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EDITORIAL
Newborn screening in Italy: a unique program of public health in Europe

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Newborn screening (NBS), also called neonatal screening, identifies shortly after birth pre-symptomatic conditions that can affect a child's long-term health or survival. Thus, early detection, diagnosis, and intervention can prevent death, disability or ameliorate the clinical manifestations of diseases, enabling children to reach their potential for health and well-being.

NBS was initiated in Europe during the 1960s for screening phenylketonuria (PKU) [1]. The introduction of tandem mass spectrometry (MS/MS) increased the technical possibility to screen more conditions using a single dried blood spot, therefore the panel of screened disorders ("conditions") gradually expanded [2].

Advances in molecular medicine contributed to enlarge the NBS panels. NBS is now performed in many countries worldwide. Where NBS is available, the number of disorders included in panels varies from one to over 40, including many inherited metabolic diseases, cystic fibrosis, severe combined immunodeficiency, and others [3]. Following the Wilson and Jungner criteria [4] several factors influence the selection of the diseases screened, including disease prevalence in the population, the availability of treatment, etc.

However, countries differ not only in the number of conditions screened, but also in the pre-screening information and support offered to parents, the time of sample collection, the accreditation status of the laboratories conducting screening and the governance, regulation and monitoring of the whole NBS pathway [5]. The major factor is represented by the health care system organization of each country.

Italy runs a universal public healthcare system since 1978, provided to all citizens; the system is organized under the Ministry of Health and administered on a regional basis.

Whereas during the past decades NBS pilot projects were available in several regions [6], in 1992 NBS became a mandatory provision of secondary prevention at national level by law [7] for the identification and early treatment of congenital hypothyroidism, phenylketonuria and cystic fibrosis.

In the years 2016-2017 a combined legislative framework established a nationwide NBS for more the 40 disorders [8-10], including genetic neuromuscular diseases, severe congenital immunodeficiencies and lysosomal storage diseases.

According to the legal framework, the NBS is funded and supported by the National Health System, and it included within the essential levels of assistance provided by the State. The framework defines the requirements in order to favor the maximum uniformity at national level of the regional implementation of NBS. Under this respect it establishes at the Istituto Superiore di Sanità (ISS) the NBS Coordination Center, coordinated by the Director of the ISS, which includes experts and representatives from central and regional institutions as well as three patient associations, Cometa Associazione Studio Malattie Metaboliche Ereditarie (Cometa A.S.M.M.E.), Associazione Italiana Sostegno Malattie Metaboliche Ereditarie (A.I.S.M.M.E.) and Associazione Immunodeficienze Primitive, on behalf of UNIAMO.

The screening program at regional level is a system articulated into four main functional structures, namely: screening laboratory, laboratory for confirmatory diagnosis, clinical centers, and regional coordination/supervision centre. The legislation also defined the panel of screening conditions, the timing for specimen collection, the screening methodology, the confirmatory tests and the clinical follow up. A periodic review of the list of conditions/diseases to be screened is set up by Ministry of Health, in collaboration with other government agencies and organizations. This task is carried out by *ad hoc* working group, co-ordinated by the Ministry of Health, including experts and representatives of institutions and patients associations, including UNIAMO. This working group has also the mission to elaborate an operational protocol including procedures for the management of positive NBS, positive diagnosis and accessing therapies [11].

The NBS Coordination Center performs the following tasks:
- promote and monitor the maximum uniformity in the implementation of newborn screenings at national level, also by identifying common standards;
- collaborate with the Regions for the dissemination of best practices;

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establish the procedures for collecting and delivering blood samples to screening centres;
- define the catchment area of each reference screening center for the Region, also in order to facilitate inter-regional collaboration (Italian Regions have quite different sizes);
- supply codified and standardized information to local services in order to inform newborns parents on the risks deriving from hereditary metabolic diseases, the benefits achievable through the screening activity, as well as the best available treatments for the specific disease;
- most important, set up a centralized archive on the results of neonatal screening in order to allow assessing the effectiveness, also in terms of cost-to-benefit, of the NBS program.

The NBS Coordination Center, with the scientific technical support of the National Centre for Rare Diseases of the ISS, works in collaboration with the Regions. Its activities are implemented through national surveys, working meetings, training courses, workshops, conferences and congresses. The results of such activities are published by the ISS as ISTISAN Reports [12-14]. The Reports also present a number of recommendations, aimed at improving the provision of information to citizens, the communication of diagnosis to parents, the consistent and uniform application of NBS on the national territory, as well as on specific technical steps (e.g., blood sampling).

Overall, the NBS is a public health action, building an organized and structured program for secondary prevention, funded by the National Health System.

The main keywords characterizing the features of the Italian NBS model are:

- Public health: NBS is an important public health action aimed at reducing the disease burden through secondary prevention; hence, public resources are devoted to its application.
- Equity: NBS is a measure of secondary prevention for all newborns of the national territory, regardless of region of birth, social status, gender, etc.
- Scientific evidence: planning, implementation and assessing the program are based on scientific evidence and exploit the consistent integration of multidisciplinary expertise.
- Consistency: in the Italian Health System, Regions have an extensive autonomy, also reflecting their different sizes and socio-demographic characteristics. Hence, the Regions, or also groups of Regions, can organize the screening services according to their requirements. Meanwhile, the legal NBS framework ensures a consistent provision of high-standard screenings throughout the whole territory, by facilitating the continuous interaction between the central and regional levels of governance and expertise.
- Assessment and review: data collection and the flow of data to the centralized archive are all important for assessing the outcomes of the program, in terms of efficacy, efficiency and consistency, and provide evidence for possible corrective actions and updates.

Last but certainly not least, participation, starting from the birth of the legal framework, that was also due to the proactive intervention by patient associations. This is reflected by the organization of the NBS. At central governance level, the patients have their place and they actively contribute, through their representatives. Indeed, the consistent and structured patient contribution, building-up from direct experience, is providing important inputs and rates among the most successful features of the Italian NBS.

In conclusion, the Italian NBS system is creating a positive exchange and a virtuous loop among Institutions, science and society, which should feed each other continuously. Assessment of uncertainties, an important aspect in the field of rare diseases [15], should facilitate and address the production of further scientific evidence. Institutions should maintain and strengthen their continuous efforts in supporting the system and maintaining and open dialogue with stakeholders; assessment of the current NBS status highlights the consistent implementation throughout the whole country as a point for attention.

The Institutions should further develop the current interchange with the European Union and EU Member States. This should be implemented at level of EU regulations, where rare diseases have already a significant place, as well as by fostering the Italian contribution to relevant technical-scientific networks and learned societies: under this respect, the European Reference Networks such as MetabERN and RITA [16] and EURORDIS [5] carry out activities of major relevance for the updating and further development of NBS, also in terms of achieving equity and innovation. On the other hand, disseminating and discussing the objectives and achievements of the Italian NBS can significantly contribute to the growth of neonatal screenings as a participated public health action at EU and international level. Society is essential in NBS implementation through advocacy and proactive participation including constructive criticisms. The involvement of patient representatives is essential for building and assessing NBS programs; in the meanwhile, beyond patient associations, citizens awareness of the value of neonatal screening is important for the NBS success.

Conflict of interest statement

The Authors declare that there are no conflicts of interest.

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