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The Frequencies of Different Inborn Errors of Metabolism in Adult Metabolic Centres: 10 Years Later, Another Report From the SSIEM Adult Metabolic Physicians Group

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ABSTRACT

There are still few centres, which specialise in the care of adults with inborn errors of metabolism (IEM). All physicians who participated in the SSIEM adult metabolic physicians group paper in 2014 were contacted to provide updated data on their IEM patients. Fifteen adult centres responded to our survey with information on their patients. Nine thousand, six hundred fifty-one patients were included in the final cohort, compared with 6182 in the previous analysis. There were 394 separate diagnoses. The most common diseases were phenylketonuria (19.6%), mitochondrial disorders (12.3%) and lysosomal storage disorders such as Fabry disease (20.1% of LSD's), Pompe disease (3.1%), and Gaucher disease (2.8%). Among the disorders that can present with acute metabolic decompensation, the urea cycle disorders (4.0%), were most common (ornithine transcarbamylase deficiency 2.6%), followed by maple syrup urine disease (1.1%) and glycogen storage disease type I (0.7%). Patients were frequently diagnosed as adults, particularly those with mitochondrial disease and lysosomal storage disorders. Many patients are only diagnosed in adulthood (>40%) and the cohort is increasing substantially with 9651 patients included in the final analysis (34% increase compared to our original paper). Thus reinforcing the need for adult specialists to be trained in this area.

1 | Introduction

The care of adults with inborn errors of metabolism (IEM) is an expanding sub-specialty due to the improved survival of children with classical IEM, the recognition of milder forms of disease diagnosed in adulthood, and late-onset disorders presenting in adulthood. Reflecting this increased interest, an Adult Metabolic Physicians working group of the Society for the Study of Inborn Errors of Metabolism (SSIEM) was formed in 2010 (http://www.ssiem.org/amp/welcome.asp). Clinical departments specialising in care for adult patient with IEM have developed in various countries; including large, centralised centres in the United Kingdom, Canada and the Netherlands, and national networks gathering many local centers such as in France the SFEIM-A—Société Française des Erreurs Innées du Métabolisme Adulte.

An initial study in 2014 was published detailing the patient cohort seen by 24 centres around the world [1]. This work described the different demographics of this cohort when compared with the traditional view of IEM seen through a paediatric lens. Many patients were diagnosed in adulthood (more than 40%), mitochondrial disorders were an important and prevalent part of the cohort, and the growth in patient numbers even over a short period of time was significant. The work also highlighted the range of clinical experience required to care for these patients, many of whom have disease specific treatment approaches and the potential to acutely decompensate.

This work extends our original study by providing a 10 year follow up data-set for 15 of those original centres.

2 | Methods

All physicians who participated in the SSIEM adult metabolic physicians group paper in 2014 were contacted to submit anonymised patient data including diagnosis, age group at diagnosis (unknown, newborn screen, neonatal (week 1 of life), infantile (0–2 years), childhood (3–10 years), juvenile (11–16 years), adult (> 16 years)), and current age. Methodology and definitions used were the same as those used in our 2014 publication. Data was also requested on whether patients were alive or deceased, and whether they were being actively followed in the clinic. Data was collected from databases held at each centre, as well as from the medical record from each individual patient. Initial data included all patients seen at each centre, hence a number of patients with diagnoses not traditionally categorised as IEM were submitted but subsequently excluded from the analysis (e.g., haemochromatosis and Beckwith-Wiedemann syndrome. An excluded diagnoses list is available from the authors on request). Patients submitted who were younger than 16 years were also excluded. Only patients with a biochemical or genetically confirmed diagnosis were included in the analysis, thus patients who were currently under investigation for a possible inborn error of metabolism were excluded. Data from Amsterdam were grouped by diagnosis as their ethical review board did not permit individual patient data to be submitted. Rotterdam now follow a large number of acute porphyria patients (292 including acute intermittent porphyria, hereditary coproporphyria and variegate porphyria patients), but data on these was not included as data collection on them was not possible at the time of final analysis. Not all centres were able to submit data detailing if patients were alive or being actively seen. Data was not submitted from Doha, Lille, Verona, Garches, Nancy, Grenoble, Angers, Strasbourg, Reims, Bordeaux or Caen who had participated in the earlier study. Data were submitted from Montpellier who had not participated in the original study.

Numbers of each disorder were counted and grouped into metabolic subtypes. The median current age and age group at diagnosis for each disorder were calculated. The numbers of patients alive, deceased or unknown were counted. The numbers of patients actively being seen were counted.

3 | Results

Fifteen centres responded with data on a total of 10 015 patients. Overall, 363 patients were excluded from analysis for diagnoses not within the IEM spectrum (for example; bone dysplasias, haemochromatosis) or for age less than 16 years, leaving 9 651 patients for final analysis. In total, 394 separate diagnoses were documented, although in some disorders there was the potential for overlap between different diagnoses or ambiguity; for example, 12 patients were labelled with hyperhomocystinaemia, 244 were labelled with homocystinuria and a single patient was labelled as homocystinuria and MTHFR deficiency (methylene tetrahydrofolate reductase deficiency). The final number of patients submitted from each centre varied from 137 to 1 478 (Table 1).

As expected, the most frequent disorder was phenylketonuria (PKU), representing 1 902 (19.7%) cases. The median age of PKU patients was 38 years, and diagnosis was predominantly in infancy. In addition to the PKU patients reported as diagnosed through newborn screening (NBS), most of the PKU patients that were labelled as diagnosed neonatally or in infancy have also most likely been diagnosed through NBS (reported by the centers as: 497 newborn screening (26%), 20 neonatal (1%), 720 infantile (38%), 394 unknown (21%)). Five PKU patients were diagnosed as juveniles and 53 as adults (2.8%). The next most common diagnosis was Fabry disease (813 patients, 8.4%), followed by adrenoleukodystrophy (X-ALD, 379 patients, 3.9%), and Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS, 360 patients, 3.7%). The 30 most common diagnoses are listed in Table 2.

Disorders of amino acid metabolism (3 384 patients, 35%) were the most frequent when data were analysed according to types of disease (Table 3). Lysosomal storage disorders (LSD's) were the next most prevalent (2 236 patients, 23%) and were predominately Fabry (813 patients, 8.4%), Gaucher (280 patients, 2.9%) and Pompe (also named GSD II) (298 patients, 3.1%) diseases.

The broad group of mitochondrial disorders was strongly represented with 1 188 patients (12%), using 77 separate mitochondrial diagnostic labels. Within these 1 188 patients, 106 did not have their phenotype described further, 371 (31%) had MELAS (m.3243A>G and unspecified mutation), 113 had m.3243A>G and 117 had Maternally inherited diabetes and deafness (MIDD)

TABLE 1 | Submitted patient numbers from each clinical centre.

Centre location	Number of patients with confirmed metabolic diagnoses in 2023	Percentage increase	Active cases	Number of patients with confirmed metabolic diagnoses in 2014
London, United Kingdom	1 478	4.2	1473	1 418
Amsterdam, Netherlands	1 284	114.0	822	600
Sydney, Australia	1 130	93.8	920	583
Nijmegen, Netherlands	1 089	143.6	874	447
Paris (Necker hospital), France	892	131.7	892	385
Vancouver, Canada	822	3.4	822	795
Rotterdam, Netherlands	800	41.8	632	564
Auckland, New Zealand	725	102.5	530	358
Paris, France (Dr Mochel)	369	296.8	369	93
Udine, Italy	223	90.6	186	117
Tours, France	215	115.0	212	100
Marseille, France	198	102.0	194	98
Dijon, France	149	204.1	149	49
Hamburg, Germany	137	−11.6	136	155
Montpellier, France	137	N/A	134	N/A
Lille, France	N/A	N/A	N/A	126
Doha, Qatar	N/A	N/A	N/A	95
Grenoble, France	N/A	N/A	N/A	43
Verona, Italy	N/A	N/A	N/A	12
Paris (Pitié-Salpêtrière hospital minus Dr. Mochel patients), France	N/A	N/A	N/A	734
Angers, France	N/A	N/A	N/A	113
Strasbourg, France	N/A	N/A	N/A	97
Reims, France	N/A	N/A	N/A	92
Bordeaux, France	N/A	N/A	N/A	63
Nancy, France	N/A	N/A	N/A	53
Caen, France	N/A	N/A	N/A	10
Country				
United Kingdom	1 478	4.2	1473	1 418
Netherlands	3 173	97.0	2328	1 611
Australia	1 103	89.2	920	583
New Zealand	725	102.5	530	358
France	1 960	170.3	1950	725
Italy	223	90.6	186	117
Germany	137	−11.6	136	155

TABLE 2 | Thirty most frequent diagnoses and ages.

Diagnosis 2023	Number	Percentage	Diagnosis 2014	Number	Percentage
PKU	1902	19.7	PKU	1048	23.7
Fabry	813	8.4	Fabry	430	9.7
X-adrenoleukodystrophy	379	3.9	Gaucher	215	4.9
Mitochondrial—MELAS	360	3.7	Homocystinuria	211	4.8
GSD II	298	3.1	X- adrenoleukodystrophy	203	4.6
OTC deficiency	256	2.7	GSD II	173	3.9
Homocystinuria	239	2.5	Mitochondrial	154	3.5
Gaucher I	236	2.4	Galactosemia	152	3.4
Galactosemia	250	2.6	TMAU	136	3.1
Porphyria—Erythroprotoporphyria	186	1.9	OTC	87	2.0
MCAD	160	1.7	Hypophosphatemic rickets	87	2.0
Alkaptonuria	153	1.6	Mitochondrial–MELAS	82	1.9
Carnitine transporter deficiency	136	1.4	Mitochondrial–CPEO	66	1.5
GLUT1	124	1.3	GSD Ia	46	1.0
Mitochondrial–MIDD	117	1.2	MSUD	45	1.0
Mitochondrial	106	1.1	MCAD	42	1.0
MSUD	103	1.1	Porphyria—acute intermittent	35	0.8
Mitochondrial–m.3243A>G	102	1.1	Carnitine transporter deficiency	34	0.8
Mitochondrial–deletion	92	1.0	MPS I	32	0.7
GSD V	91	0.9	CPT2 deficiency	29	0.7
TMAU	88	0.9	cystinosis	28	0.6
HyperPhe	82	0.8	cystinuria	27	0.6
Mitochondrial–myopathy	82	0.8	Hyperphenylalaninemia	27	0.6
CPT II	80	0.8	Argininosuccinic aciduria	27	0.6
MMA	77	0.8	MMA	26	0.6
GA I	76	0.8	MPS IV	26	0.6
Niemann Pick B	73	0.8	Alkaptonuria	25	0.6
GSD Ia	63	0.7	Niemann-Pick C	24	0.5
Porphyria–Cutanea Tarda	63	0.7	Mitochondrial–MIDD	23	0.5
Propionic Acidemia	63	0.7	Niemann-Pick B	21	0.5

Note: Six thousand, eight hundred and fifty patients are included in this group of 30 diagnoses.

(601 patients (51%) for the MELAS, MIDD and m.3243A>G groups together). In addition, 82 patients had mitochondrial myopathy, 92 had a 'deletion' and 34 had Kearns-Sayre. The age group at onset was documented for 1139 mitochondrial patients, with 127 (11%) in childhood and 920 (81%) in adulthood.

Among 444 patients with peroxisomal disorders, 379 had X-ALD. Patient numbers for each condition within the urea cycle disorders (388), disorders of fatty acid oxidation (488), mucopolysaccharidoses (253), and glycogen storage diseases (325, excluding Pompe GSD II, counted within the LSD's) are shown in Table 3.

Data for the age group at diagnosis was available for 7511 patients (Table 4). Many were diagnosed as adults (3224 patients, 43%), with the remainder predominantly diagnosed in the newborn screening, neonatal or infantile groups (2350 patients, 31.3%) and many of these patients with PKU (1306 patients). Mitochondrial diseases accounted for the largest number of adult diagnoses (920 patients) followed by Fabry disease (569 patients) and then X-ALD (183 patients). Other notable disorders diagnosed in adulthood include the porphyrias (156 patients), ornithine transcarbamylase (OTC) deficiency (106), Gaucher disease (155), alkaptonuria (98), carnitine transporter deficiency (100), Niemann Pick B (34) and Niemann Pick C (25).

TABLE 3 | Patient numbers for each diagnosis in the urea cycle disorders, fatty acid oxidation disorders, mucopolysaccharidoses, and glycogen storage diseases (excluding Glycogen Storage Disease Type II, which is counted as a lysosomal storage disorder).

Disorder	Number of patients 2023	Number of patients 2014
Urea cycle	388	199
Arginase deficiency	10	8
Argininosuccinic aciduria	60	31
Citrullinemia	4	11
Citrullinemia type I	31	2
CPS deficiency	19	7
NAGS	8	4
OTC deficiency	256	136
FAOD	531	204
CPT I	9	15
CPT II	80	43
Carnitine transporter deficiency	136	40
LCHAD	39	19
MCAD	160	48
SCAD	6	7
VLCAD	56	32
CACT	2	0
GA II/MADD	43	13
Mucopolysaccharidoses	264	141
MPS I	55	45
MPS I-H	2	0
MPS I-HS	3	0
MPS I-S	6	0
MPS II	32	16
MPS III	29	20
MPS IIIA	23	5
MPS IIIb	17	2
MPS IIIc	3	0
MPS IIId	2	0
MPS IV	53	35
MPS IVA	5	0
MPS Ivb	2	0
MPS VI	27	17
MPS VII	5	1
Glycogen storage	325	370
GSD	1	25
GSD 0	6	0
GSD I	13	7
GSD Ia	63	59
GSD Ib	28	24
GSD III	40	60
GSD IIIA	5	12
GSD IIIB	1	5
GSD IIId	1	1
GSD IV	4	4
GSD IX	35	14
GSD IXa	7	0
GSD IXb	3	0
GSD Ixc	1	0
GSD IXd	1	0
GSD V	91	145
GSD VI	21	9
GSD VII	0	4
GSD VIII	0	1
GSD XV	4	0

Note: The reduction in numbers of glycogen storage disorder patients is driven by a reduction in patients with GSD V (145 in 2014 and 91 in 2023) due to no new data submitted from the Salpêtrière centre in Paris (110 GSD V patients in 2014).

Of the conditions that may present with fatal decompensations at any time of life (Table 5), 106 patients with OTC deficiency were diagnosed as adults (age at diagnosis was available for 185 patients); however patient gender was not requested and so the proportion of these that are female is not known. Thirty-one OTC patients were diagnosed in infancy and survived to adult care. Others with potentially unstable conditions were generally diagnosed in infancy or early childhood. Exceptions to this included adult diagnosed patients with glutaric aciduria type I (13 patients), propionic acidemia (4 patients), maple syrup urine disease (MSUD 3 patients), N-acetyl glutamate synthase (NAGS) deficiency (1 patient) and Carbamoyl phosphate synthetase (CPS) deficiency (6 patients).

Conditions where some form of treatment is available, whether dietary, enzyme replacement or other pharmacological means were represented by 7560 (78%) patients. Disorders in which bone marrow transplant may be offered, such as metachromatic leukodystrophy, were not included in this 'treatable' cohort, although we appreciate that an argument could be made to include them. Disorders without other therapies where advanced

TABLE 4 | Patient age group at diagnosis.

Age group at diagnosis	Number of patients 2023	% of total with data	Number of patients 2014	% of total with data
Unknown	2140	n/a	2466	n/a
Newborn screen	703	9.4	455	22.5
Neonatal (week 1 of life)	86	1.1	44	2.2
Infantile (0–2 years)	1561	20.8	255	12.6
Childhood (3–10 years)	1362	18.1	9	0.4
Juvenile (11–16 years)	575	7.7	334	16.5
Adult (> 16 years)	3224	42.9	925	45.7

Note: French data submitted in 2014 was not included in this analysis.

TABLE 5 | Percentage of patients with decompensating disorders who were deceased and percentage diagnosed as adults.

Decompensating	Total	Percentage deceased	Percentage diagnosed as adults
Arginase deficiency	10	20.0	0.0
Argininosuccinic aciduria	55	3.6	2.4
Beta ketothiolase deficiency	11	0.0	20.0
Carnitine acylcarnitine translocase deficiency	2	100.0	0.0
Carnitine transporter deficiency	125	1.6	80.0
Citrullinemia	4	0.0	0.0
Citrullinemia type I	28	3.6	4.8
Carbamoylphosphaste synthase deficiency	19	0.0	46.2
Carnitine palmitoyl transferase I deficiency	5	0.0	62.5
Carnitine Palmitoyl Transferase II deficiency	70	0.0	60.3
Fructose-1,6-bisphosphatase deficiency	14	0.0	0.0
Glutaric aciduria type I	67	0.0	25.0
Glutaric aciduria type II	12	0.0	25.0
HMG CoA lyase deficiency	7	0.0	0.0
HMG CoA synthase deficiency	3	0.0	0.0
Isovaleric aciduria	46	0.0	0.0
Long chain AcylCoA dehydrogenase deficiency	36	0.0	10.0
Lysinuric protein intolerance	30	0.0	24.0
Multiple AcylCoA dehydrogenase deficiency	30	6.7	72.0
Malonic aciduria	6	0.0	0.0
Medium chain AcylCoA dehydrogenase deficiency	130	0.8	9.9
Methylmalonic aciduria	73	6.8	6.3
Maple syrup urine disease	101	1.0	3.8
N-Acetyl glutamate synthase deficiency	8	12.5	25.0
Ornithine transcarbamylase deficiency	235	0.9	56.7
Propionic acidemia	60	3.3	8.5
Very long chain AcylCoA dehydrogenase deficiency	46	4.3	43.5

therapeutics are in clinical trial (such as gene therapy) were likewise not included in this group.

Overall, 8156 patients were alive at the time of data collection and 378 were deceased. An additional 1410 patients from Dijon, Necker and Paris are labelled as 'unknown' for deceased status due ethical review board concerns about supplying this data, though presumably the vast majority of these patients are alive. Furthermore, 8383 patients were being actively followed in clinic (including the 1410 French patients labelled as 'unknown' for deceased status), and 1131 were labelled as inactive. Only five centres (Rotterdam, Amsterdam, Sydney, Nijmegen and Auckland) were able to provide complete data on patients lost to follow up, with the remaining centres providing data predominantly on their active patients. Analysing data from these five centres revealed that 21% (18.8% to 26.9%) of known patients were inactive, with 15% (13.7% to 12.2%) thought to be alive but lost to follow up. Table 5 shows the percentage of patients with conditions that may present with fatal decompensations that were deceased.

Change in patient numbers for each centre is shown in Table 1. The mean number of patients per centre with follow-up was 449 in our original survey and is now 567 (range 137–1483). When Montpellier is excluded from this calculation (as this centre was not included in the 2014 study), the mean number of patients for the original 14 centres participating in both studies is 598.

4 | Discussion

This paper describes follow-up of patient data seen in 15 clinical centres with a dedicated interest in adult patients with IEM. It demonstrates trends in the original 14 centres over a period of 10 years. Survey data re-iterate the wide spectrum of diseases seen and the large numbers of patients that are diagnosed in adulthood. The number of separate diagnoses followed has grown considerably, due in part to the availability of broad genomic testing increasing the ability to make specific molecular diagnoses. Increased testing availability has also resulted in a raising of awareness of rare diseases in general, also contributing to more diagnoses.

4.1 | Patient Numbers and Disease Frequencies

Newborn screening for PKU was instituted in many countries in the late 1960's and early 1970's and this in combination with its relatively high prevalence (1 in 10000 in Australia) makes it unsurprising that it is the most common disorder in this cohort, accounting for nearly 20% of patients. PKU patients were predominantly diagnosed early, whether by newborn screening or shortly thereafter. It is interesting to look at the ages of the adults who were diagnosed prior to the widespread availability of NBS (Table 6). In the dataset with individual patient ages available there were 197 people with PKU older than 55 years (thus born before 1968, and NBS was commenced in NSW Australia that year, though pilot studies occurred before this). Of these, 7 were diagnosed on the newborn screen, 2 were in the neonatal period, 17 in infancy, 70 in childhood, 1 as a juvenile and 46 as adults.

TABLE 6 | Age of diagnosis in old and young patients with PKU.

All PKU	PKU aged >55 years	PKU aged <20 years
	N = 197	*N* = 83
NBS	7	21
Neonatal	2	0
Infancy	17	41
Childhood	70	0
Juvenile	1	0
Adult	46	0
Unknown	0	21

If we compare this to those who are aged 16–20 there are 21 diagnosed by newborn screen, 41 labelled as infantile diagnoses and 21 as unknown. All centres saw patients with PKU. Overall, 2.8% of PKU patients were diagnosed as adults, though we cannot determine how many, if any, may have been missed on newborn screening rather than not having had newborn screening at all and come to diagnosis subsequently. This emphasises the known efficacy of newborn screening with our real world data but also notes that not all PKU patients have been diagnosed by NBS and it is a diagnosis of importance to consider in older persons.

The frequency of mitochondrial patients is lower than expected as various studies have indicated that around 1 in 7000 adults have a mitochondrial disorder [2]. Given this prevalence, we might have expected to see similar numbers of mitochondrial and PKU patients. However, various factors likely account for this discrepancy, primarily the fact that many patients will be seen by non-IEM centres, for example, neurologists or other specialty facilities (such as that at Newcastle upon Tyne in the United Kingdom). Also, as our study only included patients with confirmed diagnoses, patients with 'possible' or 'probable' mitochondrial disease, (a group which is expected to be significantly larger than the group of patients with a confirmed molecular diagnosis of mitochondrial disease) are not included in our data. Nonetheless, the number of mitochondrial patients followed by our centres has grown considerably. The original paper noted 425 mitochondrial patients, and in the intervening 10 years it has grown to 1188—a 279% increase. The separate diagnoses within this group have increased also. Many of these new mitochondrial diagnoses are represented by only a few patients, so the majority of the patients are still labelled with MELAS or MIDD.

This dataset remains an incomplete description of the epidemiology of adult IEM patients. The sample remains biased by the relative expertise and historical interests of each centre, and the relatively small number of centres; for example, many of the Pompe patients (GSD II) come from the Rotterdam centre (168 of the 298 patients), and other centres see fewer patients. Rotterdam also see large numbers of acute porphyria patients (292), although that data is not included in these numbers (see methods). A few Rotterdam porphyria patients were followed at the time of the 2014 study (8 EPP and 17 AHP). Since then, the increase in patient numbers is directly related to the availability

of effective treatment, recognition of Rotterdam as a centre of excellence and family counselling. A change in the guidelines, screening for complications after age 50, has also led to increased numbers of patients actively attending this clinic. Other centres in this study have not been recognised in the same way for porphyria, or have local centres of expertise such that these patients are not seen. Nijmegen is the Dutch mitochondrial centre according to their relative numbers (561), whereas in England many of these patients are seen at one of two specialist centres (neither included in this dataset). Likewise, patients with porphyria, alkaptonuria and GSD V are seen at specialty centres in England and their data was not obtained. Data was submitted from European, Canadian and Asia-Pacific centres only; hence our data may be different from patient populations seen at centres in the United States and elsewhere.

4.2 | Age Group at Diagnosis

Age group at diagnosis showed that more than 40% were diagnosed in adulthood; a similar percentage to that seen in 2014. This confirms the importance of adult physicians being aware of metabolic diseases as a diagnostic possibility. Our work along with case reports and series of other authors increasingly demonstrate that IEM can be diagnosed at any age [3]. These can be decompensating disorders, and this further underscores the need for more adult IEM physicians, adult clinics and adult training programs.

Mitochondrial disorders may present with any combination of organ dysfunctions, at any stage of life and may therefore be seen by nearly any type of specialist physician, although neurologists and endocrinologists are perhaps the most likely to be involved given the strong representation of MELAS and MIDD patients in this group. Fabry disease was also diagnosed mainly in adulthood (82% of patients with age at diagnosis data), and given its prevalence in hypertrophic cardiomyopathy, stroke and end stage renal failure cohorts [4–6], its importance to adult physicians is noteworthy.

The relative contribution of NBS differs between diagnoses and has changed with time. For example, the centres where their jurisdictions have looked for carnitine transporter deficiency (Sydney, Auckland and in the Netherlands) had significant numbers of adult diagnoses (representing maternal diagnoses made on newborn screening of the children).

There were significant numbers of patients diagnosed as adults who have disorders where acute decompensation is possible (Table 5), for example MADD (72% adult diagnoses), OTC deficiency (57% adult diagnoses) and VLCAD (43% adult diagnoses). These illustrate the spectrum of these diseases, where milder forms exist that present in adulthood, and physicians should be aware of them as effective and lifesaving treatments exist.

4.3 | Patients Deceased or Lost to Follow Up

11.8% of patients (1 134 individuals) were lost to follow up. A proportion of these were known to have died (378 patients, median age 46, range 16 to 96 years). This rate of lost to follow up is higher than that seen in the transition of patients with cystic fibrosis in the United States of around 2% [7], but in keeping with that seen in a 2 year follow up of transition of PKU patients to adult services where 9% of clinic appointments were not attended [8]. In this dataset 5.9% of PKU patients were labelled as inactive (HyperPhe 16%). Other disorders where the proportion of inactive patients was significant includes 3MCCC deficiency (35%), carnitine transporter deficiency (24%), MELAS (25%), TMAU (17%), mitochondrial myopathy (17%) and MIDD (14%). It is an interesting observation that these later disorders are ones where symptoms are rare, or where no effective treatment exists. This points towards a recognition that other 'more important' disorders are perhaps—rightly or wrongly—followed more closely. The advent of more effective telehealth clinics since COVID-19 seems a viable way of improving clinic attendance rates, but data on this aspect of care was not collected in this survey.

In the disorders where there were more than 10 patients in the database, those associated with higher proportions of deceased patients included MPS III/IIIb (38%/17% deceased), metachromatic leukodystrophy (22% deceased), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) (18% deceased), and MPS I (18% deceased). These disorders with higher mortality do not have widely available highly effective treatments, and the known natural history is in keeping with our data.

4.4 | Increasing Service Demands

Since these data was originally collected in 2014, 13 of the 14 original clinical centres has experienced growth in patient numbers (Table 1). Most clinics experienced very large increases in patient numbers, the percentage change was relative to the initial size, yet there were eight clinics growing by more than 100% and the clinic in Paris exhibiting a nearly 300% rise. The numbers listed in Table 1 include only those patients with confirmed metabolic diagnoses. Similar to paediatric services, many of the adult centres follow a large number of patients who are either in the process of undergoing diagnostic evaluation or in whom the results of such evaluation are inconclusive (personal communications with each author, data not available); such as patients with 'possible' or 'probable' mitochondrial disease, comatose patients with 'severe hyperammonemia' years after gastric bypass, or otherwise unexplained rhabdomyolysis, and these patients also need to be considered in the human resource requirements of adult clinics.

Hamburg, London and Vancouver did not grow appreciably, and this may be due to different clinicians assessing their data for this study or the introduction of newer specialty clinics in those areas. It is possible that the smaller increases from these three centres may be a more accurate reflection of patient growth. Likewise, Paris (Mochel) with a 296% increase may be skewing true growth rates upwards.

Transferral of patients from paediatric services only accounts for approximately half of this growth (as can be ascertained from the many patients with diagnoses made in adulthood). Expanded and genomic newborn screening (NBS) will change the landscape further, not only diagnosing more patients with infantile onset, but also adult-onset disease. A commitment to

funding NBS of infants therefore requires improved funding and resourcing of adult metabolic services.

Although patients with paediatric-onset IMD generally have more severe health problems related to their diagnosis, adults with IMD can be equally complex owing to the presence of more co-morbidities that can interact, requiring additional attention of the IMD specialist. In addition, adult IMD practises differ from paediatric in the sheer volume of patients. Taking PKU as an example, if we model prevalence based on incidence 1 in 10000 and mean life expectancy 78 years, then there will be nearly double the number of affected adults than children in a population. Although there are many IMDs not survivable beyond childhood, our data support substantial disease incidence for largely adult-onset diseases like Fabry disease and chronic progressive ophthalmoplegia. The needs of these patients will be distinct from those diagnosed in childhood and will require medical knowledge of the problems engendered by aging and adulthood.

The majority of patients described in this cohort potentially have some form of treatment available to them, although in some localities ultra-expensive therapies like enzyme replacement may be unavailable. The approaching era of advanced therapeutics raises further challenges as these are likely to be even more expensive and out of reach for many patients. For example the availability of givosiran, *ALAS1* siRNA, as a treatment for recurrent acute porphyria has resulted in many more referrals but remains unavailable in most countries. Medically prescribed dietary therapies remain a mainstay for many disorders and expertise in their management is something that adult metabolic clinics are best positioned to deliver. Given that many adult patients with IEM can be offered therapy, it would seem sensible that treatment be guided by physicians with expertise in these rare disorders.

Some centres care for a large number of patients with non-traditional inborn errors of metabolism not included in this study. The number of genetic diseases catalogued in OMIM continues to rise (6716 molecularly defined phenotypes as of September 2023) and many patients with ultra-rare diseases find that only the metabolic diseases clinic is equipped to provide a therapeutic home for them.

Our data has an important bias in the types of disorders seen by individual centres. Rotterdam and London see significant numbers of Pompe patients, other centres saw fewer. Vancouver and Rotterdam are designated centres for mitochondrial disease in their areas, other centres either have alternative local specialty clinics for these patients or see only a small proportion of their local patients. Similarly, with porphyria only Rotterdam is a recognised specialty centre. Future adult metabolic centres will need to take this into account when resource planning, especially if there are not disease specific centres for mitochondrial or other specialty clinics available locally.

This work raises an important question about the resources required to care for this population of patients—how do we cope with the ever increasing number of patients, and diagnostic investigation referrals? These are often lifelong conditions that rarely shorten lifespan—such as PKU, galactosemia, MSUD—and as such require specialist metabolic dietitian care. Nurses, psychologists, home adaptations are vital to allow adults to live independently. Sufficient lab staff for monitoring. Resources for pregnancy management as well as gaining a better understanding of the impact of old age, frailty, other co-morbidities and medications.

Since our initial publication there has been a call by our group for recognition that training programs for physicians who wish to care for adults with inborn errors of metabolism are needed [9], and a list of medical expert competences was published in order to help the development of accredited training programs in adult metabolic medicine worldwide [10]. These data reinforce the need of expanding a proper trained adult metabolic workforce, by showing the growth in patient numbers across the globe, the increasing complexity and breadth of diagnoses, and the continued importance of patients being diagnosed in adulthood. We aim to complete and publish a survey, exploring questions such as has staffing increased? How many (young) specialist physicians are in training and what resources are there to train them? Has there been an improvement in interdisciplinary care? We hope this forthcoming publication will further elucidate answers to these important questions.

5 | Conclusion

Our data show the wide range of paediatric and adult-onset IEM seen in these clinical centres. The increase in adult patient numbers is important to recognise, as it re-iterates the need for specialty services to be available to these patients. Specialised knowledge of these disorders is needed to provide optimal care; including up-to-date monitoring and treatments, and the ability to manage acute decompensation. We consider that care for this growing adult IEM patient population is important, as the vast majority of these people participate fully in society and the consequences of failed care can be catastrophic.

5.1 | Limitations

The quality of the data provided is dependent on the accuracy and comprehensiveness of each site's database or other mechanisms for tracking diagnoses and patient statistics (e.g., active vs. lost-to-follow-up; age at diagnosis, etc). Furthermore, it should be noted the data presented herein are not sufficient for estimating disease prevalence.

Author Contributions

Michel Tchan planned the study, analysed the data and wrote the draft article. Anna Lehman, Martin Merkel, Annalisa Sechi, Emma Glamuzina, Mirian Janssen, Janneke Langendonk, Fanny Mochel, Elaine Murphy, Jean-Baptiste Arnoux, Bryony Ryder, Elsa Kaphan, Karin Mazodier, Francois Maillot, Gonnie Alkemade, Quentin Thomas, Cecilia Marelli, Vanessa Leguy-Seguin submitted patient data and contributed to writing and editing the article.

Ethics Statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional

and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was not obtained for each participant in this study. Ethical approval was obtained for this study through the Western Sydney Local Health District Human Research Ethics Committee (2023/ETH00473).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Individual patient level data is available from Michel Tchan upon reasonable request.

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