



## ORIGINAL ARTICLE OPEN ACCESS

# Palliative Care for Children and Adults With Inherited Metabolic Disease in Europe: An Underutilised Service for Supportive Treatment and Care

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## ABSTRACT

Palliative care should be an integral part of follow-up for patients with life-limiting/life-threatening conditions, irrespective of age and diagnosis. Many patients with inherited metabolic disorders (IMD) have palliative care needs due to multi-systemic conditions without curative treatment options. To map the organisation and accessibility of palliative care across European IMD expert centres, and to explore the experiences of IMD physicians with palliative care, the European Reference Network for Hereditary Metabolic Disorders (MetabERN) invited physicians from all 103 member institutions to participate in a survey covering various aspects of palliative care. Ninety-two physicians from 63 institutions in 23 countries participated. A national plan or strategy for palliative care had been established in most countries (87%). Both children (91%) and adults (89%) had access to palliative care services. Most paediatric (86%) and many adult IMD physicians (67%) used advance care planning. A total of 284 referrals to palliative care were reported, mostly IMD patients with lysosomal and mitochondrial disorders, and neurological, respiratory, cognitive and gastrointestinal comorbidities. However, during the past 5 years, the majority of physicians (60%) had referred 20% or fewer of their deceased patients to palliative care. Although palliative care is available in most European IMD expert centres, only a small proportion of deceased IMD patients has been referred. The findings of this study indicate both a misconception and underutilisation of modern palliative care services. Addressing existing barriers is essential, and both IMD physicians and patients may need more information about available palliative care services and up-to-date indications for referral.

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## 1 | Introduction

Palliative care focuses on improving the quality of life of patients, their families and caregivers in the face of health-related suffering [1]. Paediatric palliative care includes children (age <18 years) living with life-limiting or life-threatening conditions [2].

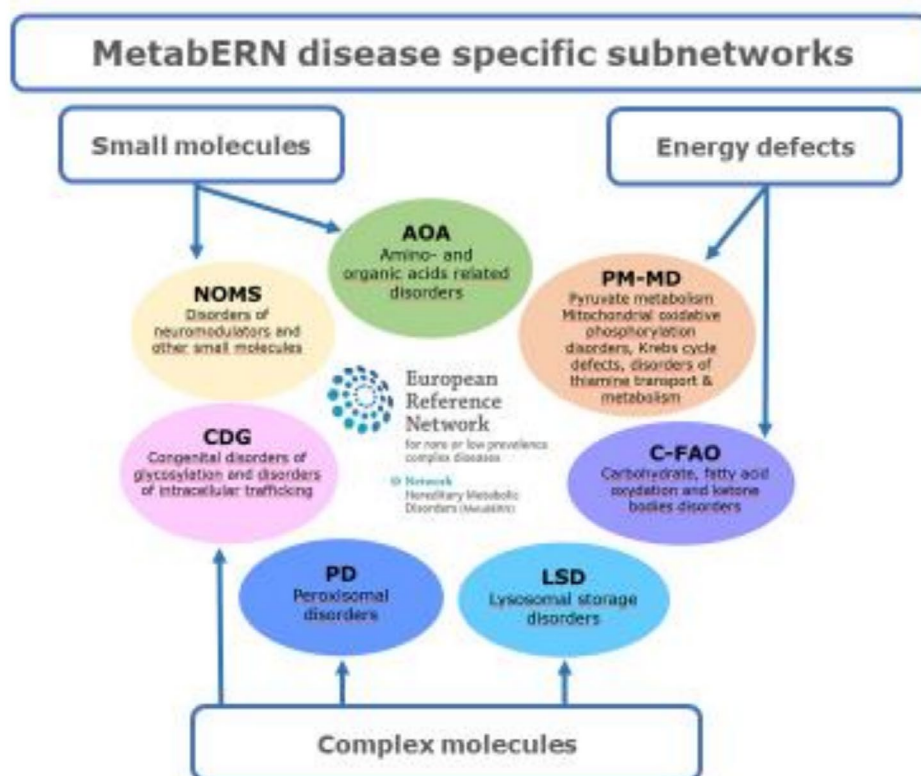
Inherited metabolic diseases (IMD) are genetic disorders causing disruption of metabolic pathways, cell trafficking and transportation [3]. The European Reference Network for Hereditary Metabolic Disorders (MetabERN) is one of the 24 European Reference Networks established by the European Commission in 2017 to facilitate access to the best available care and address cross-border needs for all patients with IMDs and their families in the EU [4, 5]. MetabERN consists of nationally certified health care partners and patient organisations from 27 European countries and is endorsed by the Society for the Study of Inborn Errors of Metabolism (SSIEM). Given the complexity of the IMD field, metabolic disorders have been divided into seven disease specific subnetworks (SNWs) within MetabERN, as illustrated in Figure 1 [6].

Globally, the birth prevalence of IMD is around 50/100,000 live births [7]. Since Sir Archibald Garrod's discovery of alkaptonuria [8], more than 1900 IMDs have been identified, with an exponential rise in the last decade following the application of new technologies [9–11]. A genomics-first diagnostic approach allows early detection of several conditions even in the absence of biochemical markers. However, curative treatment options may still be limited despite early diagnosis [12–15].

Children with congenital and neurological conditions represent the largest group in need of paediatric palliative care [16, 17]. Paediatric patients with IMD in hospital-based paediatric palliative care programs are reported to constitute between 7.2% and 19.7% of the patient population [18–20]. These patients constitute part of an expanding palliative care population [17, 21–23] with needs that may differ from those of cancer patients, especially regarding symptomatic and multidisciplinary management of neurological manifestations [24–27]. Improved disease directed and symptomatic treatment may improve life expectancy rendering more patients eligible for palliative care [13, 28–30]. Outcome may be improved by means of strict dietary interventions, enzyme replacement therapy and organ or haematopoietic stem cell transplantation, but more research is needed to determine the effects of such therapies on quality of life [31]. We know that patients with intoxication and energy metabolism disorders and their parents live with a constant threat of potentially devastating metabolic decompensations [30].

Around 40% of IMD patients are diagnosed after age 16 years [28, 32, 33]. A German study showed an annual increase of 200 patients in their adult metabolic centres [34], while a recent study by SSIEM found that the patient cohort cared for by 15 European adult IMD centres had increased by 34% since 2014 [33]. The increasing need for integrated services in the field of adult IMDs has recently been documented in 'The Statement of Udine' [35].

Palliative care research regarding adults with IMD is scarce, although these patients are encompassed by the definition of palliative care [36]. Studies have assessed the social, medical and psychological needs of IMD patients [37–39], but to our



**FIGURE 1** | Subgroups of diseases as defined by MetabERN subnetworks, combined with the simplified classification by Saudubray et al.

knowledge, no studies have focused on how the palliative care needs of these patients are met within expert centres in Europe.

To understand the current availability and practice of palliative care for IMD patients in Europe, a MetabERN working group distributed a survey across all member institutions, with the aims: (1) to obtain an overview regarding access to and organisation of palliative care services for paediatric and adult IMD patients, and (2) to explore the metabolic physician's experiences with palliative care for their patients.

## 2 | Methods

### 2.1 | Study Design

In this cross-sectional study, questionnaires were sent to all of 103 European MetabERN centres across 27 countries between July 15th 2023 and October 5th 2023. Questionnaires were distributed to paediatric and adult IMD physicians, and to collaborating physicians in Georgia, Bulgaria and Turkey. The survey was administered by the MetabERN coordination team, including two reminders.

### 2.2 | Data Collection

An online questionnaire was used for data collection. The survey template was designed by the principal authors between November 2022 and July 2023 and underwent multiple revisions within the MetabERN Working Group on Palliative Care. Feedback was obtained from SNW experts, patient representatives from the MetabERN peroxisomal SNW, and leading paediatric palliative care professionals in Europe.

The questionnaire consisted of 60 items covering 10 domains:

- a. Demographics of participating physicians
- b. Organisation of palliative care services at a national level
- c. Organisation of palliative care education at a national level
- d. Access and referral to palliative care services for IMD patients
- e. Transition of care from paediatric to adult palliative care services
- f. Palliative care services available in designated area of the IMD centre
- g. Availability of ambulatory palliative care services
- h. Proportion of IMD patients eligible for palliative care
- i. Advance care planning for IMD patients
- j. Reports on individual patients (up to 10 anonymous cases)

The survey was available in English and is included in the Appendix A. Adult palliative care was defined according to the definition of the European Association of Palliative Care (2022) [40], whereas paediatric palliative care was defined according to the definition of the National UK Charity for Children's Palliative Care 'Together for Short Lives' [41]. Advance care

planning was defined as the process of delineating a holistic treatment and management plan (including goals of care and advance directives), developed in agreement with the family/patient, available in the medical record, and regularly revised [42]. Children and adolescents (hereafter referred to as children) were defined as patients < 18 years.

### 2.3 | Ethical Considerations

The questionnaire received approval from the Institutional Patient Review Board at Oslo University Hospital, confirming that patient anonymity would be safeguarded by only requesting the associated SNW-group affiliation of included patients, rather than specific diagnoses. Additionally, only broad age categories (above and below 18 years) and no information about gender was requested from respondents.

### 2.4 | Statistical Analysis

Descriptive analysis was conducted using counts and percentages.

## 3 | Results

Aim 1: To obtain an overview across MetabERN/European expert hospitals regarding access to palliative care services for paediatric and adult patients with IMD (Domains a–i).

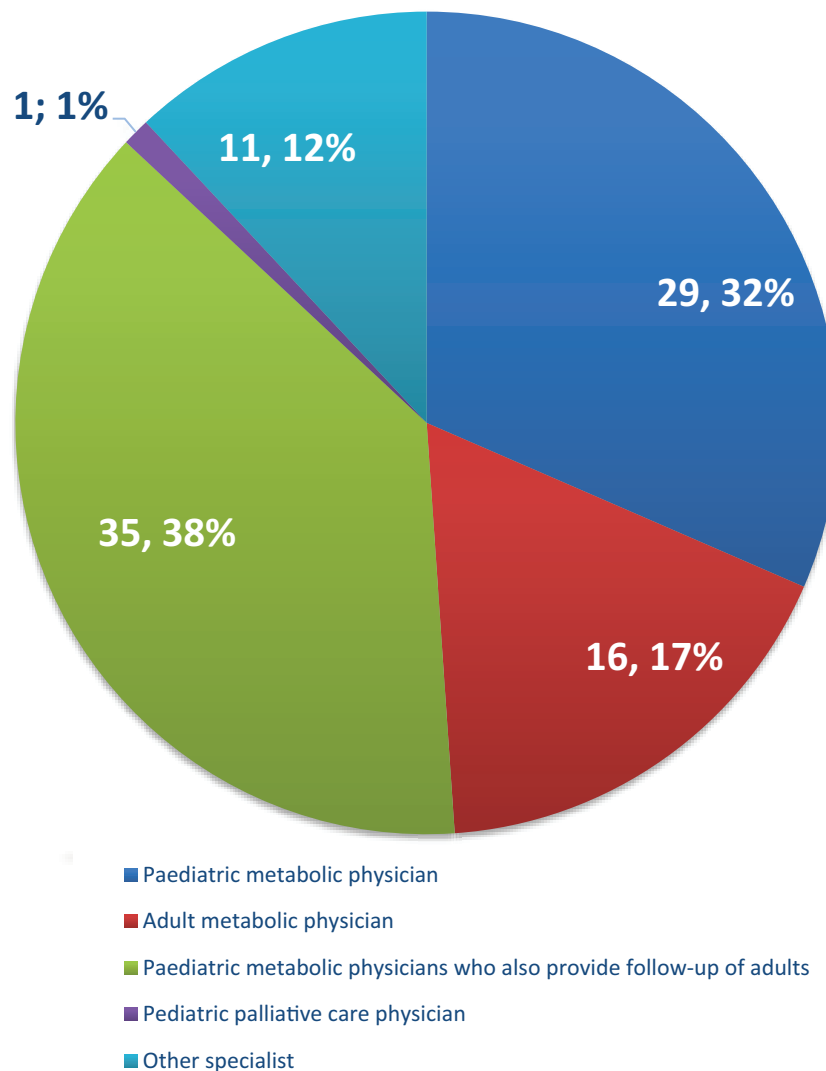
### 3.1 | Study Sample, Demographics (Domain a)

Ninety-two physicians from 63 IMD centres in 23 countries completed the questionnaire. The largest groups of respondents ( $n = 10–15$ ) represented 6–12 institutions in Italy, Portugal and Germany, whereas the second largest groups ( $n = 3–7$ ) represented 2–6 institutions in the Netherlands, Belgium, Spain, France, Norway and Denmark. The remaining countries were represented by one or two respondents each. Fifty-eight (93.5%) and four (6.5%) centres were full and affiliated MetabERN members, respectively. One centre was not a MetabERN member. Of the respondents (40% male), 65 (71%) were paediatricians and 27 (29%) were adult physicians. More than half of the metabolic paediatricians (35/64; 55%) also provided follow-up of adult patients. There was one paediatric palliative care physician among the respondents (Figure 2). Other specialists ( $n = 11$ ; 12%) included clinical geneticists ( $n = 3$ ), paediatric neurologists ( $n = 3$ ), paediatricians with a special interest in rare diseases ( $n = 2$ ), an adult endocrinologist ( $n = 1$ ), an internal medicine specialist ( $n = 1$ ) and a biochemical geneticist ( $n = 1$ ).

### 3.2 | Organisation of PC Services (Domain b)

#### 3.2.1 | National Plans and Clinical Guidelines

Respondents indicated that a national plan or strategy was established in 20/23 (87%) countries regarding paediatric (57/92; 62%) and/or adult palliative care (55/92; 60%; Table S1). One



**FIGURE 2** | Specialists ( $n=92$ ) providing follow-up of IMD patients in Europe: paediatric metabolic physician ( $n=35$ ; 38%), adult metabolic physician ( $n=16$ ; 17%), paediatric metabolic physician who also provides care for patients age  $> 18$  ( $n=29$ ; 32%), palliative care physician ( $n=1$ ), others ( $n=11$ ; 12%).

country had neither a national plan for paediatric nor adult palliative care but a national cancer plan with a section on palliative care for other diagnoses. Clinical guidelines for paediatric palliative care were available according to 49% of respondents (representing 15 countries), and for adult palliative care according to 40% of respondents (representing 14 countries).

### 3.3 | Organisation of Paediatric and Adult Palliative Care Education (Domain c)

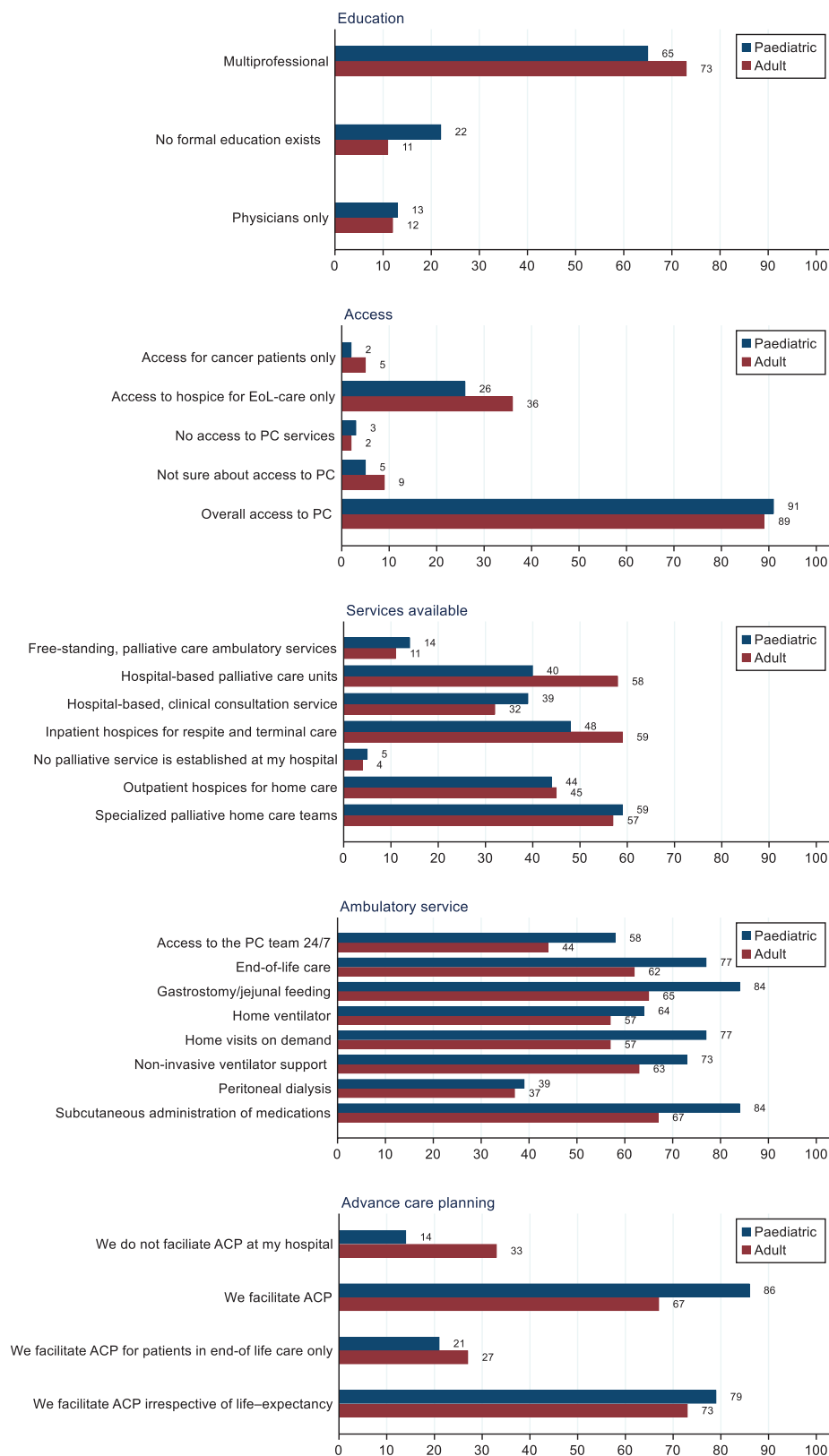
Many respondents indicated the presence of training programs for multi-professional participation regarding paediatric (65%) and adult (73%) palliative care. Some respondents (13%) reported having training programs especially for physicians, whereas 22% (representing nine countries) and 11% (representing five countries) stated that there was no formal education for either paediatric or adult palliative care, respectively, in their countries (Figure 3 and Table S1).

### 3.4 | Access and Referral to Palliative Care Services for IMD Patients (Domain d)

According to about 90% of respondents, both paediatric and adult IMD patients had access to palliative care services (Figure 3 and Table S1) and the majority of patients were eligible for palliative care regardless of diagnosis (paediatric palliative care in 85%; adult palliative care in 77% of responses). However, about one-third stated that children and adults had access to end-of-life care only. A few physicians reported that palliative care services were available exclusively for cancer patients. In most cases (76%), patients were referred to palliative care by an in-hospital specialist (Table S1).

### 3.5 | Transition From Paediatric to Adult Palliative Care Services (Domain e)

About half of the respondents (47/92; 51%) transferred paediatric IMD patients in need of palliative care to adult palliative care services at age 16–18 years (Table S1). Twenty percent of respondents



**FIGURE 3** | National plans and clinical guidelines regarding palliative care. Bars represent percentages of 92 survey respondents, answering on behalf of paediatric (blue bars) and adult (red bars) IMD patients.

stated that adult IMD patients remained in the care of paediatricians if diagnosed in childhood. Some commented that if life expectancy was limited to a few years, patients were more likely to

remain in the care of the paediatric palliative care team. About one-third of respondents confirmed that the transition from paediatric to adult palliative care service was non-existent (Table S1).



### 3.6 | Availability of Palliative Care Services Within the Designated Area (Domain f)

Various palliative care services were available to paediatric and adult IMD patients (Figure 3 and Table S1). Respondents commented that most adult palliative care services had been established around the beginning of the century, while the majority of paediatric palliative care services were developed between 2016 and 2018. A few paediatric palliative care services in Italy and Germany had been established in 2000 and 2004, respectively. In some countries, palliative care programs varied substantially between regions, and in some institutions, paediatric palliative care had initially been accessible exclusively to paediatric cancer patients.

### 3.7 | Ambulatory Palliative Care Services (Domain g)

More paediatric than adult palliative care services were accessible twenty-four seven (58% vs. 44%), and various ambulatory practical support services (enteral and parenteral feeding, subcutaneous and intravenous administration of medications, peritoneal dialysis, life-sustaining ventilatory support), including end-of-life care, were generally more accessible to paediatric than adult palliative care patients (Figure 3 and Table S1).

### 3.8 | Proportion of IMD Patients Eligible for Palliative Care (Domain h)

Half of the IMD specialists caring for paediatric IMD patients (38/77; 49%) and two-thirds of those treating adult IMD patients (40/61; 66%) estimated that fewer than 10% of their patients fulfilled the definition of a life-limiting/life-threatening condition (Table S1). A third of paediatric and a quarter of adult physicians estimated that 10%–30% of their patients were eligible for palliative care, while 13% of paediatric and 5% of adult physicians reported that 30%–50% of their patients were eligible for palliative care (Table S1).

### 3.9 | Advance Care Planning for IMD Patients (Domain i)

Advance care planning was practised by 86% of paediatric and 67% of adult IMD physicians, respectively (Figure 3 and Table S2).

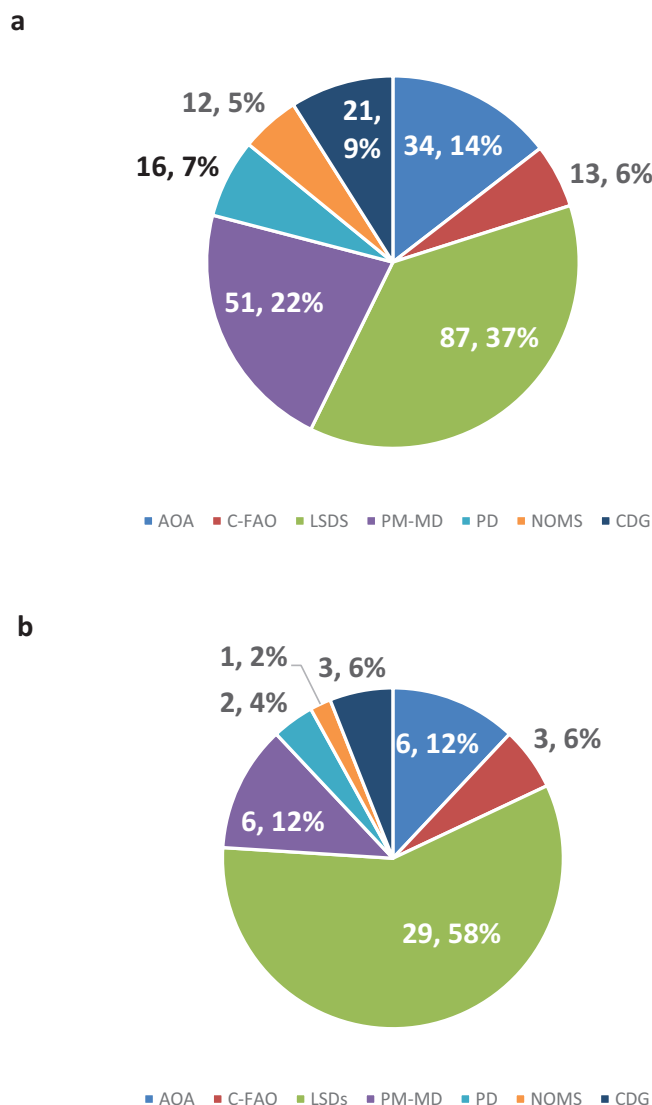
Aim 2: Experience of physicians with palliative care services for paediatric and adult patients with IMD.

Overall, 89% of respondents reported having referred at least one patient to palliative care during the past 5 years. Specifically, 36% had referred 1–5 patients, 25% had referred 6–10 patients, and 28% had referred 11–20 patients (Table S2). Regarding their deceased paediatric patients, 46% of respondents had referred 10% or fewer to palliative care during the last 5 years, whereas 35% had referred more than 50% of patients. Regarding adult patients, 43% of respondents had referred fewer than 10% of their deceased patients, whereas 22% had referred more than 50% to palliative care (Table S2). Among deceased children, home (26%), hospital ward (29%) and intensive care unit (25%) were

relatively evenly distributed locations of death. Adults more frequently died at home (35%) and less often in the intensive care unit (14%). Approximately 10% of respondents reported that both children and adults died in a hospice setting (Table S2).

### 3.10 | Reports on Individual Patients (Domain j)

During the past 5 years prior to the survey, respondents reported a total of 284 individual patients (234 children; 82%) who had been referred to palliative care. Patients with lysosomal storage diseases (LSDs) comprised the largest group both in children (87/234; 37%; Figure 4a; Tables 1 and 2) and adults (29/50; 58%; Figure 4b;



**FIGURE 4** | (a, b) Diagnosis groups stratified by MetabERN disease-specific subnetworks in 234 paediatric (a) and 50 adult IMD patients (b) referred to palliative care. Abbreviations: AOA, amino- and organic acid-related disorders; CDG, congenital disorders of glycosylation and disorders of intracellular trafficking; C-FAO, carbohydrate, fatty acid oxidation and ketone bodies disorders; LSDs, lysosomal storage disorders; NOMS, disorders of neuromodulators and other small molecules; PD, peroxisomal disorders; PM-MD, pyruvate metabolism mitochondrial oxidative phosphorylation disorders, Krebs cycle defects, disorders of thiamine transport and metabolism.

**TABLE 1** | Diagnosis groups of 284 reported patients ( $n = 234$  children; 50 adults), categorised according to the MetabERN SNWs.

Patients	Life expectancy	AOA ( $n$ )	C-FAO ( $n$ )	LSDs ( $n$ )	PM-MD ( $n$ )	PD ( $n$ )	NOMS ( $n$ )	CDG ( $n$ )	Total ( $n$ )
	> 6 months (%)								
Paediatric	71	34	13	87	51	16	12	21	234
Adult	68	6	3	29	6	2	1	3	50
Total		40	16	117	56	18	13	24	284

Abbreviations: AOA, amino- and organic acids related disorders; CDG, congenital disorders of glycosylation and disorders of intracellular trafficking; C-FAO, carbohydrate, fatty acid oxidation and ketone bodies disorders; LSDs, lysosomal storage disorders; NOMS, disorders of neuromodulators and other small molecules; PD, peroxisomal disorders; PM-MD, pyruvate metabolism mitochondrial oxidative phosphorylation disorders, Krebs cycle defects, disorders of thiamine transport and metabolism; SNWs, subnetworks.

**TABLE 2** | Diagnosis groups of 284 reported patients, categorised according to the simplified classification by Saudubray et al.

Small molecules, $n$ (%)		Complex molecules, $n$ (%)		Energy defects, $n$ (%)	
AOA	40 (14.1)	LSDs	117 (41)	C-FAO	16 (5.6)
NOMS	13 (4.6)	CDG	24 (8.5)	PM-MD	56 (19.7)
		PD	18 (6.3)		
Total	53 (18.7)		159 (56)		72 (25.3)

Abbreviations: AOA, amino- and organic acid-related disorders; CDG, congenital disorders of glycosylation and disorders of intracellular trafficking; C-FAO, carbohydrate, fatty acid oxidation and ketone body disorders; LSDs, lysosomal storage disorders; NOMS, disorders of neuromodulators and other small molecules; PM-MD, pyruvate metabolism mitochondrial oxidative phosphorylation disorders, Krebs cycle defects, disorders of thiamine transport and metabolism; PD, peroxisomal disorders.

Tables 1 and 2), followed by those with disorders related to the PM-MD SNW (disorders of pyruvate metabolism and mitochondrial oxidative phosphorylation, Krebs cycle defects, and disorders of thiamine transport and metabolism) (Figure 4a,b; Tables 1 and 2). Patients with amino and organic acid related disorders were the third largest group comprising 14% and 12% of paediatric and adult patients in palliative care, respectively (Figure 4a,b; Tables 1 and 2). Patients with a diagnosis in any of the remaining SNWs collectively accounted for 25% (Figure 4a,b and Table 2).

Regardless of age group, around 70% of patients had an estimated life expectancy of more than 6 months at the time of referral (Table 1). The main reason for referral of paediatric patients was symptom burden (76%; Figure 5), while for adult patients it was short life expectancy (68%; Figure 5). Other reasons were evenly distributed for children and adults (Figure 5). More than a third of patients (38%–42%; Figure 5) were referred due to a need for social assistance or because the physician sought advice on advance care planning. A small proportion of physicians (5%) sought a second opinion regarding life-sustaining treatment (Figure 5). Some respondents commented that assistance from the palliative care team was crucial for parental psychological support and for provision of bereavement resources.

Neurological symptoms, especially seizures and dystonia, were the most frequently reported manifestations of IMD, affecting over 75% of both children and adults referred to

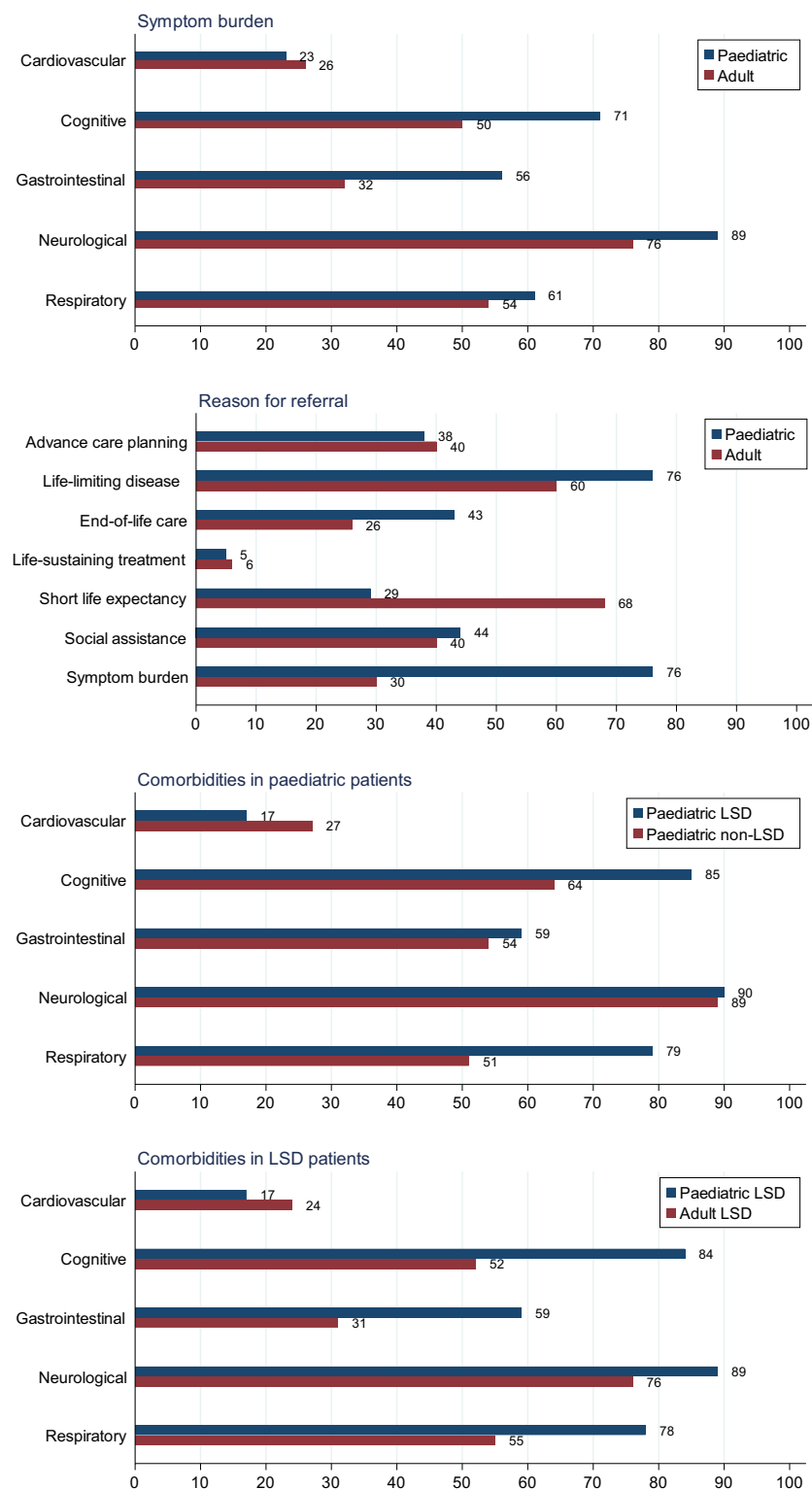
palliative care (Figure 5). Cognitive, respiratory, and gastrointestinal comorbidities were also prevalent among these patients (Figure 5). Additional contributing factors included orthopaedic and skeletal issues, secondary cancer, nutritional problems, treatment failure and multi-morbidity. When paediatric IMD patients in palliative care were stratified according to LSDs versus other IMDs, neurological comorbidity remained predominant in both groups, but respiratory and cognitive manifestations were relatively more frequently reported in patients with LSDs (Figure 5). When comparing paediatric and adult LSD patients, children appeared to be more affected by respiratory, neurological, cognitive and gastrointestinal comorbidities (Figure 5).

## 4 | Discussion

This study explored the organisation and accessibility of palliative care for paediatric and adult IMD patients across 63 MetabERN centres in 23 countries. According to the respondents of the survey, national plans or strategies for palliative care were available in 20 European countries. In countries where clinical guidelines or training programs for paediatric and adult palliative care were available, the majority of IMD patients had access to some kind of palliative care service. With reports on 284 IMD patients referred to palliative care, this study represents the largest European study on palliative care in IMD and the first to include both paediatric and adult IMD patients.

### 4.1 | Demographics of Participating Physicians (Domain a)

The majority of participating physicians were from Portugal, Italy and Germany. Germany was one of the first European countries to implement palliative care in health care services and to regulate by law the right to specialised palliative care [43]. Likewise, Italian citizens have a legal right to the best possible treatment of suffering (Law no. 38 of 2010), yet there seems to be unmet needs [44]. According to the Portuguese Association of Palliative Care, more than 70% of adult and 90% of paediatric patients do not have timely access to palliative care [45]. The many Portuguese, Italian and German survey respondents may indicate that there is a growing concern among physicians in these countries about the relative shortage of palliative care services [44, 46].



**FIGURE 5** | Symptom burden, reason for referral and comorbidities in patients with inherited metabolic disorders (IMD) reported in this survey. Bars represent percentages of 92 survey respondents, answering on behalf of paediatric (blue bars) and adult (red bars) IMD patients. Abbreviations: IMD, inherited metabolic disorders; LDS, lysosomal storage disorder.

The findings of this survey align with the results of a European regional analysis of palliative care integration indicators from 2021, which revealed that Germany and the Netherlands have the highest integration capacity score, Italy, Spain, France,

Belgium and Denmark are at an intermediate level, whereas Portugal, Sweden, and Norway have a low score, and Eastern European countries exhibit a very low integration capacity score [47].



## 4.2 | Organisation and Education (Domains b and c)

The four key components for integration of palliative care into existing health care systems are: (1) appropriate policies, (2) adequate drug availability, (3) education of healthcare workers and the public and (4) implementation of palliative care services [48]. The domains covered by this survey reflect upon these components, except for the availability of drugs typically used in palliative care (especially morphine), which is not a critical issue in most European countries [49–51].

While appropriate policies and national plans are established in most member countries of MetabERN, Eastern European countries have been slower to develop palliative care services [47, 52–54]. According to respondents of this survey, some western European countries also experience shortcomings regarding appropriate policies for implementation of palliative care.

A lack of palliative care training at basic, intermediate and specialist levels has been identified as a major barrier to accessing palliative care services [55]. In Germany, paediatric palliative care has been offered as an advanced, multi-professional course since 2005 [56], and increasing educational opportunities have led to a rise in palliative care services across all levels of care [57]. Multi-professional participation is recommended by several institutions, including the European Association of Palliative Care (EAPC) [58, 59]. Although this survey did not analyse the reasons behind the absence of palliative care training in three Eastern and two Central European countries, the lack of guidelines is unlikely to be the cause. Indeed, in 2013, the EAPC published a White Paper on core competencies in palliative care education for health and social care professionals [58], and several papers have reported on undergraduate [60–62], graduate [63] and postgraduate level palliative care education [55, 64].

Palliative care as a medical specialty is a relatively new field, especially regarding non-cancer patients, which is a patient group at risk of receiving a lower quality of palliative care than cancer patients [65, 66]. The consensus-based definition of palliative care that focuses on the relief of serious health-related suffering, regardless of age and diagnosis (2020) [1] is in line with the World Health Assembly resolution on palliative care, ‘Strengthening of Palliative Care as a Component of Comprehensive Care Throughout the Life Course’ (2014) [67], and the statements put forward by the Lancet Commission on Global Access to Palliative Care and Pain Relief (2018) [51]. The findings of this survey suggest that the modern concept of palliative care has not yet been fully adopted by IMD physicians, indicating a need to explore possible barriers. The gap between knowledge and behaviour is not unique to the field of IMD; similar discrepancies can be found in other fields of medicine [68–70].

## 4.3 | Access and Transition (Domains d and e)

In this survey, the implementation of palliative care services, the fourth key component for integration, was covered by four domains (d–g). Around 90% of respondents stated that both paediatric and adult patients had access to various palliative care

services. The countries where this was not the case were mostly the countries also lacking palliative care education.

Transition has been defined as ‘the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult-oriented health care systems’ [71]. As shown in this survey, and in accordance with previous studies [72, 73], far from all participating hospitals had a transition program within palliative care. Half of the respondents stated that paediatric IMD patients enrolled in palliative care services were transitioned to adult palliative care at the age of 16–18 years, whereas around 30% stated that patients in need of palliative care remained in paediatric care beyond the age of 18 years. However, in comparison with the first European study on transition for IMD patients, there seems to be an improvement towards more patients receiving timely transfer [72]. It was not within the scope of this study to investigate the transition process in more detail. Although patients and their caregivers highly value continuity of care, the fact that many young adult IMD patients remain in the care of paediatricians may inhibit the development of adult metabolic services [74]. In the clinical setting, the decision to transition or not should always be at the discretion of the responsible physician, tailor-made for each patient and in close dialogue with the patient and family.

## 4.4 | Availability of Hospital-Based and Ambulatory Palliative Care Services (Domains f and g)

This survey shows that hospital-based clinical consultation and ambulatory palliative care services in general are more prevalent for paediatric than for adult patients, while hospital-based palliative care units are more common for adult patients. Several factors may contribute to this discrepancy. Adult palliative care services originated from the hospice movement in the United Kingdom, where Dame Cicely Saunders founded the first hospice worldwide in 1967, integrating clinical care with education and research [75]. Hospital support teams for terminal care were established in the United Kingdom in 1976, followed by a growing number of hospital-based palliative care teams. In many European countries, specialised palliative care is provided in dedicated hospital units [49, 52].

Paediatric palliative care was first defined by the World Health Organization (WHO) in 1998 [76], and the WHO Guide to ‘Integrating palliative care and symptom relief into paediatrics’ was published in 2018 [77]. The principle of this integration is based on the numerous similarities that exist between general paediatrics and paediatric palliative care, such as the emphasis on continuity of care, integrated bio-psycho-social care, and caring for both the patient and the family. Thus, the development of paediatric palliative care builds upon already existing structures. This might explain why this survey found that ambulatory practical support including end-of-life care was more available to paediatric than adult IMD patients. Past studies have shown that children and adolescents prefer home to hospital, whenever appropriate healthcare can be delivered at home [78–81]. Home is often the preferred place for end-of-life care for both paediatric and adult patients [82, 83].

#### 4.5 | Eligibility of IMD Patients to Palliative Care (Domain h)

Somewhat unexpectedly, the majority of IMD specialists estimated that fewer than 10% of their patients had a life-limiting/life-threatening condition, thus being eligible for palliative care. This might be due to health care providers' lack of knowledge about the modern definition of palliative care [84]. However, 90% of respondents had referred at least one patient to palliative care during the past 5 years, the majority being patients diagnosed with LSDs and neurological, cognitive and respiratory comorbidities. Certainly, physicians' referral practices may vary according to the overall burden of their patient cohort. If the cohort mostly includes patients with preventable conditions detected by newborn screening, the patients may have fewer palliative care needs compared to those with symptomatic LSDs or mitochondrial disorders. According to the respondents, only a small proportion of patients who had died during the past 5 years had been referred to palliative care. In summary, these findings suggest that metabolic physicians have not fully embraced the potential benefits of access to palliative care for patients with a life-limiting/life-threatening disease, ideally initiated at the time of diagnosis [41].

#### 4.6 | Advance Care Planning for IMD Patients (Domain i)

Planning for future care in the setting of life-limiting/life-threatening conditions is not exclusively a tool for palliative care, but an essential part of patient-centred care [85]. Advance care planning includes the process of establishing overarching, long-term care goals and discussing life-sustaining treatments, taking into consideration prognostic information and patient/family values. Timely advance care planning has been shown to benefit paediatric and adult patients living with life-limiting/life-threatening conditions [86–91].

Most respondents of this survey, especially paediatricians, reported employing advance care planning. Thus, many metabolic physicians seem to have integrated key elements of palliative care, including shared decision making [85, 92]. For paediatric patients, advance care planning is often conducted with their parents. However, involving children in the process is recommended [93]. Studies have shown that young patients and their caregivers are not always on the same page regarding future treatment preferences [94]. Discussions about goals of care can lead to advance directives, enabling an overall plan for future treatment, as well as avoiding unwanted procedures and futile life-prolonging interventions at the end of life [95, 96].

Despite the benefits, barriers to advance care planning do exist [97–99]. A growing body of literature aims to guide health care providers to value advance care planning as a procedure that needs to be learned and repeatedly practised [92, 100–102]. Studies have shown that paediatric patients and their parents are more likely to have advance care planning discussions if they have been referred to palliative care [103], and that advance care planning is associated with improved parent-reported end-of-life outcomes for children, adolescents and young adults with complex chronic conditions [87].

#### 4.7 | Reports on Individual Patients (Domain j)

The respondents were asked to provide information about 1–10 of their IMD patients currently enrolled in palliative care (Tables 1 and 2). Most patients (56%) reported in this study were categorised with a disease within the group of complex molecules, which is the most prevalent patient group referred to palliative care, ranging from 48% to 65% in previous studies [19, 20, 24]. The second largest group was patients with disorders affecting energy metabolism, followed by patients with disorders of small molecules, including organic acidaemias and urea cycle defects.

Lysosomal storage disorders, mitochondrial disorders and organic acidurias, representing around 75% of the patients reported in this survey, are disease groups involving multiple organs, particularly the central nervous system. The most frequently reported comorbidities in these patients are neurological and cognitive [37, 104, 105]. Symptoms in this patient group include neuropathic pain [106–109], joint contractures and kyphosis/scoliosis [110], renal and cardiac failure and seizures [36]. However, there is significant heterogeneity between various LSDs, even among patients with the same disorder [37, 111]. Although these patients may experience challenges related to impaired intellectual capacity and communication, the approach to their care should remain consistent with that for all patients requiring palliative care; each patient is entitled to tailor-made, person-centred treatment and care—the hallmark of palliative care.

To avoid violating patient anonymity, only crude patient data were collected for this survey, limiting a granular overview of the patients' total symptom burden. Yet, the survey revealed a complex set of symptoms in IMD patients, clearly indicating a need for holistic palliative care to address the medical challenges, as well as the social, psychological and existential issues associated with severe, life-limiting/life-threatening disorders [39, 112, 113]. Apart from publications about the burden (on families and society) of adults living with IMDs [114, 115], reports on symptom burden in adult IMD patients are scarce [36, 116].

In this study, most patients had an estimated life expectancy of more than 6 months at the time of referral to palliative care. In line with WHO recommendations [77, 117], there is a clear benefit of early referral to palliative care [118–120], with 'early' meaning the patient is not imminently dying. Although most research on early involvement of palliative care has been carried out within oncology, other patient groups also benefit from early referral [121–124]. Generic trigger tools, such as the SPICT [125] for adult patients and the Paediatric Palliative Scoring Scale [126] for children with life-limiting/life-threatening conditions, could facilitate needs-based access to palliative care. Employment of such trigger tools may prevent unplanned hospital admissions and patient suffering [127].

How can IMD patients, regardless of age, benefit from palliative care? As shown in this study, these patients deal with a wide range of challenges due to their specific disorder, life-long treatments, adverse effects of treatment and the psychosocial burden for the patient, siblings, parents and caregivers [128–131]. With early referral, routine systematic screening of symptoms and needs, family-centred, holistic follow-up by a multidisciplinary

team, sibling and family support and bereavement care, IMD patients and their families could obtain better quality of both life [112, 124, 132] and death [87, 133, 134].

The reason that only 18% of patients referred to palliative care in this study were adults is most likely due to the composition of MetabERN. As reflected in both this and previous studies, MetabERN has a greater participation from paediatric metabolic physicians than adult specialists [39, 72]. A further explanation could be that adult IMD patients who survived childhood-onset disease overall may have milder phenotypes and that IMD patients first presenting in adulthood may have attenuated phenotypes compared to patients diagnosed with the same disorder during childhood.

#### 4.8 | Limitations of This Study

This survey reflected the practice of 61% of MetabERN centres. Although the findings may be representative for expertise centres, the results may not be generalised to all countries, regions and hospitals in Europe, particularly as Eastern European countries were underrepresented. Furthermore, the insights into national and organisational aspects of palliative care reported in this study are based on the knowledge of the responding clinicians, which may not fully reflect the accuracy of the information. The number of responding specialists from each country varied, and there were some conflicting responses among physicians from the same country, especially regarding organisational issues and access to various services for paediatric and adult patients. In the case of respondents working at the same institution, we cannot exclude an overlap regarding some of the reported cases.

#### 5 | Conclusion and Future Perspectives

This study shows that palliative care is a new element of care for both paediatric [19, 24, 25] and adult [36, 135, 136] IMD patients in Europe. Palliative care services are available in the majority of MetabERN expert hospitals, and the widespread use of advance care planning is a key indicator of a desired standard of care. Nevertheless, the results of this study demonstrate that palliative care services are underutilised by metabolic physicians. Identifying barriers of capability, opportunity, or motivation [137], closer integration [138] and the availability of palliative care expertise in clinical settings is crucial for fostering mutual knowledge exchange in order to improve quality of life for IMD patients and their families. Further studies are necessary to gain a deeper understanding of palliative care needs of IMD patients, especially from the perspective of patients and their caregivers.

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#### Conflicts of Interest

The authors declare no conflicts of interest.

#### Data Availability Statement

The data that supports the findings of this study are available in the [Supporting Information](#) of this article.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Characteristics of palliative care services. **Table S2:** Experiences of IMD specialists with palliative care services for their patients. **Appendix A:**