



Newborn Screening and Diagnostic Protocol for Cystic Fibrosis in New Zealand

Newborn infants have been screened for cystic fibrosis (CF) as part of the Newborn Metabolic Screening Programme (NMSP) since 1986¹⁻³. This protocol is for infants not at known increased risk for cystic fibrosis. Infants at increased risk (for examples close family members with CF, infants with meconium ileus) proceed straight to diagnostic testing.

This is done by a two-tier system from the newborn bloodspot.

Tier 1: Measurement of immunoreactive trypsin (IRT).

Tier 2: If the IRT level is in the highest 1%, this is followed by genetic analysis using a limited panel of the most common CF genetic mutations in NZ.

A positive CF screen is then notified if one of these CF mutations are identified in the bloodspot. A positive CF screen means the child is either a carrier, has CF (approximately 20%) or is CFSPID (cystic fibrosis screen positive, inconclusive diagnosis)

Figure 1: Newborn screening protocol for cystic fibrosis in New Zealand

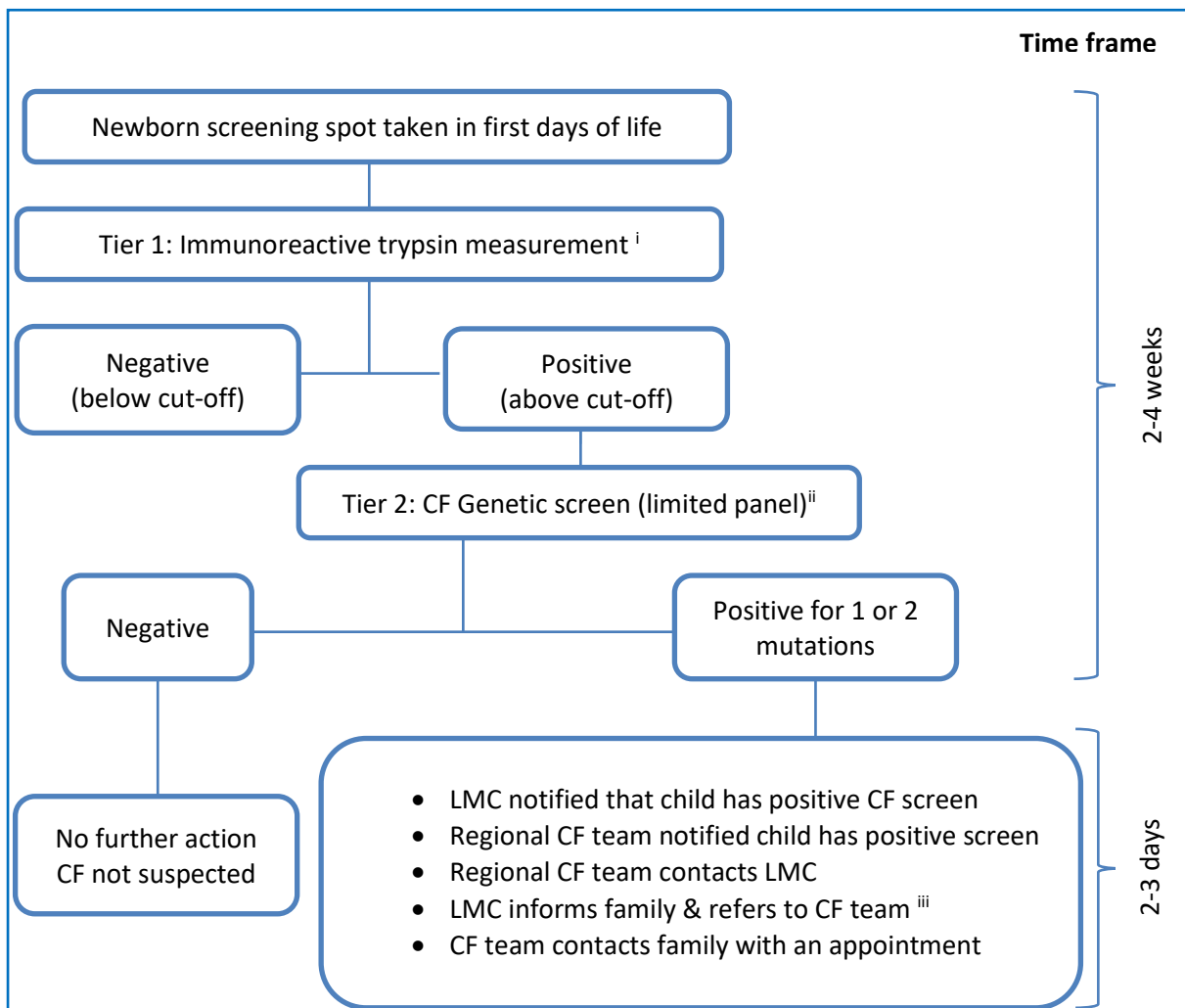
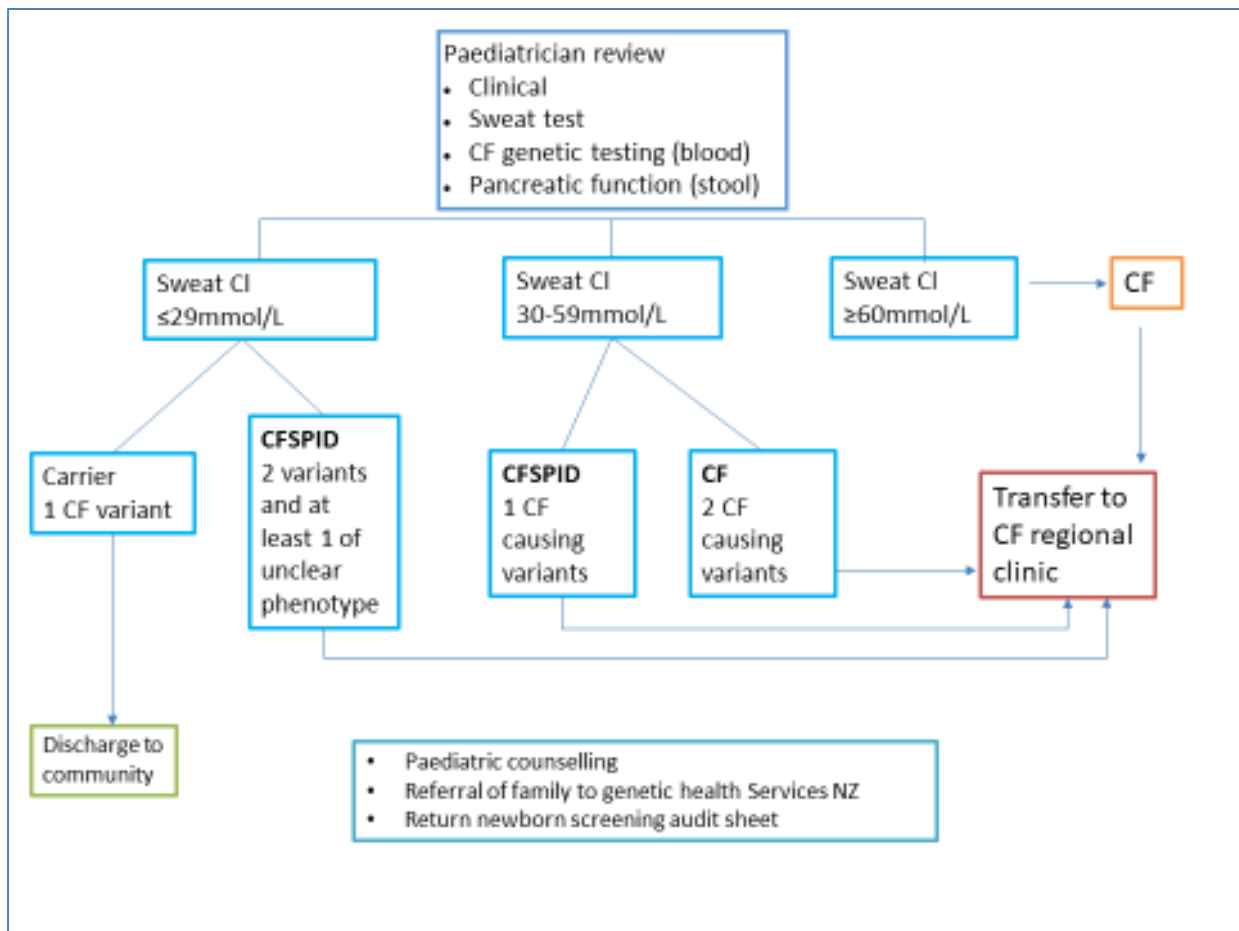


Figure 2: Newborn diagnostic protocol for cystic fibrosis in New Zealand



ⁱ Infants that have meconium ileus often have a low IRT and are missed by newborn screening. All children with meconium ileus should have CF genetic mutation analysis and a sweat test organised regardless of the newborn screening result.

ⁱⁱ The exact nature of the second tier testing has changed over time. From 2015, it has been done with genetic sequencing of the CFTR region exons 10 & 11 which cover the most common three genetic mutations seen in NZ (F508del or c.1521_c.1523delCTTT, G551D or c.1625G>A, G542X or c.1624G>T) and other rare mutations. This step may remain subject to change. *NOTE: The report to lead medical teams will remain the same regardless of exact Tier 2 technique – that is, a positive screen that includes one or two CF causing genetic mutations has been found in an infant.*

ⁱⁱⁱ The Newborn Metabolic Screening Programme testing centre notifies the lead maternity carer (LMC) and the nominated regional CF paediatrician or nurse. The nominated CF team member contacts the LMC and they plan to inform the family. The LMC informs the family, giving the family information sent by the newborn screening testing centre, and refers the child to the regional CF paediatrician. The nominated CF team member (usually the paediatric nurse) at each hospital will receive the referral, contact the family and organise review with the CF paediatrician. *NOTE: The aim is to have the shortest time possible between the family being told their baby has a positive screen for CF, and the assessment by the regional CF paediatrician. Same day contact with the family – first by the LMC then the CF team – is ideal, with the first review taking place within two days.*

^{iv} A sweat test can be done from 1 week of age onwards in a child with a weight >2kgs⁴. The main issue in the very young infant is obtaining adequate sweat weight and waiting till >3kgs will improve the first time success rate. Using the traditional Gibson-Cooke method a sweat weight of 75mg is needed⁵, using the newer Wescor Macroduct® system a sweat of 15µL is needed⁶. Not all regional paediatricians have immediate access to sweat tests⁷. The initial assessment may be clinical review, stool sample for pancreatic function (elastase) and blood genetic mutational analysis in the first instance while a sweat test is booked inter-regionally .

^v The access to this test is variable. Some areas perform sweat tests locally, elsewhere the test is either conducted locally and sent to a second region for analysis, or the child needs to travel to another centre for testing. There are three potential delay time points. Firstly the availability of sweat tests – offered a number of times per week in the centres, offered sometimes only once every four weeks in the regions. Secondly is when the result becomes available once testing is done – usually within 48 hours if done locally, up to one week if sent elsewhere. Thirdly the age at testing – in some units it has been done when the child is 6 weeks of age and >5kgs to maximise the chance of getting adequate sweat weight and a test result. Also if the child has to attend another centre, this is dependent on family timing and ability to travel, often occurring at weeks to months of age. The sweat test should be considered a priority and the child remain under review until a result obtained.

^{vi} The CFTR genetic analysis on the blood from the infant is a diagnostic test and uses a wider panel than the screening test to detect the presence of a range of genetic mutations – panels used in New Zealand are 31 and 52 CFTR mutations depending on the laboratory with both including the 23 mutations recommended by the American College of Medical Genetics with results usually available in one to two weeks.

^{vii} CFSPID is an asymptomatic infant with a positive new born screen result for CF and either a sweat chloride value <30mmol/L and two CFTR variants at least one of which has unclear phenotypic consequences, or an intermediate sweat chloride value (30-59 mmol/L) and one CF causing variant²⁰. (The global definition of CFSPID includes infants with an intermediate sweat chloride and zero CF causing variants but this scenario would not occur with the current screening protocol in New Zealand).

**See guidelines on management of CFSPID

[Cystic fibrosis screen positive, inconclusive diagnosis \(CFSPID\) \(starship.org.nz\)](http://starship.org.nz)

^{viii} Siblings of children diagnosed with CF: those with symptoms need prompt sweat testing with their own CF genetic mutational analysis if positive or intermediate sweat chloride levels determined; those without symptoms should have a sweat test when possible. This is regardless of their own newborn screening result.

^{ix} There is evidence of improved outcomes in children with early diagnosis of CF subsequent to newborn screening⁸⁻¹¹ including before 2 months of age¹².

^{xi} Regardless of outcome - the family is offered counselling – initially this may be done by the local paediatrician but all families should be referred to Genetic Health Services New Zealand for counselling on future pregnancies and cascade testing to extended family members as appropriate.

^{xii} Letters regarding the clinical review and test results will be sent from the CF paediatrician to the LMC and the family's general practitioner, usually with a copy to the family.

Children missed on newborn screening or born abroad

About 8% of children with CF are missed on newborn screening (low IRT, no CFTR genetic mutations detected, other reason for no or incorrect testing, born abroad in country without CF newborn screening). This means some children will require investigations for CF at a later age.

Please notify the screening programme of all patients diagnosed with CF who were missed on newborn screening as this allows potential modifications to the protocol, particularly regarding variants tested for. The newborn screening duty scientist can be called within working hours on 021745847 or emailed at nmsp@adhb.govt.nz

Initial clinical review

The history and/or examination may raise suspicions of a possible CF diagnosis but by the time of initial review most children remain healthy. Concerns would be early respiratory infections and failure to thrive with steatorrhoea, frequent and prolonged feeding (but many affected children at this early age will be indistinguishable from carriers).

- In a baby, CF should be excluded with; meconium ileus, rectal prolapse, salty tasting skin, prolonged obstructive jaundice, and unexplained haemolytic anaemia with hypoalbuminaemia.
- In an older child or young adult, CF is possible with: recurrent respiratory infections, nasal polyps, severe sinusitis, presence of clubbing, failure to thrive, abnormal bowel habit or recurrent abdominal pain with no other explanation.
- The isolation of *pseudomonas aeruginosa* in particular, and *staphylococcal aureus* repeatedly from respiratory tract secretions is suspicious.

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