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Short Communication

Defining key outcomes to evaluate performance of newborn screening programmes for cystic fibrosis

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1. Background

The European Cystic Fibrosis Society (ECFS) Neonatal Screening Working Group (NSWG) aims to monitor the performance of newborn bloodspot screening (NBS) for cystic fibrosis (CF) and compare protocols to optimize effectiveness, whilst reducing negative impact in agreement with published international guidelines. ¹ The NSWG has supported numerous European countries and regions to establish NBS for CF. Collecting data on the performance of programmes across Europe has been a key element in evaluating and

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improving quality.^{2;3} From collecting data over two decades, it was clear to the NSWG that outcomes needed to be better defined and focused in order to ensure consistency in data collection. There was potential in previous surveys for variation in data collected including data quality. To improve the collection of data and better enable comparison of the performance of different programmes we established key outcomes and parameters required to calculate those outcomes. It should be noted that this is an evolving field, for example, when the first NSWG survey was undertaken, the CF transmembrane conductance regulator related metabolic syndrome (CRMS)/ CF Screen Positive, Inconclusive Diagnosis (CFSPID) designation for an unclear diagnosis after a positive NBS result did not exist.

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Newborn Screening Parameters (P) to be collected by each country (or region)

- 1. Number of live births per year
- 2. Number of infants screened per year
- 3. Number of infants with an inadequate dried blood sample per year
- 4. Number of infants with positive tier 1 test (IRT or IRT/PAP) per year
- 5. Number of infants with a positive NBS result (NBS+) with 2 *CFTR* variant or 1 *CFTR* variant referred for diagnostic assessment (including sweat testing)
- 6. Number of infants NBS+ with 0 *CFTR* variant and a positive IRT safety net (if applicable) referred for diagnostic assessment (including sweat testing)
- 7. Number of infants NBS+ with a confirmed CF diagnosis per year
- 8. Number of infants NBS+ with a confirmed CF diagnosis and 2 CFTR variants identified from the NBS protocol¹
- 9. Number of infants NBS+ with a confirmed CF diagnosis and 1 CFTR variant identified from the NBS protocol¹
- 10. Number of infants NBS+ with a confirmed CF diagnosis and 0 CFTR variants identified from the NBS protocol¹
- 11. Number of infants NBS+ with a CRMS/CFSPID designation per year
- 12. Number of infants NBS+ with a pending conclusion per year ²
- 13. Number of infants who did not complete the NBS algorithm per year
- 14. Number of infants NBS+ with one *CFTR* variant ³ and sweat chloride <30mmol/L if required by the protocol (reported as a carrier)
- 15. Number of false negatives without MI: cases clinically diagnosed with CF based on symptoms, family history and without MI, born in the previous year (affected but not detected by NBS)
- 16. Number of false negatives including MI: cases clinically diagnosed with CF based on symptoms, family history and including MI, born in the previous year (affected but not detected by NBS)⁴
- 17. Total number of infants diagnosed with CF during this year (True+ and False-)⁴
- 18. Number of infants with a true negative NBS result
- 19. Number of infants NBS+ result but not diagnosed as CF or CRMS/CFSPID
- 20. Mean age (median, min and max) in days, where date of birth is day 0 and when the newborn is first assessed by a CF specialist team

Abbreviations: CF: Cystic Fibrosis; CFSPID: CF screen positive, inconclusive diagnosis; CFTR: CF transmembrane conductance regulator; CRMS: CFTR-related metabolic syndrome; IRT: Immunoreactive trypsinogen; NBS: Newborn Bloodspot Screening; NBS+: positive NBS result; MI: meconium ileus; PAP: Pancreatitis-associated protein

Fig. 1. Newborn Screening Parameters (P) to be collected by each country (or region).

2. Objective

To establish key outcomes to determine and compare the performance of NBS programmes and define parameters needed to calculate those outcomes. Sweat testing is a diagnostic tool and lies outside the remit of this guidance but is a key outcome in assigning a CF diagnosis and is included in some parameters.

3. Methods

The outcomes were determined to reflect four main algorithms identified in the last survey, but also aiming at being inclusive to new screening algorithms. A core panel of experts (AM, JB, KWS and CC) constructed a process map to determine key outcomes that would best reflect performance and illustrate the impact on the family and clinical progress. Once these outcomes were determined, all parameters required to calculate the outcomes were

listed (Fig. 1). The outcomes and parameters were further refined following consultation with the wider NSWG.

Once a template for data collection was completed, this was distributed to all key workers identified in each programme to assess the feasibility of collecting these data. Further refinements were made following this assessment.

4. Results

Eight key outcomes were established:

- 1. Coverage of the NBS programme
- 2. Proportion of samples taken on to second tier testing
- 3. Number of infants with a CF diagnosis or CRMS/CFSPID designation
- 4. Number of carriers recognised
- 5. CF cases missed by NBS (both including and not including infants with meconium ileus)

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Outcomes for CF newborn screening programmes

Filled in by (capital letters): _____ Date: -- / -- / ----

Please provide information on your ongoing NBS programme

- Pilot study:
 Established programme:
- Country National:
 Regional:
 Name of the region:
- Attach file with current algorithm including IRT cut-offs, and if applicable PAP cut-off, CFTR panel with expected detection rate within the population screened, and (if used) IRT safety net cut-off.
- Is there a centralized structure for collecting the data? NO $\hfill \label{eq:VC}$ or YES $\hfill \label{eq:VC}$

if yes, provide the name of the responsible person and email (capital letters, please)

Modalities and time period (duration since the year in which the survey takes place) used for identifying cases missed by NBS

(false negative cases)

Abbreviations: CF: Cystic Fibrosis; CFTR: CF transmembrane conductance regulator; CFSPID: Cystic fibrosis screened positive, inconclusive diagnosis; DOB: Date of birth; IRT: Immunoreactive trypsinogen; Nb: Number; NBS: Newborn bloodspot screening; NBS+: Infants with a positive NBS result; MI: Meconium ileus; PAP: Pancreatic associated protein; SCC: Sweat chloride concentration; ST: Sweat testing

Key outcome	Definition	Parameters
1. Coverage of the NBS programme	Proportion of infants screened for CF per year	P2/P1
 2. First-tier or IRT/PAP (if applicable) a) Proportion of first-tier IRT or IRT/PAP b) Proportion of repeat tests required for inadequate dried blood sample (%) 	 a) Proportion of infants with a first-tier IRT or IRT/PAP ≥ cut-off per year b) Proportion of infants with an inadequate first dried blood sample per year 	P4/P2 P3/P2
3. NBS outcome (diagnosis or designation)		
a) CF (number (%)) if applicable	 a) CF: Sweat chloride concentration (SCC) ≥60mmol/L <u>and/or</u> 2 CF-causing mutations (CFTR2 database) Number of infants with a CF diagnosis per year 	P7
b) CRMS/CFSPID (number (%))	Proportion of infants carrying 2 CFTR variants within the programme protocol ¹ Proportion of infants carrying 1 CFTR variant within the programme protocol ¹ Proportion of infants carrying 0 CFTR variant within the programme protocol ¹ b) CRMS/CFSPID: An infant with a positive NBS result and 1) SCC -30mmol/L and 2 CFTR variants (mutations), at least one of unclear phenotypic consequences QB 2) Intermediate SCC (30-59mmol/I) and 1 or 0 CF-causing variants (mutation). ^{2,3} Proportion of infants with a CFSPID diagnosis per year	P8/P7 P9/P7 P10/P7 P11/P5+P6
 c) Pending conclusion, infants screened positive for whom the CF physician needs additional information to conclude CF, no CF, CRMS/CFSPID (number (%) (i.e. waiting for ST or genetic result) 	c) Not yet with a conclusion Proportion of infants with a pending conclusion per year	P12/P5+P6
d) Lost to follow-up (number (%))		
	d) Cases screened positive on IRT that could not follow the algorithm	
	(including deaths) Proportion of infants who did not complete the NBS algorithm	P13/P4
4. Carriers (if applicable), number (%))	Infants carrying one CFTR variant with a SCC <30mmol/L if required by the protocol Proportion of infants with one CFTR variant and SCC <30mmol/L/year if required by the protocol	P14/P5
5. CF cases missed by NBS without MI (number, (%))	Cases diagnosed CF based on symptoms or family history who were screened	
Cr cases missed by NBS including MI (number, (%)) (Please record babies born in the index year and then diagnosed within two years. For example, for the 2019 data collection include diagnoses subsequently made in 2020). Please outline on the first page how you have collected these data	negative Proportion of CF cases clinically diagnosed on symptoms or family history born during the intended analysis	P15/P7 and P16/P7
6. Performances for CF		
a) Sensitivity, %	a) Proportion of cases with CF diagnosis after positive NBS out of all CF cases including clinically diagnosed CF (to calculate the sensitivity you need the number for this year which makes a follow-up of at least 1-2 years necessary until children are clinically diagnosed)	P7/P17
b) Specificity, %	b) Proportion of cases with negative NBS not CF affected out of all CF not affected	P18/P19
c) Positive predictive value, %	 Proportion of cases with CF diagnosis after positive NBS out of all NBS positive cases 	P7/P5+P6
7. Performances for CRMS/CFSPID		
Ratio CF:CRMS/CFSPID	Ratio of CF to CRMS/CFSPID	P7:P11
8.Timeliness at initial visit at a CF centre a) CF	Mean age (median, min and max) in days, where date of birth is day 0 and when newborn is first assessed by a CF specialist team (may be before age at sweat test)	P20
b) CRMS/CFSPID		

¹ Number of mutations identified through the NBS programme; further analysis being done according to clinical need.
² Farrell PM et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr 2017; 1815:54-515

³ Southern KW et al. Inconclusive diagnosis after a positive NBS result for CF; clarification of the harmonised international definition. J Cyst Fibros 2019; 18(778):780

Fig. 2. Outcomes for CF newborn screening programmes.

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- 6. Sensitivity and specificity (positive predictive value) of the NBS protocol
- 7. The ratio of CF infants to those with a CRMS/CFSPID designation.
- 8. Age at initial visit at a CF centre for infants with CF and those designated as CFSPID

Definitions were established for each outcome and a panel of 20 parameters was developed to be collected to calculate these outcomes (Fig. 2).

The form includes general information on who completes the survey, on the ongoing NBS programme either pilot or established and either national or regional; current algorithm including IRT cut-offs, and if applicable PAP cut-off, CFTR panel and IRT safety net cut-off; existence or not of a centralized structure for collecting the data and the method used for identifying cases missed by NBS.

5. Discussion

Since there is no longer a valid scientific rationale for not screening the European newborn population for CF, we highlight the importance of careful CF-NBS protocol selection with respect to achieving ECFS standards and minimizing negative impact on the population screened. The considerable variation in approach to NBS for CF is not ideal, and clear outcomes are required to rigorously assess and compare the performance of different protocols. Using a systematic approach and engaging with key stakeholders we have developed for the first time a focused number of outcomes with clear definitions. We have also established parameters required to calculate the outcomes reliably. By generating a list of outcomes with clear definitions, the collection of data from countries and regions with NBS programmes will be more consistent, enabling better evaluation of performance. Through comparison of outcomes, programmes can adapt to achieve national standards and improve quality.

6. Credit author statement

The preliminary recommendations were drafted by a core group (JB, CC, AM, KWS) and then adapted following the comments of all other authors (core committee members of ECFS NSWG). We aimed to establish key outcomes to determine and compare the performance of NBS programmes across Europe and define parameters needed to calculate those outcomes.

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References

- [1] Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, et al. ECFS best practice guidelines: the 2018 revision. J Cyst Fibros 2018;17(2):153–78.
- [2] Southern KW, Munck A, Pollitt R, Travert G, Zanolla L, Dankert-Roelse J, et al. A survey of newborn screening for cystic fibrosis in Europe. J Cyst Fibros 2007;6:57–65.
- [3] Barben J, Castellani C, Dankert-Roelse J, Gartner S, Kashirskaya N, Linnane B, et al. The expansion and performance of national newborn screening programmes for cystic fibrosis in Europe. J Cyst Fibros 2017;16(2):207–13.