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FORTY-FOUR YEARS OF NEWBORN SCREENING IN PORTUGAL: NEW CHALLENGES, THE SAME COMMITMENT TO THE COMMUNITY

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The National Newborn Screening Program (PNRN) is a systematic program aimed at all newborns (NB) born in Portugal, and currently screening for 28 conditions: Congenital Hypothyroidism (CH, since 1981), 24 Inborn Errors of Metabolism (IEM, since 2004), Cystic Fibrosis (CF, since 2013), Sickle Cell Disease (SCD, since 2021) and Spinal Muscular Atrophy (SMA, in pilot study since 2022). It was started in 1979, and for more than twenty years it only included PKU and CH screenings. Starting from 2004, other diseases were included, following technological developments and international trends. The addition of new conditions, the implementation of new screening strategies, the increasing genetic diversity of the Portuguese population, and the growing demands of modern society, represented important challenges to the program over the years.

More than 4,200,000 NB have been screened, using different strategies. Currently, immunological techniques (CH and CF), *tandem mass* spectrometry (IEM, since 2004), capillary electrophoresis (SCD), and genetic testing (CF and SMA) are used. A constant development and increasing quality control are carried out.

Over the 44 years of the PNRN's existence, many changes have been made at different levels, which lead to significant improvements in the program. These include organizational and screening strategies changes, together with the screening for new disorders.

Organizational changes: Communication with parents has been increasingly privileged, with the dissemination of information through the program's website and the distribution of flyers at collection centers, both regarding the program and the pilot studies underway. All information is currently disseminated in Portuguese and English, due to the increasing number of births to foreign parents.

Results have became available to the parents online, with the possibility of printing the respective report. This was an important achievement because it allows the parents to confirm that the samples have arrived at the laboratory and have been analyzed. An application is being tested that will allow even greater control of the arrival of samples at the laboratory, as it allows them to be recorded at the place of collection and tracked by the laboratory.

The collection date has been brought forward, which allows an earlier treatment. This is essential for some disorders in which there may be potentially fatal metabolic decompensation in the first few days of life or in which a delay in the treatment leads to irreversible consequences. It is currently recommended to do sample's **collection from 36 hours feeding**.

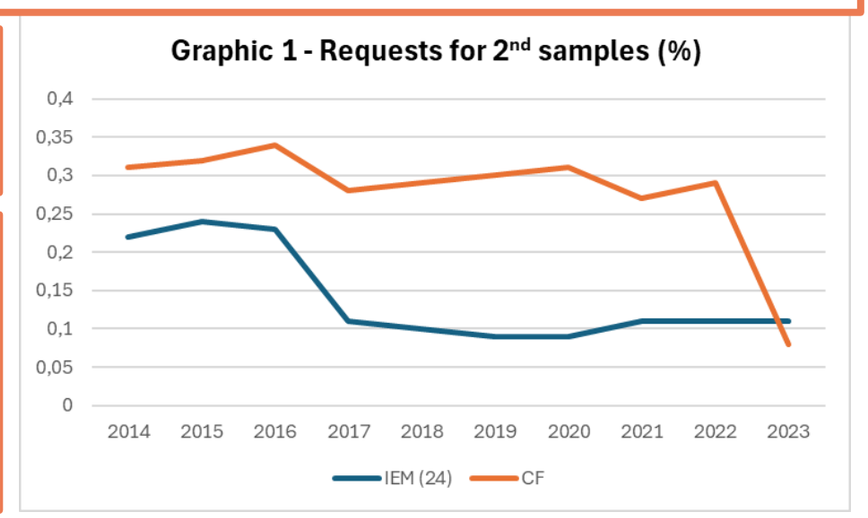
Patients are now referred for treatment to Reference Centers, for all the pathologies in which they are defined, thus guaranteeing excellent follow-up by multidisciplinary teams.

CH screening: Up to 4 additional samples are now recommended for newborns less than 32 weeks' gestation or less than 1500g weight, to avoid false-negative results due to the immaturity of the hypothalamic-pituitary axis.

The cut-off values for TSH and T4 are currently 10,0 mU/L and 9,5 µg/dL. These values have been updated several times, in line with international recommendations, to avoid miss cases. Both determinations are accredited by IPAC, in accordance with Standard NP EN ISO 15189, since 2015.

IEM screening: Since 2004, some changes have been made to several cut-off values to increase sensitivity and specificity. With the introduction of second-tier testing in 2017, the performance of this screening has improved significantly, with a substantial decrease in the rate of new sample requests (Graphic 1).

CF screening: Until 2022, this screening had the highest rate of requests for new samples, in spite of 2nd tier test (PAP) introduction. With the inclusion of the genetic study into the screening algorithm, this number has decreased significantly (Graphic 1 and Figure 1). IRT and PAP determinations are accredited by IPAC, in accordance with Standard NP EN ISO 15189, since 2019. The genetic epidemiology of CF seems to be changing in Portugal, probably due to the recent modifications in our population, and this will probably bring new implications in our screening strategy.



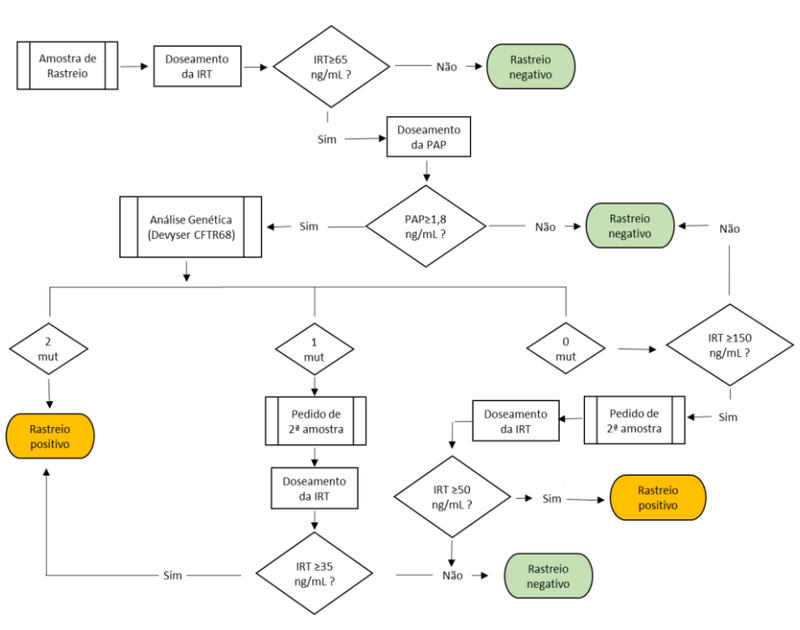


Figure 1 - CF screening since 2024

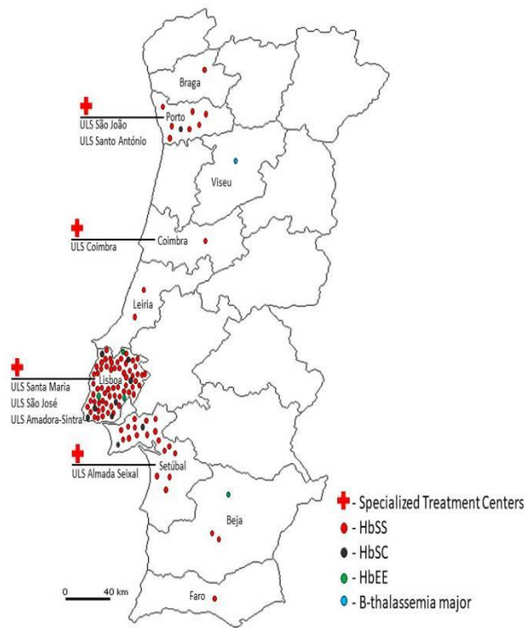


Figure 2 - Patients identified in SCD screening

Table 1 – Birth prevalence of disorders included in PNRN

Disorder	Birth prevalence
IEM (1979*, 2004)	1: 2 225
CH (1981)	1: 2 207
CF (2013)	1: 10 058
SCD (2021)	1: 2 053
SMA (2022)	1: 14 515
Total	1: 681

*Only PKU

SCD screening: After a regional pilot study, SCD screening started nationally and, as expected due to recent immigration events, several patients have been already identified outside Lisboa/ Setúbal regions (Figure 2). SCD incidence in Portugal is significantly higher than expected from former results (Table 1), but is according with recent immigration patterns.

SMA screening: this was the first genetic screening implemented in Portugal. Using the same methodology, a pilot study for SCID screening will be started next April 1st.

The PNRN is a dynamic program in constant evolution.
Over 2,700 positive cases have been identified and referred to specialized clinical centers, enabling timely therapeutic interventions, and thus benefiting both newborns and their families.
The continuous update of screening programs, with incessant adaptation to new technological challenges and to the needs of the community, is essential for their success.

The authors would like to thank all the clinicians who collaborate with the PNRN and all the families who participated in the program and agreed to take part in the pilot studies carried out.

References

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