ARIZONA DEPARTMENT OF HEALTH SERVICES

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THE INSTITUTE FOR FUTURE HEALTH

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All Black Adults SHOULD Be Offered Genetic Screening for TTR Amyloidosis

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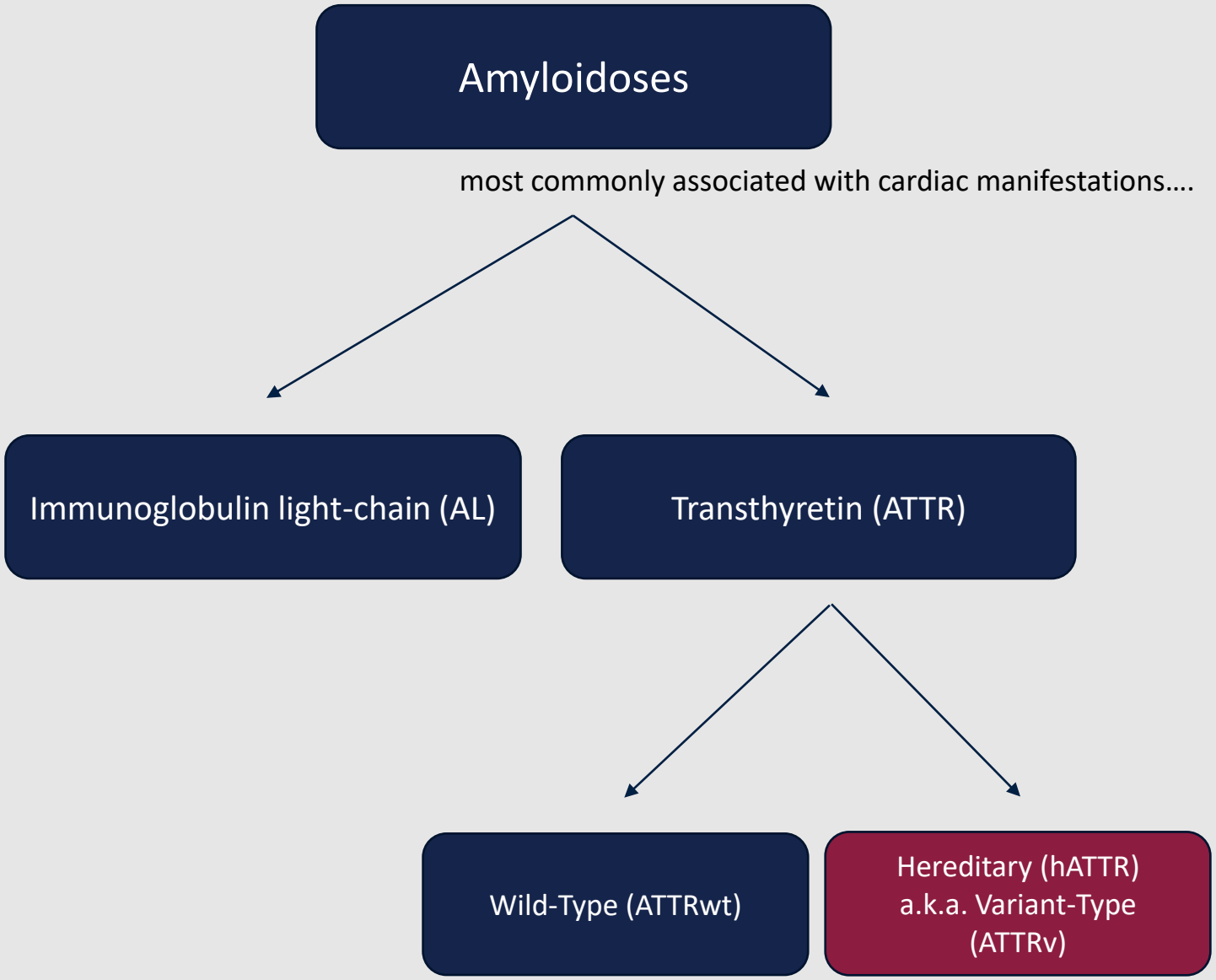
Racial Disparities in Cardiac Disease

Compared to White patients, Black Americans...

- Are more likely to develop CHF and to do so at an earlier age
- Have a 2.5x increased risk of hospitalization for heart failure
- Have higher rates of myocardial infarction and worse outcomes after acute coronary events
- Are 30% more likely to die from heart disease

ATTR-CM is a life-threatening disease that disproportionately affects older adults and people of African descent.



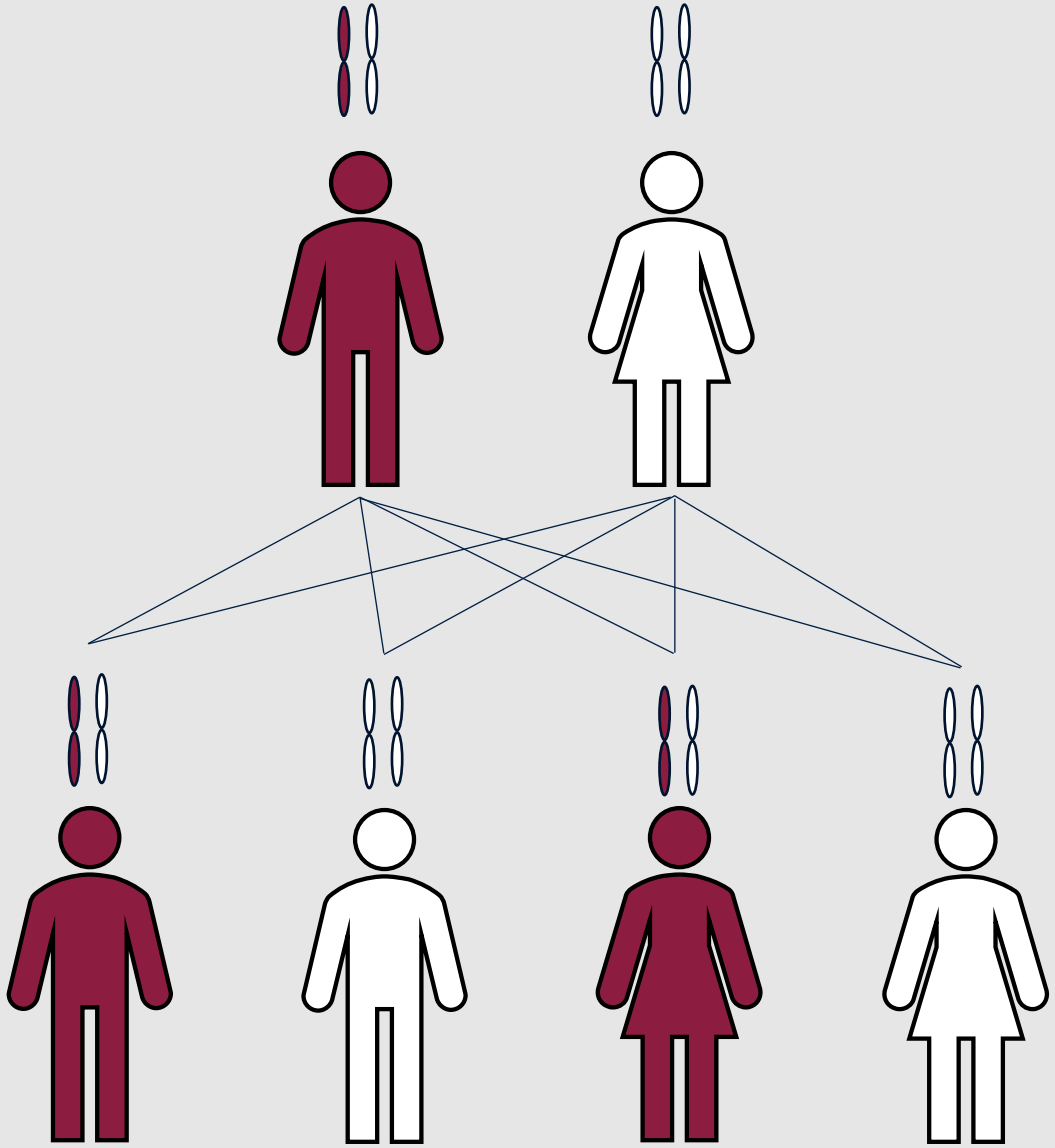
TTR Gene

- Located on chromosome 18q12.1
- Encodes for **transthyretin protein**
  - Homo-tetrameric carrier protein
    - Thyroid hormone transport
    - Retinol transport
  - Other potential intracellular involvement…
    - Proteolysis, nerve regeneration, autophagy, glucose homeostasis
- Pathogenic variants -> amyloid deposition
  - Predominantly affects peripheral nerves and heart

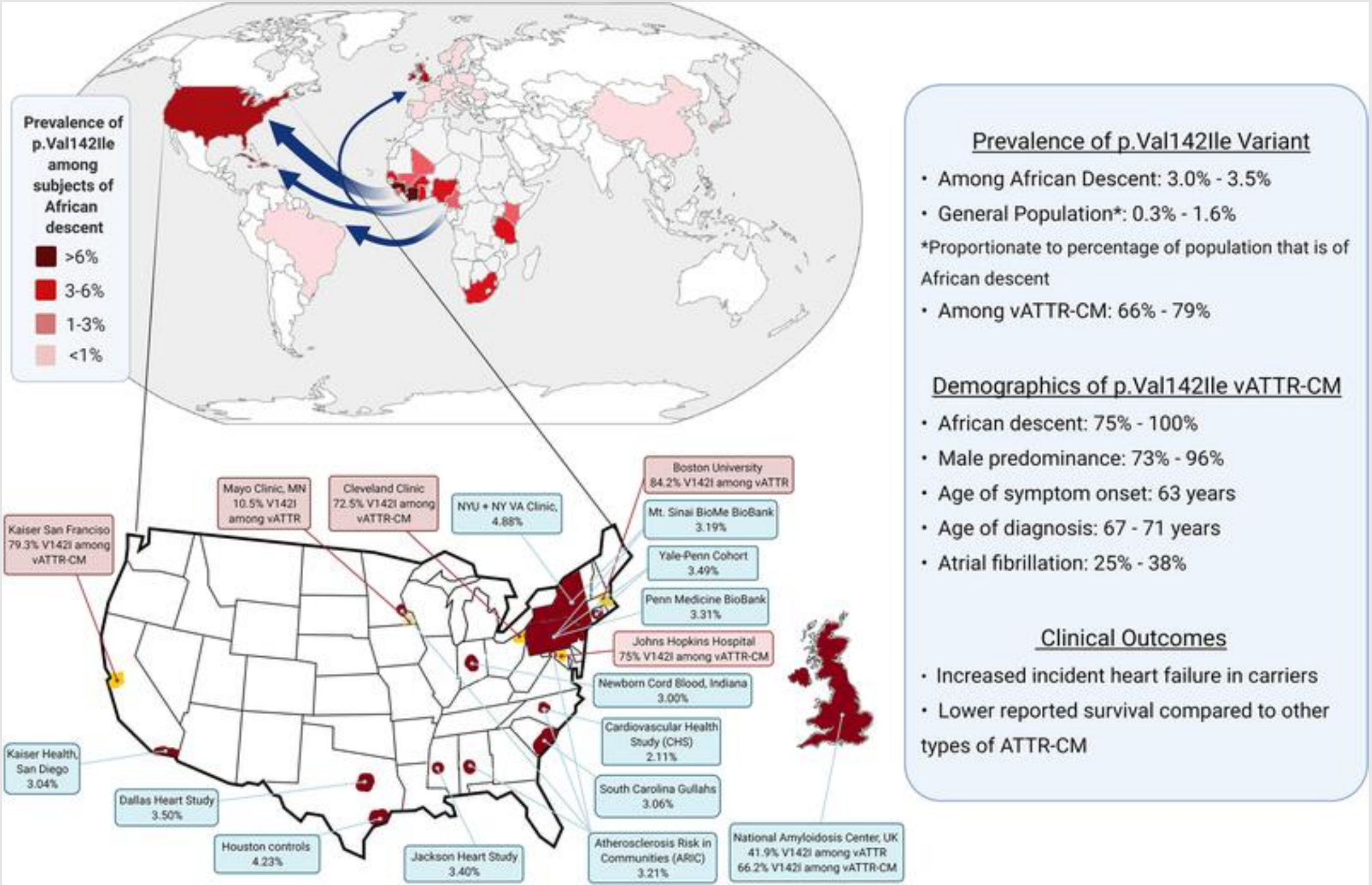
Image from: https://en.wikipedia.org/wiki/Transthyretin

hATTR Inheritance

- Autosomal Dominant
  - 50% risk to children
  - Expected 50% risk to other first-degree relatives (sibs, parents)
- ~150 hATTR-causing variants have been identified
- Incomplete penetrance
- Variable expressivity



Geographical Distribution of p.Val142Ile Variant Prevalence (Chandrashekar et al., 2021 – Figure 1)



Prevalence of p.Val142Ile Variant

- Among African Descent: 3.0% - 3.5%
- General Population*: 0.3% - 1.6%

*Proportionate to percentage of population that is of African descent

- Among vATTR-CM: 66% - 79%

Demographics of p.Val142Ile vATTR-CM

- African descent: 75% - 100%
- Male predominance: 73% - 96%
- Age of symptom onset: 63 years
- Age of diagnosis: 67 - 71 years
- Atrial fibrillation: 25% - 38%

Clinical Outcomes

- Increased incident heart failure in carriers
- Lower reported survival compared to other types of ATTR-CM

Racial Disparities in Cardiac Amyloidosis

African Americans with hATTR...

- Present with more advanced disease compared to Caucasians with ATTRwt despite having a non-invasive method for early detection (genetic testing)
- Have a median survival of 25.6 months (p.V142I hATTR) vs 43 months (ATTRwt)
- Have twice the risk of incident heart failure compared to non-carriers
- Are disproportionately underrepresented in relevant clinical trials
    - Despite the high burden of ATTR-CM among Black individuals, most clinical data for ATTR-CM are from North America and Europe.

Benefits of Early Detection

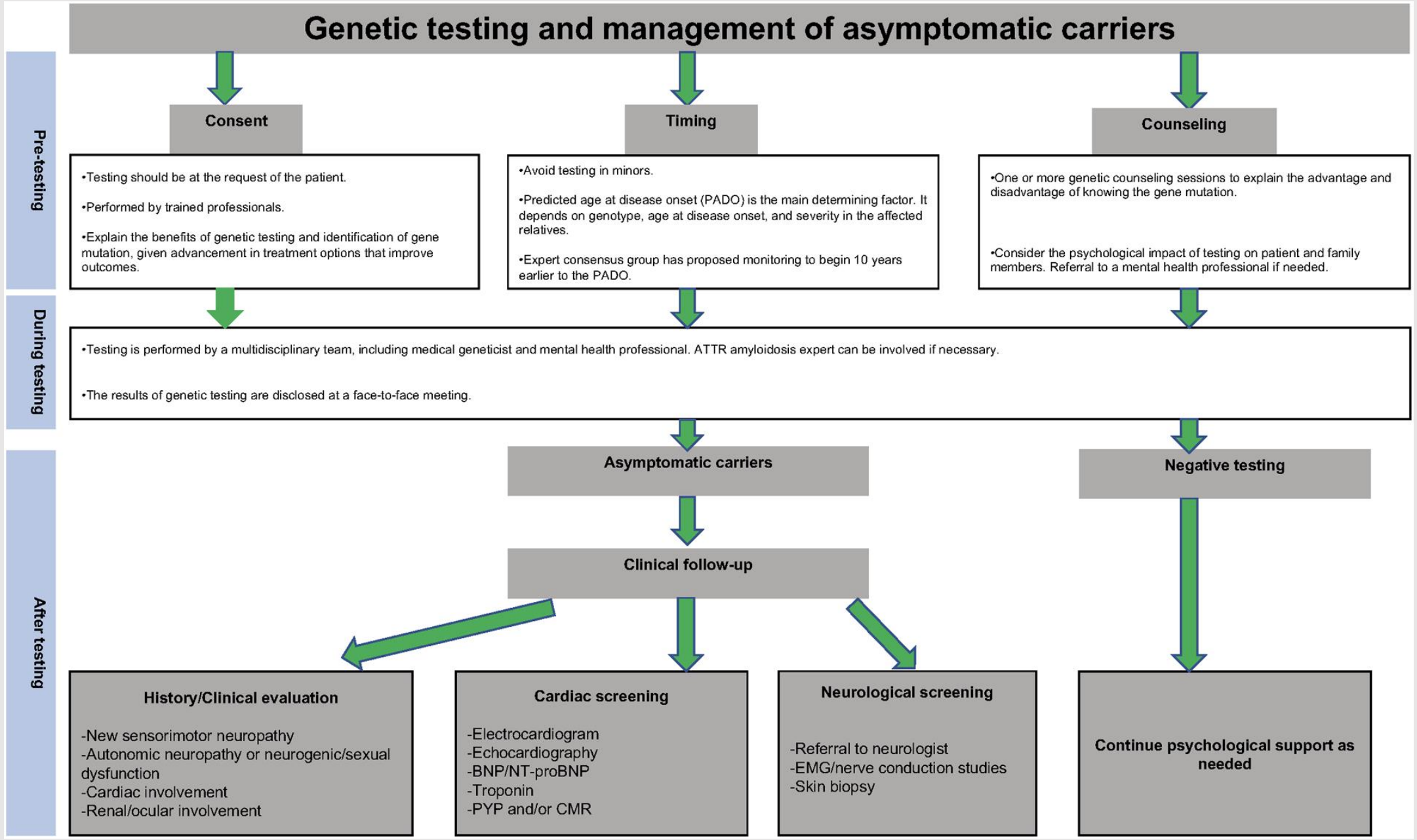
- Early education
  - Awareness of signs, symptoms, resources
  - Notification of at-risk relatives & cascade testing
- Efforts to prevent progressive clinical disease
  - Baseline and serial surveillance to implement treatment at initial onset
    - One expert consensus group suggests begin monitoring 10 years prior to predicted age of onset to establish baseline then annual follow-up with increased frequency if needed
  - Active research into potentially preventative meds/supplements (Glavonoid)
- Avoidance of misdiagnosis as other forms of heart failure (HCM, RCM, etc.)
- Involvement in clinical trials if interested

Currently: When to Consider Genetic Testing

- All patients with established diagnosis of ATTR cardiac amyloidosis
  - Differentiate between ATTRwt and ATTRv to better characterize:
    - Clinical manifestations
    - Prognosis
    - Treatment selection
    - Importance of screening family members

- Family members of individuals with known *TTR* variant interested in predictive genetic testing

Suggested Approach to Pre-Symptomatic Genetic Testing (Alreshq & Rubert, 2021 – Figure 1)



Limitations in Current Practice

- Seemingly negative family history may hide the presence of a risk variant
- Inheritance may be masked by...
  - Failure to recognize the condition
  - Early death of a parent before symptoms
  - Later onset of disease in a parent
  - Incomplete penetrance

- *TTR* gene analysis is already available on direct-to-consumer (DTC) testing
  - Often report on presence of 3 most common variants – including p.Val142Ile
  - Individuals may not be expecting risk result or prepared to process its significance

Genetic Testing: simpler and more accessible than ever

- Sample can be collected via blood draw or at-home saliva kit
- Commercial send out labs often have convenient insurance billing assistance
  - Alternative $250 self-pay cost
- Sponsored testing programs
  - No-charge genetic testing
  - Eligibility criteria based on personal and/or family history
- Expanded genetic counseling services
  - Local hospitals/clinics
  - May be offered by testing laboratory
  - Partnership with independent telehealth company
  - National Society of Genetic Counselors: www.findageneticcounselor.com

Case Example: 45yo Male

History

- Self-referred to discuss *TTR* p.V122I variant on DTC testing
- Reported Nigerian and other West African ancestry
- No personal or family history of related symptoms

Considerations

- Clinical confirmatory testing
- Family letter for cascade testing
- Age-dependent penetrance
- Follow-up education, evaluation, & screening with multi-disciplinary amyloid team

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