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Original Article

The expansion and performance of national newborn screening programmes for cystic fibrosis in Europe

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Abstract

Background: Newborn screening (NBS) for cystic fibrosis (CF) is a well-established public health strategy with international standards. The aim of this study was to provide an update on NBS for CF in Europe and assess performance against the standards.
Methods: Questionnaires were sent to key workers in each European country.
Results: In 2016, there were 17 national programmes, 4 countries with regional programmes and 25 countries not screening in Europe. All national programmes employed different protocols, with IRT-DNA the most common strategy. Five countries were not using DNA analysis. In addition, the processing and structure of programmes varied considerably. Most programmes were achieving the ECFS standards with respect to timeliness, but were less successful with respect to sensitivity and specificity.
Conclusions: There has been a steady increase in national CF NBS programmes across Europe with variable strategies and outcomes that reflect the different approaches.

Keywords: Cystic fibrosis; Newborn bloodspot screening; IRT; PAP; CFSPID; Carriers

1. Introduction

Over the last 50 years, European countries have introduced newborn bloodspot screening (NBS) programmes for a range of inherited diseases as an important public health programme [1,2]. Increasingly, cystic fibrosis (CF) has become a core component of these programmes. The rationale for NBS for CF is well established and there is a robust evidence base to support this strategy, however the challenges of this public health initiative are well documented [3].

In 2004, the European CF Society (ECFS) established the Neonatal Screening Working Group (NSWG) to track current

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practices in NBS, support implementation of NBS and establish consensus on issues arising in NBS. The first survey of the NSWG was performed in 2004/2005 and identified a wide variety of CF NBS programmes across Europe [4]. Of 26 programmes reported in this publication, two were nationally co-ordinated (France and Austria). In 2008, the NSWG published guidelines for CF NBS and recognised the wide variance in protocols. They suggested that given the geographic, ethnic, and health economic variations between countries, complete harmonisation of protocols was not appropriate, and every country had to evaluate and optimise their approach to CF NBS in light of the health structure and population screened [5].

In this study, we aim to provide 1) an update on CF NBS programmes in Europe, 2) describe and discuss differences between protocols, 3) identify barriers to establishing national NBS programmes, and (4) compare the performance with the recently published *ECFS Standards of Care Best Practice Guideline* [6].

2. Methods

An important early task of the ECFS NSWG was to identify a key worker in each country to provide information and act as a local co-ordinator. This was achieved and enabled complete coverage for the purpose of this exercise. The Core Committee of the NSWG developed three distinct questionnaires; for countries with national NBS programmes, regional NBS programmes, and without NBS (Appendix). The questionnaire for the national programmes was divided into 3 sections: (A) questions about the screening protocol, (B) the performance of the protocol in the year 2014, and (C) the structure of NBS in the country. The first section (A) included questions regarding the screening protocol with description of the specific algorithm, proportion of the screened population, sample collection (collection day), details of immune-reactive trypsinogen (IRT) measurement, second tier used including details of DNA analysis and/or pancreatitis-associated protein (PAP), procedure for one mutation and safety net strategy. The second section (B) included questions about the performance of the protocol in the year 2014 (if available), including the number of population screened, percentage above cut-off, percentage of referrals for clinical assessment (sweat test), CF diagnosis, inconclusive diagnosis, carrier detection, safety net, average and median age for diagnosis, first appointment in a CF centre, and number of false negatives and false positives. The third section (C) included questions regarding the processing of results including number of NBS laboratories in the country and details of informed consent. The questionnaires were sent to the key worker in each country in summer 2015. In some cases, they were not able to complete the survey and were encouraged to forward the survey to an appropriate colleague.

2.1. Data analysis

Performance of national programmes was assessed through data obtained from the 2014 survey and subsequent follow-up questionnaires to determine sensitivity by accurately reporting false negative cases. Data from our 2016 survey were also included to provide a more accurate assessment of practice in 2016, but not an assessment of performance of those programmes.

The data were presented graphically. Positive predictive value (PPV) was calculated as the number of true positive cases as a proportion of all positive NBS results (presented as a percentage). A positive NBS result was defined as an infant referred for clinical and diagnostic assessment (sweat testing). We also collected data about children screened positive for CF but their further clinical and diagnostic assessment was inconclusive, and these children were labelled as having an "inconclusive" diagnosis [7]. These infants are designated as CF Screen Positive, Inconclusive Diagnosis (CFSPID) in Europe [8]. We have included PPV calculations with and without CFSPID infants.

Programmes were asked to report the number of affected but not detected infants (false negatives) born in the year 2014. These numbers were used to calculate the sensitivity of the protocol in that year (the number of infants diagnosed with CF as a proportion of all infants with CF born in 2014). Infants who presented clinically (meconium ileus) but had a false negative NBS result were not included in the sensitivity calculation as this presentation does not delay diagnosis. We re-approached the 13 national programmes in 2016 to enquire if any additional false negative NBS results had been reported from 2014.

3. Results

3.1. Description of the current status of NBS for CF across Europe

A total of 31 countries provided data for 2014–2015 (16 returns from national programmes, 4 from regional programmes and 11 from countries not screening). Fifteen countries did not provide a full data reply, but confirmed that the situation had not changed (no plans for NBS). Overall, this represents a considerable increase in NBS programmes over a sixteen-year period, in particular national programmes (Fig. 1). In 2007, the Working Group reported two national programmes in Austria and France, although programmes in Northern Ireland and Wales described as regional at that time should now be considered national, as those countries have become devolved authorities within the UK. At end of 2015, there were 17 national programmes in Europe, including the most recent, Denmark (2015 data were not available for this country). Four countries (Spain, Italy, Germany and Serbia) report regional programmes. In Spain, there is complete coverage of the population, but each region uses a distinct NBS protocol. Germany has announced to start the national programme in September 2016. Twenty-five countries have no current programme. Ten were considering and planning for NBS programmes for CF. The most frequently reported barrier to implementation was a lack of financial support (4/11 countries). Other barriers included ethical concerns, a preference for antenatal screening and methodological arguments. In 2016, NBS for CF is undertaken in 21 countries in Europe. For the 13 national programmes that provided complete 2014 datasets, this corresponds to 2.7 million screened babies per year, compared to 1.6 million who were being screened annually ten years ago [4]. Bearing in mind that 2014 data do not include

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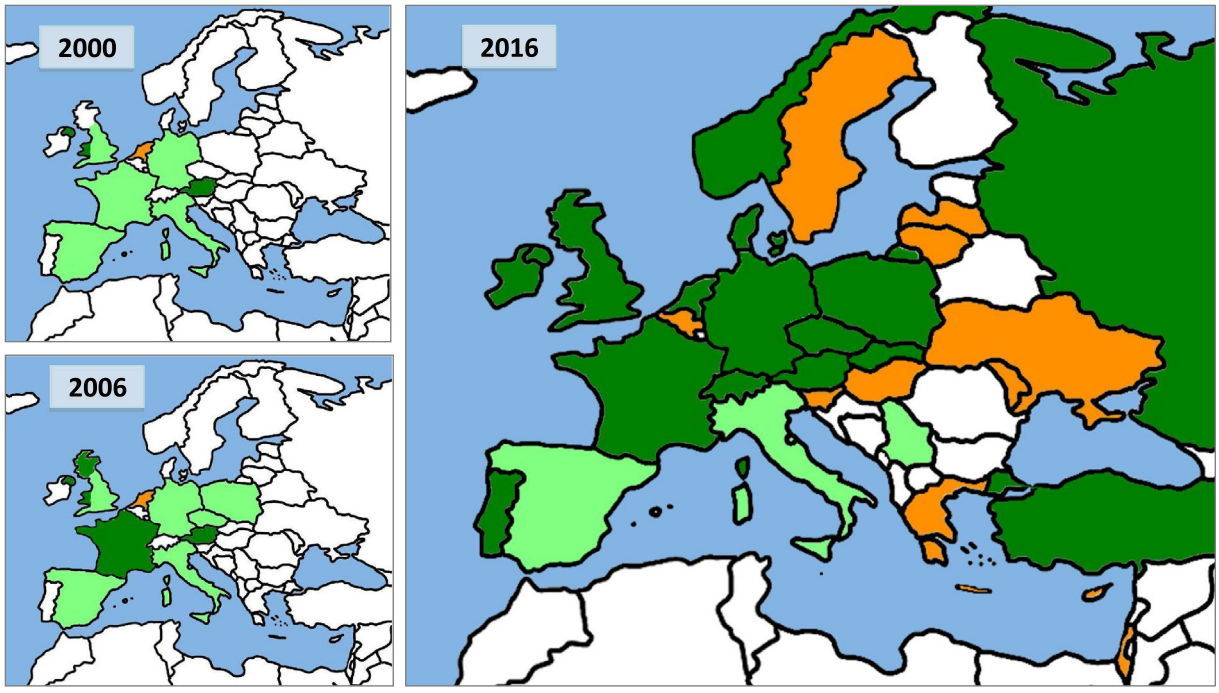

Fig. 1. The status of NBS for CF in Europe in 2000, 2006 and 2016. National programmes are coloured dark green and regional programmes, light green. Countries considering or planning NBS for CF are coloured orange and those with no plans, white.

regional programmes, this represents a considerable increase over the time period.

3.2. Structure of national NBS protocols in Europe

There continues to be considerable variability in structure of NBS programmes. The sixteen programmes that provided data on structure all report a distinct algorithm (Table 1). All programmes use measurement of IRT as the starting point (IRT-1). This measurement is undertaken on a dried bloodspot sample (DBS) taken in the first week of life (median day 3, ranging from days 2 to 8). Ten programmes report a fixed cut-off for IRT-1 ranging from 60 to 90 ng/ml (median 65). Six programmes report a floating cut-off to achieve a set percentage of samples sent for the next level of testing (ranging 99.0th to 99.5th centile). Nine programmes report exclusively using the Auto Delfia™ technology for IRT measurement.

The main factor contributing to the variability of programmes is the approach taken to second tier testing. In four programmes, a second sample is obtained at 14–21 days of age for a second IRT measurement (IRT-2). In these IRT-IRT programmes, a persistently raised IRT-2 value represents a positive NBS result and infants are referred for diagnostic assessment. Two programmes measure pancreatitis associated protein (PAP) on the initial DBS in combination with the IRT-1 result to establish the need for further testing. In one programme this is combined with subsequent DNA analysis, but in the other a combination of raised IRT and PAP values constitutes a positive NBS result. Most programmes (n, 10) report using a DNA panel as the second tier test. The initial panel size ranges from 4 to 644 mutations. Four programmes report undertaking further IRT testing at day 21 (IRT-2) for infants with one mutation recognised. In these programmes, infants with a low IRT-2 value are reported as carriers with a low likelihood of CF. In three programmes, extended gene sequencing (EGS) is undertaken on samples in which one mutation has been recognised on the initial panel. This provides opportunity for increased specificity if only mutations that are recognised as CF causing are reported as positive NBS results.

Ten countries employ a strategy which is called a “safety net” (also known as failsafe or ultra-high IRT). For this strategy, infants with a high IRT but no mutation recognised are referred for further testing. In most programmes, this involves a referral for sweat testing. In four programmes a repeat DBS is taken at day 21 and the infant referred only if this is raised. In France, in the absence of parental written consent for DNA analysis, the infant screened positive is referred for a second IRT at day 21.

3.3. Managing the interface with the family

Written informed consent is mandatory in six (38%) countries (Supplemental Table 1). In most countries the consent (oral or written) is obtained by a midwife or community nurse. In four countries, consent is obtained by a doctor. The DBS is obtained in the hospital (8 countries) or family home [6], by a nurse or midwife. In one country, the sample is taken in a GP surgery (office) by a Primary Care Physician and in another at the local health centre by a nurse.

A positive NBS result is most frequently reported by the CF centre [9], and in most cases [10] this is by a phone call. The result may be reported to the family by a CF Physician, a specialist CF nurse, a community Nurse or a Family Doctor [3]. In two countries, the NBS laboratories inform the family of the positive

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Table 1
The structure of 16 national NBS programmes for CF in Europe in 2015.

	Northern Ireland	Wales	Austria	France	Scotland	England	Russia
Initiated (year)	1984	1996	1997	2002	2003	2007	2007
Protocol (2015)	IRT DNA IRT	IRT DNA	IRT IRT	IRT DNA IRT	IRT DNA IRT	IRT DNA IRT	IRT IRT
Day of IRT-sampling	5	5–8	3	3	5	5–8	4–5
IRT method	Auto Delfia	Auto Delfia	Auto Delfia	Auto Delfia & Cisbio & *GSP	Auto Delfia	Auto Delfia	Manuel Delfia & Auto Delfia
IRT-1 fixed value in ng/ml	Y ≥62	N	Y 65	Y 65 (*60)	N	N	Y 70
IRT-1 floating centile (%)	N	Y 99.5%	N	N	Y 99.5%	Y 99.5%	N
PAP cut-off	N	N	N	N	N	N	N
Initial DNA panel (no. of mutations)	29	8	NA	29	4 + 29	4 + 50	NA
Further testing if one mutation identified	IRT-2 (day 21)	ST	–	ST	IRT-2 (day 21)	IRT-2 (day 21)	–
Safety net threshold if tier 2 is negative	IRT-1 ≥ 99.9%	IRT-1 > 170	–	IRT-1 > 100	IRT-1 > 99.9%	IRT-1 > 99.9%	–
Safety net strategy	IRT-2 (day 21)	ST	–	IRT-2 (day 21)	IRT-2 (day 21)	IRT-2 (day 21)	–

result. In three countries the result is given in the home and in three countries the family are informed by letter, although in two this is accompanied by a phone call. For subsequent genetic advice, this was undertaken by Genetic Counsellors in 12 countries, with the CF Physician in three and exclusively by the Physician in four.

3.4. Performance of national programmes

Thirteen national programmes provided performance data for the year 2014 (Table 2). A wide variance in performance is reported and there are consistent themes that can be recognised. The incorporation of DNA analysis into a protocol results in an improvement in positive predictive value (PPV), with fewer false positive infants being referred for sweat testing. The variance in PPV was considerable (range, 3 to 75%). Whilst the use of extended gene sequencing is associated with improved PPV, this is at the expense of increased recognition of infants with an unclear diagnosis. For some countries, inclusion of CFSPID infants results in a considerable improvement in PPV (for example, in Poland from 23 to 42%). The ratio of infants with CF compared to CFSPID ranged from 1.2:1 (Poland) to 32:1 (Ireland). Programmes incorporating DNA analysis were more likely to recognise a higher proportion of infants with CFSPID (Table 2). The median age of the infants diagnosed with CF when they are first seen by a CF team was 26 days (range, 15–53). There was no relationship between the algorithm employed and age when seen at the CF centre (Table 2). Sensitivity ranged from 81 to 100%. In total, 12 infants with meconium ileus had IRT-1 values below the cut-off. These infants were excluded from the sensitivity calculations.

When comparing the results to published ECFS standards, only one programme was not achieving the minimum standard for timeliness. However, four programmes did not achieve the minimum 95% standard for sensitivity, and five programmes had a PPV that was lower than the minimum standard of 30% (Table 3).

4. Discussion

There has been a steady increase in NBS for CF across Europe over the past ten years. Primarily this reflects the emergence of national programmes. At the end of 2015, NBS for CF is undertaken in 21 countries in Europe, 17 of them within a national screening programme. Germany started their national programme in September 2016 (Table 2), and Italy and Spain continue to have extensive coverage of their populations with regional programmes, with a wide variety of screening protocols and outcomes. To compare protocol performance, we restricted our analysis to national programmes with centralised data collection, although it is appreciated that some regions in Spain and Italy have considerable experience of NBS for CF and sizeable populations to screen.

Despite expansion of NBS for CF across Europe, we identified 25 European countries without NBS, including some countries with well-established CF care programmes. Barriers to implementation are predominately reported as political and financial, as NBS for CF is now recognised as a valid public health strategy for European populations [3].

The national programmes recorded in this survey report 16 different approaches to screening. This variance is a consistent theme across the world [3]. The variability of approach reflects a number of issues; 1) different health service models in individual countries, 2) lack of a comprehensive bioethical tool for assessing overall performance of CF NBS, 3) financial implications and 4) barriers to change. The majority of programmes [11] incorporate DNA analysis as a second tier test, as per "Best Practice" recommendation, and five national programmes report using biochemical tests only, either a repeat IRT measurement at days 14–21 or measurement of PAP in parallel to IRT-1. Ten programmes that use DNA analysis have incorporated a "safety net" for infants with a very high IRT and no mutations recognised. For most this involves a direct referral for sweat testing, although in the UK and Switzerland, the

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Slovakia	Czech Republic	Poland	Ireland	Nether-lands	Switzer-land	Norway	Turkey	Portugal
2009	2009	2009	2011	2011	2011	2012	2015	2015
IRT	IRT	IRT	IRT	IRT	IRT	IRT	IRT	IRT
IRT	DNA	EGS	DNA	PAP	DNA	EGS	IRT	PAP
	IRT			DNA	IRT			IRT
				EGS				
3–4	2–3	2	3–5	3–7	3–4	2	2	3–6
Neo IRT ILMA kit	Auto Delfia	IRT-neo-natal, IBL	Auto Delfia	Auto Delfia & GSP neonatal	GSP neo-natal IRT	GSP neo-natal IRT	Manuel Delfia	Auto Delfia
Y	Y	N	N	Y	N	Y	Y	Y
70	65			60/100		59.5	90	65/100
N	N	Y	Y	N	Y	N	N	N
		99.4%	99.0%		99.2%			
N	N	N	N	Y	N	N	N	Y
				3.0/1.6				1.6/0.5
NA	50	644	38	35	18	92	NA	NA
–	ST	EGS	ST	EGS	ST	EGS	–	–
–	IRT-1 > 200	–	–	IRT-1 > 100	IRT-1 > 60	IRT-1 > 400	–	IRT-1 > 150
–	ST	–	–	EGS	IRT-2 (day 21)	ST	–	ST

programmes undertake a second IRT measurement on a day 21 sample and only refer if that value is raised. Three programmes (Poland, Netherlands and Norway) are using extended gene sequencing for samples in which one mutation is recognised on the initial panel.

The direct impact of NBS for CF on a family is considerable and it is clear from the responses to this survey that there is significant variability in how different programmes interact with parent/carers. Informed consent is stated as a principle for all programmes, orally in ten programmes and as written consent for six. Consent is most frequently obtained by a midwife or community nurse, although in some countries it is the responsibility of a doctor. Processing a positive result is again an area of variability, but there are some common themes, with most reporting that the result is processed by the CF centre using a phone call to make the first contact. In most cases the programmes

Table 2
The performance of 13 national NBS programmes for CF in 2014.

	Northern Ireland	Wales	Austria	France	Scotland	England	Slovakia	Czech Republic	Poland	Ireland	Nether-lands	Switzer-land	Norway
Population (millions)	1.8	3.1	8.2	66.3	5.3	54.3	5.4	10.5	38.5	4.6	16.8	8.2	5.2
Birth per year	24,000	34,000	77,000	828,000	56,000	666,000	55,000	110,000	375,000	68,000	175′,000	86,000	60,000
Number of babies with IRT-1 > cut off	120 (0.50%)	170 (0.53%)	500 (0.60%)	3141 (0.39%)	405 (0.72%)	3842 (0.57%)	848 (1.54%)	942 (0.90%)	2558 (0.60%)	670 (1%)	1004 (0.56%)	524 (0.61%)	491 (0.8%)
Number of babies with positive NBS result (referred for sweat test)	16	27	130	409	24	255	181	98	291	72	31	108	16
CF diagnosis	4	9	25	139	18	157	5	15	66	32	21	34	10
CFSPID	0	0	1	17	NA	15	0	2	55	1	2	2	4
Carriers	15	18	NA	190	17	139	NA	80	170	40	6	46	58
PPV													
CF diagnosis only	25%	30%	20%	34%	75%	67%	3%	15%	23%	44%	68%	31%	63%
CF & CFSPID	25%	30%	19%	38%	75%	73%	3%	17%	42%	46%	74%	33%	88%
Ratio CF:CFSPID	0	0	25:1	8:1	NA	10.5:1	0	7.5:1	1.2:1	32:1	10:1	17:1	2.5:1
First seen in CF centre (days, median)													
CF diagnosis	22	21	30	34	24	22	15	31	53	23	25	18	26
CFSPID	–	–	30	54	38	22	–	85	55	23	25	25	29
Safety net													
Investigations	10	3	-	559	29	321	-	40	-	-	79	209	2
CF diagnosis	0	0		7	0	6		0			1	1	0
False negatives													
Without MI	0	1	1	8	0	3	0	1	0	0	5	1	3
Including MI	1	3	2	11	1	4	0	2	0	1	5	2	0
Sensitivity (without MI)	100%	90%	96%	95%	100%	98%	100%	94%	100%	100%	81%	97%	91%

Abbreviations: IRT, immune-reactive trypsinogen; NBS, newborn screening; CFSPID, CF screen positive, inconclusive diagnosis; PPV, positive predictive value; MI, meconium ileus.

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Table 3
A comparison of the performance of 13 national programmes with ECFS standards.

Standards of ECFS Care Guidelines (abbreviated)	Number of countries (%) achieving standards	Range of performance
1.3. The number of requests for repeat dried blood samples should be less than 0.5%	Not available	Not available
1.4. Positive predictive value (PPV) above 30%	8 (62%)	3–75%
1.5. Sensitivity above 95%	9 (69%)	81–100%
1.6. The sweat test should be analysed immediately and reported on the same day.	Not available	Not available
1.7. Infants with a confirmed diagnosis after NBS should be seen by the CF specialist team by 35 days (no later than 58 days after birth)	12 (92%)	15–53 days

report referral to a genetic counsellor if required, but in four programmes this information is provided by CF physicians.

With respect to the performance of the reported programmes, it can be seen that the majority are achieving acceptable sensitivity. The ECFS Standards of Care suggest that a sensitivity of 95% is a minimum requirement, however four programmes reported results that did not achieve this standard (Table 3). Some caution must be exercised as false negative (affected but not detected) results are challenging to collect, requiring reliable data collection systems. Also, some of these children born in 2014 may not have been recognised and diagnosed yet, although programmes were approached for these data again in 2016. A standardised approach for collecting false negative data would be of benefit for projects comparing performance across countries. It is well recognised that infants with meconium ileus regularly have IRT-1 values below the cut-off and disproportionately contribute to false negative datasets. In practical terms, these infants do not impact on performance as the CF diagnosis is made clinically in the first weeks of life. We have included sensitivity calculations without meconium ileus cases, as per the ECFS standards.

With respect to standards for timeliness; that an infant should be seen by the CF team within five weeks, only one programme was routinely failing to achieve this standard (Table 3). Despite this, programmes should not be complacent and should continue to strive to minimise systematic delays in their programmes. Programmes that are regularly reviewing infants after four weeks should critically assess their performance even though they are within current ECFS standards.

Programmes are performing less well with respect to PPV, with only 62% achieving the PPV standard of 30%. For families this equates to an acutely stressful time, as the false positive NBS result is confirmed by sweat testing [9]. Overall protocols that include DNA testing had higher PPV than biochemical protocols; however this was not a completely consistent result, with some IRT-DNA programmes not achieving the standard. Although additional infants with CF were identified through various safety net strategies, this was at the expense of a negative impact on PPV.

The data from this survey highlight the complexity of NBS for CF and the relationship between different components of algorithms and performance. Often a strategy that will improve one aspect of performance will have a negative impact on another, for example using more extensive DNA testing may improve specificity but at the expense of increased carrier recognition and the recognition of infants with CFSPID. There are not sufficient data available to confidently assess the impact of a CFSPID designation on families, but the general consensus is that recognising these infants is not an aim of NBS for CF [10]. As the initial data collection was undertaken in 2014 before a clear definition of CFSPID was available, programmes have been approached again to reassess their CFSPID numbers. Although this resulted in minimal change to the initial data presented, it would have been preferable for these infants to be designated in a more prospective manner, raising the possibility that CFSPID numbers were underestimated by this survey. Another outcome from CF NBS that generates debate is the recognition of carriers, with some arguing that this is beneficial to parents and even the individual [11]. Again there are not sufficient data to confidently assess the impact of carrier status on an individual or their family, but the consensus is that carrier recognition should be minimised in a public health screening programme [12]. Health services are under pressure to consider increasingly complex DNA based protocols for NBS for CF. It may be that this approach ultimately leads to improved PPV and timeliness, however at present our data suggest this may be at the expense of increased carrier and CFSPID recognition. Policymakers need to carefully consider the impact of such strategies on their population.

The expansion of NBS for CF across Europe has been a success story, with most programmes performing adequately with respect to international standards. This survey highlights the challenges and the need for continued quality improvement exercises. Programmes need to reflect critically on their performance and embed data collection systems to evaluate their outcomes prospectively. Large datasets are required to confidently assess the performance of a NBS programme on a specific population. Programmes should avoid altering cut-offs and other aspects, for example the safety net, unless the impact is carefully considered over time on a large dataset, but should also be willing to embrace change if that will improve performance. The main barrier to implementation is political inertia and CF advocacy groups have been critical in overcoming this hurdle. There is no longer a valid scientific rationale for not screening a European population, although the results of this study highlight the importance of careful protocol selection with respect to achieving ECFS standards and minimising negative impact on the population screened.

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Conflict of interest

There are no conflicts of interest.

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