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Evaluation Report 2020 Cystic Fibrosis Newborn Screening

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September 2021

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Abbreviations

CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CFSPID	Cystic Fibrosis Screening Positive, Inconclusive Diagnosis
CHUV	Centre hospitalier universitaire vaudois
DNA	Deoxyribonucleic Acid
DOL	Day of Life
EGS	Extended Genome Sequencing
FOPH	Federal Office of Public Health
IRT	Immunoreactive Trypsinogen
ISPM	Institute of Social and Preventive Medicine
mmol/L	Millimoles per litre
NBS	Newborn Screening
ng/L	Nanograms per litre
NPV	Negative Predictive Value
PAP	Pancreatitis Associated Protein
PPV	Positive Predictive Value

Terms

Guthrie Card / Test	A screening test usually performed on day 4 of life consisting of a heel-prick blood test that tests for several rare genetic diseases including CF
False Negative Rate	The probability that a child with CF will be have a negative screening test result
False Positive Rate	The probability that a child without CF will have a positive screening test result
Incidence	The number of new diagnoses of CF divided by the number of children born alive in Switzerland in the year 2020
Negative Predictive Value	The percentage of children who screen negative and do not have CF
Positive Predictive Value	The percentage of children who screen positive and have CF
Recall rate	The number of children that are recalled to have a second IRT test due to an initial high IRT with no genetic mutations found on DNA testing
Safety net	An added step in the screening process which results in referral of children to a CF centre if their initial IRT is high and no genetic mutations are found on DNA testing
Sensitivity	The percentage of children who have CF and screen positive among children with CF (true positive rate)
Specificity	The percentage of children who do not have CF and screen negative among children who do not have CF (true negative rate)
Linear regression coefficient	Parameter of a linear regression model which indicates the direction of a relationship between an outcome variable and an explanatory variable. A positive regression coefficient indicates that the outcome variable increases when the explanatory variable increases. A negative regression coeffienct indicates that the outcome variable decreases when the explanatory variable decreases.
95% confidence interval	Range of values that can be said with 95% confidence to contain the true parameter.

Foreword

Newborn screening for Cystic Fibrosis is a well-established, cost-effective and integral part of cystic fibrosis management that improves short and long-term clinical outcomes (Castellani, C et. al. Lancet 2016.) With the knowledge that there is an accepted and clear rational for the role of CF NBS in public health screening strategies, CF NBS was introduced in Switzerland in 2011. During the first 10 years it has been gradually adapted to further improve its performance.

The Cystic Fibrosis Newborn Screening Evaluation Report 2020 differs from that of previous years. This report does not only evaluate the performance of CF NBS in Switzerland in 2020 but expands on this by evaluating the past 10 years of CF NBS in Switzerland. Furthermore, it broadens its perspectives by including data collected from the ECFS surveys to compare CF NBS in Switzerland with other countries in Europe.

The report will as such be divided into three main sections.

The first chapter of this report evaluates the current state of CF NBS in Switzerland including current screening algorithms and results from data collected over 2020.

The second chapter of this report evaluates the past 10 years of CF NBS in Switzerland. This chapter focuses on comparing changes that have been implemented to the CF NBS algorithms during this time. It also includes an evaluation of its performance over the past 10-year period.

The third chapter of this report compares the Swiss CF NBS to other screening programmes across Europe. Most importantly, we examine the lessons we can learn from this comparison to other European screening programmes and discuss ways forward in the optimisation of the CF NBS programme in Switzerland.

Participating Institutes

Table 1: Participating Institutes and Responsible Persons

Institute	Centre	Responsible Person
Newborn Screening Laboratory	Kinderspital Zürich	PD. Dr. Ralph Fingerhut (until July 2020) Dr. Susanna Sluka (since Aug 2020)
CF Centres	Pädiatrisches CF Zentrum Kantonsspital Aarau	Dr. med. Peter Eng
	CF Zentrum Universitäts-Kinderspital beider Basel	Prof. Dr. med. Jürg Hammer
	Pädiatrisches CF Zentrum Inselspital Bern	Prof. Dr. med. Philipp Latzin
	CF Zentrum Hôpital Universitaire Genève	Prof. Dr. med. Constance Barazzone
	CF Zentrum CHUV Lausanne	Dr. med. Sylvain Blanchon
	Pädiatrisches CF Zentrum Luzerner Kantonsspital	Prof. Dr. med. Nicolas Regamey
	Regionales CF Zentrum Lugano	Dr. med. Maura Zanolari
	CF Zentrum Ostschweizer Kinderspital St. Gallen	Prof. Dr. med. Jürg Barben
	CF Zentrum Kinderspital Zürich	Prof. Dr. med. Alexander Möller
Genetic Laboratory	Kinderheilkunde Inselspital Bern	Dr. phil. nat. Javier Sanz
Institute of Social and Preventive Medicine	University of Bern	Prof. Dr. med. Claudia Kuehni Dr. med. Daria Berger Dr. phil. Eva Pedersen

Chapter 1

1 Newborn Screening for Cystic Fibrosis in Switzerland in 2020

The annual evaluation of cystic fibrosis newborn screening by the ISPM is an important part of the ongoing success of the CF newborn screening programme in Switzerland. This evaluation commenced in 2011 during the initial pilot phase of the CF NBS programme. It provides the office of the FOPH with an up-to-date reflection of the performance of the screening programme. Importantly, it provides recommendations for the adjustments required to the screening programme in order to optimise its performance. Past recommendations to screening programme adjustments have included increasing the IRT cut-off percentile and changing the second safety net IRT level in order to reduce unnecessary recalls and maintain the same performance of the study (Torresani et.al. 2013, Journal of Cystic Fibrosis).

The aim of this chapter is to describe the current screening process for Cystic Fibrosis in Switzerland and present results from the 2020 screening period.

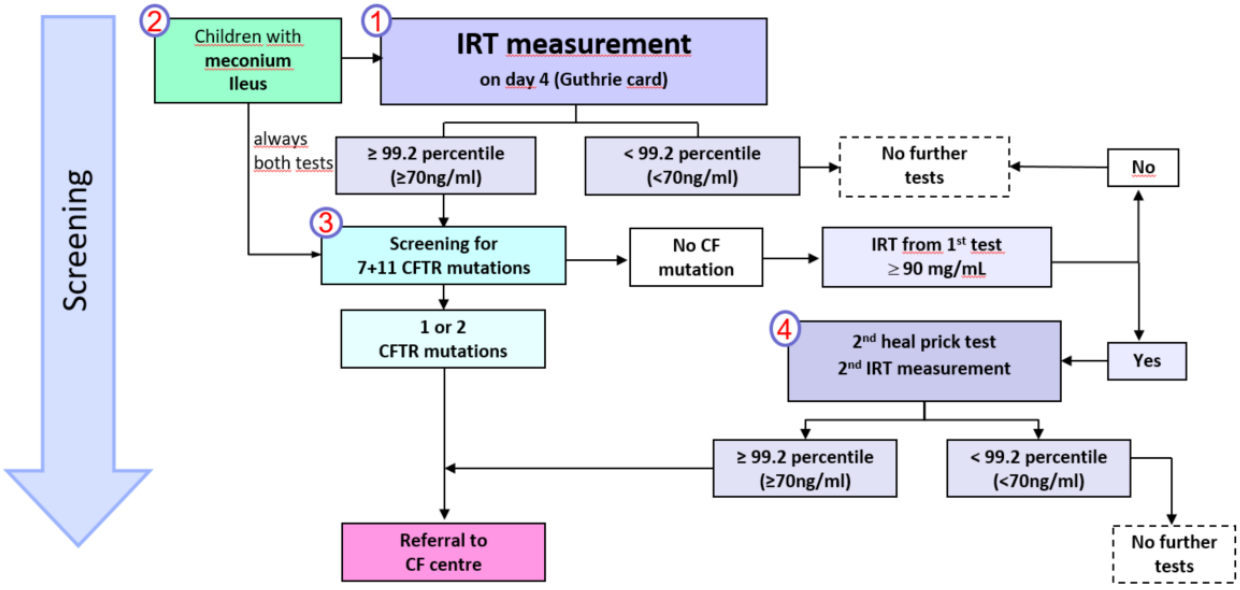
In this chapter we first discuss in detail the processes behind the current screening protocol including the processes in the newborn screening laboratory and the CF specialist centres. Secondly, we describe the way in which the newborn screening laboratory collaborates with CF centres to insure timely referral and review in cases of suspected CF. Thirdly, we describe data collection methods used in capturing CF NBS data including the way in which the ISPM, CF centres and laboratories collaborate to insure accuracy of data collection. We then go on to define the terms used in screening evaluation. Finally, we discuss the results of the evaluation of the CF NBS programme for the year 2020.

1.1 Current Newborn Screening Laboratory Algorithm

The current screening algorithm has remained unchanged over the preceding 12 months and is described in detail in Figure 1 below. When a positive screening result is identified, the Zurich central laboratory directly informs the appropriate CF centre by telephone. A suspicion of a CF diagnosis is flagged as urgent to a CF centre if two CFTR mutations are identified on screening. Due to current legislation the actual genetic mutations are not revealed.

The aim at this stage of the algorithm is for the child and family affected by the positive screening result to be seen by a CF specialist within a short time frame. Consultation with the CF specialist team allows for expert discussion regarding any diagnostic uncertainty and is particularly important in alleviating the stress caused in cases where screening is positive but diagnosis is ultimately negative for CF. This process also allows for an indepth discussion and planning regarding ongoing management of children with an unclear diagnosis (Cystic Fibrosis Screening Positive, Inconclusive Diagnosis, CFSPID). Review with the CF team is also essential as even if 2 CFTR mutations have been identified, a diagnosis must be confirmed by demonstrating that the CFTR gene is dysfunctional.

Figure 1: Newborn Screening for Cystic Fibrosis 2020



1. The initial IRT measurement is derived from a heel prick Guthrie card blood test on day 4 of life. If this test is positive (i.e. higher than 99.2nd centile, see Figure 1), a genetic test for a panel of the most common CFTR mutations is performed using the same blood sample as collected on the initial heel prick test.

2. In exceptional circumstances such as clinical suspicion of CF, meconium ileus or significant family history of CF the genetic testing is performed regardless of the IRT.

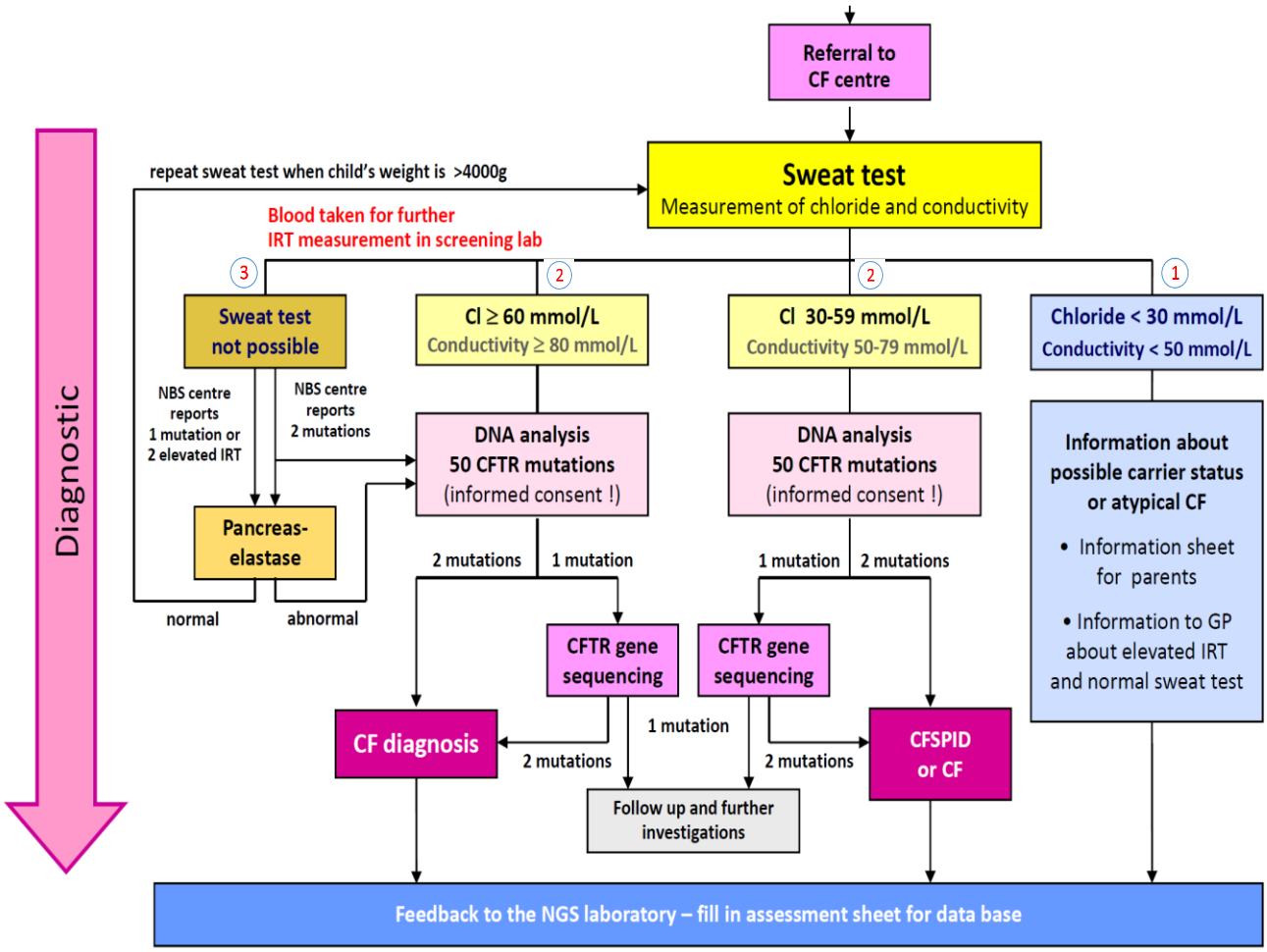
3. In the case of a positive genetic screening result i.e. the presence of one or two known CFTR mutations, the newborn screening algorithm is considered to be positive and the child is referred to a CF centre immediately. This allows for timely review by a CF specialist in order to clarify the diagnosis with reference standard testing including a sweat test.

4. In the case of a negative genetic screening result and an initial IRT result above 90 ng/ml, a second Guthrie test is performed. If the second IRT result is above the 99.2nd centile, the child is referred to a CF specialist in order to clarify the diagnosis with reference standard testing including a sweat test. This process is known as the safety net.

1.2 CF Centre Diagnostic Algorithm

Once a positive CF NBS result is identified, the child is referred to a CF centre specialist. The diagnostic process that takes place at the CF centre is demonstrated in Figure 2. The initial diagnostic testing offered by the CF centre is the Macroduct sweat test (reference standard). Subsequent tests such as Nanoduct sweat testing as well as faecal pancreatic elastase or extended genetic sequencing are performed depending on the results of the initial Macroduct sweat test and are determined by the treating clinician.

Figure 2: Diagnostic Process in the Cystic Fibrosis Centre



1. Negative Macroduct Sweat Test

If the chloride level of the Macroduct sweat test is less than 30 mmol / L, the test is considered negative and no further testing is performed. If CF mutations are present the family receives professional genetic counselling regarding their possible CF carrier status. Additionally, the family doctor is informed of this outcome.

2. Positive or Borderline Macroduct Sweat Test

The macroduct sweat test is considered positive if the chloride level is measured above 60 mmol / L and further genetic analysis can be performed at this stage if CFTR mutations are not yet identified.

If the chloride level of the macroduct sweat test is measured between 30 and 59 mmol / L, the test is considered equivocal and the child is reviewed by a CF specialist for further consultation, examination and testing as required. For example, if genetic testing detects only one or no CFTR mutations an extended genetic analysis to detect further mutations is performed.

3. Sweat Test Unable to be Performed

If the sweat test cannot be performed, a faecal pancreatic elastase test is performed. If the pancreatic elastase test is normal, the sweat test is repeated when the child weighs at least 4,000g. However, if the pancreatic elastase result is pathological or two known CFTR mutations were identified on screening the child is referred for further extended genetic analysis as in the case of borderline cases.

1.3 Data Collection Methods

The communication process and feedback loop regarding the evaluation of CF NBS in Switzerland is demonstrated in Figure 3. Initially, the results of the Cystic Fibrosis Newborn Screening process are collected at the Kinderspital Zürich Newborn Screening laboratory. These initial results are entered directly into the current ISPM CF database by the responsible newborn screening laboratory staff. Consent for participation in the CF database is collected by the CF specialist at the CF centre visit and sent to the ISPM team. In the case of consent being denied the results of CFTR mutations are entered directly into the ISPM CF database by those responsible from the genetic laboratory.

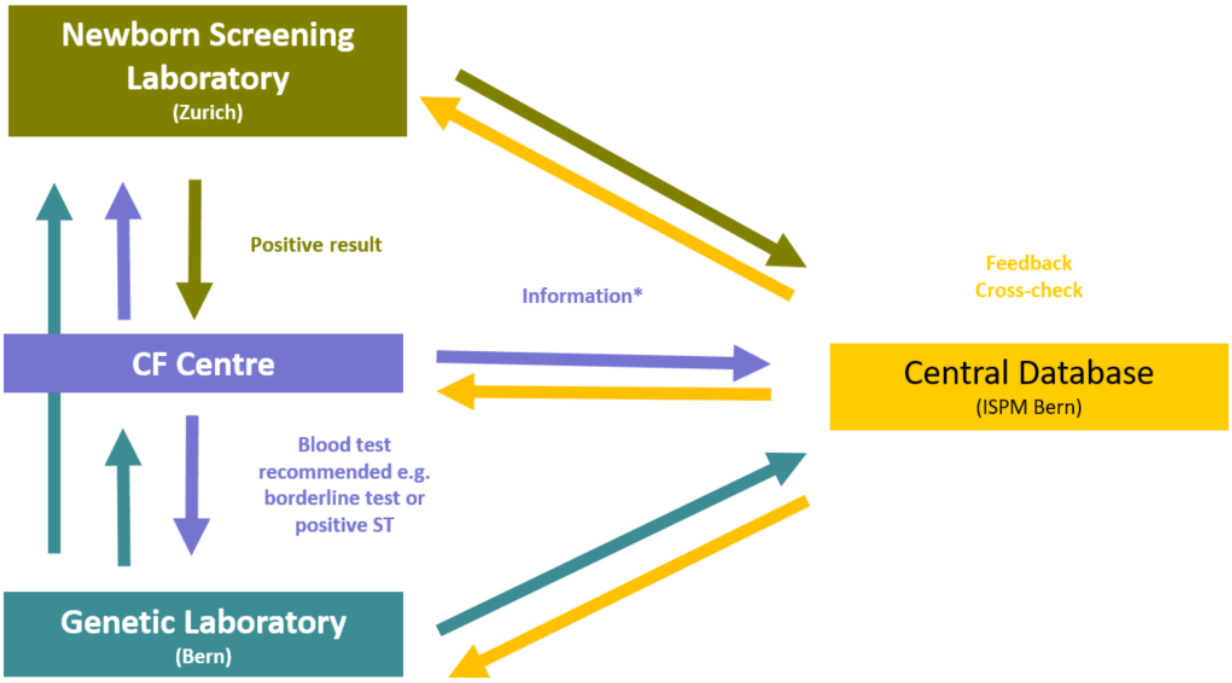
Additional information about the diagnostic process is sent to ISPM staff by the CF specialists in the form of a completed CF assessment sheet. This assessment sheet is sent regardless of the result of the sweat test. Further diagnostic clarification is sought by the ISPM data manager who requests missing information directly from CF specialists in the form of further assessment sheets or individual data. Missing data is then added to the ISPM CF database.

In the case of a false negative screening result, the CF specialist informs the ISPM CF database manager directly. However, the ISPM CF database manager also send a reminder to the CF centres regularly to insure that data is collected for children with a false negative screening result. False negative cases are formally discussed at the annual CF specialist conference.

Having the database located separately to the newborn screening laboratory and CF centres aids the ISPM team in successfully performing the independent quality evaluation of the CF screening algorithm performance. It also allows the ISPM to provide feedback directly to CF centres and laboratory staff on data quality.

Figure 3 provides an overall summary regarding the ways in which the newborn screening laboratory, genetic laboratory, CF centres and central database communicate in order to ensure data collection accuracy.

Figure 3: Feedback Communication Loop for Cystic Fibrosis Newborn Screening Evaluation



**Information: assessment sheet, follow-up assessment sheet, informed consent form*

Figure 3 demonstrates the communication between the newborn screening laboratory, the CF centres, the Genetic laboratory, and the central database. The central database holds an important role for the correct and complete collection of data from all sites. This is vital to optimise the Cystic Fibrosis newborn screening algorithm.

1.4 Evaluation Parameters

The parameters used for the evaluation of the CF newborn screening programme have been adapted from those recommended by the ECFS Guidelines. The parameters used for the evaluation of the CF NBS programme are the following:

Parameters associated with the timing of screening to timing of diagnosis:

- Days since birth to CF centre specialist review
- Days since birth to genetically confirmed diagnosis

Parameters associated with evaluating screening performance to optimise the algorithm:

- Recall rate
- Sensitivity
- Specificity
- Positive Predictive Value (PPV)
- Negative Predictive Value (NPV)
- Number and incidence of CF cases

These parameters are used and reviewed during the annual CF NBS evaluation performed by the ISPM. The parameters allow for consistent comparison in evaluations performed on CF NBS in Switzerland across the years as well as comparison to other CF NBS programmes across Europe. Consistency with the reporting parameters used in the annual CF NBS evaluation is one of the strengths of the CF NBS programme in Switzerland.

1.5 Evaluation Results 2020

In 2020, an IRT test was performed via Guthrie heel prick test in 88,717 children (Figure 4). Of these children, 1,016 (1%) had an elevated IRT or meconium ileus and underwent genetic screening for CFTR mutations. There were 80 children (8% of the 1,016) that had one or two CFTR mutations identified. There were 643 children (63% of 1,016) who had no CFTR mutations identified and who consequently underwent a second IRT heel prick blood test. In 619 of these 643 children, the second IRT test was below the cut-off and as such these children received a negative screening result. The remaining 22 children had an IRT higher than the cut off and were referred to the appropriate CF centre for diagnostic clarification. Two children were referred due to meconium ileus or by clinical discretion. Overall, the number of children who were recalled for further testing after the initial heel prick test was 723 (80 + 643) giving a recall rate of 0.8% (723 / 88,717).

In total, 104 children were referred to a CF centre for further diagnostic clarification (referral rate of 0.1% of 88,717). Of these 104 children, CF was definitively diagnosed in 19 children (PPV 18% - Table 2). A diagnosis of CF was excluded in 80 children after further testing. The diagnosis of CFSPID was made in 2 children. No further diagnostic clarification was possible in 3 cases due to: illness, loss to follow up and pending further testing. The incidence of CF was 1 in 4,295 children over the 1-year screening period.

There was one false negative case identified in 2020. This child screened negative and eventually was seen in a CF centre at approximately 7 months of age for diagnostic work up in the context of failure to thrive. The child was subsequently diagnosed with CF after a positive sweat test.

During 2020 there was a median of 19 days before a child was seen in a CF centre after birth. Genetic confirmation of CF diagnosis occurred at a median of 23 days from birth.

Every child identified in the 2020 period is receiving care at an appropriate CF centre.

Figure 4 below demonstrates the overall numbers of children participating in each screening step from Guthrie test to diagnosis in Switzerland 2020.

Figure 4: Number of Children who Participated in Each Screening Step from Guthrie test to Diagnosis in Switzerland 2020.

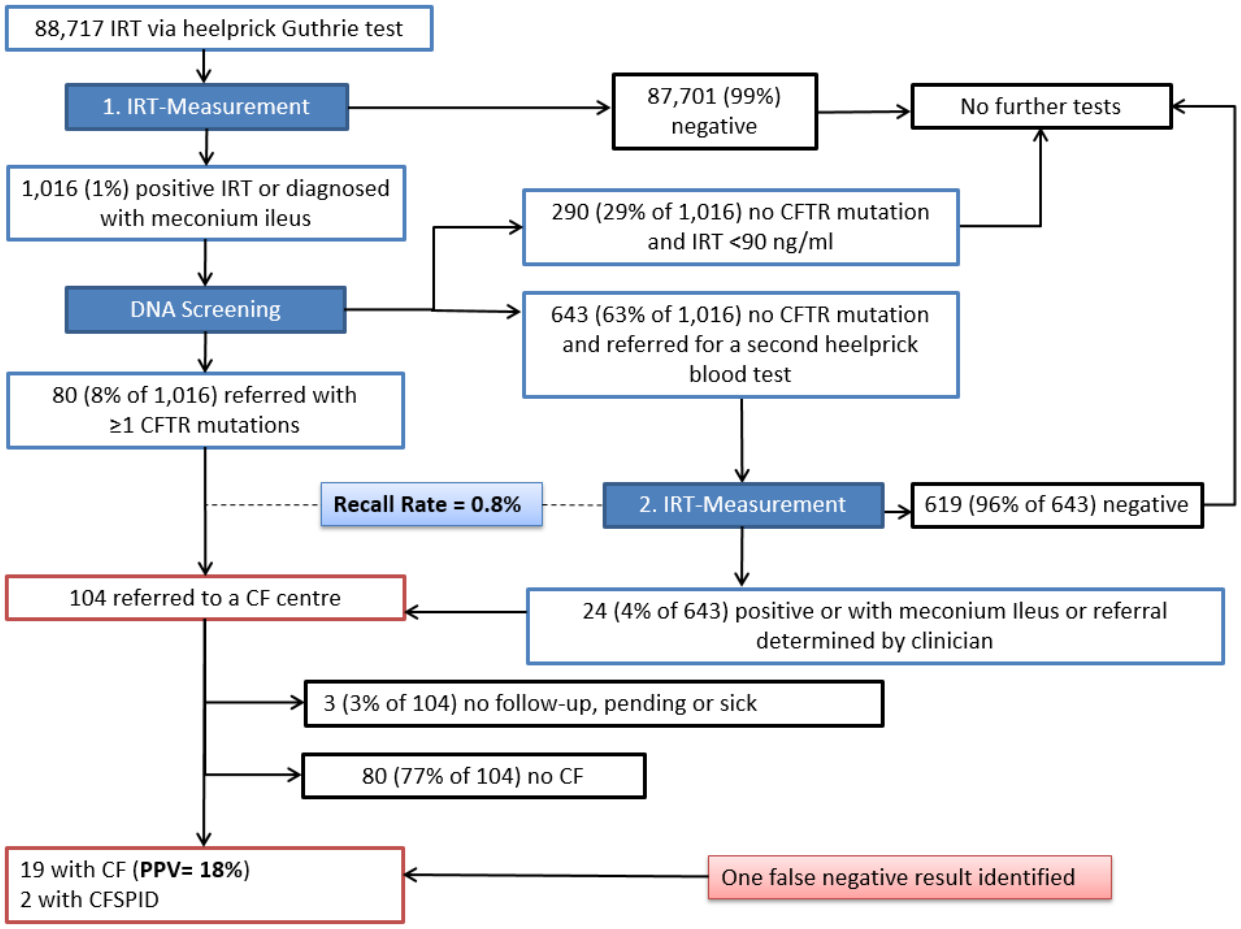


Table 2 demonstrates the outcomes of the evaluation parameters for CF diagnosis using the CF NBS in Switzerland over the period of 2020.

Table 2: Evaluation Parameters for CF diagnosis using the Cystic Fibrosis Newborn Screening Programme in Switzerland, 2020

		True Diagnosis		
		CF	**No CF**	**Total**
Screening Result	**CF**	19 *(True positive)*	85* *(False positive)*	104
	No CF	1 *(False negative)*	88,612 *(True negative)*	88,613
		20	88,697	**88,717**

*CF was excluded in 80 children referred to a CF centre, 2 children were diagnosed with CFSPID, 2 children were too sick to undergo reference standard testing, 1 was lost to follow up

Screening Parameters for 2020		
Sensitivity	True positive rate: 19/20	95%
Specificity	True negative rate: 88,612/88,697	99.9%
False negative rate	1 - sensitivity	5%
False positive rate	1 - specificity	0.01%
Positive predictive value	True positives/screened positive: 19/104	18%
Negative predictive value	True negative/screened negative: 88,612/88,613	99.9%
Recall rate	723 / 88,717	0.8%
Incidence of CF	CF cases/live births: 20 / 85,914	1:4,295
Incidence of all diagnoses (CF+CFSPID)	22 / 85,914	1:3,905
Time from birth to review at a CF centre	Median (range)	16 Days (12-22)
Time from birth to genetic diagnosis of CF	Median (range)	26 Days (21-37)

Discussion

In 2020 the Cystic Fibrosis Newborn Screening programme in Switzerland continued to perform an integral role in the care of children with Cystic Fibrosis. During this past year, a total of 19 children were diagnosed with Cystic Fibrosis as a direct result of the screening programme. Consequently, these children were able to directly access important disease altering medication and intervention improving their quality of life as well as short and long term health outcomes.

During the same period, one child was missed through the CF NBS process and as such was designated a false negative screening result. The false negative rate of the CF newborn screening process in Switzerland in 2020 was thus 5% which is at the limit of what is considered acceptable by the ECFS. However, given the low absolute numbers, results from a single year are strongly influenced by chance and thus have to be interpreted by looking at data over several years. This data is presented in chapter 2.

Two children were diagnosed with CFSPID in the 2020 period. There were 3 children who did not have a diagnosis of CF excluded despite a positive screening result. Reasons for this include: loss to follow up and severe illness.

The positive predictive value of the screening process in 2020 was 18%. This is below the international standard. The CF NSB laboratory team uses a floating cut-off for identifying abnormal IRT values. This refers to a percentile threshold above which the IRT cut off is determined to be too high. As such, the IRT cut off value used in the algorithm changes depending on the observed distributions of sampled IRT values. In late 2020, it was observed that the IRT cut off of 70 was capturing far more children than previously. The reasons for this are unknown although fluctuations and seasonal variations in IRT levels have been known to occur. Consequently, effective from late 2021, the IRT cut off level for the floating percentage of 99.2 was changed from 70 to 95 while the 99.5th percentile cut off was changed from 90 to 110. Further trends of the PPV over the 10-year period as well as other underlying reasons for the observed changes in PPV are discussed further in chapter 2 including possibilities for adjustments to the algorithm.

The sensitivity of the screening algorithm in 2020 performed highly with an overall value of 95% and the time period to definitive CF diagnosis and time seen by CF specialist (median of 26 and 16 days respectively) has remained within the recommended.

In the next chapter, we review and discuss the past 10 years of screening in Switzerland to better understand how to uptimise the current screening algorithm.

Chapter 2

2 Ten Years of Newborn Screening for Cystic Fibrosis in Switzerland

The year 2020 marks 10 years since the beginning of NBS for CF in Switzerland. Newborn screening was first introduced in Switzerland in 2011. The initial pilot phase lasted from January 2011 to December 2012. During this time the programme was closely monitored and evaluated. The evaluations have helped to direct adjustments made to the programme. The programme has also undergone changes to its algorithm determined by advances in newborn screening methods. At this 10-year milestone, it is time to reflect on the progress of the CF NBS programme in Switzerland and identify ways in which it can be optimised for the future.

As such, the aim of this chapter is to describe the changes to the screening process for Cystic Fibrosis in Switzerland over the past 10-year period and present an evaluation that analyses data over the entire 10-year period.

In this chapter we first discuss changes in the Swiss CF NBS algorithms over the past 10-year period. Secondly, we demonstrate findings of our 10-year performance evaluation using the same performance parameters that we have used throughout this screening programme. Third, we will describe the observed fluctuations in CF incidence in Switzerland over the 10-year period. Finally, we explore the role of the safety net in the overall performance of the screening programme.

2.1 Changes to the Screening Algorithm 2011-2020

Over the preceding 10-year period the CF NBS in Switzerland has undergone changes to the way in which the screening process is performed. The majority of these changes occurred in the early pilot and establishment phase of the project between 2011 and 2013 during which adjustments were made to improve key parameters such as PPV and sensitivity and reduce unnecessary tests on healthy children.

Following this period, the protocol remained consistent until 2019 when the laboratory test system used to assess IRTs was changed which resulted in the adoption of new IRT cut off values. The summary of these changes over the 2011 to 2020 period can be seen in Table 3 below.

Table 3: Changes to the Cystic Fibrosis Newborn Screening Algorithm 2011 to 2020

Year	Screening Component Affected	Change Made
2011	IRT	Cut-off increased from 45ng/mL to 50 ng/mL
2011	Second IRT	Threshold for second IRT was changed from 50ng/mL to 60 ng/mL
2011	DNA	Genetic screening was carried out simultaneously to IRT measurement in children with meconium ileus
2011	Referral to CF centre	Reporting of screening result to CF centres adjusted to "screening positive" regardless of mutation
2011	Sweat Test	Genetic analysis was performed immediately if sweat test was invalid
2013	DNA	DNA kit for genetic screening in the NBS laboratory changed as the components of the "in house test" were no longer available and a commercial test kit with 18 CFTR mutations had to be used.
2013	Database management	Further separation of database following Human Research Act amendments
2013	Faecal pancreatic elastase	Faecal pancreatic elastase performed in the CF-centres in the case of invalid sweat test and 0 or 1 CFTR mutations to avoid CFSPID cases; sweat test was repeated when child had a weight > 4,000g
2014	DNA	Diagnostic genetic analysis expanded to the most common 50 CF-causing CFTR mutations in the CF centers
2014	Nomenclature	Equivocal CF diagnosis removed and CFSPID definition introduced
2014	Database management	Access provided to the newborn laboratory
2015	Database management	Access provided to the genetic laboratory
2019	IRT	Laboratory system changed from Perkin-Elmer to Labsystems affecting absolute IRT values

2.2 Evaluation Results 2011-2020

During the 10-year period of CF NBS in Switzerland from 2011 to 2020, a total of 873,273 children had an initial IRT test result after undergoing the Guthrie test as a newborn (Figure 5).

Of these 873,273 children, a total of 949 children were referred to a CF centre for further diagnostic clarification (referral rate of 0.1%). Of these 949 children, CF was definitively diagnosed in 244 children (PPV 25.6% Table 4). A diagnosis of CF was excluded in 657 children after further testing. The diagnosis of CFSPID was made in 29 children. No further diagnostic clarification could be performed in 19 cases due to: illness, loss to follow up and pending further testing. The incidence of CF was 1 in 3,357 children over the 10-year screening period.

In total during the 10-year screening period there were ten false negative cases identified. The number of months of delay to be diagnosed ranged from 1 to 30 months. The summary of these cases can be found in Table 5.

During the 10-year period there was a median of 16 days (inter-quartile range 12-22) from birth before a child was seen in a CF centre. There was a median of 26 days (inter-quartile range 21-37) after birth before a child received genetic confirmation of a CF diagnosis.

Figure 5 demonstrates the overall numbers of children participating in each screening step from Guthrie test to diagnosis in Switzerland from 2011 to 2020 without 2013 represented in parts due to variations in the algorithm during the time. Table 4 demonstrates the outcomes of the evaluation parameters for CF diagnosis using the CF NBS in Switzerland over the period of 2011-2020. Table 5 summarizes the false negative cases that were missed by the cystic fibrosis newborn screening over the last 10 years.

Figure 5: Number of Children who Participated in Each Screening Step from Guthrie test to Diagnosis in Switzerland 2011-2020*

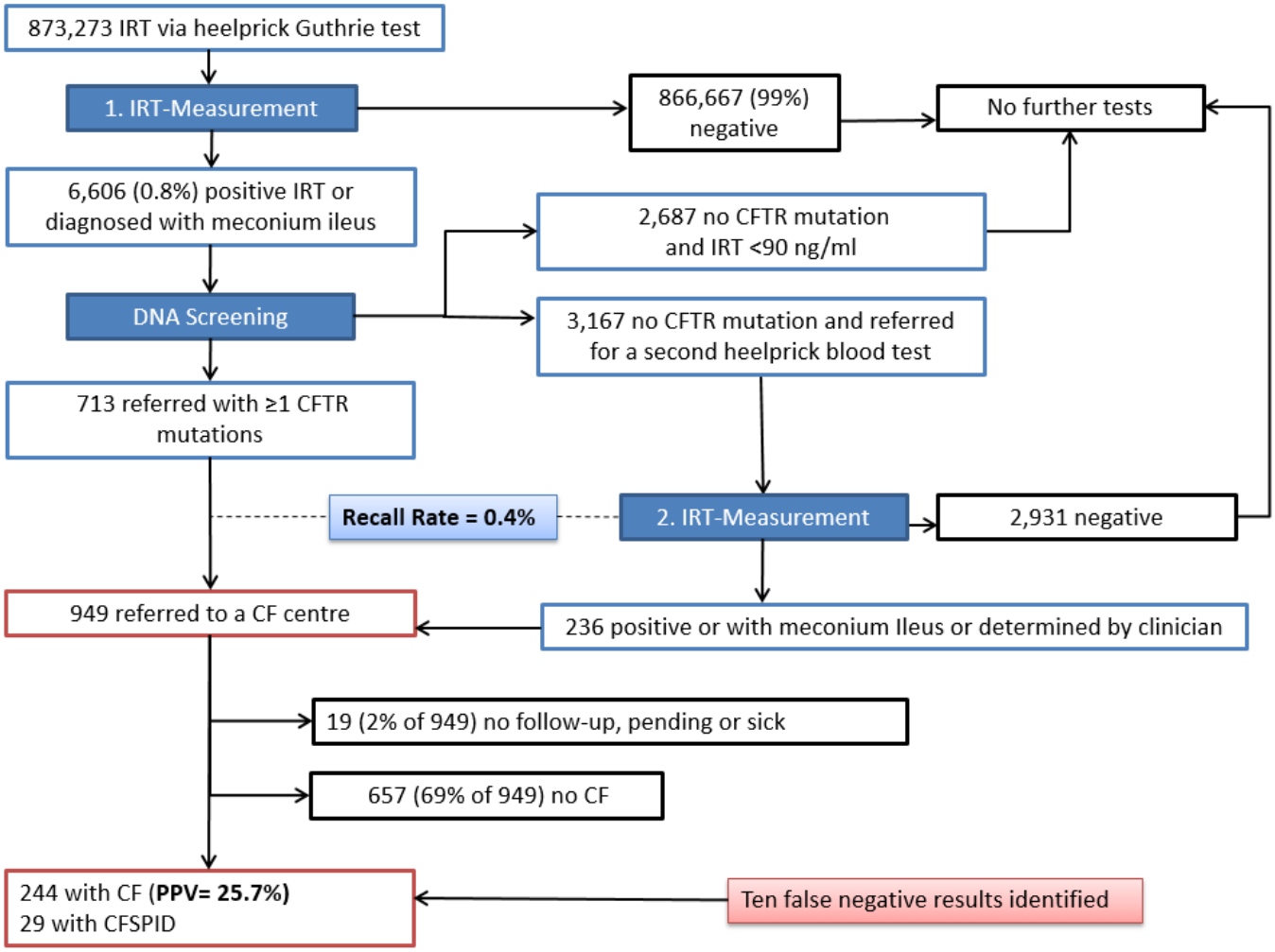


Table 4: Evaluation Parameters for CF diagnosis using the Cystic Fibrosis Newborn Screening Programme in Switzerland, 2011-2020

		True Diagnosis		
		CF	**No CF**	
Screening Result	**CF**	244 *(True positive)*	705* *(False positive)*	949
	No CF	10 *(False negative)*	872,314 *(True negative)*	872,324
		254	873,020	**873,273**

*CF was excluded in 657 children referred to a CF centre, 29 children were diagnosed with CFSPID and 19 children had an elevated IRT in the context of another disease (such as multiple organ failure, trisomy 21 or heart defects) or were lost to follow up

Screening Parameters for 2020		
Sensitivity	True positive rate: 244 / 254	96%
Specificity	True negative rate: 872,314/ 873,020	99.9%
False negative rate	1 - sensitivity	4%
False positive rate	1 - specificity	0.01%
Positive predictive value	True positives/screened positive: 244 / 949	25.7%
Negative predictive value	True negative/screened negative: 872,314 / 872,324	100%
Recall rate	3,880 / 873,273	0.4%
Incidence of CF	CF cases/live births: 254 / 852,750	1:3,357
Incidence of all diagnoses (CF+CFSPID)	283 / 852,750	1:3,013
Time from birth to review at a CF centre	Median (range)	18 Days (9-56)
Time from birth to genetic diagnosis of CF	Median (range)	26 Days (13-94)

Table 5: Summary of False Negative Cases Missed by Cystic Fibrosis Newborn Screening over the period 2011 to 2020[+]

No.	Delay in diagnosis (months)	IRT-1 (dol)	IRT-2 (dol)	CFTR mutation 1	CFTR mutation 2	Sweat chloride [mmol/L]	Faecal elastase [ug/g]	Symptoms
1	5	73.6 (4)	34.1 (25) *	2789+5G >A	2789+5G >A	62	340	Severe metabolic acidosis after diarrhoeal illness
2	23	16.9 (5)	-	F508del	R1158X	95	<15	Failure to thrive and steathorrhoea
3	2	49.6 (4)	53.6 (61) **	F508del	F508del	101	<15	Prolonged RSV bronchiolitis and failure to thrive
4	4	132.1 (4)	***	R347P	Q525X	107	521	Chronic cough
5	7	49.6 (4)	-	F508del	F508del	81	<15	Failure to thrive
6	8	37.4 (4)	-	R352Q	2184insA	61	<15	Chronic cough & failure to thrive, Pseudo-Bartter syndrome
7	30	34.9 (4)	-	1548delG	H139L [#]	95	501	Nasal polyps and recurrent bronchitis
8	4	49.1 (4) +		F508del	F508del	94	<15	Chronic cough and failure to thrive
9	1	45.6 (5) +	-	3905insT	R1066H	66	47	CF diagnosis at birth due to family history
10	7	69 (3)	-	F508del	3849+10 kbC>T	79	71	Weight loss, failure to thrive, Pseudo-Bartter syndrome

*2nd IRT performed as no CFTR mutation was found on genetic screening **Due to clinical suspicion of CF a 2nd heel prick tests was performed ***Due to communication barriers no 2nd IRT was performed, [#]Not yet reported in the CFTR2 database, dol = day of life, [+]table based on publication under submission by Fingerhut, R. et. al.

Figure 6: Number of cases of CF, CFSPID and false negative results per year from 2011 to 2020

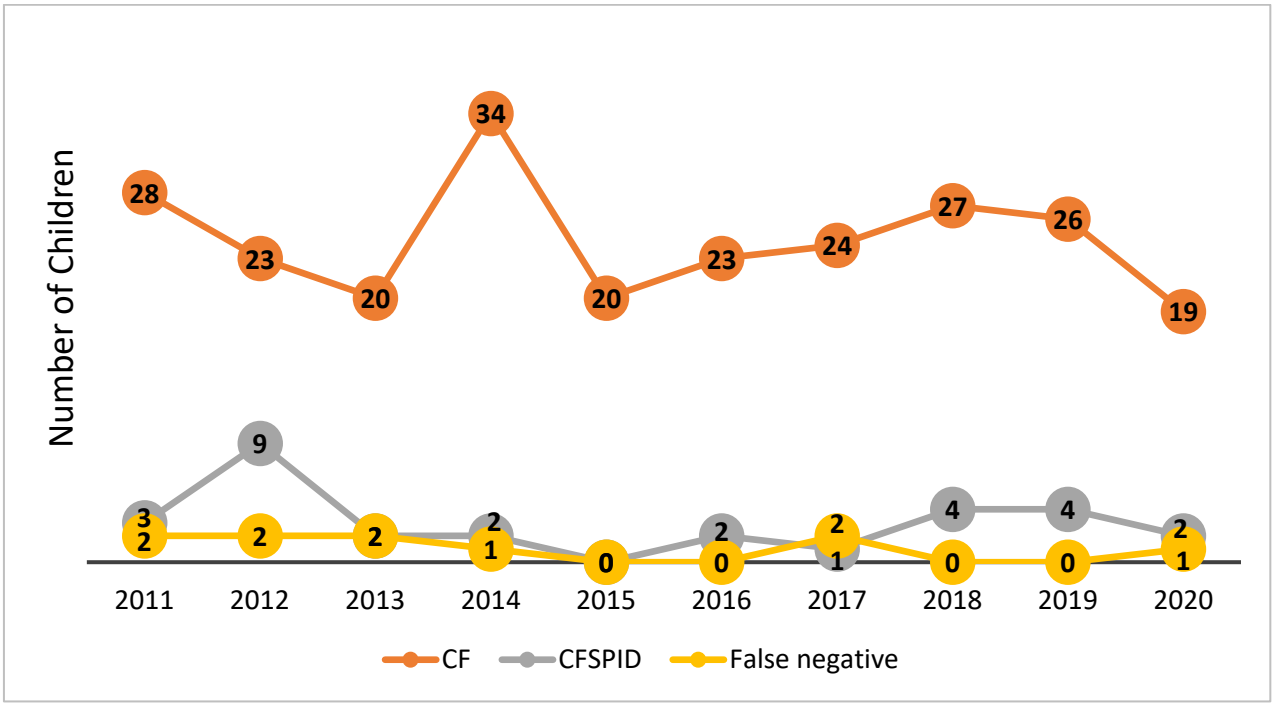


Figure 6 demonstrates the total number of CF, CFSPID and false negative cases over the 2011 to 2020 CF NBS period in Switzerland. Numbers over the entire time period remained stable with only minor fluctuation which was within expected patterns. The total number of CF cases diagnosed over the 10-year period was 244. The total number of CFSPID cases diagnosed over the same period was 29 while the total number of false negatives was 10. These overall numbers have changed slightly compared to previous evaluations due to data updates.

To improve our understanding of the role of the safety net in the CF NBS algorithm we examined the number of children who underwent safety net screening during the 10-year period. The results of this can be seen in detail in Figure 7.

Figure 7: **Number of Children Referred** to a CF Centre after Positive Screening Result due to Safety Net and Number Diagnosed with CF due to Safety Net, 2011 to 2020

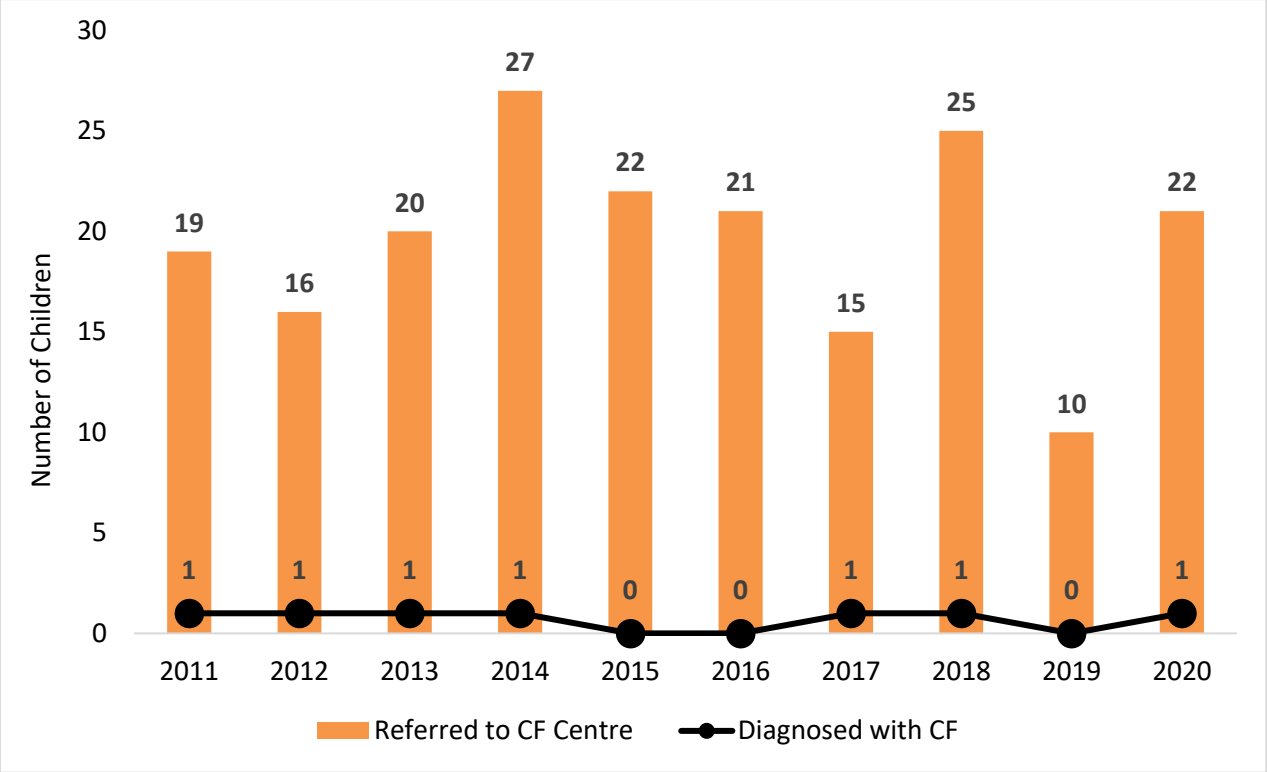


Figure 7 demonstrates the safety net process between 2011 and 2020. The black dot represents the total number of children diagnosed with CF per year as a result of the safety net process. A total number of 197 children participated in the CF NBS safety net process and 7 CF diagnoses were made as a result of this process. Without the safety net process, these children would have potentially missed an early diagnosis.

The PPV of the CF NBS is a key outcome measure. The ECFS has set an international standard for PPV for CF NBS at 30%. As such, we decided to examine the performance of the CF NBS PPV over time and in comparison to the international standard of 30%. The findings of this evaluation can be seen in Figure 8.

Figure 8: **Positive Predictive Value (%)** of the CF NBS in Switzerland over the period 2011-2020 with the International Standard Threshold of 30% for Comparison and the estimated regression line

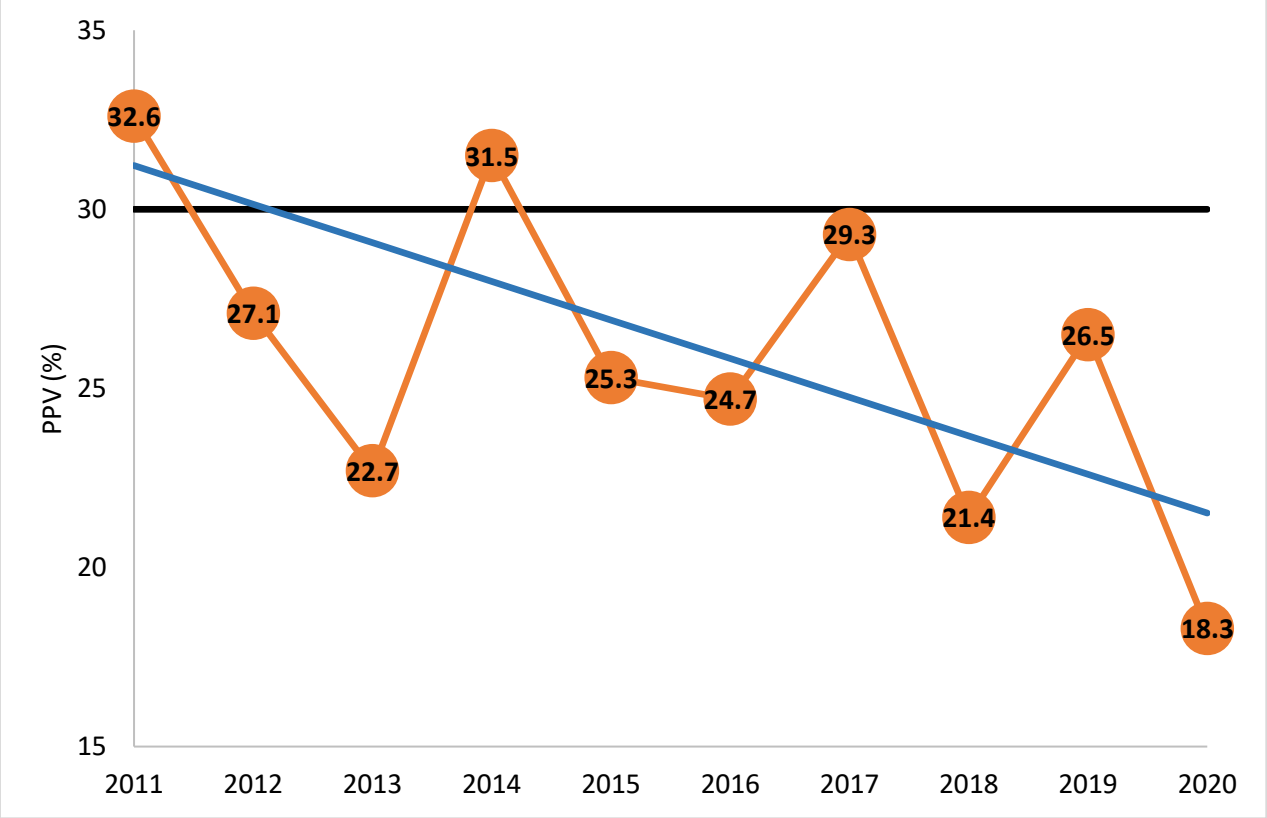
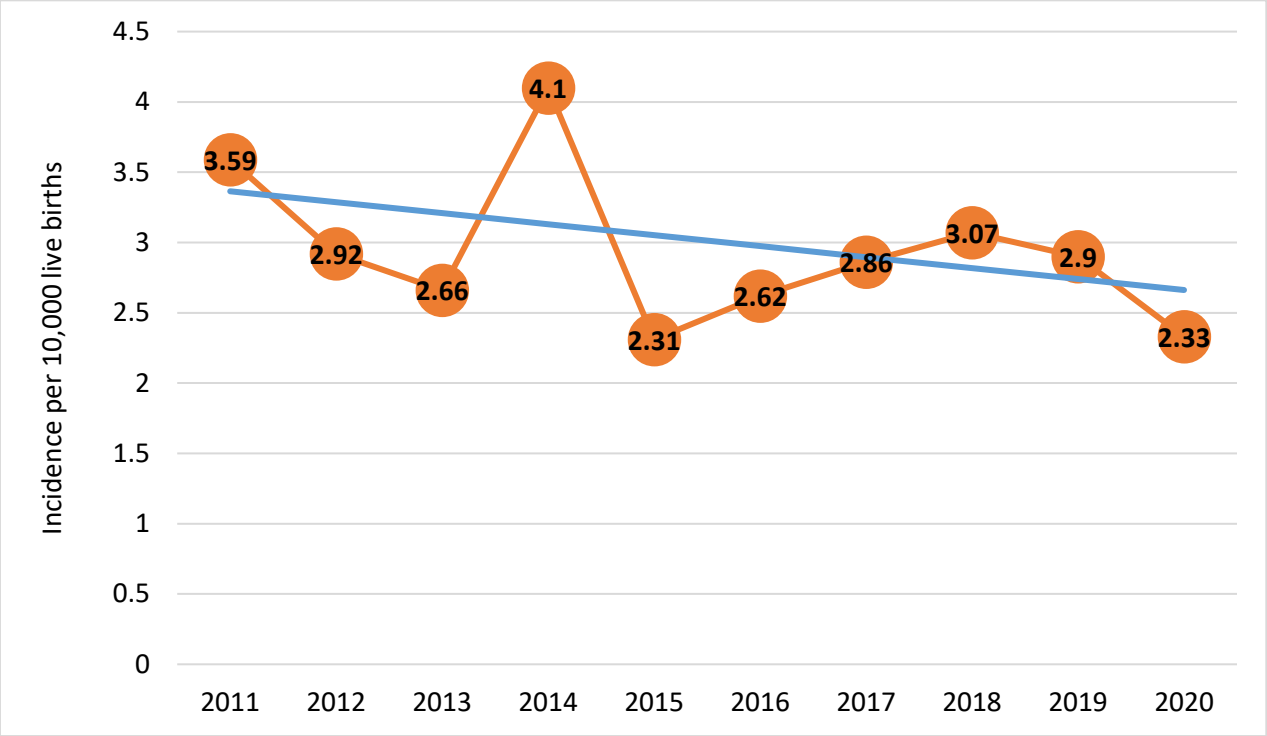


Figure 8 demonstrates the PPV of the CF NBS programme in Switzerland over the 2011 to 2020 period. The black line represents the 30% PPV threshold as defined by the ECFS standards. In order to achieve the international standard, the PPV (orange dot) should lay above the black line. The overall trend of the PPV over the past 10 years has been to decrease. The blue regression line demonstrates that the decrease over time has been at a rate of approximately 1% per year over the 10-year period (linear regression coefficient: -1.08, 95% confidence interval: -1.97 to -0.18, R-squared 0.49). The PPV of any screening programme depends on the prevalence of the particular disease that is being screened in the population. In diseases such as CF which are rare and affect very small numbers of the population the PPV value may be low due to overall low cases numbers in the population.

We compared incidence rates of CF over the 10-year period during which the CF NBS programme was running in Switzerland in order to achieve an understanding of patterns of CF disease in the population. The results of this can be seen in Figure 9. The incidence rate describes the number of newly diagnosed cases of a specific disease over a specific time period.

Figure 9: Incidence rate of CF per 10,000 Live Births in Switzerland with regression line over the period of 2011 to 2020



The incidence rate of CF diagnoses per 10,000 live births in Switzerland over the period of 2011 to 2020 is demonstrated in Figure 9. Over this 10-year time period the incidence rate has remained relatively stable with minor fluctuations. We used linear regression analysis with incidence rate as outcome and year as explanatory variable to see whether there was a decreasing tendency during the 10-year period. We found no evidence of a decreasing trend in the incidence rate (Regressions coefficient: -0.08; 95% confidence interval: -0.21 to 0.06; R-squared 0.18).

Time to diagnosis was analysed to assess trends over the 10-year period for the number of days to diagnosis and to CF centre review. The number of days to CF centre review and definitive genetic diagnosis is a parameter defined by the ECFS guidelines. According to these international standards, an infant with a positive NBS result should be seen by a CF specialist team by 35 days of life and no later than 58 days of life. The results of this analysis can be seen in Figures 10 and 11.

Figure 10: Minimum, Median, Interquartile range and Maximum Days of Life when Seen by a Cystic Fibrosis Specialist

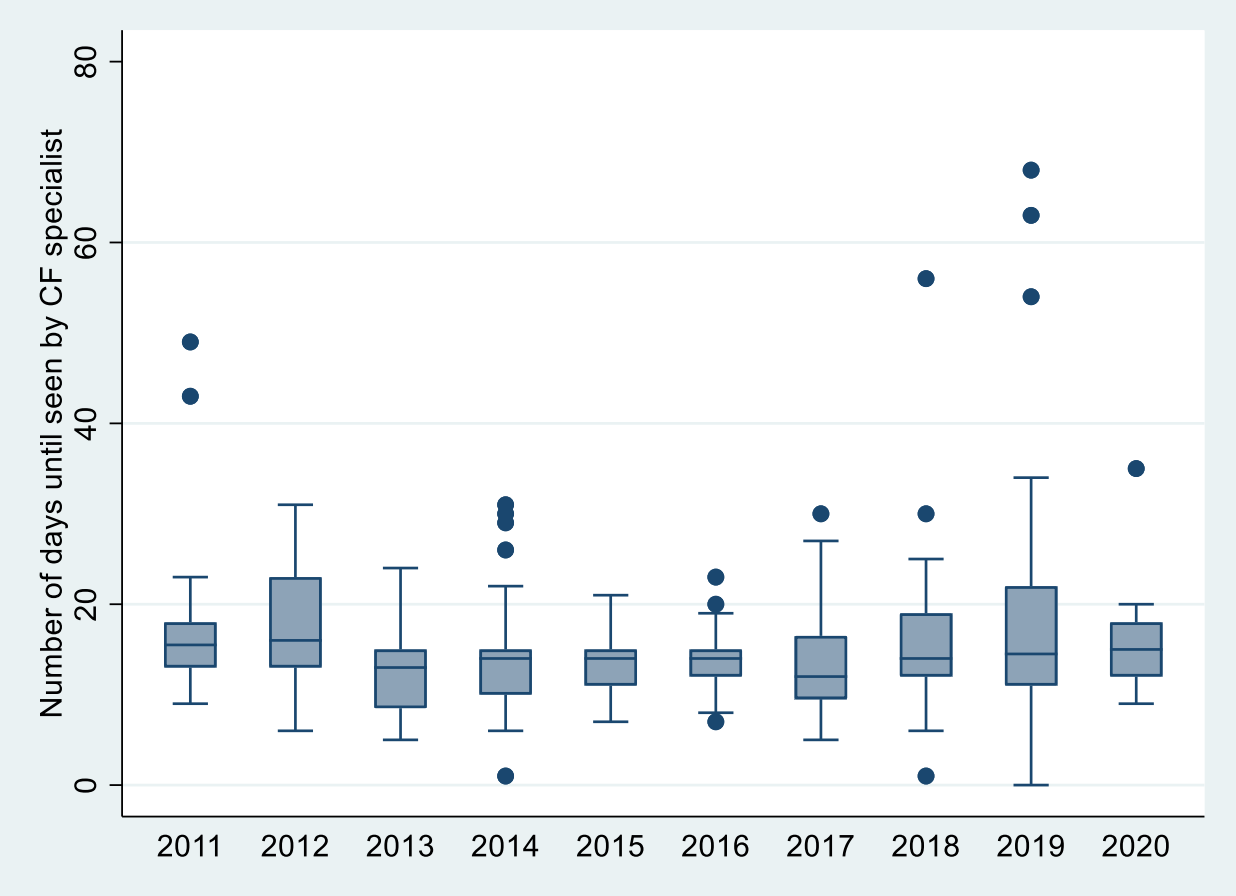


Figure 10 demonstrates the median age in days at which point a child is seen by a CF specialist. If a child tests positive for suspected or confirmed CF through the CF NBS algorithm, they are immediately referred to a CF centre. The figure also includes the range of minimum to maximum days of life. Overall, the median number of days has remained stable and well within the recommended international standards. The additional aspect to note here is that despite the COVID-19 pandemic numbers remained stable.

Days of life (i.e. age in days) when a child receives a genetically confirmed CF diagnosis is shown in the following Figure 11.

Figure 11: Minimum, Median, Interquartile Range and Maximum Days of Life when Genetically Diagnosed with CF in Switzerland 2011 to 2020

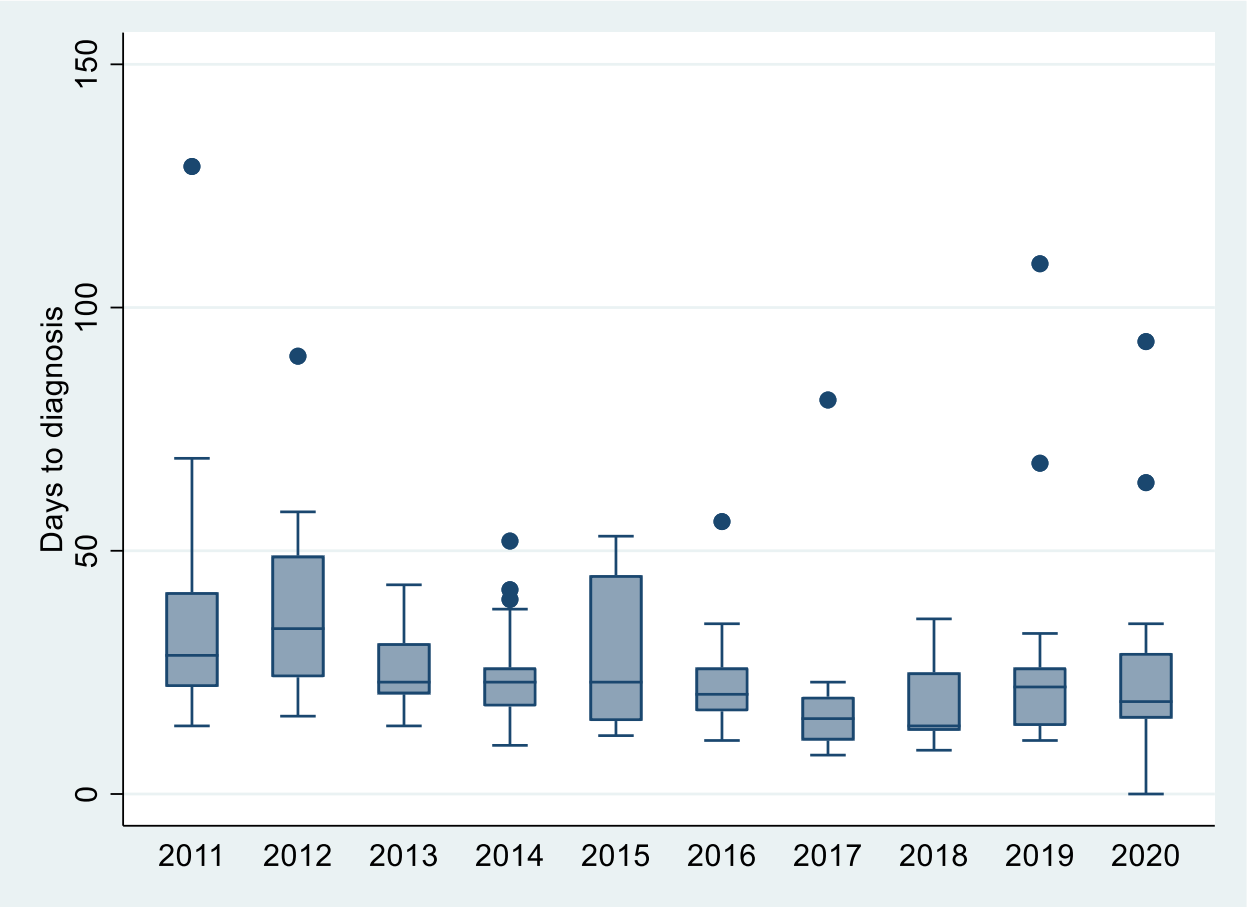


Figure 11 demonstrates the median number of days of life (i.e. age in days) when a child received a genetic diagnosis of CF 2011 to 2020 in Switzerland. The figure includes the range of minimum to maximum days of life. The median sits well within the international standard of 35 days of life and has trended down slightly over time. This reflects a good level of communication across the various institutes involved in the CF NBS programme. The additional aspect to note here is that despite the COVID-19 pandemic numbers remained stable.

Discussion

The introduction of Cystic Fibrosis Newborn Screening in Switzerland in 2011 has transformed the care of children with CF in this country over the past 10 years. Between 2011 and 2020, a total of 244 children were early diagnosed with Cystic Fibrosis as a direct result of the screening programme. Consequently, these children were able to quickly access important disease altering medication and interventions improving their quality of life as well as short and long term health outcomes.

During the same 10-year period a total of 10 children with CF were missed by the CF NBS process. Seven of these 10 cases occurred between 2011 and 2014. The false negative rate of the screening algorithm over the 10-year period of 4% is below the 5% limit determined by the ECFS guidelines. This low false negative rate emphasises the role of the careful selection of the IRT cut-off level. Of these 10 children with a false negative results, 1 had been already diagnosed in the antenatal period. The remaining children presented to health practitioners with a variety of symptoms. These symptoms include: failure to thrive, weight loss, chronic cough, prolonged lower respiratory tract infections, diarrhoea and severe electrolyte abnormalities. The diagnosis of CF was made in this group of children with false negative screening results over a range of 1 to 30 months of age. Unfortunately, false negative results occur in any screening programme.

The aim of CF-NGS in Switzerland has always been to avoid as many cases with unclear diagnoses (CFSPID) as possible and to only screen for clear CF cases for whom early treatment is possible. In the last 10 years, only 29 children with CFSPID had been diagnosed in Switzerland. The diagnosis CFSPID is an unintended consequence of any CF newborn screening programme. The consensus definition of CFSPID, which includes the designation CRMS (CFTR-related metabolic syndrome), is: a positive NBS result with either a borderline sweat test with 0 or 1 CFTR mutations or a negative sweat test with 0 or 1 CFTR mutations. The rate of conversion from CFSPID to a CF diagnosis is unclear and thought to range between 11% and 44% (*Munck, A et. al International Journal of Neonatal Screening, 2020*). The diagnosis of a CFSPID case always leads to a high burden of stress to the families who require close medical follow up to identify emerging symptoms early while striking the balance of avoiding overmedicalisation of a child that may otherwise be healthy. A study is currently underway in Switzerland to find out how these children with CFSPID are doing in Switzerland today and who is looking after them.

In evaluating the role of the safety net there are clear benefits and shortfalls. Although a total of 7 children were diagnosed with CF as a consequence of the safety net, there were conversely 190 healthy children who were referred to a CF centre for further testing (out of 3,167 children who had a 2nd heel prick test because of an elevated initial IRT and no mutations found) and who did not have a CF diagnosis. Weighing up the ongoing role of the safety net will need to take into account the benefits of early identification of CF with the stress caused to otherwise healthy children and families as well as health care costs. Overall, there have been few changes to the CF NBS algorithm over the past 10-year period with the majority of changes having been made in the primary pilot and programme establishment period. In future, changes could be made to the algorithm that remove or modify the safety net in order to improve screening benefits and reduce the associated shortfalls.

A closer look at the overall picture shows a declining PPV over the 10-year period of CF NBS in Switzerland. The average PPV over the 10-year period of 25.7% is below the accepted international standard of 30%. The fluctuations of PPV observed over the 10-year period reflect normal fluctuations in CF case prevalence in the community as well as changes to the CF NBS screening algorithm and safety net cut off values. Nevertheless, in the last 10 years a total of 705 children and their families were sent to a CF centre for further investigations after a false positive screening result in which CF was then excluded by CF specialists. Setting the specifics of the algorithm cut-off points is a balancing act between missing cases of CF and reducing the exposure of healthy children and families to unnecessary medicalisation and stress. Both aspects have to be observed and evaluated for ongoing optimisation of the protocol.

The main reason for the low PPV is the safety net. A total of 3,167 children had a 2nd heel prick test, of which 197 were then referred to a CF centre because they had a 2nd elevated IRT value. A further 32 children were referred due to meconium ileus and the remainder were referred by clinician discretion. Of these, only 7 children were diagnosed with CF due to rare mutations. Two of these children would have been identified through the CF NBS if screened with the current 18 CFTR mutations protocol.

Optimisation of the PPV can occur by increasing the specificity of the algorithm or by abolishing or changing the safety net. Possible strategies for this include: incorporation of an extended genetic sequencing component thereby identifying a broader range of CFTR mutations, increasing the IRT threshold, including additional tests such as PAP (pancreatitis-associated protein) or targeting the screening to a population at higher risk. However, making these adjustments will also ultimately affect the sensitivity of the screening algorithm and increase the number of CFSPID diagnoses.

The sensitivity of the screening algorithm also performs highly with an overall value of 96%. This is in the setting of an overall stable incidence of CF during the 10-year period. Additionally, the time period to definitive CF diagnosis and time seen by CF specialist (median and inter-quartile range of 26 (13-94) and 18 (9-56) days respectively), has remained stable over the 10-year period. This shows that the underlying processes behind the CF-NBS in Switzerland have remained effective.

Overall, the bigger picture indicates that the Swiss CF NBS has been performing well over the past 10-years. This is also reflected in the way in which the Swiss CF NBS is accepted within the ECFS as a good example of an effective screening programme with a good and effective evaluation programme (resulting in many publications in scientific journals). Not only does the algorithm perform close to acceptable international standards, the integrated effort of all involved services to insure excellent data quality and communication plays a key role in its success. The annual evaluation of the Swiss CF NBS over the past 10 years also means that minor adjustments can be made to the algorithm which will further optimise the screening programme.

Chapter 3

3 A Comparison of Swiss Newborn Screening to Other European Countries

This 10-year evaluation of CF NBS in Switzerland has provided a deeper understanding of the way in which the programme has evolved over this time. This 10-year period of screening has also coincided with European wide surveys of national and regional CF NBS programmes, which are coordinated by the ECFS. Using the published information from these surveys, it is possible to gain further insight into the performance of the Swiss CF NBS within the greater context of other CF NBS programmes across Europe.

The aim of this chapter is to compare the Swiss CF NBS to other protocols in Europe. We first introduce basic information regarding selected CF newborn screening programmes across Europe including outcomes of an evaluation of CF NBS in Europe published by the ECFS. Secondly, we describe the updated planned survey currently in the process of collecting data. In conclusion, we describe the lessons learned from the evaluation of CF NBS on a European scale and how these can help in the optimisation of CF NBS in Switzerland.

3.1 Newborn Screening for Cystic Fibrosis in Europe

From 2014 to 2015, the ECFS conducted a survey of European countries performing CF NBS. This followed on from a previous survey conducted in 2004. It identified that by 2016, CF NBS was undertaken in 21 countries across Europe, including Switzerland. This survey demonstrated an approximate increase in the number of children undergoing CF NBS from 1.6 to 2.7 million over the preceding 10-year period (*Barben, J et.al. Journal of Cystic Fibrosis 2017*).

Across Europe, CF NBS has been widely adopted with wide variation in the protocols used. Choices regarding protocol details are generally made during an initial pilot phase of evaluation and take into account local patterns of disease, health care resources, ethical concerns and participant engagement. The wide variability of screening protocols used can be seen in Table 6.

As with the CF NBS in Switzerland, regular evaluation of the CF NBS programmes across Europe plays an integral role in their ongoing optimisation. As a part of the 2014-2015 survey, the ECFS presented performance data on 13 of the national NBS programmes that were running over the 2014 period. These data provide a snapshot over the one-year data-collection period. Included in this survey were data on PPV, sensitivity, false negatives and the ratio of the number of CF to CFSPID cases. These selected data can be seen in Table 7.

Table 6 demonstrates examples of the protocols used in Europe during 2015 to highlight the variability in chosen methods.

Table 6: Protocols for Cystic Fibrosis Newborn Screening in Europe in 2015*

Country	Year Initiated	Protocol (2015)
Northern Ireland	1984	IRT / DNA / IRT
Wales	1996	IRT / DNA
Austria	1997	IRT / IRT
France	2002	IRT / DNA / IRT
Scotland	2003	IRT / DNA / IRT
England	2007	IRT / DNA / IRT
Russia	2007	IRT / IRT
Slovakia	2009	IRT / IRT
Czech Republic	2009	IRT / DNA / IRT
Ireland	2011	IRT / DNA
Netherlands	2011	IRT / PAP / DNA / EGS
Switzerland	2011	IRT / DNA / IRT
Norway	2012	IRT / EGS
Turkey	2015	IRT / IRT
Portugal	2015	IRT / PAP / IRT

**values taken from Barben J. et. al. The expansion and performance of national newborn screening programmes for cystic fibrosis in Europe, Journal of Cystic Fibrosis 16 (2017) 207-213.*

Table 6 demonstrates the wide variability in CF NBS protocols that were being used across Europe in 2015. The table presents only basic information on the variability in protocols. Within each protocol there is great variability in the selected IRT and PAP cut-off points, sampling and processing methods, number of mutations included in the DNA panel and days of age at which the testing is performed. It is also clear in table 6 that CF screening has only recently started in several parts of Europe over the past 10-year period.

Table 7 demonstrates available performance data for several national NBS programmes that were running in 2014 (Barben, J et al. 2017, Journal of Cystic Fibrosis).

Table 7: Performance Data for Cystic Fibrosis Newborn Screening in Europe in 2014*

Country	PPV	Sensitivity	False Negatives	CF to CFSPID Ratio
Northern Ireland	25%	100%	0	0
Wales	30%	90%	1	0
Austria	20%	96%	1	25:1
France	34%	95%	8	8:1
Scotland	75%	100%	0	
England	67%	98%	3	10.5:1
Slovakia	3%	100%	0	0
Czech Republic	15%	94%	1	7.5:1
Ireland	44%	100%	0	1.2:1
Netherlands	68%	81%	5	10:1
Switzerland	31%	97%	1	17:1
Norway	63%	91%	3	2.5:1

**values taken from Barben J. et. al. The expansion and performance of national newborn screening programmes for cystic fibrosis in Europe, Journal of Cystic Fibrosis 16 (2017) 207-213.*

Table 7 demonstrates the wide variability in performance standards across CF NBS programmes in Europe in 2014. The PPV ranges from 3% to 75% depending on the population undergoing the screening test and type of protocol used. Sensitivity appears adequate with most countries achieving above the international standard of 95%. Additionally, only few false negative cases were missed by screening across the entirety of the participating CF NBS sites. The CF to CFSPID ratio differed widely across sites. A higher ratio of CF to CFSPID is considered a better outcome compared to a lower ratio.

The expansion of NBS for CF across Europe has been a success story, with most programmes performing adequately with respect to international standards. This 2014 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.

In the conclusion of the 2014 ECFS survey, the authors recommend, that 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. 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.

One problem with the data collection for the 2014 survey was that there was no standardised data collection in the different European countries. As a consequence, the ECFS Newborns screening Working Group (NSWG) has now defined the key outcome parameters (published by Munck, A. et. al. in Journal of Cystic Fibrosis, 2021) and launched a new survey in 2021, the results of which are expected in 2022.

Discussion

Neonatal Screening for Cystic Fibrosis is a well-established, cost-effective public health prevention strategy that has been increasingly implemented in many European countries including Switzerland (Barben J, et al. Journal of Cystic Fibrosis 2017). Combining the information learned from this 10-year evaluation of the Swiss CF NBS with the performance outcomes collected from the regular snapshots provided by European wide ECFS surveys, we can optimise the Swiss CF NBS performance. The information gained through this evaluation is vital given the growing number of regional and national programmes in Europe that are using increasingly complex and diverse screening protocols. Despite the huge variation in screening protocols there are few countries, including Switzerland, that are able to persistently achieve the ECFS guidelines for standards of CF NBS programmes.

Most countries and regions used an IRT / DNA / IRT based protocol. However, even within this protocol the positive predictive value differs across countries from 15% to 75%. There are several reasons that can explain the variation seen which will now be discussed.

Although each protocol begins with an IRT test performed on the 3rd to 4th day of life as part of the heel prick Guthrie test for newborns, this common first step quickly diverges. Even at this early stage, errors in collection and storage of the Guthrie card can influence IRT results. The first IRT test has a different cut-off point depending on the local laboratory protocol. For example, the IRT cut-off point can be a fixed value (e.g. > 90ng/mL) or a floating percentage value (e.g. 99.2nd percentile). The IRT can also be measured using different methods. The threshold used in the initial IRT protocol has a direct impact on the number of CF cases that are positively identified or missed as a false negative result.

There are also differences in the timing of performing the second IRT test. Depending on the CF NBS programme, this test is carried out at different ages and assigned its own cut-off value. In this case, a child with an initially borderline IRT result will undergo further testing at a specific age in days. If this second IRT result is above the threshold for the second IRT this child will be referred for further review at a CF centre.

The role of the DNA test in the protocol is to use the original Guthrie card blood sample to simultaneously identify a specific group of known CFTR mutations that are linked to CF. In this case, if a child has a borderline initial IRT and no DNA mutations, they may have a second IRT test. The spectrum of DNA test kits used is extensive and ranges from testing a panel of 4 known mutations to over 600 known mutations. To date 2,104 *CFTR* variants are known (www.genet.sickkids.on.ca - last update 25.4.2021) and only 442 are characterised, of them 360 CF-causing (www.cftr2.org - last update 31.7.2020). Using a broader range of known CFTR mutations tested can improve the overall positive predictive value of the protocol as it helps the screening programme to target the high-risk population. However, using a broader range of genetic mutations associated with Cystic Fibrosis in the screening algorithm also comes at the cost of identifying a higher number of children and families with CF carrier status i.e. those that only carry one mutation and CFSPID i.e. those with mutations but normal or borderline sweat test results.

Additional issues include the possible misdiagnosis of CF. The use of extended genetic sequencing in CF screening also raises questions on variant interpretation and important ethical issues (Bergougnoux A, et al. International Journal of Neonatal Screening 2020). Currently, only two sites across Europe: Poland and Norway, have adopted the extended genome sequencing protocol which has lead to a higher number of CFSPID cases in these two locations.

The data from the ECFS 2014 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.

3.2 What we can learn

Ten years after the introduction of CF screening for newborns in Switzerland, the screening programme continues to play an integral role in CF care in Switzerland. There are several strengths of the current Swiss CF NBS model including: communication, evaluation and optimisation.

Firstly, communication across teams is efficacious. Working in a small nation, the specialists at each institute involved in CF care in Switzerland are well-known to each other. Each institute has clear leadership and responsibilities which means that communication continues to work well. The overall success in communication across institutes is also reflected in the fact that the initiator of the Cystic Fibrosis Newborn Screening programme in Switzerland, Prof. Jürg Barben, has also been the head of the Newborn Screening Group of the ECFS for several years. Addionally, during the COVID-19 era of online meetings, communication across teams has become even easier and new team members are able to be introduced to the CF NBS team officially during taskforce meetings that occur remotely.

Secondly, the annual evaluation of the CF NBS in Switzerland is performed by an external group of epidemiologists at the ISPM. The ISPM staff collect data from every institute involved in the CF NBS programme. Data has been continuously collected since the beginning of the programme in 2011 and reliably reported using clear key outcome measures. Additionally, missing data is identified and sought and errors in data entry identified. The role of the ISPM as a third party assessor provides a reliable perspective from which to assess the CF NBS and give recommendations for optimisation.

Thirdly, optimisation of the CF NBS in Switzerland occurs regularly. Good communication across CF participating institutes combined with the annual evaluation of the CF NBS allows for the ongoing optimisation and adjustment of the screening process to achieve the best outcomes for children with CF. Following on from each annual evaluation, the ISPM makes recommendations regarding possible changes to the algorithm. These recommendations are carefully considered by those responsible and are able to be efficiently implemented as they are reliable and able to be clearly communicated across institutes. The current 10-year CF NBS evaluation provides additional information on the performance of the programme

since it started which is a valuable contribution to the ongoing optimisation of the CF NBS programme in Switzerland.

Overall, with its detailed independent evaluation and good communication, the CF NBS in Switzerland is judged to be a leading example of screening within Europe. However, there are also weaknesses to the current CF NBS programme. These weakness include: low overall PPV and the unnecessary psychological stress caused due to CFSPID diagnoses and false positive screening outcomes.

Unfortunately, any screening programme independent of its focus, would encounter the same difficulties as faced by the CF NBS in Switzerland. However, there are two strategies that can improve the current overall PPV of the Swiss CF NBS (Figure 12). Our main recommendation to improve the PPV is to consider changing or eliminating the current safety net. An alternative second recommendation would be to include more CFTR-mutations in genetic screening. However, this second strategy would come at the cost of detecting more CFSPID cases and carriers which contributes more psychological stress to those with an unclear diagnosis and uses valuable health care resources. Currently, the Swiss CF NBS algorithm is effective in minimising the number of CFSPID cases and carriers identified and this must be balanced with the overall performance of the CF NBS algorithm.

Figure 12: Recommendations for Consideration to Changes to the CF NBS Algorithm

1. Change or eliminate the safety net procedure
2. Include more CFTR-mutations in genetic screening

The 2020 Evaluation of the Cystic Fibrosis Newborn Screening programme provides an extensive assessment to the current screening programme in Switzerland. Currently, no changes are advised to the screening process. However, in order to improve PPV, changes or elimination of the safety net can be considered. We commend the various institutes involved in the CF NBS in Switzerland for their excellent communication over the past 10-years as this has played an integral role in the success of the programme to date and its ongoing role in the future.

Chapter 4

4 Publications and Conferences

4.1 Scientific Publications in Peer-Reviewed Journals

Fingerhut R, Rueegg C, Imahorn O, Pedersen ESL, Kuehni CE, Gallati S, Regamey N, Barben J. **I**mmunoreactive trypsinogen (IRT) levels in healthy newborns and infants with CF and CRMS/CFSPID. Submitted to *J Cyst Fibros.*

Newborn Screening for Cystic Fibrosis (Book). Edited by Jürg Barben & Kevin Southern. mdpi.com/books/pdfview/book/2841. ISBN 978-3-03936-991-1

Barben J, Southern KW. Why Do We Screen Newborn Infants for Cystic Fibrosis? *Int J Neonatal Screen* 2020 Jul 8;6(3):56.

Barben J, Chudleigh J. Processing Newborn Bloodspot Screening Results for CF. *Int J Neonatal Screen*. 2020 Mar 25;6(2):25

Barben J, Castellani C, Munck A, Davies JC, deWinter K, Gartner S, Kashirskaya N, Linnane B, Mayell SJ, McColley S, Ooi CY, Proesmans M, Ren CL, Salinas D, Sands D, Sermet-Gaudelus I, Sommerburg O, Southern KW, For the European CF Society Neonatal Screening Working Group (ECFS NSWG). Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID). *J Cyst Fibros*. 2020 December. doi: 10.1016/j.jcf.2020.11.006

Southern KW, Barben J, Gartner S, Munck A, Castellani C, Mayell SJ, Davies JC, Winters V, Murphy J, Salinas D, McColley SA, Ren CL, Farrell PM. Inconclusive diagnosis after a positive newborn bloodspot screening result for cystic fibrosis; clarification of the harmonised international definition*. J Cyst Fibros.* 2019 Nov;18(6):778-780

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Ruegg CS, Kuehni CE, Gallati S, Jurca M, Jung A, Casaulta C, Barben J. Comparison of two sweat test systems for the diagnosis of cystic fibrosis in newborns. *Pediatr Pulmonol*. 2019; Mar;54(3):264-272.

Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, Sermet-Gaudelus I, Southern KW, Barben J, Flume PA, Hodková P, Kashirskaya N, Kirszenbaum MN, Madge S, Oxley H, Plant B, Schwarzenberg SJ, Smyth AR, Taccetti G, Wagner TOF, Wolfe SP, Drevinek P. ECFS best practice guidelines: the 2018 revision. *Journal of Cystic Fibrosis*. 2018;17(2):153-178.

Barben J, Castellani C, Dankert-Roelse J, Gartner S, Kashirskaya N, Linnane B, Mayell S, Munck A, Sands D, Sommerburg O, Pybus S, Winters V, Southern KW. The expansion and performance of national newborn screening programmes for cystic fibrosis in Europe. *Journal of Cystic Fibrosis;* 2017;16(2):207-213

Kuehni CE, Schindler M, Mazur A, Malzacher A, Hornung R, Barben J. Feasibility and normal values of an integrated conductivity (Nanoduct™) sweat test system in healthy newborns. *Journal of Cystic Fibrosis.* 2017;16(4):465-470

Barben J, Southern K. Cystic Fibrosis Screen positive inconclusive diagnosis. *Curr Opin Pulm Med* 2016; 22: 617-22.

Barben J, Rueegg CS, Jurca M, Spalinger J, Kuehni CE, and the Swiss CF Screening Group. Measurement of fecal elastase improves performance of newborn screening for cystic fibrosis. *Journal of Cystic Fibrosis*. 2016; 15(3):313-7.

Rueegg CS, Barben J, Hafen GM, Moeller A, Jurca M, Fingerhut R, Kuehni CE, and the Swiss CF Screening Group. Newborn screening for cystic fibrosis - The parent perspective. *Journal of Cystic Fibrosis*. 2016; 15(4):443-51.

Rueegg CS, Kuehni CE, Gallati S, Baumgartner M, Torresani T, Barben J. Neugeborenen-Screening auf Cystische Fibrose - Evaluation nach einem Jahr*. Paediatrica*. 2013;24(3):26-31

Rueegg CS, Kuehni CE, Gallati S, Baumgartner M, Torresani T, Barben J. Dépistage néonatal de la mucoviscidose – évaluation après une année*. Paediatrica*. 2013;24(2):8-12

Rueegg CS, Kuehni CE, Gallati S, Baumgartner M, Torresani T, Barben J. One-year evaluation of a neonatal screening program for cystic fibrosis in Switzerland; *Deutsches Aerzteblatt International* 2013; 110(20):356-63. (Der Artikel wurde auf Deutsch und Englisch publiziert und jeweils in einem Editorial zusammengefasst)

Torresani T, Fingerhut R, Rueegg CS, Gallati S, Kuehni CE, Baumgartner M, Barben J. Newborn Screening for Cystic Fibrosis in Switzerland – Consequences after Analysis of 4 Months Pilot Study; *Journal of Cystic Fibrosis* 2013; doi:pii: S1569-1993(13)00067-2. 10.1016/j.jcf.2013.04.008

4.2 Published Abstracts in Peer-Reviewed Journals

Jurca M, Kuehni CE, Rueegg CS, Fingerhut R, Gallati S, Torresani T, Baumgartner M, Barben J, and the Swiss CF Screening Group. Newborn screening for cystic fibrosis in Switzerland – Evaluation after 5 years. *J Cystic Fibrosis* 2016; 15 (Suppl. 1): S36-37.

Mazur A, Kuehni CE, Loher J, Malzacher A, Hornung R, Barben J. Values and failure rate of sweat conductivity using Nanoduct sweat analysis system in healthy infants aged 4 days and 4 weeks. *J Cystic Fibrosis* 2015; 14(Suppl. 1):S60

Jurca M, Kuehni CE, Rueegg CS, Fingerhut R, Gallati S, Torresani T, Baumgartner M, Barben J, and the Swiss CF Screening Group. Newborn screening for cystic fibrosis in Switzerland – performance after 4 years. *J Cystic Fibrosis* 2015; 14(Suppl. 1):S22

Torresani T, Rueegg CS, Baumgartner M, Fingerhut R, Barben J, and the Swiss CF Screening Group. Age related cut-off levels for Immunoreactive Trypsin (IRT) in healthy newborns in the first two months of life. *Journal of Cystic Fibrosis.* 2014; 13(Suppl. 2):23s

Rueegg CS, Barben J, Hafen GM, Moeller A, Gallati S, Torresani T, Baumgartner M, Fingerhut R, Kuehni CE, and the Swiss CF Screening Group. National newborn screening for cystic fibrosis in Switzerland – a parents' perspective. *Journal of Cystic Fibrosis.* 2014; 13(Suppl. 2):48s

Rueegg CS, Spalinger J, Hafen GM, Moeller A, Gallati S, Kuehni CE, Torresani T, Baumgartner M, Fingerhut R, Barben J, and the Swiss CF Screening Group. Change of algorithm in the CF centers influences the amount of equivocal CF diagnoses in the newborn screening program in Switzerland. *Journal of Cystic Fibrosis.* 2014; 13(Suppl. 2):23s

4.3 Contributions to National and International Conferences

4.3.1 Oral Presentations at National and International Conferences

Barben J, Castellani C, Dankert-Roelse J, Gartner S, Kashirskaya N, Linnane B, Mayell S, Munck A, Sands D, Sommerburg O, Pybus S, Winters V, Southern KW. The expansion and performance of national newborn screening programmes for cystic fibrosis in Europe.
European Cystic Fibrosis Society Conference, Seville, Juni, 2017.

Jurca M, Kuehni CE, Rueegg CS, Fingerhut R, Gallati S, Torresani T, Baumgartner M, Barben J, and the Swiss CF Screening Group. Newborn screening for cystic fibrosis in Switzerland – Evaluation after 6 years. *Swiss Society for Paediatrics, St. Gallen, 1-2 June, 2017*

Fingerhut R, Jurca M, Sluka S, Kuehni CE, Barben J. Newborn screening for cystic fibrosis in Switzerland – Evaluation after 5 years. *International Society for Neonatal Screening, Den Haag 11.-14.9.2016*

Cirilli N, Buzzetti R, Southern K, Barben J, Nährlich L, Munck A, Wilschanski M, De Boeck K, Derichs N, on behalf of ECFS Diagnostic Network Working Group. Real life practice of sweat testing in Europe: results from an ECFS-wide survey. *European Cystic Fibrosis Society Conference, Basel, Juni 8-11, 2016.*

Jurca M, Kuehni CE, Rueegg CS, Fingerhut R, Gallati S, Torresani T, Baumgartner M, Barben J, and the Swiss CF Screening Group. Newborn screening for cystic fibrosis in Switzerland – Evaluation after 5 years. *European Cystic Fibrosis Society Conference, Basel, Juni 8-11, 2016.*

Jurca M, Kuehni CE, Rueegg CS, Fingerhut R, Gallati S, Torresani T, Baumgartner M, Barben J, and the Swiss CF Screening Group. Newborn screening for cystic fibrosis in Switzerland – performance after 4 years. *European Cystic Fibrosis Society Conference, Brussels, Juni 10-13, 2015.*

Barben J. Erfahrungen und Stand des Neugeborenen-Screenings für CF in der Schweiz. *Jahreskongress der Deutschsprachigen Gesellschaft für Pädiatrische Pneumologie, Basel, March 5, 2015.*

Barben J. Neugeborenenscreening auf cystische Fibrose. *Deutscher CF-Kongress Würzburg, November 21, 2014.*

Torresani T, Rueegg CS, Baumgarter M, Fingerhut R, Barben J, and the Swiss Cystic Fibrosis Screening Group. IRT cut-off levels related to age of sampling. International Society for Neonatal Screening (*ISNS) Anaheim, October 27-30, 2014.*

Barben J. Quality assurance of CF newborn screening. *Scientific Meeting Mukoviszidose e.V., Mainz. September 25-26, 2014.*

Torresani T, Rueegg CS, Baumgarter M, Fingerhut R, Barben J, and the Swiss Cystic Fibrosis Screening Group. Age related cut-off values for immunoreactive Trypsin (IRT) in healthy newborns in the first two months of life. *European Cystic Fibrosis Society Conference, Gothenburg, Juni 11-14, 2014.*

Rueegg CS, Spalinger J, Hafen GM, Moeller A, Gallati S, Kuehni CE, Torresani T, Baumgarter M, Fingerhut R, Barben J, and the Swiss Cystic Fibrosis Screening Group. Change of algorithm in the CF centers influences the amount of equivocal CF diagnoses in the newborn screening program in Switzerland. *European Cystic Fibrosis Society Conference, Gothenburg, Juni 11-14, 2014.*

Fingerhut R, Torresani T, Gallati S, Schoeni MH, Kuehni CE, Rueegg CS, Baumgartner M, Barben J, and the Swiss Cystic Fibrosis Screening Group. Newborn screening for cystic fibrosis in Switzerland – Evaluation after two years. *Joint Meeting of the Newborn Screening and Genetic Testing Symposium and International Society for Neonatal Screening (NBSGTS-ISNS), Atlanta, May 5-10, 2013*

Barben J, Rueegg CS, Gallati S, Kuehni CE, Baumgartner M, Torresani T, Schoehni MH, on behalf of the Swiss Cystic Fibrosis Screening Group. Comparison of two sweat test systems (Macroduct versus Nanoduct) for the diagnosis of cystic fibrosis in the newborn screening program in Switzerland*. Annual Congress of the Swiss Pulmonology Society, Bern, April 17-19, 2013*

Rueegg CS, Torresani T, Baumgartner M, Gallati S, Schoehni MH, Kuehni CE, Barben J. Newborn-screening for cystic fibrosis in Switzerland – Evaluation after one year. *Swiss Public Health Conference, Lausanne, August 30-31, 2012*

Rueegg CS, Barben J, Torresani T, Baumgartner M, Kuehni CE, for the Swiss CF Screening Group. Newborn screening for cystic fibrosis in Switzerland – Feedback from parents. *Swiss Society of Paediatrics Annual Conference, Lucerne, May 31-June 1, 2012*

Barben J, Rueegg CS, Gallati S, Kuehni CE, Baumgartner M, Torresani T, Schoeni MH and the Swiss CF screening group. Newborn screening for cystic fibrosis in Switzerland – Comparison of Nanoduct versus Macroduct sweat test in the diagnosis of CF. *Swiss Society of Paediatrics Annual Conference, Lucerne, May 31-June 1, 2012*

Barben J, Fingerhut R, Gallati S, Schoeni MH, Kuehni CE, Baumgartner M, Torresani T. Newborn screening for cystic fibrosis in Switzerland – Evaluation after one year. Annual Congress of the Swiss Pulmonology Society, Crans Montana, April 17-19, 2012
Awarded: GlaxoSmithKline – Prix Glaxo 2012 for the best communication in Paediatrics

4.3.2 Poster Presentations at National and International Conferences

Imahorn O, Frauchiger B, Pedersen E, Kuehni C, Gallati S, Fingerhut R, Blanchon S, Jung A, Mornand A, Müller D, Regamey N, Trachsel D, Latzin P, Barben J. Follow-up of Children with Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID) in Switzerland. *44th European Cystic Fibrosis Conference 9-12.6.2021.*

Fingerhut R, Murca M, Sluka S, Kuehni CE, Barben J. Newborn screening for cystic fibrosis in Switzerland – Evaluation after 5 years. *International Society for Neonatal Screening, Den Haag 11.-14.9.2016.*

Cirilli N, Buzzetti R, Southern K, Barben J, Nährlich L, Munck A, Wilschanski M, De Boeck K, Derichs N, on behalf of ECFS Diagnostic Network Working Group. Real life practice of sweat testing in Europe: results from an ECFS-wide survey. *39th European Cystic Fibrosis Conference Basel 9.-12.6.2016.*

Mazur A, Kuehni CE, Loher J, Malzacher A, Hornung R, Barben J. Values and failure rate of sweat conductivity using Nanoduct sweat analysis system in healthy infants aged 4 days and 4 weeks. *European Cystic Fibrosis Society Conference, Brussels, Juni 10-13, 2015.*
Awarded: Best Poster Award

Jurca M, Kuehni CE, Rueegg CS, Fingerhut R, Gallati S, Torresani T, Baumgartner M, Barben J, and the Swiss CF Screening group. Newborn screening for Cystic Fibrosis in Switzerland – Evaluation after four years. *Jahreskongress der Deutschsprachigen Gesellschaft für Pädiatrische Pneumologie, Basel, March 5-7, 2015.*

Simon Pybus S, Barben J, Castellani C, Dankert-Roelse J, Gartner S, Kashirskaya N, Linnane B, Mayell S, Munck A, Sands D, Sommerburg O, Winters V, Southern K. Updated survey of newborn screening for cystic fibrosis. *European Cystic Fibrosis Society Conference, Gothenburg, Juni 11-14, 2014*.

Rueegg CS, Spalinger J, Hafen GM, Moeller A, Gallati S, Kuehni CE, Torresani T, Baumgarter M, Fingerhut R, Barben J, and the Swiss Cystic Fibrosis Screening Group. National newborn screening for cystic fibrosis in Switzerland – a parents' perspective. *European Cystic Fibrosis Society Conference, Gothenburg, Juni 11-14, 2014.*
Awarded: Best Poster Award; 2nd place: Highly Commended Research

Gallati S, Barben J, Rueegg CS, Fingerhut R, Hafen G, Kuehni CE, Moeller A, Mornand A, Schoeni MH, Torresani T, and the Swiss CF Screening Group. Genotype-phenotype associations in babies with a positive cystic fibrosis (CF) newborn screening (NBS) test. *ERS Annual Congress, Barcelona, September 7-11, 2013*

Barben J, Rueegg CS, Gallati S, Kuehni CE, Baumgartner M, Torresani T, Schoeni MH and the Swiss Cystic Fibrosis Screening Group. Comparison of two sweat test systems (Macroduct versus Nanoduct) for the diagnosis of cystic fibrosis in the newborn screening program in Switzerland. *36th European Cystic Fibrosis Society Conference, Lisbon, June 12-15, 2013*

Barben J, Rueegg CS, Gallati S, Kuehni CE, Baumgartner M, Torresani T, Schoeni MH and the Swiss CF Screening Group. Comparison of Nanoduct versus Macroduct sweat test for the diagnosis of cystic fibrosis in the newborn screening programme in Switzerland. *ERS Annual Congress, Vienna, September 1-5, 2012*

Barben J, Gallati S, Fingerhut R, Schoeni MH, Rueegg CS, Kuehni CE, Baumgartner M, Torresani T and the Swiss CF Screening Group. Newborn screening for cystic fibrosis in Switzerland – Evaluation after one year. *35th European Cystic Fibrosis Society Conference, Dublin, June 6-9, 2012*
Awarded: Cesaro Romano Award for Cystic Fibrosis Research

4.4 Other Invited Lectures

Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID. *European CF Society, DNWG Meeting* 23.9.2020 (Jürg Barben)

Addressing timeliness in the processing of a CF screening result. *European CF Conference*, Liverpool, 8.6.2019 (Jürg Barben)

Newborn screening for CF - benefits and pitfalls. Jahrestagung der Schweizerischen Gesellschaft für Klinische Chemie, Bern 15.11.2018 (Jürg Barben)

Newborn screening for CF. *European Respiratory Society Meeting*, Paris 15.9.2018 (Jürg Barben)

Practical aspects for improvement of CF diagnosis in Europe. Hands-on Training Workshop Schweisstestseminar Kinderspital Zürich, 25.10.2018 (Jürg Barben, Andreas Jung)

Is it time to unwrap the Nanoduct? European CF Society Diagnostic Network Meeting in St. Gallen, 9.2.2018. (Jürg Barben)

Protocols and performance; lessons from the 2015 survey. ECFS Neonatal Screening Working Group, European CF Conference Seville, June 7, 2017 (Jürg Barben)

Bedeutung des Schweisstests im Rahmen des CF-Neugeborenen-Screenings. Universitätskinderklinik Zürich, 11.8.2016 (Jürg Barben)

What is a presumptive diagnosis after newborn screening. 39th European CF Conference Basel 9.6.2016 (Jürg Barben)

Maintaining a high-quality sweat test. 39th European CF Conference Basel 9.6.2016 (Jürg Barben)

Erfahrungen nach Einführung des CF-Screenings in der Schweiz. Jahrestagung der Deutschen Gesellschaft für Neugeborenenscreening, Heidelberg, 4.6.2016 (Jürg Barben)

CFTR related disorder - extended use as label for multiorgan CF-like disease. ECFS Diagnostic Network Meeting, London 12.2.2016 (Jürg Barben)