Screening in cystic fibrosis

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Background

PRENATAL SCREENING

CFTR gene cloning has made screening for CF possible. Prevention for CF offers prenatal diagnosis for carrier couples (“at risk”) with selective pregnancy termination.

A few trials on prenatal CF carrier screening have been performed assessing what proportion of pregnant women are likely to be offered screening and what proportion are likely to accept the test if it is offered free by their own physician (Rowley PT, 1997; Loader S, 1996). A paucity of experience-database is available on CF carrier screening and to terminate CF affected pregnancies. Women found to be carriers generally followed through with partner testing and, if they were found to be at risk, with prenatal diagnosis. Women who would not consider pregnancy termination for CF generally decline screening.

In a paper reporting the experience of an Italian Prenatal Diagnosis Center for beta-thalassemia (BT), CF and other rare genetic disorders (Maruotti GM, 2013) all the couples referred to the center from January 1993 to May 2013 were analyzed retrospectively for Prenatal Diagnosis (PD). 1269 PD were performed for genetic disorders. The majority of the people were screened for CF carrier after the birth of an affected child or through the cascade screening, while large-scale screenings for rare genetic conditions are not available and people were screened only if they have a positive familial history. Women who would not consider pregnancy termination for CF generally decline screening.

Regarding the still unsolving 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 NS.

NEWBORN SCREENING

The relevance of newborn screening in CF has been recently pointed out in a series of editorial/reviews (Massie J, 2016; Farrell PM, 2016; Castellani C, 2016; De Boeck K, 2017; Stephenson AL, 2017; Farrell PM, 2017).

Newborn screening (NS) is feasible and recommended worldwide. Best practice guidelines of European Cystic Fibrosis Society Standards of Care support NS for CF.

NS 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.

Until now no “ideal” protocol has been challenged. Quite different stage protocols based on a second IRT test with or without subsequent genetic analyses have been developed in USA (Caggana M, 2017) and in Europe (Barben J, 2017) to reduce the false positive diagnoses associated with one stage IRT testing.

Recently (Baker MW, 2011) it has been proposed a panel selection of 23 mutations to optimize sensitivity in US. The IRT cut-off value, however, is actually more critical than DNA in determining CF newborn screening sensitivity and focus on identifying key IRT testing issues has been recently discussed (Therrell BL, 2012). A study from France suggests that newborn screening programmes should have a centralized monitoring process to warrant adjustments for improving performance in terms of early diagnosis and reducing of pending diagnosis (Munck A, 2017). A new screening protocol (Sommerburg A, 2017) has been implemented in Germany using immunoreactive trypsinogen (IRT) as first and pancreatitis associated protein (PAP) as second tier. Gene analysis with a panel of 31 CFTR-mutations is 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 show that this protocol has a better performance, decreasing number of false-positively detected with the previous protocol, leading to less consultations including sweat tests, reducing anxiety in parents, and finally resulting in less costs after screening. Thus advantages and disadvantages have been registered for each NS program 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, 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 patients with mild disease who might not have presented clinically and exposing them to unnecessary treatments or interventions.

Regarding to genetic analysis recent data from California (Currier RJ, 2017) showed that using third-tier CFTR gene sequencing may improve CF detection following an initial elevated immunoreactive trypsinogen and detection of only one mutation on a second-tier panel, improving the utility of his approach in states that have diverse multiethnic populations.

NBS should focus on the rationalisation and optimisation of existing programmes, with particular attention to bioethical implications such as unwanted detection of carriers and inconclusive diagnoses.

Regarding the still unsolving 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 NS.
further evidence based 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 and had confirmed CF, and were followed up the first 12 months of life showed a significant improvement in nutritional status, with normalization of weight in the first year of life, as remaining common length stunting (Leung DH, 2017).

Generally, as newborn screening not only saves lives but can also yield net societal economic benefit, calculations of net economic benefit from newborn screening are performed including the monetary equivalent of avoided deaths and reductions in costs of care for complications associated with late-diagnosed individuals minus the additional costs of screening, diagnosis, and treatment associated with prompt diagnosis. The experience of the Washington State Department of Health has been recently published including data on newborn screening of CF (Grosse SD, 2016).

CARRIER SCREENING
Newborn screening for CF can improve the experience of diagnosis for parents.
Advantages can lead to testing of parents and family members as carriers, and possible affected future siblings.
Potential disadvantages of screening at individual and population levels can inadvertently identify newborn infants as ‘genetic carriers’ that could provide unjustified anxiety about the health of the carrier newborn for 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.

Issues

PRENATAL SCREENING
● To evaluate the way to screen couples before the birth of an affected child
● To evaluate what is the cost per CF birth (cost-effective analysis)
● To evaluate what is this cost of carrier screening balanced by costs of medical care (cost–benefit analysis)
● To define what are future technological changes to adopt for CF carrier screening (cost –effectiveness

NEWBORN SCREENING
To address whether NS for CF:
● improves survival;
● reduces the number of respiratory complications and improves overall respiratory status;
● improves nutritional status;
● reduces long-term complications such as CF–related diabetes and liver cirrhosis;
● 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);
● 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 misconceptions of results, as well as the effect that an early diagnosis has on the quality of life of the child and parent (cost–utility analysis)
● is a more economic way of achieving a diagnosis of CF as when diagnosed clinically.

CARRIER SCREENING
● To advance in technology enhancing the expansion of newborn blood spot screening and raised expectations of informed consent and disclosing test results.
● 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.

What is known

PRENATAL SCREENING
Regarding to prenatal screening one RCT (Miedzybrodzka ZH, 1995) reported comparative evaluation of stepwise and couple approaches to antenatal carrier screening for CF including 2002 women (couples) with no family history of CF. An increased maternal distress was associated to identification as carrier, although this disappeared when a negative result in her partner became available. In part to avoid such distress and the associated need for counselling, screening of couples was proposed.

Since prenatal screening sensitivity test is generally reported under 78% (Grosse SD, 2004) in several countries of Caucasian population where prenatal screening has been adopted, despite of a decrease of neonates born with CF, no strategies have been still promoted worldwide.
Prenatal CF carrier screening engages for widely medical, social, and ethical perspectives (Castellani C, 2016). A cost-effectiveness
analysis of prenatal carrier screening is in favor of this strategy (Weilers-Poppelaars FA, 2005).

Recently (Norman R., 2012) a cost-effectiveness of prenatal carrier screening for CF was detected in Australia to evaluate benefit of information from pregnancy to pregnancy, including both initial and subsequent pregnancies. Beyond reduced annual incidence of CF births, results reported reduced incidence of CF in subsequent pregnancies at low additional costs.

Routine prenatal CF carrier screening may increase the utilization of carrier screening and ultimately increase competition among laboratories, reducing the cost of testing. Furthermore, increasing efficient screening for large numbers of mutations may reduce costs.

Despite a highly cost-effective a national In vitro-Fertilization (IVF)-Preimplantation-Genetic–Diagnosis (PGD) program could be a novel modality of preventive medicine and would avoid most births of individuals affected with CF (Reprod Biomed Online, 2010) taking into account that reproductive decisions are complicated by the diversity of disease-causing variants in the CFTR gene and by complexity of correlations between genotypes and associated phenotypes.

Recently (Girardet A., 2016) on behalf of the EuroGentest Network, eighteen experts in PGD and/or molecular diagnosis of CF from seven countries builded on 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, genetic counseling, PGD strategy and reporting of results.

NEWBORN SCREENING

Only 1 CDSR on NS was update at 2009. 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 (Chatfield S., 1991; Mischler EH., 1998).

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 reported 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 have been reported:

1) 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 to 10.38) and for height was 4.62 (95% CI 1.69 to 12.61) in the control group.

2) 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 data are not conclusive.

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 suggest that, even within the context of modern care at specialized centres for patients with CF, the early diagnosis by NS 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.

In a recent overview (Salvatore D., 2010) in order to define the role of NS on better prognosis and survival over 30,000 people with CF were evaluated from registries including very heterogeneous clinical trials.

Taking into account that comparison between screened and not screened subjects could be influenced by different plan of care for subjects diagnosed by NS in recent years, despite of adjusting the analysis for possible confounding factors, the main results are as follow:

- no data are conclusive related to the impact of early diagnosis on respiratory function;
- NS is effective in promoting better nutritional status and lowering morbidity;
- early diagnosis by NS could positively impact on a lower number of adverse events as growth failure, delayed culture positive for PA, and hospitalization rate, although inclusion of mild forms of CF could overestimate these results;
- the cost of care of patients diagnosed by NS 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 reduces the costs to laboratories and insurance companies but has 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 7350,000 newborns in Germany has been obtained as an acceptable alternative to genetic CF-NBS (Sommerburg O, 2015);
- more recently (HTA-32012000676, 2012) a review of clinical and cost-effectiveness of NS for CF was performed with the aim to estimate the accuracy of eight different NS protocols and to compare costs of IRT/IRT protocol to IRT/DNA protocol. Despite the review documented a lower cost of the first protocol, decision of which NS panel to use should be made considering the benefits of an early treatment related to accuracy of early diagnosis.

CARRIER SCREENING
No controlled trials about disclosing carrier status have been found. 1 CDSR updated to 2008 assessed whether psychological interventions for CF provide significant psychosocial and physical benefits in addition to standard care: only one paper was included (Cheuvront B, 1998), reporting gene pre-test education counseling within a screening program for relatives of individuals diagnosed with CF. One approach was clinic-based where a qualified genetic counselor delivered education and a technician took the mouth swab sample. The primary outcome indicator was level of knowledge retained about genetic aspects of CF.

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. When NBS program identifies a carrier status this may have implications for the baby's future reproductive choices, but it is still unclear whether this information can be reliably remembered, or recorded and retained by the family or child. In a recent Australian study (McClaren BJ, 2010) the uptake of testing for eligible non-parent relatives was 12%.

Unresolved questions

PRENATAL SCREENING

Setting up a national prenatal screening program for CF is timely and should be implemented. Otherwise, further studies are needed to define the best prenatal 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.

NEWBORN SCREENING

Many questions remain to be resolved:

- To update 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 define the most suitable diagnostic molecular analysis kit for achieving the highest detection rate in a NS program in each geographical region (Bauca JM, 2015), considering the relevance of multiethnic populations shared with Caucasian populations.
- To highlight factors that could account for a missed diagnosis of CF (Baker MW, 2011).
- To carefully assess methodological quality of trials in clinically defined groups.
- To provide proper methods for quality improvement of communication and psychosocial outcomes after NBS in families of infants with carrier status, as recently described (Farrell MH, 2011) or in families of infants with inconclusive diagnosis (Ooi CY, 2015).
- To update NS guidelines in terms of sensitivity, specificity, costs and outcomes.

CARRIER SCREENING

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 (Castellani C, 2009). There is some more difficult for disclosure of carrier status for mild mutations. No studies are available concerning the benefits on medical, social and ethical perspectives. Setting computer programs that can successfully educate individuals considering genetic testing for CF have to be implemented (Castellani C, 2011).

Keywords

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