Influence of newborn screening on the age of diagnosis in cystic fibrosis patients
K. Zyber1, M. Mielus1, E. Mierzejewska2, M. Oltarzewski1, D. Sanda1, 1Institute of Mother and Child, Cystic Fibrosis Center, Warsaw, Poland; 2Institute of Mother and Child, Department of Epidemiology, Warsaw, Poland; 3Institute of Mother and Child, Screening Department, Warsaw, Poland

Background: Cystic Fibrosis Newborn screening (CFNBS) as a pilot study started at the Institute of Mother and Child (IMC) Centre in 1999 and 444 063 newborns were examined until 2003. Current CFNBS has started gradually in Poland in 2006, covering the whole country in 2009 and is ongoing. 582 693 children were screened until the end of 2011. During CFNBS different protocol’s strategies were used.

Aim: Impact of the implementation of NBS on the age of CF diagnosis.

Methods: The study involved children diagnosed and treated only in IMC CF Centre (from 1999 until the end of 2011). Three groups were formed:
1. Pilot group (p-NBS) – 56 children, according to protocol strategy IRT/IRT and IRT/DNA only, F508del mutation was assessed;
2. Current group (c-NBS) – 92 children, IRT/IRT/DNA and IRT/DNA protocol, with expanded DNA analysis panel;

Moreover, DNA analysis in c-NBS group contains also frequent mutation in Polish population: 3849+10kcC>T, which is combined with low sweat test values. All patients underwent sweat tests.

Results: The age of diagnosis was significantly lower (both p<0.001) in p-NBS (mean 1.4 months) and c-NBS (mean 0.8 month) than in non-NBS group (mean 20.1 months). Median for the 3 groups was 1 month, 1 month and 7 months respectively. During the first month of life 7.1% of children were diagnosed in p-NBS, 20.1% in c-NBS and 12% in non-NBS group. C-NBS was characterized by higher incidence (6.5%) of 3849+10kcC>T than p-NBS and non-NBS group (both 0.9%).

Conclusion: IRT/DNA strategy with extended DNA analysis provides an opportunity of earlier CF diagnosis even in children with normal sweat test values.

Cystic fibrosis newborn screening (CF NBS): 4 year experience of the Prague Centre with the IRT/DNA/IRT protocol
A. Holubová1, V. Kružliaková1, V. Skalická1, F. Votava3, P. Dejmek3, M. Balašáková1, T. Piskáčkova1, J. Bartošová2, E. Kinclová2, M. Macek1, V. Krulísová1, V. Skalická1, F. Votava1, P. Dejmek3
1University Children’s Hospital, Prague, Czech Republic; 2Institute of Mother and Child, Prague, Czech Republic; 3Charles University 3rd Faculty of Medicine and University Hospital Královořecká Vinoř, Department of Pediatrics, Prague, Czech Republic

Objectives: The Czech nationwide CF NBS scheme, based on IRT/DNA/IRT protocol, has been operational since X2009. We evaluated its screening outcomes in Bohemia (western region of the Czech Republic) accounting for 2/3 of the entire population) until XII 2013.

Methods: Annual summaries from CF NBS and internal diagnostic database were used.

Results: From the total of 313,666 screened newborns 3,406 (1.09%) underwent DNA testing (DT). 337 children were identified with positive NBS (1 or 2 detected mutations, IRT recall) of which 48 children with positive sweat test (ST) had CF (38 with 2 CF-causing mutations in trans, 10 with 1 mutation). None of the children where no mutation was identified and whose IRT recall value was above the recall cut-off level (i.e. fail safe strategy) had positive ST. Extended DT revealed an additional mutation (Q1476X) in an infant with 1 CF mutation and repeatedly borderline ST. 199 children with positive NBS had negative ST, including 9 children with equivocal diagnosis of CF (most of whom had R117H/V585T/7 complex allele). ST was not performed in 8 screening positive children due to parental non-compliance or in deceased infants. In 5 instances CF NBS failed to identify CF: 3 cases had meconium ileus with IRT below the cut-off and 2 instances had rare mutations not present in the screening panel accounting for over 90% of all population specific alleles.

Conclusion: Current CF NBS protocol is an effective tool for early diagnosis of CF. However, we plan to adopt IRT/PAP/DNA protocol in a future to improve sensitivity and to reduce costs of CF NBS by limiting DT. Supported by CZ.2.16/3.1.00/24022/OPPK and 00664203 and PRVOUK P31.

The first date with patients detected by newborn screening – what do we see?
J. Hammermann1, K. Ulbrich1, B. Schulte-Hubbert1, 1University Children’s Hospital, TU Dresden, CF Center, Dresden, Germany

Objectives: Newborn screening for cystic fibrosis is done in eastern Saxony since 18 years now. We detected 53 babies with cystic fibrosis through that time. 50 of them we saw in our cystic fibrosis center for sweat testing and confirming the diagnosis. We looked for clinical signs and symptoms of cystic fibrosis and need for special therapy at this early stage of life.

Methods: Babies screened positive for cystic fibrosis are seen between 2 and 8 weeks of life for sweat testing in our center. We ask for medical history, do a weight and height measurement, look for fecal elastase and do a clinical assessment at this first visit.

Results: 18% of the children diagnosed with cystic fibrosis had a meconium ileus in their history, 84% had pancreatic insufficiency diagnosed by absence of fecal elastase in their stool. More than the half of children showed gastrointestinal symptoms as stool abnormalities, meteorism, abdominal pain and failure to thrive. But also pulmonary symptoms like cough, crackles in auscultation and wheezing were seen in nearly half of the children.

Conclusion: Most of the babies detected by newborn screening show clinical signs of cystic fibrosis even in their first weeks of life and need special therapy. Without newborn screening in many of them those signs would not have been correlated to cystic fibrosis and specially treated without newborn screening.

Newborn screening for cystic fibrosis – Polish experience with CFTR sequencing strategy
A. Sobejczynska-Tomaszewska1,2,3, K. Czerska1,2,3, M. Oltarzewski2, K. Wertheim-Tysarowska2, J. Bal3, CF Screening Working Group, 1MedGen Medical Centre, Warsaw, Poland; 2Institute of Mother and Child, Warsaw, Poland; 3GENOMED, Warsaw, Poland

Newborn screening for CF in Poland was started in 2006. According to our previous experience, the commercial assays are not appropriate for the Polish population due to high heterogeneity of the CFTR mutations in our CF patients. That is the reason of CFTR/DNA-strategy sequencing strategy implementation. In the first step of analysis the most frequent mutations in seven exons were analyzed according to the recommendation of the Polish Society of Cystic Fibrosis. Since 2010 protocol was developed by introduction of second step in which automatically analysis of the remained CFTR exons is provided for newborns with one identified mutation. The aim of this study was evaluation of the effectiveness of the expanded CFTR analysis in screening programme. Definition “rare mutation” was determined for a variant which is not included in the common commercial assays. The group of 9443 newborns was directed for genetic analysis. In first basic step of genetic analysis two pathogenic mutations were found in 223 cases, in 25 (11.2%) rare or novel mutations were discovered. A group of 303 newborns with one identified mutation were directed for expanded CFTR analysis. In 59 cases second mutation was identified, and in 42 cases (71.2%) there were rare or novel ones. The 2184insA, 3600+2insT, L997F, 2789-2insA, R1102X and K710X (included in one commercial assay) mutations should be considered as potential candidates for inclusion to the Polish CFTR panel as frequent mutations. Summarizing, strategy based on DNA sequencing seems to be accurate method for screening programme in Poland even at the risk of detection novel variants without confirmed clinical significance.