothyroidism.
- Keratitis, ichthyosis, deafness (KID) syndrome.
- Mauriac's syndrome (malnutrition of).
- Protein-calorie malnutrition.
- Pseudohypoaldosteronism.
- Psychosocial failure to thrive / Environmental deprivation.
- Systemic lupus erythematosus.
- Triosephosphate isomerase (TPI) deficiency.