

# POSITION PAPER ON EXTENDED NEWBORN SCREENING DRAFTED BY THE ASSOCIATIONS OF PEOPLE LIVING WITH RARE DISEASES

## 1 Extended newborn screening

Extended newborn screening is one of the most important public programs of secondary preventive medicine currently available in Italy. Based on the provisions of Law no. 167/2016, thanks to a test carried out with a simple blood sample from a newborn's heel, it is now possible to early identify about 40 rare genetic hereditary metabolic pathologies. This test offers hope for survival and a better quality of life for the newborn and the family, as these are very difficult diseases to recognize, since they give symptoms similar to other diseases, and quickly degenerative.

### 1.1. What it is and what it is used for

In Italy, newborn screening is a preventive, free and mandatory health activity since 1992, when Law no. 104 has provided mandatory screening for three diseases: phenylketonuria, congenital hypothyroidism and cystic fibrosis.

Since 2016, Law no. 167 has extended mandatory newborn screening to about 40 other hereditary metabolic diseases (expanded newborn screening), hitherto applied heterogeneously and not in all regions. The metabolic genetic pathologies detectable thanks to the expanded newborn screening, which is not a genetic but biochemical test, are diseases for which special diets and treatments are available. If applied in the first days of life, before that symptoms occur, they can very significantly improve the quality of life or prevent death.

Some regions have already included other diseases in their screening programs, in addition to those of the official panel provided for by Law no. 167/2016 and the related Ministerial Decree 13/10/2016, which can be treated effectively if diagnosed early, such as, for example, congenital adrenal hyperplasia, some lysosomal storage diseases, severe combined immunodeficiency (SCID), GAMT deficiency, some hemoglobinopathies. Other pathologies such as Adrenoleukodystrophy X Linked, Metachromatic Leukodystrophy, Argininosuccinic Aciduria, OCT deficiency Ornithinacetyltransferase, other immunodeficiencies / trek may also be added to these in the coming months.

The Budget Law 2019 (Law 30 December 2018, n. 145. "State budget for the financial year 2019 and multi-year budget for the three-year period 2019-2021"), amended the Law 167/2016 by expanding the extended newborn screening, to neuromuscular diseases of genetic origin, severe congenital immunodeficiencies and lysosomal storage diseases. Thus these latter are included in the panel, in addition to hereditary metabolic diseases.

### 1.2. Information and possible informed consent for parents

Before the test is carried out, an operator / doctor of the birth point gives the family information that illustrates the purposes and methods and presents the diseases being screened. The test is free and mandatory, therefore informed consent from parents is not required. Informed consent is instead requested only if the Region where the child was born has added additional new pathologies to the test

which are not yet part of the panel of the 40 provided for by Law no. 167/2016 and if the storage and retention of the filter paper with the biological material is scheduled for a period exceeding two years.

### **1.3. How it works**

Between 48 and 72 hours of life, before the discharge from the birth point, a small blood sample is collected from the heel of the new-born. If the mother and the new-born are discharged earlier (24 hours after childbirth) they are called back to the birth point. The same sampling - blood spot - which was used up to now to screen only 3 pathologies (phenylketonuria, congenital hypothyroidism and cystic fibrosis), is used to screen also the other about 40 pathologies. No larger or further blood sample are therefore necessary; the test is not invasive and cannot harm the new-born in any way. After taking the sample, the drops of blood are deposited on a special absorbent paper (filter paper), part of a card (specimen collection device) containing the identification data of the new-born. The card with dried blood is sent to the regional screening laboratory where tests are carried out to rule out any pathologies.

If the test is positive, the parents are promptly called back by the Birth Point or Regional Screening Centre and invited to take the new-born to the Birth Point or to the reference care centre for further checks. If it is not an immediately degenerative pathology, the new-born can be called back to carry out a second in-depth test in more extended times. If, on the other hand, the pathology is among those that require immediate clinical intervention, the new-born is immediately sent to the reference clinical centre, where the symptoms of the pathology are promptly contained with targeted treatments and diets and the genetic confirmation of the suspected diagnosis is carried out.

The extreme sensitivity of the equipment, in addition to some conditions, can determine the positivity of the test, for example a premature birth, a low birth weight, taking medications, etc. Therefore, a positive test does not always mean that the new-born is affected by the disease: only subsequent tests will allow to confirm or not the diagnosis.

## **2. The position of associations of people with rare disease**

With respect to the issue of new-born screening UNIAMO, the Italian Federation of Rare Diseases, and many Patient Organisations have created follow-up courses, meetings and debates, both to raise awareness of the importance of the test and to outline the needs of pre and post blood sample. The ideas that emerged were collected and systematized in this position document in a sort of "decatalogue" of what is our ideal path on this topic.

### **2.1 The 10 recommendations on expanded neonatal screening**

**1.** Ensure the protection of human rights in the processes of carrying out expanded neonatal screening. For this reason, screening tests for rare diseases must be:

- timely: be carried out within the times indicated by the regulations;
- specific: obtain a low number of false positives to avoid unnecessary anxiety and stress to parents;
- sensitive: obtain a low number of false negatives to reduce diagnostic delays;
- predictive: have a high probability that a positive test is an indicator of the disease;
- acceptable: foresee a low level of risk and inconvenience provided:

Extended neonatal screening programs must:

- eliminate or minimize any harm to the newborn;
- guarantee the right to privacy and self-determination;
- consider the social, ethical and legal aspects.

**2.** Ensure the timely inclusion, in the panel of expanded newborn screening ,of all hereditary metabolic pathologies, of neuromuscular diseases of genetic origin, of severe congenital immunodeficiencies and of lysosomal storage diseases or in any case of all those pathologies for which there is scientific evidence of therapeutic efficacy for the pharmacological or dietetic therapy or for which there is scientific evidence that an early diagnosis, in neonatal age, entails an advantage in terms of access to therapies in an advanced state of trial, also of dietary type.

**3.** Ensure full implementation of new-born screening path in all the Regions / Autonomous Provinces also through inter-regional agreements. It must therefore be ensured the functioning of:

- I. new-born screening laboratory with an adequate pool of target population;
- II. laboratory for confirmatory diagnostic tests;
- III. clinical centre for screened diseases;
- IV. regional or interregional coordination of the screening system.

At regional / provincial level, the following must also be guaranteed:

- I. the presence in the regional panel of all the pathologies identified by Law no. 167/2016 and subsequent updates in the panel of pathologies;
- II. the identification of a regional contact person for the regional program of expanded new-born screening;
- III. the implementation of a regional archive on the results of new-born screening that regularly feeds the national archive;
- IV. updating of the Regional / Interregional Registries of rare diseases with the positive cases of expanded new-born screening for which the diagnosis has been confirmed followed by the their submission to the National Register of Rare Diseases

**4.** Provide for and guarantee uniformity in the implementation of expanded new-born screening throughout the national territory (in the collection devices, in the information collected, in the transport, in the laboratory methods, in the number of diseases subject to screening, in the timing, in the information given to parents and in the management of information / informed consent, ...) through the issue of recommendations .

**5.** Provide for and guarantee training on expanded new-born screening of all health professionals involved in the birth path (gynaecologists, neonatologists, consultants, nurses, etc.), including paediatricians and General Practitioners, as well as the professionals and operators involved in the screening process who relate to the parents from the pre- conception period to the time of the test.

**6.** Provide for and ensure adequate information on expanded new-born screening to citizenry and in particular to families, from the pre-conception period to the time of the test

**7.** Provide for and ensure adequate communication of the results of expanded new-born screening to parents, providing for timings, methods, settings and professionals that facilitate the parents' understanding and ensure their possible and appropriate genetic counselling.

**8.** If the outcome of the expanded new-born screening is positive:

a) ensure a timely recall

b) in the event of subsequent diagnostic confirmation, ensure adequate and timely take in charge, with the identification of the reference centre, follow-ups and hospitalizations with the formulation of the treatment and / or diet and the relationship between the reference centre and the Paediatricians / GPs.

**9.** Provide a communication to the parents also in case of negative test result.

**10.** Based on Law 11/01/2018 n. 3 art. 1 paragraph f and Legislative Decree 14 May 2019 n. 52, Art. 1 B, provide for the possibility of consciously opting for the retention, distribution and use of the residual biological material of the screening and personal data for research purposes, also in an epidemiological perspective, and for further diagnosis, even over 2 years from execution of the test, after acquiring informed consent, as required by European legislation (EU Reg. n.679 / 2016, Law 3/2018, paragraph f). In this regard, it is necessary to specifically regulate the methods of retention and use, for research purposes, of the residual material of the neonatal screening. It is hoped that the samples can be stored in a biobank (preferably in a national biobank that is part of the BBMRI network) to ensure uniformity of storage conditions and access methods.

## **2.2 A starting point for starting a shared reflection**

We hope for the opportunity to include new genetically transmissible diseases, even if currently incurable, in the panel of expanded new-born screening, in order to ensure informed decisions by parents in the procreative field.

### REFERENCE REGULATIONS

- Legislative Decree 14/05/2019 n. 52 "Implementation of the mandate for the reorganization and reform of the legislation on clinical trials of medicinal products for human use, pursuant to article 1, paragraphs 1 and 2, of the law 11 January 2018, n. 3
- Law n. 145 of 30 December 2018 "State budget for the financial year 2019 and multiannual budget for the three-year period 2019-2021", Article 1, Paragraph 544
- Law 11.1.2018 n. 3 "Mandate to the Government on clinical trials of medicines as well as provisions for the reorganization of the health professions and for the health management of the Ministry of Health"
- Decree of the Ministry of Health of 13 October 2016 "Provisions for the launch of newborn screening for the early diagnosis of hereditary metabolic diseases"
- Law n. 167 of August 19, 2016 "Provisions on mandatory newborn diagnostic tests for the prevention and treatment of hereditary metabolic diseases"

- Law n. 190 of 23 December 2014 "Provisions for the formation of the annual and multiannual state budget (2015 Stability Law)", Article 1, Section 167
- Law n. 147 of 27 December 2013 "Provisions for the formation of the annual and multiannual state budget (2014 Stability Law)", Article 1, Section 229

#### REFERENCE DOCUMENTS

- Taruscio D., Kodra Y., Amicosante AMV, Bacco G., Battilomo S., Burlina A., Privitera MG, La Marca G., Leonardi A., Salvatore F., Segato A., Vaccarotto M., Del Favero A., "Expanded Newborn screening in Italy: state of the art as of 30 September 2018"
- UNIAMOF.I.M.R., "MonitoRare. Fifth report on the condition of the person with rare disease in Italy "(2019)
- Taruscio D., Kodra Y., Amicosante AMV, Bacco G., Battilomo S., Burlina A., Conti S., La Marca G., Minelli G., Leonardi A., Salvatore F., Segato A., Vaccarotto M., Del Favero A. "Expanded Newborn screening in the Regions: monitoring of the implementation of the Ministerial Decree of 13 October 2016. State of the art at 30 June 2017" (ISTISAN reports 18/811) (2018)
- UNIAMO F.I.M.R., "Proposal of patient and parent associations for a national model of information on newborn blood drop screening" (2018)
- SIMMESN, "Technical Report on Newborn Screening Programs in Italy", (2014, 2015, 2016, 2017, 2018)
- Eurordis, "Eurordis policy fact-sheet - Newborn Screening" (2013)
- )• Wilson JMG, Jungner G., "Principles and practice of screening for disease", WHO (1968).

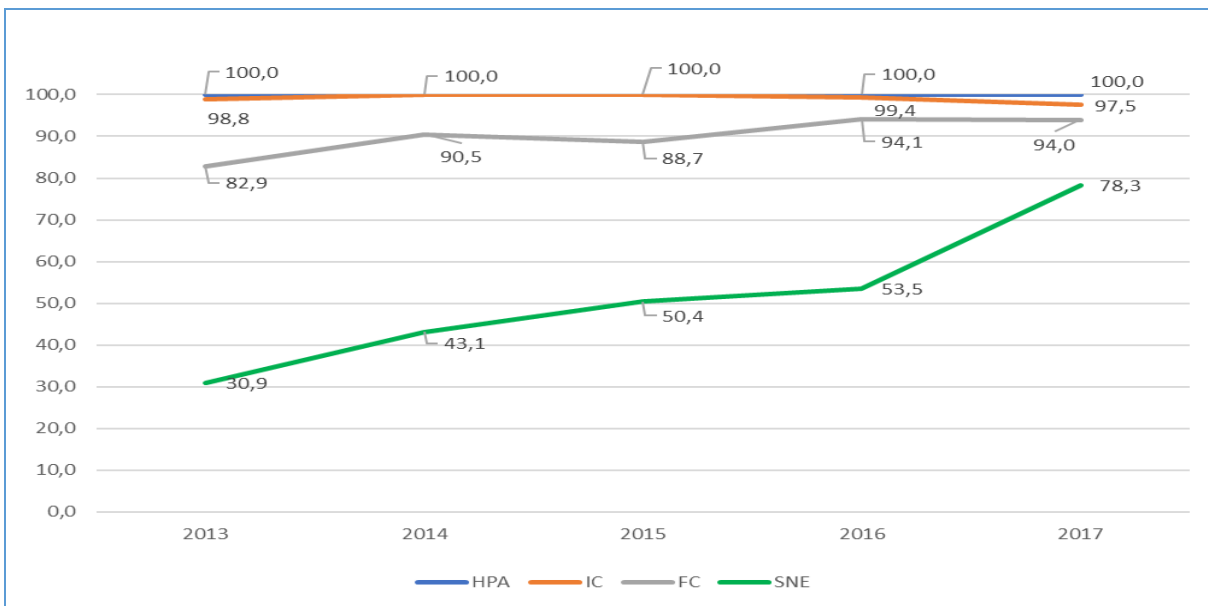
Figure 1. Status of implementation of the ENS Regional System as of 30.09.2018

REGION/PA	State of implementation of the ESN regional system as of 30.09.2018	Presence of one or more regional representatives of the ENS program	Presence of a Regional Coordination Center of the Screening System
ABRUZZO	Operative	yes	yes
BASILICATA	Operative, in agreement with other Regions	yes	yes
CALABRIA	Being implemented in agreement with other	yes	No

REGION/PA	State of implementation of the ESN regional system as of 30.09.2018	Presence of one or more regional representatives of the ENS program	Presence of a Regional Coordination Center of the Screening System
	regions		
CAMPANIA	Operative	yes	No
EMILIA ROMAGNA	Operative	yes	yes
FRIULI V.G.	Operative, in agreement with other Regions	yes	yes
LAZIO	Operative	yes	yes
LIGURIA	Operative	yes	yes
LOMBARDIA	Operative	yes	yes
MARCHE	Operative	yes	yes
MOLISE	Operative, in agreement with other Regions	yes	No
P.A. BOLZANO	Operative, in agreement with other Regions	yes	No
P.A. TRENTO	Operative, in agreement with other Regions	yes	No
PIEMONTE	Operative	yes	No
PUGLIA	Operative	yes	yes
SARDEGNA	Operative	yes	No
SICILIA	Operative	yes	yes
TOSCANA	Operative	yes	yes
UMBRIA	Operative, in agreement with other Regions	yes	No
VALLE D'AOSTA	Operative, in agreement with other Regions	yes	No
VENETO	Operative	yes	yes

Source: "Expanded Newborn screening in Italy: state of the art as of 30 September 2018", 2019 (Reference tools 19 / S2)

Figure 2. Coverage for Hyperphenylalanemia (HPA), Congenital hyperthyroidism (IC), Cystic fibrosis (CF) and Expanded newborn screening (SNE) from 2013 to 2017 in Italy



Source: our processing of data from the "Technical Report on Neonatal Screening Programs in Italy", Years 2013-2017 (SIMMESN)