• Aismme calls for ENS in Europe
• Training for Medical Doctors is missing, a letter to Minister Grillo
• Project NS2: new challenges, new services

Launched by UNIAMO FIMR, partner of non-profit organisation Mitocon - Together to study and treat mitochondrial diseases - and Aismme, and co-sponsored by the Ministry of Labour and Social Policies (under Article 72 of Decree n. 117 of July 3, 2017)
“Expanded Newborn Screening: it’s up to Europe now”

Aismme in Brussels to tell the story of Italian excellence of Law 167/2016

Aismme was at the European Parliament in Brussels on January 30 to present law 167/2016 to Europe, a law that makes Italy a pioneer in the whole continent in terms of number of metabolic diseases screened at birth for all newborns. A right to health supported in all regions and financed by the National Healthcare System, envisaging the screening for 40 hereditary metabolic diseases for which a therapy exists. Severe pathologies for which a delay in the diagnosis, which can come even 7 years after the first symptoms, leads to severe disability and even death.

Law 167 was strongly supported by Aismme, that also contributed to its drafting. “We have worked intensely over the years to raise awareness on the need to identify at birth pathologies that can get worse rapidly if they are not identified immediately, with severe consequences for the baby – Manuela Vaccarotto, Vice President of the association, explained to MEPs - We have involved the medical and scientific world, alongside with national and local decision makers, leading to a pioneering law in Europe. Owing to this law, 2018 saw 350 early identified newborns. These babies were able to have a future and a discrete quality of life. Their families did not have to face the long quest for a diagnosis and did not have to cope with lives marked by their baby’s death or severe disability.” “Being in Brussels to represent the patients and to tell the path that led to the approval of this law has been an honour for us – Manuela said - We are proud to bring the Italian expertise to Europe, an anchorage and a starting point to bring justice and qual rights to millions of babies being born in our continent every year, where huge gaps in terms of screened diseases exist. It’s up to Europe now!”

The european situation

On the newborn screening, the European situation is not homogeneous, with enormous differences between States in terms of screened diseases, laboratories capable of carrying out the screening, and the percentage of children with access to the service. Furthermore, each State has envisaged a different time range to screen the newborns, and a different time limit to preserve the blood samples.

The list illustrates the number of pathologies enlisted in experimental or national screening programs.

- 40 in Italy;
- 29 in Polonia;
- 26 in Hungary;
- 24 in Portugal;
- 19 in The Netherlands;
- 18 in Czech Republic;
- 17 in Denmark;
- 16 in Germany;
- 14 in Switzerland and Slovakia;
- 12 in Russia;
- 9 in the UK;
- 8 in Ireland;
- 7 in Spagna;
- 5 in France and Luxembourg;
- 4 in Greece and Lithuania;
- 2 in Malta and Romania.

Aismme’s commitment to broaden the newborn screening panel evenly over the European Countries: the stages

- **May 2018**: Aismme presents a poster on the beginning of expanded newborn screening in all Italian birth centres during the European Conference on Rare Diseases in Vienna
- **January 2019**: Aismme is at the European Parliament in Brussels to present the Italian excellency of L.167.
- **April 2019**: Aismme takes part to the MetabERN Board in Frankfurt. Over the different sessions, it presents the Italian experience and calls for greater attention to the implementation of ENS in Europe
- **May 2019**: Aismme sends a letter to the Eurordis Board, the alliance of more than 800 patients associations from 70 Countries, that gathers in Bucharest, asking to enact the Italian screened diseases panel in the remaining EU Countries. The Board enlists ENS in Europe among its priorities.
- **May 2019**: Aismme is contacted by an Irish father working to raise awareness in his Country’s Government to implement the expanded panel. Aismme offers its expertise and writes a reminder, inviting the Irish Minister of Health to Italy, to visit the screening labs and see the concrete enactment of L.167 in Italy. Late in May, the father submits the report he had drafted about ENS in Italy to the Irish Minister of Health and the Prime Minister, who warmly welcome it and pledge to treat the path to activate the expanded screening.

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ENS extended to further pathologies

A big mobilisation by patients associations, including Aismme, has backed the Parliamentary procedure of the amendment presented by Rt. Hon. Leda Volpi, envisaging the widening of the Expanded Newborn Screening panel to include lysosomal storage diseases, genetic neuromuscular diseases, and severe congenital immunodeficiencies. Letters of appeal to all Parliamentarians and to Minister Grillo, mass media mobilisation and lobbying actions that finally led to the goal: December 3 saw the approval of the amendment, and the open Board at Istituto Superiore della sanità (ISS) is currently working to include the new diseases in the panel. The amendment also mandates to update the panel every two years, hence keeping health policies at pace with scientific ongoing progress. “We are moved, really happy – Patients associations have commented - Starting today, newborn screening, a crucial secondary prevention tool, will be extended to genetic neuromuscular diseases, severe combined immunodeficiencies and lysosomal storage diseases. Up until today, this would have been impossible, and the newborns affected by such pathologies couldn’t have hoped to receive timely, life-saving treatments. It is a big civil achievement, just two years after the introduction of newborn screening for metabolic diseases under Law 167/2016”.

The interview to Hon. Leda Volpi
XII Commission (Social Affairs), Parliamentary Commission for childhood and adolescence

Neurologist at the University of Pisa, a background of studies on neuromuscular diseases in partnership with Telethon and several Patients associations, MP Leda Volpi (M5S) is the author of the amendment enabling to widen the panel of screenable diseases within the expanded newborn screening under L.167/2016 enlistng new categories of diseases: genetic neuromuscular diseases, severe combined immunodeficiencies and lysosomal storage diseases.

The initiative has stemmed from the awareness of the impact the integration could have had on newborns, and from the enthusiasm that all of us, Medical Doctors, researchers and patients feel owing to the steps forward made by the research, which is providing us with therapies and treatments for diseases that had been considered untreatable just a few years ago – Ms Volpi says - A full-fledged revolution that calls for the Legislator’s commitment to keep pace with medical progress and to properly meet the needs of people with a disease, be they present, or yet to be born.

The cornerstone two months after being elected, meeting Famiglie Neurologi on Spinal Muscular Atrophy), thence the presentation of the amendment.

It was a gamble. We had been dissuaded to try and include it in the Budget Bill, as it was likely to be rejected. Nonetheless, we decided to put it forward, to avoid alternative means whose procedures would have been much longer. When we received the financial backing and the support from all political forces we understood we could make it. Following upon that, the path was downhill.

The next steps shall be the enactment of the implementing decree, even though it might be possible to use the active decree for L.167, hence speeding up the procedure. After that, a discussion with all regions and the taking charge by the Board previously activated under L.167, where representatives from the Ministry of Health, the Istituto superiore della Sanità (ISS), the medical and patients world sit together.

Among the contents of the amendment, I wish to recall the requirement to lower from three to two years the enlisting of new pathologies in the panel of screened diseases. Research is moving fast, in particular on the field of gene therapies. We must keep pace with new therapies and treatments, hence making it possible to identify all treatable diseases at birth and limiting the impact on babies – she concludes – the advantage lies both in curbing the costs connected to disabilities that become chronic and in the quality of life of patients and their families.

Lysosomal diseases: early diagnosis is crucial

A specific therapy already exists for these pathologies, and their frequency matches, or outnumber, pathologies already included by law in the screening. Which is why several regions, including Veneto, had already included the four pathologies in the screening panel.

Pompe disease and Mucopolysaccharidosis type 1: if the onset is in the neonatal period, they can be deadly, hence newborn screening means survival. Life-saving therapies are available for these two extremely severe diseases. Alongside with the transplant, the therapies may spell the difference between life and death.

Gaucher disease: the most frequent lysosomal pathology in Italy. For this disease, the enzyme replacement therapy has been available for many years, and it is now coupled by the opportunity (for some patients) of an oral therapy.

Fabry disease: usually marked by a late onset, an early diagnosis gives a chance to have a careful follow-up and a family screening.

SMA (Parents association for research on Spinal Muscular Atrophy), hence the presentation of the amendment.

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The good news

Pathologies included
- genetic neuromuscular diseases
- severe congenital immunodeficiencies
- lysosomal storage diseases

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“There are no doctors and practitioners to treat newborns with metabolic hereditary diseases”

Aismmeme’s appeal to Minister Grillo

With a letter issued last March 27, Aismmeme asked the Minister of Health Giulia Grillo rapid intervention to address the lack of practitioners in metabolic diseases, in particular paediatric doctors, and the lack of Post graduate institutions for doctors willing to become practitioners in metabolic diseases.

“At Present, there are 15 active Regional Centres for ENS in Italy, with 300/350 diagnosed newborns per year. The number of patients is deemed to be on the rise, also thanks to the increased number of screened pathologies in the panel, and throw treatment centres into crisis, especially considering that even at present such centres cannot cater for all patients – the letter reads - The Ministry of Health and all the right institutions must activate policies to boost resources and increase the hiring of practitioners for these diseases, alongside with new post graduate schools to train practitioners in metabolic diseases”.

The situation is alarming.

• there is no post graduate course/ school nor any other type of training for hereditary metabolic diseases in Italy;
• there are no applicants to public competitions for practitioners in metabolic diseases due to the complexity and peculiarity of the diseases and because there are very few practitioners in this field;
• many practitioners managing the few existing Centres of expertise are approaching retirement age, many have already retired, taking years of expertise on the field with them;
• many young doctors in treatment centres benefit from coaching from practitioners because of grants or because they are privately funded by patients associations, with no hope to have a permanent contract due to the stop to the turnover. Therefore, a few, yet precious, training years are lost, among the many years an expert practitioner needs to manage the taking charge of newborns and adults affected by these highly complex diseases;
• there are no practitioners for adult patients, who are currently being followed by paediatric practitioners in metabolic diseases from the very few Treatment Centres that have activated this service;
• there are no contract incentives nor peculiar job placements for young doctors, such initiatives may encourage those who choose to treat metabolic patients;
• the lack of medical personnel is a critical factor in nearly all health structures, and health managers are forced to ask practitioners in metabolic disorders to endure very hard work shifts and exhausting night shifts at first aids, hence increasing the already burdening workload that practitioners in metabolic diseases already have. This leads many of them to leave patients with metabolic diseases, because they can take no more.

“If there are no practitioners, there are no treatments, and if practitioners are not highly qualified, patients with metabolic diseases cannot be adequately cared for – Aismmeme points out - To prevent the positive effects brought about by Law 167 from vanishing, We ask you to commit your Ministry to invest resources aimed at boosting treatment centres, and work to activate post graduate courses for young doctors”.

Minister Grillo’s replies during ‘Question time’ at the Health Commission last June 6 on the lack of practitioners

“Extraordinary measures have been implemented to address the lack of practitioners originated by the inadequate forecast about the demand. Starting the turnover, increasing post graduate grants, the opportunity to hire post-graduate students on their last training year with a permanent contract once their training is complete, the opportunity, for those enrolled to general practitioner training courses to take part to the allocation of conventional mandates, though subordinated to those already entitled, these are concrete actions implemented to cater for the emerging estimated demand. A structural reform will be necessary for the future, with a post graduate course hinged upon a timely planning of the demand and type of practitioners across the Country, with education enabling the young practitioner to access the labour market overcoming the steps that currently cause a far too long waiting time between post graduate courses and access to the professional world. Over these years there have been 10,000 annual graduates from medical schools, and 7,000 post graduate positions, hence excluding about 3,000 practitioners from the post graduate course. An educational funnel has come into place. We need to consider our young practitioners and create an education-labour continuum for them, providing dignity and security on their workplace. We are aware that the low participation to public competitions is often due to unacceptable working conditions (…). Our goal must be to guarantee quality of education and a future for our young practitioners, with a timely, ongoing turnover to bring back dignity and respect to the health profession and to all the professionals that are the backbone of the welfare in our Country”.
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News

From Italy

Rare diseases: social costs

Analysis on social costs of rare diseases carried out by the Economic Evaluation and HTA (EEHTA) of the Centre for Economic and International Studies (CEIS) from the faculty of Economics of "Tor Vergata" University, in Rome, has underlined the trend in costs and applications for healthcare services connected to rare diseases and tumours. Over the period between 2009 and 2015, the estimated cost amounted to 600 million euros (a yearly average of about 100 million euros). The rare diseases group calculated, for disability allowances, an annual average cost of about 13.5 million euros and a 3% annual average cost increase. For Invalidity pensions, the average annual cost amounted to 10.5 million euros, with a 6.7% average annual increase. With regard to rare tumours, the average annual cost for disability allowances amounted to 42.6 million euros, with a 4.7% annual average increase. The average annual cost for Invalidity pensions amounted to 15.2 million euros, with a 2.9% average annual increase.

These data put the problem of early taking charge and early diagnosis for rare diseases under the spotlight: a late diagnosis and a not so prompt taking charge of patients leads to an increase in the disability, which equals to an increase in the number and costs for Invalidity pensions. Conversely, an early diagnosis and a timely taking charge, in case of rare tumours, is leading to a significant reduction in the number and costs of Invalidity pensions.

National Plan for Rare Diseases: new Board members appointed

On February 20, Minister Grillo appointed the members of the new Board that shall approve the second National Plan for Rare Diseases. The previous Plan had expired in 2016 and, partly owing to the complete lack of funds, it had not been enforced. Here are the new members:
- Bruno Dallapiccola, scientific manager of Children's Hospital Bambino Gesù in Rome
- Paola Facchin, coordinator of the interregional technical board for rare diseases
- Tommasina Iorno, president of Uniamo FIMR onlus
- Luca Li Bassi, general manager of AIFA (Italian Medicines Agency)
- Francesca Pasinelli, general manager of Telethon
- Patrizia Popoli, drugs department of Istituto Superiore di Sanità (ISS)
- Armando Magrelli, Italian representative at EMA Committee for Orphan Drugs
- Domenica Taruscio, director of the National Centre on Rare Diseases of ISS
- director of Ufficio 3 of Programazione Sanitaria (Healthcare planning, Office 3), to date Andrea Piccioli MD, and director of Healthcare planning Office 5, to date Silvia Arcà MD. Following upon her retirement, the role will be taken by Rosanna Mariniello MD.

Dallapiccola suggests a platform to gather all RD specialists and the updating of the National Plan

Prof. Bruno Dallapiccola, scientific manager at Children's Hospital Bambino Gesù and member of the National Plan for Rare Diseases, has identified three important goals to pursue before the new Plan is developed: strong attention on financial-economic aspects, an administrative management system to boost performance available for families, and a European perspective for the development of the Plan, with special care for ERNs, to bring the Italian excellency to Europe. “We need to bridge the gap that has followed the 2016 – Dallapiccola claims - The working group from the previous Consiglio Superiore di Sanità (Superior Health Council) had created an interesting paper, a
good starting point providing food for thought. It outlined the situation about rare diseases in Italy, it highlighted practical problems and drafted solutions. It only needs updating”. Furthermore, he has suggested creating a “Platform for rare diseases, a pivotal element for all specialists. At its core, shared services. In the Platform, centres with expertise on the diagnosis and the taking charge of patients shall have a coordinated organisation. There is no need to come up with much, just implement a little review of the organisation”.

ISS: Del Favero’s mandate has expired

Angelo Lino Del Favero’s mandate as general manager of ISS, started in 2014, has expired. Competencies have now been handed over to Prof. Silvio Brusaferro as President of ISS, and to Andrea Piccioli MD as general manager.

Patients associations involved in the clinical trials. The law decrees are still missing

Approval for legislative decrees to Law Lorenzini on the reform of professional associations and clinical trials of January 2018 is still pending. The reform has stated the need to identify the requisites for centres entitled to carry out clinical trials from stage I to IV, giving preference to Centres ensuring, during stage IV, the involvement of patients associations to define research protocols, in particular when it comes to rare diseases. In fact, more than 18 months after its approval, the Minister has explained that “the technical complexity of the matter will certainly require a longer period for the legislative decree to come into force, therefore, an extension of the deadline shall be necessary”.

Meanwhile, at AIFA (Italian Medicines Agency), the National Coordination Centre for territorial ethical committees for clinical trials on human drugs and medical appliances has been set up. It plays an addressing and monitoring role for assessments over ethical aspects of clinical trials, and it includes representatives suggested by the most representative patients associations at a national level: Cittadinanzattiva, Uniamo, and Federazione Italiana Associazioni genitori onco-ematologia pediatrica FIAGOP (Italian Federation of Parents Associations for Child Oncohematology).

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The White Paper on the Italian Law “After Us”
The White Paper including proposals for concrete enhancement of Law 112/16, better known in Italy as “After Us” is now available on Uniamo website. Promoted by UNIAMO-FIMR (Italian Federation for Rare Diseases), the paper has been jointly drafted within the project “Social Rare – Social framework, new actions and proposals for people with rare diseases”, with contributions, among others, by ANFFAS (National Association of Families of Persons with Intellectual and/or Relational Disability) and the National Council of Notaries.

Ddl Bologna (Bologna draft law): “Supporting research and ensuring treatment for rare diseases”
Last March 6 marked the beginning of the review for the Bologna draft law (ddl Bologna of M5S) by the Commission for Social Affairs. It calls for a rare disease certificate with unlimited validity across the nation, full reimbursement for drugs and services for people affected by rare diseases, the set up of a National research fund in the sector at the Ministry of Health, with 20% of funds provided by pharmaceuticals and incentives to carry out research to produce orphan drugs.

From Europe
Brussels strives for accessible online medical records in the 28 EU countries
Making medical records accessible online across all 28 EU states to simplify treatments in case of accidents or illness for citizens abroad, but also reducing healthcare costs and boosting medical research. That is the aim of the recommendations the EU Commission submitted last February to broaden the digital healthcare registry of European citizens. The system is already being used, but only in a few countries and for electronic prescriptions. The proposal extends access to healthcare information of European citizens, such as analysis, hospital reports and medical reports for X-rays or CT scans, under EU privacy laws. The goal is to have faster, more accurate treatments, prevent redundancy of X-rays, hence reducing costs, and, only under prior consent, provide new data for research on neurodegenerative diseases. The countries in the online healthcare registry (currently 22, including Italy) shall coordinate to draw the practical guidelines to implement the registry.

UE: a shared platform to support diagnosis and treatment
During the Rare Diseases Day, the European Commission presented the “European Platform on Rare Diseases Registration”, the new online platform aimed at collecting and exchanging data from over 600 European registries and databases containing patients’ information to support diagnosis and treatment for over 30 million people with rare diseases in Europe. The platform includes the European Directory of Registries, providing an overview of each participating registry; the Central Metadata Repository, memorising all variables used by the registries; a data-protection tool, ensuring that patients’ data are stored using a pseudonym, so that information cannot bring back to the individuals.

News from the Regions
Basilicata
ENS active since January
January saw the beginning of the Expanded Newborn Screening activity for metabolic diseases on all newborns in the Birth centres in the region. Samples are collected and analysed by the Simple Operative Unit of the Screening Regional Centre of “Giovanni XXIII” Children’s Hospital in Bari, and by the clinical centre of the Complex Operative Unit for Metabolic diseases and Clinical Genetics. Positivity to the screening is the starting point of an integrated, multidisciplinary path between Birth Centres, the Screening Centre of the Basilicata Region at Hospital San Carlo in Potenza, the Clinical Centre for first referral at the Intensive Care Unit for newborns at San Carlo and the Complex Operative Unit for Metabolic Diseases and Clinical Genetics of Giovanni XXIII” Hospital in Bari.
ERNs 4th Conference in Brussels
The point and future strategies

On November 21-22, the 4th ERNs Conference was held at the European Commission in Brussels. The event gathered more than 400 participants, representing all stakeholders (national authorities, healthcare providers, members of ERNs, health professionals, hospital managers, patients representatives, EU institutions). The Conference was a great opportunity to trade opinions and strengthen mutual bonds between those who are working to achieve better diagnosis, rare diseases care and assistance, while facing inequalities between differing EU countries. One of ERNs fundamental goals is to foster movement of competences rather than patients. This is possible owing to the Clinical Patient Management System (CPMS), an IT solution enabling cross-border discussion of medical cases. Over 250 patients have already benefited from this opportunity, yet, financing for time dedicated to online consulting is a problem that may be solved under the cross-border healthcare directive. It will be necessary to detect possible savings on virtual expertise and consultations for the NHS and to overcome barriers such as data protection and content regulations. As to the sustainability of the ERNs model, over the next months and years, it will be necessary to prioritise the commitment of individual countries and private-public funding models for certain activities, without compromising ERNs independence.

For the integration within national care systems, the solution lies partly in the increase of representativeness and participation of Member States to ERNs, yet all NHS will need to embody the ERN concept itself. This shall be achieved through national strategies for rare diseases and it shall be integrated immediately into the healthcare provider work to re-orient organisation and funds towards a more rational, efficient, less segmented access to the best expertise available for ERNs patients with rare diseases in all countries. ERNs shall also play a key role in drawing and disseminating good clinical practices, drawing new guidelines when deemed necessary, while assessing and updating the existing ones. To this goal, a public bid has been set up to support ERNs on this challenging task. Drawing guidelines will not be enough, though: the dissemination of best practices and expertise is fundamental to enhance care for patients with rare diseases, irrespective of their countries of origin. Some ERNs have already developed education programs (via webinars) and grants, initiatives that will spread to other ERNs. Moreover, the development of new competencies in Countries underrepresented in ERNs shall be encouraged. (from Omar)

Holistic Person-Centred Care
The new document by Eurordis

May 2019 saw the publication of the Position paper “Achieving Holistic Person-Centred Care to Leave No One Behind” by Eurordis. The paper presents evidence, stemming from European research, on the unmet everyday needs of people living with a rare disease, while also offering a synthesis on policy and recommendations to achieve holistic care for rare diseases and integrate clinical and social aspects. The ambition is to have holistic care provided to the 30 million people living with a rare disease in Europe, and their families, by 2030, and to see these people integrated in a society that leaves no one behind, working together, with all stakeholders. Therefore, Eurordis and its members are inviting the EU, all European Countries and all stakeholders within the health and social sector to spread this new paper and act in accordance with its 10 recommendations.

Recommendations
1. Making full use of EU instruments and European networks to implement holistic care for rare diseases.
2. Creating a supportive political environment at national level for holistic care for rare diseases.
3. Gathering and disseminating knowledge and good practices, to ensure that the needs of people living with a rare disease and their carers are adequately addressed by specialised and mainstream services.
4. Implementing specific mechanisms that ensure integrated care provision to rare diseases.
5. Guaranteeing meaningful engagement of organisations and representatives of people living with a rare disease in the design and implementation of policies and services.
6. Implementing specific measures that ensure access of people living with a rare disease and their carers to adequate social services and social protection.
7. Ensuring the recognition and adequate compensation of the disabilities experienced by people living with a rare disease.
8. Creating the conditions for people living with a rare disease and their carers to access adapted and sustainable employment.
9. Implementing specific mechanisms that empower people living with a rare disease and their carers, in co-creation and co-delivery with organisations representing people living with a rare disease.
10. Eliminating all types of discrimination, ensuring that people living with a rare disease have access to social, labour, educational, leisure inclusion on equal footing with other citizens.

EURORDIS: Recommendations for ERNs

How to better integrate ERNs into NHS: this is the point of new recommendations presented by Eurordis during the ERNs 4th conference. Eurordis believes it is necessary to raise awareness among stakeholders about ERNs and their value, to integrate ERNs in national healthcare policies and focus further on rare diseases and on the patients community, to create national networks of centres specialised on rare diseases and patients communities to set up national networks fitting ERNs diseases groups; to gather new members and partners to bridge the geographical and/or competence gaps of ERNs; to set up national coordination and focus centres; to streamline applications, to fast-pace access to diagnosis and professional opinions; to set up a fund-raising system to finance on-line consulting and, finally, to develop a national-level mechanism to acknowledge and adopt the clinical guidelines reviewed and adopted by ERNs.
“Juggling care and daily life”

EURORDIS: the first survey across 48 European Countries on the capability of patients and their carers to live their daily lives with a disease

The survey aimed at exploring social needs of people living with a disease and their carers, particularly aiming at: Assessing the impact of rare diseases on mental, social and physical functions, on the family budget, occupation and working career, family life and wellbeing; assessing the access rare diseases patients have to social and health services and exploring the challenges connected to the coordination of the treatments.

The sample distribution was: 79% women and 21% men; 92% diagnosed and 8% non-diagnosed; 62% patients, 37% parent of a child with rare disease, 4% brother/sister, 2% husband/wife, and 1% aunt/uncle of a person living with a rare disease. Polled patients are enlisted in the Rare Barometer Voices database, a EURORDIS tool to perform quantitative polling, made up by a community of more than 5,000 people, across 48 countries, who live with a rare disease.

The data

Irrespective of the different pathologies, results show that a wide majority of patients, 85% of the sampled individuals, believes the rare disease has a huge impact on everyday life, and 8 out of 10 find it difficult to carry out simple daily tasks. 52% of patients and their relatives feel like the rare disease has a severe (30%) or very severe (22%) impact on their daily life. Pathologies are complex, and symptoms may vary over time.

62% of the polled complained that information about their conditions was given in the wrong way, 33% defined the information as extremely wrong. More than 70% feel underinformed about their rights connected to the consequences of the pathology, about possible financial aids and important health services they may have access to.

The complex nature of most of the rare diseases make it so that patients need assistance from a wide variety of healthcare professionals: 65% of patients stated that they had to face differing, often independent professionals turns out to be a challenge for most of the polled: 51% of them stated that contacting differing professionals is a difficult activity to manage.

Most rare diseases are untreatable, and even existing treatments are not able to curb the disabilities such diseases cause; therefore, services to help patients face their daily challenges are fundamental. Unfortunately, it is very often the case that patients’ needs such as those helping them maintain their autonomy or an autonomous management of the disease, including rehabilitation services (48%), psychological support (47%), aids to adapt their homes to the new needs (30%), medical devices (28%), and suitable transportation (23%) remain unmet.

The surveyed expressed huge difficulties in combining their professional lives with the organisation connected to the rare disease. Being affected by such pathologies can have a huge impact on several aspects connected to jobs. High percentage of absence from work (21% of the polled declared their absence from work amounted to 90 days over the year before); 7 patients out of 10 had to reduce, or interrupt their professional life. 35% of them had to work part-time, as against to 17% of the overall population, with a higher percentage among women. Finally, 76% of the polled declared that being affected by a rare disease had caused crucial limitations to their professional choices and to promotions at work (67%).

One of the most important problems perceived by the relatives of patients with disabilities is the sense of isolation from their friends or relatives; moreover, 52% of the polled state that the pathology often leads to attrition and tension within the family. People who live with a rare disease and their relatives/carers say they feel three times more depressed than the overall population: 37% of the polled declare they often (19%) or really often (17%) feel miserable or depressed, as against 11% of the overall population.
Patients consultation on drugs
The Italian Medicines Agency AIFA sets up a permanent Board

“In compliance with the guidelines of the Paper on pharmaceutical governance, the Italian Medicines Agency has decided to set up a permanent consultation board with patients associations within Open AIFA”, the Medicines Agency has said. Therefore, the Agency invites patients, gathered as associations or as individual citizens on drug-related themes (i.e. access, research, safety), to contact it through the website openaifa@aifa.gov.it and visit the dedicated web page to read and subscribe its participation rule book.

“Opening this channel for dialogue – AIFA underlines - is a valuable contribution to regulatory action, bearing real life experiences and competences that will ease the path to achieve AIFA’s primary goal, promoting and safeguarding the health of citizens. The agenda and memorandums of the Agency will be available on the institutional web portal. The Farmaciline channel is open every day to the public, to individual patients and healthcare operators, to provide an independent, timely information service on issues connected to authorised drugs”.

The US experience
The Food and Drug Administration (Fda) has published the paper “Benefit-risk assessment in drug regulatory decision-making”, confirming its will to more effectively incorporate the patient perspective into the decision-making processes. The US Agency program to integrate the patient perspective into the drug-approval process is based upon four main points:
1. public meetings with patient communities to develop a systematic way to collect their perspectives on the disease and available therapeutic options;
2. encouraging patients to organise autonomous meetings – such initiatives may serve, for instance, to provide food for thought on areas non envisaged by the FDA;
3. providing patients, caregivers, and advocates with more communication channels and opportunities to be heard within the regulatory process;
4. cooperating with the scientific-medical community to design clinical studies that are less burdens on patients – for example using pharmacogenomics to carefully select patients more likely to respond positively to therapies.

The European experience
In 2014 the European Medicines Agency (Ema) launched a pilot project to involve patients into some steps of the works of the Committee for Medicinal Products for Human Use (Chmp). The main recommendation stemming from this experience was about the opportunity to use several tools – public consultations, questionnaires, referring to specific doubts, and even participation to the Committee’s works – to constantly integrate patient perspectives into the regulatory path.

Rare diseases, stop to extra LEA (Essential Levels of Care) services
Patients may suffer discrimination

Many patients associations and newspapers have spoken about the vicissitudes in Puglia on the decision, by the Ministry of Health, to list out extra LEA (Essential Levels of Care) services for patients affected by a rare disease. The legal-aid centre of O.Ma.R. has tried to clarify the situation referring to Institutional acts. As envisaged by DPCM (Prime Ministerial Decree) January 12, 2017 “Definition and updating of essential levels of care”, people affected by a rare disease enlisted in appendix 7 of the Decree are entitled to free-of-charge healthcare services. The new DPCM has included, besides A Class drugs, even prosthetic aids and appliances, leaving out, on the other hand, C Class drugs, supplements, medications and more. Such products, non reimbursable by the NHS, hence being entirely paid for by patients, are very often prescribed to people affected by a rare disease and, to some patients, they are necessary, non-fungible drugs. As envisaged by the Ministry “Regions, as they have been doing so far, will be entitled to provide further services as against those included in LEAs, using their own resources”. Yet, the Ministry also clarifies that only financially sound Regions will be entitled to grant ‘extra LEA’ services, excluding several Italian Regions: Puglia, Abruzzo, Sicily, Calabria, Campania, Lazio and Molise. Therefore, patients from these regions may suffer discrimination, as they may have to pay for drugs and supplements that are needful for their health. A further information note from the Ministry then clarified that patients affected by cystic fibrosis will be granted access to extra LEA drugs, irrespective of their Region of origin. Yet, the case remains open for other pathologies. The interregional board on rare diseases has suggested a possible solution to the problem. “A feasible, quick system strategy that the Italian Medicines Agency (AIFA) itself shall define, using its executive resolution and under law 684/1996, a specific list of consolidated drugs for rare diseases, whose effectiveness has been scientifically proved - Giuseppe Annichiarico MD, responsible for Rare diseases coordination in Puglia explains - AIFA has already drawn up similar lists for oncology, cardiology and nephrology. Alternatively, AIFA could, with its executive resolution, reclassify those drugs. The interregional board on rare diseases of the Health Commission has issued the list of Class C drugs for each disease enlisted in the DPCM harming LEA. The Board, supported by technicians and clinicians from differing Italian Regions, using data from national registers and thanks to the global scientific literature review, can provide AIFA and the Italian Government with a quality, fitting tool. The goal is to benefit not only Regions that are still catching-up, but also financially sound Regions, and provide equal, holistic treatments”.

(From Omar)
Report of OSSFOR: Orphan drugs are on the rise, with shorter time required for authorisation

Research and development of treatments for rare diseases are thriving. 2018 saw 9 new drugs being granted marketing authorisation, amounting to a total of 95 orphan drugs marketed in Italy. At a national level (AIFA-Italian Medicines Agency), there has been a significant reduction in the duration of the approval process over the last years: from authorisation by the EMA (European Medicines Agency, to pricing and reimbursement, the time span passed from 35 months in the 2003/2005 period, to 11 months in the 2015/2017 period.

Positive data that were underlined in the 2nd Report of the Orphan Drugs Observatory (OSSFOR), published last November, analysing the economic impact of rare diseases and orphan drugs on the Healthcare System, and monitoring the evolution of healthcare policies, regulations, and the management of rare diseases. “The growth of orphan drugs comes largely from innovation and the natural progressive uptake of new molecules. – Francesco Macchia, OSSFOR coordinator, has explained – Increased consumption and expenditure depend mainly on the marketisation of new generation drugs over the last three years, while expenditure for older drugs has lowered, for the first time, of about 5%. International and national safeguards in this sector are finally bearing fruit: in the future, stability in this sector will play a fundamental role to provide answers to more than 6,000 rare diseases for which a proper therapy still does not exist.” Widening the list of exemptions has led to a 6% increase of rare disease patients recognised with exemptions; the “new cases” are mainly among the prevalence of ultra rare diseases, with an average expenditure per capita 23.4% higher than the average of rare disease patients. As for expenditure incurred by the NHS, the annual average expenditure per capita of rare disease patients with exemption ranges between €4,217 - 5,384, and includes exemption drugs and File F drugs, diagnostics, laboratory testing, medical examinations, hospitalisations and day hospital services. Data from the report enable to assess that the average expenditure for rare disease patients does not differ significantly from that of chronic patients with two comorbidities.

OSSFOR suggests creating a Board on orphan drugs

An institutional, multi-professional Board dedicated to using the Health Technology Assessment (HTA), governing market access and reimbursement for technologies. The Board should be aimed at collecting further evidence on social preferences on equal allocation of public resources, and through collective decision-making involving all the stakeholders, issuing recommendations on the system. This is the proposal described in the second Position Paper by OSSFOR (Orphan Drugs Observatory) titled “HTA dei piccoli numeri” (HTA of small numbers). “There is a growing consensus by the international community that a wider use of the Health Technology Assessment (HTA) is necessary in the field of orphan drugs and, in general, of rare disease technologies - Barbara Polistena and Federico Spandonaro, from University of Roma Tor Vergata have explained - Though being aware of the difficulties that lie in the application of a multidimensional and multidisciplinary approach, such as the HTA, that is needful to assess the social and organisational impact, at the technical Boards organised by OSSFOR with panels of experts, the use of HTS is clearly fundamental even in the field of rare diseases and in situations marked by “small numbers”. Today, more than ever, it is necessary to organise a task force to outline HTS rules of application..

Expenditure for orphan drugs

According to the latest report by Evaluate Pharma, the worldwide increase of expenditure for orphan drugs (therefore, not all and not only rare disease drugs) will be of 11% per year, more than the overall expenditure for drugs. In Italy, the share of expenditure incurred by the NHS for orphan drugs as against the overall expenditure has increased from 3.5% in 2002 to 7.2% in 2007.

Rare diseases: new, increasingly specific therapies are coming

Ideas from the conference “Market access for rare disease drugs: new challenges and priorities for the NHS” organised last April 15 by the Italian Society of Pharmacology at Istituto Superiore di Sanità (ISS) in Rome

“Over the last years, there has been the approval, or the beginning of clinical studies, for innovative therapies based on molecular, cellular and gene strategies to treat severe rare genetic diseases - has underlined Anna Maria De Luca, Professor of pharmacology at the Department of Pharmacy and Drug Science at the University of Bari and member of the board of directors of the Italian Society of Pharmacology. Several groups of Italian pharmacologists are carrying out research on innovative therapies and orphan drugs for rare genetic diseases. The Italian Society of Pharmacology is particularly committed to promoting debate on these topics, from baseline and pre-clinical research, to clinical studies. Among the steps deemed necessary for the future, we believe that priority must go to allocating incentives and resources to the research and further awareness raising among all stakeholders, to grant rare disease patients with access to effective, safe therapies”.

“Advanced therapies (gene, cellular and tissue regeneration therapies) known as ATMPs (Advanced Therapy Medicinal Products), provide further therapeutical approaches that do not replace traditional therapies entirely, but can support traditional drug therapies - added Prof. Canonico, Director of the Department of Drug Science of Università del Piemonte Orientale A. Avogadro in Novara - Since many rare diseases have a genetic origin, approaching them via gene therapy may prove particularly positive in case of certain diseases. To sum up, there is a new weapon at our disposal against specific diseases”. The problem of rare diseases has both social and clinical relevance, and has been addressed by all regulatory agencies to foster research of new therapeutical options. “Clinical and pre-clinical research needs boosting, newborn screenings have to be performed - Canonico underlined - and we must identify excellence centres for specific diseases, implementing cooperation between political decision-makers and patients associations. To this goal, a fundamental role is played by the central coordination of Istituto Superiore di Sanità (ISS) to discover the epidemiology and incidence of such diseases”, (from www.dire.it)
Legislative tools in Italy for early access to drugs with pending authorisation

In many cases, the use of an experimental drug or of drugs not yet marketed in Italy for patients with severe, highly disabling diseases is the only tool that can save their lives or enhance their health conditions. Which is why legislative tools have been introduced in Italy to enable early use of an orphan drug recommended for a rare disease, even though authorisation by the European Medicines Agency is still pending. Here below are the regulations.

**Law 648: enlisted drugs are reimbursed by the NHS**

Law 648/1996 states that some orphan drugs that are still unmarketed can join a specific list and be provided, paid for by the NHS, to all patients with that particular disease. Such drugs are innovative and marketed in other states; non authorised drugs undergoing clinical trial for which stage II results from clinical studies are available; drugs whose use is for an indication other than that authorised in Italy but with stage II results already available. Even when an effective therapy already exists (Law 79/2014, Art. 3), these drugs can enter Law 648 List (hence be paid for by the NHS) of drugs whose use is for an indication other than that authorised by the Regional Council to the applicant healthcare structure), AIFA reimburses all paid invoices.

**Decree May 8 2003: «Compassionate use» of investigational drugs**

Therapeutic use of a drug under clinical trial (the so-called compassionate use, first introduced in Italy through Decree May 8 2003) is allowed for «the treatment of patients with severe, rare diseases, rare tumours or life-threatening illnesses that cannot be included in other clinical trials, diseases for which no other therapeutic options are available, or to provide therapeutic continuity, for patients who had benefited from a previous, concluded clinical trial» (Article. 2 Decree of September 7, 2017 published in the Gazzetta Ufficiale n. 256/2017). Compassionate use, the law reads, means free supply by the drug company of: drugs unauthorised in Italy, but undergoing clinical trials, produced by drug companies or imported in compliance with import regulations and requirements by law; drugs marketed with use for indications other than those authorised; authorised drugs that are not marketed in Italy, despite being granted “Com” classification (Non-negotiable classification). AIFA’s website provides information on procedures, documentation to submit to the Agency and the list of programs for compassionate use.

**Law 94/1998: Access to Off label drugs**

Law 94/1998, also known as Di Bel-la law, envisages that for each individual case, a doctor can prescribe, under his own, direct responsibility and with a patient’s informed consent, marketed drugs for off-label use, provided that there be positive results from documented and concluded clinical studies, if the doctor believes the patient cannot be successfully treated with drugs previously approved for that therapeutic indication or administration. (from www.corriere.it)

**Expanded Newborn Screening**

Following upon 2006, Aismme has been working to make this life-saving test, which can detect over 40 rare metabolic diseases immediately after birth, a right for all newborns in Italy. Thanks to Law 167/2016, drafted with Aismme’s support, Expanded Newborn Screening is now mandatory and free-of-charge. For further information www.aismme.org
Genetic testing on newborns: the British project by Genomics England has started

The 100,000 Genomes Project was defined as the biggest genetic project in the world, envisaging DNA sequencing for all British newborns, alongside with further medical tests. The goal is to early identify cancer and other severe diseases, like cystic fibrosis, to treat them early and save many lives. To date, the project has sequence 100,000 genomes of people, including children and adults, that will rise up to 5 million people over the next five years. Thanks to this technique, 4,000 individuals have already discovered they have one or more diseases among the 1,200 severe genetic or very rare diseases, and have received specific treatments. Genetic tests may replace newborn screening based on blood samples collected from newborns’ feet. 

Debate on this latest frontier of genomic medicine, on when it is really necessary and when it may be aversive, is still open. Discussions on an international stage also dwell on the chance and occasion to use DNA sequencing as a screening test for all newborns within public health systems. In fact, the prospect is to ‘shed light’ on the entire genome of a baby, and on the information it can contain, with just one test: not only information on the likelihood to develop potentially severe childhood-onset diseases to be treated as soon as possible, but also on the risk of developing diseases during adulthood (from some forms of cancer to Alzheimer’s disease), or on the individual’s pharmacogenetic profile that describes body capabilities on the metabolism of drugs. 

There are some situations where this approach is already being acknowledged. “For instance, facing a newborn in critical conditions, with severe diseases that may have a genetic origin whose diagnosis cannot be achieved via traditional tools, such as step-by-step genetic tests”, explains Professor Alessandra Renieri, manager of the Medical Genetic Unit at the Hospital in Siena, and among the authors of the joint paper on this topic, issued by several Italian genetic and pediatric scientific companies. 

At present, discussion is not about replacing the “old” biochemical test, but to flank it: “Even though sequencing techniques have undergone huge breakthroughs in terms of speed, accuracy and reduction of operative costs, they cannot be used comprehensively, on entire populations, to detect genetic defects that may give rise to the first symptoms within hours” Giancarlo La Marca, manager of the newborn screening lab at Meyer Hospital in Florence, has commented. “In this regard, biochemical tests remain the most effective ones, also because they generate fewer interpretation problems”. 

According to a paper published in the summer of 2018 by the ethics committee of the US NSIGHT project, exploring public implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period, this approach leads to a successful diagnosis rate of 40-60%. These data confirm the first, preliminary results stemming from the Rare (Rapid Analysis for Rapid Care) project in Bergamo, aimed at assessing the clinical utility and the cost-effectiveness ratio of exome sequencing for urgent diagnosis of rare genetic diseases for children in critical conditions hospitalised in newborn or paediatric intensive care units. “So far, the analysis has been carried out on 49 young patients, showing encouraging results - Maria lascone, the contact person of the medical genetic laboratory at Hospital Papa Giovanni XXIII, among the first in Italy to include new generation genome sequencing in the diagnostic routine, has said - definitive diagnosis was achieved in 50% of cases, requiring on average 9 days, as against 35% of cases and a 4-month average waiting time for the traditional system. The test has identified extremely rare diseases, atypical forms of known diseases, or disorders so diverse that can require years to diagnose. In 20% of diagnosed cases it has been possible to implement a specific drug or dietary treatment, while in other cases having a name for the disease has influenced the clinical care of the babies, for instance providing useful information to decide if a young patient needed a heart transplant or not”. 

Counting on a huge genetic information load may seem a fantastic idea. Yet, the challenges from a scientific, ethics and logistics point of view are huge. In fact, as early as 2015, the European Society on Human Genetics had listed the areas that needed further investigation to properly assess utility and feasibility of this approach on a public level. It is the same path the ethics committee of NSIGHT project is following, currently proving sceptic about this option, underlining that “benefits from screening the population to detect genetic risks remain a hypothesis”, hence suggesting a nuanced approach towards the rising technology of gene sequencing. An approach “that can counter the idea of genetic information as the absolute good, fuelled by unfettered scientific optimism and commercial interests”. 

Newborn Screening, a possible life-saver for 8 million children across the world

In 2006, March of Dimes, the American foundation created by President Roosevelt in 1983 to fight pox, published a report on the global burden of congenital disorders. The report revealed that about 8 million children are born with a rare congenital disorder every year (Christianson et. al., 2006). Among the five most common diseases, congenital heart disorders were first, haemoglobin disorders, thalassaemia and sickle cell anaemia ranked third, while glucose-6-phosphate dehydrogenase deficiency (G6PD), also known as Favism, was fifth. All these disorders can be diagnosed and managed thanks to newborn screening. This was revealed by a recent international study, published on the Molecular Genetics and Metabolism Journal. The report also noted that 70% of congenital disorders can be prevented, or that affected children can be provided with life-saving treatments to obliterate the burden of disability. These are the fields where the true potential of newborn screening can and must be achieved. Making it so that all children, irrespective of their place of birth, are granted equal access to quality ENS, is a challenge. Even more when considering the high incidence of congenital disorders in middle and low income countries, where 94% of these children are born and 95% of them die. 

As early as 2010, the WHO called upon UN Member States to develop national plans and implement effective actions, including newborn screening, aimed at preventing and managing congenital disorders. Yet, this call for action has gone widely unheard across middle and low income countries, where only one child out of three had access to any kind of organised screening in 2014 (Thevrell et. al., 2015).
Adrenoleukodystrophy
Providing an early diagnosis
From the Italian Association on Adrenoleukodystrophy, a project to raise awareness among endocrinologists

Before discovering they have adrenoleukodystrophy (ALD)/Adrenomyeloneuropathy (AMN), a significant percentage of people is diagnosed with Addison disease or adrenal insufficiency, a delay which may jeopardise the likelihood of undergoing a bone-marrow cells transplant within the pre-symptomatic window, before irreversible brain damage occurs. This has led the Italian Association on Adrenoleukodystrophy to launch a project to raise awareness among doctors and endocrinologists on ALD/AMN and prevent late diagnosis or misdiagnosis.

"Considering the dramatic consequences of a late diagnosis for Adrenoleukodystrophy - says Valentina Fasano, President of AIA (Italian Association on Adrenoleukodystrophy) - it is crucial to implement knowledge and awareness in the medical community. In particular, as it is being done in other countries, this must be the case for endocrinologists, to reach patients who may receive an early diagnosis, especially considering that adrenal insufficiency in adrenoleukodystrophy and adrenomyeloneuropathy is often detected during childhood and adolescence."

In particular, according to specialists, ALD and AMN are crucial and potential underlying diseases to consider on boys and men with idiopathic (inexplicable) adrenal insufficiency/Addison's disease: this is when testing patients is important, when adrenal antibodies cannot be detected and there is no other clear cause for adrenal insufficiency.

To this purpose, it is emblematic to tell a family story connected to the Italian Association on ALD (IALD): who had not been able to have a diagnosis for a long time. It is a family of eight, two parents and their six children: five males, three of which have developed Adrenoleukodystrophy, and a female who, like her mother, is a carrier. The diagnosis was reached after detecting a rare disease called "Addison's disease".

Their story
"It all started when our fourth child - the parents say - started showing fatigue, loss of appetite, darker areas of skin colour, and, every now and then, his need to ingest grains of coarse salt. At first we believed it was normal, since it happened during sumertime: we went to the beach and thought the darker skin was due to the sun, and fatigue was connected to the heat".

Later, though, the parents began to notice behavioural changes in their fourth son: he no longer ate, not even his favourite food, his weight loss progressed. Further tests were carried out later on, recommended by an endocrinologist at the Hospital in Chieti. She had recently attended a conference on the diagnosis of adrenoleukodystrophy, and her life-saving intuition steered the family towards the right path, enabling them to achieve, also thanks to a further intervention by Hospital Bambin Gesù in Rome, a definitive diagnosis of adrenoleukodystrophy.

"My children and my wife – the father says - immediately began the therapy, and were given a diet to follow, restricting saturated fats to three grams per day. It is a sacrifice for our children in particular, who cannot eat the food they love the most. Yet, we are happy because we have a path to follow, and we know we are in good hands".

Dr. Valentina Fasano
President of the Italian Association
of Adrenoleukodystrophy

X-linked adrenoleukodystrophy
Newborn screening in the UK may save half a million euros

Three and a half million euros saved every year by the NHS in the UK, as against a cost of 463,000 euros if newborn screening for X-linked adrenoleukodystrophy were activated. This was stated by a team of researchers from Sheffield University, hence confirming sustainability of the screening for this disease, with patients on the winning side in terms of healthy years of life to live.

Results of the study, published on Orphanet Journal of Rare Diseases, included healthcare, social assistance and education costs, together with Quality Adjusted Life Years (QALY), a cost-utility analysis measure including both the quality and the quantity of life lived.

Screening 780,000 newborns per year would lead to detect 18 boys with X-ALD, of which would then develop CCALD (Childhood Cerebral Adrenoleukodystrophy). The model only assessed males. Yet, should it be extended to females, 17 more cases of X-ALD would be detected. Estimates say the cost of the program is about £402,000 (about 463,000 euros) with an overall saving of £3,040,000 per year (about 3,502,000 euros). Moreover, patients with CCALD may obtain 0.5 QALY each. Information worth bearing in mind, in case Italy decided to start a debate on the introduction of this disease in the ENS.

Adrenoleukodystrophy
Adrenoleukodystrophy is a rare genetic disorder affecting peroxisomes (intracellular organelles which compartmentalise enzymes crucial for processes such as β-oxidation), counting several forms: ALD, neonatal or Childhood cerebral ALD (one possible expression of Zellweger syndrome), and the most diffused X-linked adrenoleukodystrophy.

In some cases the disease causes deterioration of the myelin, a complex fatty acid in the tissues that covers many nerve cells of the central and peripheral nervous system. Without myelin, the nerves cannot transmit impulses, leading to a growing disability, while myelin disruption keeps growing and increasing. It mainly affects children between 4 and 8 years old, while milder forms are detected in adults also. The latter is also called adrenomyelopathy (AMN), with onset in early to mid-adulthood, when individuals are in their 20s or 30s. The disease primarily affects males.

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder causing cerebral demyelination and axonal dysfunction of the bone-marrow. It can cause spastic paraparesis, adrenal insufficiency, and, at times, testicular dysfunction. It affects 1 individual out of 20,000 newborns (males and females). Molecular newborn analysis of ABCD1 gene can be carried out, and some countries provide preimplantation genetic testing (PGT).
**Gene therapy: hope for treatment of MLD (together with early screening)**

Metachromatic leukodystrophy (MLD) is a severe genetic disease that can have an early infantile onset and leads to the decline of acquired motor and cognitive skills. It is caused by a lack of an enzyme that breaks down substances whose accumulation becomes toxic for the nervous system. To date, there are no effective treatments, but a great hope lies within gene therapy: the protocol developed at San Raffaele-Telethon Institute in Milan (SR-Tiget) has proved capable of producing a significant change in the natural progress of the disease. The gene therapy, currently undergoing advanced clinical trial, may be available over the next years thanks to Orchard Therapeutics, which has secured its license. Haematopoietic stem cells taken from the patient are corrected in the laboratory using viral vectors containing one or more functioning gene copies, then reinfused into the blood: once they are back into the organism, engineered cells are able to counter the build-up of toxic substances, hence enabling a normal development and growth. All of this, provided that the therapy be given when the damage is not severe, ideally before the onset: such an early diagnosis is very unlikely, though, unless there has been a previous case in the family. Which is why newborn screening would be a proper cornerstone, enabling doctors to diagnose the disease within the first months after birth, the stage in which gene therapy can bring about its maximum benefits. At present, MLD is not in the list of diseases screened at birth: the necessary, but not sufficient condition, is to have a reliable, affordable test, like the one developed in the newborn screening lab at Meyer’s children’s Hospital in Florence. Involved researchers are currently committed to starting a pilot study to validate the test and confirm its reliability on a vast scale. An important project, supported by patients association “Voa Voa! Onlus – Amici di Sofia” (www.voavoa.org) with its crowdfunding campaign “Gocce di Speranza” (www.goccedisperanza.it).

Alessandro Aiuti, Deputy Director of San Raffaele-Telethon Institute for gene therapy, Milan

Giancarlo La Marca, Manager of the newborn screening laboratory of Meyer’s children’s Hospital, Florence

Below: A. C., 8 years-old from Brazil, affected by metachromatic leukodystrophy, like her brother Carlos, who passed away a few years ago, but “thanks to whom” she was able to undergo gene therapy very early, about a year and a half after birth. Next to her, Dr. Francesca Fumagalli, neurologist at Sr-Tiget Institute.
You can provide 0.5% pre-tax donations to Aismme using tax code 92181040285.
The quality of life of patients with Fabry disease

Aiaf Onlus presented the results of the National inquiry during the National Meeting of Anderson Fabry Patients 2019

A present of fatigue, severe and chronic pain and motion difficulties, together with a future of looming more severe symptoms, physical disability, dysfunction of vital organs, and the risk of leaving work, or being unable to find a job. This, to sum up, is the picture drawn by “The quality of life of patients with Fabry disease”, the 2018 national enquiry carried out on behalf of Aiaf, the reference association of patients, by C.R.E.A. Sanita – of Tor Vergata University in Rome, with the non-conditioning support of Amicus Therapeutics and presented at the National Meeting of Anderson Fabry Patients, held in Rimini last March 22-23.

106 questionnaires collected from as many patients, 40.6% females and 59.4% males, aged 42 on an average, and diagnosed at an average of 31.6 years of age.

As regards the quality of life, 40.6% of patients believe their health conditions are decent, while 12.3% think conditions are bad. In fact, for most of the polled (55.7%), health conditions are jeopardised by the disease, 11.3% believe conditions are extremely jeopardised. Unfortunately, the young are like-minded: among polled aged 25-34, 60% declare their health conditions are either or very jeopardised.

Among the problems caused by the disease, the first is fatigue, felt by 65% of patients, followed by temporary severe pain (48%) and 40% of the polled feeling, quite or pretty much, chronic severe pain, in addition to motion difficulties (25%). Primarily, the disease impacts on the decision to have children (4 surveyed out of 10), triggers anxiety on almost 50% of the surveyed, while 25% fears being judged by others.

In particular, 28.3% of the polled believe the disease makes it rather difficult to walk, while 0.9% are bedridden. Only 7.5% find it difficult to wash themselves and get dressed (0.9% are not able to do it), and 45.3% have difficulties in their daily routines (1.9% have huge difficulties). Pain remains one of the main problems: only 22.6% don’t feel it. 68.9% consider it moderate, while 8.5% of the polled say it is extreme. The picture illustrates that 50.9% of patients live with moderate anxiety and depression, while 6.6% feel extremely anxious and depressed. A wide majority of patients accepts the disease trying to carry out their lives as they did before (42.5%) or try and cope with it at their best (36.8%). 1.9% of the polled, though, feel unable to react, almost 1% react with denial, and 18% live between acceptance and denial.

The future is often looked at with concern: because of increasingly severe symptoms (75%), dysfunction of body organs (85%), pain (44%), and the prospect of physical disability (9%). More than half the patients are also pessimistic about the likelihood of finding an occupation or being forced to leave their job. The impacts appear particularly heavy in the field of occupation: 45% of the polled declared they had to reduce their working hours, 20% had to leave their job, and 18% had to change it. School or working days that patients lost per year amount to an average of 19.1, with 6.6 days lost per year by their friends and family members. Productivity was jeopardised for almost 50 days per year. The figure was quite high even about the days when patients had to give up doing sports, going out or enjoying leisure time activities due to the limitations connected to the disease: 54 days.

Finally, while the families are quite supporting (34%), together with friends (24%) and parents associations (36%), the disease is not recognised by the National Institute for Social Security (INPS), that doesn’t give eligibility to receive disability benefits under Law 104 to one applicant out of three. Only one patient out of three receives them, while one out of three does not even submit the application. Severe disability status is recognised in 45.7% of cases.

Fabry disease

Possible contribution to the treatment from the Nephrology Group in Padua

Professor Lorenzo Calò, and his research group of the Nephrology department in Padua, documented oxidative stress (OxSt) activation and the altered reaction to it in Fabry patients. Results of the study were published in the scientific journal PLoS ONE in October. They suggest that, in addition to enzyme replacement therapy, OXSt and Rho kinase inhibition by either pharmacological or nutritional measures, is likely to prove useful for the prevention/treatment of Fabry patients’ cardiovascular-renal remodelling. OXSt activation in the disease has been documented in Fabry disease patients currently undergoing enzyme replacement therapy (ERT), which stabilises and halts the progress of the disease. Yet, there is no evidence as to ERT’s ability to halt cardiac, renal and cerebrovascular natural deteriorations, in particular when the diagnosis has not been carried out at an early stage.
The helplines

One of the targets of Project NS2 is to boost present association helplines for people with rare diseases. Helplines are being used increasingly often in several health communication initiatives because of the easy access they can grant to wide groups of people. Even more so when dealing with rare or ultrarare diseases or patients, bound for life to a centre of expertise due to the impacts the disease can have on a daily basis. Work is currently being done, aimed at:

- mapping and uploading existing association helplines by means of an extended preliminary investigation among all associations in the sector;
- enabling association helplines to provide quality services, by means of training professionals and volunteers dedicated to the service itself, even on ENS;
- testing innovative channels for the listening, information and orientation services on rare diseases, by means of video-conferences. The video consultation grants access to a direct contact with the caregiver or the patient, providing welcoming and proximity that are fundamental for those who, like rare disease patients, often feel bewildered, alone and overwhelmed by a social healthcare system that is not always easy to approach.
- creating a guidebook on association helplines.

- strengthen the helplines for people with a rare disease;
- activate a line dedicated to remote psychology support/consultation for people with a rare disease and their relatives, through an innovative web platform – a dedicated on-line video conference system (malatirLive!) - in the web portal www.malatirari.it, to overcome the distance that separates people with rare diseases;
- train patients and contact people to ensure updated information on the news about regulations, deeper knowledge on LEAs, ENS, ERNs, etc.;
- provide an information channel dedicated to Expanded Newborn Screening to inform and orientate families in the correct way;
- develop empowerment of people with rare diseases and their contact people, enabling them to carry out active-citizenship programs through auditing on ENS regional networks and institutional regional helplines on rare diseases. This shall be achieved by developing shared models to assess the quality of regional ENS networks, aimed at drafting a factsheet summing up the stances of associations of people with rare diseases towards ENS;
- organise 5 Open Days in ENS centres, so that citizens can see the services dedicated to ENS.
“Stars don’t bother being mistaken as fireflies: together for Hereditary Metabolic Diseases”

Patients, families and healthcare operators from Verona gathered with Aismme in May

Last May 11, Aismme promoted a day of in-depth analysis and trade of ideas among families of young patients and adults from the Verona Health Centre, practitioners and operators to help them getting acquainted. The meeting dealt with several approaches to the pathologies, the situation of the Treatment Centre and the Screening Centre, and Aismme’s activity to support practitioners and patients. Attendance was good at an event which, on its second edition, wishes to become a schedule to keep for Verona.

Manuela Vaccarotto, Vice President of Aismme, presented an overview of the Association’s activity at a national and European level, then she spoke about the financial support it provides to the Screening Centre and the Treatment Centre in Verona, enabling them to purchase appliances and materials, and the grants and private funds for research and clinical education of young doctors and dietitians, professionals who, led by Dr. Bordugo MD, have raised quality standards of treatments. Cristina Vallotto, President of Aismme, illustrated the projects dedicated to patients in the Centre, and asked their families to give their contribution to go on and support the work of practitioners, technicians and operators. Among bibliography events with Irene Monge, the floor was also taken by Marta Camilot, responsible for the Newborn Regional Screening Lab, Giulia Rodella, Geneticist and Metabolic practitioner, Alice Dianin and Roberta Nurti, Dietitians, Katia Tinazzi, Psychologist, Trombetta, Endocrinologist, and Tonin, Neurologist. These latter, in cooperation with Dr. Bordugo, also treat adult patients with metabolic diseases, something only very few treatment centres in Italy do.

To conclude, experiences from two fathers whose children received different diagnosis for the disease. On the one hand, an early diagnosis with ENS, and a family going through anxiety and dismay after the diagnosis, getting to the relief from identifying the disease a few hours after birth, enabling an early treatment. On the other hand, a late detection of the disease, seeking an answer that comes late, the baby’s worsening conditions, the family feeling powerless, and, finally, the diagnosis and treatment in Verona, improving the situation dramatically.

At the end of the day, attendees enjoyed a snack with seasonal fruit, very good aprotic and hypolipidemic food and delicious aprotic homemade ice-cream. See you again next year!

“Verona is a point of reference for rare diseases in newborns: 80 diagnosed patients over 5 years” (from www.veronaeconomia.it)

The Integrated University Hospital in Verona has been studying Rare Diseases since 2014, and to date it is one of the main excellences at a national level and beyond. This is owing to the expanded newborn screening project, that has turned Verona into one of the main centres for this kind of research, not only at a National, but also at a European level. In particular, it is a project led by Dr. Laura Camilot, and managed by a team of good researchers who can count on pioneering appliances. Thanks to these protagonists, the laboratory can diagnose a rare disease from a single drop of a newborn’s blood with the aim of using such an early diagnosis to monitor these disorders adequately, preventing the development of more severe consequences. Furthermore, data seem to confirm the quality of this project: from 2014 to 2018 (hence over the last 5 years), the Hospital in Verona has diagnosed 80 rare newborns with rare diseases, with 450 further diagnosed patients, including children and adults. It is no coincidence that Verona has been acknowledged as Metab Centre for ERN, the European Reference Network on Rare Bone Disorders, Rare and Complex Connective Tissue and Musculoskeletal Diseases, Rare Haematological Diseases and Pulmonary Diseases.”
Aismme for Verona

2014 saw the birth of the Clinical centre in Verona, managed by metabolism specialist Dr. Bordugo, which joins the already existing Screening Centre. Aismme immediately acknowledged the excellency of the Centre and started supporting the laboratory and the clinical department alike, financing activities of highly trained and specialised personnel. “Over 300 patients come to the Centro di Cura Italia (Italy Treatment Centre)— Cristina Vallotto, President of Aismme, explains – a growing number thanks not only to the screening work carried out by the laboratory, an excellency performing 125,000 screening tests per year for 40 metabolic and endocrine disorders, but also (and mainly) because of the kind-heartedness and the ability to sympathise with adult and baby patients alike”. For 2 years, Aismme has been financing a grant for dietitians, geneticists and metabolism specialists, six doctors in total. It is currently financing Dr. Giulia Rodella, geneticist and metabolism specialist, Dr. Roberta Nurti, dietitian, and Irene Monge, data manager. For the Screening centre, it has purchased appliances to carry out the second-tier test and tandem mass spectrometry. Among other activities, it has promoted the Aurora Project, envisaging remote psychological support, and it has covered the costs of whole-exome sequencing tests for two children. Every year, it organises the Metabolic Cooking, a day dedicated to babies and their families who need to be on special diets, and a meeting to gather doctors, patients, families and Aismme. All of this thanks to funds coming from pre-tax donations, donations, and events such as concerts, theatre plays, stalls at Christmas markets, social media campaigns, etc.

Aismme’s Aurora Project

A remote video consultation service where parents can find answers and support

It means remote psychological support to help new-parents accept their baby's disease, to take awareness and widen their consciousness on the pathology and its management; a follow-up to better face the problems connected to coping with the disease, the parent-child and the brother-child relationship, the processing of the pathology by the entire family and, last but not least, the life-saving diet, sometimes very strict, that these babies need to follow from birth and during all their lives. The project is also the missing link between the home and the treatment centre, between clinical recommendations and their enforcement into “Best home practices” for all-round management of a hereditary metabolic disease whose treatment is highly complex. Progetto Aurora, suggested and financed by Aismme, embodies all this. Its trial will be starting over the next months and shall be dedicated to caregivers and families of baby and adult patients of the Centro di Cura delle malattie metaboliche ereditarie (Treatment centre for hereditary metabolic diseases) of the University Hospital in Verona – Borto Trento. The psychological support service for families and adult patients is already active within the Centre. Yet, it is carried out by the personnel during regular Day-Hospital hours or during hospitalisation. Families, therefore, often feel abandoned due to a lack of local counselling and psychological support services. The project enables to care for the families at home, providing them concrete attention and psychological support via telephone or video consultation. On the phone, or through a digital platform, a professional can arrange a consultation service for one or more people at the same time. The service can also be dedicated to groups of families whose children suffer from the same pathology to share experiences, and solutions to problems connected to the management of a baby and his disease. Should it be necessary, a person can be followed by a psychotherapist, or be given psychological and/or psychiatric support at a local level. The professional remains at user's service to guide him through this stage and identify a suitable path, relieving the person's solitude and bewilderment as much as possible. Progetto Aurora wishes to be a further step in the networking job carried out within the treatment centre: further analysis of the demand will enable to spotlight collective needs only partly catered for by the healthcare system and the health and social services. Aurora Project has been possible thanks to the unconditioned support by Sobi.
Aismme at Telethon

Last December 15, Cristina Vallotto and Manuela Vaccarotto, representing Aismme, participated at the Telethon marathon on RAI (Italian National Broadcasting Channel). On Saturday morning, during the TV program ItaliaSi on Rai2, they spoke about ENS and the importance of parents approaching it with confidence. The speech is available on Aismme’s website.

January-June 2019
We participated at...

- January 18/20 Madrid, Spain: XLH International alliance meeting of European and American associations of XLH patients associations.
- January 30 Bruxelles, European Parliament: Convention “Expanded Newborn Screening Programme: creating a European common model. The positive example of the Italian system”
- February 28 - March 1 Rome: “3rd International Homocystinurias Patient-Expert Meeting”
- April 4/7: Frankfurt, Germany: Annual MetaBeERN Board Meeting (Aismme is epags of the Net)
- Report on: Fabry, Gaucher and Niemann Pick disease (with Prof. La Marca). Sponsored by Aismme.
- May 16-17 Rome: Member of the jury “5th Workshop on drug pricing” Award for the 5th Market Access Award
- June 19/21 Salzburg, Austria: XLH International alliance meeting of European and American associations of XLH patients associations

Aismme is part of the National Coordination for Newborn Screening at Istituto Superiore di Sanità (ISS) in Rome. Aismme representative, Vice President Manuela Vaccarotto, attended the meetings on the following dates:

- December 20, 2018
- January 29, 2019
- April 10, 2019
- May 10, 2019
- June 6, 2019