Response to the reviewers

Reviewer 1*:* The paper admirably aims to improve and standardize data collection in regard to missed cases of Cystic Fibrosis in Europe in order to gain more knowledge on how to reduce the number of missed cases. Overall it is a nice paper, but the text could be a bit more cohesive. Before the manuscript is ready for publication, there is some issues that need to be addressed.	
1. The authors states in the "result" section, that sensitivity should be calculated as total number of missed cases both including and not including meconium ileus (MI). In the "background" section, the authors list the results of a recent survey and they provide the sensitivity found in different countries with and without DNA analysis. The authors state, that the recommended sensitivity should be no less than 95%. The authors refer to ECFS best practice guideline 2014 and the 2018 revised version. In the 2014 version MI is not addressed, whereas the 2018 version states that sensitivity should be calculated both including and not including MI. It is not clear whether the calculated sensitivity is including or not including MI cases. If the 2018 version of the European guidelines is referenced, the authors should provide both of the sensitivity calculations or at least address why one was not preformed	Mainly because this is a short communication, it was difficult to discuss on this aspect. In the revised version (reference 4) it is clearly mentioned on page 158: 3.5. What is an acceptable number of false negative NBS results? *These are infants with a negative NBS test that are subsequently diagnosed with CF (a delayed diagnosis)* *a. Programmes should aim for a minimum sensitivity of 95%. Sensitivity is the number of true positive NBS results as a percentage of the total CF population (true positive and false negatives not including meconium ileus, see below).* Thus, we did not add a sentence on this aspect but we provide the information when reviewer 2 tackled this aspect (last comment)
2. The authors reference Rock et al (reference 5) stating that the paper lists many factors accounting for CF cases missed by NBS. The referenced paper only focuses on infants with a false positive screening result and primarily investigate the correlation between low apgar score and false positive IRT. The authors should consider changing the reference	We thank very much the reviewer and we apology for this error. The correct reference is: Rock MJ, Levy H, Zaleski C, Farrell PM. Factors accounting for a missed diagnosis of cystic fibrosis after newborn screening. *Pediatr Pulmonol*. 2011;46(12):1166-74. doi:10.1002/ppul.21509
3. paragraph 2. The Authors summarize the results of 15 surveys in regard to missed cases. They then state, that in Europe little is known about the demographics and overall factors that account for missing cases. As some of the 15 survey comes from European countries, this statement seems a bit overstated and should perhaps be nuanced.	We agree with the reviewer (6 European countries reported their data) and thus we modified the sentence accordingly (in red): *In Europe, only few countries reported about their age range at diagnosis, demographics, symptoms, factors accounting for missed cases and their CFTR variants.*
4. In regard to Pre-analytical issues 1. Dried blood spot sample not obtained/lost. It might be reasonable to distinguish between samples not obtained due to errors from heath personnel and samples not obtained because the parents have opted out of newborn screening. The first category is in essence unacceptable errors that needs to be addressed whereas the latter is difficult to address and a category of missed cases that we cannot avoid.	We agree with the reviewer, that it would be nice to distinguish between a refusal of parents to opt out of a NBS from all other reasons of not obtained samples. However, it is difficult to get this information. Anyway, if NBS is mandatory in a country, measures should be in place to do it anyway, so it is a missed case. But if NBS is not mandatory, it is not a missed case and NBS was not done

Reviewer 2: This brief report from the ECFS NSWG is very important to improve the collecting of data on missed cases of CF. It represents the results of the process of finding consistent definitions and data acquisition in different countries and for various algorithms. In my opinion, the report is well written and almost ready for publication	
I have only few comments on Table 1: The (n) for total cases should be in the first column and omitted after Total cases in the second	We have re-arranged Table 1
As in all other parts the second line should read: Median age at diagnosis, n (%) and describe the n for the different columns (132/138 54/54 78/84) here and not as "number" in the 4th line	We have made the changes in Table 1
The % figures for the sweat test results are missing	% have been added
It would be interesting to have some information about children with meconium ileus in this table. At least it should be mentioned whether these cases are included in the reasons for missed cases with IRT<cut off or not	We thank the reviewer for this comment. In the text we added a sentence in brackets (Background paragraph 3, in red): *Since 2000, there have been 15 surveys where individual patient data were reported for 138 missed cases (we excluded cases with meconium ileus as CF diagnosis is not delayed) following a negative NBS result.*