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Mini-symposium: CF in the age of modulators

Revisiting a diagnosis of cystic fibrosis – Uncertainties and considerations

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Educational Aims

The reader will be able to:

- Understand when the CF diagnosis should be revisited.
- Understand why the situation may have arisen.
- Know how best to broach the issue with the patient and family.

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ABSTRACT

There is now increased knowledge and experience of newborn screening around the world. There is also a better understanding of CF gene analysis, informed by international databases. This has resulted in a small number of children and adults having their diagnosis of CF reversed. This article illustrates this issue with three cases. It considers how best to tell children and adults with their families, and the reactions that may be encountered. It also discusses practical issues of removing the diagnosis.

INTRODUCTION

Usually when a patient and their family receive a diagnosis associated with multiple co-morbidities, burdensome treatments, and reduced survival, the reaction is understandably negative. This is commonly the reaction with cystic fibrosis (CF), a life-limiting genetic condition. There is growing recognition that retraction of this diagnosis can also evoke challenging emotions, driven by uncertainty and a loss of both the patient's and possibly the family's identity, and longstanding support networks.

This article discusses the issue of reversing the diagnosis of CF in children and young adults. It is focussed on patients for whom there may have already been diagnostic doubt, or where lack of symptoms results in diagnostic re-evaluation. This appears to be relatively rare but has increased in recent years. In our paediatric CF unit, out of 640 patients over the past 8 years, we have reversed the diagnosis in 11 (1.7%) children. This is largely due to advances in understanding of CF genetics, emergence of international databases of CF variants, and our experience gained from the UK newborn screening (NBS) program. Meanwhile the concepts of CF-Screen Positive Inconclusive Diagnosis [1], and CFTR-related disorders [2] have been established.

PAEDIATRIC CASE – *ILLUSTRATING THE UNCERTAINTIES ENCOUNTERED WHEN A CONCLUSIVE REVERSAL IS NOT POSSIBLE*

The baby had a normal immunoreactive trypsin on NBS in 2007, 4 months after the start of national newborn screening. She was referred aged 14 months with a history of an early chest infection followed by frequent cough and wheeze. She had slow weight gain but normal stools. Examination was unremarkable although her weight was 2-9th centile (height 25th centile). A chest radiograph was normal, stools had occasional fat droplets, sweat chloride was 30 mmol/L. Her parents had been told her CF gene analysis was normal. We said it was 'most unlikely she had CF'.

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Retrospective testing of the NBS sample identified the single p.Phe508del variant so the extended genotype was analysed. This identified 3 variants – p.Phe508del (c.1521_1523del); p.Thr582Ile (c.1745C > T, T582I); and 1249-27DelTA (c.1117-26_25delAT). The Regional Genetics laboratory indicated p.Thr582Ile was CF-causing whilst 1249-27DelTA was a variant of unknown clinical significance. Her parents were tested and one had p.Phe508del and 1249-27DelTA *in cis*, the other carried the p.Thr582Ile variant, confirming the child had the p.Phe508del and p.Thr582Ile variants *in trans*. The Regional Genetics laboratory concluded 'this result is likely therefore to provide a molecular confirmation of CF'. Her parents were informed she had CF.

Bronchoscopy showed a slightly narrowed right main bronchus, lavage isolated *H. influenzae* with neutrophilia (16%). Repeat sweat chlorides were normal at 26 and 24 mmol/L, stool elastase was normal (>500 mcg/g). She was started on co-amoxiclav prophylaxis and regular physiotherapy, and within 2 months her parents felt she was the best she had ever been. Over the next year she remained well, with negative cough swabs. At 3 years she had a ventilation scan showing a defect in the left upper lobe that cleared with 2 months of oral antibiotics. At 4 years she was having abdominal pain with constipation; weight had risen above the 90th centile. At 6 years prophylactic antibiotics were stopped, she was started on nebulised dornase alfa (our routine practice); FEV_1 was 104%. At 7 years, lung function drifted to the 80s with no response to azithromycin, so she had a bronchoscopy (RSV isolated). She had intravenous antibiotics and her lung function recovered.

At 8 years, we started to question the diagnosis as she remained so well, and a repeat sweat chloride was 23 and 24 mmol/L, stool elastase remained normal. By then the CFTR2 database was available but had no information about the 1249-27DelTA variant (same in 2021). This doubt was discussed with her parents, who did not want her to know immediately in case we changed our minds. Her parents were keen to continue physiotherapy (but with reduced frequency) as they felt it had been so beneficial in her early years; dornase alfa was stopped. She continued to see the same consultant but in a general respiratory clinic. Lung function remained normal (FEV_1 92%), with normal Lung Clearance Index of 6.77; weight on 90–98th centile.

She then had a nasal potential difference (NPD) test that was expected to be normal. She had a raised skin PD of −55 mV. She had a normal basal PD of around −19 mV, a delta amiloride of 11 mV but a very low chloride secretory response of ∼4 mV in total to zero chloride and Isoprenaline. Results were reviewed in the combined difficult diagnosis clinic to ensure consensus. The unanimous interpretation was that CFTR function within her airways was suboptimal, but not completely absent and may explain why she remains so well.

This was disappointing to her parents, and we state on clinic letters the diagnosis –

- No CF disease (normal sweat tests, no symptoms)
- Uncertainty about some aspects of CFTR function (abnormal nasal potential difference)
- CF genotype of uncertain significance

Over the next year, she developed occasional chest pains due to a breathing pattern disorder that resolved with physiotherapy support. She had constipation and abdominal discomfort that took a year or two to resolve. She also had intermittent headaches. She is now 13 years old and remains under 6–9 monthly follow up and is very well with a good level of exercise. We plan to repeat the NPD.

Box 1 The parents of this case have kindly set out their thoughts on this difficult process –

After seven years of physio, medication, and hospital visits, being told that our daughter might not have CF after all was a relief but, at the same time, unsettling. She had been so sick as a baby and within weeks of starting treatment she was happy, healthier than she had ever been and developing well – could we risk stopping that treatment? What if she deteriorated? Would we be to blame? If she stayed well, had we subjected her to this rigorous treatment regime for all these years for nothing? Having CF was a part of who she was, how would this change impact on her own sense of identity? We had always been scrupulous about maintaining her physio, twice every day, and this was just part of her life that she accepted, usually without any fuss; if we stopped, and it turned out she did have CF after all, how easy would it be for her to start again, having had that taste of freedom? All these questions were whizzing round our heads as we tried to make sense of what we were being told. We needed time to adjust and so did our daughter. We also wanted certainty – we didn't want to tell her, or stop the treatment, until we knew for sure that the situation would not change again. Life (and medicine) is never quite that simple though. Although she would have the NPD test, there was a long wait and so we tentatively reduced and then stopped the physio – hoping for the best but fearing the worse – and began trying to explain to the situation to her. She stayed well, and we felt able to relax.

Then, of course, came the blow of receiving the news that, contrary to all expectations, the NPD was abnormal, that the consensus was that the diagnosis could not be removed and that, whilst there was a good chance that she would remain healthy, there was also a chance that she would get sick again as she got older. This hit us quite hard as we once again had to face the prospect of an uncertain future.

Explaining the situation to others was also not easy. When she was admitted to our local hospital for emergency appendicectomy, the plan was to have 'key-hole surgery' until it was noted from her medical record that she had CF. When we tried to explain that she was well and that the diagnosis was being removed, the doctors smiled kindly, assuming we had misunderstood, and explained that 'CF isn't something that you get better from'. It continues to be difficult to explain the situation to others, including health professionals for whom this seems to go against everything they have learnt about CF.

Despite amazing support from the healthcare team, the last few years have been difficult for all of us with some real high points followed by some big lows – and an awful lot of confusion. Now things seem more settled – we realise there is uncertainty but that's just the way it is. We are delighted that she is extremely well now and can live a 'normal' life and we remain hopeful that she will stay that way".

PAEDIATRIC CASE – *ILLUSTRATING AN EASIER DECISION TO REVERSE THE DIAGNOSIS WHEN A DESIGNATION OF CF-SPID IS MORE APPROPRIATE*

A male infant born in 2008 was positive on NBS (IRT 167 mg/L and p.Phe508del/*Asp1152His*). Sweat chlorides were 12 and 16 mmol/L and stool elastase confirmed pancreatic sufficiency (443 mcg/g). He was diagnosed with CF with a likely good prognosis. At that time, our practice was to perform bronchoscopy for surveillance within the first few years of life; this revealed a neutrophilia (>50%) but no cultured pathogens. Over the next few years, he had several positive cultures of *S. aureus* and

P. aeruginosa, the latter treated with oral and inhaled antibiotics. Spirometry remained normal (>100% predicted) as did lung clearance index. At the age of 9 years, based on very good health and increasing understanding of his mutation (*Asp1152His* was categorised on CFTR2 database as a variant of variable clinical consequence rather than definitively CF-causing), his diagnosis was revisited: most recent sweat test still showed chlorides of 16 and 17 mmol/L. Nasal potential difference demonstrated raised basal (−60 mV) and amiloride response (40 mV) but preserved chloride secretion (total −12 mV). In the context of his good health, normal sweat tests and chloride phase of nPD, we considered a CFSPID label more appropriate. He had CF treatments gradually withdrawn and remains clinically well under follow up in the general respiratory clinic.

ADULT CASE – *ILLUSTRATING HOW DIFFICULT THE REVERSAL IS FOR AN ADULT FOLLOWING DECADES OF BELIEVING THEY HAD CF*

A 41 year old woman re-presented to our CF service after being lost to follow-up for six years. Her original presentation was as an infant with failure to thrive, loose stools and recurrent lower respiratory tract infections. Aged 7 years (pre-dating the discovery of *CFTR*), her family was told she had CF based on an abnormal sweat test (sweat sodium of 48 & 70 mmol/L). Her height and weight were on the 75th centile. When genotyping became possible, aged 19 years, she was found to carry the p.Phe508del variant with no second mutation identified (on a limited CFTR panel). Her weight had increased to 79.4 kg (BMI 27.5 kg/m^2) – her fat soluble vitamin levels were within the normal/high range (faecal elastase not checked due to weight gain and absence of steatorrhoea). At that point the term 'mild CF' was used. Sputum cultures were intermittently positive for *Staphylococcus aureus* and *Haemophilus influenzae* but she remained stable, with excellent lung function (FEV_1 3 L; 89%). Her sweat test was repeated (sodium 48 and 40 mmol/L). When she returned to our service aged 41 years her weight had increased further to 116 kg (BMI 40.1 kg/m^2) and her lung function was stable. She still produced sputum (with predominantly negative cultures apart from a one-off growth of *S. aureus*) but importantly there was no evidence of bronchiectasis (or bronchial wall thickening) on chest CT. A further CF diagnostic evaluation was undertaken. Sweat chlorides were 34 and 35 mmol/L. NPD demonstrated a skin PD of −44 mV with a normal basal PD and amiloride response of −21 mV and 4 mV, respectively, followed by a good chloride response (total 9 mV). Whole DNA sequencing of CFTR and the epithelial sodium channel (ENaC) identified only the p.Phe508del variant. As a result of this evidence, the CF diagnosis was withdrawn, and she remains under follow-up in a general respiratory clinic. Withdrawing the diagnosis precipitated anger, upset and disbelief. Much of this related to her loss of identity, particularly as this had significantly influenced life choices, including her parents deciding not to have any more children. She was also angry about her weight gain as she put some of this down to following a traditional CF diet from a young age. These emotions were prolonged, requiring counselling and psychological support.

HOW IS CF CURRENTLY DIAGNOSED

The gold-standard test for CF, first developed over 60 years ago, is measuring the concentration of salt in the sweat. Genetic mutations lead to non/poorly-functional CFTR protein, an ion channel on the apical surface of multiple epithelial-lined organs. In the CF sweat gland, this leads directly to failure of chloride (Cl^-) reabsorption and high sweat Cl^-concentrations. This electrolyte imbalance, in turn, leads to sodium (Na^+) retention in the sweat. Early sweat analysers measured Na^+, but Cl^- concentration has been shown to be more reliable and discriminatory, and is the current standard [3]. Sweat conductivity is not recommended and performs less well, although is still used in some countries. People with CF have sweat Cl^- levels above 60 mmol/l, those <30 mmol/l are considered normal, with a grey area in between [3]. Testing requires two samples with quality criteria for reproducibility and should be undertaken by teams in centres with a critical mass of patients [4].

Although in many parts of the world sweat testing is performed in a patient presenting with symptoms in whom CF is suspected, the diagnosis of CF in many regions is now made following NBS on the neonatal heel prick test. Globally, different approaches are taken to this; in the UK our algorithm involves an initial immunoreactive assay for the pancreatic enzyme, trypsinogen. Samples above a certain threshold are cascaded for a limited panel *CFTR* mutation screen [5]. Either two mutations, or a repeated high IRT in the face of 1 or 0 mutations may lead to a 'CF suspected' referral to a CF tertiary centre for confirmation of the diagnosis. Even in cases with two confirmed CF-causing mutations, sweat testing will be undertaken. A diagnostic sweat chloride in an infant with fewer than 2 disease-causing gene mutations, will be sufficient to support the diagnosis, although full CFTR sequencing will remain important, particularly to assess suitability for future CFTR modulator drugs.

HOW THE DIAGNOSIS HAS EVOLVED

NBS was adopted nationally in the UK in 2007. Over the subsequent 14 years, there have been substantial advances in our understanding of CFTR variants, aided by the CFTR2 project (https://cftr2.org/). This seeks to curate numerous CFTR variants into categories: CF-causing, variant of variable clinical consequence (VVCC) and non-CF-causing, based on clinical, functional, and epidemiological data gathered from patient registries. Before this new characterisation, the finding of 2 CFTR mutations may have been considered sufficient for a diagnosis to be confirmed, whereas under updated guidelines, a CF diagnosis in patients with one or more VVCC's now requires a sweat Cl^- in the abnormal range, evidence of established disease or a CFTR functional abnormality from advanced testing (NPD; or intestinal current measurement (ICM) on rectal biopsy) [6,7]. Of particular relevance here is the splice variant, Arg117His; the amount of functional CFTR produced by an allele encoding this mutation is closely related to an associated variant in intron 8. The 7 T repeats leading to high protein expression, whereas the 5 T variant it is much lower [8]. The former is classified as a VVCC, whereas the latter is CF-causing.

As a direct consequence of this increased understanding, a new term, CF screen-positive, inconclusive diagnosis (CFSPID) has been coined (in the US, the term used is CFTR-related metabolic syndrome (CRMS)) [6]. This is a term used as a holding label for babies presenting screen-positive, with fewer than 2 CF-causing mutations and with sweat chlorides in the normal or borderline range. Investigations and management of this group, the majority of whom will not go on to fulfil CF diagnostic criteria, have recently been updated [1,6]. There is of course a population of older children and adults who did not undergo NBS or whose genetic analysis is incomplete (*e.g.* no analysis of the intron 8 polyT status with an Arg117His) who would, under current criteria, have been more appropriately designated CF-SPID; some of these are the cases in whom the CF diagnosis may appropriately be withdrawn.

RE-THINKING THE DIAGNOSIS

As CF is a lifelong *progressive* condition, clinical stability (and/or lack of development of disease in other organs), particularly over many years, is a key feature which should trigger re-

consideration of the diagnosis. When a child presents with non-specific symptoms such as failure to thrive, loose stools or a cough, this should always trigger CF investigations, but as our cases show, care in the interpretation of equivocal sweat test results (and non-diagnostic genetics) is vital, as only a proportion will actually have CF. Over time (even decades) if lung function has remained stable, bronchiectasis has not developed and the pancreatic function tests (*e.g.* faecal elastase) have remained normal, then the likelihood of CF is very low.

Moreover, older individuals with an original diagnosis based purely on a sweat test and/or with only one (or even no) CFTR mutation, should have their diagnostic information re-examined and potentially repeated. This is particularly salient if a historically limited CFTR genotype panel was used, and if sweat Na^+ was measured rather than Cl^-. Not only is this important to secure the diagnosis, but it is critically important to enable access to genotype specific CFTR modulator therapies. When there is still uncertainty over the diagnosis, additional diagnostic modalities that measure epithelial ion transport should be used [3].

It should also be noted that as different organs have different susceptibility to abnormal CFTR function, the lack of abnormality is a positive diagnostic discriminator. This is particularly relevant to the vas deferens, which is the most sensitive organ to abnormal CFTR function ($\geq$50% wild type function causes disease compared with $\geq$90% for pancreatic insufficiency) – so it is incredibly rare for a male patient *with* CF to have an intact vas deferens ($\sim$1%) [2]. Such a scenario should raise suspicion and trigger a review of the diagnostic information.

INFORMING THE CHILD AND THEIR CARERS

There is no question that one must be completely open and honest that the CF diagnosis is now in question, whilst endeavouring to be as certain as possible of the facts at the same time as understanding that it is uncertainty which is likely to engender negative emotions [9]. The conversation cannot be rushed, and a detailed letter should follow, summarising the discussion, copied to the GP. Whether the child should be present at the initial discussion depends on their age and level of understanding; for children under 12 years, it is helpful to give the parents/carers a choice. Certainly, the child will need to be informed and support can be offered to the parents with this if required.

It is important for the family to realise that our medical understanding of the CF diagnosis has changed over the last 15 years, as we have gained experience with NBS and as the genetics has evolved. Some of the variants previously thought to be CF-causing are now known to be variants of uncertain consequence. The notion of atypical CF is no longer valid, the cut off for a normal sweat test has lowered (40 to 30 mmol/L), and the concept of CF-SPID has come into existence. One should not feel guilty about a change of diagnosis, a mistake was not made. The science has evolved, and it is good practice to constantly evaluate a patient's diagnoses.

Nevertheless, the response of parents to the news differs. Whilst clinicians would regard undoing a CF diagnosis as good news, uncertainty is difficult and will likely involve change with loss as well as gain. Uncertainty is never good for parents and patients. The effect of having a chronic and life limiting condition leads to major changes in self-perception by the patient as well as the family's perception of the patient and their own lives [10]. Furthermore, many parents are invested in the CF community, including online forums, parent groups and fund raising. The CF MDT is often a big part of the family, and support from the CF MDT is essentially withdrawn. There may also be financial issues as the Disability Living Allowance for children is likely to be withdrawn and changes in employment and housing allowances for adults may follow. Interestingly, these effects are also being reported by some patients following significant improvement in health due to CFTR modulator therapy.

The experience of one CF centre in the USA in whom 18 patients had been misdiagnosed elsewhere (between 1970 and 1994), found that parents expressed great disbelief (mothers more so than fathers) and there was a correlation between length of misdiagnosis and the degree of problem in undoing the diagnosis [10]. The undoing occurred in a new centre so there was great distrust in the physician and a lot of anger; repeated tests were requested for months afterwards and there was resistance to stopping the therapies. They found it took one to three years for the family to accept normalcy, but many felt the child was still vulnerable if they developed minor symptoms such as a viral cold. Another US centre reviewed 271 patients from over a 15-year period (1971–1985), and found 8 patients who subsequently had normal sweat tests (despite initial abnormal ones) [11]. They found that the families were relieved but not elated and one family was extremely angry; another family denied the new diagnosis and only accepted it a year later after retesting in two other CF centres. In another UK 1987 series, 7/179 children had the diagnosis reversed [12]. In two cases the families refused to accept the diagnosis (one with a maternal cousin and one with a sibling with CF); one family who had received considerable welfare benefits and a trip to Disneyland attempted to sue the paediatrician, and when they finally accepted it appeared in a newspaper saying the child had been cured of CF. It should be noted that these papers are quite old and predated routine extended genetic analysis. A more recent paper from Germany found the diagnosis had been withdrawn nationally in 51 patients between 1989 and 2004 [13]. They found most parents and patients showed understanding but about 1 in 4 refused to believe it. They said CF teams should expect some families to be confused and to blame the CF teams for previous overtreatment.

TELLING ADULTS

In the majority of situations, the patient is already aware that the diagnosis is in question – previous labels such as 'mild CF' or 'atypical CF' or even 'possible CF' may have been used (all of which are usually unhelpful and we would advise against this, unless 'possible CF' is being used during the diagnostic work-up period). The diagnostic process itself in the context of such 'difficult' cases is often a staged process over many weeks (due to the time waiting for specialist tests or the processing time for extended genetic analysis) so the patient already has had time to contemplate this. It is important to explain why the diagnosis has been withdrawn similarly to with paediatric patients (see above).

Nevertheless, withdrawing the diagnosis of CF from an adult patient is usually met with incredulity and frequently with anger and denial. This is usually because this diagnosis has been with them for years, if not decades. It has been part of their identify and often shaped life decisions, as outlined in the adult case example above. Although no one wants a genetic disease, when symptoms are present, it is far easier to accept them when there is an explanation, so if a diagnosis is removed and there is no clear alternative explanation, this can be challenging, particularly whilst losing MDT support. In our experience, with appropriate support, reassurance and psychological input, this can be overcome; eventually there is a realisation of the wider benefit, *e.g.* reducing some of the burden of treatment frequently associated with CF, and removal of some of the social and economic disadvantages (*e.g.* life insurance).

PRACTICAL OUTCOME OF REVERSING THE DIAGNOSIS IN CHILDREN

Clearly some of the treatments need to be withdrawn, particularly if they are specific to CF. What remains will depend on

whether the child is still symptomatic but with a different diagnosis, or whether the treatments are being given to a well child who was having routine CF therapies. In the latter case, examples of drugs to stop would be dornase alfa, prophylactic antibiotics, and vitamin supplements. Airway clearance physiotherapy would also stop. It may be better to withdraw gradually, and usually one therapy at a time to reassure the parents that the child will remain symptom free, especially if the therapy has been given for some years. Interestingly, although physiotherapy is usually the least popular treatment in CF (due to the time it takes), it is physiotherapy in our experience that parents find hardest to stop. CFTR modulators should clearly not continue either.

We recommend that the child is moved into a general respiratory clinic, ideally remaining under the same consultant. They will no longer be provided with support from the CF MDT, so involvement of a paediatric respiratory nurse specialist is recommended. Physiotherapy and dietetic provision should be provided only if there is a clinical need. A clinical psychologist may be able to support the transition process and offering a referral is recommended.

OUTCOME IN ADULTS

Similarly, to children, treatments will need to be scrutinised and potentially rationalised. Therapies for bronchiectasis – such as nebulised dornase alfa – only have a strong evidence base in CF (as opposed to other causes of bronchiectasis) so may need to be withdrawn [14]. Inhaled antibiotic therapies have also largely been developed for CF-bronchiectasis although benefits in other conditions are likely [15]. Each patient will need careful case-by-case consideration, although access and funding to such medications may be more challenging. CFTR modulators are not licensed for such individuals either [16]. The underlying pathology and 'new' diagnosis will dictate where and how the patient should be managed and followed up. For example, if they do have bronchiectasis then follow-up in a non-CF general bronchiectasis service may be the optimal choice. Providing clarity to the patient and reassuring them of the follow-up plan and who to contact if there are issues, is key to successful next steps.

FUTURE TESTS

Withdrawing CF as a diagnosis can be very challenging for the patient and their family. Clearly avoiding this in the first place should be the priority, although very few medical tests, if any, are 100% accurate. The sweat test is likely to remain at the core of the diagnostic process, but other related modalities are under investigation, such as sweat stimulation testing [17]. The wide equivocal range for sweat chloride values and the association of certain CFTR pathogenic mutations with a normal (<30 mmol/L) sweat chloride will always limit the value of this for these rare difficult cases [18]. Broadening access to NPD and ICM will also be important, particularly now that both tests are integrated into internationally accepted consensus diagnostic guidelines [3]. Rapidly advancing technology and access to next generation sequencing platforms may hold the key, particularly when whole gene analysis is performed, but even with this it is possible that variants will be missed, or their clinical significance unknown [19]. An emerging research area is the use of rectal tissue-derived organoids. These *ex vivo* spheroidal cellular structures recapitulate CFTR activity producing different 3-dimensional configurations dependent on CFTR genotype. Work is ongoing to investigate their accuracy as a diagnostic test with early results looking promising [20].

CONCLUSIONS

Diagnosing CF is usually straight forward, but at times can be rather complex. Newborn screening and extended genotype analysis have thrown up a number of dilemmas, and as our knowledge and experience have increased, it has become clear that a small number of children and adults should no longer be considered as having CF disease. Reversing the diagnosis is generally regarded as good news, but this change can understandably result in feelings of regret, loss, and frustration as well as practical repercussions for both the patient and their family. The issue needs to be verified and planned well and communication handled with sensitivity and understanding.

DECLARATIONS OF INTEREST

None.

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DIRECTIONS FOR FUTURE RESEARCH

- How best to psychologically support patients and their families.

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