INFORMATION FORM
FOR PARENTS/LEGAL GUARDIANS
Version 2 of 15/12/2022

Title of the study: Newborn screening for the diagnosis of Metachromatic Leukodystrophy (MLD)
Protocol code: NBSMLS2020
Promoter: Prof. Giancarlo la Marca, U.O. Newborn Screening Laboratory, Biochemistry and Pharmacology, AOU Meyer
Local Principal Investigator(at the Birth Centre): *indicate the name, surname, affiliation of the birth centre*
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Dear Parents/Legal Guardian,
We ask you to accept to participate in the trial described below only after carefully reading this information sheet and having had a comprehensive interview with the investigator who will have to devote the necessary time to fully understand what is being proposed.
If you wish, your child/daughter can participate in a trial sponsored by AOU Meyer and to which this Birth Centre has decided to adhere. This study involves several hospitals in Tuscany.
Once you have read this form, you have received answers to any questions, and if you allow your son/daughter to take part in the trial, you will be asked to sign the consent form.

What is the purpose of the trial
The aim of the trial is to identify, at an early stage (at birth), infants affected by **Metachromatic Leukodystrophy**, a rare genetic disease, characterised by severe and progressive demyelination of the central and peripheral nervous system, with the arrest of psychic and motor development, epileptic seizures and ataxia. Metachromatic leukodystrophy belongs to the group of lysosomal storage diseases, many of which are already subject to expanded mandatory screening according to National Law 104/92 and Regional Law 909/2018.
Expanded Newborn Screening is an important instrument of public precautionary medicine that allows early detection, possibly in the pre-symptomatic phase, of the subjects at risk of many diseases, allowing to establish the appropriate therapy at an early stage (dietary, vitamin, pharmacological therapy) and resulting in changes of the natural history of the disease and a better prognosis.
The clinical diagnosis of Metachromatic Leukodystrophy is currently following the clinical suspicion (onset of signs and symptoms compatible with the disease) and the presence of suggestive findings in the brain MRI (Magnetic Resonance Imaging). The confirmatory test is carried out with genetic analysis to identify mutations in the gene encoding the Arisulfatase A (ARSA) enzyme .
There are four clinical variants based on the age of the onset of symptoms: Late Infantile(LI); Early Juvenile(EJ) and Late Juvenile(LJ); Adult Disease(AD). The Late Infantile form is the most frequent (death is generally within 5 years of the onset of the first symptoms).

What therapies are available today for metachromatic leukodystrophy?

Until recently, no therapeutic approach other than symptomatic and supportive therapies was available. However, recent studies have shown that hematopoietic stem cells transplant is able to delay the onset or slow the progression of the disease especially in the late-juvenile and adult forms, in the asymptomatic phase. Furthermore, studies have shown a relative efficacy of experimental treatments for metachromatic leukodystrophy including the intrathecal enzyme replacement therapy and the gene therapy with hematopoietic stem cells. At the Tiget San Raffaele Institute in Milan, a clinical trial of gene therapy with hematopoietic stem cells was conducted and completed on patients diagnosed with metachromatic leukodystrophy, in pre-symptomatic patients with late infantile or early juvenile form and in patients affected by the early juvenile form with early clinical manifestations of the disease. In clinical trials, stem cell gene therapy showed more efficacy in patients who had not yet developed symptoms. Once they received the medicine, their cognitive and motor performance was maintained and comparable to that of their healthy peers during the observation period.

Having regard to the results, the European Medicines Agency (EMA) and subsequently, in May 2022, the Italian Medicines Agency (AIFA) approved the marketing of the gene therapy medicinal product, which is currently available in Italy as Libmeldy.

What does participation in the trial involve?

If you decide to participate in the study, specific tests will be carried out on some molecules, called sulfatides, which more commonly accumulate in the blood of patients suffering from metachromatic leukodystrophy. The test will be carried out on the capillary blood drops (Dried Blood Spot) collected from the newborn's heel for the mandatory newborn screening required at national and regional level (that will be carried out anyway, as routine). The child will not be subjected to other punctures or blood samples specific to the project. The study will be proposed to all infants born in Tuscany and it will last for 3 years.

What will happen to our child's biological sample?

Your child's blood cards will be sent for analysis to the AOU Meyer Screening Laboratory as a regional reference for the diagnosis of metabolic diseases. The cards will be stored for 10 years from the end of the trial under the responsibility of Prof. Giancarlo la Marca, Head of the Screening Laboratory and promoter of the study. After this period, the samples will be destroyed.

At any time you can exercise your right to request the destruction of the remaining sample. Only a limited number of people, authorized by the Promoter, will have access to the biological sample of your child.

How will we be informed of the metachromatic leukodystrophy test results?

The screening test results will be available within seven working days of collection date.

In case of negative results, as for all other mandatory neonatal screening, there is no communication and/or re-evaluation.

In case of a positive screening test or dubious result of the first blood sample, there is a confirmation algorithm that involves contacting you parents to carry out a check sample at the birth centre, always with a drop of blood from the baby's heel on the card. In case of a second positive test, you will be directed to the AOU Meyer for an interview with paediatricians who will visit your son/daughter and take a new blood sample to both him/her and parents, for genetic analysis of metachromatic leukodystrophy confirmation by ARSA gene analysis, always carried out at the AOU Meyer (Molecular Biology Laboratory of Neurometabolic Diseases). The doctors of the centre will provide you with all necessary information.

Due to the purpose of the screening, the test may also give rise to unexpected news, that is to say, it could signal the suspicion of a pathology other than those examined, that can be recognized by the test itself.

Even in this case, AOU Meyer doctors will give you all the necessary information before proceeding with further diagnostic tests to confirm or rule out the suspicion of disease.

How to proceed if our child is affected by metachromatic leukodystrophy?

If the child is affected by the late infantile or juvenile form, without clinical manifestations of the disease, he/she could be a candidate for gene therapy at the San Raffaele Hospital in Milan; in the case of other forms, he/she will be followed up every six months at the Meyer Hospital for the clinical and instrumental assessments necessary for the ongoing evaluation of the disease.

Benefits of participating in the trial

Early detection of metachromatic leukodystrophy, especially in severe form, allows to start a specific treatment process in order to reduce the progression of the disease. In other forms, however, it will be important to take charge of a specific clinical-care management.

Potential risks from participation in the trial

There is no direct physical risk associated with participation in the project, since the blood samples collected for the trial are not additional to those for mandatory neonatal screening.

What if you decide not to take part in the trial

Participation in the trial is entirely voluntary.

If you decide not to allow Your child to participate in the study, you will not need to provide any explanation and there will be no change in the medical treatment at the birth centre.

How personal data relating to your child's identity will be protected

With regard to the processing of personal data, in compliance with the provisions of current legislation on the protection of personal data, pursuant to art. 13 and 14 of EU Regulation of 27/04/2016, n. 679 (General Data Protection Regulation - GDPR), your data and your child's biological samples will be processed only to the extent that they are indispensable for the objective of the study and we inform you, as of now, that the independent data Controller is the Meyer University Hospital of Florence (as Promoter and principal investigator), and the Birth Centre that will be appointed, pursuant to art. 28 of the GDPR, is the Data Controller. In short some essential information:

I. Data Controller and Data Protection Officer

The Data Controller is the Meyer University Hospital, with registered office in Viale Pieraccini n. 24, 50139 - Florence, PEC meyer@postacert.toscana.it. Pursuant to art. 37 of the GDPR, the Data Protection Officer (DPO) has been appointed at the Meyer University Hospital, available for any clarification at the email address: privacy.dpo@meyer.it.

II. Purposes and Categories of Data Processing

The processing of personal data will be carried out:

a) in order to carry out the study indicated in the introduction;
b) for the purpose of diagnosis, healthcare or therapy, if the preliminary test is positive.

The conduct of the study determines the treatment of the following categories of your personal information:

- Common data (e.g. personal and contact details) including personal identification number.
- Special categories of personal data mentioned in art.9 of the GDPR (e.g. health data) and eventually genetic data (i.e., data relating to the hereditary characteristics of an individual).

III. Legal basis of the processing and nature of the contribution

The legal basis of the processing described above is to be found mainly in the consent, pursuant to art. 9, 2 comma, lett. a) of the Regulation. Participation in this trial is voluntary and the consent to the processing for the purposes described above is free and optional. Denying your consent will not affect your right to use other medical services provided by the institution where the child is being treated.

However, we must make it clear that consent for the purpose referred to in point IIa is necessary to be able to participate in this trial. If the biological data and samples indicated for this purpose are not provided, it will not be possible to participate in the trial.

If the test conducted for the purposes referred to in point IIB is positive and if the necessary conditions are met, you will have the opportunity to submit the minor to therapeutic treatment at the San Raffaele Hospital in Milan.

Therefore, you will be asked right now for consent to the communication of data by AOU Meyer to the San Raffaele Hospital in Milan, that from that moment will treat them as an independent data controller.

The Data Controller (AOU Meyer) may need to communicate the results at the Birth Centre to comply with the patient's health care request and for legal obligations regarding the storage of administrative and health documents.

IV. Methods of processing

The purposes, referred to in point II, foresee collection, registration, storage and management of personal data using paper and computer tools with reasons strictly connected to the same purposes in order to assure security and confidentiality of the data, pursuant to art. 32 of the GDPR.

For the collection of the biological sample and the consent to the trial, the owner will avail of the help of birth centres punctually identified in the trial protocol and that will previously appoint data processors, pursuant to art. 28 of the GDPR.

The subjects in charge of data processing will pay specific attention in differentiating the data collected for medical/clinical purposes from those collected for experimental purposes in compliance with the protection of the rights and dignity of the patient.

V. Categories of subjects to whom data may be disclosed

The Data Controller undertakes not to disseminate particular and genetic data and not to use biological samples for purposes other than those provided for in point II.

With your consent to participate in the trial, the Data Controller will carry out the tests at its Newborn Screening Laboratory, Biochemistry and Pharmacology.

AOU Meyer will not use the samples for purposes other than those indicated in the trial protocol and undertakes to communicate, where appropriate, to third parties and the scientific community, only aggregated and anonymised data.

The data from the results of the genetic test will be made known directly to you, if they bring a concrete and direct benefit in terms of therapy, prevention or awareness of your future choices; only with your consent the data can be disclosed to different subjects or communicated to different Data Controllers (San Raffaele Hospital in Milan).

VI.Storage of personal data.

The data you provide will be stored for a period of time necessary to fulfil the purposes for which it was collected and processed. The blood spot will be stored for 10 years, a period considered necessary for the performance of any control and verification of the health of the newborn.

As regards the data emerging from this study will be kept within the limits established by the laws governing the subject.

VII. Extra EU transfer of personal data

The data, object of the trial, will not be processed in countries outside the European Union.

VIII.Exercise of the rights

You may exercise the rights granted to you, pursuant to and within the limits of art. 15-21 of Regulation (EU) 2016/679, including the right to request access to your personal data, their modification or their deletion, as well as to limit and oppose their processing and data portability.

We also specify that any expressed consent is freely given and is revocable at any time, without causing any disadvantage or prejudice and without compromising the processing lawfulness based on consent given before the withdrawal.

If you decide to withdraw your consent to the data processing for the purposes in point IIa, you will be able to obtain the destruction of your biological sample and your genetic data will be deleted, unless, originally or after treatment, the sample or information can no longer be attributed to an identified or identifiable person and/or unless the cancellation of the data seriously undermine the achievement of the research objectives.

Inquiries related to exercising of these rights can be sent to the Data Protection Officer by writing to the e-mail address privacy.dpo@meyer.it or by writing to the Data Controller at the address listed in point I.

Finally, if you believe that the processing of your child's personal data violates the Regulation (EU) 2016/679 or Legislative Decree 196/03 s.m.i., you have the right to lodge a complaint with the Supervisory Authority, as provided for in art. 77 of the Regulation (EU), or to appeal to the appropriate courts (Art. 79 of the Regulation).

Additional information

There are no additional costs for you arising from participation in the trial and you will not receive any financial compensation for participation in the trial. The study has been arranged in accordance with the rules of Good Clinical Practice and the Declaration of Helsinki, and has been approved by the Ethics Committee of the Region of Tuscany-Pediatric Section.

For further information or clarification about the research project or if you would like to withdraw your consent for participation in the trial and/or to have your Son's biological sample destroyed, please contact the following addresses:

Tel: 055-5662988

Email: giancarlo.lamarca@meyer.it