Cystic Fibrosis Frequently Asked Questions

Does newborn screening improve early lung function in cystic fibrosis?

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Keywords: Cystic fibrosis, newborn screening (NBS), infant lung function, spirometry, lung clearance index

Competing interests: GD reports personal fees from Chiesi Limited, unrelated to the current work.

Funding: GD was supported by the UCL Wellcome Institutional Strategic Support Fund 3 [Grant Reference 204841/Z/16/Z]. All research at Great Ormond Street Hospital NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the NIHR Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

Educational aims

The reader will come to be able:

- To review the literature relating to lung function in the evaluation of NBS for CF
- To discuss that the choice of outcome measure is important in this population
- To recognise the limitations in the literature relating to measurement of pulmonary outcomes and significant changes that have been made in clinical management, infection control measures, and wider public health.
- To appreciate the yet unknown additional benefit of being able to detect CF in the first weeks of life in relation to disease modifying treatments targeting the underlying molecular defects responsible for CF.

Abstract

Despite evidence showing an improvement in nutritional outcomes following diagnosis by newborn screening (NBS) for cystic fibrosis (CF), the impact on pulmonary outcomes has been less clear. In this review the approaches to measurement of early lung function and knowledge gained from NBS CF cohorts will be described. Studies which have compared outcomes in those diagnosed by NBS to those diagnosed following symptomatic presentation will be presented. Compiling the evidence base used to evaluate the impact of NBS on pulmonary outcomes has been complicated by improvements in clinical management, infection control practices, as well as public health interventions (such as tobacco smoking bans in public places) that have evolved substantially over recent decades. Forced expiratory volumes have been used as the main outcome but it is important not to draw conclusions for 'early lung function' from tests such as spirometry alone, which lack sensitivity in early lung disease. There is, at present, insufficient evidence to draw firm conclusions about the effect of NBS on early lung function. In an era of highly effective treatments targeting the underlying molecular defect responsible for CF, future opportunities for early initiation of treatment may mean that the impact of NBS on early lung function may yet to be realised.

Introduction

Newborn screening (NBS) for cystic fibrosis (CF) has been widely adopted across the globe where CF is prevalent and appropriate diagnostic and clinical infrastructure is in place[1]. It permits early diagnosis predating symptoms, and the opportunity for nutritional and pulmonary interventions with the aim of preserving health. In turn, this provides an opportunity to prevent harm and long term lung damage at an earlier stage than in symptomatically diagnosed populations. The greatest morbidity and mortality in CF is from the respiratory system, largely due to bronchiectasis, small airway obstruction and progressive respiratory failure[2]. Whilst benefits in nutritional outcomes have been demonstrated [3-12], the impact of NBS on lung function outcomes has been less clear [13-18]. Advances in clinical management, and wider societal and environmental changes, have occurred over the same period. Any comparison to historical cohorts may be influenced by these factors in addition to any impact of NBS per se.

This review will summarise the literature relating to NBS and early lung function outcomes, and the important methodological considerations when comparing outcomes in patient cohorts separated in time, location, and clinical management. It will describe how we measure early lung function, and put this in the context of a rapidly changing therapeutic environment with the advent of highly effective cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy (HEMT). Although this current review focuses on early lung function, other outcomes reported in the literature include infection (particularly in relation to acquisition of *Pseudomonas aeruginosa*) [6, 10, 14, 17, 19, 20], pulmonary exacerbations [6, 7], and survival [3, 4, 16, 21, 22]. Early diagnosis by NBS has been shown, in general, to have more favourable clinical outcomes than children whose access to routine CF care was as a result of later diagnosis [18].

Measuring lung function in the early years

Early lung function tests aim to detect evidence of early lung disease. This is important for targeting appropriate treatment, and also because of its association with adverse outcomes in later childhood

[23-25]. One of the challenges is that “early lung function”, within the first years of life, is often not routinely measured in clinical practice.

Measurement of infant lung function requires specialist expertise and is generally carried out in the research setting rather than being a component of routine clinical care [26, 27]. In NBS infants with CF, $FEV_{0.5}$ — measured by the raised volume rapid thoraco-abdominal compression (RVRTC) technique — is normal in the vast majority of infants[28, 29], yet more sensitive outcomes such as lung clearance index (LCI) — measured using the multiple breath washout (MBW) technique — are significantly raised in comparison to healthy controls despite still (overall) remaining within the normal range [29]. Although a nitrogen multiple breath washout (N_2 MBW) is recommended from pre-school age range and beyond [26], LCI in infants has, in general, been measured using an MBW technique with SF_6 as the tracer gas rather than a nitrogen washout. Historic preferences for SF_6 has centred on concern that breathing in 100% oxygen will alter the respiratory drive and result in hypoventilation[30, 31], and impact on the variability of tidal volumes [32]. N_2 MBW overestimates LCI in comparison to SF_6 methodology [33], but although more research is required to understand the relationship between infant N_2 MBW and N_2 MBW at pre-school and later childhood, feasibility of this method in infants has been demonstrated [33].

Measurement of lung function in pre-school children is, like infant lung function testing, largely restricted to the research setting although spirometry is often attempted in routine clinical practice before 5 years to get young children accustomed to the technique. The Global Lung Function Initiative (GLI) spirometry reference equations can be used from pre-school age upwards, and allow comparison using %predicted or z scores [34]. LCI can be undertaken in pre-school children and the N_2 method is recommended [26], although again this is restricted to the research setting. Evidence for lung function outcomes in the pre-schoolers with CF therefore comes from a relatively small number of clinical settings and cohorts.

Routine spirometry measurements in clinical practice are feasible from around 5 years, and performed according to international ATS/ERS recommendations [35]. As well as a role in routine clinical care and in clinical trials, spirometry outcomes such as FEV_1 and FVC are also collected on national CF Registries, providing a rich resource for longitudinal follow up in the real world setting. Both spirometry and LCI measured by the MBW technique have been assessed longitudinally in a longitudinal cohort studies of children with CF diagnosed by NBS.

In an era of treatments with the potential for disease modifying capability initiated at an ever-decreasing age, greater sensitivity for pulmonary function measures are required. Modalities such as hyperpolarized gas ventilation magnetic resonance imaging (ventilation MRI) can detect early lung function abnormalities not evident on spirometry, or MBW indices such as LCI which instead assess a global measure of ventilation inhomogeneity [36-38]. The feasibility and ability to detect longitudinal change in children and adults with CF has been demonstrated [39-41].

Evidence from NBS cohorts

Several cohorts are prospectively following up infants with CF diagnosed by NBS. Although protocols and clinical management vary, within each cohort there exists an opportunity to track pulmonary (and other) outcomes over time. They do not assess the direct impact of NBS on lung function, but are important in understanding the evolution of lung disease in a NBS population.

These cohorts aim to understand the relationship and tracking of outcomes during infancy and early childhood, and how they relate to disease trajectories in the longer term. Examples of NBS cohorts include the London Cystic Fibrosis Collaboration (LCFC), the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF), and the Swiss Cystic Fibrosis Infant Lung Development (SCILD) cohort. The LCFC recruited a NBS cohort between 2009-2011[28, 42]**.** This was a second cohort for the LCFC, the first involved children with symptomatic presentation prior to the introduction of NBS for CF in the UK (introduced nationally in 2007 although several regional programmes were in place prior to this). To date, the LCFC NBS cohort has been followed up at 3mth, 1yr, 2yr and 3-6 years. In

LCFC infants with CF diagnosed by NBS, mild deficits in lung function were detectable by 3 months of age [42], with improvement in $FEV_{0.5}$ between 3 months and 1 year of age [28]. By 2 years of age, there was no significant difference in $FEV_{0.5}$ between CF and contemporaneous healthy controls [29], with the vast majority of infants with $FEV_{0.5}$ in the normal range. In contrast, LCI was able to discriminate between NBS children with CF and healthy controls. Although LCI generally remained within the normal range, it remained significantly elevated in 2yr old children with CF [29].

The Australian AREST CF group has an ongoing programme of recruitment to its NBS cohort following diagnosis, with a much larger cohort and duration of follow up than LCFC. Their protocol includes annual lung function (RVRTC, forced oscillation and LCI in infants, and then forced oscillation and spirometry from preschool age), high resolution chest CT, and bronchoscopy with bronchoalevolar lavage. This has led to a rich data resource which has given important insights into risk factors for progression of lung disease [43-45]. They have reported lung function results in infants and young children with CF, with much greater deficits in infant RVRTC outcomes than observed in the LCFC cohort[46]; however, direct comparisons between the LCFC and AREST CF early lung function results in their NBS cohorts is challenging [47], and more important is the follow up and interpretation of results *within* each cohort. Another example is the SCILD cohort which has, since 2011, recruited infants with CF diagnosed by NBS from across Switzerland [48]. A recent cohort profile publication reported that 70 infants had been recruited to the cohort, with data collection to include questionnaires, lung function measurements, telephone interviews, nasal swabs and magnetic resonance imaging.

Clinical trials of NBS

There have been two randomised controlled trials of NBS for CF (from the UK [49] and Wisconsin, US [9, 12]). The Wisconsin CF Neonatal Screening Project was the only randomised clinical trial included in a Cochrane systematic review evaluating the evidence base for NBS (published in 2009) [50], as it was not possible to combine results from the two trials due to differences in study design and

outcomes. The Wisconsin trial involved infants born in the state of Wisconsin, US between 1985 and 1994 having an immunoreactive trypsinogen (IRT) test (and both IRT and DNA analysis from 1991-1994). Randomisation was to either the care team being informed of the screening results, or storing this information until 4 year of age unless there was a positive family history or clinical symptoms suggestive of CF in the interim. It sought to investigate whether an early diagnosis of CF through NBS was associated with better nutritional status without major risks (e.g. adverse impacts through procedural/laboratory errors or psychosocial morbidity). In addition to assessing nutritional status, pulmonary outcomes were assessed by chest x-rays, high resolution chest computed tomography, and pulmonary function tests. The Cochrane review of the Wisconsin trial concluded that NBS is associated with improved nutritional outcomes and the potential for improved lung function outcomes but confounding factors influenced long term pulmonary prognosis[50], including that NBS was associated with earlier age of first acquisition of *Pseudomonas aeruginosa. Pseudomonas aeruginosa* is associated with respiratory morbidity and faster decline in lung function [51], and in the Wisconsin trial, children attending a centre in an urban location with opportunity to mix with other patients with CF in clinic had a significantly earlier age of first acquisition of *Pseudomonas aeruginosa* [52].

The UK NBS trial was undertaken in Wales and the West Midlands in infants born between 1985 and 1989. This trial used a methodology which included screening infants on alternate weeks according to week of birth, and thereby identifying two groups in each region [49, 53]. Their initial report described outcomes relating to age at diagnosis, growth, and admissions to hospital at 4 year follow up, and did not include any measures of early lung function[49]. The results were not reported according to an intention to treat analysis, and therefore interpretation of results is compromised[54].

Observational studies

In addition to limited clinical trials of NBS, other studies have compared geographically distinct contemporaneous populations with and without NBS, or NBS-diagnosed with historical cohorts prior to screening[55]. Other methodologies have included comparing outcomes in children with a late diagnosis of CF despite NBS with children diagnosed after a positive NBS, for example as undertaken by Coffey *et al* in children from New South Wales, Australia 1998-2010[15].

The majority of these studies have reported favourable outcomes in NBS groups [5, 6, 8, 15, 56, 57]. For example, an observational study in Australia compared outcomes up to 10 years of age in those diagnosed in a three year period after the introduction of newborn screening (n = 60; birth years mid 1981 to 1984) with those born in the 3 years immediately prior to its introduction (n = 57; birth years 1978 to mid-1981)[5]. Waters *et al* [5] reported that mean % predicted FEV_1 was significantly higher in the screened cohort at 5 and 10 years of age (average difference 9.4% (95% CI 0.8, 17.9) at 10 years). Not all observational studies have reported better lung function in NBS populations (a French study by Sirat *et al* did not detect any difference [7]). A challenge in the interpretation of these observational studies is with confounding and other bias. These include differences in clinical care and advances in management and a 'cohort effect' with CF outcomes improving sequentially over recent decades, in addition to wider public health interventions (e.g. smoking bans in public places, or bans on smoking in cars carrying children) within regions or nations in the interim. This relates both to within periods used for comparison, but also in the interpretation of these results in the context of standard care today.

It is often difficult or inappropriate to compare outcomes between countries or centres, and this is particularly relevant for early lung function measurement whereby differences in equipment or testing methodology may be responsible for some of the discrepancies between NBS cohorts reported in the literature. There is a difference in age at diagnosis between NBS and symptomatically diagnosed groups, and in studies comparing outcomes between these groups the median age of the latter variable across studies from one month to over one year [18]. However,

the age at diagnosis for NBS infants is also not uniform, with median age at diagnosis is dependent on the screening algorithm followed and infrastructure supporting communication of results.

Registry-based evaluation of impact of NBS on early lung function

As Registry data relies on measurement of outcomes in routine clinical practice, lung function outcomes within national CF registries are currently restricted to spirometry, with FEV_1 recorded at least annually from around 5-6 years of age onwards. A recent UK CF Registry study by Schluter *et al* has investigated lung function outcomes at age 5-6 years in UK NBS infants in comparison to those diagnosed by other means[17]. Although NBS for CF was introduced nationwide in 2007, it was already established in several regions for many years and therefore the authors were able to take advantage of this in their analysis as information relating to mode of diagnosis is routinely collected in the UK Registry. Introduction of NBS programmes on a national (or regional) level themselves will change the demographics of the CF population within a CF Registry, with an impact on overall patient numbers including those with a mild phenotype with pancreatic sufficiency who may not have been diagnosed until later in childhood or adulthood. This is an important consideration when comparing any difference in outcomes between the NBS and clinically diagnosed populations within a Registry. Groups must be comparable, and not biased by the inclusion of 'milder' phenotypes in NBS cohorts, however VanDevanter reported that a favourable impact of NBS on clinical outcomes persisted even when this is accounted for [18].

In their recent analysis of the UK CF Registry, Schluter *et al* [17] investigated the association of early diagnosis by NBS with clinical outcomes including lung function trajectories. Although not so 'early life' as the NBS longitudinal cohorts, this gives an important insight at the population level. They found that NBS children have a small but statistically significant 1.6% predicted FEV_1 advantage at age 5-6 years over those diagnosed clinically (and also a later onset of chronic *Pseudomonas aeruginosa* infection and increased early weight (at age 1 year)). They propose that this may be due to reduced lung disease (less airway obstruction) or reflect improved lung growth [58, 59]. However,

they did not find any association between NBS status and subsequent rate of change of lung function (i.e. lung function trajectory) throughout childhood, i.e. the magnitude of this difference remained static[17]. The finding that NBS was found to be protective for chronic *Pseudomonas aeruginosa* infection, with their data from an era of stricter policy relating to the prevention of cross-infection, contrasts to the Wisconsin trial from previous decades [52]. Lower rates of *Pseudomonas aeruginosa* in NBS diagnosed have also been reported by a Canadian registry study [60].

In a prior UK study, Sims *et al* utilised the CF Database (pre UK CF Registry) to analyse clinical and radiological outcomes in NBS, early- or late-clinically diagnosed (defining the latter as beyond the reporting window of diagnosis for NBS) in a cross sectional analysis of patients with F508del homozygote variants[61]. This was prior to national newborn screening in the UK, but regional screening programmes were in place in some areas. They found that NBS children were taller and had reduced morbidity and number of chronic medications but no difference in lung function between groups [61].

A US Registry study including data up until the year 2000 investigated the mode of CF diagnosis with survival, including meconium ileus, prenatal or neonatal screening, positive family history only, and symptoms other than meconium ileus [21]. They found diagnosis through symptoms at presentation beyond one month of age was associated with a significantly reduced survival in comparison to those diagnosed by NBS. However, they also reported that if diagnosis on the basis of symptoms was made within the first month of life, then survival was not significantly different to the NBS group (and was significantly better than those diagnosed on the basis of symptoms between 1 month and 10 years of age)[21]. Another US Registry study from the start of the millennium reported improved lung function (FEV_1) in NBS patients when compared to symptomatic/meconium ileus presentation [6] but again is confounded by historical comparisons.

Lung function outcomes in childhood according to mode of diagnosis have also been compared between national CF Registries. Martin *et al* [11] analysed cross sectional data from the US and

Australian CF Registries to compare growth and pulmonary outcomes between children with a diagnosis after newborn screening with those diagnosed after symptomatic presentation. Using data from the 2003 Registries, they found that children diagnosed after NBS had a higher FEV_1% predicted (mean (95% CI) difference 5.3% (3.6-7.0) in addition to a higher BMI [11]. They also investigated whether this advantage in lung function was dependent on country, and found that NBS was associated with a greater lung function advantage in US than Australian children. At the time of their study, Australian patients were significantly more likely (65.8% vs 7.2%; *P* <.001) to have been diagnosed after NBS than those from the US.

How does lung function in early childhood relate to later measures?

This review focuses on early lung function, but the relationship of these early measures to those in later life is important to put results in context. All of the observational studies comparing long term outcomes according to whether or not diagnosis was via NBS (either in observational studies or clinical trials) have used FEV_1 as the main lung function outcome. McKay *et al* reported 15-year outcomes from the cohort of children with CF diagnosed by NBS on pulmonary outcomes in New South Wales Australia [57]. These children had been studied at 1, 5 and 10 years of age[5] as described above, and were then followed up age 15 using data collected during their routine clinical annual review. Children diagnosed by NBS were found to have a survival advantage and higher lung function (%predicted FEV_1 and FVC) than those in the symptomatically diagnosed group.[57]. The differences continued to be detectable in early adult life [13]. The previously observed benefits in the screened group were maintained, with FEV_1% predicted 16.7% (95% CI: 10.3% to 23.1%) higher at transition to adult care at 18 years of age. Each 1% improvement in FEV_1% was associated with a 3% reduced risk of death at age 25, and a significant difference in survival at age 25 was detectable between groups.

Long term follow up data from the Wisconsin RCT provides an opportunity to determine the significance of prior results from this cohort. At a follow up between 8-18 years of age, chest x-ray

scores were worse in the screened group but there was no difference in either these or spirometry following adjustment for pancreatic insufficiency and *Pseudomonas aeruginosa* status [62]. At 10 year follow up, nutritional outcomes favoured the NBS group but there was no difference in lung function, and chest x-ray scores were worse in the screened group, again associated with an earlier age of acquisition of *Pseudomonas aeruginosa* [63]. Spirometry was however well preserved in both groups. At follow up between 8-18 years of age, chest x-ray scores were worse in the screened group but there was no difference in either these or spirometry following adjustment for pancreatic insufficiency and *Pseudomonas aeruginosa* status [62]. A recently published long-term follow up of the original Wisconsin cohorts utilises the US Cystic Fibrosis Foundation Patient Registry (CFFPR) to investigate longer term pulmonary (%predicted FEV_1 decline over time) outcomes, and mortality [16]. Barreda *et al* report a significantly increased rate of decline in % predicted FEV_1 in the NBS group of 1.76% per year (95% CI: 1.62 to 1.91%) in comparison to 1.43% (95% CI: 1.26 to 1.60%) in the control group over a twenty year period from childhood. This significant difference persisted after adjusting for pancreatic status, *Pseudomonas aeruginosa* status, and age at diagnosis. Barreda *et al* suggest that "while NBS is effective at identifying cases of CF and early diagnosis of CF by NBS with subsequent management of nutrition can lead to improved nutritional and growth outcomes [12, 64], NBS may be insufficient to improve pulmonary and mortality outcomes for patients with CF." The contrasting results from the recent Registry study by Schluter *et al* [17] do not have a long enough duration of follow up to be able to determine whether the small improvement in FEV_1% predicted in those diagnosed by NBS that they observed is sustained into later life, but also use FEV_1 %predicated as the main outcome.

One of the challenges in detecting any difference in the rate of change between NBS and symptomatically diagnosed groups is a low expected rate of %predicted decline in FEV_1 in both groups. The combination of relatively short term follow up and use of annual review data (rather than more granular encounter-based data) add to these challenges, but spirometry is unlikely to be the best method of comparing pulmonary outcomes between groups. Instead, more sensitive

outcomes such as LCI are required, but at present this is not routinely captured in all CF centres nor recorded in national CF Registries.

LCI is more sensitive than FEV_1 at detecting early lung disease [65], and is better correlated with structural change on chest CT in children with CF than FEV_1 z score [66]. The significance of an elevated LCI at pre-school age is becoming clearer, with increasing evidence that measures at this age can track disease and relate to lung function in later childhood. Hardaker et al [67] reported that LCI at preschool (measured by Exhalyzer® D, EcoMedics AG) was a strong predictor of spirometry outcomes in childhood. The progression of LCI in pre-school (2.5 to 6 years) children with CF, in comparison to stability of this measurement in healthy controls, has also been demonstrated by Stanojevic et al in their study of serial measurements of LCI over a 12 month periods in 156 participants from 3 North American CF centres (Chapel Hill, Indianapolis, and Toronto), at 4 time points designed to mimic routine care and clinical trials [24]. Of note, not all children with CF in this study were diagnosed by NBS; 62/78 (79%) were NBS diagnosed. In those diagnosed following clinical presentation (predating NBS), LCI at preschool predicts LCI at school age [23], and is associated with LCI at adolescence [25].

Future opportunities and a rapidly changing therapeutic environment

Highly effective CFTR modulator therapies (HEMT) such as elexacaftor-teazacaftor-ivacaftor are transforming the therapeutic landscape in CF [68, 69]. The field is rapidly evolving, with clinical trials of elexacaftor-tezacaftor-ivacaftor involving 6-11 year olds at the time of writing. Currently licensed in the US and undergoing approval by the European Medicines Agency for adults and children aged 12 years and over with either F508del/F508del or F508del/minimal function variants, clinical trials in children age 6-11 years are in progress. There is an expectation that this will rapidly expand to young age groups as occurred for ivacaftor. For ivacaftor, approvals in pre-school children and infants were granted on the basis of safety data alone [70], and it is now licensed from 6 months of age. As the safety and efficacy of these medicines that target the underlying molecular defect is evaluated in

ever-younger CF populations, early diagnosis by NBS assumes a potentially greater significance. The timing of initiating therapy e.g. prior to symptoms and within a certain number of weeks from birth may be important to maximally preserve lung health.

In parallel with these rapid therapeutic advances, we are also understanding more about the importance of lung function measures in early life from longitudinal follow up of NBS infants, and how pre-school and early school age measures relate to those made in later life. Follow up of existing NBS cohorts such as the AREST CF and LCFC cohorts will help understand the relationship between sensitive early lung function outcome measures and later clinical outcomes following diagnosis by NBS. Analysis of national Registry data using spirometry outcomes will also be important in the absence of LCI, or any contemporaneous randomised controlled trials of NBS. These approaches will help better understand which investigations are best able to detect and monitor early lung disease in NBS CF populations. This will enable a heightened opportunity to preserve lung health. The specific algorithm used for NBS within a country or region, and corresponding age at diagnosis of CF, may be critical.

Conclusion

Infants and young children with CF diagnosed by NBS have well preserved lung function, but mild deficits are detectable between those with CF and healthy controls in the first years of life with sensitive measures such as LCI. Irrespective of screening status, pulmonary outcomes for those diagnosed within the first weeks of life, with early instigation of CF-specific management, in general, have better outcomes by school age than those with a later diagnosis. There is insufficient evidence to draw firm conclusions about any direct effect of diagnosis by NBS on early lung function outcomes. This may reflect the quality of the underlying evidence base. In addition to significant changes in the design and delivery of CF care over recent decades, use of spirometry in the Wisconsin trial and observational studies rather than newer, more sensitive measures such as LCI that are now available may have underestimated or missed any effect.

The age at which treatment with highly effective CFTR modulators is initiated is likely to decrease over the coming years. As this encroaches towards the age of diagnosis following NBS and precedes that of diagnosis following symptomatic presentation, NBS may facilitate the opportunity to further improve early lung function outcomes.

Future directions for research

NBS for CF has been integrated into standard care and further clinical trials seem unlikely, although the age at which CFTR modulators should be initiated, taking into account a risk-benefit profile, may indirectly determine whether this is in a window that would pre-date diagnosis following symptomatic presentation. Ongoing recruitment and follow up to longitudinal CF NBS cohorts permits an evaluation of the evolution of CF lung disease and how lung function measures in early life track through the life course. Crucially, this needs to use methods that are sensitive to detect mild CF lung disease.

Highlights

- NBS now widely introduced as standard of care
- Clear pulmonary benefits for NBS have not been demonstrated
- Nutritional benefits for NBS are well established
- Most studies used FEV_1 to compare outcomes, but lacks sensitivity in early disease
- Impact of very early introduction of disease modifying treatments awaited

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