Prevention

Screening in cystic fibrosis

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Background

A) PRENATAL SCREENING

CFTR gene cloning in 1989 has made prenatal diagnosis for CF possible. Direct analysis of mutations by current methods (chorionic villi sampling) plays a key role in the prevention of CF. Prenatal diagnosis may be offered at least to CF carrier couples ("at risk") with selective pregnancy termination. As alternative to this approach non-invasive prenatal diagnosis for CF (Guissart C et al, 2017) has been proposed, determining the presence or absence of paternally inherited foetal allele p.Phe508del by detecting the presence or absence of a p.Phe508del allele by Mutant Enrichment with 3'-Modified Oligonucleotide PCR coupled to Fragment Length Analysis (MEMO-PCR-FLA) or detecting the p.Phe508del allele with classical Multiplex Fluorescent PCR including five intragenic and extragenic STR markers of the CFTR locus and a specific SRY sequence. Furthermore, in order to facilitate the process of cell-based non-invasive prenatal testing (NIPT) a low-cost next-generation sequencing method has been evaluated, including CF (Zhuo X et al, 2021). Cell-based NIPT could accurately state the fetal variant status and distinguish fetal trophoblasts from maternal cells. Clinical reports (Jeppesen LD

Recently an Italian researchers group (Giambona A et al, 2024) reported celocentesis as a new procedure for prenatal diagnosis available from 7 weeks in case of couples at risk for genetic diseases.

Despite a still high cost-effective ratio a national In vitro-Fertilization (IVF)-Preimplantation-Genetic –Diagnosis (PGD) program could be a novel preventive medicine tool in alternative to conventional current methods and would avoid most births of individuals affected with CF, taking into account that reproductive decisions are complicated by the diversity of disease-causing variants in the CFTR gene and by the complexity of correlations between genotypes and associated phenotypes. A CF French genetic Center experienced an applicable test to 98% of couples at risk of transmitting CF (Girardet A et al, 2015). Further (Girardet A, 2016), on behalf of the EuroGentest Network, eighteen experts in PGD and/or molecular diagnosis of CF from seven countries published the best practice guidelines for amplification-based PGD established by ESHRE (European Society of Human Reproduction and Embryology), in order to contribute to a better harmonization of practices across Europe. Different topics were covered including variant nomenclature, inclusion criteria for accessing to test, genetic counseling, PGD strategy and reporting of results.

B) CARRIER SCREENING

Experience-database has been recently evaluated on couples to assess what proportion of pregnant women are likely to be offered carrier screening for CF and what proportion are likely to accept the test if it is offered free by their own physician (Lee E et al, 2025). Women found to be carriers generally followed through with partner testing and, if they were found to be at risk, through with prenatal diagnosis. Women who would not consider pregnancy termination for CF generally decline screening.

Further advantages for carrier screening can lead to test parents and family members as carriers, and possible affected future siblings.

Conversely, potential disadvantages of carrier screening at individual and population levels can inadvertently identify newborn infants as 'carriers' that could provide unjustified anxiety about the health of the baby for the parents and ethical problems concerning the child's future reproductive choices.

In several cases screening can reveal that the putative father is not the biological father.

So there is an urgent need to develop a clear guidance as how to respond to the carrier screening program. Recently a review of current guidelines for CF carrier screening has been published (Hopkins MK et al, 2022), including results of 2 medical society committee opinions and 15 additional peer-reviewed journal articles. The American College of Obstetricians and Gynecologists recommends to expand correct information on options for carrier screening, and outlined the complexity associated with carrier screening for CF, including indications for referral to certified genetic counselors or maternal-fetal specialists

The question whether heterozygotes are at increased risk for many of the same conditions as homozygotes for CFTR causing-mutations, including chronic pancreatitis, atypical mycobacterial infections, and bronchiectasis, is unresolved. There is a need to estimate the real risk attributable to the CF carriers across the lifespan, as recently discussed (Polgreen PM and Comellas AP, 2022).

C) NEWBORN SCREENING

The relevance of newborn screening (NBS) for CF has been pointed out in a series of editorials/reviews (Massie J et al, 2016)(Farrell PM et al, 2016)(Castellani C et al, 2016)(De Boeck K et al, 2017)(Stephenson AL et al, 2017)(Farrell PM et al, 2017)(Farrell PM, et al 2020)(Farrell PM et al, 2020) (Shteinberg M et al, 2021) in the last ten years.

NS is feasible and recommended worldwide. Best practice guidelines of European Cystic Fibrosis Society Standards of Care updated in 2018 support the relevance of NS in CF.

However, while NBS for CF has clearly improved the outcome for those with a 'classical' CF phenotype, understanding CFTR gene has become more complex and prognostication more challenging for some individuals that carry mutations that may result in minimal or no disease burden (Course CW, 2019). In the last years NBS programs selected also carriers and babies who do not meet all the criteria for a CF diagnosis, having inconclusive diagnostic sweat chloride (SC) and/or DNA results.These infants are classified as CF screen positive, inconclusive diagnosis (CFSPID) in Europe (Munck A, 2015) and as CF transmembrane conductance regulator-related metabolic syndrome (CRMS) in the North-America (Ren CL, 2017). The two terms have been harmonized through international

communications introducing the definition of CRMS/CFSPID, in an attempt to improve diagnostic appropriateness in the presence of unclear results, and analysis of clinical outcomes and management have been retrospectively described in several cohorts (Terlizzi V, 2019); (Terlizzi V et al, 2021); (Dolce D et al, 2022)(Salinas DB et al, 2023). An updated guidance on the management of children with CFSPID has been proposed (Burgen J et al, 2021).

NBS programs for CF represent a complex strategy involving laboratory quality control in specimen collection and analysis (IRT/DNA/sweat testing), genetic counseling and communication, and follow-up. Several critical points have been focused in the last years. First, defining the immunoreactive trypsinogen (IRT) cut-off value was previously discussed to identify key IRT testing issues (Therrell BL, 2012). Second, to date no "ideal" protocol has been challenged. Different stage protocols based on a second IRT test with or without subsequent genetic analyses have been developed in USA (Caggana M et al, 2017) and in Europe (Barben J et al, 2017) with the attempt to reduce the false positive diagnoses associated with one stage IRT testing. A study from France suggests that NBS programmes should have a centralized monitoring process to warrant adjustments for improving the performance in terms of early diagnosis and reducing pending diagnosis (Munck A et al , 2017). An alternative screening protocol (Sommerburg A et al, 2017) was implemented in Germany using IRT as first tier and pancreatitis associated protein (PAP) as second tier. Gene analysis with a panel of 31 CFTR-mutations was used as third tier to increase the positive predictive value (PPV) which is known to be low in pure biochemical IRT/PAP protocols. Main results showed that this protocol has a better performance and a decreasing number of false-positives, leading to less consultations including sweat tests, reducing anxiety in parents, and finally resulting in less costs after screening. Recently, the European CF Society Neonatal Screening Working Group (ECFS NSWG) (Munck A et al, 2022) assessed that different NBS programmes impact differently on performance and larger data are needed to evaluate their role on clinical outcomes.

In general, advantages and disadvantages have been registered for each NBS program worldwide (Turkey, Denmark, UK, France, Italy, Catalona, Ireland, Brazil, Cuba) in terms of specificity and sensitivity, costs, false-positive results, that may adversely affect the parents relationship with their baby, or false-negative screening tests, that may delay diagnosis (Kharrazi M et al, 2022) with false reassurance that may lead to delays in clinical diagnosis and loss of an opportunity to give genetic counseling at an appropriate time. In addition, there may be a risk of “labelling” as CF those patients with mild disease who might not have presented with clinical symptoms and exposing them to unnecessary treatments or interventions.

Regard carefullness of genetic analysis included in NBS programmes previous data from California (Currier RJ et al, 2017) showed that using third-tier CFTR gene sequencing may improve CF detection following an initial elevated IRT associated to detection of only one mutation on a second-tier panel, improving the utility of this approach in states that have diverse multiethnic populations as US (McGarry ME et al, 2023). A recent cohort study of infants with CF born in California between 2007 and 2021 (McGarry ME et al, 2024) confirmed that larger CFTR panels in NBS improved the detection of CF in all races and ethnicities.

Issues

PRENATAL SCREENING

- To define what are future technological changes to adopt for prenatal CF diagnosis.

CARRIER SCREENING

- To identify acceptable ways of disclosing carrier status depending on the condition for which screening is offered.
- To identify acceptable ways of not disclosing carrier status depending on the condition for which screening is offered.

NEWBORN SCREENING

- -To advance in technology enhancing the expansion of newborn blood spot screening
- -To address whether NS for CF:

1. improves survival;
2. reduces the number of respiratory exacerbations and improves overall respiratory status;
3. improves nutritional status;
4. reduces long-term complications such as CF–related diabetes and liver cirrhosis;
5. is associated with significant adverse effects in the CF group diagnosed by NS (including delay in clinical diagnosis of ’missed’ cases because of false-negative tests and ’labelling’ of those with mild disease, as well as early colonization by gram-negative bacteria);
6. is associated with significant adverse effects in the screened population (including psychological damage following false-positive tests, interference with developing family relationships and misconceptions and miscommunication of results, as well as the effect that an early diagnosis has on the quality of life of the child and the parents (cost–utility analysis);
7. is a more economic way of achieving a diagnosis of CF than through signs or symptoms.

What is known

PRENATAL SCREENING

Regarding prenatal diagnosis only one CDSR (Hussein N, 2021) was assessed to evaluate the effectiveness of systematic preconception genetic risk to enable autonomous reproductive choice and to improve reproductive outcomes in women and their partners who are both identified as carriers of thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease in healthcare settings when compared to usual care. No RCTs were found. While RCTs are desirable to inform evidence?based practice and robust recommendations, the ethical, legal and social implications associated with using the trial design must also be considered. In addition,

rather than focusing on single gene?by?gene carrier testing preconception expanded genetic screening should also be included in future searches as a more pragmatic strategy. The research evidence for current international policy recommendations is limited to non?randomised studies.

CARRIER SCREENING

No controlled trials about disclosing carrier status have been found.

1 CDSR was updated to 2008 for assessing whether psychological interventions for CF provide significant psychosocial and physical benefits in addition to standard care: only one paper reported gene pre-test education counseling within a screening program for relatives of individuals diagnosed with CF. The primary outcome indicator was level of knowledge retained about genetic aspects of CF.

In a retrospective study (Dotan M et al, 2023) a population genetic carrier screening (PGCS) for CF has been offered to couples in Israel since 1999 to evaluate the impact of PGCS on CF incidence, genetic and clinical features. Demographic and clinical characteristics of children with CF born in Israel between 2008 and 2018 were derived from the national CF registry and from patients' medical records. Data on CF births, preimplantation genetic testing (PGT), pregnancy termination and de-identified data from the PGCS program were collected. Results indicate that the birth of children with CF decreased markedly. Residual function variants and pancreatic sufficiency were more common suggesting that a broader genetic screening panel and increased PGCS utilization may further decrease the birth of children with CF. Main results showed that CF births per 100,000 live births decreased from 8.29 in 2008 to 0.54 in 2018 (IRR = 0.84, $p < 0.001$). The CF pregnancy termination rate did not change (IRR = 1, p= 0.9) while the CF-related PGT rate increased markedly (IRR = 1.33, $p < 0.001$). One hundred and two children were born with CF between 2008 and 2018 with a median age at diagnosis of 4.8 months, range 0-111 months. Unlike the generally high uptake nationally, 65/102 had not performed PGCS. Even if all had utilized PGCS, only 51 would have been detected by the existing genetic screening panel. Clinically, 34 % of children were pancreatic sufficient compared to 23 % before 2008 ($p = 0.04$).

The preconception carrier screening test for CF is usually performed using ethnically targeted panels of selected mutations. Expanded, ethnically indifferent, pan-population panels for preconception carrier screening testing might achieve higher preconception detection rates, as revealed by a study from Israel where populations carry a wide heterogenous range of CFTR mutations beyond the ones included in the CFTR2 database (Behar DM, 2017). Canadian carrier genetic screening recommendations updated to 2016 (Wilson RD, 2016) comprised not only the costs of these programs for the national healthcare system, but also the social, financial, psychological, emotional costs for the families.

NEWBORN SCREENING

The Wisconsin CF Neonatal Screening Project provided robust evidence of the nutritional benefits of early diagnosis (Shenoy A et al, 2025). This randomized control trial followed 650,341 children over 2 decades, demonstrating that patients with CF identified by CF NBS had significantly higher weight, height, and head circumference. On the contrary data on the pulmonary benefits of GF NBS havebeen inconsistent. Only one randomized trial reported better chest radiographic score in NBS diagnosed children compared to children diagnosed clinically, but there were no differences in the FEV1.The ultimate goal of CF NBS is early diagnosis and treatment of newborns with CF.

In the past a Cochrane Database Systematic Review (CDSR) on NBS was update at 2009 in order to evaluate whether NBS improves clinical outcomes, quality of life and survival. Searches of this CDSR identified six trials. Two trials involving 1.124.483 screened neonates (210 with CF) with a maximum follow up of 17 years were eligible for inclusion. 552.354 (49.1%) were allocated to the screened group and 572.129 (50.9%) to the control group. A total of 210 CF participants were included in the analysis. The participants ranged from 0 to 16 years of age. Length of follow up ranged from one year to 16 years. Varying study designs, outcomes reported and summary measures precluded calculation of pooled estimates and only data from one study were analyzed.

Main results pointed out that:

- severe malnutrition was less common among screened participants. Compared with screened participants, the odds ratio of weight below the 10th percentile was 4.12 (95% CI 1.64; 10.38) and for height was 4.62 (95% CI 1.69; 12.61) in the control group.
- at age seven, 88% of screened participants and 75% of controls had lung function parameters within normal limits of at least 89% predicted. At diagnosis chest radiograph scores were significantly better among screened participants: 33% of screened versus 50% of control participants, but over time chest radiograph scores were worse in the screened group. Results were no longer significant after adjustment for genotype, pancreatic status, and Pseudomonas aeruginosa (PA) culture results. In screened participants colonization with PA occurred earlier (but this result was related to minimal prevention measures for segregation).

For issues 1,4,5,6 previously raised collected data of CDSR are not conclusive. In particular, results on long-term pulmonary prognosis are biased by confounding factors such as infection and pancreatic status and make difficult analysis of results.

Overall these results suggested that, even within the context of modern care at specialized centres for patients with CF, the early diagnosis by NBS appears to offer global advantages. Regarding the pulmonary outcomes described in both trials, screened participants at the time of diagnosis had better chest radiograph scores and more participants in the screened group had lung function tests within the normal limits at 7 years of age, although differences in lung function parameters were not statistically significant between groups. However, differences between screened and control participants regarding the several lung function parameters in the longitudinal analyses were not specified. Over time chest radiographs were worse in the screened groups and long-term differences in lung function were statistically not significant between groups.

A multicenter study (Pagani S et al, 2019) showed differences in height, weight, and BMI between NBS children and LD children at diagnosis in a cohort of subject followed for several years. Despite these differences were not statistically significant at median level, LD children were found to have reduced weight, height, and BMI values compared to NBS children, confirming that the LD children were at a disadvantage compared to the NBS group at diagnosis. During longitudinal observation this discrepancy was not registered. In 2021 (Barreda CB, 2021) a retrospective analysis of the RCT cohort derived from the Wisconsin Cystic Fibrosis Neonatal Screening Project was performed to assess whether early diagnosis of CF via newborn screening may impact on long-term pulmonary and mortality outcomes. The analysis showed that NBS alone does not improve pulmonary outcomes in CF. Among the 145 subjects who

consented to the original study, 104 subjects met inclusion criteria and had adequate data in the CFFPR. The rates of ppFEV$_1$ decline were 1.76%/year (95% CI 1.62 to 1.91%) and 1.43%/year (95% CI 1.26 to 1.60%), respectively (p<0.0002) in the screened group (n= 57) and in the control group (n=47). Pseudomonas aeruginosa acquired before 2 years was partially responsible. There was no difference in mortality rate between the two groups.

In the past other papers reported that

- the cost of care of patients diagnosed by NBS is significantly lower than the cost of treatment of patients diagnosed by symptoms requiring fewer therapeutic interventions and, overall, less intensive therapy (Sanders DB, 2012);
- the IRT/IRT screening algorithm reduced the costs to laboratories and insurance companies but had more system failures. IRT/DNA offers other advantages, including fewer delayed diagnoses and lower out-of-pocket costs to families (Wells J, 2012);
- a purely biochemical IRT/PAP protocol obtained in a large cohort of 330000 newborns in Germany was accepted as an alternative to genetic CF-NS (Sommerburg O, 2015);
- an historical cohort study (Zhang Z, 2016) assessed pubertal height growth and adult height after newborn screening. Early linear growth benefits of NS were sustained through puberty, leading to a better adult height in CF;
- a systematic review (Schmidt M, 2018) revealed that all screening strategies are cost-effective compared with no-screening option; the IRT/PAP seems to be the most cost-effective screening strategy.

NGS can be used with IRT as an effective method of identifying infants at risk for CF, adding value for facilitating equity, enhancing sensitivity and detecting more CF patients with 2-variants during the NBS program (Rock MJ et al, 2023).

Unresolved questions

PRENATAL SCREENING

Setting up a national prenatal screening program for CF is timely and should be implemented (Banzi R et al, 2023).

CARRIER SCREENING

Further studies are needed to define the best carrier screening method, to evaluate the net cost of screening, the effect on quality of life in terms of anxiety associated with testing, the potential benefits related to information of risk for any subsequent pregnancy, and for alerted relatives (Castellani C, 2016). There is a need to develop and evaluate the effects of interventions to support the disclosure of carrier status to parents and relatives following newborn screening, focusing on genetic counseling and epidemiology, as well as on decreasing in the incidence of CF. There is some more difficulty for disclosure of carrier status for mild mutations . No studies are available concerning the benefits on medical, social and ethical perspectives. A wide variability in how reproductive carrier screening is offered across the globe is updated, including factors that contribute to variation as geographical status, genetic conditions and local health care, financial, cultural, and religious factors (Delatycki MB et al, 2020).

Population-based screening programs are encouraged rather than selective screening tests for individuals already known to be at high risk. The information for carriers may be of no immediate benefit to their health or treatment.

NEWBORN SCREENING

NBS for CF should be considered as a relevant tool in order to increase survival in CF. The integration of NBS within well-established CF care structures, supporting interaction of obstetricians, primary caregivers, pediatricians, CF centers, and health authorities is mandatory in the future (Naehrlich L, 2021).

Many questions remain to be solved:

- to update the best cut-off of screening test (IRT) for different laboratories in different geographic regions in order to take account also of seasonal fluctuation of IRT;
- to highlight factors that could account for a missed diagnosis of CF (Kharrazi M et al, 2022);
- to provide proper methods for quality improvement of communication and psychosocial outcomes after NS in families of infants with carrier status, as described in the past (Farrell MH, 2011) or in families of infants with inconclusive diagnosis (Tosco A et al, 2023);
- to update NS guidelines in terms of sensitivity, specificity, costs and outcomes.

In the era of new therapies women with CF may plan pregnancies and for men with CF, CF-associated infertility can be mitigated with assistive reproductive technology. So practice recommendations regarding reproductive counseling and care in CF, including the role of genetic counseling, preconception and prenatal counseling, carrier screening, teratogen counseling, in vitro fertilization and pre-implantation genetic diagnosis, are needed via a multidisciplinary, patient-centered approach (McGlynn J et al, 2023).

Regarding the still unresolved problem whether the marked increase in the life expectancy of people with CF registered over the past 30 years could be attributed to improvements in therapy and/or to early treatment in asymptomatic children with CF diagnosed by NBS further evidence based on new studies should be implemented. The Baby Observational and Nutrition Study (BONUS), a multicenter, longitudinal, observational cohort study conducted at 28 US Cystic Fibrosis Foundation-accredited Care Centers from January 2012, through May 2015, including 231 infants younger than 3.5 months who underwent NBS with confirmed CF, and followed up the first 12 months of life showed a significant improvement in nutritional status, with normalization of weight, but not height in the first year of life (Leung DH, 2017). A recent review (Davies D, 2020) confirmed that at present there is insufficient evidence to draw firm conclusions about the effect of NBS on early lung function. These conclusions have been confirmed in a recent review (Davies G, 2022).

Recently (Felton I et al, 2024) the potential impact of CFTR modulators on maternal, fetal and long-term offspring outcomes following CFTR modulator use has been reviewed, as constituent therapy components have been found in fetal circulation in humans, and there could be implications for maternal continuation or cessation of treatment. A potential therapeutic impact of targeting CFTR-related organ dysfunction in CF-fetuses via maternal-administration of CFTR modulators has been suggested.

Keywords

Carrier Status; Genetic Predisposition to Disease; Heterozygote; Screening;