30* Quality improvement in newborn screening for cystic fibrosis by process failure mode effects analysis (PFMEA)

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Cystic fibrosis (CF) newborn screening (NBS) in the US has expanded rapidly to include all states except one, but issues have arisen regarding quality assurance. To address the entire CF NBS process we have completed a quality improvement (QI) project integrating methods used in other industries such as aviation but never previously applied to NBS, namely PFMEA exercises. Specifically, we drafted a flowchart of the entire CF NBS process, as well as a best IRT/DNA practices protocol, then generated a list of potential errors in this multi-step system, and rated them on a 1 to 10 scale each for severity, occurrence probability, and detectability; the product of these is the Risk Priority Number or RPN. Rating a list of 112 potential errors in Denver CO, Boston MA, and Madison WI by groups of NBS experts (N = 22) revealed that the most severe potential problems (RPN values) are: (1) parents misunderstand genetic counseling information (203); (2) missed babies due to NICU transfer (180); (3) IRT cutoff errors leading to false negative outcome (165); (4) babies with confusing or similar names (160); (5) primary care physicians not understanding NBS results and being unable to accurately explain them to parents (159); (6) birth hospitals entering the wrong data, i.e., clerical errors (158); (7) primary care physicians understanding the NBS results but not how to communicate properly without a scripted message (157); (8) babies never screened (153); (9) nurses or lab technicians obtaining and processing the wrong NBS card (153); (10) false negative NBS test results (148). It was revealing, surprising, and significant that 60% of the most serious potential errors relate to communication challenges. These results will help with QI efforts.

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31* Cystic fibrosis Heelprick among a newbOrn Population in the Netherlands: the CHOPIN-study

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Background: Although newborn screening for CF (NBSCF) is included in many routine newborn screening programs, there is no ideal test.
Aim: to assess the test characteristics of 2 new strategies for NBSCF.
Methods: In 2008 NBSCF was added to routine NBS in 4 Dutch provinces. In each sample screening was performed by 2 strategies. The 1st strategy used immunoreactive trypsin (IRT) and pancreatitis-associated protein (PAP). The test was considered positive with concentrations of IRT = 50 and PAP = 1.8 or IRT = 100 and PAP = 1.0 (all μg/l). For the 2nd method samples with IRT = 50 were analyzed for 36 CF-mutations. An extended gene-analysis (EGA) was performed in samples with 1 CF-mutation. Tests were positive when 2 CF-mutations were identified.
Results: Of the 72874 screened neonates 127 had a positive test with the IRT-PAP, among those 10 CF patients were identified. With the IRT-DNA-EGA 18 positive tests identified 11 CF-patients. IRT-DNA-EGA also revealed 84 carriers and 7 compound heterozygotes with R117H-7T as 2nd mutation. To assess the sensitivity a retrospective analysis with the 2 strategies was performed in heel prick samples of 18 known CF-patients. The IRT-PAP identified 13, the IRT-DNA-EGA 18 patients. Specificity and PPV for the IRT-PAP were 99.8 and 8.2%, while for the IRT-DNA-EGA these were 99.99 and 61%. Sensitivity calculated on the results of the screening program and the retrospective analysis was 82 respectively 100%.
Conclusion: Compared to current NBSCF-strategies, an improved test performance of the IRT-DNA-EGA strategy was found, but not of the IRT-PAP strategy.

32* Cystic Fibrosis (CF) Newborn Screening (NBS) – Comparison of an IRT-PAP with an IRT-DNA based protocol in a German population

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The effect of NBS for CF has been extensively studied. Today there is evidence that CF patients diagnosed by NBS show less nutritional deficiencies and a reduced morbidity compared to clinically diagnosed CF patients. In Germany there is so far no nationwide routine CF NBS program.
All current CF NBS protocols start with quantification of immunoreactive trypsinogen (IRT) as 1st tier in dry blood. In case of elevated IRT most NBS protocols analyse a region dependent panel of CF causing mutations as 2nd tier (IRT-DNA). If 1 or 2 mutations are detected, sweat testing is performed as confirmation. The disadvantage of IRT-DNA is the detection of healthy carriers. Recent data (Sarles et al. Pediatrics 2005) show that consecutive analysis of IRT and pancreatitis associated protein (PAP) may represent an alternative method (IRT-PAP).
The aim of our study is to compare both protocols in a German population (NBS Centre Heidelberg). The tests are carried out in heel prick dry blood spots from routine screening after written parental consent. Is IRT elevated (>99.0 P.) a parallel detection of PAP and a screening for 4 CF causing mutations (delF508, G551D, R553X, G542X) follows. A positive result in either of the protocols results in a sweat test performed in a certified CF centre. From April until November 2008 28663 children were screened for CF. 324 (1.1%) showed an elevated IRT, 61 (0.21%) of them were tested positive in a 2nd tier. In 7 children (0.024%) CF was confirmed.
We expect important information about the feasibility and reliability of a biochemically based CF NBS in comparison to a DNA based screening. Furthermore, the project represents a milestone on the way to a nationwide CF NBS in Germany.

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33 Revealing potential plasma lipid biomarkers of cystic fibrosis by mass spectrometry

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Biomarkers obtained by rapid and non-invasive methods could be used in the precocious detection of exacerbations or as prognostic indicators in CF. Our goal was to search for lipid signatures characteristic of CF patients in blood plasma. Samples from 121 individuals (53 CF patients, 18 healthy children and 49 healthy parents – heterozygotes) were collected at the Institute for Mother and Child (Warsaw). Organic extraction was followed by elution through SepPak-C18 cartridges by methyl formate. Extracts were analyzed by mass spectrometry (MALDI-TOF). Data were acquired in the positive and negative reflector mode between 200 and 1500 m/z. Ion signatures were compared by the ClinProTools software (Bruker Daltonics). Twenty one peaks, found statistically significant, were analyzed by LC-ESI-MS/MS for identification. Twelve of them were consistently upregulated (3) or downregulated (9) in CF patients as compared to heterozygotes and healthy subjects. Downregulated signatures were identified as seven phosphatidylcholine and two lysophosphatidylcholine species, some of them containing polyunsaturated acyl chains. Upregulated ions included a triglyceride adduct (m/z 881.8), and two ion signatures (m/z 335.1 and 337.1) coincident with the masses of a number of arachidonic acid derivatives. These results are consistent with the altered arachidonic acid metabolism and fatty acid profiles characteristic of CF patients, and show MALDI-TOF and ClinProTools, together with LC-ESI-MS/MS, as a suitable methodology for the search of lipid markers in CF.

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