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Original article

Key lessons from the first international treatment eligibility committee: the case of metachromatic leukodystrophy

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A B S T R A C T

Background: Treatment decisions in metachromatic leukodystrophy (MLD), a rare life-threatening neurological disease, are challenging. Hematopoietic stem cell transplantation or autologous stem-cell-based gene therapy can be life-changing but come with uncertainties, risks, and high costs. To address this, the international MLD treatment eligibility panel was established in collaboration with the European Reference Network on Rare Neurological Diseases. The panel reviews and discusses individual MLD cases and provides consensus-based recommendations on whether to treat and which treatment modality. The goal is to streamline international care and treatment counseling by providing uncomplicated access to expert opinion.
Methods: The panel operates according to a published standard operating procedure and was evaluated between September 2021–2024. Case data were recorded in a Castor EDC-based system and, with consent, included in the MLD Initiative (MLDi) patient registry. Physicians' experiences were assessed via EUsurvey, and patients' feedback was collected through an MLDi registry survey.
Findings: The panel discussed 43 cases, recommending treatment in 20, abstaining in 19, and reaching no consensus in 4. Open questions regarding cognitive function and lack of outcome data caused challenges in treatment recommendations in late-onset MLD patients. All treatment recommendations were followed. Physicians reported positive experiences with the panel.
Interpretation: The MLD treatment eligibility panel demonstrates how international expert advice can be streamlined across Europe for a rare disease like MLD, where disease-specific guidelines are still in development. By balancing complex clinical, social, and ethical parameters, the panel aids in encouraging appropriate use of innovative and costly therapies and guarantees accessibility to expert advice irrespective of country of origin.

1. Introduction

Innovative treatments such as gene therapy can drastically change the management of a rare disease but also introduce new challenges. [1,2] Uncertainties about long-term effectiveness, safety, and eligibility criteria coupled with high costs and unclear cost-effectiveness, can hinder access. [3,4] The highly specialized care necessary for treatment leads to organizational challenges and may require cross-border referrals of patients. [5] These clinical, organizational and financial challenges need to be addressed to ensure adequate implementation of innovative treatments in daily practice. We illustrate these issues using the case of metachromatic leukodystrophy (MLD) and evaluate how streamlining international care and treatment counseling could benefit the care for this rare disease.

MLD is a neurodegenerative disorder caused by biallelic pathogenic variants in the *ARSA* gene, which leads to impaired sulfatide degradation. [6] Sulfatide accumulation damages the central and peripheral nervous systems and causes diverse neurological symptoms. Birth prevalence in Europe is estimated at 0.38 – 1.85 per 100,000 live births. [7] Disease onset is highly variable, typically within the first decade of life but ranging up to the fourth or fifth decade. Different MLD subtypes can be distinguished based on age at onset. Early onset forms (late-infantile <2.5 years and early juvenile 2.5-6 years) cause rapid deterioration with a predominant motor phenotype, whereas late-onset forms (late-juvenile 7-16 years and adult ≥16 years) present with a mixed or cognitive presentation. [8] If untreated, patients will lose all their abilities and eventually die prematurely. [6] Predicting phenotype based on the genotype and residual arylsulfatase A activity is promising, but needs further refinement. [9,10] For example, intra-familial variability in late-onset MLD forms is not yet fully understood.

Early-stage treatment with allogeneic hematopoietic cell transplantation (HSCT) or autologous ex vivo hematopoietic stem cell gene therapy (HSCT-GT, atidarsagene autotemcel, brand name: Libmeldy™), have demonstrated benefits in delaying or stopping disease progression in MLD patients. [11-16] Once substantial neurodegeneration is present, these therapies not only fail to halt disease progression but may, in some cases, exacerbate the speed of decline. [11] The risks associated with allogeneic transplantation are supposed to be higher than those of HSCT-GT because of potential graft-versus-host disease, but both HSCT-GT and HSCT are invasive treatments.

Determining eligibility for HSCT or HSCT-GT poses a considerable challenge due to the phenotypic heterogeneity of MLD and the lack of robust biomarkers for disease staging. HSCT-GT is registered for pre-symptomatic late-infantile MLD and pre- or early-symptomatic (before the onset of cognitive decline) early-juvenile MLD. HSCT-GT is being investigated in late-juvenile MLD where pre-symptomatic cases are eligible when there is a symptomatic sibling and early-symptomatic cases when they have normal cognitive function and are able to walk independently. Official eligibility criteria for HSCT are lacking but often include a late-juvenile or adult MLD subtype with substantial cognitive function, i.e. an intelligence quotient (IQ) above 70 or 85, and the ability to walk independently. [11,16-18] Limited evidence on precise eligibility as well as lacking robust long-term outcome and safety data adds uncertainty to clinical decision-making.

Beyond the clinical complexities, the significant treatment costs underscore the importance of appropriate treatment decisions. Recently, negative reimbursement decisions have delayed or hampered access to the HSCT-GT in various European countries. [19] HSCT for MLD is available in most European countries, although gaps remain. [18] Thus, given the high budget impacts of HSCT and HSCT-GT, determining the right candidates is also relevant from a health economic perspective.

To address these challenges, an international treatment eligibility expert panel for MLD was established through collaboration between the MLD Initiative (MLDi) and the European Reference Network for Rare Neurological Diseases (ERN-RND). [20] The MLDi, a primarily European collaborative network of MLD experts, maintains a patient registry for

Table 1
Cognitive impairment categories.

Cognitive impairment categories	Criteria
Normal cognition	• Total IQ or DQ ≥ 85
Estimated normal cognition	• No clinical symptoms of cognitive decline in pre-symptomatic patients
Borderline cognitive impairment	• Total IQ between 70 and 84, or • in the case of a lacking total IQ score: three normal index scores (≥85) with a low processing speed (<70)
Estimated borderline cognitive impairment	• MoCA scores between 11 and 25, or • an estimated IQ of 70–85 measured with incomplete/screening tests
Significant cognitive impairment	• Total IQ below 70, or • in the case of a lacking total IQ score: two or more index/IQ scores <70
Estimated severe cognitive impairment	• Clearly symptomatic patients with cognitive decline indicated as language regression (ELFC-MLD ≥3) or MoCA scores <11, or • an estimated IQ below 70 measured with incomplete/screening tests.

MLD. The ERN-RND provides an infrastructure for sharing expertise and improving care for patients with rare neurological diseases. [21] The panel convenes ad hoc to review and discuss individual MLD cases, offering consensus-based recommendations on whether to treat and streamlining international care and treatment counseling.

In this study, we evaluate the performance of the MLD treatment eligibility panel by reviewing the experiences of physicians and the outcomes of the cases discussed. We assess the panel's consistency and predictive value to enhance the decision-making process and improve clinical and economic outcomes.

2. Methods

2.1. Standard operating procedure treatment eligibility panel

Panel activities between *September 2021* and *September 2024* were evaluated for this study. Data from the cases discussed during this period were collected using a Castor EDC-based survey for the referring physicians. The treatment eligibility panel operates according to the standard operating procedure as published in *January* 2023. [20] Cases eligible for discussion include patients with a confirmed diagnosis of MLD for whom possible benefits of treatment with hematopoietic stem cell transplantation or HSCT-GT are not straightforward. Also, pre-symptomatic cases or cases where a reimbursement authority requests an expert-supported advice can be discussed. The panel consists of a minimum of 3, but preferably ≥5 experts with a varying composition of pediatric and adult neurologists, metabolic pediatricians and internists, and transplant specialists/hematologists.

Generally, the Clinical Patient Management System (CPMS) [22] was used for convening panels and distributing pseudonymized clinical information among the panelists before the meeting. Patients' or legal guardians' consent was obtained as appropriate for both discussing their case in the panel and to be included in the MLDi registry for the purpose of care and research respectively. The panels' metadata were collected in a Castor EDC-based [23] database and the clinical follow-up data were obtained through the Castor EDC-based [23] MLDi registry.

The panel discussions were moderated by a representative from the ERN-RND (TM) or the MLD initiative (DHS). The referring physician presents a detailed overview of the patient's and family's history and clinical status, including neurological and neurodevelopmental examination, genotype, arylsulfatase activity, MRI, nerve conduction studies and neuropsychological assessment. In all panels, the criteria TIQ ≥85 and Gross Motor Function Classification for MLD (GMFC-MLD) [24] <2 were explicitly considered. The official eligibility criteria for HSCT-GT were followed, including the fact that HSCT-GT is only commercially available for early-onset MLD and is being investigated in late-juvenile MLD. [25,26] Additional aspects necessary for successful treatment were considered as well, such as the rate of decline, the support network of the patient, the coping and ability to follow strict instructions (i.e. spending weeks in isolation during myeloablation), and donor availability. During the discussion a clear advice was formulated, and all the attending physicians were explicitly asked for their opinion. The minutes had a fixed format and were taken by the panel moderator. The minutes were sent for accordance to the referring physician afterwards.

Table 2
Descriptive results of the treatment eligibility panels.

Total number of panel discussions – N	43 (100 %)
Referring centers – n(%)	
Tübingen University Hospital (Germany)	9 (21 %)
Assistance Publique Hôpitaux de Paris(France)	7 (16 %)
Leipzig University Hospital (Germany)	6 (14 %)
Amsterdam UMC (the Netherlands)	6 (12 %)
Hamburg University Hospital (Germany)	3 (7 %)
Oslo University Hospital (Norway)	2 (5 %)
Oulu University Hospital (Finland)	2 (5 %)
Hospital in Mödling (Austria)	2 (5 %)
San Raffaele Hospital (Italy)	1 (2 %)
St. Anna Children's Hospital Vienna (Austria)	1 (2 %)
Heidelberg University Hospital (Germany)	1 (2 %)
The Hospital for Sick Children Toronto (Canada)	1 (2 %)
University Hospital Lyon (France)	1 (2 %)
Fakultní Thomayerova nemocnice Prague (Czech Republic)	1 (2 %)
Panel composition[a] (n = 38)	
Average number of experts – mean (range)	9 (3–16)
Pediatric neurologists represented – n(%)	38 (100 %)
Adult neurologists represented – n(%)	27 (71 %)
Metabolic physicians represented – n(%)	28 (74 %)
Transplant specialists/hematologists represented – n(%)	32 (84 %)
All key specialties represented (pediatric/adult neurologist, metabolic physician, and transplant specialist)	23 (60 %)
Average number of days between request and panel discussion meeting – median (IQR)	8 (6.75–12)
Average follow-up time after panel meeting at the time of evaluation in years – mean (SD)	1.3 (0.92)
Recommendation	
Treatment with HSCT or HSCT-GT is recommended – n(%)	20 (47 %)
HSCT – n	9
HSCT-GT – n	15
Treatment with HSCT or HSCT-GT is not recommended – n(%)	19 (44 %)
No consensus – n(%)	4 (6.8 %)
Advice followed when recommendation was to treat	
Yes (patient is treated) - n	14
No (patient is not treated) - n	0
Decision on (timing of) treatment not yet made - n	6
Advice followed when recommendation was **not** to treat	
Yes (patient is not treated) - n	19
No (patient is treated) - n	0
Treatment when there was no consensus	
Patient is treated with HSCT - n	2
Patient is not treated - n	2
Causal treatment at follow-up	
HSCT - n	7
HSCT-GT - n	9
Not treated - n	21
Decision on (timing of) treatment not yet made[b] - n	6

[a] For six panels, no information on panel composition was available.
[b] Treatment was recommended but not yet performed.

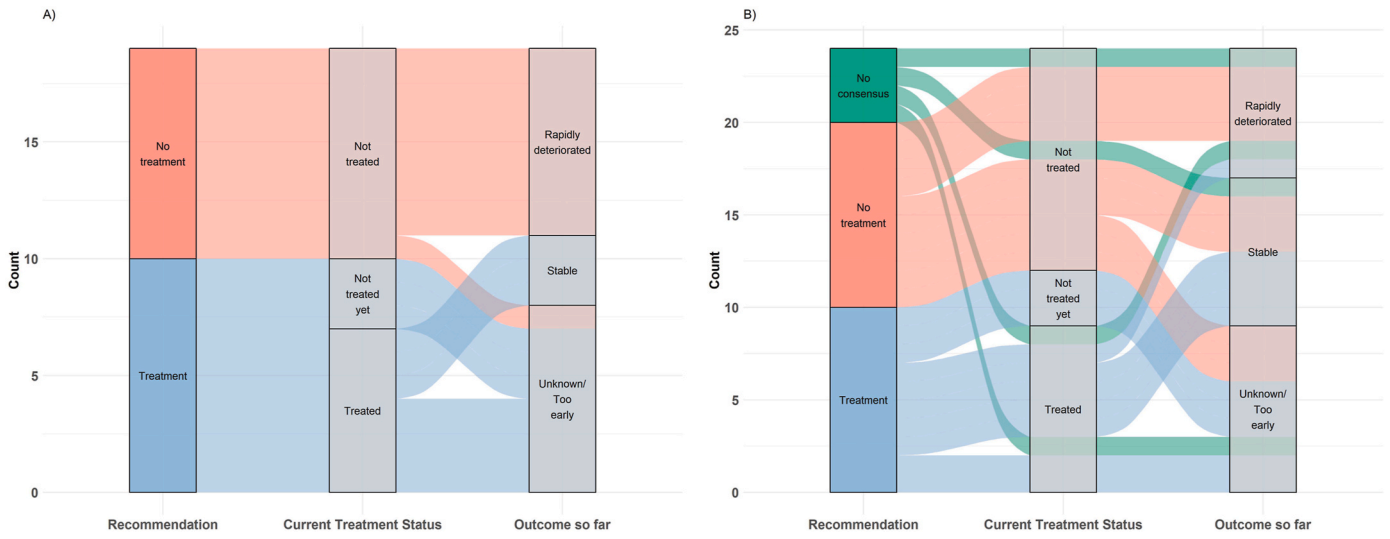

Fig. 1. Sankey Diagram of recommendations, current treatment status and outcome so far. The category 'Not treated yet' for the current treatment status, includes cases that are being monitored with an intention to treat the patient in the future. A) shows the outcomes for early-onset cases and B) shows the results for late-onset cases and the three cases with an uncertain phenotype (these three received a positive treatment recommendation).

The treatment decision was discussed with the patient/caregivers by the referring physician. After a minimum time of six months after the initial panel discussion, a follow-up survey was sent to physicians to collect information on the treatment decision and current clinical status of the patient.

2.2. Physicians' experiences

A questionnaire consisting of 11 multiple-choice questions about awareness of the MLD treatment eligibility panel and experiences with this panel using a 5-point Likert scale was set up with the software tool EUsurvey (Version 1.0, 2020/06/10). The questionnaire was distributed among all ERN-RND expert centers via the network-internal newsletter ('bulletin') and a reminder email to centers who did not respond to the general newsletter.

2.3. Analysis

Cases were categorized as either rapidly progressive, defined by a change of $\geq$2 points in GMFC-MLD, or stable, defined by $\leq$ 1 point change in GMFC-MLD and stable IQ (within margin of error +/- 5 points) or stable Montreal Cognitive Assessment (MoCA) at $\geq$1.5 year follow-up. For cases with a follow-up period of less than 1.5 years, the time window only allowed us to categorize as rapid progression if the criteria for this category were met. In case formal IQ testing was not (yet) repeated, a clinical impression by an MLD expert as either stable or rapidly progressive disease was sufficient. Phenotype categorization was based on manifestations at symptom onset, with a motor phenotype defined as isolated motor symptoms, cognitive phenotype defined as isolated cognitive symptoms, and a mixed phenotype as a combination of motor and cognitive symptoms. Cases were considered pre-symptomatic as long as they had no cognitive decline and no neurological signs and symptoms of the disease.

The total IQ or development quotient (DQ) was measured with the Wechsler Intelligence Scales for Children or Adults, or the Bayley Scales of Infant and Toddler Development, respectively. The IQ test results and MoCA scores [27] were categorized into six impairment categories: *normal cognition, estimated normal cognition, borderline cognitive impairment, estimated borderline cognitive impairment, significant cognitive impairment, or estimated severe cognitive impairment* (Table 1). Total IQ could not be reliably calculated in all cases due to incomplete tests or disharmonic profiles.

IBM SPSS statistics 28 was used for data analysis. The figures were created with RStudio 4.2.1. Normality was visually assessed using a histogram and/or Q-Q plots and tested with the Shapiro-Wilk test. Descriptive statistics were given as a mean with a range and/or SD for normally distributed data and as a median with interquartile ranges (IQR) for non-normal data. We used Fisher's Exact Test to assess the relation between stable or rapidly progressive disease and the treatment decision. A p value < 0.05 was considered statistically significant.

3. Results

3.1. Descriptive results of the panels

A total of 43 MLD cases with referring physicians from 10 countries were discussed in the treatment eligibility panel (Table 2). The panel quorum was reached for all cases and in the 23 (60 %) (child) neurologists, metabolic physicians and transplant specialists were all represented. Overall, the median time between a request and the meeting was 8 (IQR 6–12.5) days. This was 7 (IQR 5 – 11) days for the urgent panels. Except for four late-onset cases, a consensus-based recommendation could be formulated. Treatment was recommended in 20 (47 %) cases, whereas abstaining from treatment was recommended in 19 (44 %) cases. Fig. 1 shows an overview of treatment recommendations, treatment decisions, and outcomes so far.

3.2. Descriptive results of the discussed cases

Among the discussed cases, all MLD subtypes were represented, but the majority were early-symptomatic juvenile cases (Table 3). There were 19 (44 %) early-onset cases, 21 (49 %) late-onset cases, and 3 (7 %) cases with an uncertain MLD subtype. Thirty-one (72 %) patients were pediatric, and 12 (28 %) were adult cases. The diagnosis of the cases was made after symptom onset in 30 (69 %) cases and after a family screening because of an affected sibling in 11 (26 %) cases. One case was diagnosed after the detection of gall bladder abnormalities, and for one case, the reason for the diagnosis was missing. In total 34 (79 %) of the cases were symptomatic at the time of the panel discussion. Presenting symptoms were diverse, but cognitive decline and problems with either balance or coordination were the most prevalent, i.e. in 17 (40 %) and 16 (37 %) of the cases, respectively. At the time of the panel discussion, an MRI was available for 35 (81 %) cases. Information about IQ or MoCA was available in 24 (56 %) and 3 (7 %) of the cases, respectively.

Table 3
Descriptive results of the discussed cases.

Total number of cases - N	43 (100 %)
Sex at birth	
Female	23 (53 %)
Male	20 (47 %)
MLD subtype	
Late-infantile	6 (14 %)
Early-juvenile	13 (30 %)
Late-juvenile	12 (28 %)
Adult	9 (21 %)
Unknown[a]	3 (7 %)
Pre-symptomatic	9 (21 %)
Symptomatic	34 (79 %)
Age at onset[b], years – median (IQR)	8.6 (3.6–16.0)
Age at diagnosis, years – median (IQR)	7.8 (3.4–20.1)
Age at the time of panel discussion, years – median (IQR)	7.9 (3.7–21.2)
Which situation gave rise to the diagnosis	
Manifested symptoms	30 (69 %)
Family screening because of affected sibling	11 (26 %)
Other	1 (2 %)
Missing	1 (2 %)
Presenting symptoms[c]	
Gross motor signs	16 (37 %)
Balance and coordination problems	16 (37 %)
Loss of developmental milestones	4 (9 %)
Cognitive decline	17 (40 %)
Language regression	3 (7 %)
Behavioral changes	11 (26 %)
Psychiatric symptoms	4 (9 %)
Deterioration in school performance	7 (16 %)
Signs of polyneuropathy	11 (26 %)
Gall bladder related symptoms	3 (7 %)
Other	10 (24 %)
Predominant phenotype	
Motor phenotype	9 (21 %)
Cognitive phenotype	10 (23 %)
Mixed phenotype	13 (30 %)
Not applicable or unknown	11 (26 %)
Gross Motor Function Classification for MLD	
Level 0	17 (41 %)
Level 1	19 (44 %)
Level 2	4 (9 %)
Missing	3 (7 %)
IQ data available	24 (56 %)
Total IQ - median (IQR)	76 (67–92)
MRI available	35 (81 %)
MRI severity score – median (IQR) (n = 15)	17 (14–20)

[a] For some pre-symptomatic cases the MLD subtype could not be determined.
[b] Calculated based on the age at onset of the symptomatic patients.
[c] Each patient could have multiple presenting symptoms.

Detailed clinical information about motor function was available for all cases and a formal GMFC-MLD score for 40 (93 %) cases.

3.3. Panel recommendations

Of the 20 cases receiving a recommendation to treat, 15 (75 %) cases met both eligibility criteria (GMFC-MLD <2 and TIQ ≥85). For 9 of these 15 cases, formal IQ testing was not (yet) available at the time of the panel discussion, but all were classified as pre-symptomatic. Five (25 %) cases received a positive treatment recommendation for HSCT despite an IQ below 85 (Fig. 2). One patient had preexistent primary developmental delay explaining the low IQ, judged to be unrelated to MLD. The other four were late-juvenile or adult MLD patients and had borderline or significant cognitive impairments (Table 4).

Of the 19 cases receiving a negative treatment advice, 18 (95 %) did not meet one or both criteria (GMFC-MLD <2 and TIQ ≥85). One (5 %) case formally met the criteria of GMFC-MLD <2 and DQ/TIQ ≥85, but this was a symptomatic late-infantile 2.3-year-old patient. For this subtype, treating in a pre-symptomatic stage is essential for success. [16] For four late-onset cases, no clear consensus could be reached on whether to treat. Three of these patients had a TIQ below 85, and for one patient, formal IQ test results were not available.

Fig. 2 shows the categories based on cognitive level and the treatment recommendation. When examining all patients with a documented or estimated borderline or significant cognitive impairment (n = 10 and n = 15 respectively), treatment was not recommended in 17/25 (68 %) patients and no consensus was reached for 3/25 (12 %) of these patients. Only 5/25 (20 %) late-onset MLD patients received a recommendation that HSCT might be beneficial, of which three had a documented borderline and two a documented significant cognitive impairment (Table 4).

3.4. Follow-up

At the time of evaluation, the average follow-up time after the panel meeting was 1.3 years (SD 0.92, n = 43). The panel's advice to treat or not to treat was followed in 33 (77 %) cases. Six patients who received a recommendation to treat were not yet treated. These patients were either discussed very recently (n = 1) or are still monitored to determine optimal treatment timing (n = 5). Of the four cases for whom no consensus was reached, two were treated and two were not.

For 26 cases the overall outcome 6-36 months after the panel meeting could be determined. Of these, 8 patients with a recommendation to treat had received treatment: 7 were stable, 1 adult patient deteriorated during the 36 months after HSCT without relevant peri-interventional complications. Fifteen patients received a recommendation not to treat: 3 were stable (1 late-juvenile, 2 adult patients), 12 had deteriorated. Of the patients without consensus-based advice 1 remained stable so far, and 2 rapidly deteriorated. There was a significant association between treatment advice and outcome ($p < 0.05$). Seventeen cases had a follow-up of <1.5 years or there were insufficient follow-up data, definite categorization was therefore not yet possible.

3.5. Physicians' experiences

A total of 38 physicians involved in the care for leukodystrophy patients responded to the survey. The responders were employed in 29 different ERN-RND expert centers located in 16 European countries (Austria, Belgium, Czechia, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Malta, Netherlands, Poland, Slovenia, and Spain). Except for one physician, all (n = 37, 97 %) were aware of the possibility of discussing rare disease patients with an expert panel using CPMS within the EU. The majority, 29 (76 %) physicians, were aware of the existence of the MLD treatment eligibility panel. 24 (63 %) of the physicians indicated that they never consulted the MLD treatment eligibility panel. A total of 7 (18 %) responding physicians had discussed one (n = 3) or multiple (n = 4) patients. All physicians who discussed a case were positive about their consultation (Fig. 3). One referring physician judged the amount of time needed for the preparation of the panel as negative.

4. Discussion

HSCT and HSCT-GT for MLD are life-changing therapies for this severely progressive rare disease. When treated early in the disease course, deterioration can be slowed or stopped. On the other hand, these treatments involve high risk procedures and are expensive. Deciding whether to treat with HSCT or HSCT-GT deserves careful evaluation. The international MLD eligibility panel was established to provide consensus-based treatment recommendations for individual MLD patients. The panel offers a route to make clinical decisions in uncertain situations, leveraging the explicit and implicit knowledge of MLD experts. The panel consists of dedicated experts as reflected by the swift median response time of 8 days between the request and meeting. Treatment advice was considered useful and is adhered to in all cases. Treatment recommendations in slowly progressive late-onset MLD presenting with cognitive decline was particularly challenging.

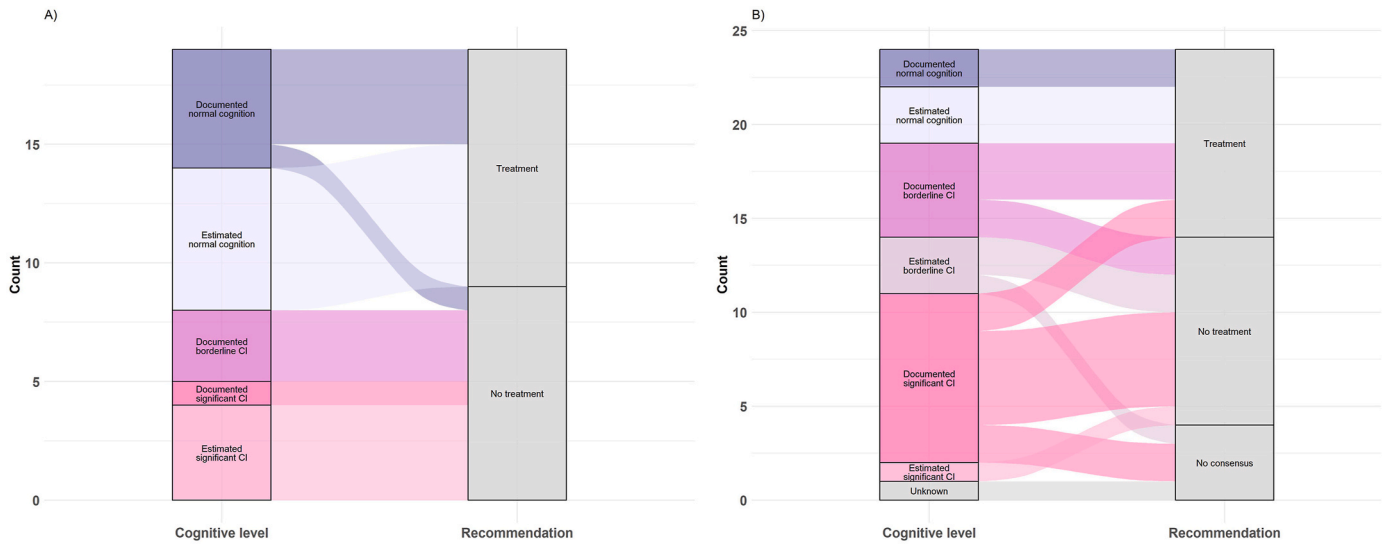

Fig. 2. Sankey Diagram of the cognitive levels and recommendations. A) shows the results for early-onset cases. Please note that in early-onset MLD, HSCT-GT was recommended when the patient had no cognitive decline. B) shows the results for late-onset cases and the three cases with an uncertain phenotype (these three received a positive treatment recommendation). In late-onset MLD, HSCT may have been recommended despite cognitive impairments. Abbreviations: CI = cognitive impairment.

The MLD treatment eligibility panel serves as an example of how international expert advice can be streamlined and made accessible across Europe for a rare disease like MLD. Due to the low prevalence numbers, most physicians, even those working with rare neurological disorders, may only encounter MLD cases occasionally or not at all in their clinical practice. [18] By fostering a network of internationally recognized specialists, the latest scientific advancements and best practices in MLD care become more widely accessible. Our survey results underscore the success of this approach: nearly all respondents were familiar with CPMS, and the majority were aware of the MLD treatment eligibility panel. This suggests that such initiatives may be helpful to improve access to expert consultation and reduce healthcare disparities. Additionally, HSCT-GT is a highly specialized treatment and is only available in a limited number of qualified treatment centers, requiring cross-border referral. Centralized expert consultation not only facilitates adequate treatment decisions, but could also aid the organizational logistics of this cross-border care. [21,28].

The panel supports appropriate use of innovative and costly therapies in MLD where evidence-based guidelines are not yet available. Data on treatment benefits remain limited, especially for late-onset patients. [11-13,16,29,30] All studies show that treating early is essential for success. As shown in other medical fields, inappropriate use of invasive treatments in patients who do not benefit from these treatments poses both health and financial risks. [31] Families are in desperate situations and often contact multiple international experts to seek treatment options. Some centers offer HSCT for patients in advanced disease stages or in late-infantile MLD, which is ineffective. [18] Recently, a paper of gene therapy in advanced MLD was published, which may increase false hope among families. [32,33] The panel advised against treatment in approximately half of the cases with all recommendations followed, demonstrating its effectiveness in preventing potential harm from ineffective invasive treatments. The association between deterioration and the treatment recommendation was significant. Still, from the six treated patients for whom a follow-up could be determined, one deteriorated shortly after treatment, emphasizing the importance of more data and structured follow-up of patients in the MLDi registry.

To harmonize and structure panel discussions, two criteria (TIQ $\geq$85 and GMFC-MLD $<$2) were explicitly assessed and registered in the minutes, but these proved insufficient for comprehensive treatment eligibility evaluations. The MLD experts in the panel weigh therefore a complex set of clinical, diagnostic and social parameters in the treatment decision, which requires MLD expertise. For young patients in a pre-walking age, the GMFC-MLD is not applicable. At the other end of the spectrum, some late-onset patients will never develop motor symptoms, or only in advanced disease stages, implying limited relevance of this criterion for decision-making in this group. [34] The official eligibility criteria for HSCT-GT include also that late-infantile patients should be completely pre-symptomatic and early-symptomatic early-juvenile patients should be treated before the onset of cognitive decline. Factors like rate of decline, age at onset, daily functioning, support network, and the ability to understand and comply with treatment procedures were considered but not formally documented. Future panels should incorporate these details into registration and minutes, ensuring criteria remain dynamic and based on the latest scientific insights.

In a substantial part (44 %) of the panel discussions, a neuropsychological assessment and full-scale IQ was not available at the time of the panel meeting. Logistic challenges regarding scheduling all relevant clinical assessments and the urgency to make treatment decisions may be explanations Besides that, the importance of assessing a full-scale IQ in MLD patients as early as possible in the diagnostic pathway gained more attention only relatively recently with the introduction of HSCT-GT. [16].

The most challenging patient group were the late-juvenile and adult MLD patients with borderline to significant cognitive impairments. Those patients typically still function relatively well in daily life but already show severe deficits during neuropsychological assessment around the time of the diagnosis. The results show that the panel did not strictly apply the total IQ $\geq$ 85 cut-off when HSCT was recommended. This is partially explained by the fact that MLD patients often have disharmonic intelligence profiles with severely affected processing speed while verbal comprehension is relatively preserved. This leads to relatively low total IQ scores compared to patients' verbal abilities. More guidance on neuropsychological assessments and profiles in complex neurodegenerative diseases such as leukodystrophies is therefore necessary. In addition, investigating the predictive value of biomarkers as quantitative MRI parameters and neurofilament light chain protein in larger cohorts of patients is important. [35-37].

The rationale behind using strict IQ cut-offs as a criterion for treatment eligibility deserves further consideration, especially in late-onset MLD. It may be better to focus on comprehensive counseling, where

Table 4
Complex cases. Five cases (1–5) with a positive treatment recommendation despite TIQ <85 and 4 cases (6–9) without a consensus-based recommendation.

Case	MLD subtype	Cognitive assessment	Considerations and recommendation	Follow-up
1	4,5 year old, pre-symptomatic, uncertain subtype	• Primary developmental delay • Total IQ 55.	Treatment with HSCT or HSCT-GT is recommended. Timing of treatment depends on onset. Monitoring until subclinical evidence for onset is recommended. The expected benefits and risks need to be realistically balanced and discussed.	Being monitored, not yet treated.
2	Adult	• Total IQ: 76 • Working memory index: 70 • Verbal comprehension index: 95 • Perceptual reasoning index: 72 • Processing speed: 76	HSCT is recommended if comprehensive counseling is done and a compatible donor is found. The patient appears to be clinically stable, is largely independent in daily living activities, and maintains a job. Some executive dysfunction, including difficulties in managing money responsibly, is present.	HSCT performed. Stable 28months after meeting, 16 months after treatment.
3	Late-juvenile	• Verbal IQ: 84 • Performance IQ: 60 • Working memory index: 67.	This patient is considered mildly symptomatic, and HSCT is recommended. Total IQ was stable over the past three months.	HSCT performed. Stable 20months after meeting, 18 months after treatment.
4	Late-juvenile	• Verbal IQ: 89 • Performance IQ: 96 • Working memory index: 94 • Processing speed: 56	This patient is considered early-symptomatic, and treatment with HSCT-GT within a clinical trial is recommended but not available. There are doubts whether HSCT will be efficacious and timely enough. The panel emphasizes the need for appropriate counseling of the family concerning HSCT, including the high probability of (rapid) deterioration before a potential stabilization.	HSCT performed. Too early for a follow-up.
5	Adult	• Total IQ: 71 • Verbal comprehension index: 95 • Perceptual reasoning index: 79 • Working memory index: 67 • Processing speed: 45	Treatment with HSCT is recommended. The patient appears to be slowly progressive, is largely independent in activities of daily living, and maintains household activities and care for a child. It is difficult to predict whether the patient will deteriorate and become ADL-dependent or will stay relatively stable after treatment. This uncertainty should be part of the treatment counseling.	HSCT performed. Patient deteriorated from GFMC-MLD 0 to 2 and experiences increasingly emotional and cognitive difficulties in daily life during the 36 months after treatment.
6	Adult	• After the meeting full scale IQ testing was done. • Total IQ: 83 • Verbal IQ: 88 • Performance IQ: 82 • Processing speed index: 86	A mild cognitive decline is observed and the MRI abnormalities are relatively mild. Half of the panel recommended to decide upon reviewing the IQ and half of the panel recommended HSCT after comprehensive counseling. No consensus-based recommendation could be formulated. No full IQ testing was done (which was recommended by the panel).	HSCT performed and rapid deterioration <6 months after treatment.
7	Adult	• Total IQ: 65 • Working memory index: 65 • Verbal comprehension index: 83 • Perceptual reasoning index: 75	No consensus-based recommendation is formulated. There is doubt concerning the IQ test results due to discrepancy with reports of high functionality in daily life. It is generally concluded that HSCT may be beneficial and could be offered to the patient if strongly wished for, after critical counseling of the patient and family concerning the uncertain outcome and high risks. If the patient decides to pursue therapy, this should be timely initiated and the patient should be re-evaluated after a compatible donor is found. Should strong cognitive decline occur within 3–4 months, treatment should be aborted.	HSCT performed, too early for follow-up.
8	Late-juvenile		No consensus-based recommendation is formulated. No full IQ testing was done, but screening tests suggest an IQ of 79. Five panelists did not recommend HSCT, two panelists would suggest to offer HSCT given that the parents of the patient are counseled appropriately and informed about the risk of decline after the procedure.	Not treated. Stable 21months after meeting.
9	Adult	• Verbal comprehension index: 63 • Perceptual reasoning index: 52 • Working memory index: 45 • Processing speed: 45	No consensus-based recommendation is formulated. Generally, the panel is hesitant towards treatment because of the cognitive decline that is already present and due to the pregnancy-related delay.	Not treated. Deteriorated 34 months after meeting.

patients are informed about potential outcomes of both treatment and non-treatment options for functioning in daily life. In other medical fields, more advanced tools to support clinical decision-making have already been developed, such as Patients Like Me, where the outcome data of similar patients are presented in an easy-to-understand way. [38, 39] Similarly, in the context of MLD, working towards adequate counseling, where sketching a realistic projection of patient outcomes may prove more valuable than simply focusing on the likelihood of a

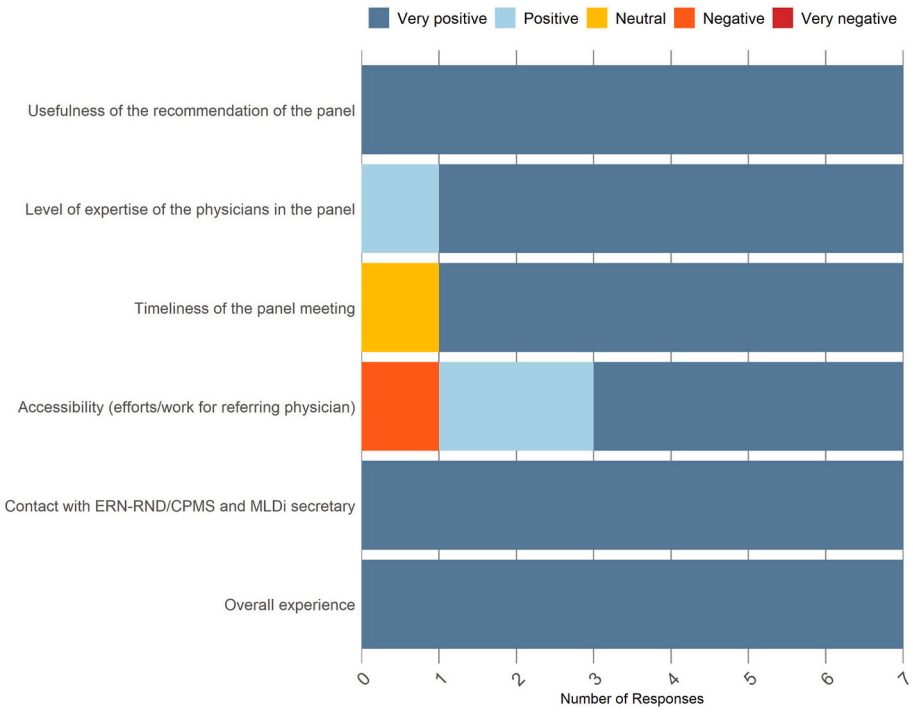

Fig. 3. Physicians' experiences.

"favourable" or "unfavourable" outcome. Importantly, such a tool should be developed within academic and patient advocacy initiatives without commercial interests.

The MLD eligibility panel was rapidly initiated when HSCT-GT as additional treatment option for MLD emerged and has turned out to be a valuable tool in navigating intricate treatment decisions. The results of the evaluation of the panel emphasize that treatment decisions of this degree of complexity require a thorough understanding of the medical and ethical nuances and should be guided by physicians with the expertise in MLD and its treatments. This study demonstrates that physicians, with support of experienced colleagues, can make well-considered choices including refraining from providing therapy when it is medically futile. In the near future, cases identified through newborn screening will gain the attention of the panel, especially to discuss treatment timing. [17,40] Continuous evaluation of case outcomes and panel recommendations is necessary to improve panel counseling and ensure alignment with the latest scientific insights. This approach may also serve as a template for clinical decision making in other complex rare disorders.

Authors' contributions

DHS, NIW, HG, and TM established the MLD treatment eligibility panel and designed this study. HD was involved in the design of the study as a patient advocate. DHS, NIW, TM, MABCA, MD, SB, and CEMH were part of the operational team of the MLD treatment eligibility panel. DHS drafted the manuscript, performed the analysis, and created the figures under the supervision of NIW. Referring physicians that presented the cases, obtained informed consent, and collected clinical information were MIF, SG, CK, AØ, CS, FF, CGB, PV, AB, JU, MAH, KB, ES, HP, RL, EAE, FM, and NIW. MLD experts who took part in the panel in varying compositions were: SG, AØ, CS, CAL, CK, FF, CGB, AB, EAE, FM, LAA, LL, JJB, VC, AD, AG-C, AZ, SWG, PMH, SAJ, TJK, DR, LS, and NIW. The manuscript has been reviewed and provided with feedback from all authors. All authors approved the final version of this manuscript.

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References

[1] C.L. Mackall, C.M. Bollard, N. Goodman, C. Carr, R. Gardner, R. Rouce, et al., Enhancing pediatric access to cell and gene therapies, Nat Med 30 (7) (2024) 1836–1846.
[2] A. Deticek, I. Locatelli, M. Kos, Patient access to medicines for rare diseases in European countries, Value Health 21 (5) (2018) 553–560.
[3] R.A. Vreman, H. Naci, W.G. Goettsch, A.K. Mantel-Teeuwisse, S.G. Schneeweiss, H. G.M. Leufkens, et al., Decision making under uncertainty: comparing regulatory and health technology assessment reviews of medicines in the United States and Europe, Clin. Pharmacol. Ther. 108 (2) (2020) 350–357.
[4] EURORDIS, Access to Affordable Medicines for Rare Diseases – towards an Equitable European Ecosystem, 2021.
[5] B. Tumiene, H. Graessner, Rare disease care pathways in the EU: from odysseys and labyrinths towards highways, J Community Genet 12 (2) (2021) 231–239.
[6] M. Cesani, L. Lorioli, S. Grossi, G. Amico, F. Fumagalli, I. Spiga, et al., Mutation update of ARSA and PSAP genes causing metachromatic leukodystrophy, Hum. Mutat. 37 (1) (2016) 16–27.
[7] S.C. Chang, A. Bergamasco, M. Bonnin, T.A. Bisono, Y. Moride, A systematic review on the birth prevalence of metachromatic leukodystrophy, Orphanet J. Rare Dis. 19 (1) (2024) 80.
[8] C. Kehrer, S. Elgun, C. Raabe, J. Bohringer, S. Beck-Wodl, A. Bevot, et al., Association of age at onset and first symptoms with disease progression in patients with metachromatic leukodystrophy, Neurology 96 (2) (2021) e255–e266.
[9] M. Trinidad, X. Hong, S. Froelich, J. Daiker, J. Sacco, H.P. Nguyen, et al., Predicting disease severity in metachromatic leukodystrophy using protein activity and a patient phenotype matrix, Genome Biol. 24 (1) (2023) 172.
[10] V. Santhanakumaran, S. Groeschel, K. Harzer, C. Kehrer, S. Elgun, S. Beck-Wodl, et al., Predicting clinical phenotypes of metachromatic leukodystrophy based on the arylsulfatase A activity and the ARSA genotype? - chances and challenges, Mol Genet Metab 137 (3) (2022) 273–282.
[11] S. Groeschel, J.S. Kuhl, A.E. Bley, C. Kehrer, B. Weschke, M. Doring, et al., Long-term outcome of allogeneic hematopoietic stem cell transplantation in patients with juvenile metachromatic leukodystrophy compared with nontransplanted control patients, JAMA Neurol. 73 (9) (2016) 1133–1140.
[12] D.F. van Rappard, J.J. Boelens, M.E. van Egmond, J. Kuball, P.M. van Hasselt, K. J. Oostrom, et al., Efficacy of hematopoietic cell transplantation in metachromatic leukodystrophy: the Dutch experience, Blood 127 (24) (2016) 3098–3101.
[13] A.A. Boucher, W. Miller, R. Shanley, R. Ziegler, T. Lund, G. Raymond, et al., Long-term outcomes after allogeneic hematopoietic stem cell transplantation for metachromatic leukodystrophy: the largest single-institution cohort report, Orphanet J. Rare Dis. 10 (2015) 94.
[14] J. Beschle, M. Doring, C. Kehrer, C. Raabe, U. Bayha, M. Strolin, et al., Early clinical course after hematopoietic stem cell transplantation in children with juvenile metachromatic leukodystrophy, Mol Cell Pediatr 7 (1) (2020) 12.
[15] A. Biffi, E. Montini, L. Lorioli, M. Cesani, F. Fumagalli, T. Plati, et al., Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy, Science. 341 (6148) (2013) 1233158.
[16] F. Fumagalli, V. Calbi, M.G. Natali Sora, M. Sessa, C. Baldoli, P.M.V. Rancoita, et al., Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access, Lancet 399 (10322) (2022) 372–383.
[17] L. Laugwitz, D.H. Schoenmakers, L.A. Adang, S. Beck-Woedl, C. Bergner, G. Bernard, et al., Newborn screening in metachromatic leukodystrophy - European consensus-based recommendations on clinical management, Eur. J. Paediatr. Neurol. 49 (2024) 141–154.
[18] D.H. Schoenmakers, F. Mochel, L.A. Adang, J.J. Boelens, V. Calbi, E.A. Eklund, et al., Inventory of current practices regarding hematopoietic stem cell transplantation in metachromatic leukodystrophy in Europe and neighboring countries, Orphanet J. Rare Dis. 19 (1) (2024) 46.
[19] Schoenmakers DH, Wolf N.I., Van Hasselt P., Lindemans C. . Dutch doctors on the reimbursement decision for Libmeldy: patients with this rare disease lose out 2023 [Available from: https://medicijnvoordemaatschappij.nl/no-reimbursement-libmeldy/.
[20] MLDi. Treatment eligibility panel [Available from: https://www.mldinitiative.com/for-professionals/treatment-eligibility/.
[21] C. Reinhard, A.C. Bachoud-Levi, T. Baumer, E. Bertini, A. Brunelle, A.I. Buizer, et al., The European reference network for rare neurological diseases, Front. Neurol. 11 (2020) 616569.
[22] Clinical Patient Management System (CPMS) [IT Platform for Clinical Consultations between ERN Members]. Available from: https://cpms.ern-net.eu/.
[23] C. Edc, Castor Electronic Data Capture, 2019.
[24] C. Kehrer, G. Blumenstock, C. Raabe, I. Krageloh-Mann, Development and reliability of a classification system for gross motor function in children with metachromatic leucodystrophy, Dev. Med. Child Neurol. 53 (2) (2011) 156–160.
[25] EMA, Libmeldy - Autologous CD34+ Cells Encoding ARSA Gene, European Medicines Agency, 2020. www.ema.europe.eu. (Accessed 5 July 2021). https://www.ema.europa.eu/en/medicines/human/EPAR/libmeldy.
[26] OTL-200 in Patients With Late Juvenile Metachromatic Leukodystrophy (MLD) - NCT04283227: Orchard Therapeutics; [Available from: https://clinicaltrials.gov/study/NCT04283227.
[27] Z.S. Nasreddine, N.A. Phillips, V. Bedirian, S. Charbonneau, V. Whitehead, I. Collin, et al., The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment, J. Am. Geriatr. Soc. 53 (4) (2005) 695–699.
[28] Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the Application of Patients' Rights in Cross-Border Healthcare. [Internet]. Available from: https://eur-lex.europa.eu/eli/dir/2011/24/oj.
[29] X. Chen, D. Gill, P. Shaw, R. Ouvrier, C. Troedson, Outcome of early juvenile onset metachromatic leukodystrophy after unrelated cord blood transplantation: a case series and review of the literature, J. Child Neurol. 31 (3) (2016) 338–344.
[30] L.D. de Hosson, B.P. van de Warrenburg, F.W. Preijers, N.M. Blijlevens, B.A. van der Reijden, H.P. Kremer, et al., Adult metachromatic leukodystrophy treated by allo-SCT and a review of the literature, Bone Marrow Transplant. 46 (8) (2011) 1071–1076.
[31] F. Brinkhuis, W.G. Goettsch, A.K. Mantel-Teeuwisse, L.T. Bloem, High cost oncology drugs without proof of added benefit are burdening health systems, BMJ 384 (2024) q511.
[32] Z. Zhang, H. Jiang, L. Huang, S. Liu, X. Zhou, Y. Cai, et al., Lentivirus-modified hematopoietic stem cell gene therapy for advanced symptomatic juvenile metachromatic leukodystrophy: a long-term follow-up pilot study, Protein Cell 16 (1) (2024) 16–27.
[33] D.H. Schoenmakers, S. Beerepoot, L.A. Adang, M.A.B.C. Asbreuk, C.G. Bergner, A. E. Bley, et al., Gene therapy in advanced metachromatic leukodystrophy: tempering expectations, Protein Cell 16 (1) (2024) 12–15.
[34] Beerepoot DHS. Shanice, Francesca Fumagalli, Samuel Groeschel, Ludger Schöls, Raphael Schiffmann, Sheila Wong, Odile Boespflug-Tanguy, Caroline Sevin, Yann Nadjar, Annette Bley, Fanny Mochel, Morten A. Horn, Cristina Baldoli, Sara Locatelli, Holger Hengel, Lucia Laugwitz, Carla E.M. Hollak, Volkmar Gieselmann, Marjo S. van der Knaap, Nicole I. Wolf, ARSA Variants Associated with Cognitive Decline and Long-Term Preservation of Motor Function in Metachromatic Leukodystrophy - Submitted Manuscript, 2024.
[35] S. Beerepoot, H. Heijst, B. Roos, M.M.C. Wamelink, J.J. Boelens, C.A. Lindemans, et al., Neurofilament light chain and glial fibrillary acidic protein levels in metachromatic leukodystrophy, Brain 145 (1) (2022) 105–118.
[36] D.F. van Rappard, A. Klauser, M.E. Steenweg, J.J. Boelens, M. Bugiani, M.S. van der Knaap, et al., Quantitative MR spectroscopic imaging in metachromatic leukodystrophy: value for prognosis and treatment, J. Neurol. Neurosurg. Psychiatry 89 (1) (2018) 105–111.

[37] S. Groeschel, C. i Dali, P. Clas, J. Bohringer, M. Duno, C. Krarup, et al., Cerebral gray and white matter changes and clinical course in metachromatic leukodystrophy, Neurology 79 (16) (2012) 1662–1670.
[38] J. Frost, M. Massagli, PatientsLikeMe the case for a data-centered patient community and how ALS patients use the community to inform treatment decisions and manage pulmonary health, Chron. Respir. Dis. 6 (4) (2009) 225–229.
[39] C.M. Cramer-van der Welle, E.A. Kastelijn, B.C. Plouvier, C.F. van Uden-Kraan, F. Schramel, H.J.M. Groen, et al., Development and evaluation of a real-world outcomes-based tool to support informed clinical decision making in the palliative treatment of patients with metastatic NSCLC, JCO Clin Cancer Inform 5 (2021) 570–578.
[40] L. Laugwitz, T.P. Mechtler, N. Janzen, P. Oliva, A.R. Kasper, C.E. Teunissen, et al., Newborn screening and presymptomatic treatment of metachromatic leukodystrophy, N. Engl. J. Med. 391 (13) (2024) 1256–1258.