THE PATHCARE NEWS

NEW CYSTIC FIBROSIS 50 VARIANT PANEL

PathCare is pleased to offer a cystic fibrosis (CF) panel of 50 *CFTR* gene variants (CF 50 panel). This panel includes the common South African variants, commonly known as delta F508 and 3120+1G>A.

The CF 50 panel is more comprehensive and more informative than testing for a single variant (e.g. delta F508), AND more affordable than full *CFTR* gene sequencing (~half the cost). There is also the advantage of a quick turnaround time of 2-3 weeks vs 6-8 weeks for full *CFTR* gene sequencing.

As from 12 August 2024, all delta F508 requests will be transferred to the CF 50 panel.

If there is a strong clinical suspicion (e.g. positive sweat chloride test) for CF following a negative CF 50 panel or if the CF 50 panel only picks up one *CFTR* variant (heterozygous), then more comprehensive *CFTR* testing (full *CFTR* gene sequencing) would be indicated to confirm a molecular diagnosis.

PathCare currently offers a local, as well as an international referral service for full *CFTR* gene sequencing. Please see our lab update on cystic fibrosis for more clinical details.

CF 50 panel variants included:

Traditional/ Legacy name of CF variants tested		
CFTRdele2,3	I507del	2789+5G>A
E60X	F508del	Q890X
P67L	1677delTA	3120+1G>A
G85E	V520F	3272-26A>G
394delTT	1717-1G>A	R1066C
444delA	G542X	Y1092X(C>A)
R117C	S549R(T>G)	M1101K
R117H	S549N	D1152H
Y122X	G551D	R1158X
621+1G>T	R553X	R1162X
711+1G>T	R560T	3659delC
L206W	1811+1.6kbA>G	3849+10kbC>T
1078delT	1898+1G>A	S1251N
R334W	2143delT	3905insT
R347P	2184delA	W1282X
R347H	2347delG	N1303K
A455E	W846X	* 3 x poly TG tract alleles

Please feel free to contact our Genetics Team if you have any questions on:
(021) 596 3655 or geneticconsult@pathcare.net

THE PATHCARE NEWS

GENETIC TESTING FOR CYSTIC FIBROSIS

Cystic fibrosis (CF) is an autosomal recessively inherited genetic condition that primarily affects the epithelia of the respiratory tract, exocrine pancreas, intestine, hepatobiliary system, and exocrine sweat glands, causing sticky, thick mucus to build up in these organs, particularly in the lungs and pancreas.

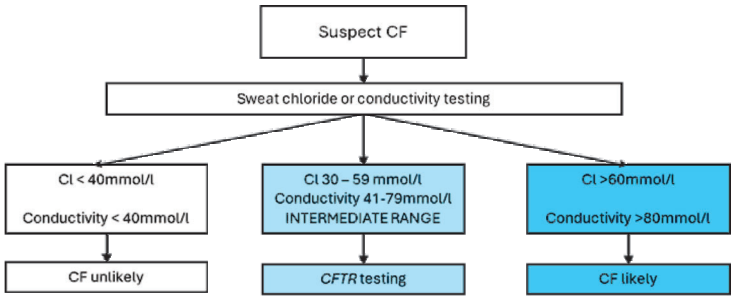
Genetics

CF is caused by disease causing (pathogenic) variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. An individual with CF will have two pathogenic variants in their *CFTR* gene – one inherited from each parent. Full siblings of an individual with CF will have a 25% chance of also having CF. More than 2000 *CFTR* variants have been identified; however there are two variants that are more common in the South African (SA) population: **delta F508** (prevalence of 76%) and **3120+1G>A** (prevalence of 46%) [1].

Diagnosis

The diagnosis of CF is established in an individual with one of the following:

- Positive newborn screen
- Signs and/or symptoms suggestive of CF (see below)
- Family history of CF in a first-degree relative (typically a sibling)



AND one of the following:

- Elevated sweat chloride value ≥60 mmol/L on sweat chloride testing
- Identification of two *CFTR* pathogenic (or likely pathogenic) variants via molecular genetic testing

Table 1: Findings suggestive of CF

Clinical findings	
Pulmonary	Chronic wet or productive cough, recurrent pneumonia, bronchiectasis, nasal polyposis
Pancreatic	Exocrine pancreatic insufficiency, recurrent pancreatitis
Intestinal	Meconium ileus, rectal prolapse, distal intestinal obstructive syndrome, steatorrhea
Infectious	Respiratory infection with Pseudomonas aeruginosa or other atypical gram-negative organisms, allergic bronchopulmonary aspergillosis
Nutritional/metabolic	Poor weight gain, growth deficiency
Musculoskeletal	Digital clubbing
Hepatic	Protracted neonatal jaundice, biliary cirrhosis
Genitourinary	Obstructive azoospermia
Laboratory findings	Hyponatremia, hypochloremia, hypokalemia, hypoproteinemia, chronic metabolic alkalosis, deficiency of fat-soluble vitamins

Differential diagnosis

Genetic disorders of interest in the differential diagnosis of CF include:

- Primary ciliary dyskinesia
- X-linked agammaglobulinemia
- Common variable immunodeficiency
- Isolated hyperchlorhidrosis
- Shwachman-Diamond syndrome
- X-linked severe combined immunodeficiency
- Pseudohypoaldosteronism type I

NEWBORN SCREENING

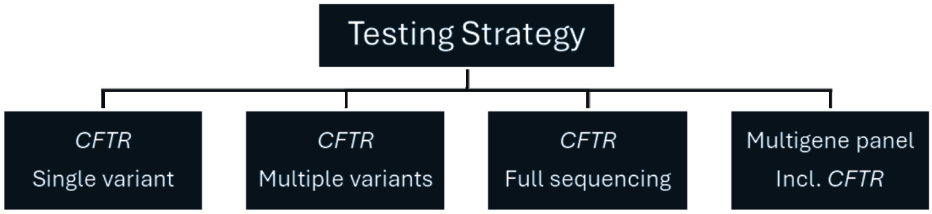
Newborn Screening (NBS) is a blood test that requires only a few drops of blood, collected 1-3 days after a baby's 1st feed. NBS tests for a group of disorders called inborn errors of metabolism (IEM), some endocrine disorders and CF. Infants with CF have increased immunoreactive trypsinogen (IRT) levels on NBS; however, IRT levels is a screening test only and follow up with definitive testing is needed.

SWEAT CHLORIDE TEST

The sweat chloride test is the gold standard for diagnosis of CF. It checks for increased levels of salt in the sweat. A clinical work up for suspected CF should **always** start with a sweat chloride test, where possible. Neonatal use of a sweat test may be limited by nasal oxygen and prematurity. Reliable sweat chloride tests are available in the main cities in SA.

Genetic testing for CF

There are various approaches to genetic testing for CF including single variant, multivariant, single gene and multigene panel testing:



When a diagnosis of CF is suspected, a panel approach, or full *CFTR* gene sequencing, whereby many variants are tested simultaneously, is recommended.

LOCAL testing for CF

(The benefit of local testing is that medical aid may cover the cost of testing)

- **CF 50 panel:** Multiple variant testing that analyses 50 frequently detected *CFTR* variants, including the common SA variants, delta F508 and 3120+1G>A. This testing is more comprehensive and informative than testing for a single variant (e.g. delta F508), but more affordable than full *CFTR* gene sequencing and has the advantage of a quick turnaround time (2 – 3 weeks).
    - If the CF 50 panel is negative, or only picks up one *CFTR* variant, and a strong clinical suspicion of cystic fibrosis remains (e.g. positive sweat chloride test), then full gene sequencing of the *CFTR* gene would be indicated.
- **Full *CFTR* gene sequencing**: most comprehensive *CFTR* gene test

International send-away testing

PathCare offers an international referral service to Invitae in the USA and Centogene in Germany. Both laboratories offer multigene panels that test for several genes simultaneously, including *CFTR*.

Table 2: Quick guide to testing

	LOCAL		INTERNATIONAL	
Laboratory	**PathCare**		**Invitae**	**Centogene**
Location	South Africa		United States of America	Germany
Description	**CF 50 variant panel**	*CFTR* full gene sequencing	Single gene: • Invitae Cystic Fibrosis Test (*CFTR* gene only) Multigene panels that include the *CFTR* gene, e.g.: • Primary Ciliary Dyskinesia Panel (~42 genes) • Cholestasis Panel (~136 genes) • Inborn Errors of Immunity and Cytopenias (~574 genes)	Multigene panels that include the *CFTR* gene: • Pancreatitis Panel (~29 genes) • Pulmonary Panel (~101 genes) • CentoNephro Panel (~504 genes)
TAT	2 - 3 weeks	6 – 8 weeks	~3 – 4 weeks	~ 6 weeks
Cost	Medical aid quotations can be requested		USD 399* + Handling fee R1000*	From USD 435* + Handling fee R750*
Advantage	Medical aid may cover the cost		Free family testing for 150 days after index report	

** Pricing is correct and valid for 2024. Costs are subject to change. Please contact the PathCare genetics team for confirmation of current prices.*

Genetic counselling

It is internationally recognised and strongly recommended that genetic testing be offered in the context of appropriate pre- and post-test genetic counselling by a genetics professional. PathCare can provide you with contact details for genetic counsellors in SA. Please contact our Genetics Team for a list of HPCSA-registered genetic counsellors who you can refer your patients to for a consultation.

Please feel free to contact our Genetics Team if you have any questions on:
(021) 596 3655 or **geneticconsult@pathcare.net**

References:

1. Zampoli, M., Verstraete, J., Frauendorf, M., Kassanjee, R., Workman, L., Morrow, B. M., & Zar, H. J. (2021). Cystic fibrosis in South Africa: spectrum of disease and determinants of outcome. ERJ open research, 7(3), 00856-2020. https://doi.org/10.1183/23120541.00856-2020
2. Savant A, Lyman B, Bojanowski C, et al. Cystic Fibrosis. 2001 Mar 26 [Updated 2023 Mar 9]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1250