The cost of disease progression in ATTRv amyloidosis

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The cost of disease progression in ATTRv amyloidosis

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My disclosures

- Advisory work for
  - Pfizer
  - Alnylam
  - Eidos
- Avisory work in the past for
  - GSK
  - Neurochem

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Estimating the cost of disease

Different types of direct and indirect costs:[1,2]

- Classic approach: Calculating health care resource utilization = HCRU
  - Hospital service usage: outpatient services, inpatient admissions and emergency room visits
  - Physician visits, pharmacy, home health care, assistance devices
- Additional approaches:
  - Productivity loss & early retirement (expressed in terms of disability-adjusted life years; DALYs), loss of paid taxes
  - Societal services; loss of work and income of caregivers

1. Choi H-J & Lee E-W. Methodology of Estimating Socioeconomic Burden of Disease Using National Health Insurance (NHI) Data, Evaluation of Health Services, Sandeep Reddy and Aida Isabel Tavares, IntechOpen. December 2019. Available from: https://www.intechopen.com/books/evaluation-of-health-services/methodology-of-estimating-socioeconomic-burden-of-disease-using-national-health-insurance-nhi-data; 2. Jo C. Clin Mol Hepatol. 2014;20:327–37.

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Estimating the cost of disease

Specific factors in ATTRv amyloidosis:

- The long and winding road in non-familial patients diagnosis along multiple specialists[1,2]
- The longer the road the more progressed is disease at diagnosis[1,2]
- Both age at disease onset and rate of progression vary considerably among patients[2]
- Disease spectrum with different clinical pictures at both ends: heart vs. nerves (with a mixed type in between)[2,3]

In order to obtain a clear picture of the costs of progression of the disease itself, the use and effect of disease-modifying drugs (TTR tetramer stabilizers and *TTR* gene-silencers) have not been looked at in this presentation

ATTRv, hereditary transthyretin amyloidosis; TTR, transthyretin

1. Lane T et al. Circulation 2019;140:16–26; 2. Adams D et al. J Neurol 2020; doi: 10.1007/s00415-019-09688-0 [Epub Jan 6]; 3. Wixner J et al. Orphanet J Rare Dis 2014;9:61.

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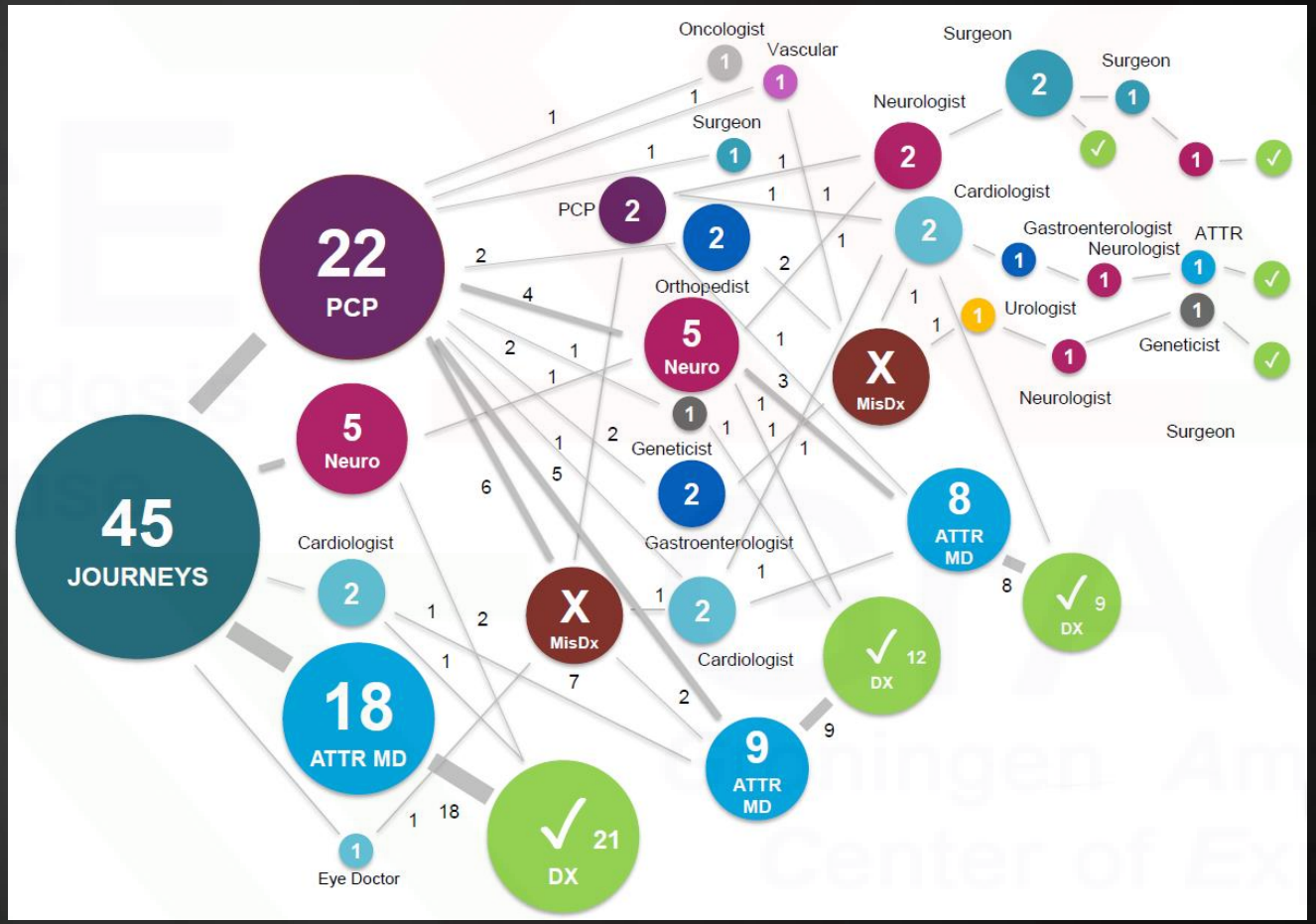
A complicated path to diagnosis

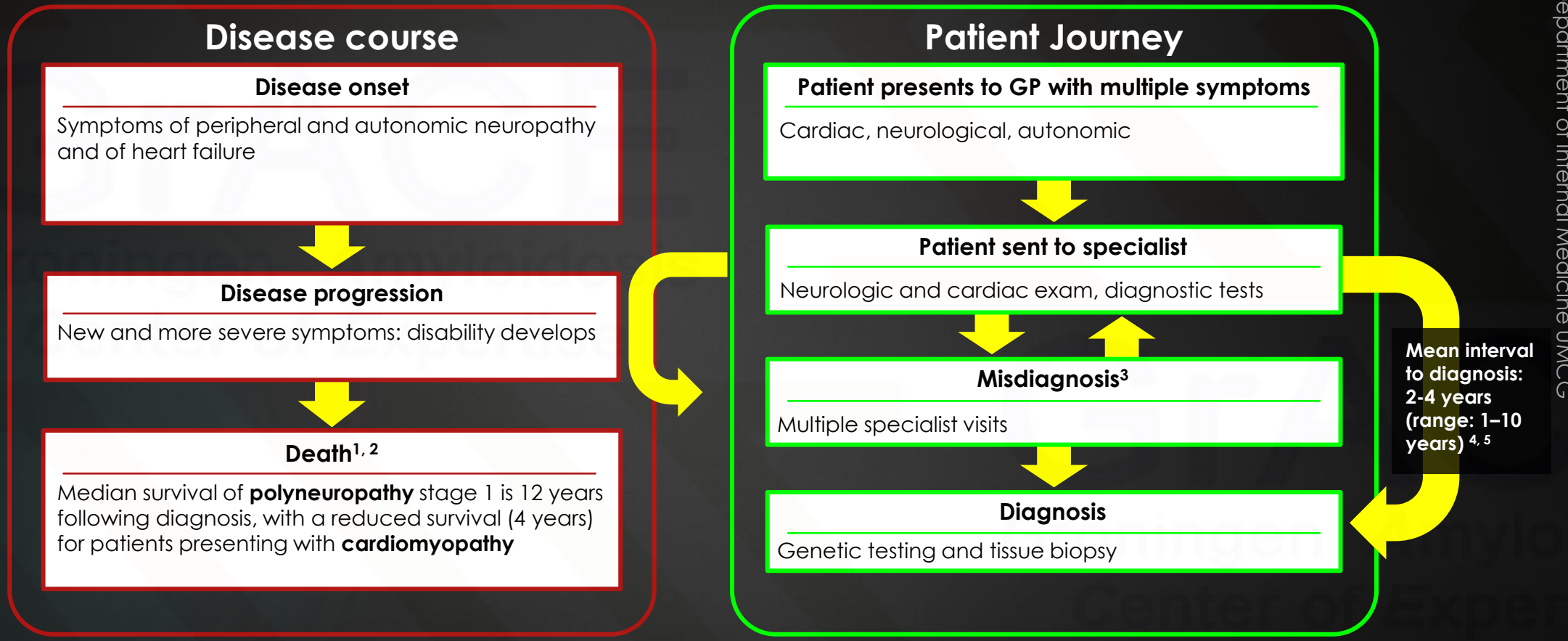
Often a long journey to diagnosis

- Visits to multiple specialists over many years
- Disease symptoms continue to progress as diagnosis is delayed



Alnylam® data on file (hereditary transthyretin (hATTR) amyloidosis: disease background) 2019.

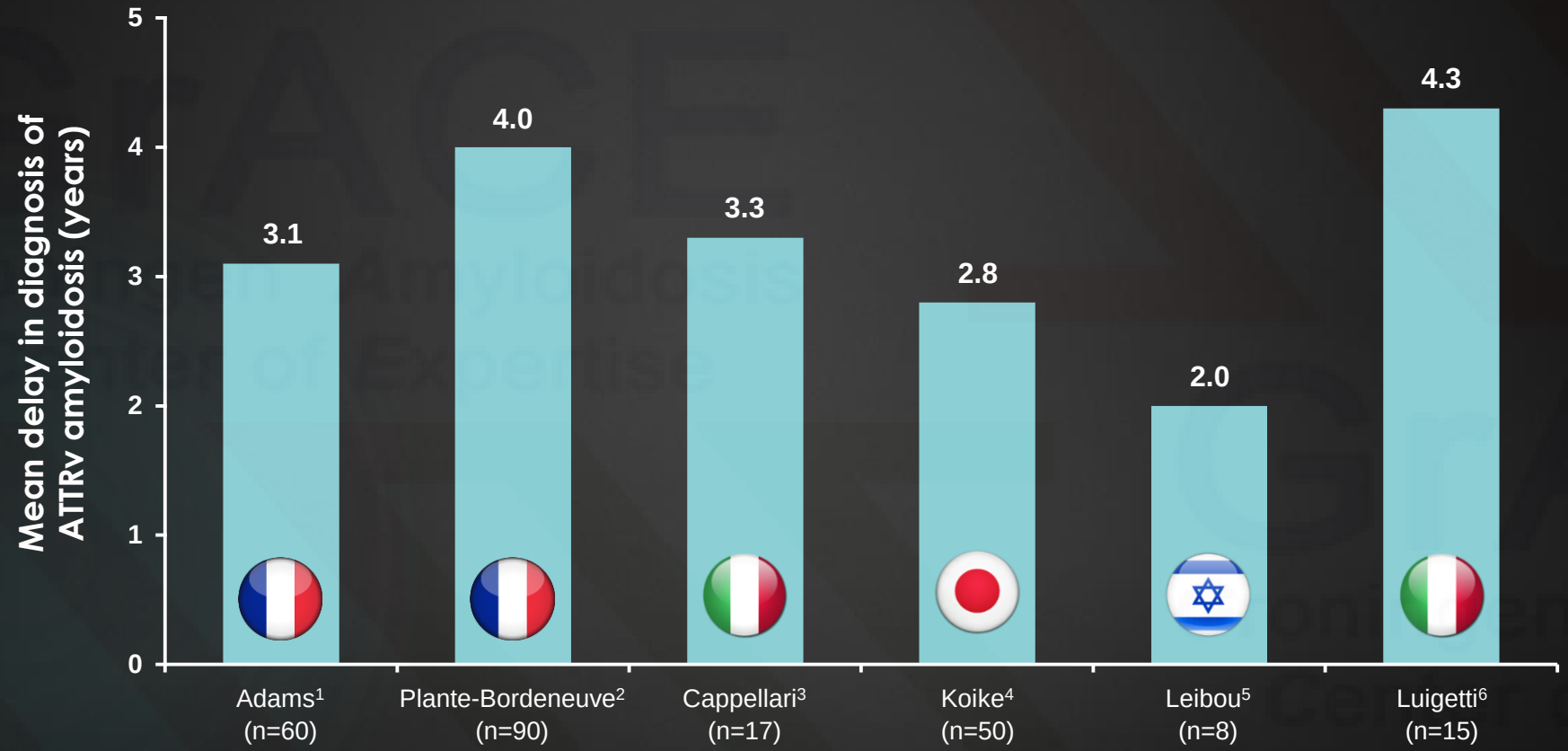
Patient journey in the diagnostic delay period



GP = general physician.

1. Coelho T, et al. Neurology. 2018 Nov 20;91(21):e1999-e2009. 2. Klaassen SE, et al. Am J Cardiol 2018; 121:107-12. 3. Plante-Bordeneuve, et al. *Lancet Neurol.* 2011;10:1086-1097. 4. Plante-Bordeneuve, et al. *Neurology*. 2007;69(7):693-698. 5. Leibou et al. Isr Med Assoc J 2012;14:662–5.

Mean interval until diagnosis is 2-4 years in ATTRv patients without a family history

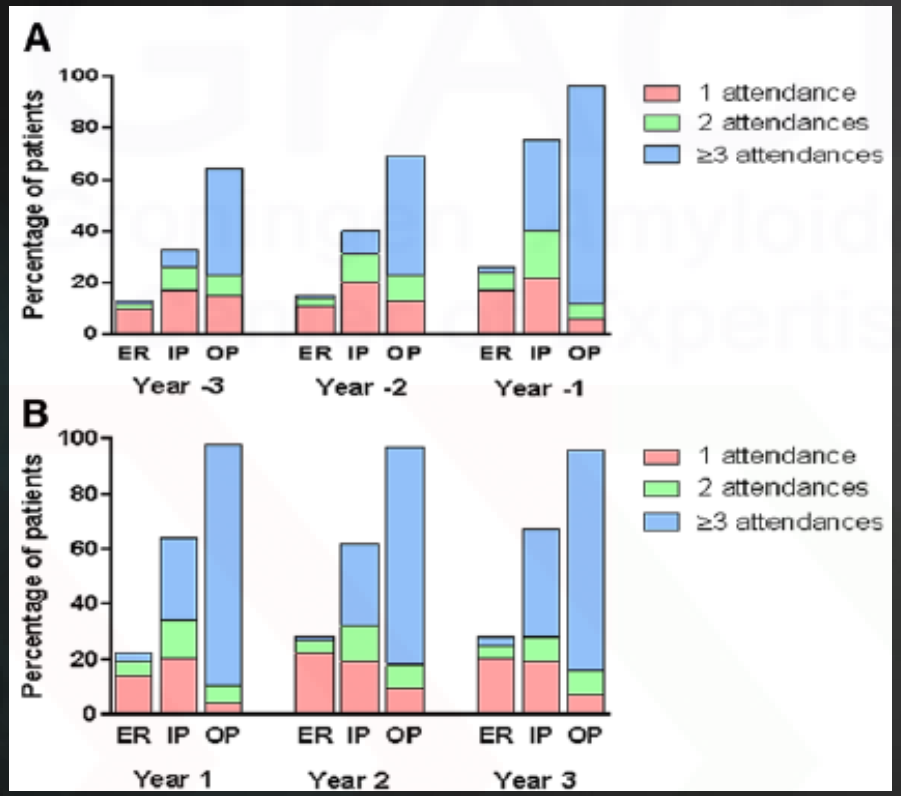


ATTRv, hereditary transthyretin amyloidosis

1. Adams et al. *Amyloid* 2012;19(Suppl. 1):61–4; 2. Plante-Bordeneuve et al. *Neurology* 2007;69:693–8; 3. Cappellari et al. *J Peripher Nerv Syst* 2011;16:119–29; 4. Koike et al. *J Neurol Neurosurg Psychiatry* 2012;83:152–8; 5. Leibou et al. *Isr Med Assoc J* 2012;14:662–5; 6. Luigetti et al. *Neurol Sci* 2013;34:1057–63.

Delayed diagnosis in cardiac ATTR is associated with HCRU[1]

Health care resource utilization (HCRU) in 3 years before diagnosis (A) and 3 years after diagnosis (B)



- Diagnostic delay: median 25 months (IQR 4–60) for ATTRv-cardiomyopathy

During the 3 years prior to diagnosis:

- Patients attended hospital a median of 17 times (IQR 9–27)
- Patients experienced a median of 3 inpatient admissions (IQR 1–5)

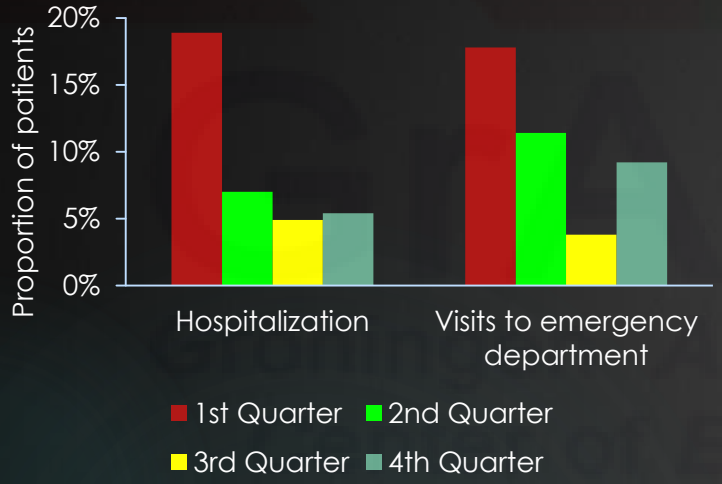
During the first year after diagnosis:

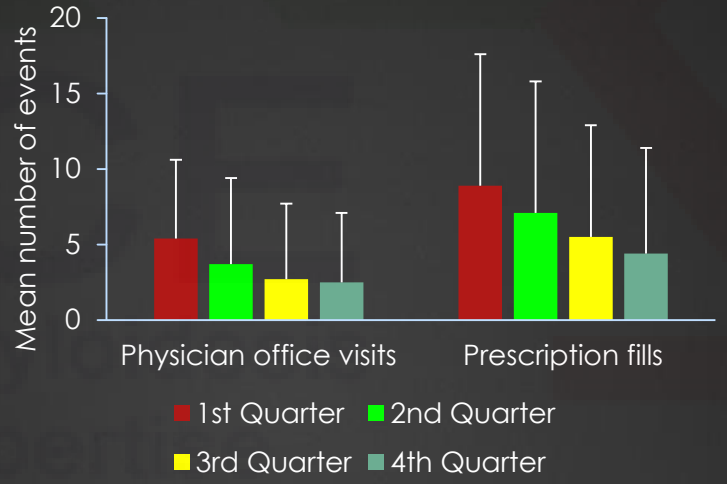
- 30% of patients were admitted ≥3 times

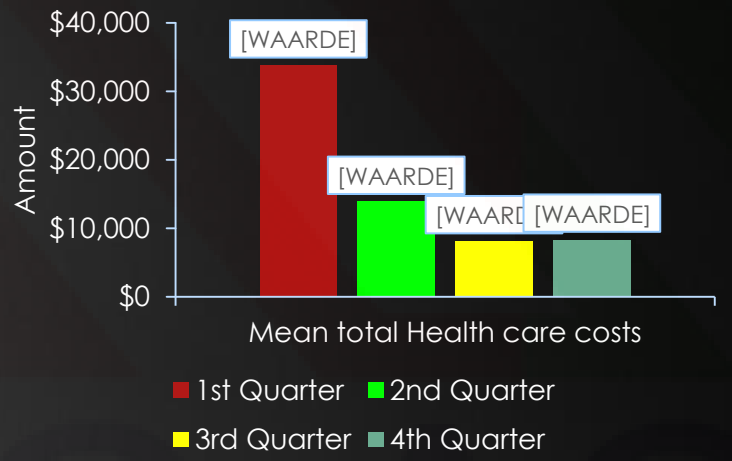
ER, emergency room; IP, inpatient admissions; OP, outpatient services.
IQR, interquartile range

1. Lane T et al. Circulation 2019;140:16–26.

Increased HCRU increases costs[a]





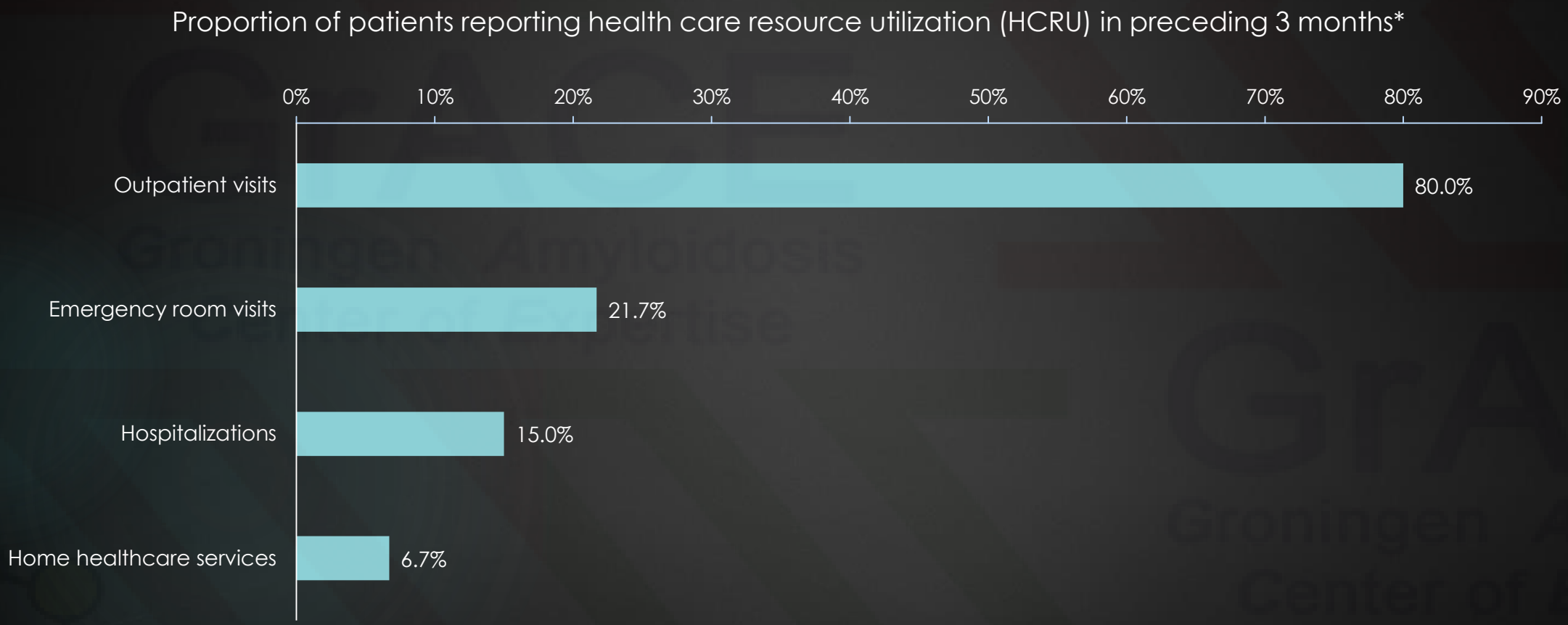


Newly diagnosed ATTRv patients (N=185) have substantial HCRU and costs in the first year[1]

Total HCRU $64,066: inpatient services $34,461, outpatient services $ 23,853, pharmacy $5752

[a]Retrospective study based on US medical claims data; physician office visits and prescription fills show mean + standard deviation.
ATTRv, hereditary transthyretin amyloidosis; HCRU, health care resource utilization.
1. Reddy SR et al. Neurol Ther 2020; [Epub ahead of print].

Most ATTRv patients use HCRU[1]

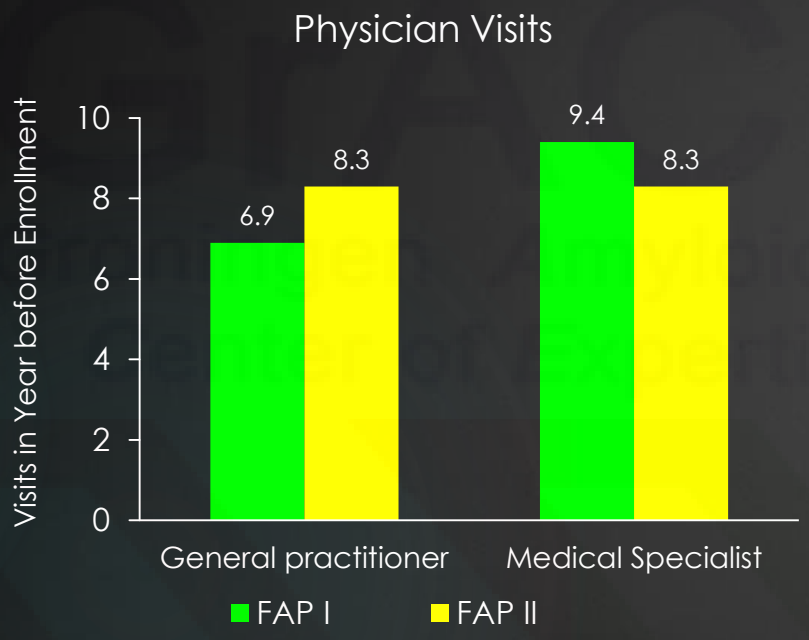


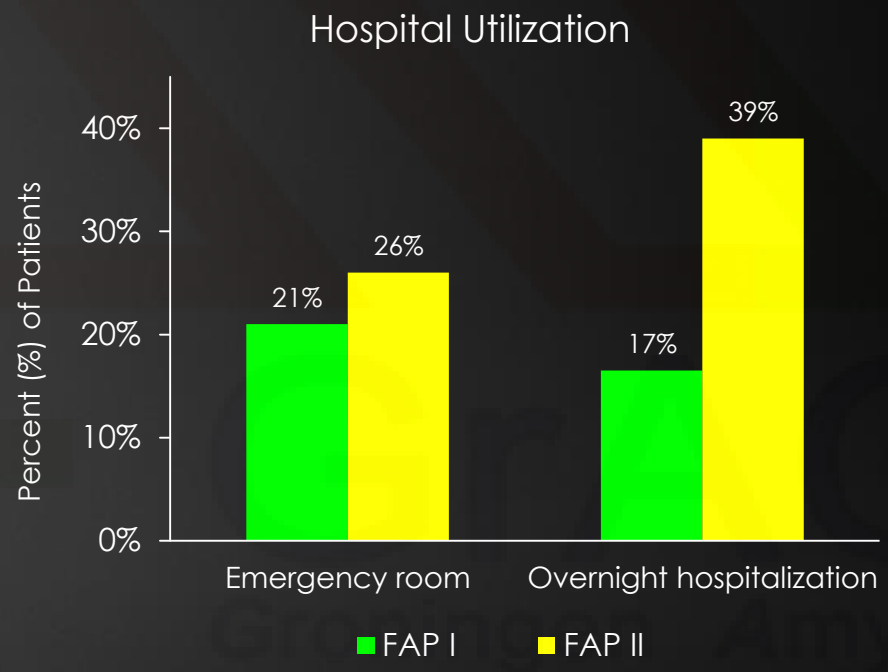
[a]Data from cross-sectional non-interventional survey in patients from USA (n=44) and Spain (n=16); *in the 3 months preceding taking the survey.

1. Stewart M, et al. Neurol Ther 2018;7:349-64.

ATTRv patients: increased use of HCRU

HCRU use in the year prior to enrolment in the APOLLO trial





On average, patients require ≈15-16 visits per year, split by general practitioners and specialists

About 1 out of 4 patients with ATTRv require hospital emergency care and/or hospitalization

ATTRv = hereditary transthyretin amyloidosis; FAP = familial amyloidotic polyneuropathy, staged I and II; HCRU, health care resource utilization.
Schmidt H, et al. Presented at: The International Symposium on Amyloidosis (ISA) 2018; March 2018; Kumamoto, Japan.

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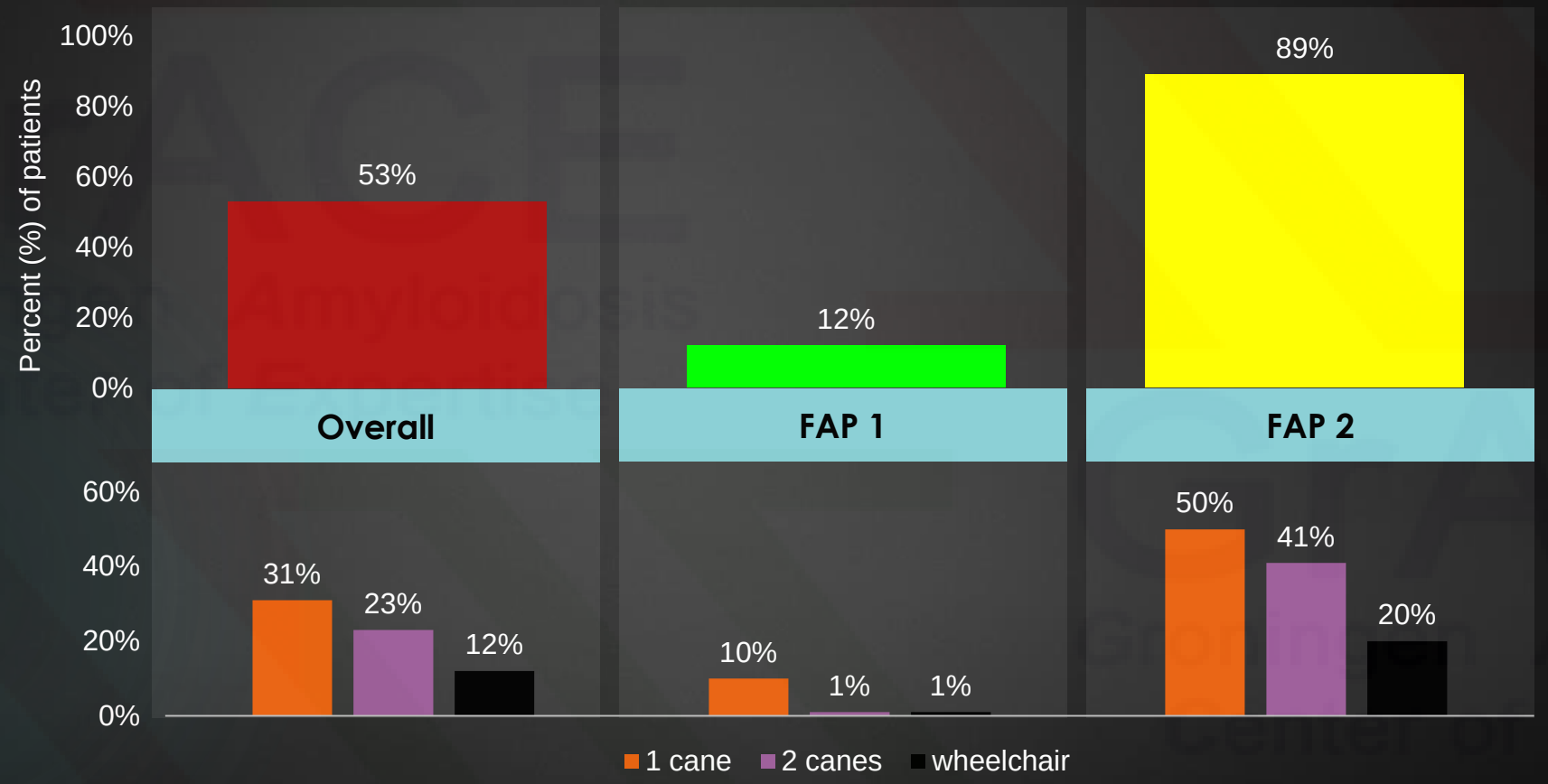
ATTRv amyloidosis: increased use of aids

Patient-Reported need for assistance devices at baseline (APOLLO trial)

Any mobility assistance device

Mobility assistance devices breakdown



ATTRv = hereditary transthyretin amyloidosis; FAP = familial amyloidotic polyneuropathy, staged I and II.
Schmidt H, et al. Presented at: The International Symposium on Amyloidosis (ISA) 2018; March 2018; Kumamoto, Japan.

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The cost of ATTRv-polyneuropathy[1]

- In a Portuguese study[1] a prevalence-based approach including direct and indirect costs was focused on health care resource use (HCRU)
- The burden of disease was expressed in terms of disability-adjusted life years (DALYs)
- The total annual cost-of-illness (COI) of ATTRv-PN in Portugal in 2016 was ≈ €50,000,000 (N≈1850) and the mean cost per patient was ≈ €30,000 (80% direct; 20% indirect costs)
- Treatments accounted for ≈ 50% of total costs, while ≈ 0.2% were devoted to disease prevention. A total of ≈ 2,000 DALYs were lost, 25% due to disability and 75% due to death
- Annual costs and burden of ATTRv-PN were considerable but within the range of other rare diseases

ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy.

[1]Inês M, et al. Societal costs and burden of hereditary transthyretin amyloidosis polyneuropathy. Amyloid. 2020; 27:89-96.

Table 1. Costs per ATTRv-PN patient (€, 2016) in Portugal.

	Users	Total annual cost	Annual mean cost per user	Annual mean cost per patient	% Total cost
Genetic counselling visits	109	10,137	93	5	0.02
Medically assisted reproductive interventions	18	83,906	4661	45	0.16
Drugs	1865	27,120,879	14,542	14,542	51.66
Medical tests	1537	206,507	134	110	0.39
Medical and Nurse visits	2551	657,702	257	352	1.25
Hospitalisations	493	3,287,260	6667	1762	6.26
Health material	1865	949,781	509	509	1.81
Healthcare transport	2338	545,251	233	292	1.04
Direct healthcare costs	–	32,767,382	–	17,569	62.59
Professional formal caregiver and social services	68	99,721	1461	53	0.19
Informal caregiver	1481	8,711,216	5882	4670	16.59
Direct non-healthcare costs	–	8,810,938	–	4724	16.78
Direct costs	–	41,672,364	–	22,344	79.37
Sick leave	438	4,442,382	10,142	2382	8.46
Early retirement	469	6,389,549	13,614	3,426	12.17
Indirect costs	–	10,831,931	–	5808	20.63
Total costs	–	52,504,295	–	28,152	100.00

ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy.
From: Inês M, et al. Societal costs and burden of hereditary transthyretin amyloidosis polyneuropathy. Amyloid. 2020; 27:89-96.

HCRU and costs by PND stage and NT-proBNP level in the UK[1]

Costs of polyneuropathy-related resources by PND stage

	PND 0	PND I	PND II	PND IIIa	PND IIIb	PND IV
Average cost per patient per 6 months	£233	£1,825	£2,499	£4,553	£7,203	£14,114
Average one-off costs per patient	£0	£0	£2,997	£8,075	£9,938	£10,783
Resources with highest average cost per patient per 6 months	1. Physician 2. Psychologist 3. Assistant nurse	1. Doxepin 2. Hospitalization 3. Physician	1. Doxepin 2. Physician 3. Orthotics	1. Homecare 2. Doxepin 3. Physician	1. Homecare 2. Doxepin 3. Parenteral nutrition	1. Homecare 2. Hospitalization 3. Special housing

Costs of cardiomyopathy-related resources by NT-proBNP level

	NT-proBNP <3000 ng/mL	NT-proBNP >3000 ng/mL
Average cost per patient per 6 months	£5,559	£7,991
Resources with highest average cost per patient per 6 months	1. Cardiac resynchronization therapy 2. Sinoatrial node ablation 3. Rivaroxaban	1. Cardiac resynchronization therapy 2. Hospitalization days 3. Sinoatrial node ablation

Note: All costs estimates are additive and mutually exclusive.
NT-proBNP, N-terminal pro b-type natriuretic peptide; PND, polyneuropathy disability.
1. Alnylam data on file (Patisiran for the treatment of hereditary transthyretin amyloidosis) 2019.

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Modelling of the fiscal life course[1]

Using a public economic framework for the Netherlands. The economic impact per person between ages 40-80. Looking at:

- Total money transfers:
  - Health costs (HCRU)
  - Disability payments (government transfers)
  - Pensions
- Lifetime earnings
- Gross tax:
  - Direct tax
  - Indirect tax

1. Connolly MP et al. Orphanet J Rare Dis 2019;14:220

The fiscal life course of ATTRv amyloidosis can be modelled

Using a public economic framework for the Netherlands[1]

Scenario 1

- Early onset (age 45, PND Stage 1)
- Median progression
- Death at age 55 (PND Stage 4)
- No severe cardiomyopathy

"Early PN, median progression"

Scenario 2

- Early onset (age 45, PND Stage 1)
- Slow progression
- Death at age 65 (PND Stage 4)
- No severe cardiomyopathy

"Early PN, slow progression"

Scenario 3

- Late onset (age 60, PND Stage 1)
- Median progression
- Death at age 70 (PND Stage 4)
- No severe cardiomyopathy

"Late PN, median progression"

Scenario 4

- Late onset & diagnosis (age 60, PND Stage 2)
- Severe cardiomyopathy
- Death within 4 years (PND Stage 3b)

"Late onset, severe CM"

ATTRv, hereditary transthyretin amyloidosis; CM, cardiomyopathy; PN, polyneuropathy; PND, polyneuropathy disability

1. Connolly MP et al. Orphanet J Rare Dis 2019;14:220

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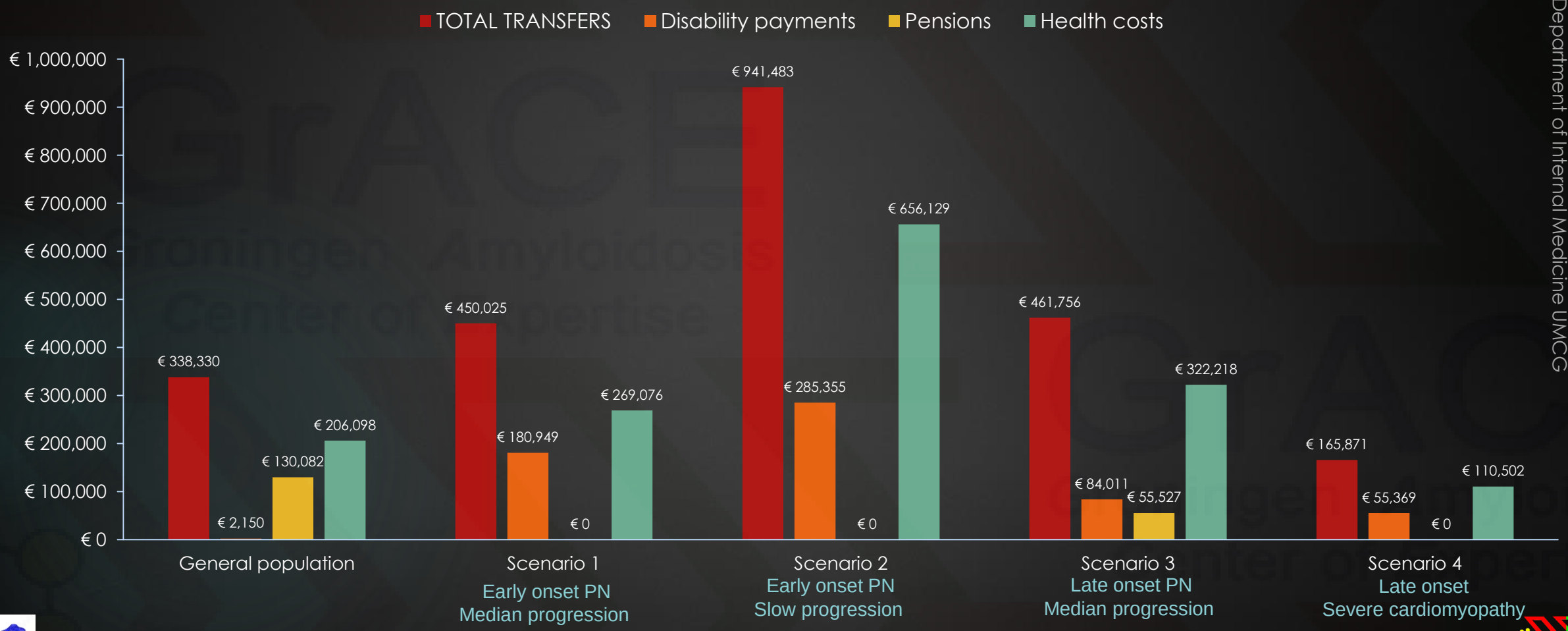
Indirect costs depend on duration of illness

Transfer payments: Patients living longest with the disease incur the highest total transfers[1]

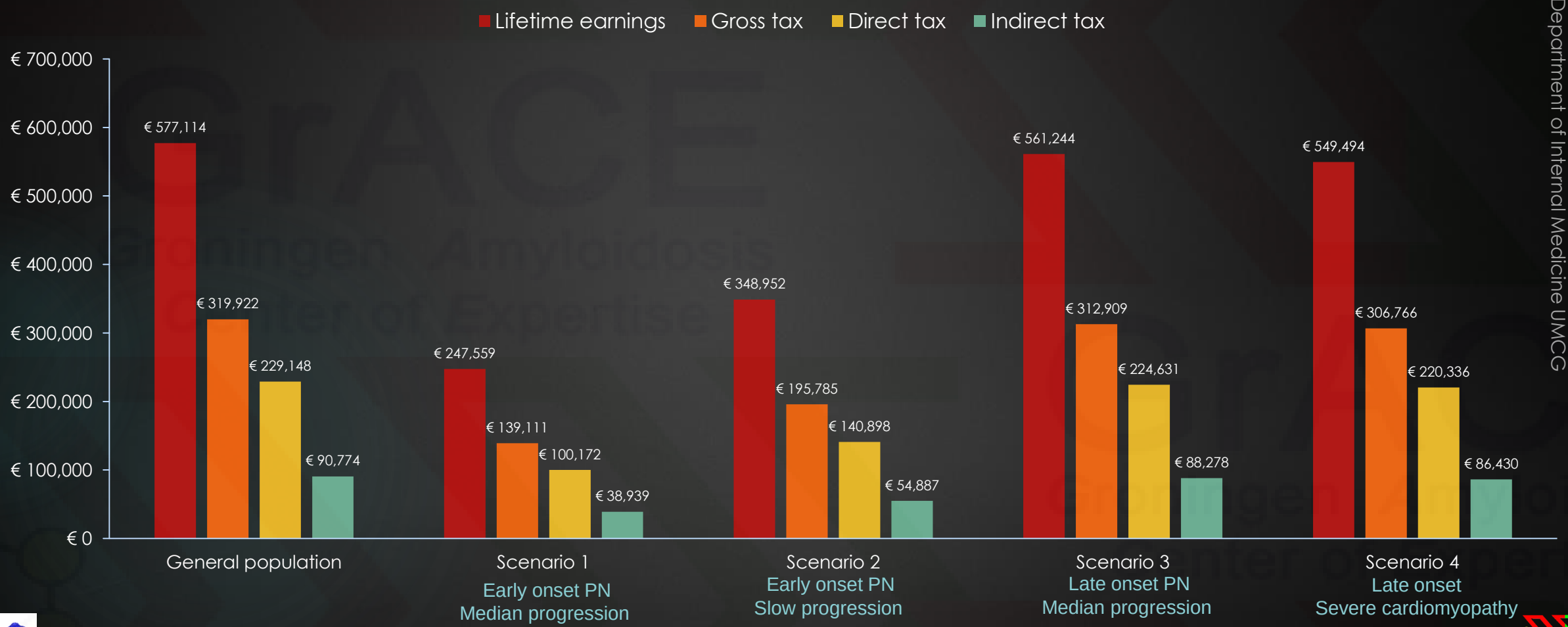


PN, polyneuropathy

1. Connolly MP et al. Orphanet J Rare Dis 2019;14:220

Earnings and taxes paid depend on disease onset

Patients with early onset disease have lowest lifetime earnings and pay least total taxes[1]

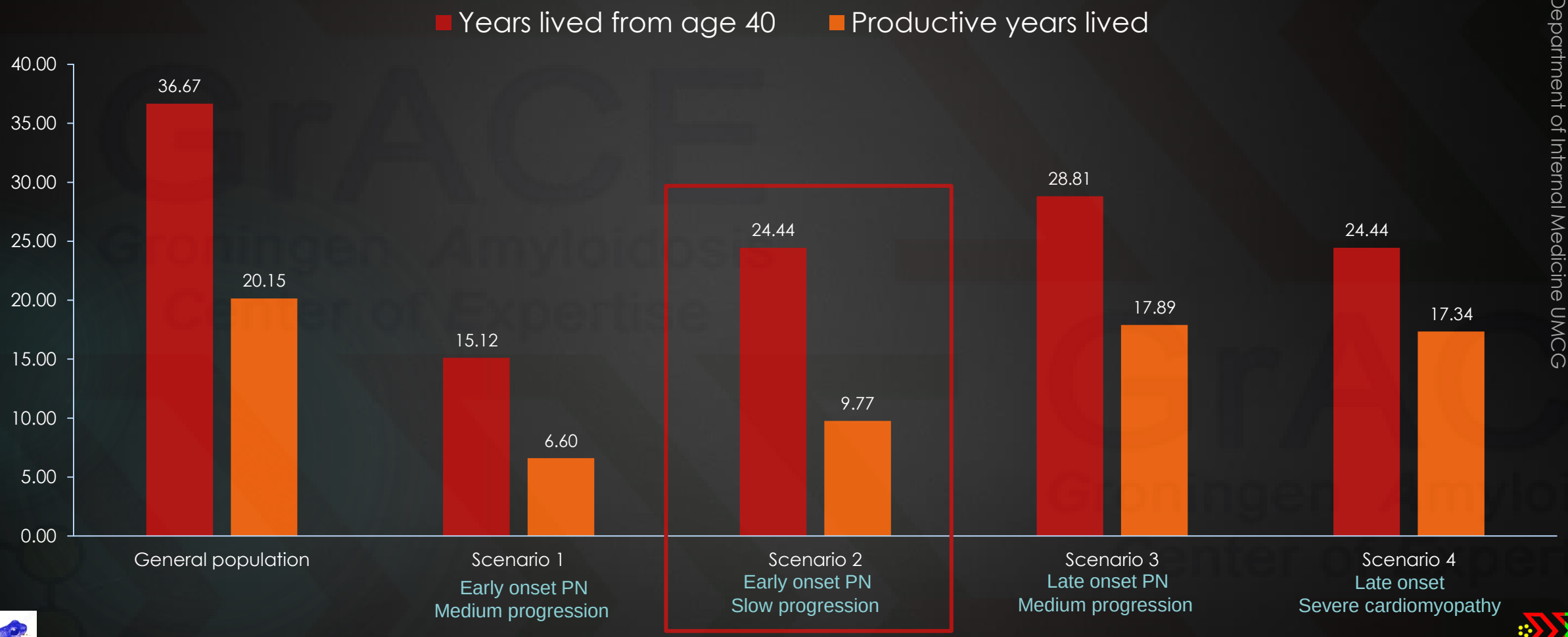


PN, polyneuropathy

1. Connolly MP et al. Orphanet J Rare Dis 2019;14:220

Productive years are least in patients with early onset disease

Only 40% of life aged ≥40 is productive in patients with early onset and slow progression[1]



PN, polyneuropathy

1. Connolly MP et al. Orphanet J Rare Dis 2019;14:220

Early onset disease presents the highest fiscal burden

Halting disease progression **early** would generate economic benefits alongside health benefits[1]

Scenario 1: "Early PN, median progression"

- Have lowest lifetime earnings
- Pay least in total taxes
- Have fewest years alive after age 40 with second lowest proportion of productive years (44%)

Scenario 2: "Early PN, slow progression"

- Live longest with disease and require most public funding
- Incur highest health costs/disability payment
- Have lowest proportion of productive years after age 40 (40%)

Scenario 3: "Late PN, median progression"

- Have highest lifetime earnings
- Pay most in total taxes
- Live longest after age 40 with second highest proportion of productive years (62%)

Scenario 4: "Late onset, severe CM"

- Incur the lowest government spending
- Have second highest lifetime earnings and total taxes paid
- Have highest proportion of productive years after age 40 (71%)

CM, cardiomyopathy; PN, polyneuropathy

1. Connolly MP et al. Orphanet J Rare Dis 2019;14:220

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Societal burden:

Direct costs to the patients, families and care givers

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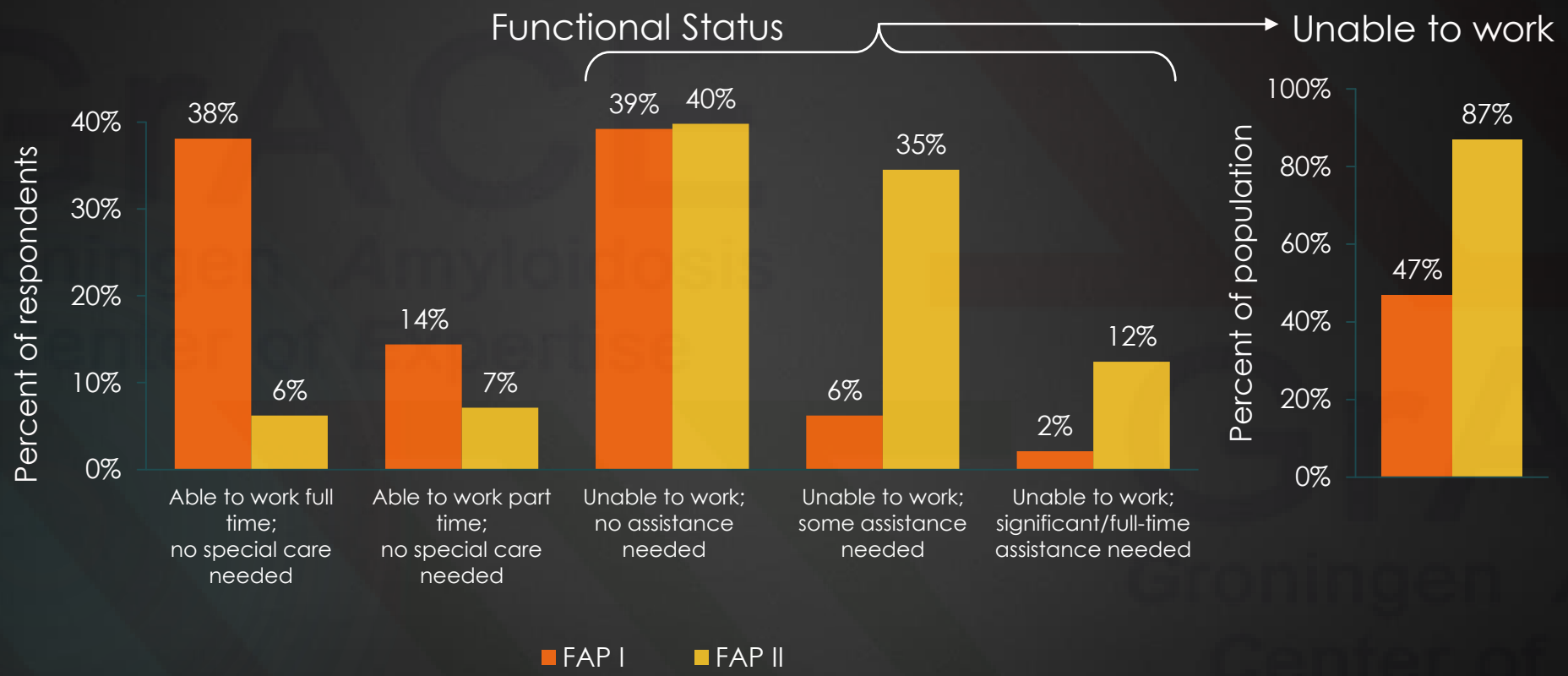
69% of those in the APOLLO trial reported being unable to work

Patients' functional status and ability to work by FAP stage

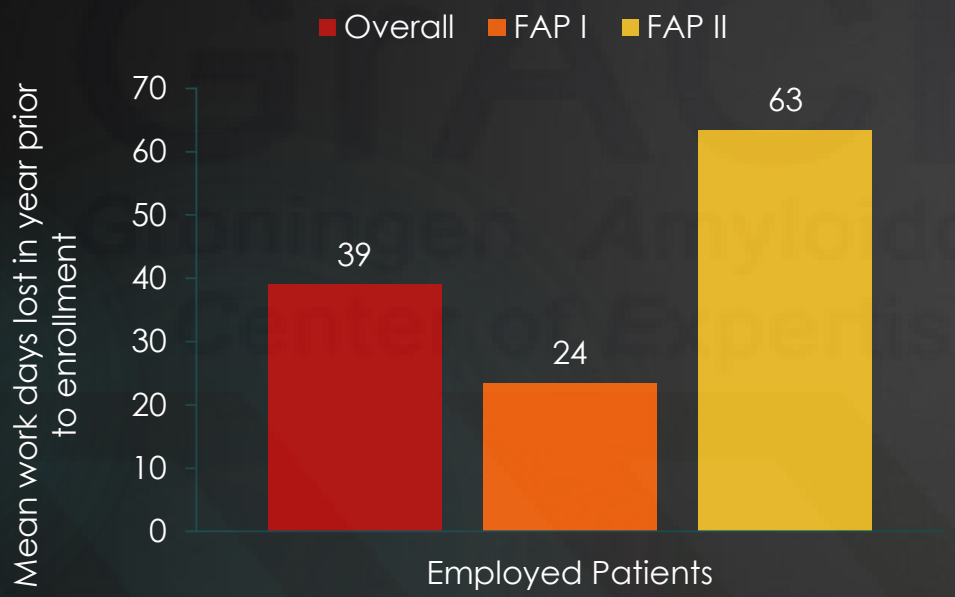


Ability to work and requirement for assistance to live independently were associated with FAP stage, increasing from **47%** unable to work to **87%** between FAP stages **I** (no aids) and **II** (one or more canes)

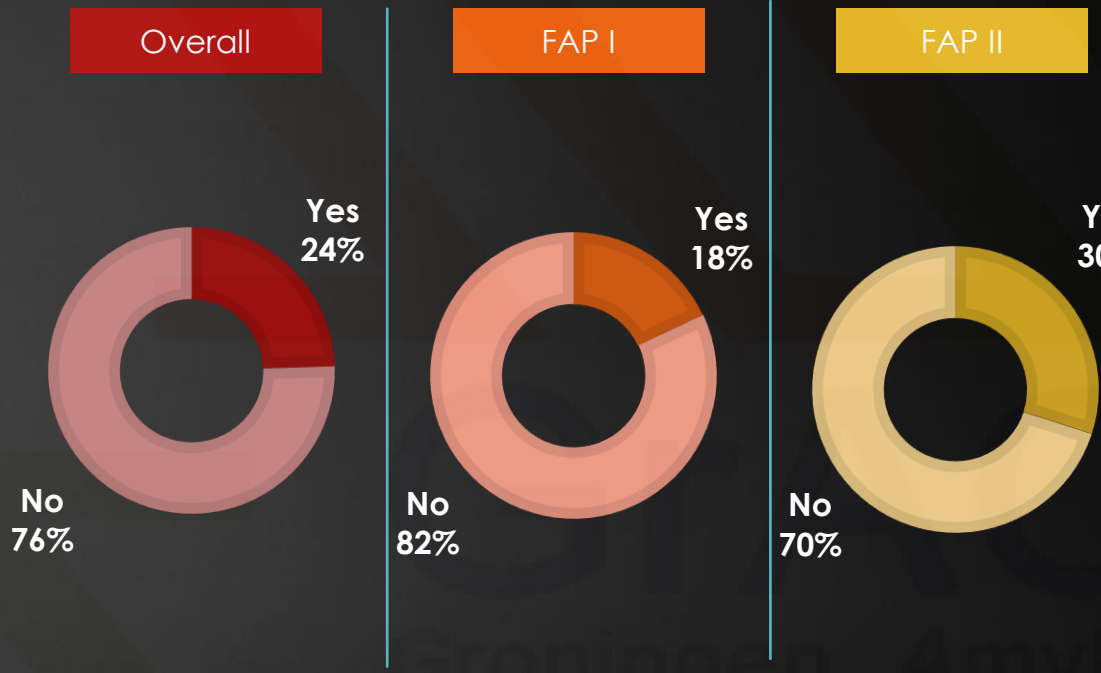
FAP, familial amyloidotic polyneuropathy, staged I and II.
Berk JL, et al. Presented at: The International Symposium on Amyloidosis (ISA) 2018; March 2018; Kumamoto, Japan.

Patients in the APOLLO trial reported an average of 39 work-days lost, and 24% received government compensation

Patient work-days lost



Government compensation received due to illness



Lost work days numerically increased from 24 to 63 days in FAP stage I vs FAP stage II (P=0.061)

Need for government compensation increased from 18% to 30% in FAP stage I vs stage II (P=0.03)

FAP, familial amyloidotic polyneuropathy, staged I and II.

Berk JL, et al. Presented at: The International Symposium on Amyloidosis (ISA) 2018; March 2018; Kumamoto, Japan.

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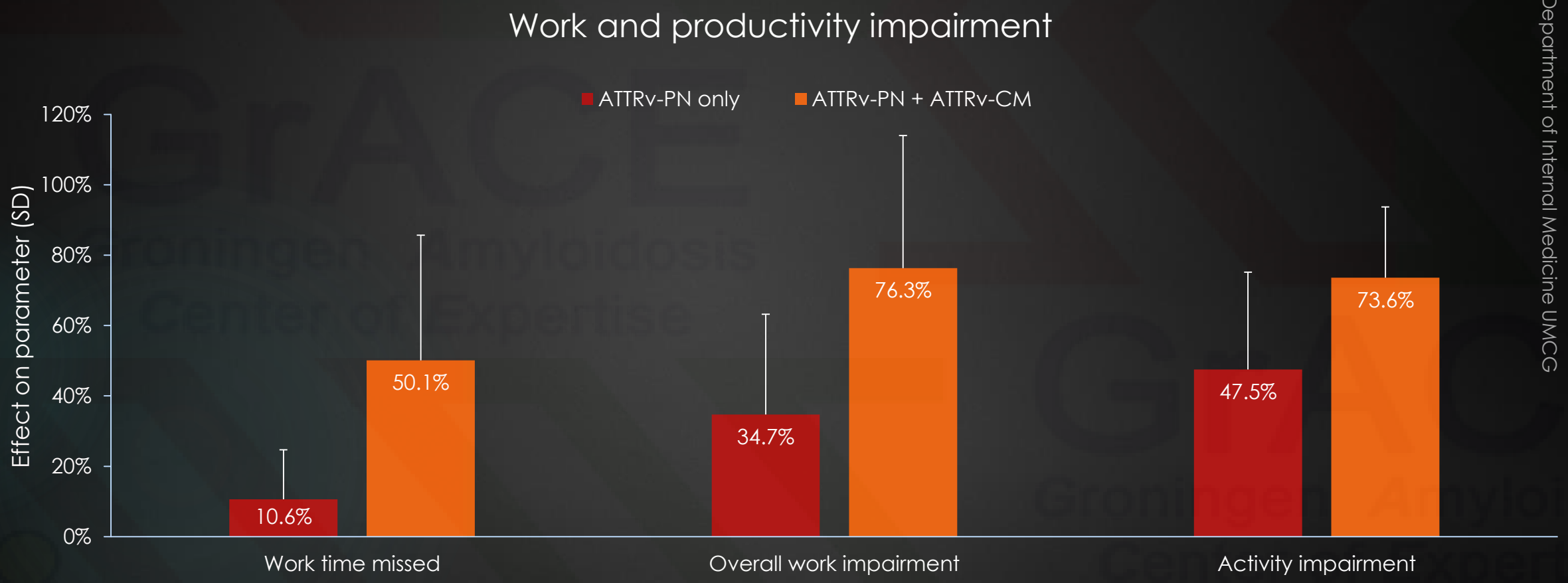
Productivity is impaired in patients with ATTRv amyloidosis[a]

Patients who have both neuropathy and cardiac symptoms are most affected[1]

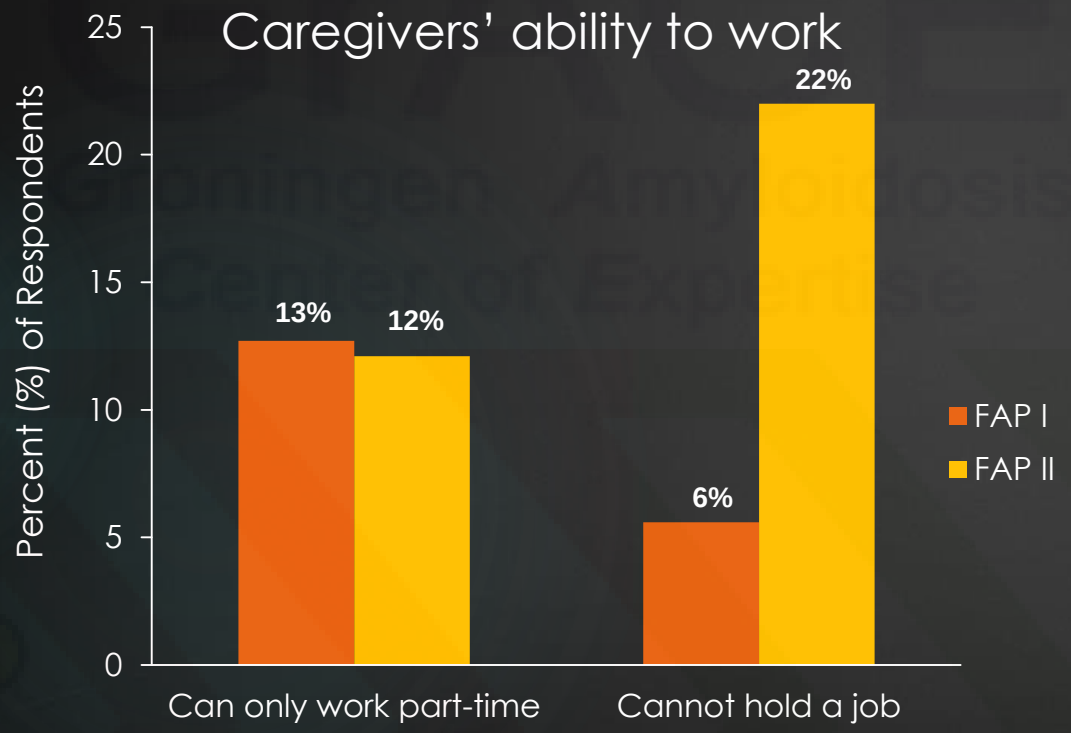


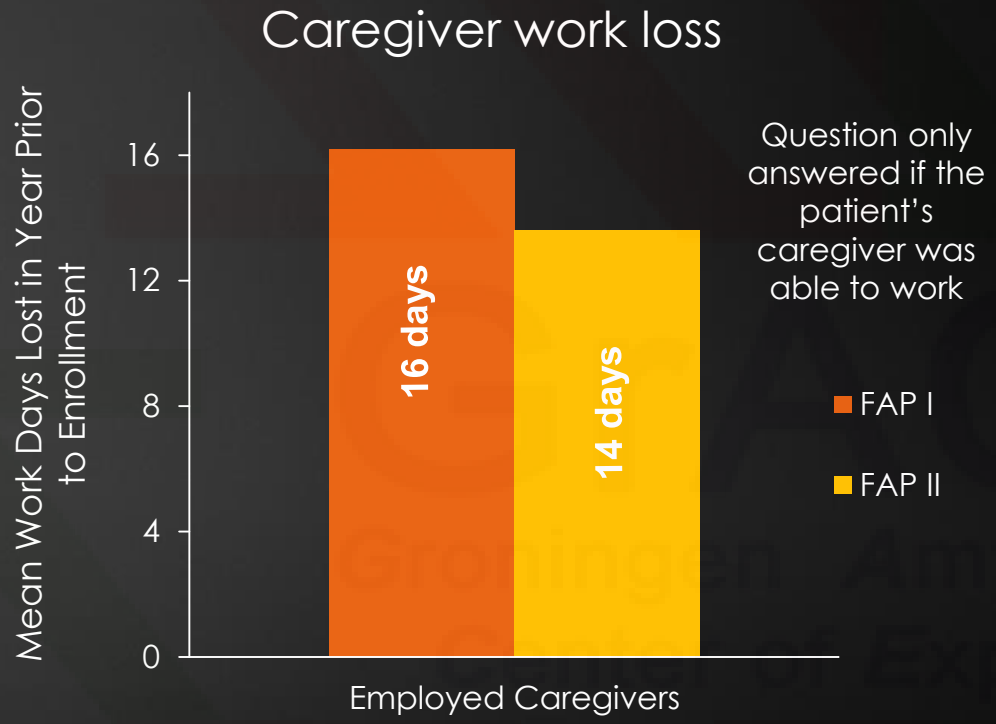
[a]Data from cross-sectional non-interventional survey in patients from USA (n=44) and Spain (n=16).
ATTRv-PN, transthyretin amyloidosis with peripheral neuropathy; ATTRv-CM, transthyretin amyloidosis with cardiomyopathy; SD, standard deviation.

1. Stewart M et al. Neurol Ther 2018;7:349-64.

ATTRv amyloidosis impacts on **caregivers'** ability to work[1]

Inability to hold a paying job rose from **6%** to **22%** for those caring for a patient with FAP stage **I** vs Stage **II** in the year prior to enrolment in APOLLO





ATTRv = hereditary transthyretin amyloidosis; FAP, familial amyloidotic polyneuropathy, staged I and II

1. Berk J et al. Presented at International Symposium on Amyloidosis (ISA); Kumamoto, Japan; March 26–29, 2018. Poster.

Learning Points

For patients, healthcare systems and society

- The cost of disease progression is not only related to HCRU, but also to societal support, loss of productivity, early retirement, loss of taxes, and work loss of caregivers
- The long and winding road to diagnosis in non-familial cases is expensive before diagnosis and increases risks of progressed disease and costs at diagnosis
- Age at onset, rate of progression and organ dominance (heart vs. nerves) are important determinants of the costs of disease
- HCRU costs rise with progression of polyneuropathy and of cardiomyopathy

HCRU, health care resource use.

Learning Points

For patients, healthcare systems and society

- Productivity is most impaired in patients with both polyneuropathy and cardiomyopathy
- Patients living longest with the disease incur the highest total transfers
- Patients with early onset disease have lowest lifetime earnings and pay least total taxes

- Complete stabilization of early disease by early detection and highly effective treatment will - alongside obvious health benefits - reduce the current economic and societal burden of the disease

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Relevant references used in the presentation (1)

Literature:

- Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A, et al. Natural history, quality of life, and outcome in cardiac transthyretin Amyloidosis. Circulation 2019;140:16–26.
- Reddy SR, Chang E, Tarbox MH, Broder MS, Tieu RS, Guthrie S, et al. The Clinical and Economic Burden of Newly diagnosed hereditary transthyretin (ATTRv) amyloidosis: a retrospective analysis of claims data. Neurol Ther 2020; [Online ahead of print].
- Stewart M, Shaffer S, Murphy B, Loftus J, Alvir J, Cicchetti M, et al. Characterizing the High Disease Burden of Transthyretin aAmyloidosis for patients and caregivers. Neurol Ther 2018;7:349-64.
- Inês M, Coelho T, Conceição I, Landeiro F, de Carvalho M, Costa J. Societal costs and burden of hereditary transthyretin amyloidosis polyneuropathy. Amyloid 2020; 27:89-96.
- Connolly MP, Panda S, Patris J, Hazenberg BP. Estimating the fiscal impact of rare diseases using a public economic framework: a case study applied to hereditary transthyretin-mediated (hATTR) amyloidosis. Orphanet J Rare Dis 2019;14:220.

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Relevant references used in the presentation (2)

Poster presentations at The International Symposium on Amyloidosis (ISA); March 2018; Kumamoto, Japan:

- Schmidt H, Lin H, Agarwal S, Merkel M, Gollob J, Berger A, et al. Impact of hereditary transthyretin-mediated amyloidosis on use of health care services: an analysis of the APOLLO Study. PC034, Abstract book page 449.
- Berk JL, Lin H, Agarwal S, Merkel M, Gollob J, Berger A, et al. Impact of hereditary transthyretin-mediated amyloidosis on daily living and work productivity: baseline results from APOLLO. PC035. Abstract book page 450.