Cystic Fibrosis (CF) is one of the commonest life-shortening autosomal recessive diseases in Caucasian populations, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Aggressive treatment of lower respiratory tract infections and nutritional support are the cornerstones of management and are required lifelong following diagnosis. The therapeutic landscape is being transformed by treatments which target the underlying molecular defect in CFTR; however these remain prohibitively expensive for many healthcare organisations and patients worldwide.

CFTR has many actions, and in the airways it plays a crucial role in regulation of chloride ion transport across epithelial cells. Dysfunctional or absent CFTR results in altered airway hydration and impaired mucociliary clearance, with inflammation and chronic infection leading to progressive lung disease. As a marker of CFTR function, measurement of chloride concentration in sweat is of pivotal importance in diagnosing CF. The sweat test, first described in 1959(1), remains the gold standard for diagnosis and international recommendations state that diagnoses associated with CFTR mutations be established by evaluation of CFTR function with a sweat chloride test(2).

In the UK the incidence of CF is around 1:2500 live births, and average life expectancy is 47 years with a median age at death of 31 years(3). Across the globe, many countries with a relatively high prevalence of CF (Europe, North America and Australasia) have population-wide CF screening programmes for asymptomatic newborn infants. Despite a lower carrier frequency, CF is increasingly recognised in people from the Indian subcontinent and is likely to be both underrecognised and underdiagnosed.

In this issue, Singh and colleagues publish results of a single centre study evaluating the detection of ‘aquagenic wrinkling’ as a screening test for cystic fibrosis (CF)(4). The terminology used is important. Wrinkling of the palms after water immersion is a normal physiological response,
occurring in health after an average of 11.5 minutes (5). In contrast, aquagenic wrinkling of the palms (AWP) is a rare dermatosis characterised by rapid excessive skin wrinkling and white papules on the palms within three minutes of immersion in water. The majority of case reports for AWP in the literature are from European populations, however it has also been reported in India (6). It is known to be associated with CF (in children and adults), and in CF carriers (7, 8). Singh suggests that immersion of the hands in water to test for ‘aquagenic wrinkling’ could be used as part of the diagnostic work up in children with symptoms consistent with CF, as a positive test results in a higher likelihood of confirming a diagnosis of CF on a subsequent sweat test. It was back in 1974 that Elliot first suggested that ‘three minutes and a bowl of water might provide a cheap screening test’ for CF (9).

In the literature, the proportion of patients with CF with AWP is reported to be between 41% and 84% (8, 10, 11). Singh et al (4) report a prevalence of aquagenic wrinkling of 81% within 3 minutes and 95% within 5 minutes. Gild et al (7) found that AWP occurs in around 25% CF carriers. Unexpectedly, Singh et al (4) found that time to skin wrinkling in ‘carriers’ was longer than in controls. The inclusion of ‘carriers’ in the study by Singh et al (4) introduces a number of variables which make it difficult to compare results between groups. As presumed heterozygotes for CFTR, the pragmatic ‘carrier’ group was made up of parents of the children with CF, who were therefore significantly older (median age 36 vs 9 years) aside from any additional variation introduced by an absence of mutation analysis. Further investigation of confirmed paediatric CF carriers in India will be crucial to understanding these results. In addition, the results in controls reported by Singh et al (4) (56% specificity for aquagenic wrinkling by 3 minutes) greatly contrasts with existing literature where time to skin wrinkling in controls is significantly longer, and Arkin et al reported 0% prevalence of AWP in 25 paediatric controls (8). The influence of ethnicity on time to skin wrinkling in controls is unknown. Non-CF causes of AWP should also be considered and it has been reported to occur with marasmus in infants (9), an important differential in India as despite decreasing prevalence it remains more common than CF.

The possibility of a minimal cost ‘screening test’ which can be performed outside the specialist setting is attractive, particularly as sweat testing requires technical expertise and is only performed in a small number of specialist centres across India. However the relatively poor sensitivity and specificity reported in this study preclude the use of AWP for whole population CF screening. Alternatively there may be a role for the test to assist diagnosis in symptomatic children. Should a simple ‘three minutes and a bowl of water’ test be used to improve estimates of the likelihood of a CF diagnosis in symptomatic patients lacking access to sweat testing and CFTR mutation analysis? Should it be used to ‘triage’ referrals to specialist centres (whereby patients with a positive test are
referred for sweat testing and those with symptoms but no AWP are not)? A negative result must not preclude referral for sweat testing in those with symptomatology consistent with CF, as some of these children will have CF. Children with recurrent respiratory tract infections and failure to thrive are at risk of long term illness and require close follow up, even if they don’t have CF. The availability of resources will likely dictate response – in an ideal world all children with clinical suspicion of CF would have a sweat test. However, given that in India this situation is some way off, Elliot’s test represents an extremely simple method of aiding clinical decision making when CF is considered clinically likely and yet referral for sweat test complicated by geographical, financial or access to appropriate expertise. However for accurate diagnosis and to improve population-wide data on the number of patients with CF in India, the goal must remain for definitive diagnostic testing. In an era of rapid progress with drugs which target the underlying molecular defect in CFTR, accurate diagnosis is increasingly important.

References