Transthyretin Familial Amyloid Polyneuropathy.
hATTR-PN

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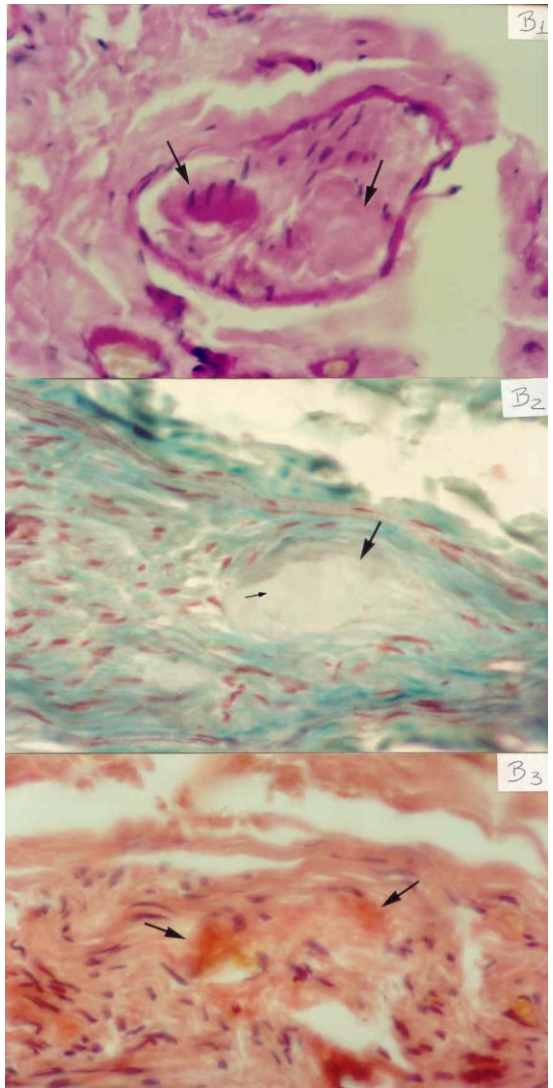
Hospital Universitário Clementino Fraga Filho

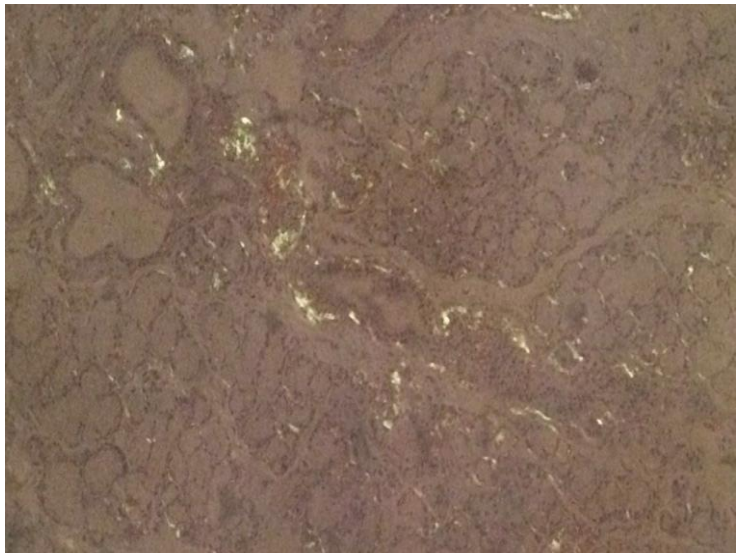
CEPARM

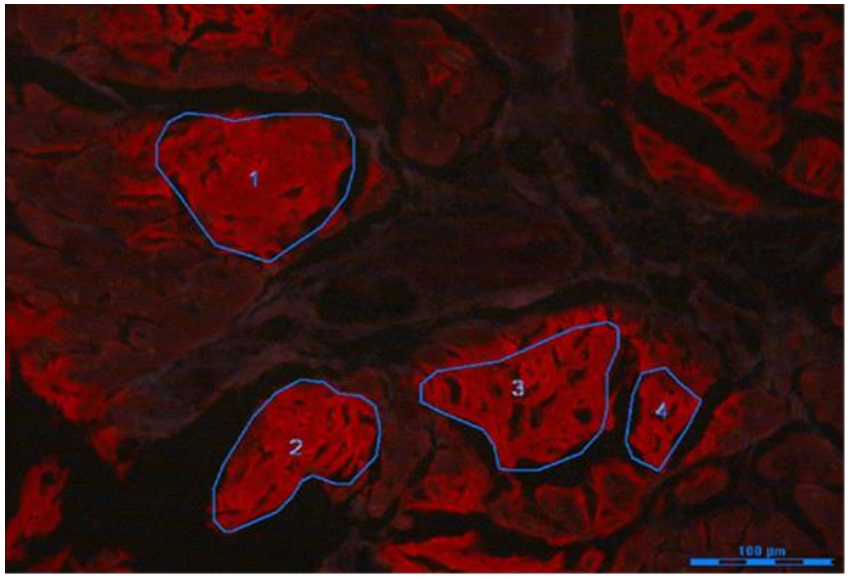
Disclosures

- Márcia Waddington Cruz received honorarium from, NHI, Prothena, FoldRx, Pfizer, Alnylam, Ionis, PTC, Astra Zeneca and Genzyme for travel expenses related to presentations at medical meetings, for acting as a consultant member.
- All images from patients and exams are original from Márcia Waddington Cruz and permission to use was given by the patients.
- Márcia Waddington Cruz was an author of all related articles and presentations.

Amyloid deposit in different tissues





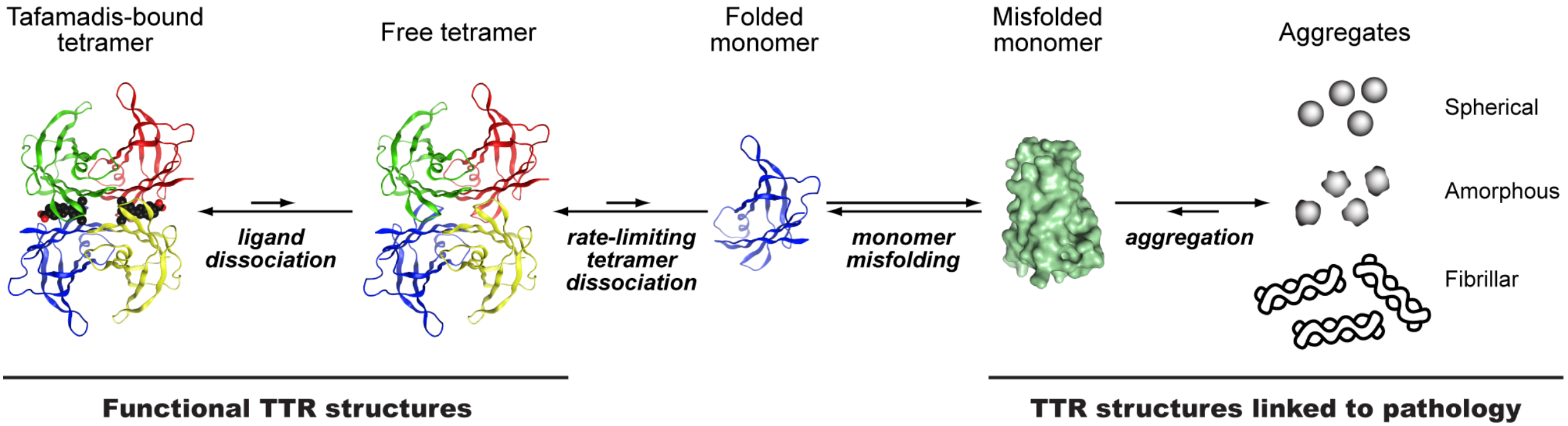


TTR transport vitamin A and tyroxin.

98% production in the liver

> 120 mutations

V30M most common



Courtesy from Dr. Jeffrey Kelly.

TTR Amyloidosis is a Severe, Progressive and Fatal Disease Affecting Multiple Organs

Ocular Manifestations

- Vitreous opacities
- Glaucoma
- Abnormal conjunctival vessels
- Papillary abnormalities

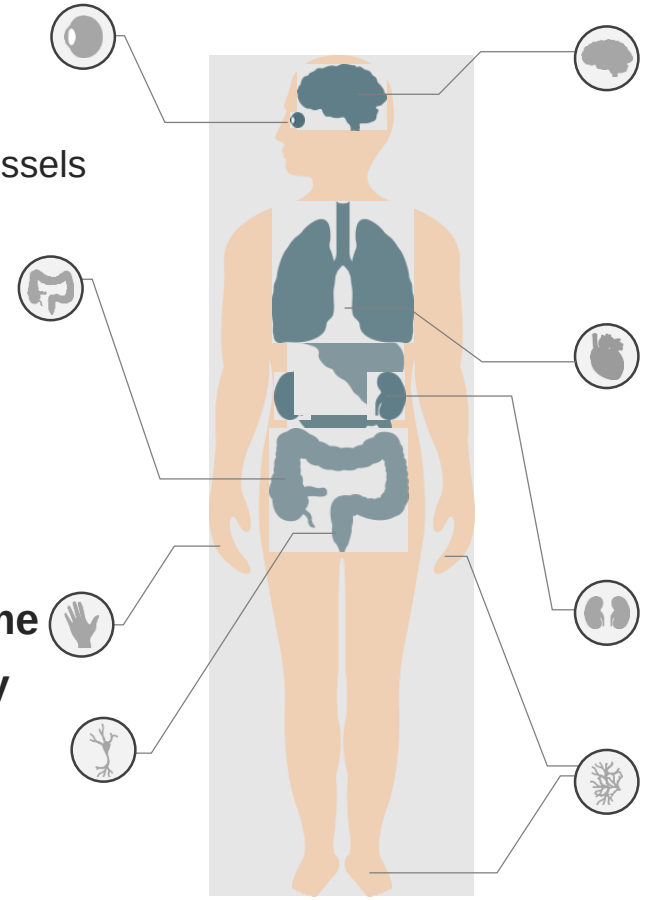
GI Manifestations

- Nausea & vomiting
- Early satiety
- Diarrhea
- Severe constipation
- Alternating episodes of diarrhea & constipation
- Unintentional weight loss

Carpal Tunnel Syndrome

Autonomic Neuropathy

- Orthostatic hypotension
- Recurrent urinary tract infections (due to urinary retention)
- Sexual dysfunction
- Sweating abnormalities



Cerebral Amyloid Angiopathy

- Progressive dementia
- Headache
- Ataxia
- Seizure
- Spastic paresis
- Stroke-like episode

Cardiovascular Manifestations

- Conduction blocks
- Cardiomyopathy
- Arrhythmia

Nephropathy

- Proteinuria
- Renal failure

Peripheral sensory-motor neuropathy

- Typically axonal, fiber-length-dependent, symmetric, and relentlessly progressive in distal to proximal direction

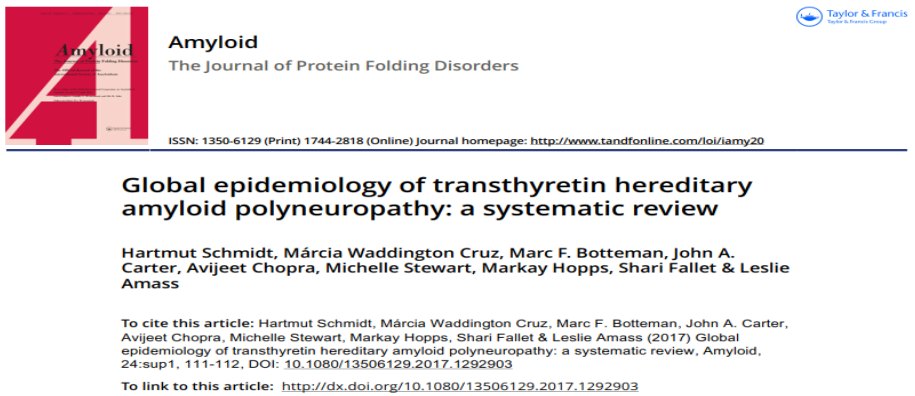
Adapted from: Conceicao et al, First Congress of the European Academy of Neurology (EAN), June 20-23 2015, Berlin, Germany (#P1184)

TTR-FAP is a rare disease with areas of identifiable clustering around the world

Published prevalence estimates of TTR-FAP from key countries

- **Portugal**
  - 19.23[1] - 163.12[2] per 100,000 individuals
- **Sweden**
  - 2.6[1] - 104.0[3] per 100,000 individuals
- **Japan**
  - 0.10[4] - 1.5[5] per 100,000 individuals
- **Brazil**

5.000 to 15.000 individuals

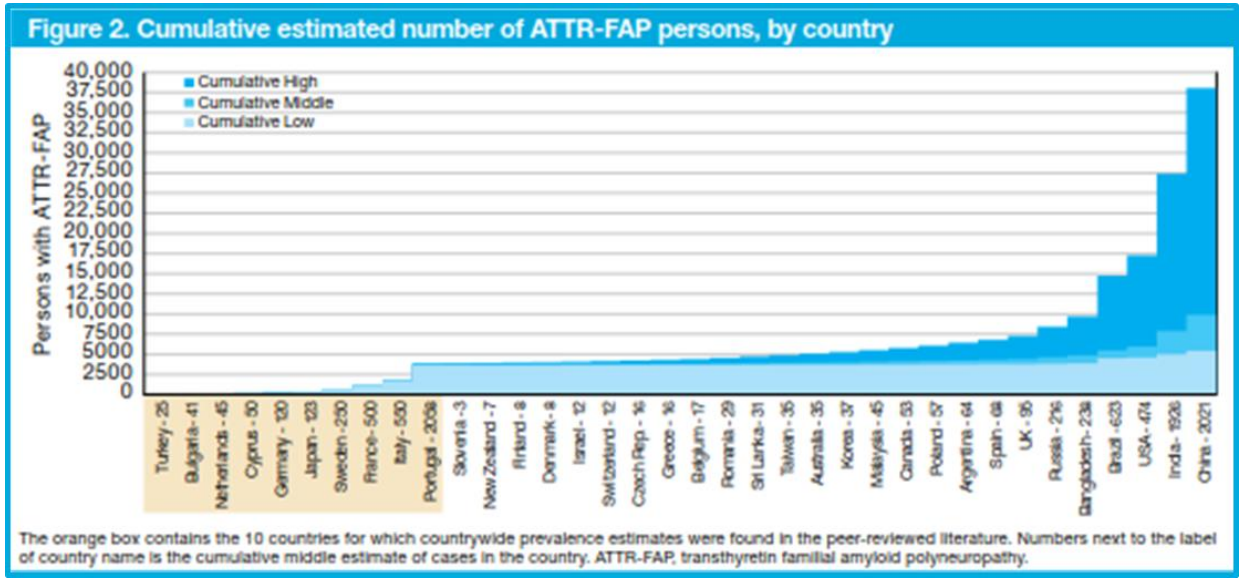

Amyloid
The Journal of Protein Folding Disorders
ISSN: 1350-6129 (Print) 1744-2818 (Online) Journal homepage: http://www.tandfonline.com/loi/iamy20

Global epidemiology of transthyretin hereditary amyloid polyneuropathy: a systematic review

Hartmut Schmidt, Márcia Waddington Cruz, Marc F. Botteman, John A. Carter, Avijeet Chopra, Michelle Stewart, Markay Hopps, Shari Fallet & Leslie Amass

To cite this article: Hartmut Schmidt, Márcia Waddington Cruz, Marc F. Botteman, John A. Carter, Avijeet Chopra, Michelle Stewart, Markay Hopps, Shari Fallet & Leslie Amass (2017) Global epidemiology of transthyretin hereditary amyloid polyneuropathy: a systematic review, Amyloid, 24:sup1, 111-112, DOI: 10.1080/13506129.2017.1292903

To link to this article: http://dx.doi.org/10.1080/13506129.2017.1292903



1. Parman, 2016 2. Ines, 2015 3. Andersson,1976 4. Kato-Motozaki, 2008 5. Arakai, 1968 6. Planté-Bordeneuve, 2011

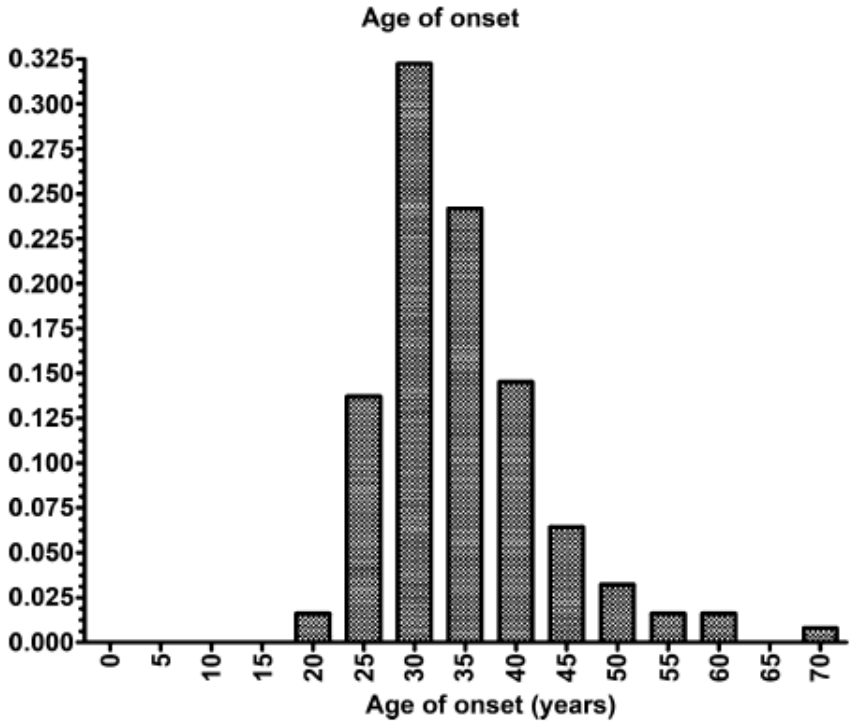
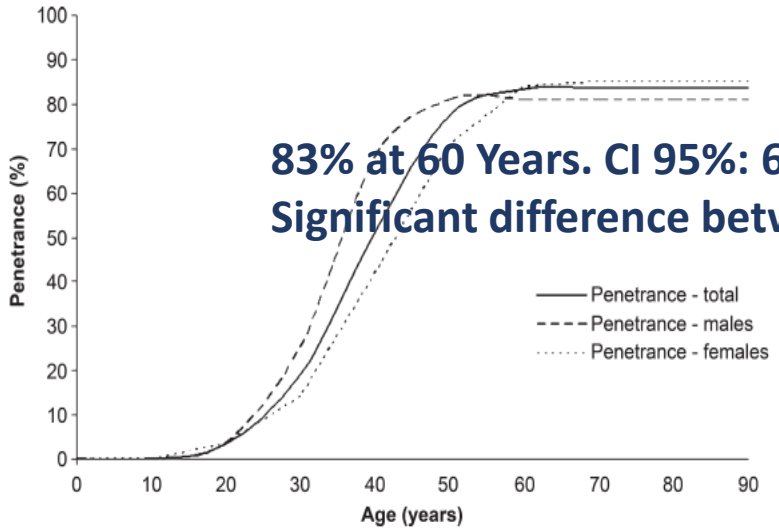


Figure 1 Distribution of age of onset of familial amyloid polyneuropathy in Brazilian families.



83% at 60 Years. CI 95%: 66 – 100
Significant difference between sexes (p < 0,001)

Age (years)	30	40	50	60	70	80	90
Sample	19	51	77	83	83	83	83
CI 95%	(11–26)	(36–62)	(56–93)	(65–99)	(66–99)	(66–99)	(66–100)
Males	25	68	81	81	81	81	81
Females	14	42	71	84	85	85	85

Figure 2 Penetrance estimates according to age and gender.

European Journal of Neurology 2009, **16:** 337–341 doi:10.1111/j.1468-1331.2008.02429.x

Penetrance estimation of TTR familial amyloid polyneuropathy (type I) in Brazilian families

M. A. C. Saporta[a], C. Zaros[b], M. W. Cruz[a], C. André[a], M. Misrahi[b], C. Bonaïti-Pellié[c,d] and V. Planté-Bordeneuve[e]

[a]*Department of Neurology, University Hospital, Federal University of Rio de Janeiro, Brazil;* [b]*Laboratoire de Biologie cellulaire et moléculaire, CHU Bicêtre, Paris, France;* [c]*INSERM U535, Villejuif, France;* [d]*Université Paris-Sud, IFR 69, Villejuif, France; and* [e]*Service de Neurologie, CHU Henri Mondor, Paris, France*

In previous work from our center a common haplotype was demonstrated in Portuguese and Brazilian patients from 22 families and the calculation of the most recent common ancestor in 13 families demonstrated that it has occurred at 26 past generations about 650 years ago hence before the time of Brazil`s discovery (1500) [1].

Haplotype analysis

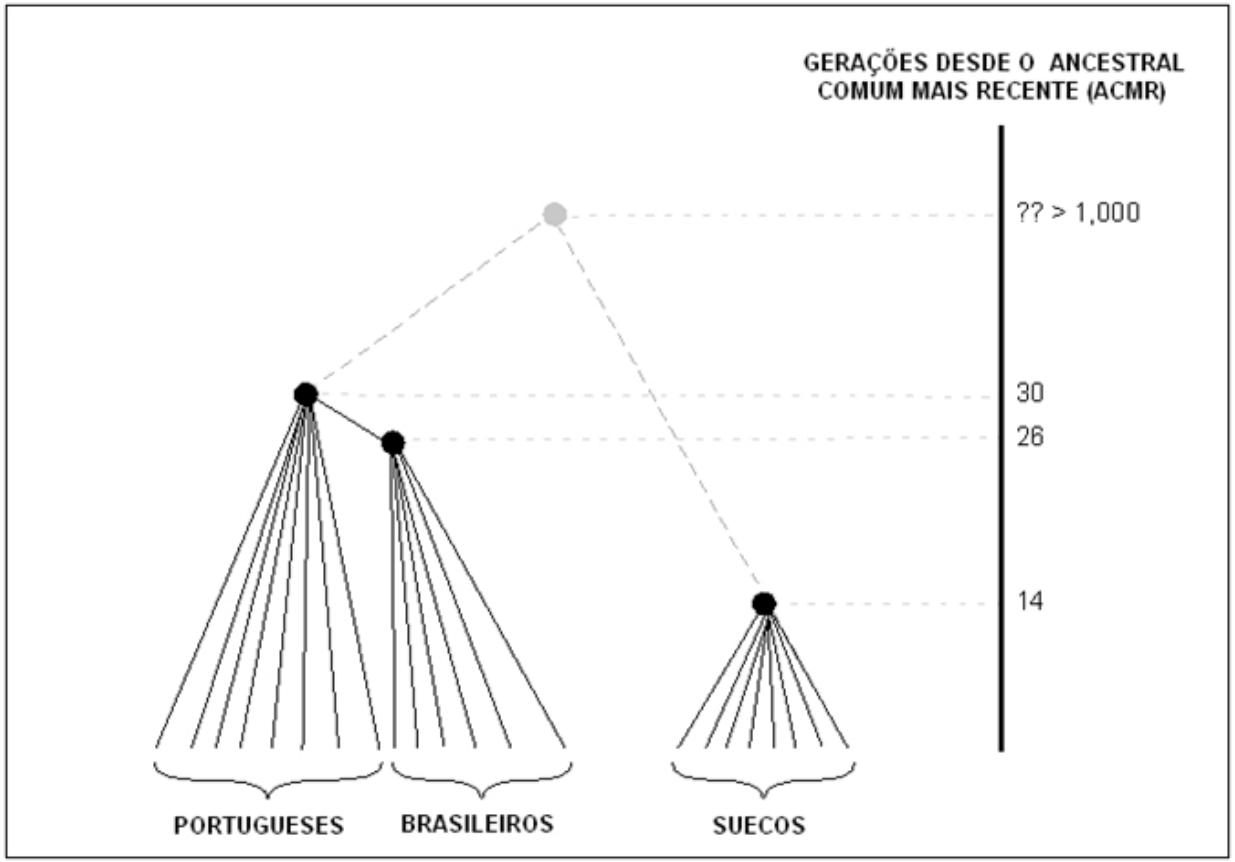
13 families

MRCA :

26 generations (CI 95%: 17 – 40)

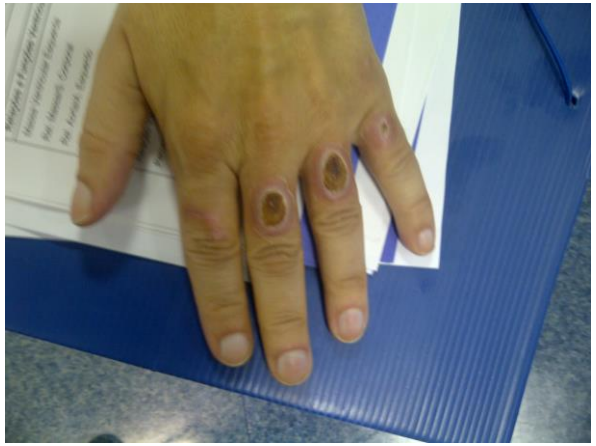
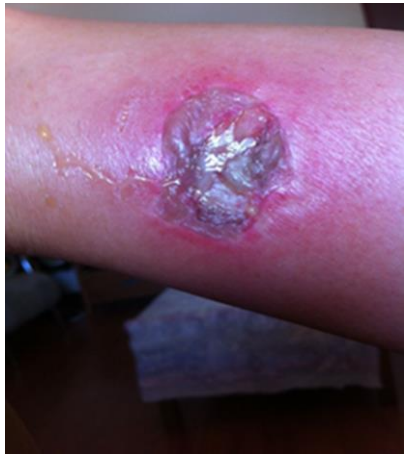
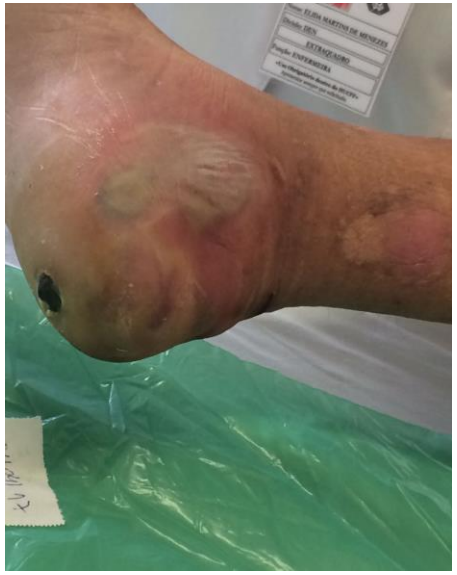
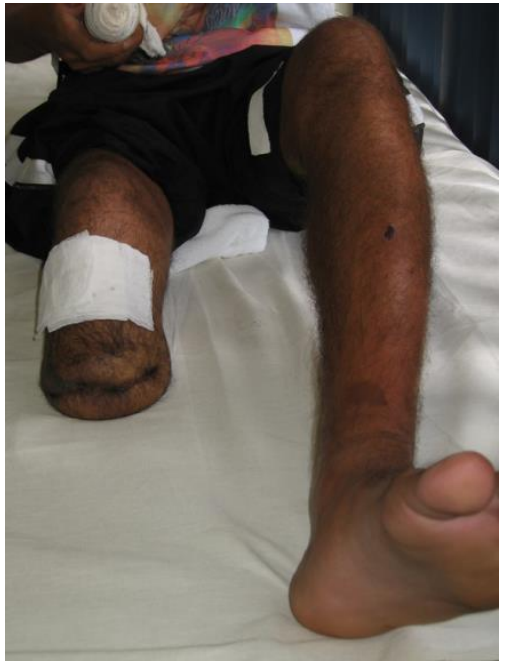
650 years (CI 95%: 425 – 1000)

Mais de 25 milhões de Luso descendentes

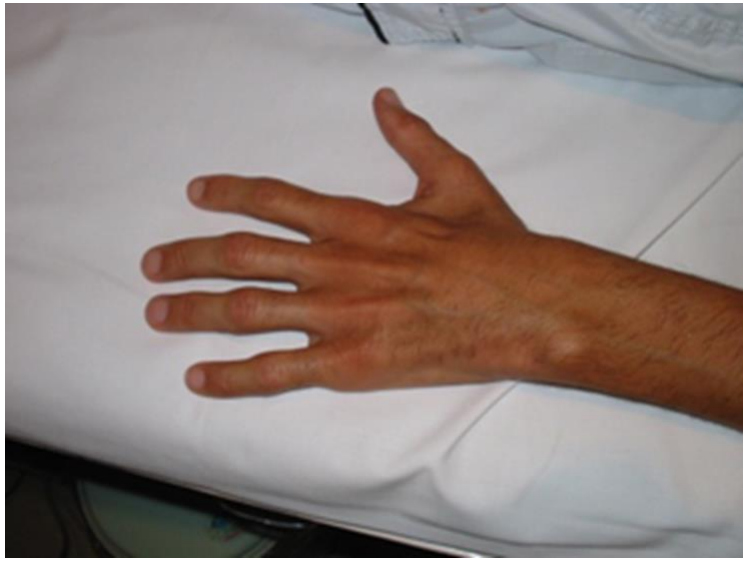


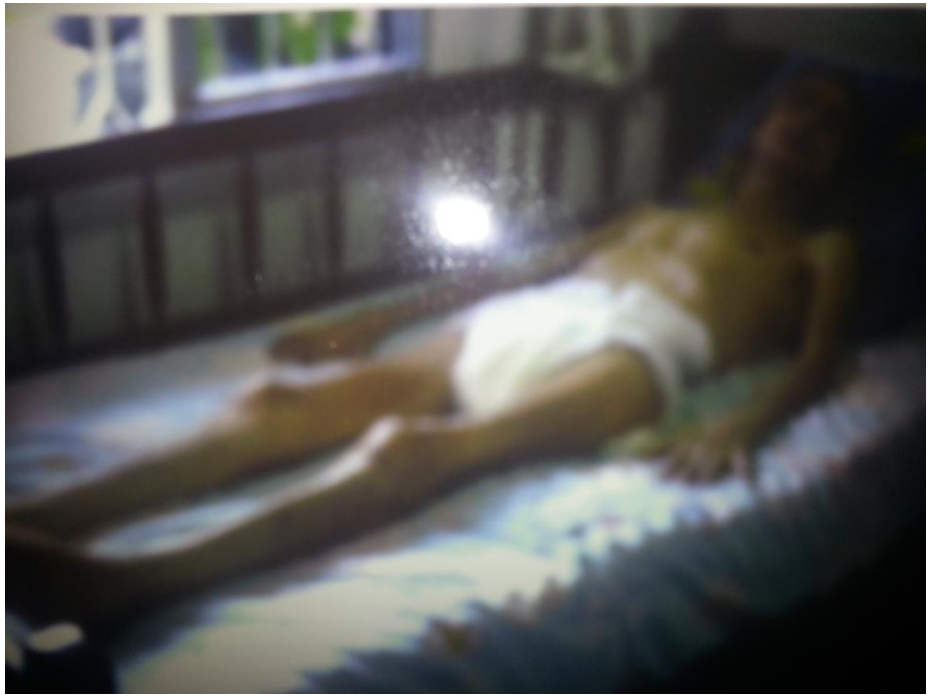
TTR-FAP disease progression

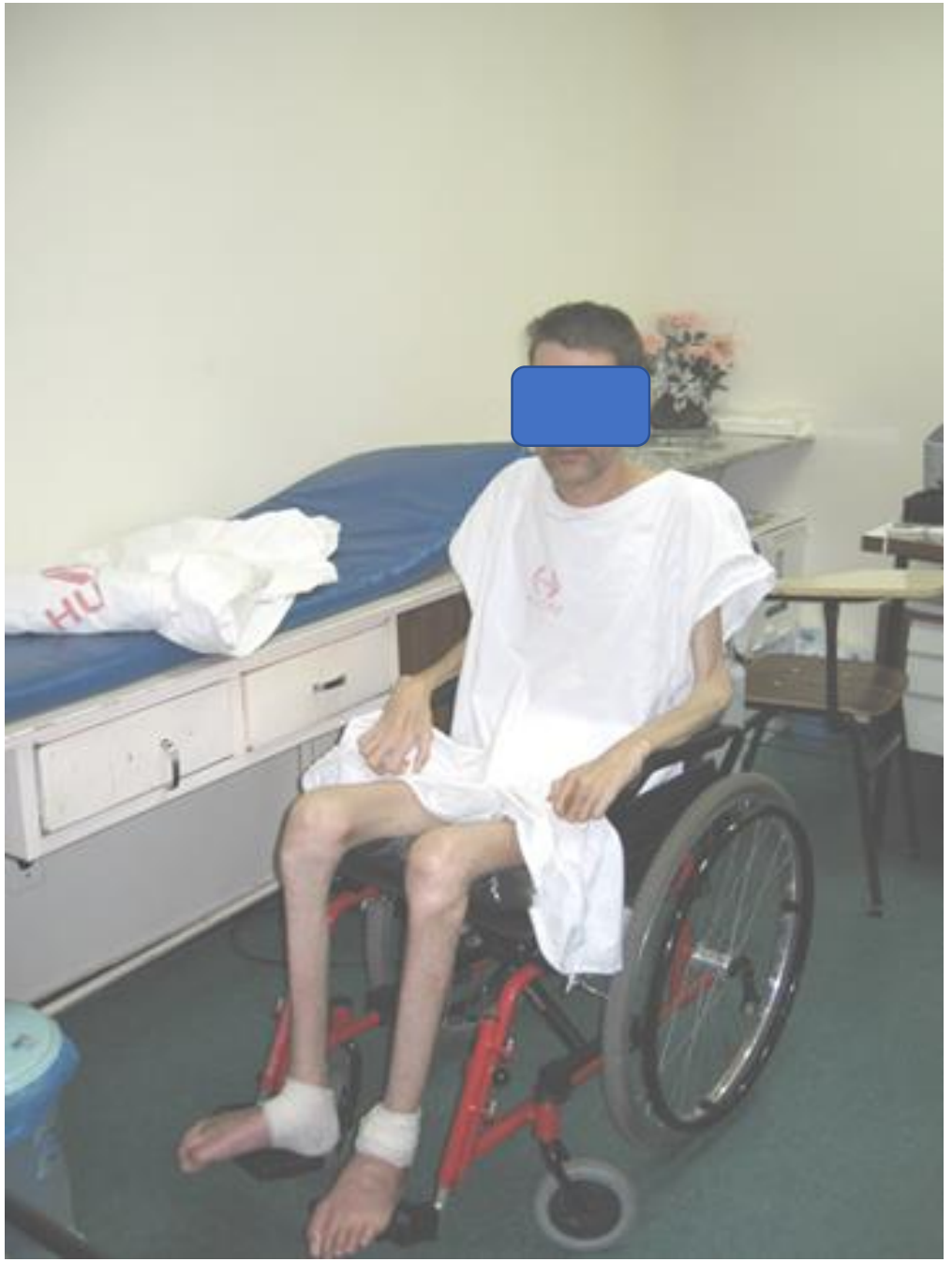
- Patients with TTR-FAP experience a progressive loss of sensory, motor, and autonomic nerve function[2]

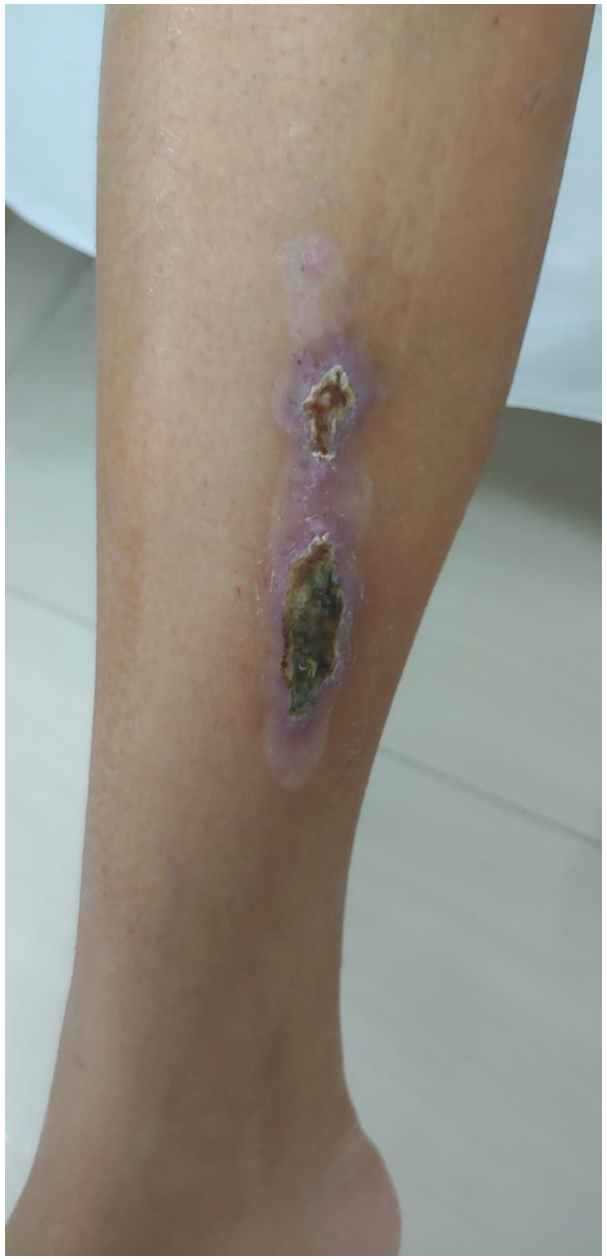





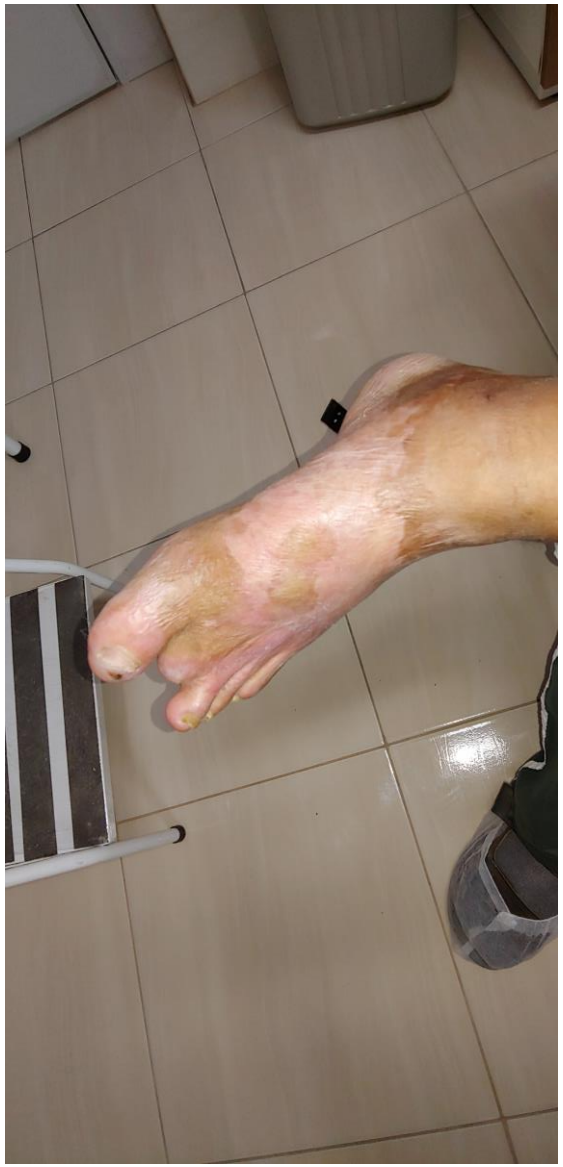
1. Ando Y et al., *Orphanet J Rare Dis.* 2013; doi: 10.1186/1750-1172-8-31; 2. Adams D, et al., *Curr Opin Neurol.* 2016; 29(Suppl 1):S1–S2.

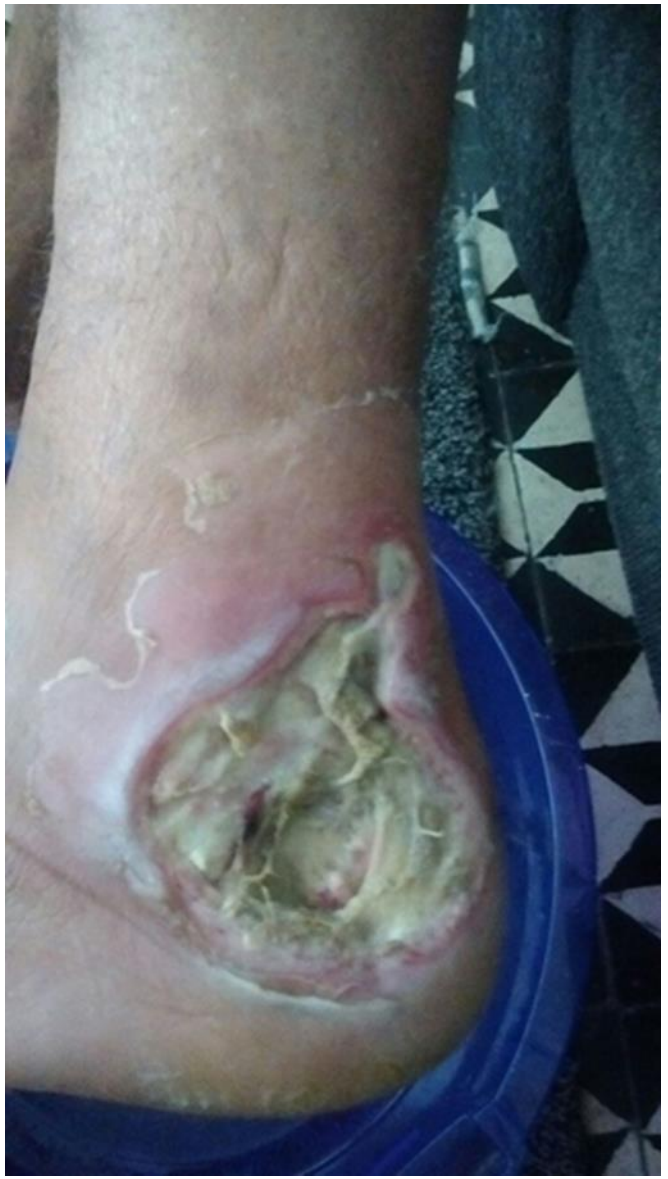


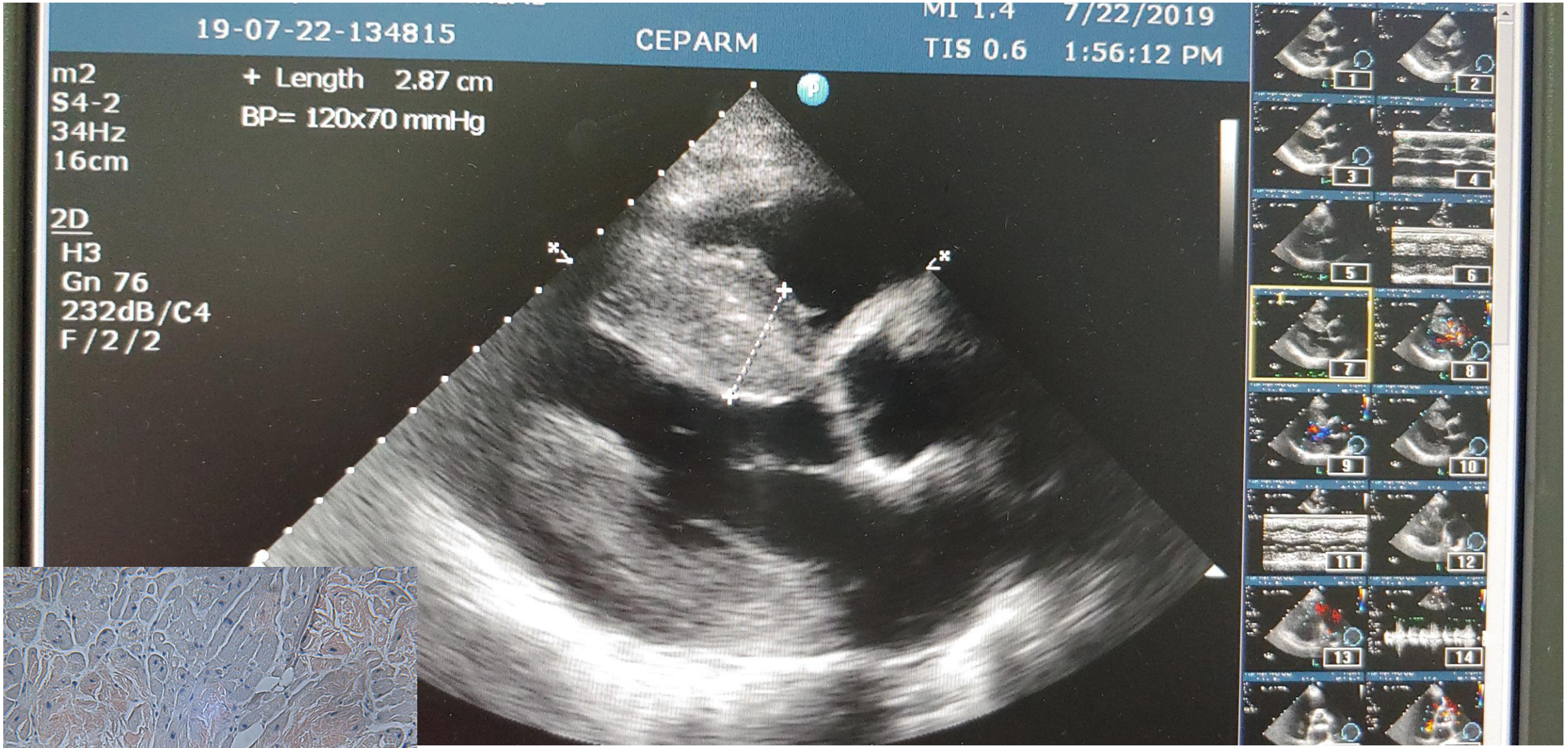








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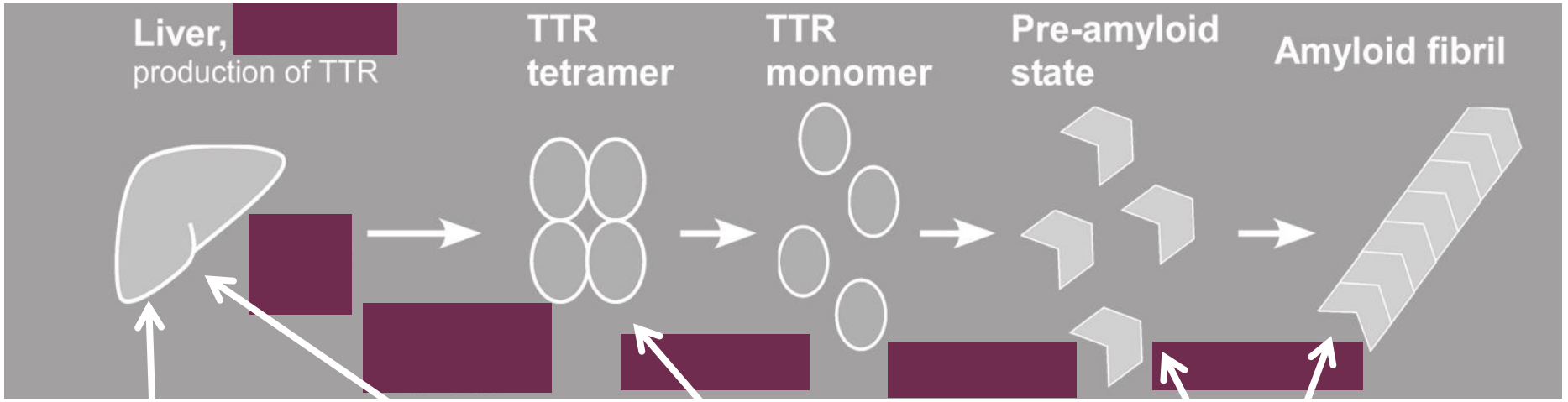
CEPARM
MI 1.4
TIS 0.6
7/22/2019
1:56:12 PM
m2
S4-2
34Hz
16cm
+ Length 2.87 cm
BP= 120x70 mmHg
2D
H3
Gn 76
232dB/C4
F/2/2

Therapeutic strategies for TTR-FAP



Liver transplant

Gene silencing

ASO, siRNA, etc

TTR stabilizers

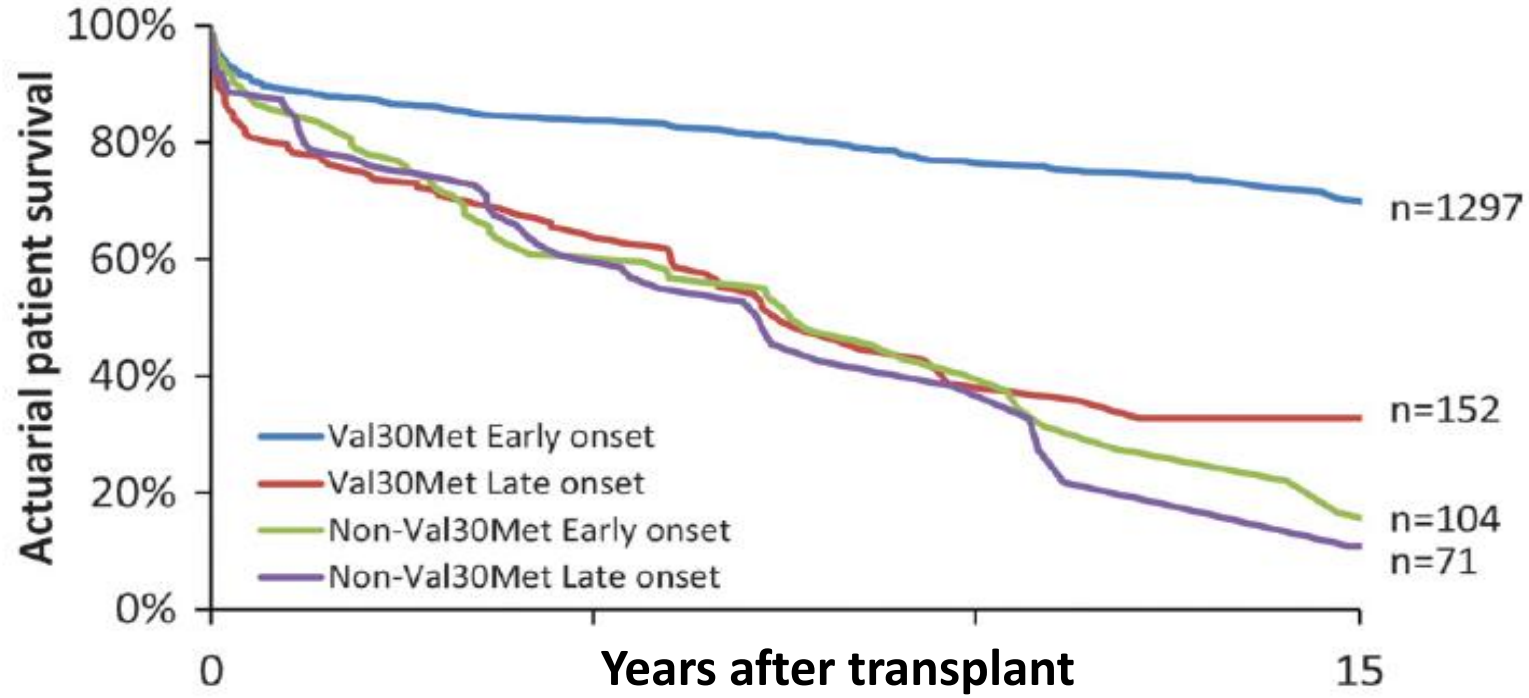
Tafamidis
Diflunisal

Antibody therapy, vaccination

Amyloid breaker

1. Ando Y, *et al. Orphanet J Rare Dis, 2013; 1-13*

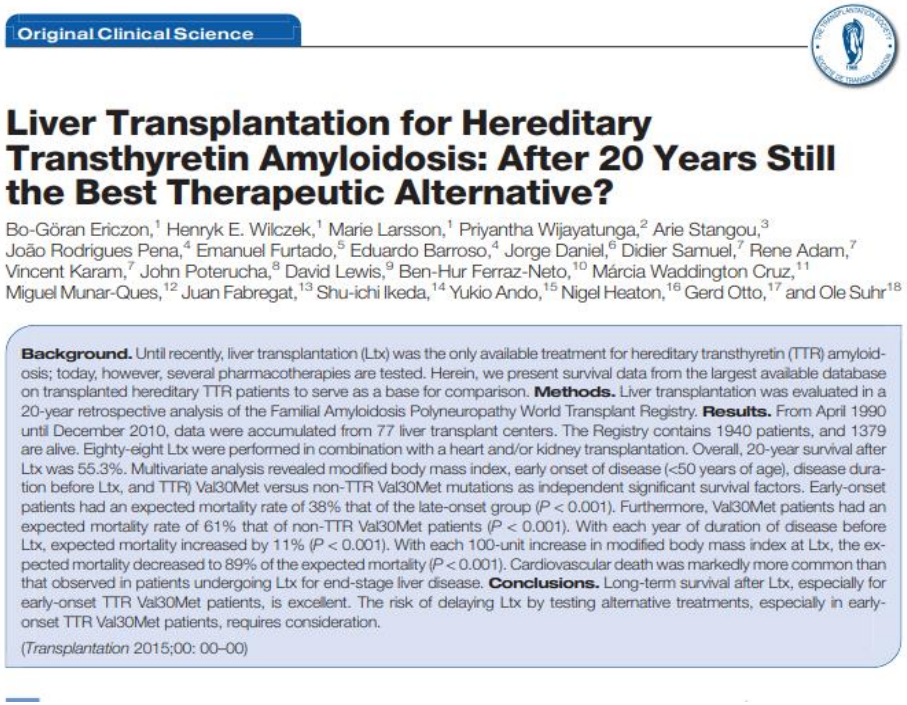
Survival of TTR-FAP patients
post-liver transplant is influenced by disease onset and mutation group[1] (1990-2010).
After 20 years 55% in total pop.



1. Ericzon BG et al. 2015. *Transplantation* 99:1847-1854.

Problems

- Availability of donnor organs.
- Mortality.
- Morbidity.
- Progression.



Original Clinical Science

Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative?

Bo-Göran Ericzon,[1] Henryk E. Wilczek,[1] Marie Larsson,[1] Priyantha Wijayatunga,[2] Arie Stangou,[3] João Rodrigues Pena,[4] Emanuel Furtado,[5] Eduardo Barroso,[4] Jorge Daniel,[6] Didier Samuel,[7] Rene Adam,[7] Vincent Karam,[7] John Poterucha,[8] David Lewis,[9] Ben-Hur Ferraz-Neto,[10] Márcia Waddington Cruz,[11] Miguel Munar-Ques,[12] Juan Fabregat,[13] Shu-ichi Ikeda,[14] Yukio Ando,[15] Nigel Heaton,[16] Gerd Otto,[17] and Ole Suhr[18]

Background. Until recently, liver transplantation (Ltx) was the only available treatment for hereditary transthyretin (TTR) amyloidosis; today, however, several pharmacotherapies are tested. Herein, we present survival data from the largest available database on transplanted hereditary TTR patients to serve as a base for comparison. **Methods.** Liver transplantation was evaluated in a 20-year retrospective analysis of the Familial Amyloidosis Polyneuropathy World Transplant Registry. **Results.** From April 1990 until December 2010, data were accumulated from 77 liver transplant centers. The Registry contains 1940 patients, and 1379 are alive. Eighty-eight Ltx were performed in combination with a heart and/or kidney transplantation. Overall, 20-year survival after Ltx was 55.3%. Multivariate analysis revealed modified body mass index, early onset of disease (<50 years of age), disease duration before Ltx, and TTR) Val30Met versus non-TTR Val30Met mutations as independent significant survival factors. Early-onset patients had an expected mortality rate of 38% that of the late-onset group ($P < 0.001$). Furthermore, Val30Met patients had an expected mortality rate of 61% that of non-TTR Val30Met patients ($P < 0.001$). With each year of duration of disease before Ltx, expected mortality increased by 11% ($P < 0.001$). With each 100-unit increase in modified body mass index at Ltx, the expected mortality decreased to 89% of the expected mortality ($P < 0.001$). Cardiovascular death was markedly more common than that observed in patients undergoing Ltx for end-stage liver disease. **Conclusions.** Long-term survival after Ltx, especially for early-onset TTR Val30Met patients, is excellent. The risk of delaying Ltx by testing alternative treatments, especially in early-onset TTR Val30Met patients, requires consideration.

(*Transplantation* 2015;00: 00–00)

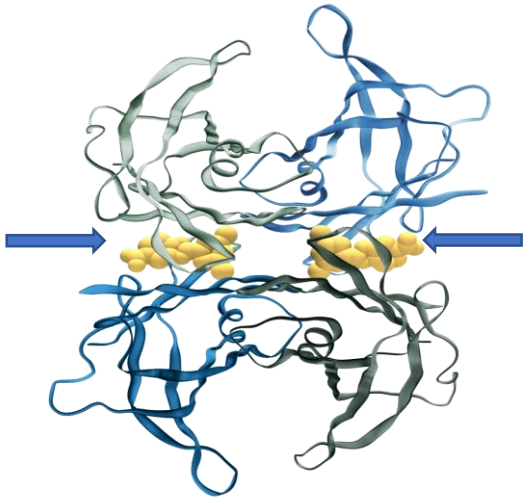
Aggregation of native TTR in previous amyloid deposits after LT (Suhr, 2002);

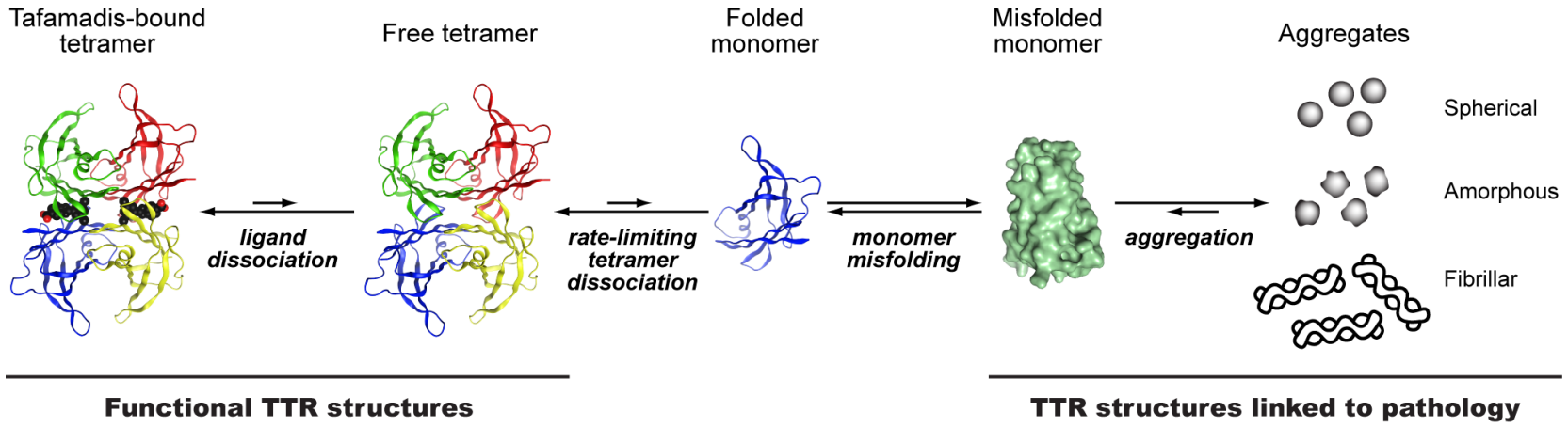
Continuous production of mutated TTR in retina and choroid plexus (Ando, 2001);

And in the Brain (Maia, 2014).

Tafamidis (VYNDAQEL) linked to ligand sites of tyroxin at TTR.

- VYNDAQEL is a new and selective TTR stabilizer.[1]
- VYNDAQEL links to ligand sites of T4 at TTR[1]





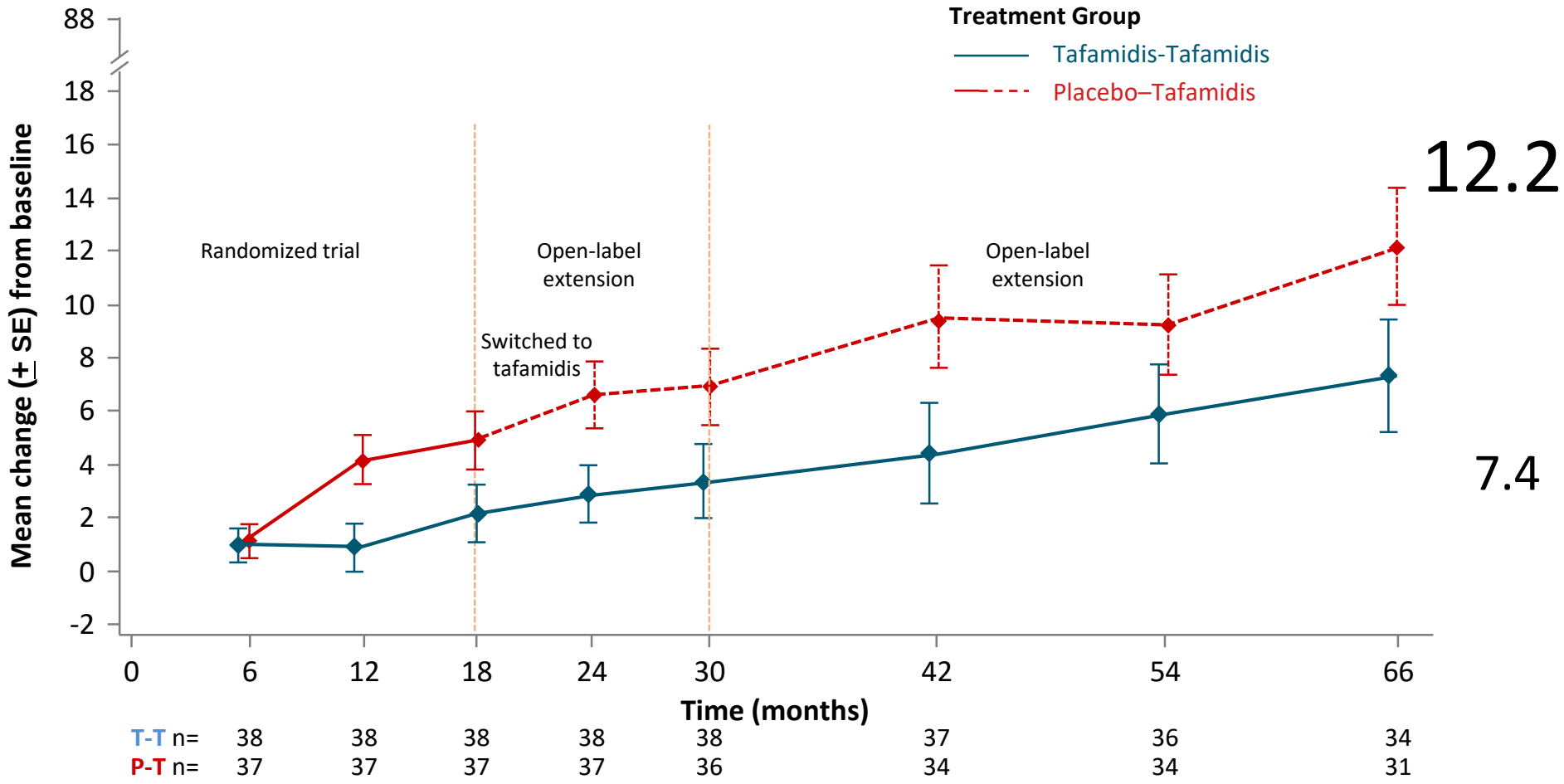
Courtesy from Dr. Jeffrey Kelly.

1. VYNDAQEL (tafamidis). Summary of Product Characteristics. 2013.

18

Change from baseline in NIS-LL total score in V30M patients

Pop V30M em estágio inicial



1. Barroso F et al. Amyloid 2017;24(3);194–204.

From 18 months all patients were assigned to tafamidis

Amyloid
The Journal of Protein Folding Disorders
ISSN: 1350-6129 (Print) 1744-2818 (Online) Journal homepage: http://www.tandfonline.com/loi/iamy20

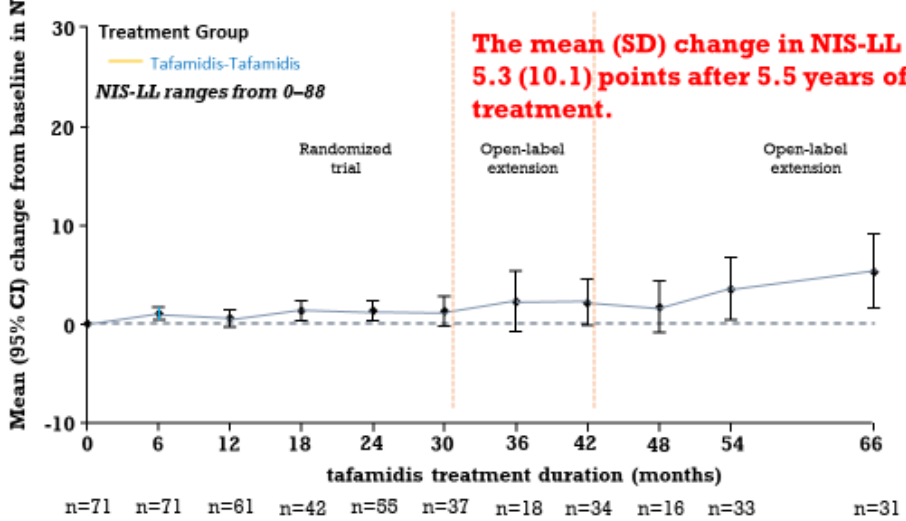
Early intervention with tafamidis provides long-term (5.5-year) delay of neurologic progression in transthyretin hereditary amyloid polyneuropathy

Márcia Waddington Cruz, Leslie Amass, Denis Keohane, Jeffrey Schwartz, Huihua Li & Balarama Gundapaneni

NIS-LL Total Score — V30M

Low baseline disease severity at treatment initiation. N=71

Change from baseline in NIS-LL total score in V30M patients with a low baseline disease severity at treatment initiation (NIS-LL ≤10)



The mean (SD) change in NIS-LL from baseline was 5.3 (10.1) points after 5.5 years of tafamidis treatment.

The rate of change in NIS-LL during 18 months of placebo treatment in the registration trial was approximately 4 points/year in the sub-population of patients who switched from placebo to tafamidis after completing that trial (n=33).[1]

Waddington-Cruz M et al. *Amyloid*. In press.

From 18 months all patients were assigned to tafamidis

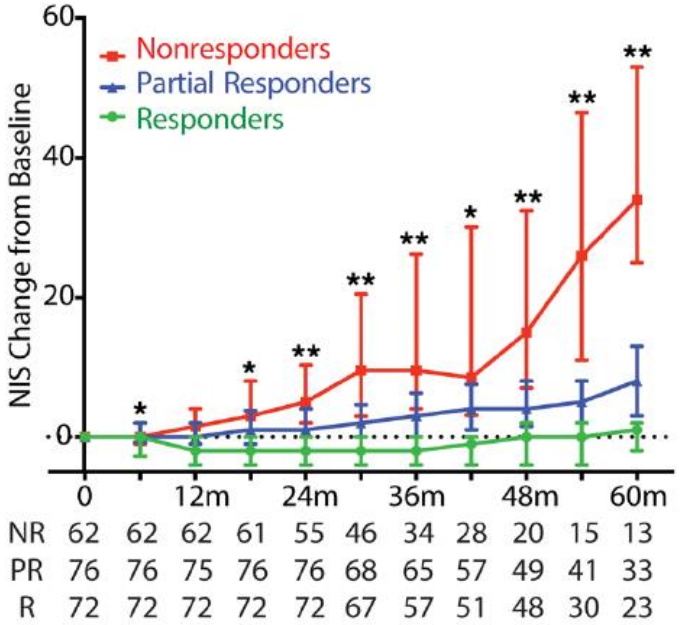
JCI insight

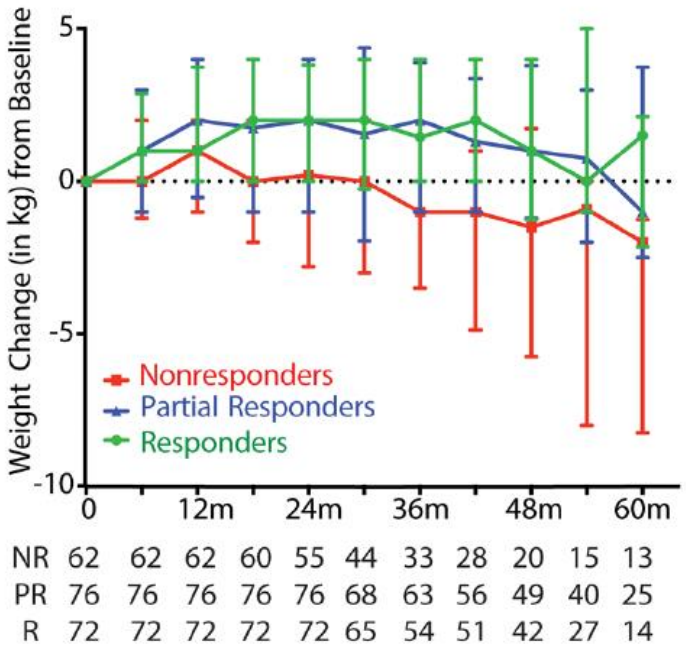
Predictive model of response to tafamidis in hereditary ATTR polyneuropathy

Cecília Monteiro, … , Teresa Coelho, Jeffery W. Kelly

JCI Insight. 2019;4(12):e126526. https://doi.org/10.1172/jci.insight.126526.

Clinical Medicine | Neuroscience | Therapeutics





11 patients out of 31 were considered non-responders based on a NIS increase >10 points

REAL-WORLD EXPERIENCE WITH TAFAMIS AT CEPARM UNIVERSITY HOSPITAL. FEDERAL UNIVERSITY OF RIO DE JANEIRO. BRAZIL.

P. 86

Waddington M; Pedrosa R; Gomes CP; Pinto MV; Pinto LF; Dias M; Santa Rosa R; Amorim, G; Accioli P, Guedes P.
National Amyloidosis Referral Center, CEPARM.

ΔNIS

Δt (months)

Necessidades não atendidas

- Não respondedores ao tafamidis.
- Pacientes em estágio 2 ou 3.
- Pacientes com mutação não V30M.

Journal of Neurology
https://doi.org/10.1007/s00415-022-11276-8

ORIGINAL COMMUNICATION

Long-term efficacy and safety of inotersen for hereditary transthyretin amyloidosis: NEURO-TTR open-label extension 3-year update

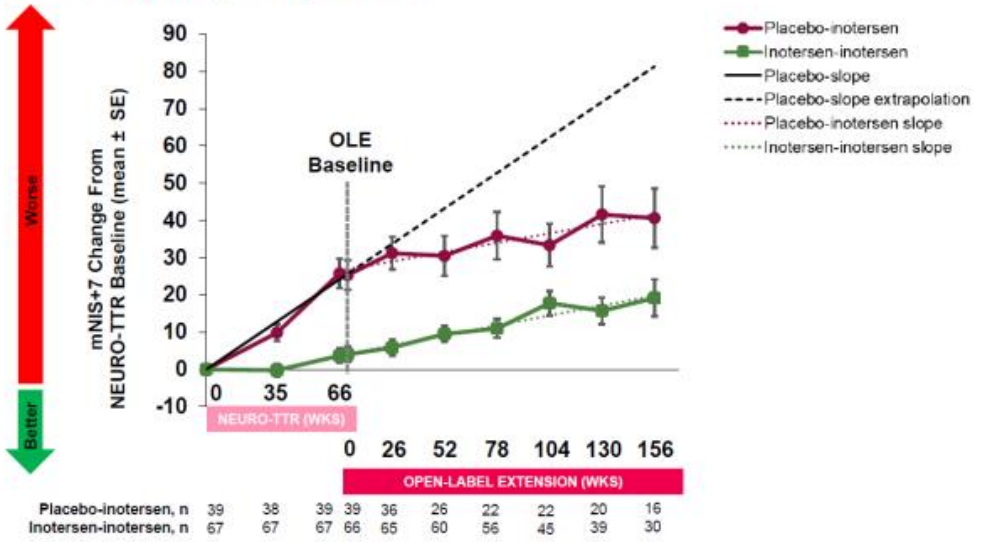
Thomas H. Brannagan[1] · Teresa Coelho[2] · Annabel K. Wang[3] · Michael J. Polydefkis[4] · Peter J. Dyck[5] · John L. Berk[6] · Brian Drachman[7] · Peter Gorevic[8] · Carol Whelan[9] · Isabel Conceição[10] · Violaine Plante-Bordeneuve[11] · Giampaolo Merlini[12] · Laura Obici[12] · Josep Maria Campistol Plana[13] · Josep Gamez[14] · Arnt V. Kristen[15] · Anna Mazzeo[16] · Luca Gentile[16] · Arvind Narayana[17] · Kemi Olugemo[17] · Peter Aquino[17] · Merrill D. Benson[18] · Morie Gertz[5] · for the NEURO-T. T. R. Open-Label Extension Investigators

Received: 16 March 2022 / Revised: 7 July 2022 / Accepted: 8 July 2022

NIS +7.

População abrangente V30 e não V30.
Diferentes estágios da doença.

Patients Who Switched From Placebo to Inotersen Demonstrated Sustained Improvement in Neuropathy Progression



mNIS+7, modified Neuropathy Impairment Score +7 neurophysiologic tests composite score; OLE, open-label extension; SE, standard error.
NEURO-TTR week 66 data are shown for patients who enrolled in the OLE study. Patients from Europe and North America only. Data on file, Akcea Therapeutics, Inc.

Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study

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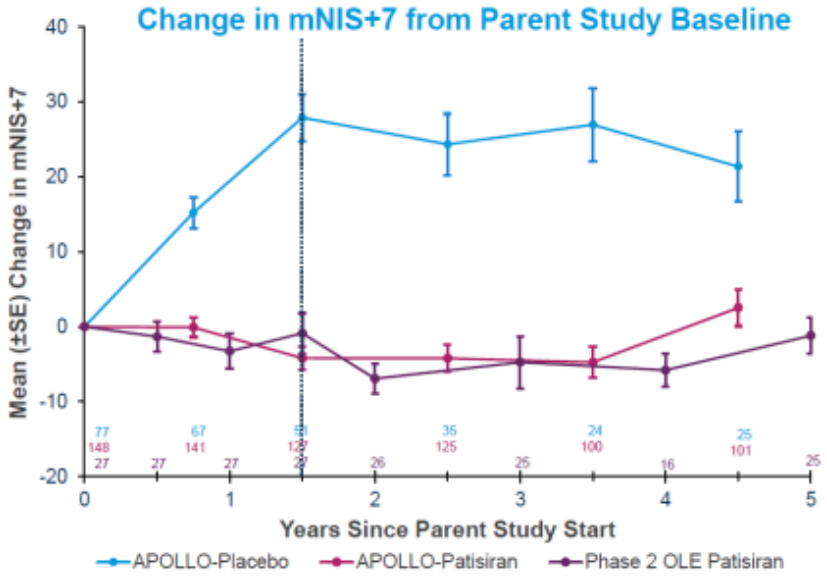
Alnylam@20

Results

Durable Efficacy of Patisiran at Global OLE Month 36

- In the APOLLO-patisiran and Phase 2 OLE groups, mNIS+7 remained stable from parent study baseline; mean (SE) change from parent study baseline was 2.53 (2.45) and –1.18 (2.46), following 4.5 and 5 years of treatment, respectively
- In the APOLLO-placebo group, a decrease in mNIS+7 was observed from Global OLE baseline following initiation of patisiran; mean (SE) change from Global OLE baseline was –5.99 (3.60)
  - However, patients did not return to parent study baseline



Mean (SD) mNIS+7 at parent study baseline was 74.6 (37.0) for the APOLLO-placebo group, 80.9 (41.5) for the APOLLO-patisiran group, and 53.0 (35.6) for the Phase 2 OLE group.

23 **Abbreviations:** mNIS+7, modified Neuroimpairment Score+7; OLE, open-label extension; SE, standard error.

NIS +7.

População abrangentes V30 e não V30.
Diferentes estágios da doença.

- Approved by ANVISA in 26/02/2020.

Stage 1 and 2 PNP.

Não incorporado

Approved by ANVISA in 24/10/2019.

Stage 1 and 2 PNP.

Não incorporado