# Amyloidosis Roundtable: Unmet Needs in the Management of Cardiac Amyloidosis

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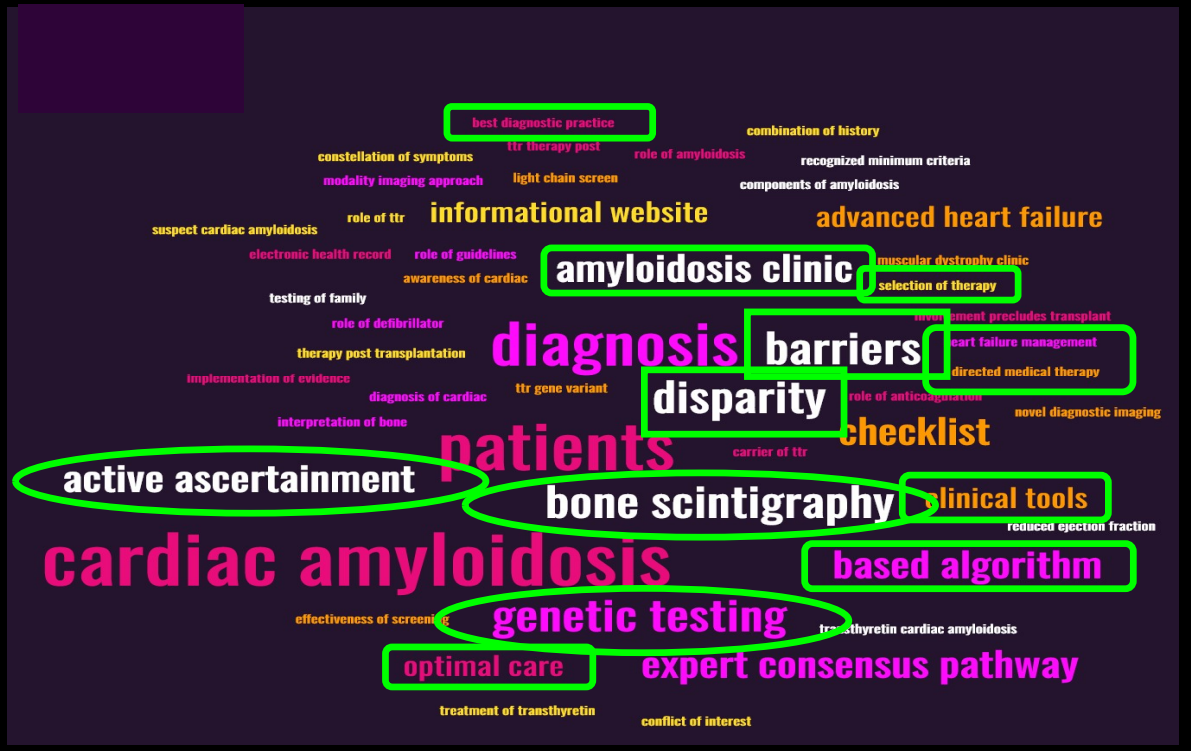
# Disclosures

- I have research support for my research from:
  - NIH/NIA/NHLBI
  - Eidos, Inc
  - Ionis Pharmaceuticals
  - Pfizer, Inc.
  - -Akcea
  - -GSK
  - -Alnylam
  - -Intellia

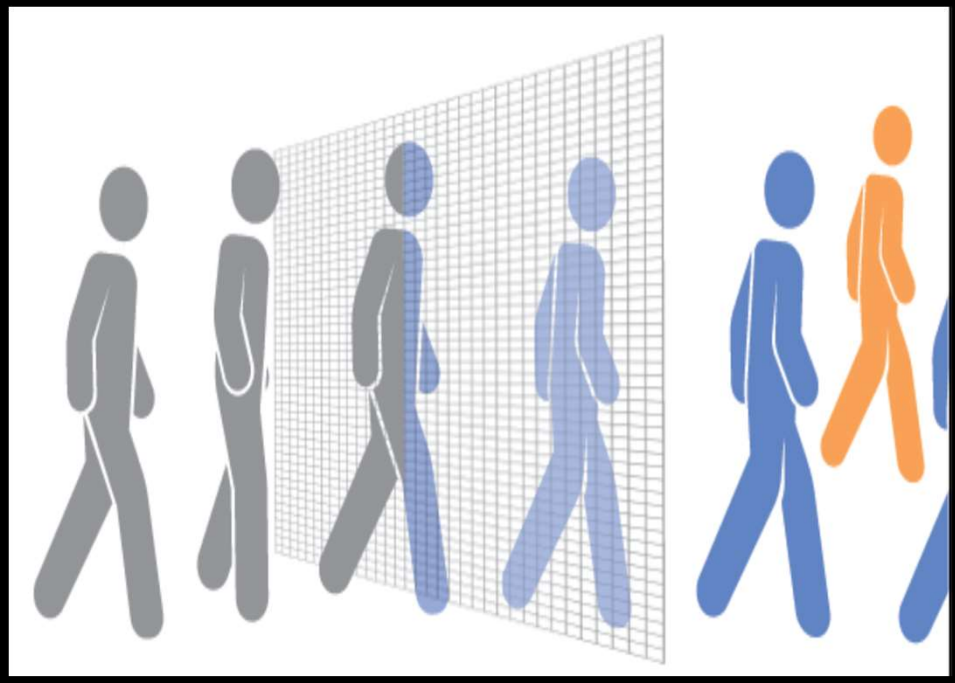
# Topics for Brief Discussion

- Active Ascertainment/ Screening
- Health Disparities
- Emerging Treatments
  - Cost and Selection
  - Progression of Disease
- Multidisciplinary Care



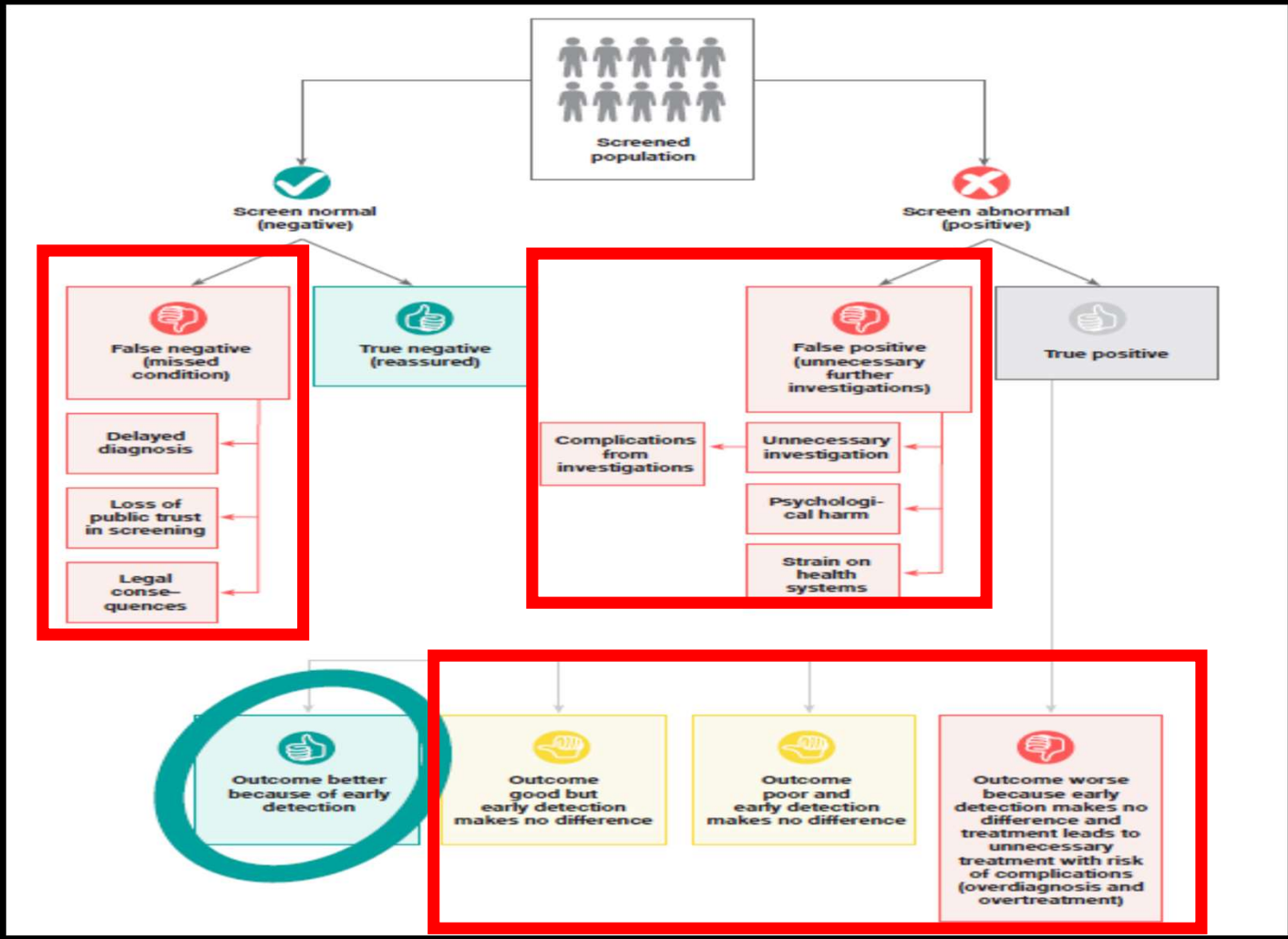
# What is screening?

Screening is a process aimed at identifying people in an ***apparently healthy population*** who are at higher risk of a health problem or a condition, so that an early treatment or intervention can be offered and thereby reduce the incidence and/or mortality of the health problem or condition within the population.

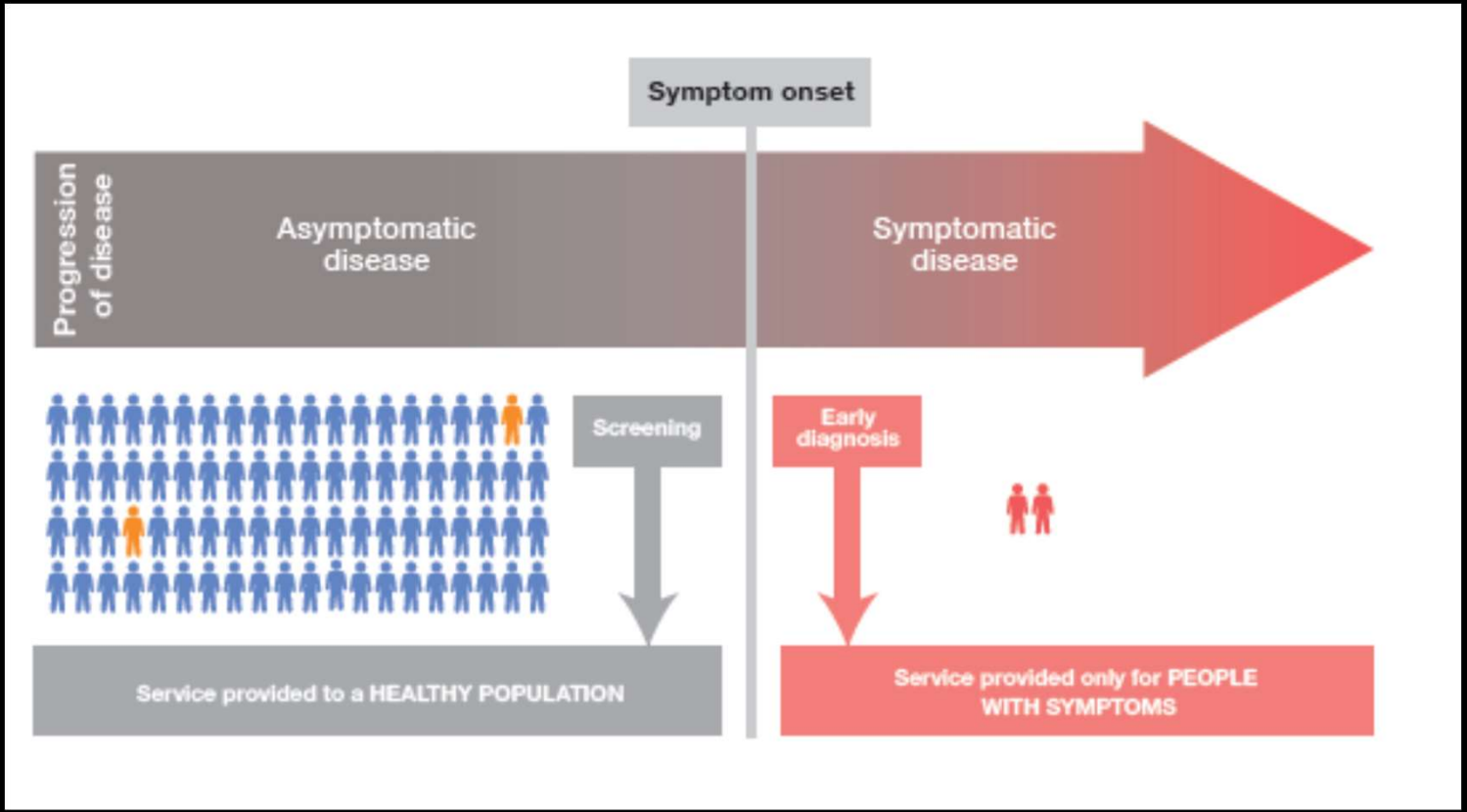


World Health Organization 2020

# There are many potential negative consequences of screening programs

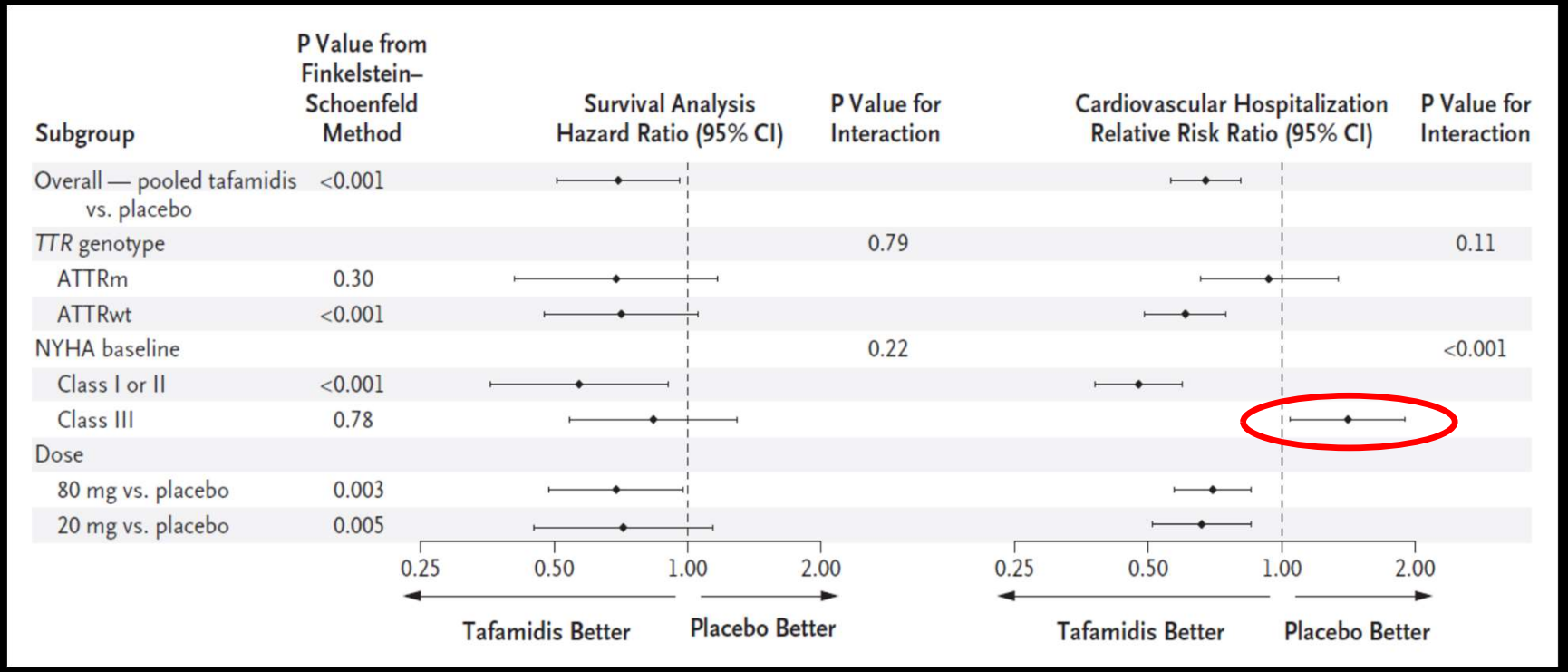


# Screening versus Early Diagnosis in TTR Cardiac Amyloidosis




World Health Organization 2020

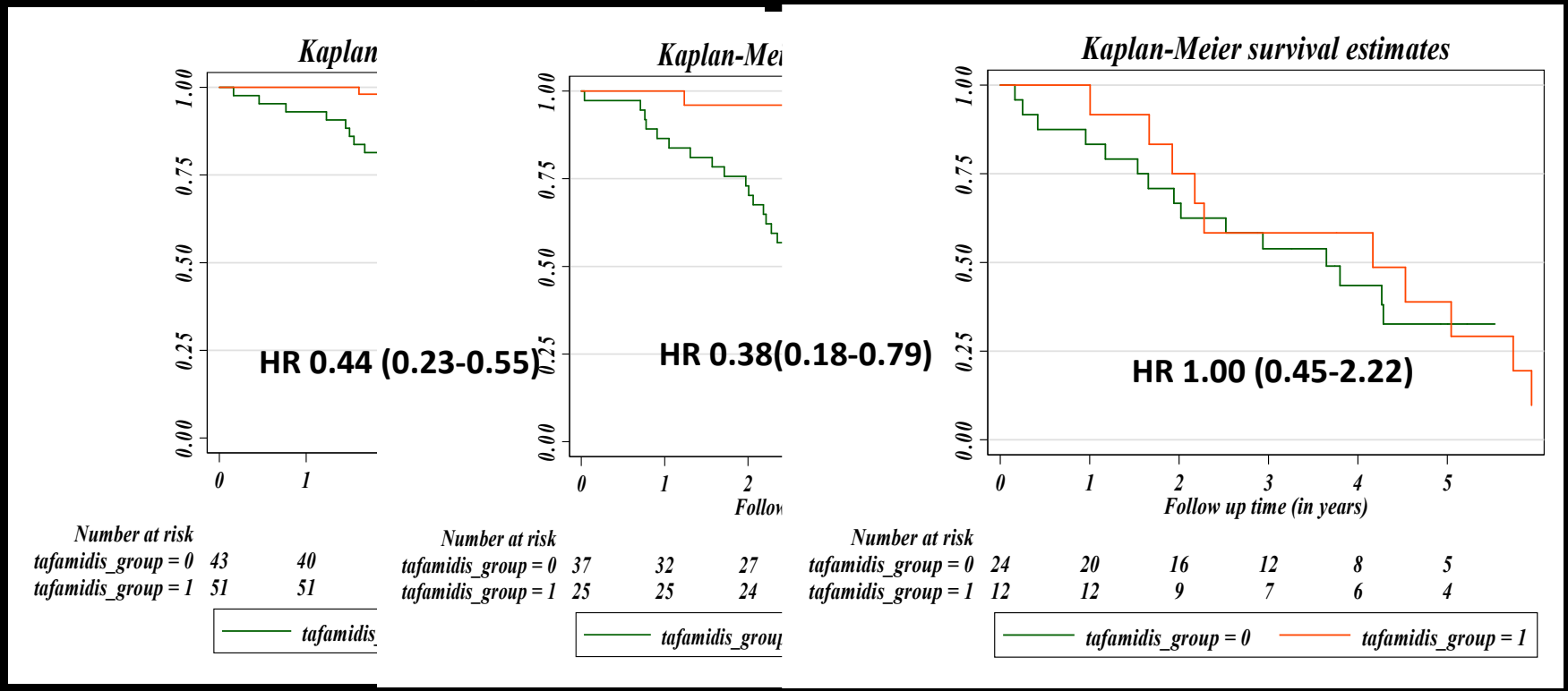
# ATTR-ACT trial provides evidence that early diagnosis is important in leveraging beneficial effects of stabilizers.




Maurer MS, et al. N Engl J Med. 2018 Aug 27.

# Real World Data for Tafamidis in ATTRwt: The Earlier the Better!!!

Mayo Stage I Mayo Stage 2 Mayo Stage 3



# Problems of Spectrum and Bias in Evaluating the Efficacy of Diagnostic Tests

Clinical investigations of the efficacy of diagnostic tests have often produced misleading results so that tests initially regarded as valuable were later rejected as worthless.

- Alvan Feinstein, MD, NEJM 1978

N Engl J Med 1978; 299:926-930

# Prevalence of ATTR-CA in Previous Studies of Nuclear Scintigraphy is Very High

| Study | # of Participants | Prevalence |
|---|---|---|
| Gillmore, EMB subgroup | 374 | 70% |
| Gillmore, Overall | 1217 | 51% |
| Castano, et al. | 171 | 71% |
| Columbia Nuclear Lab | 757 | 36% |
| University of Pittsburgh | 233 | 26% |
| Mayo Screening Study | 286 | 6% |
| SCAN-MP | 800 (planned) | ~10% |

Circulation. 2016;133(24):2404-1; JAMA Cardiol. 2016;1(8):880-889;
JACC Cardiovascular Imaging, 2020 Nov 12; Circ Cardiovasc Imaging. 2020 Feb;13(2):e010249;
JAMA Cardiol. 2021 Aug 25:e213070..

# Impact of Prevalence of ATTR-CA on Positive Predictive Value of Scintigraphy

## High Prevalence

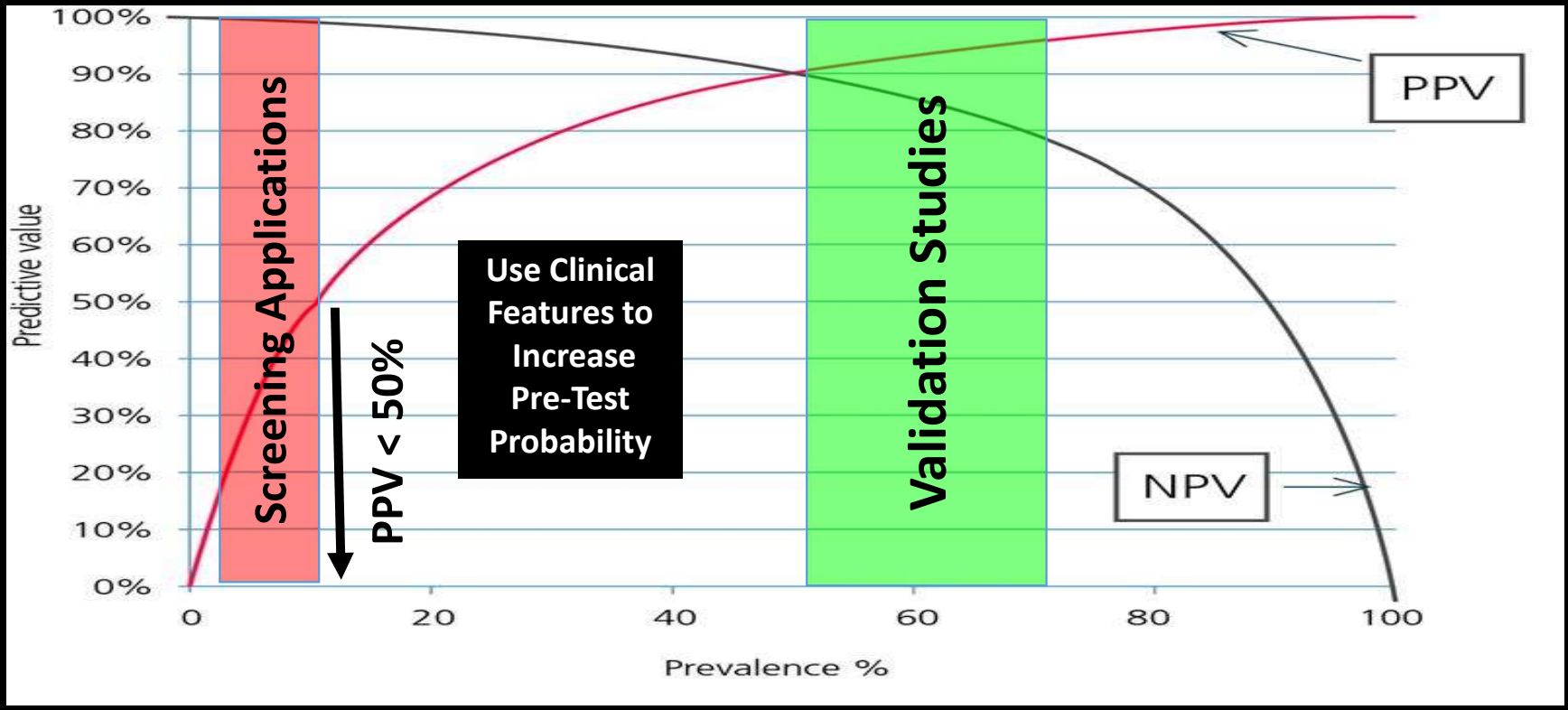
| | ATTR-CA+ | ATTR-CA - |
|---|---|---|
| +Scintigraphy | 666 | 34 |
| -Scintigraphy | 62 | 667 |
| | 728 | 701 |
| Prevalence | 50.9% | |
| Sensitivity | 91.5% | |
| Specificity | 95.1% | |
| False Positive Rate | 4.9% | |
| False negative Rate | 8.5% | |
| PPV | 95.1% | |
| NPV | 91.5% | |

## Low Prevalence

| | ATTR-CA+ | ATTR-CA - |
|---|---|---|
| +Scintigraphy | 92 | 93 |
| -Scintigraphy | 8 | 1807 |
| | 100 | 1900 |
| Prevalence | 5.0% | |
| Sensitivity | 92.0% | |
| Specificity | 95.1% | |
| False Positive Rate | 4.9% | |
| False negative Rate | 8.0% | |
| PPV | 49.7% | |
| NPV | 99.6% | |

*Circulation*. 2016;133:2404-2412.

# Impact of Prevalence of ATTR-CA on Positive Predictive Value of Scintigraphy



# Criteria Required for Adoption of Screening: Have we met the criteria for ATTR-CA?

| Criteria | Yes/No |
|---|---|
| Important health problem | Yes |
| Methods / Facilities to diagnose are available | In some areas |
| Diagnostic test is acceptable to those at risk | Yes |
| Test has appropriate sensitivity/specificity | Unknown |
| Favorable cost / benefit analysis | Unknown |
| Treatment exists for the condition | Yes, but costly |
| Appropriate timing of intervention | Unknown |

Adopted from Wilson & Jungner,. Principles and practice of screening for disease. Geneva: World Health Organization; 1968

# Opportunity to address Health Disparities

| | Val122Ile | ATTRwt |
|---|---|---|
| **Age – Median (IQR)** | 77 (72–80) | 79 (73–83) |
| **Black Race** | 98% | 10% |
| **EF –Median IQR** | 49 (39–62) | 58 (45–71) |
| **Survival (median)** | 2.6 years | 4.8 years |
| **6MWT distance** | 260 (141–364) | 345 (230–415) |

Circulation. 2019 Jul 2;140(1):16-26

# ATTR Cardiomyopathy without Neuropathy Phase 3 Trials

- AG10- ATTRIBUTE-CM
  - Oral compound
  - Phase 3 trial -– fully enrolled
  - 510 Participants Planned
  - 2:1 Randomization
  - Co-Primary Endpoints
    - 6MWTD at 12 months
    - Mortality and CV hospitalizations at 30 months
- Patisiran – APOLLO-B
  - IV administration every 3 weeks
  - 300 participants - Anticipated enrollment closed in Q2 of 2021
  - 1:1 randomization
  - Change in 6MWT at 12 months
- AKCEA-TTR-$L_{RX}$: CardioTTRansform
  - SQ compound dose 1 a month
  - 750 participants
  - 1:1 Randomization
  - Primary - hierarchical composite endpoint of cardiovascular mortality and recurrent CV clinical events (CV hospitalizations and urgent HF visits)
- Vutrisiran – Helios B
  - SQ Compound dose every 3 months
  - 600 participants
  - 1:1 Randomization
  - All-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits).

# ATTR-CM ongoing trials:
## Will the evidence be sufficient to guide clinical care?

| Study | Arms | Combination Therapy | % Using Combination |
|---|---|---|---|
| APOLLO-B | Patisiran vs. Placebo | Patisiran + Tafamidis | Up to 30% |
| ATTRIBUTE-CM | Acoramidis vs. Placebo | Acoramidis + Tafamidis | Unknown |
| HELIOS-B | Vutrisiran vs. Placebo | Vutrisiran + Tafamidis | Up to 30% |
| CardioTTRansform | Eplontersen vs. Placebo | Eplontersen + Tafamidis | No limit |

# Cost* of therapy is already high, and combination may be prohibitory.

| | Diflunisal | Tafamidis | Patisiran | Inotersen |
|---|---|---|---|---|
| Diflunisal | $324 | $225,324 | $450,324 | $450,324 |
| Tafamidis | $225,324 | $225,000 | $675,000 | 675,000 |
| Patisiran | $450,324 | $675,000 | $450,000 | No rationale |
| Inotersen | $450,324 | $675,000 | No rationale | $450,000 |

* Yearly costs based on Wholesale Acquisition Costs (WAC)

# Engaging a multi-disciplinary team: What are the impediments?

- Cardiologist*
- Neurologist*
- Genetic Counselors*
- Gastroenterologist
- Pathologists*
- Nephrologist
- Ophthalmologist
- Orthopedists/Physiatrists

*Key team members

# Summary

- Targeted programs at “early diagnosis” of ATTR-CA in those with extra-cardiac manifestations requires rigorously conducted studies to determine if they are beneficial.
- Well designed, ongoing phase III trials will provide important data to determine the risk/benefit profile of stabilizers and silencers and their combination but will likely not provide definitive scientific guidance.
- We need to develop approaches in cardiac amyloidosis that address disparities in care.