Clinical implications of cystic fibrosis

**P244** EXTENDED CFTR SCREENING FOR PATIENTS WITH A CLINICAL DIAGNOSIS OF CF BUT ONLY ONE GENE ON INITIAL SCREENING

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Introduction Standard CF genotyping only identifies 94% of CF genes, resulting in the emergence of a "cystic fibrosis screen positive, inconclusive diagnosis" (CFSPID) designation. This, and the advent of genotype-specific CFTR directed therapies has highlighted the need for more comprehensive genotyping, particularly to identify rarer genes when only a single gene is found on initial screening. However, extended CFTR screening is an expensive investigation and we wished to assess its use and yield.

Methods Between 2014 and 2016 we identified 40 people with CF attending our large regional adult unit without two known pathogenic CFTR genes and offered them extended CFTR screening. We looked at the yield in terms of additional genes identified and their clinical significance in 37 of these (3 refused/did not attend).

Results A new molecular diagnosis (i.e., two pathogenic genes) was made in 18 (48.5%) people with CF. Genes associated with CFTR related disorders were found in a further 2 (5.5%), genes of uncertain pathogenicity were found in 3 (8.1%), and one or no genes were found in 14 (37.8%). Of the 18 people with CF with additional identified genes, 8 had those associated with responsiveness to the CFTR potentiator ivacaftor (4 × 3272–26 A2G, 1 × 711+3 A2G, 1 × R347H, 1 × 2789+5G→A, 1 × S945L) and 2 of these (R347H and S945L) have recently been approved for ivacaftor use by the U.S. Food and Drug Administration.

Conclusions In people with a clinical diagnosis of CF but only one pathogenic gene on initial screen, extended CFTR screening identified a second gene in nearly half of cases. Furthermore, a significant proportion of the identified genes have been reported to respond to ivacaftor. It is therefore important that all people with CF without two known mutations undergo extended mutation screening in order to establish who may benefit should the current license for ivacaftor be expanded in the UK.