Functional outcomes in untreated patients with thymidine kinase 2 deficiency (TK2d) aged ≤12 years at TK2d symptom onset: findings from the largest international TK2d dataset

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TK2d is an ultra-rare, progressive, debilitating and often life-threatening mitochondrial myopathy[1]

- Autosomal recessive pathogenic *TK2* variants lead to mitochondrial DNA depletion and/or multiple deletions[2]
- TK2d manifests as a continuous clinical spectrum with varying ages of symptom onset[1,2]
- Typically, the earlier that TK2d symptoms appear, the faster the disease progresses, with patients with age of TK2d symptom onset ≤12 years tending to experience rapid disease progression resulting in early death[1,2]
- Currently, there are no approved treatments for TK2d, and management is limited to supportive care; standards of care do not appear to change the progressive disease trajectory[3,4]
- Data on TK2d natural disease progression are scarce and no TK2d-specific registries comparable to the dataset described here have been completed

Objective: to characterize functional outcomes in untreated patients with TK2d with age of symptom onset ≤12 years

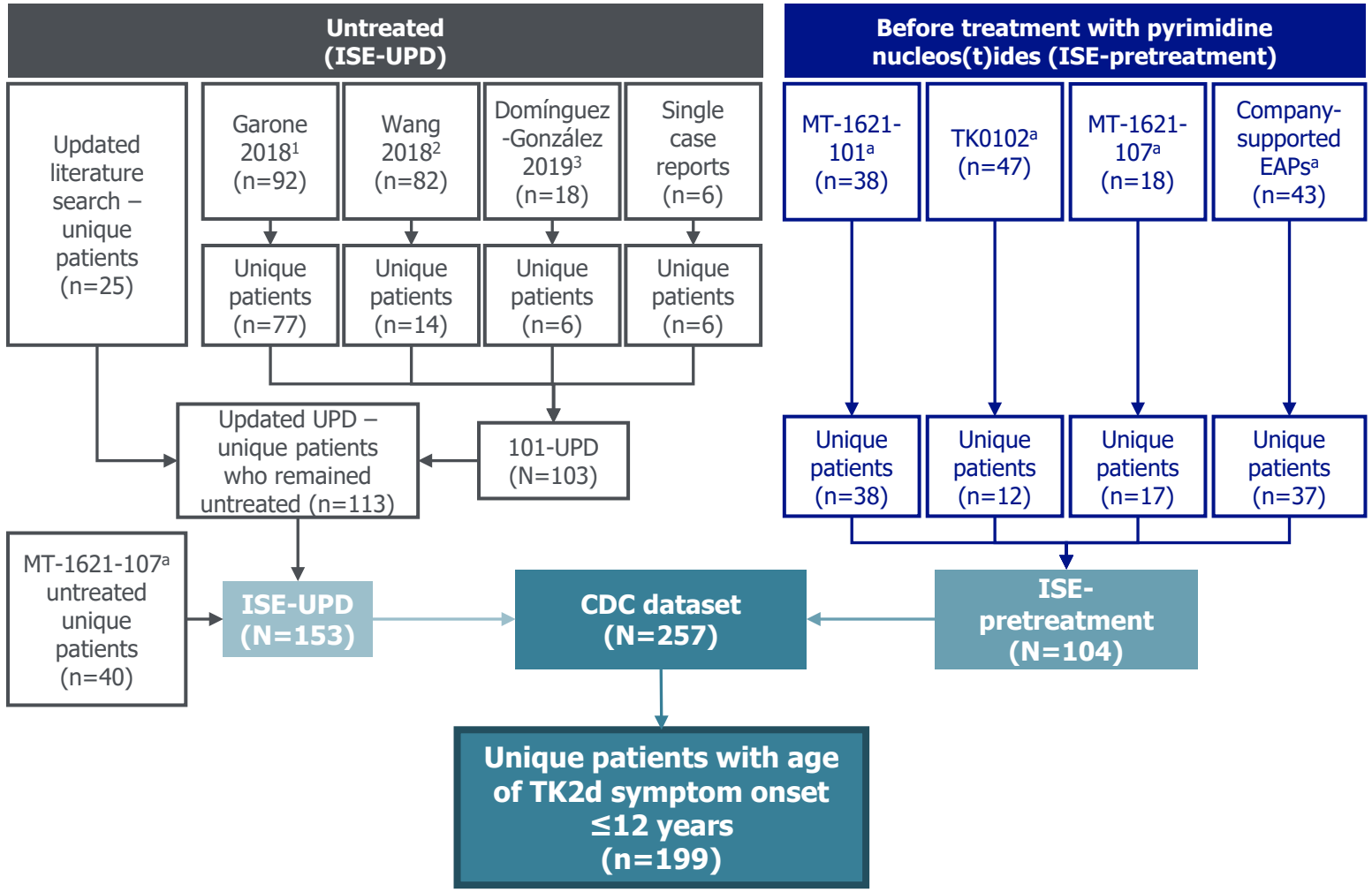
Survival data are presented in poster number 196 at the EPNS congress

EPNS, European Paediatric Neurology Society; *TK2*, thymidine kinase 2 gene; TK2d, thymidine kinase 2 deficiency

1. Garone C, *et al. J Med Genet* 2018;55:515–21; 2. Berardo A, *et al. J Neuromuscul Dis* 2022;9:225–35; 3. Wang J, *et al.* 2018. In: Adam MP, *et al.*, editors. GeneReviews® [internet]. Seattle (WA): University of Washington, Seattle; 2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK114628/ (Accessed 2 April 2025); 4. de Barcelos, *et al. Curr Opin Neurol* 2019;32:715–21

The CDC dataset is the largest single source of natural history data for patients with TK2d

- The **CDC dataset** of patients with TK2d was generated from:
  1) Comprehensive literature reviews and a retrospective chart review study of untreated patients (ISE-UPD)
  2) Data from three clinical studies and company-supported EAPs before patients started treatment (ISE-pretreatment)
- Individuals who participated in multiple studies are only counted once, although their data from across studies is included



199/257 patients (77.4%) from the CDC dataset had an age of TK2d symptom onset ≤12 years and were included in this study[b]

[a]Data from TK0102 (NCT03845712) and company-supported EAPs were collected prospectively; data from MT-1621-101 (NCT03701568) and MT-1621-107 (NCT05017818) were collected retrospectively.
[b]Some patient cohorts did not have data for all outcomes examined
CDC, Comprehensive Disease Course; EAP, Expanded Access Program; ISE, Integrated Summary of Efficacy; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database
1. Garone C, *et al. J Med Genet* 2018;55:515–21. 2. Wang J, *et al. Genet Metabol* 2018;124:124–30. 3. Domínguez-González C, *et al. Orphanet J Rare Dis* 2019;14:100

Outcomes included developmental motor milestones, and use of ventilatory and feeding tube support

Developmental motor milestones initially achieved, lost and regained, reflective of those described by the World Health Organization,[1] included the ability to:

- hold head upright, unassisted
- sit upright, unassisted
- stand, unassisted and assisted
- walk, unassisted and assisted
- climb stairs, unassisted and assisted
- run

Use of ventilatory support, included:

- mode of support (invasive [tracheostomy or no tracheostomy] or non-invasive [e.g. BiPAP, CPAP])
- age at which support was used
- number of hours per day and total number of days using support

Use of feeding tube support, included:

- type of feeding tube (nasogastric, gastrostomy)
- age at which support was used
- reasons for insertion or removal of feeding tube
- duration of feeding support

- Not all outcomes were captured in all sources, with data for developmental motor milestones, longitudinal ventilatory support use, and use of feeding tube support unavailable for any patients in the updated-UPD

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; UPD, Untreated Patient Database

1. Wijnhoven TM, *et al. Food Nutr Bull* 2004;25:S37–45

Demographic and disease characteristics of patients with TK2d with age of symptom onset ≤12 years

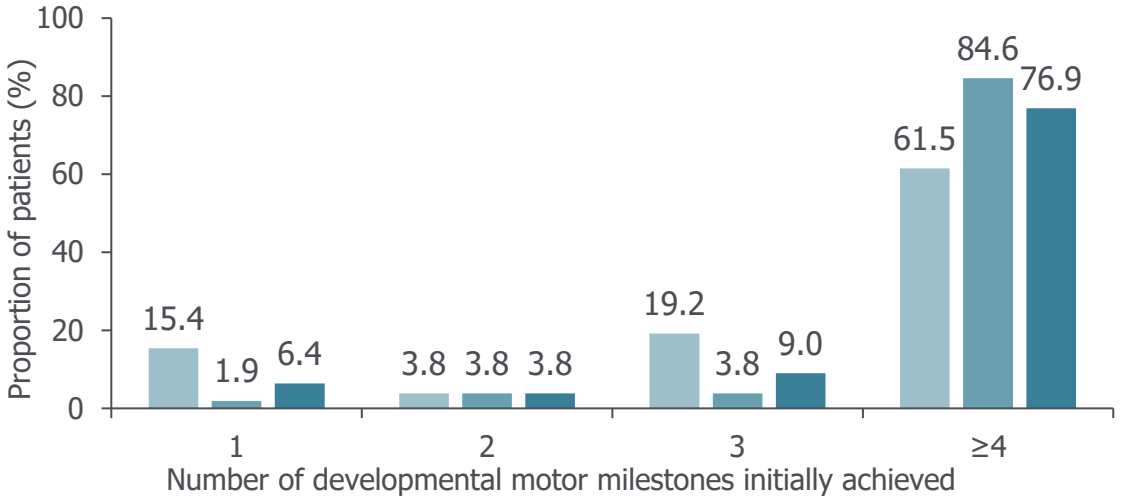
	ISE-UPD (N=117)	ISE-pretreatment (N=82)	CDC (N=199)
Sex, n (%)			
Male	62 (53.0)	46 (56.1)	108 (54.3)
Female	53 (45.3)	36 (43.9)	89 (44.7)
Missing	2 (1.7)	0 (0)	2 (1.0)
Race,[a] n (%)			
White	24 (20.5)	67 (81.7)	91 (45.7)
Other[b]	2 (1.7)	11 (13.4)	13 (6.5)
Missing or not reported	91 (77.8)	4 (4.9)	95 (47.7)
Geographic region of residence,[a] n (%)			
Europe	20 (17.1)	27 (32.9)	47 (23.6)
Rest of world	48 (41.0)	55 (67.1)	103 (51.8)
Unknown or missing	49 (41.9)	0 (0)	49 (24.6)
Age of TK2d symptom onset, years			
Median (min, max)	1.2 (0.0, 11.0)	1.5 (0.0, 11.7)	1.4 (0.0, 11.7)
Q1, Q3	0.5, 2.0	1.1, 2.4	0.8, 2.3
Age at genetic confirmation, years	n=59	n=77	n=136
Median (min, max)	5.2 (0.0, 56.4)	3.2 (0.1, 35.3)	4.1 (0.0, 56.4)
Q1, Q3	2.0, 14.4	1.6, 8.3	1.7, 10.3
Time from TK2d symptom onset to genetic confirmation, months	n=59	n=77	n=136
Median (min, max)	38.1 (–5.9, 556.4)[c]	12.3 (–59.9, 359.9)[c]	24.7 (–59.9, 556.4)[c]
Q1, Q3	9.4, 129.1	4.3, 64.7	6.3, 90.1

[a]Owing to the ultra-rare nature of TK2d and the small number of patients, some details relating to race and country of residence were grouped for reporting purposes to minimize risk of patient reidentification. [b]Includes American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other and Multiple. [c]Negative values for time from TK2d symptom onset to genetic confirmation indicate that genetic confirmation took place before onset of disease symptoms

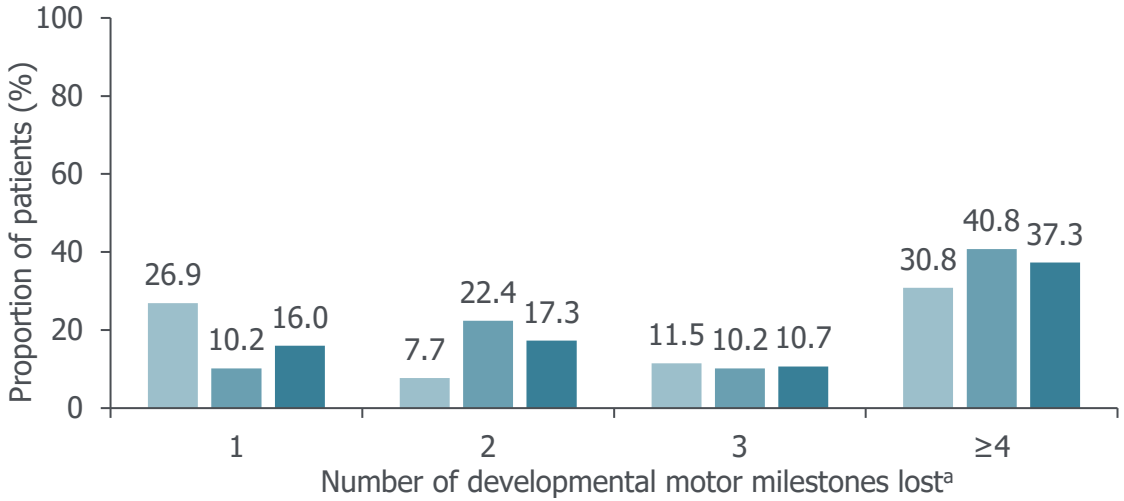
CDC, Comprehensive Disease Course; ISE, Integrated Summary of Efficacy; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database

In patients with age of TK2d symptom onset ≤12 years, loss of developmental motor milestones was frequent

- Of the 78 patients with available motor milestone data in the CDC:
  - 75 (96.2%) initially achieved at least one milestone
  - 60 (76.9%) initially achieved at least four milestones



- Of the 75 patients in the CDC who initially achieved at least one motor milestone:
  - 61 (81.3%) subsequently lost at least one milestone



	ISE-UPD	ISE-pretreatment	CDC
At risk for milestone achievement:	n=26	n=52	n=78
At risk for milestone loss:	n=26	n=49	n=75

Spontaneous regain of lost motor milestones was rarely seen
Of the 61 patients in the CDC who lost at least one milestone, 3 (4.9%) later regained a previously lost developmental motor milestone (ability to stand, assisted [n=1]; ability to walk, unassisted [n=1]; ability to run [n=1]). These 3 patients overall experienced declining motor function

Developmental motor milestones include ability to hold head upright, unassisted; sit upright, unassisted; stand, assisted; stand, unassisted; walk, assisted; walk, unassisted; climb stairs, assisted; climb stairs, unassisted; and run.
[a]Percentages for number of developmental motor milestones lost calculated based on number of patients initially achieving a milestone (ISE-UPD, n=26; ISE-pretreatment, n=49; CDC, n=75).
CDC, Comprehensive Disease Course; ISE, Integrated Summary of Efficacy; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database

Use of ventilatory support in patients with age of TK2d symptom onset ≤12 years was widespread

- In the CDC dataset, ventilatory support was used by 81/199 patients (40.7%)

	ISE-UPD (N=117)	ISE-pretreatment (N=82)	CDC (N=199)
Ventilatory support used at any time,[a] n (%)	50 (42.7)	31 (37.8)	81 (40.7)
No ventilatory support data (no record or not collected), n (%)	44 (37.6)	29 (35.4)	73 (36.7)
Mode of ventilatory support (first occurrence),[b] n/N[c] (%)			
Invasive (tracheostomy or no tracheostomy)	6/50 (12.0)	9/31 (29.0)	15/81 (18.5)
Non-invasive (e.g. BiPAP, CPAP)	7/50 (14.0)	21/31 (67.7)	28/81 (34.6)
Missing	37/50 (74.0)	1/31 (3.2)	38/81 (46.9)
Age at first ventilatory support,[b] years	n=42	n=31	n=73
Median (min, max)	3.0 (0.0, 44.0)	4.0 (0.4, 35.2)	3.0 (0.0, 44.0)
Q1, Q3	1.1, 9.0	1.3, 14.5	1.3, 10.0
Amount of ventilatory support used (first occurrence),[b] hours/day	n=8	n=28	n=36
Median (min, max)	24.0 (10.0, 24.0)	11.0 (8.0, 24.0)	12.0 (8.0, 24.0)
Q1, Q3	16.0, 24.0	10.0, 24.0	10.0, 24.0
Duration of ventilatory support,[c] days	n=27	n=31	n=58
Median (min, max)	730.6 (0.0, 6594.0)	218.0 (14.0, 9490.0)	499.8 (0.0, 9490.0)
Q1, Q3	152.1, 3287.1	61.0, 1215.6	105.0, 2633.0

[a]For treated patients, any time refers to the time up to treatment start. bIn patients with at least one record of ventilatory support. [c]Total duration of all ventilatory support used per patient during the pretreatment or non-treatment phase. [c]N is the number of patients with at least one record of ventilatory support use

BiPAP, bilevel positive airway pressure; CDC, Comprehensive Disease Course; CPAP, continuous positive airway pressure; ISE, Integrated Summary of Efficacy; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database

Feeding tube support was used by some patients with age of TK2d symptom onset ≤12 years despite limited data availability

- In the CDC dataset, feeding tube support was used by 28/199 patients (14.1%); feeding support data were not available for 121 patients (60.8%)

	ISE-UPD (N=117)	ISE-pretreatment (N=82)	CDC (N=199)
Feeding tube (gastrostomy or nasogastric) support used at any time,[a] n (%)	8 (6.8)	20 (24.4)	28 (14.1)
No feeding support data (no record or not collected), n (%)	91 (77.8)	30 (36.6)	121 (60.8)
Age at first feeding support, years	n=7	n=20	n=27
Median (min, max)	2.5 (1.0, 13.0)	1.7 (0.5, 16.3)	1.9 (0.5, 16.3)
Q1, Q3	1.3, 13.0	1.1, 4.1	1.2, 5.2
Tube insertion reason for first occurrence, n/N[b] (%)			
Supplemental oral intake	2/8 (25.0)	2/20 (10.0)	4/28 (14.3)
Dysphagia	4/8 (50.0)	9/20 (45.0)	13/28 (46.4)
Dysphagia, supplemental oral intake	0/8 (0)	6/20 (30.0)	6/28 (21.4)
Other	2/8 (25.0)	3/20 (15.0)	5/28 (17.9)
Missing	0/8 (0)	0/20 (0)	0/28 (0)
Total duration of feeding support,[c] days	n=7	n=20	n=27
Median (min, max)	1154.0 (49, 5844)	140.5 (6, 3855)	156.0 (6, 5844)
Q1, Q3	194.0, 3318.0	44.0, 219.0	45.0, 1154.0

[a]For treated patients, any time refers to the time up to treatment start. [b]N is the number of patients with at least one record of feeding tube support use. [c]Total duration of all feeding support received per patient during the pretreatment or non-treatment phase

CDC, Comprehensive Disease Course; ISE, Integrated Summary of Efficacy; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database

Conclusions and outlook

The CDC dataset represents the largest single source of natural disease course data for patients with TK2d to date, capturing data from a substantial proportion of the known global population of patients with TK2d

Our findings demonstrate the severe clinical burden of disease in patients with TK2d and age of symptom onset ≤12 years

- High levels of motor function loss and use of ventilatory and feeding tube support highlighted the heavy, progressive disease burden in these patients and were comparable between ISE-UPD and ISE-pretreatment groups
- Loss of a developmental motor milestone is never considered to be normal and prompts further workups and attention

These data suggest that the current standard of care remains insufficient to meaningfully affect morbidity associated with TK2d

Understanding the natural disease course of TK2d may aid management strategies and inform the development of studies to investigate new treatment options

CDC, Comprehensive Disease Course; ISE, Integrated Summary of Efficacy; TK2d, thymidine kinase 2 deficiency; UPD, Untreated Patient Database

Survival outcomes for untreated patients with TK2d aged ≤12 years at TK2d symptom onset are presented in poster number 196 at this congress

EPNS, European Paediatric Neurology Society; TK2d, thymidine kinase 2 deficiency

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Thank you for your attention

Do you have any questions?