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Solid organ transplant: *when & which variants do best?* Trials – *when?*

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Patient Workshop
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Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

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Hereditary systemic amyloidoses

Fibril name	Mutated precursor Protein	Target Tissues
ATTR	Transthyretin	PNS, ANS, heart, eye, leptomeninges, tenosynovium
AFib	Fibrinogen α-chain	Kidney
ALys	Lysozyme	Kidney, primarily
AApoAI	Apolipoprotein A-I	Heart, liver, kidney, PNS, testis, larynx, skin
AApoAII	Apolipoprotein A-II	Kidney
AGel	Gelsolin	PNS, cornea
ACys	Cystatin C	PNS, skin
ABri	Abri-PP	CNS
Aβ2M	β2-microglobulin	Musculoskeletal system

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Strange truths about hereditary amyloidosis

- For most types, the source of the ‘disease driving’ building blocks (mutant proteins) is the liver,
- For most types, the disease driving organ (liver) doesn’t ‘appear’ sick

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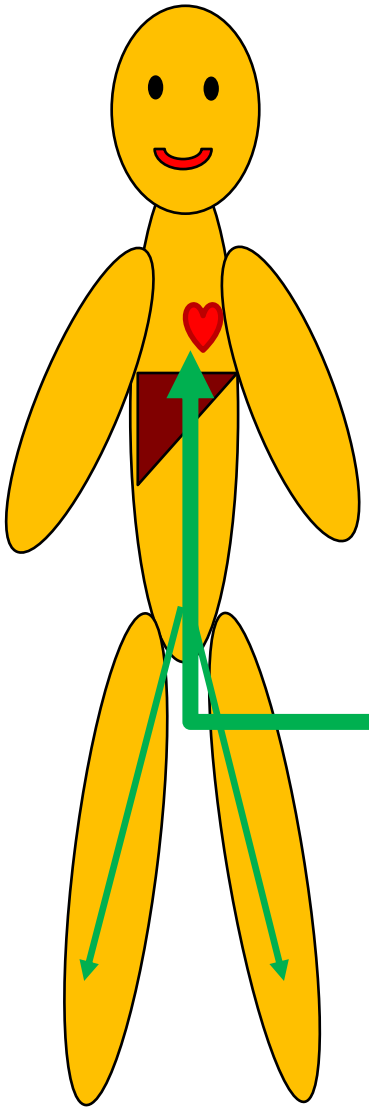
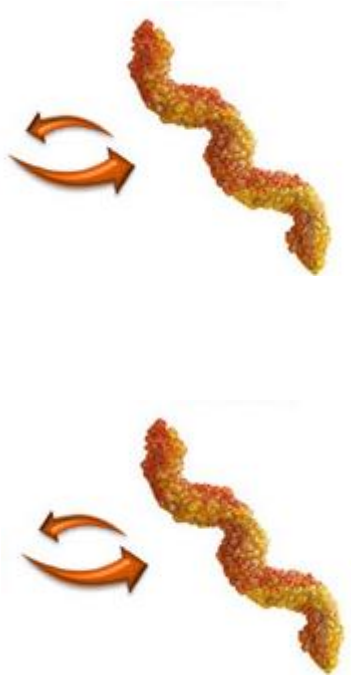
Person

Site of production

Blood

Tissues





Amyloid fibrils

TTR amyloid

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Transplant Approaches

1. **Remove mutant protein producer**
   - **Liver transplant**
2. **Replace symptomatic organ**
   - **Possible for kidney or heart**
   - **Not possible for nerve or guts**
3. **Do both**

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ATTR Transplant Trivia

- First OLT for ATTR in 1990
- First domino liver transplant in 1995
- Partial liver transplants since 1995
- ATTR patients do not meet criteria for liver transplant since “normal” liver

Results from the Familial World Transplant Registry

- **Male 57%**
- **Age at transplant: 38.2 (range 21-73)**
- **Duration of disease: 3 years (0-30 years)**

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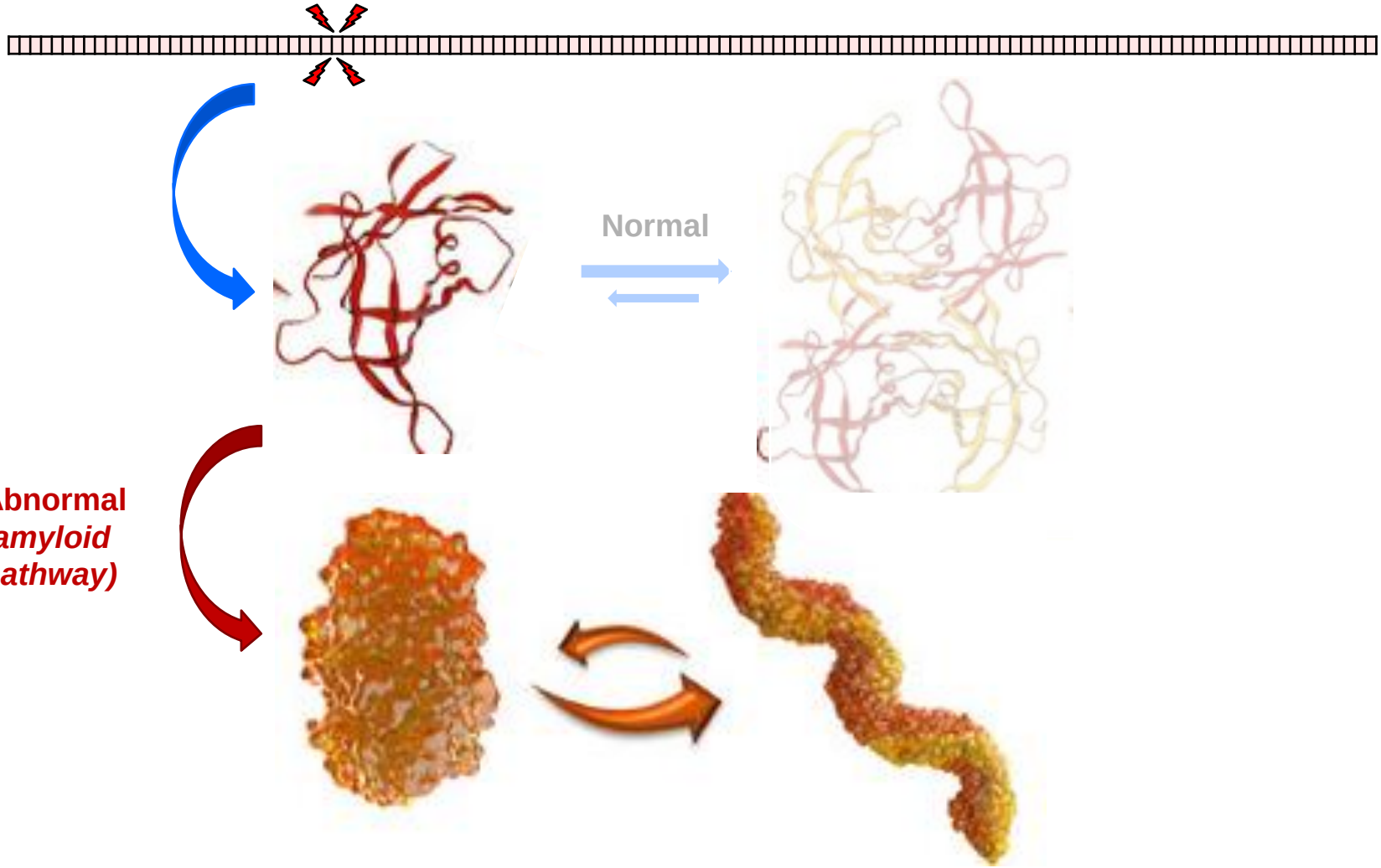
Mutation in protein

Transthyretin protein *(127 amino acids) stretched out*



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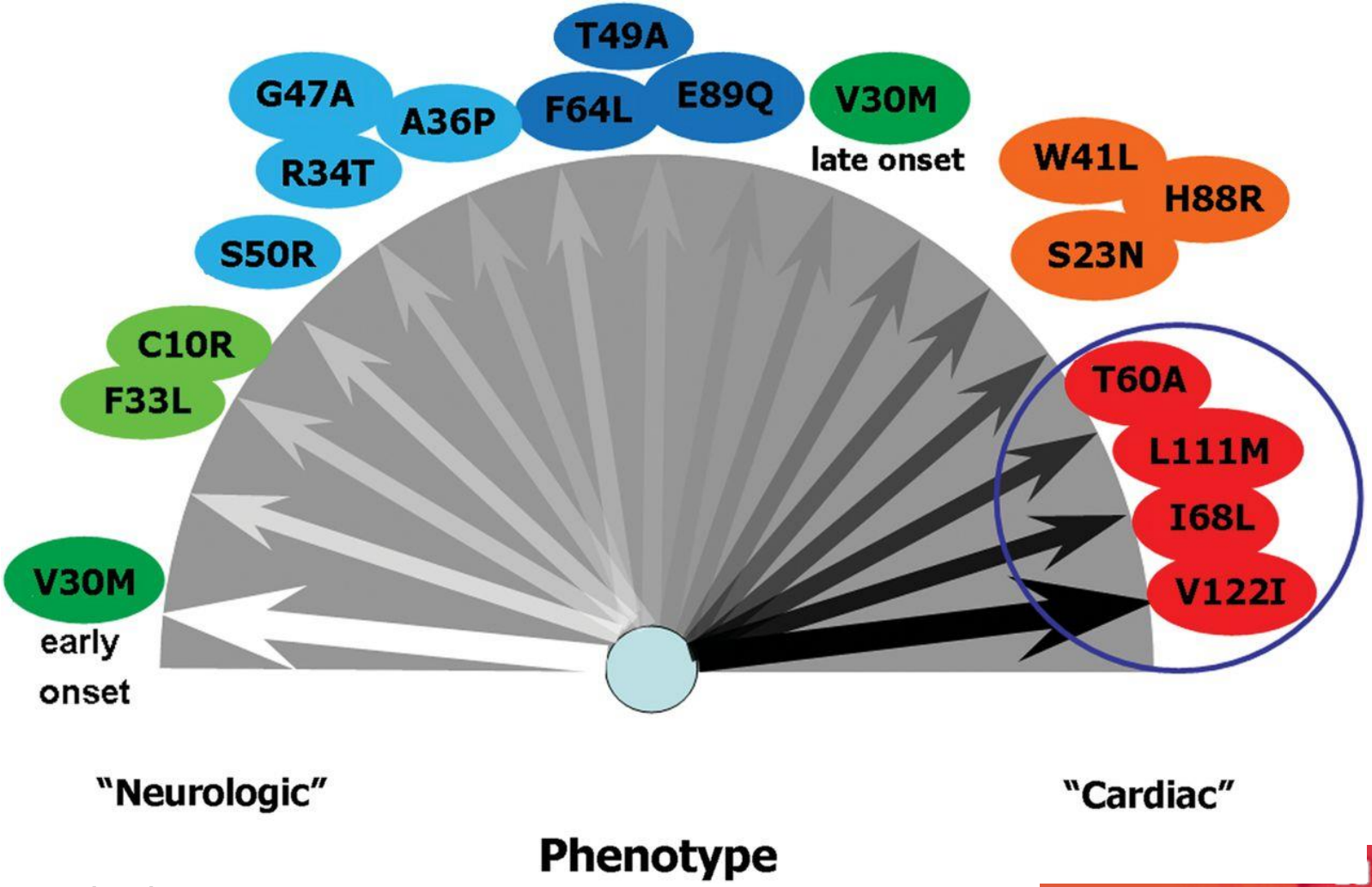
Spectrum of genotype–phenotype correlations in transthyretin-related amyloidosis.

112 mutations causing disease (2013)



Claudio Rapezzi et al. Eur Heart J 2013;34:520-528

European Heart Journal

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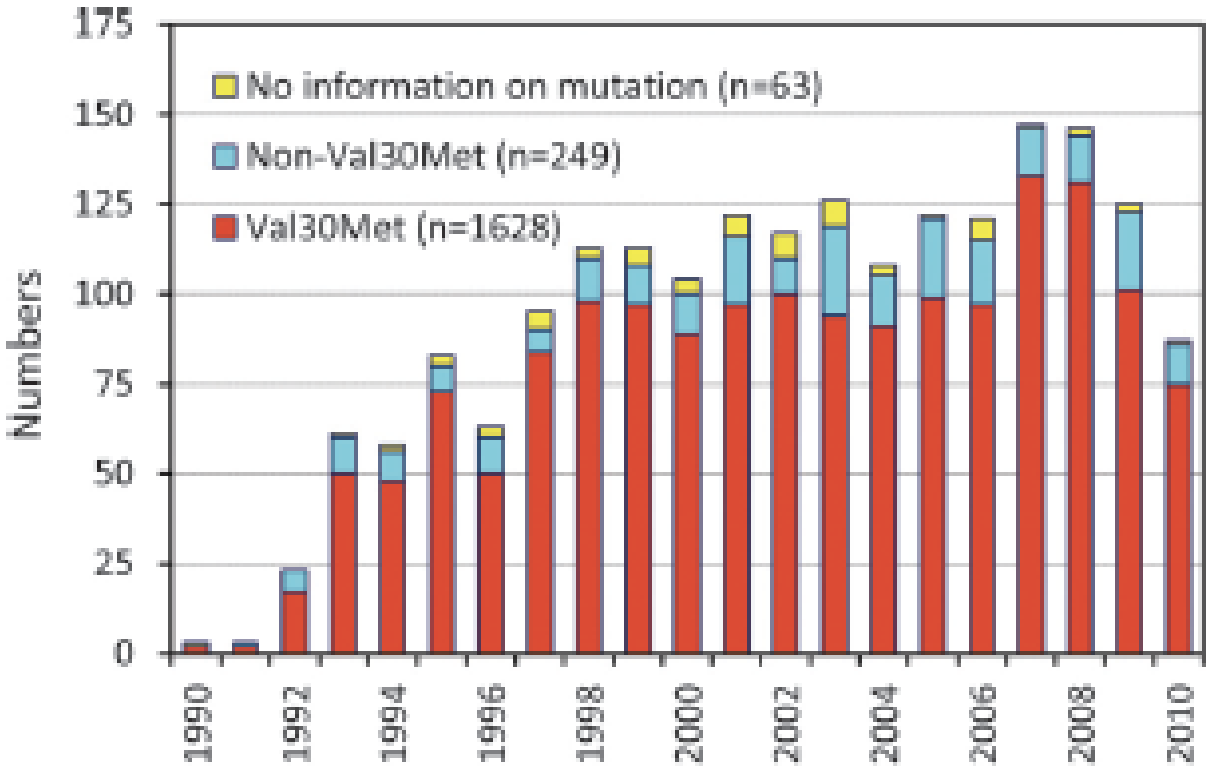
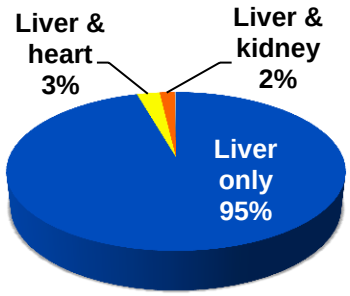
Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative?

1940 patients undergoing 2127 liver transplants





Ericzon, B.G., et al., Transplantation, 2015. 99(9): p. 1847-54.

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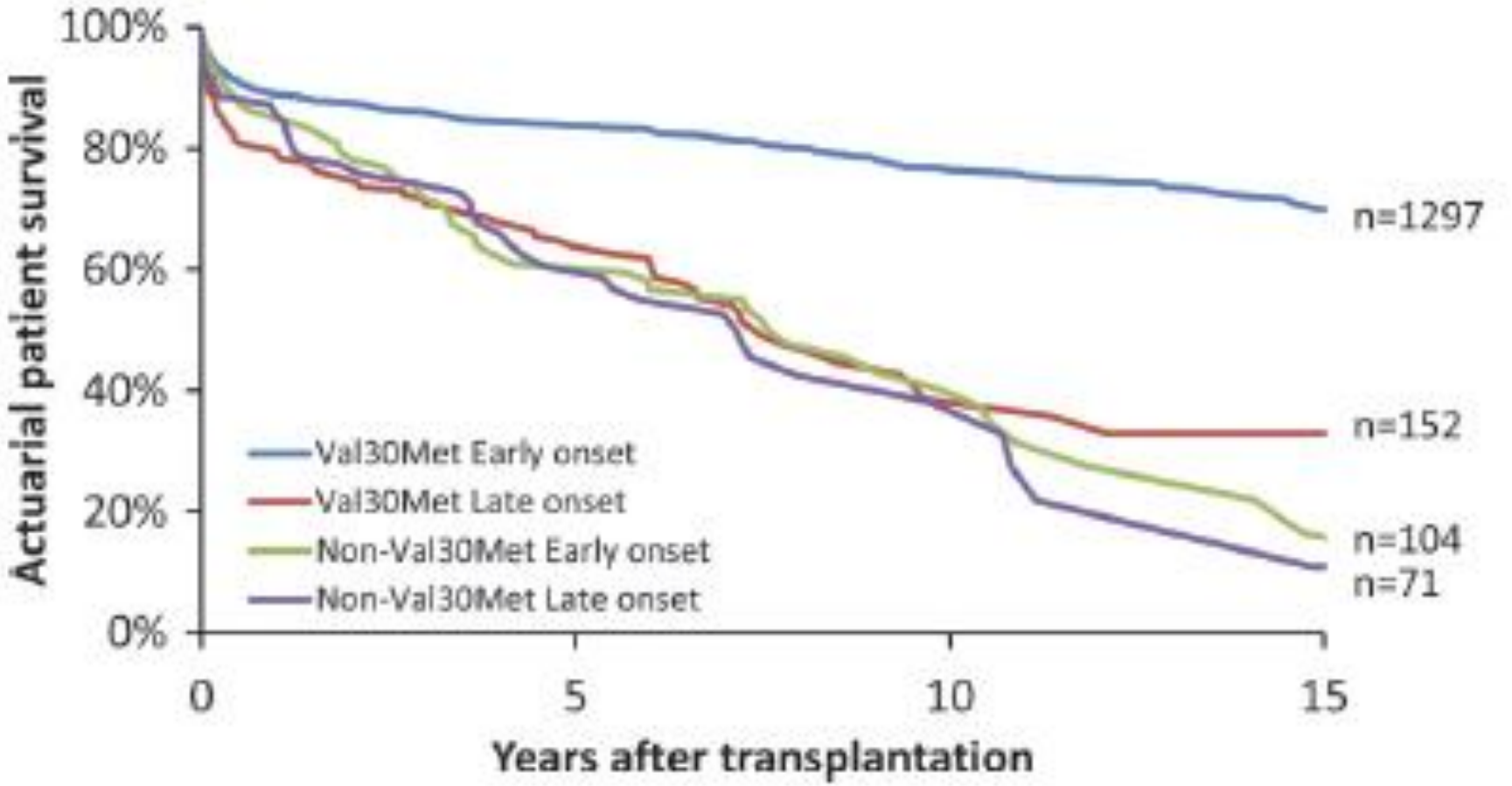
Survival post-OLT for Familial ATTR by mutation



Ericzon, B.G., et al., Transplantation, 2015. 99(9): p. 1847-54.

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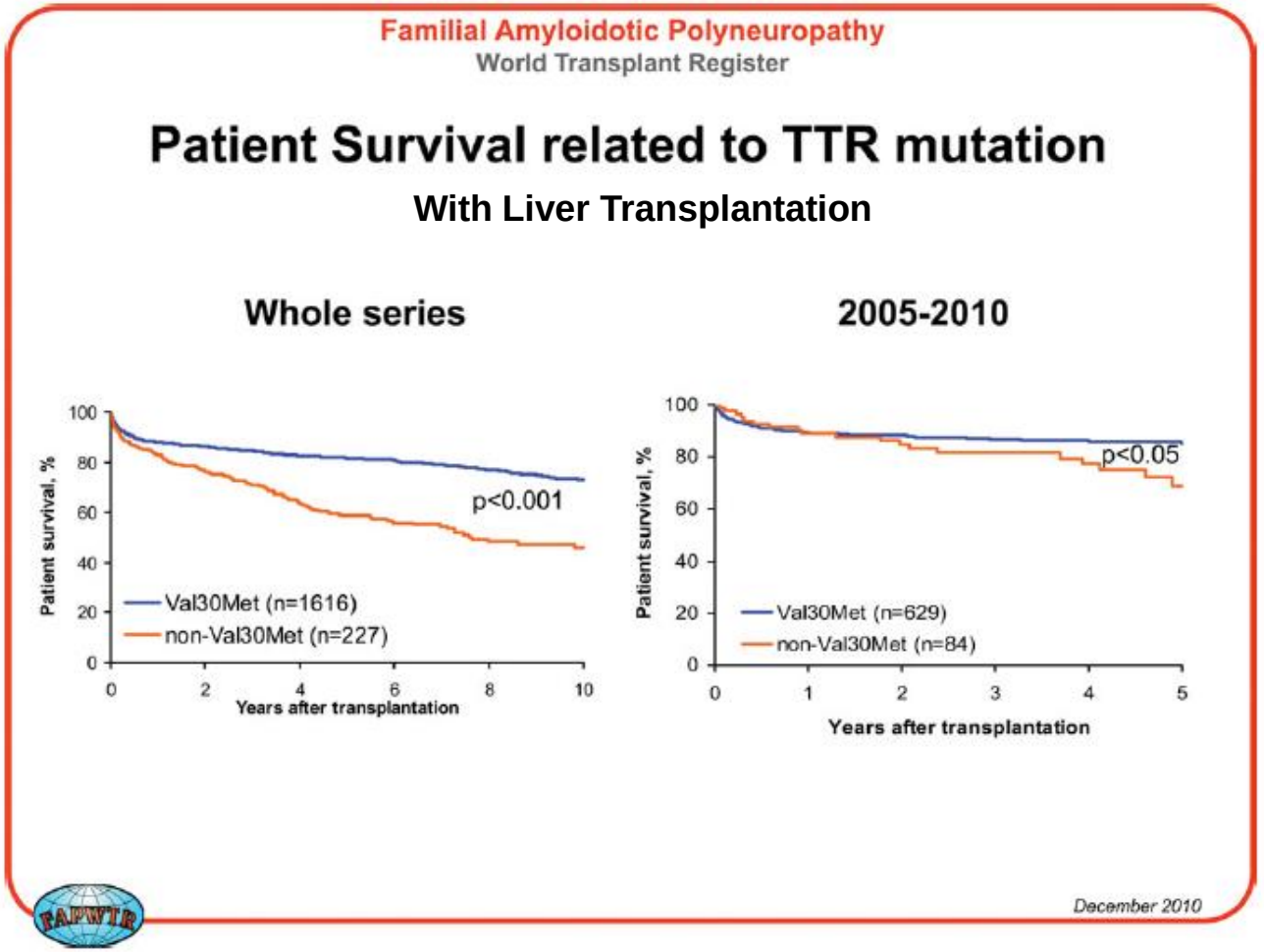
10 year Survivorship Post-OLT

focusing on most common variants

- Val30Met early onset 85%
- Val30Met late onset 45%
- Val71Ala (N) 85%
- Leu111Met (H) 83%
- Leu58His (H/N) 76%
- Thr60Ala (H/N) 36% if liver Tx only
  58% if heart & liver
- Fewer than 50% alive: Ser50Arg, Ser77Phe, Ser77Tyr, Glu89, Gln, Tyr114Cys

Ericzon,, et al., Transplantation, 2015. 99(9): p. 1847-54. Suhr et al Transplantation 2016;100(2):373-381.



Progression noted in heart, vitreous opacities, autonomic nervous system
Typically less cardiac deposition if heart transplant done same time

Benson, M.D. Muscle & nerve, 2013. 47(2): p. 157-62.

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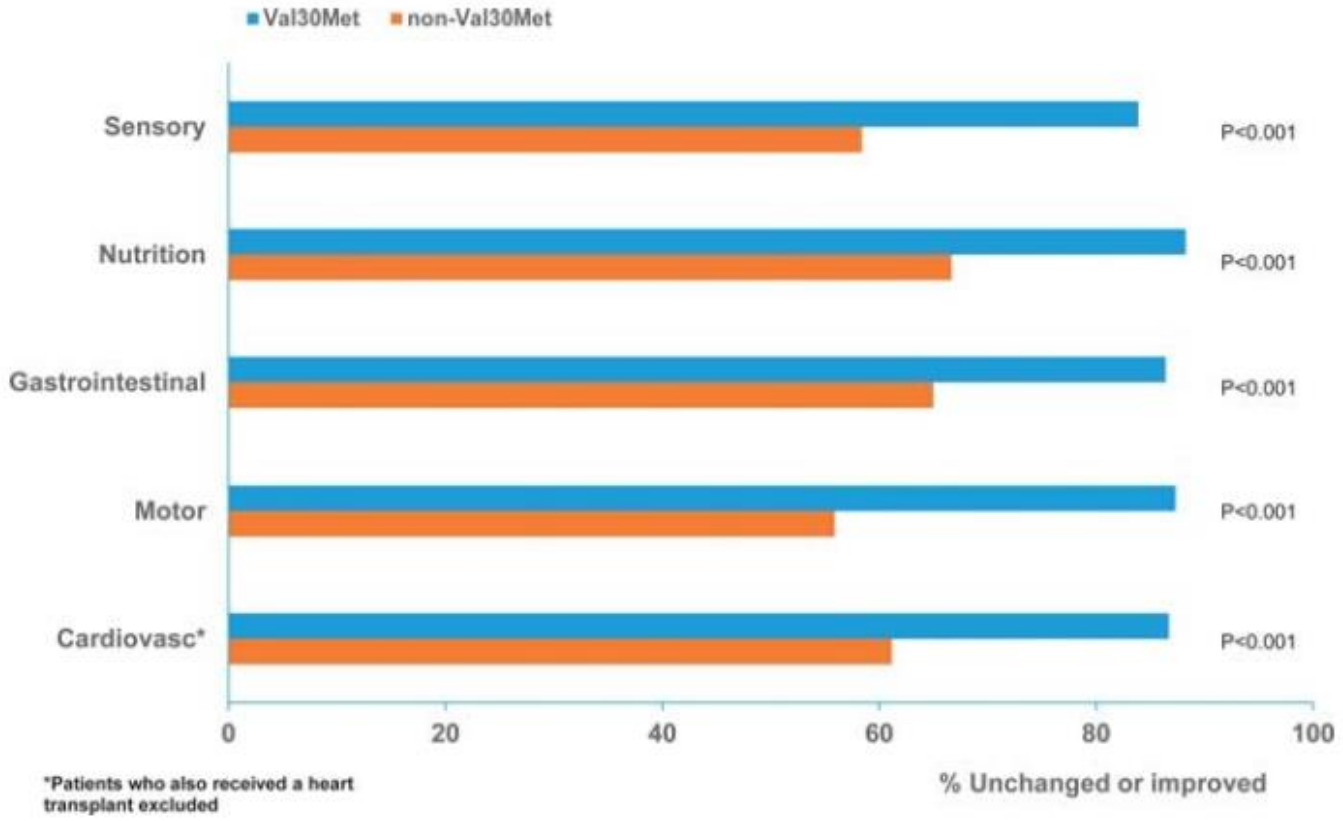
Stabilization of symptoms better in Val30Met Patients than non-Val30Met Patients with Liver Transplantation



Suhr OB, et al. Transplantation 2016;100(2):373-381.

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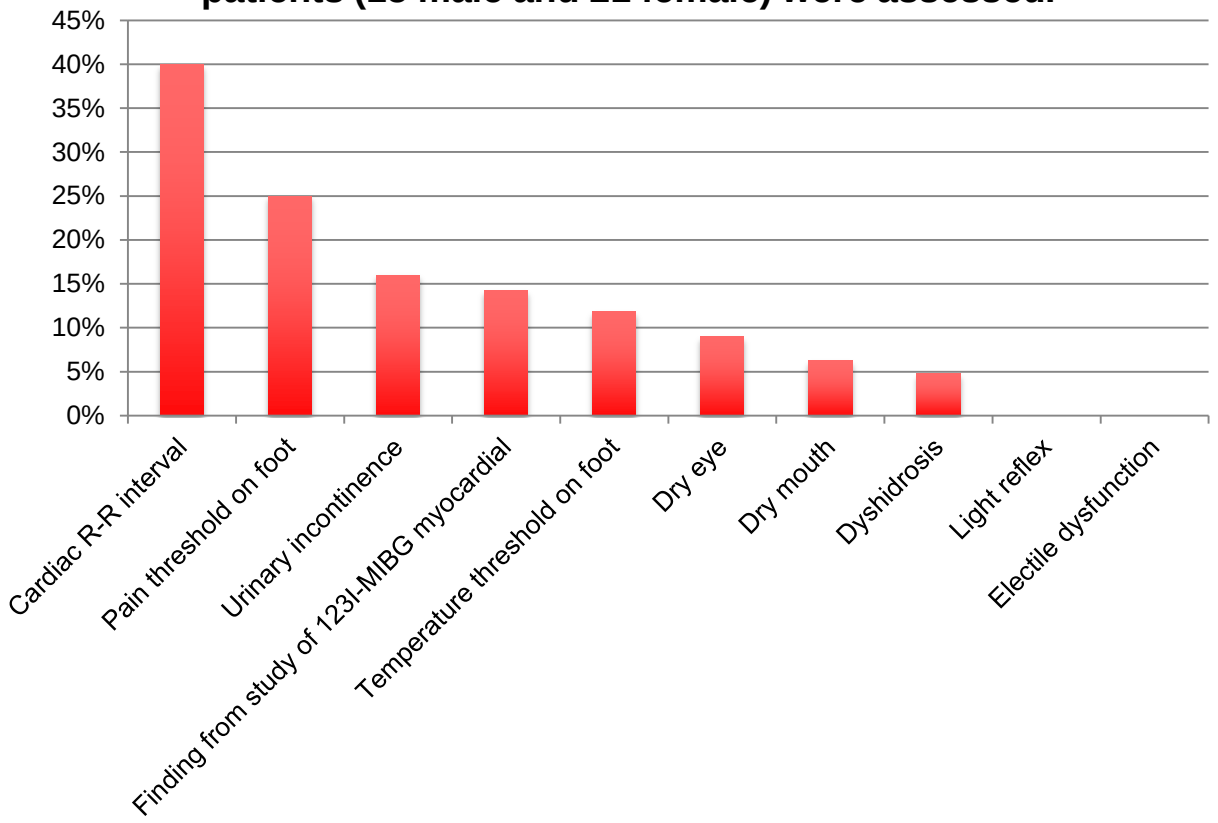
Improvement in Autonomic Function after Liver Transplant

Thirty-six Japanese transplanted FAP ATTR V30M patients (15 male and 21 female) were assessed.



Diarrhea and orthostatic hypotention could not be assessed due to large variation.

Ando Y, et al. Lancet 1995;345:195–6.

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Val30Met Outcomes

- Neuropathy stable or improved in up to 40%
- Nutrition improves in up to 80%
- Cardiac progresses in ~50%
- Kidney involvement unaffected
- Eye deposits progress

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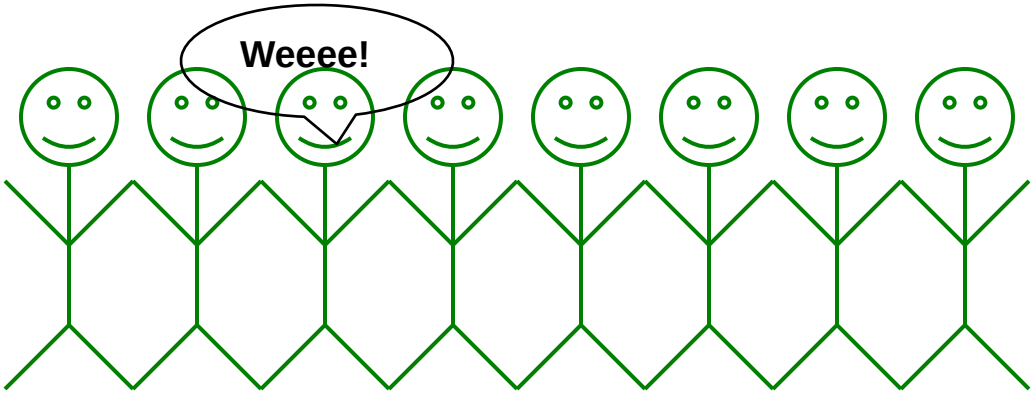
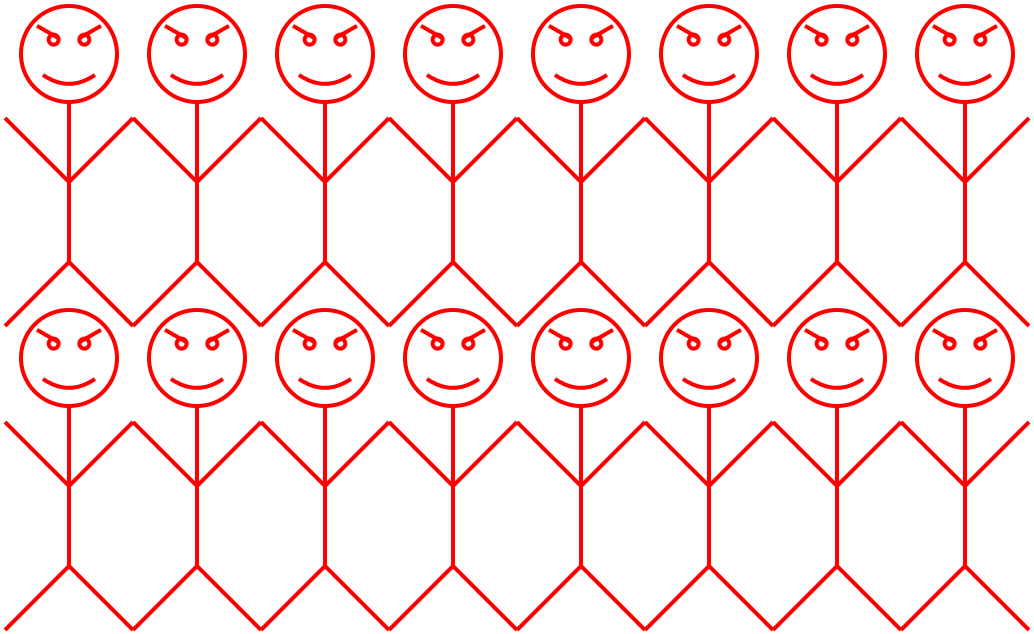


Normal ATTR
joining the party



Mutant ATTR fibrils
Made of mutant TTR

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Heart Transplantation for Hereditary ATTR

- **Trend for a superior overall survival among those receiving heart and liver transplant versus those receiving liver transplant only**
- **Mayo Clinic data, and**
- **Similar finding in the FAPTR registry**

Banerjee D, et al. *Progress in Transplantation*. 2017;27(3):246-250.
Suhr, O, et al. *Transplantation*. 2016;100(2):373-381.

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Cardiac-Related Death in Liver Transplant Patients

- 212 patients underwent LTx alone
  - 119 (56%) patients died.
  - 45 (38%) of the deaths were heart related
- 52 had combined LTx/HTx
  - 20 (38%) patients died
  - 3 (15%) of the deaths were heart related

Suhr OB, et al. Transplantation 2016;100(2):373-381.

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What Does It All Mean?

- **Known:**
  - **Survival improved with liver transplant in V30M**
  - **Most effective if early**
  - **Major benefit is nutrition**
  - **Combined liver + heart and liver + kidney feasible**

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What Does It All Mean?

- **Unknown:**
  - **When is it futile?**
  - **Which mutations benefit?**
  - **If heart involved need combined heart + liver?**
  - **Is amyloid halted, slowed, reversed or accelerated?**

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In a perfect word, there would be no liver transplant…

- **…Safe, effective, affordable drugs would help take care of the problem**

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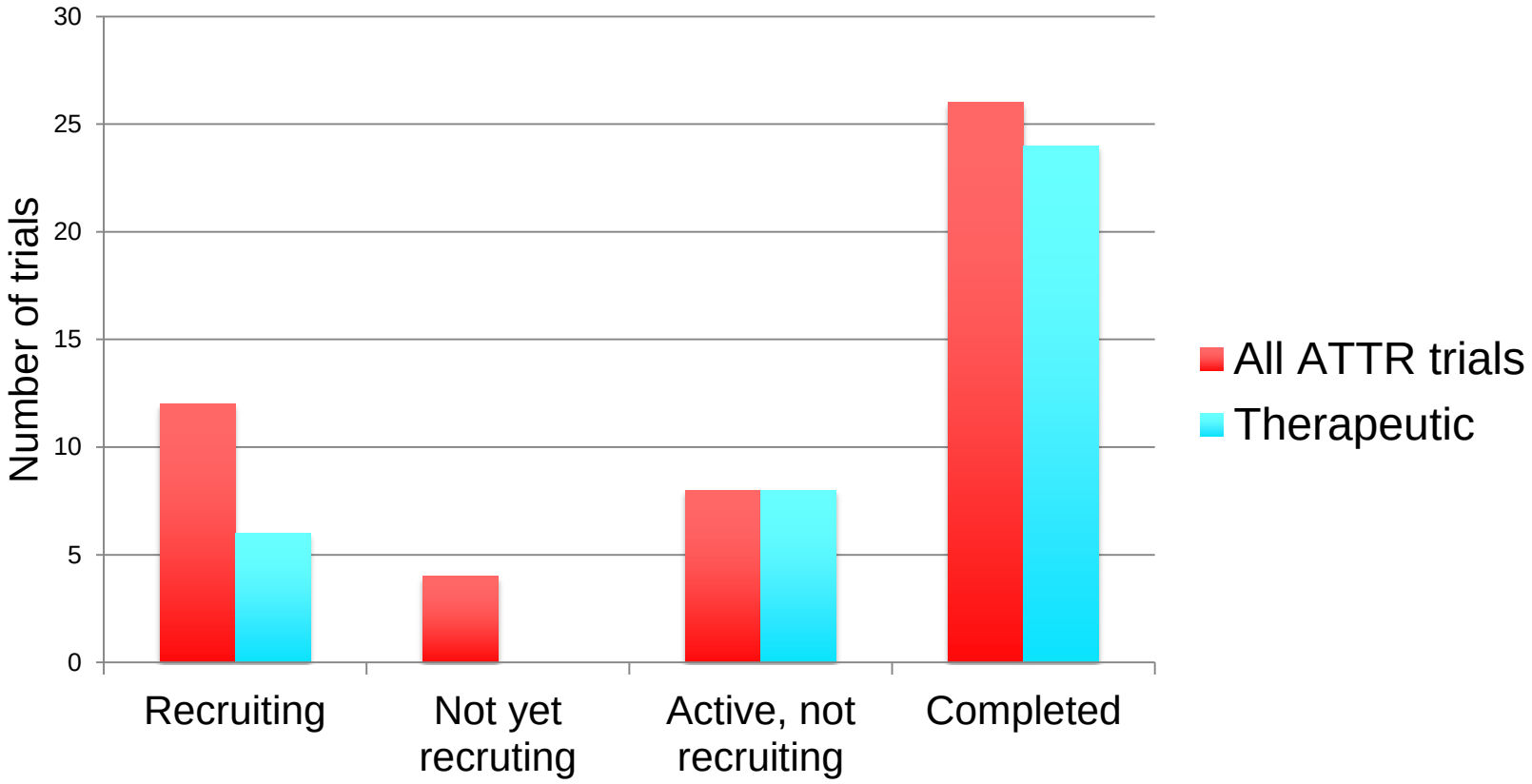
Number of ATTR Clinical Trials Registered on Clinicaltrials.gov



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Hereditary, systemic amyloidoses

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ALys	Lysozyme	Kidney, primarily
AApoAI	Apoli	
AApoAII	Apoli	
AGel	Gelso	
ACys	Cystat	
ABri	Abri-PP	CNS
Aβ2M	β2-microglobulin	Musculoskeletal system

Made entirely in the liver

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Fibrinogen A α

- Most common of hereditary renal amyloidoses (Ostertag 1932)
- First mutation described by Dr. Benson, 1993
- Middle age presentation
- If kidney replacement alone, graft fails in 1-7 years with 10-year graft survival of 5% (vs 65%)

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First Report of Liver Transplant without Kidney Transplant for Fibrinogen A alpha chain Renal Amyloidosis

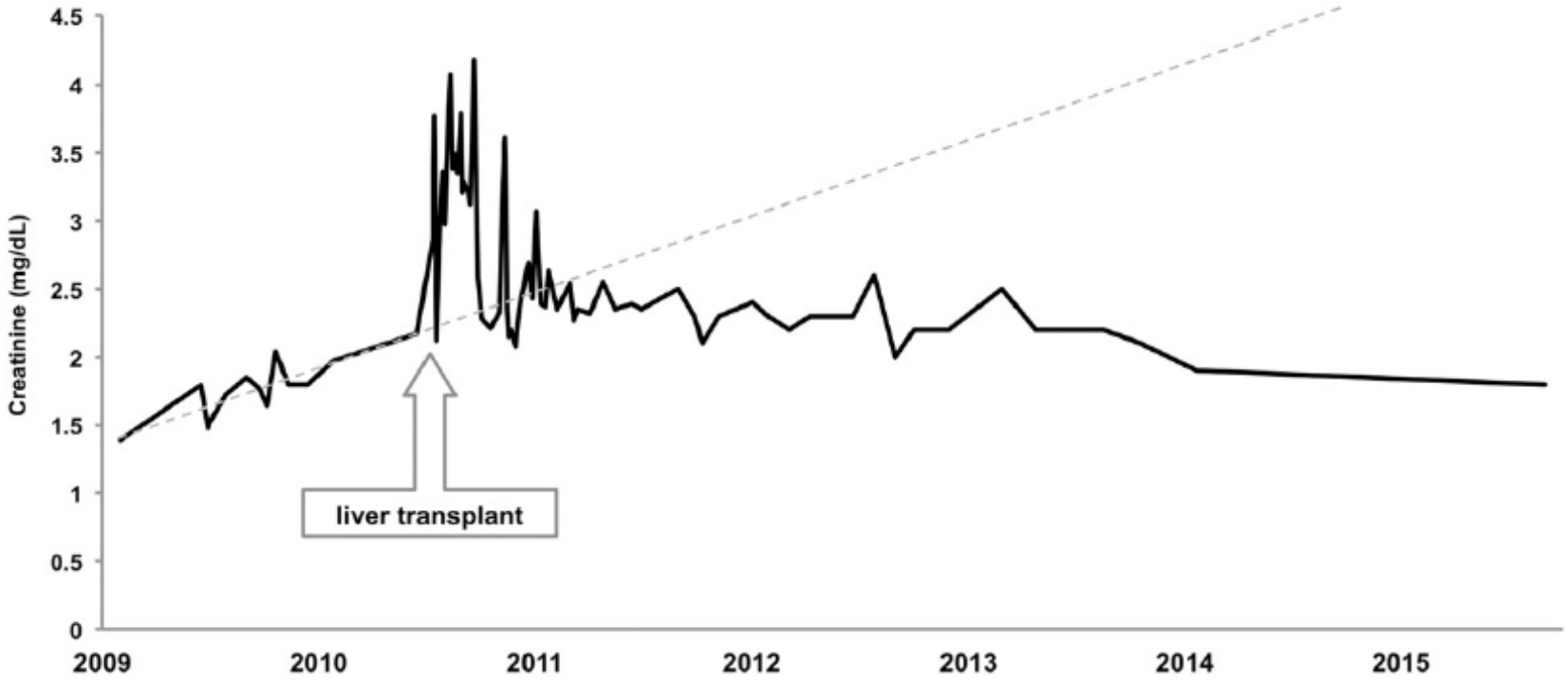

Figure 1. Time course of serum creatinine level in patient with liver transplantation without kidney transplantation.

***Fix et al. Amyloid*. 2016;23(2):132-133.**

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Conclusions

- Liver (± heart) transplant still plays a role in ATTR ValMet30 patients
  - Other mutations, less certain
- Exciting that other means of reducing the ATTR may be on the horizon
- For AFIB, liver + kidney is best
- Early diagnosis, better data collection is imperative regardless