# Atrial Fibrillation -
## Can we use polygenic risk to inform clinical care?

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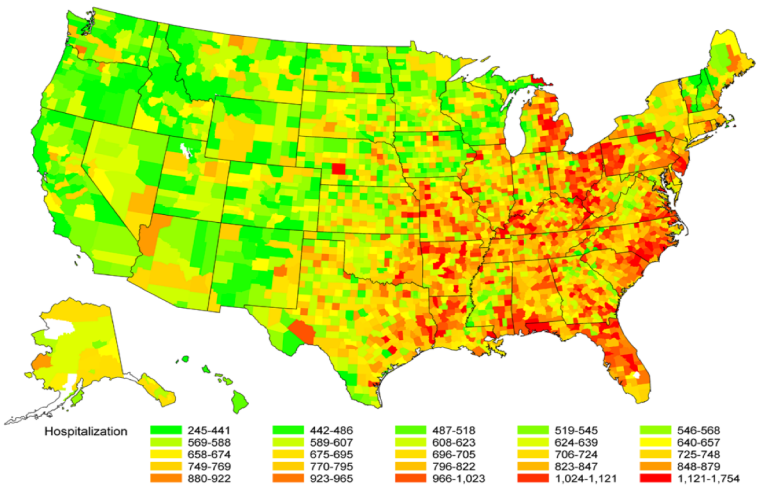
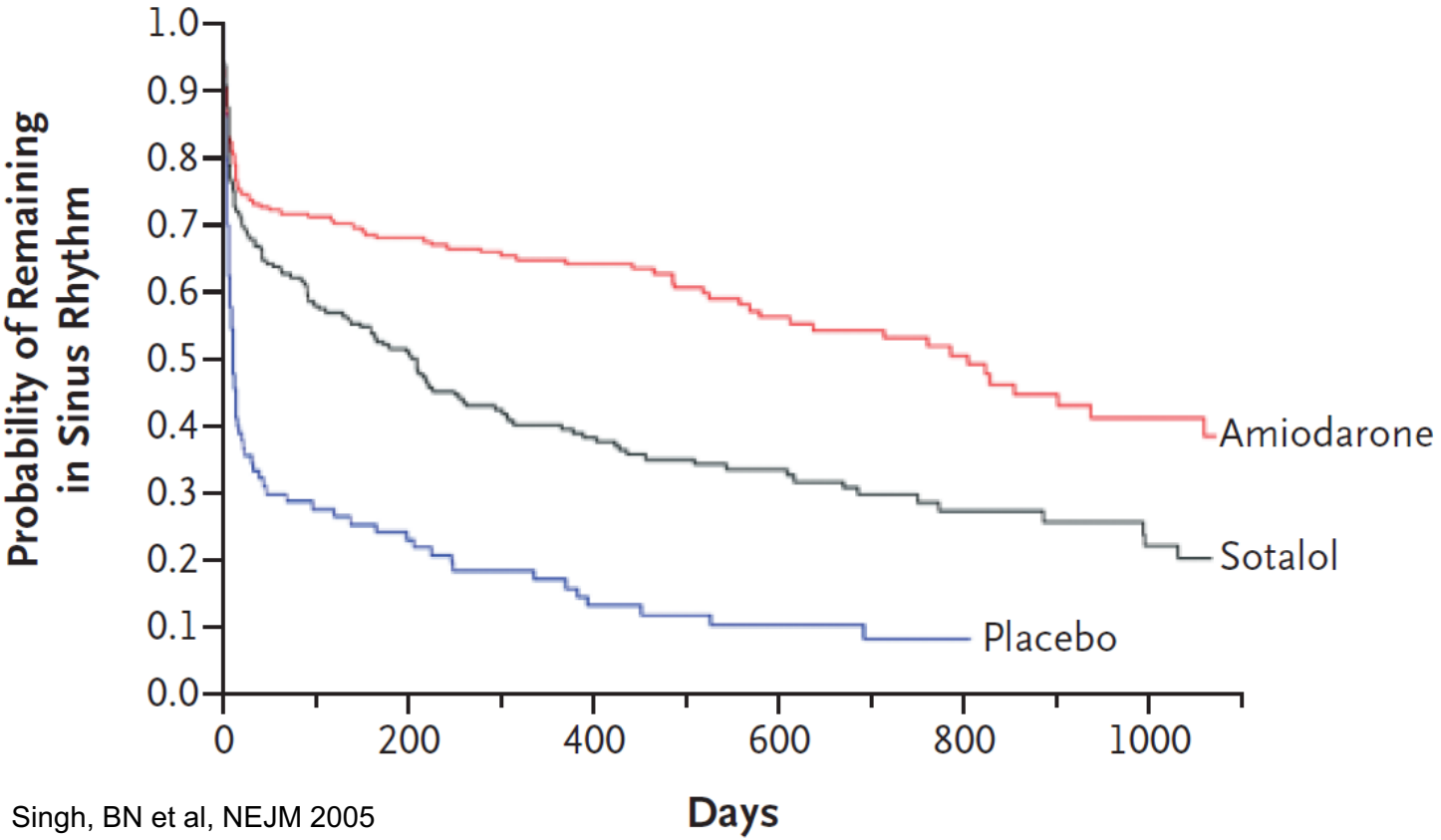
# Why do we care about atrial fibrillation?

- Most common arrhythmia
- 33 million people worldwide
- Increased risk of stroke, heart failure, dementia, and death
- Treatments are limited

**2013**



# We clearly need new treatments for AF




Singh, BN et al, NEJM 2005

Use genetics to identify underlying mechanisms of AF

# Current AF resources

| | AF | Controls | Status |
|---|---|---|---|
| **GWAS** | 120K | >1M | Available |

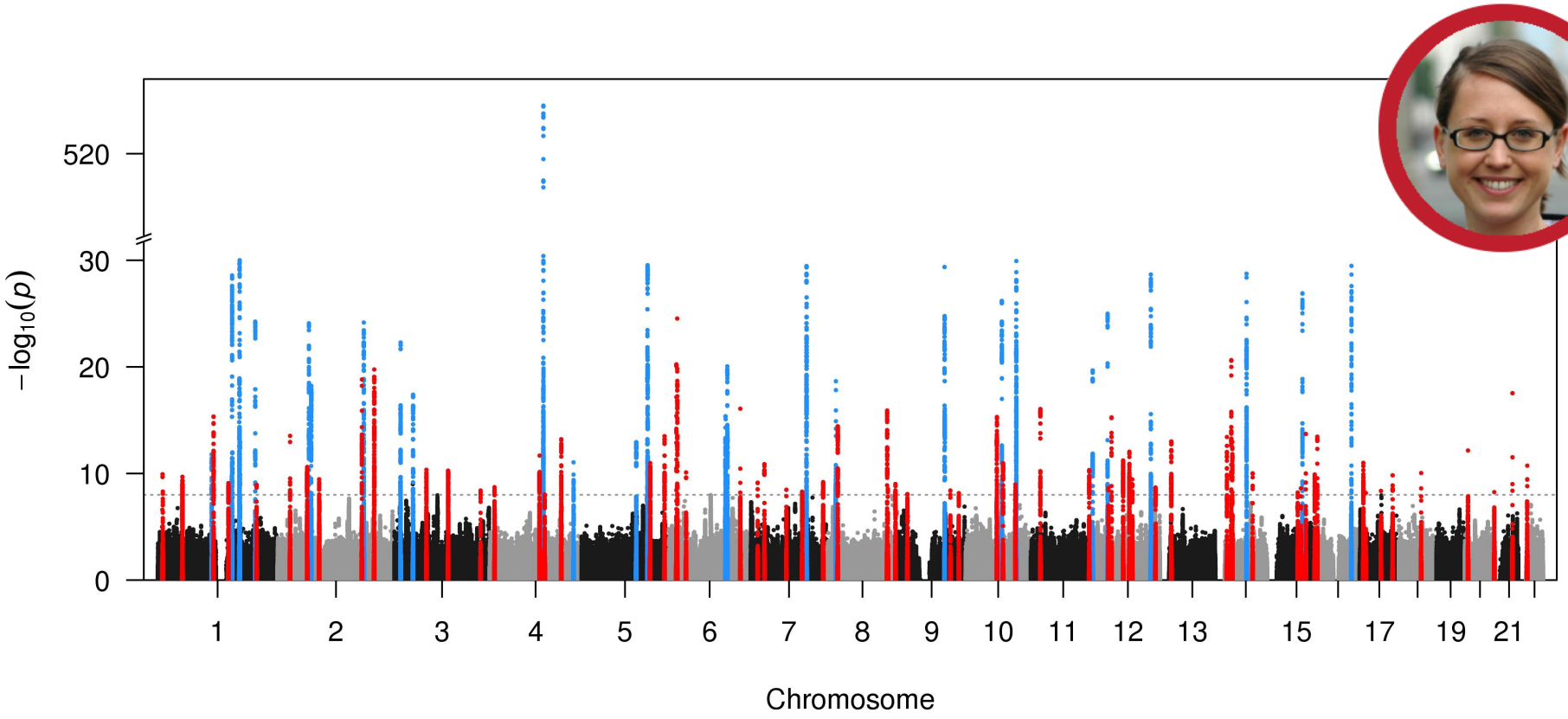

Broad AF Study

biobank uk
Improving the health of future generations

BIOBANK JAPAN

Engage AF
TIMI 48

# 2018: 65K individuals, ~100 loci






known locus
novel locus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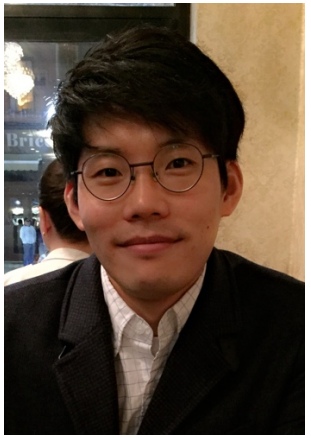
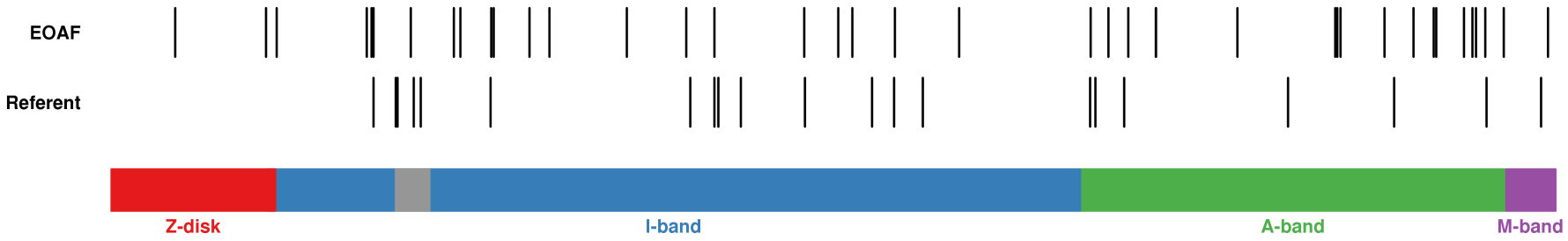
**Roselli, Chaffin, et al *Nature Genetics*, 2018**

# *TTN* loss of function mutations in early-onset AF

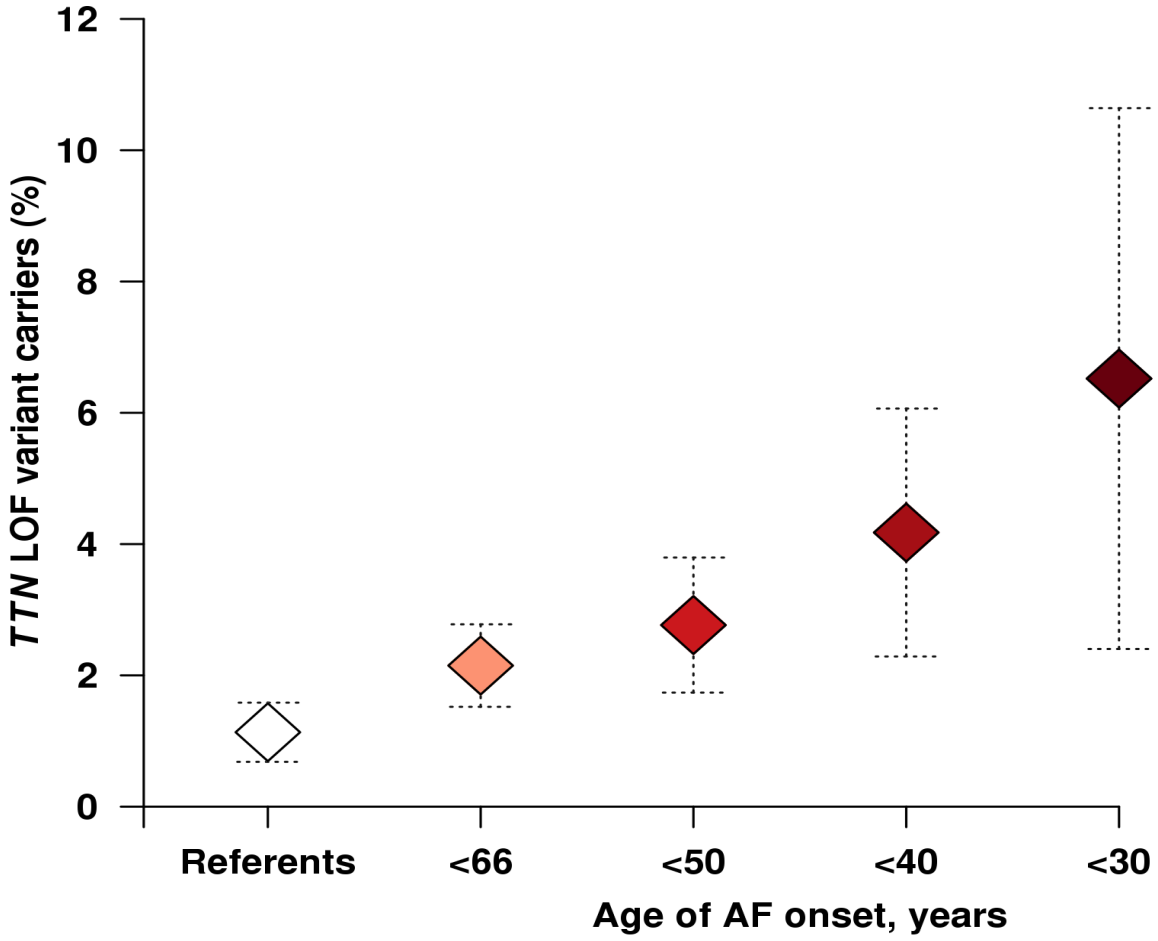
2800 AF cases + 5000 controls






Choi et al *JAMA*, 2018

# Increasing frequency of *TTN* loss of function variants with decreasing age of AF onset




**AF onset <30 yrs**

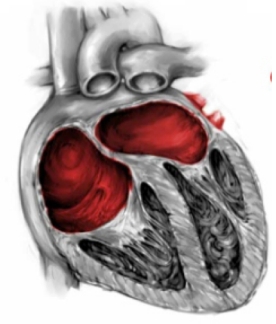
OR 5.94

CI 2.64-13.36

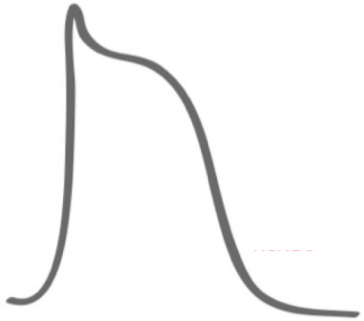
$p=1.64 \times 10^{-5}$

Choi et al *JAMA*, 2018

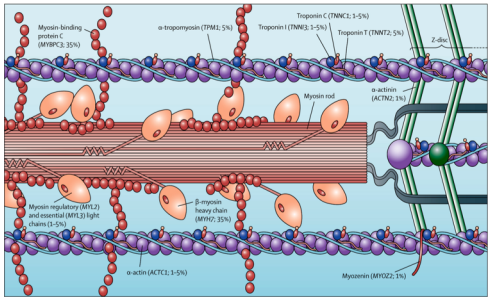
# Some expected pathways have emerged



Atrial development



Ion channels




Contractile proteins

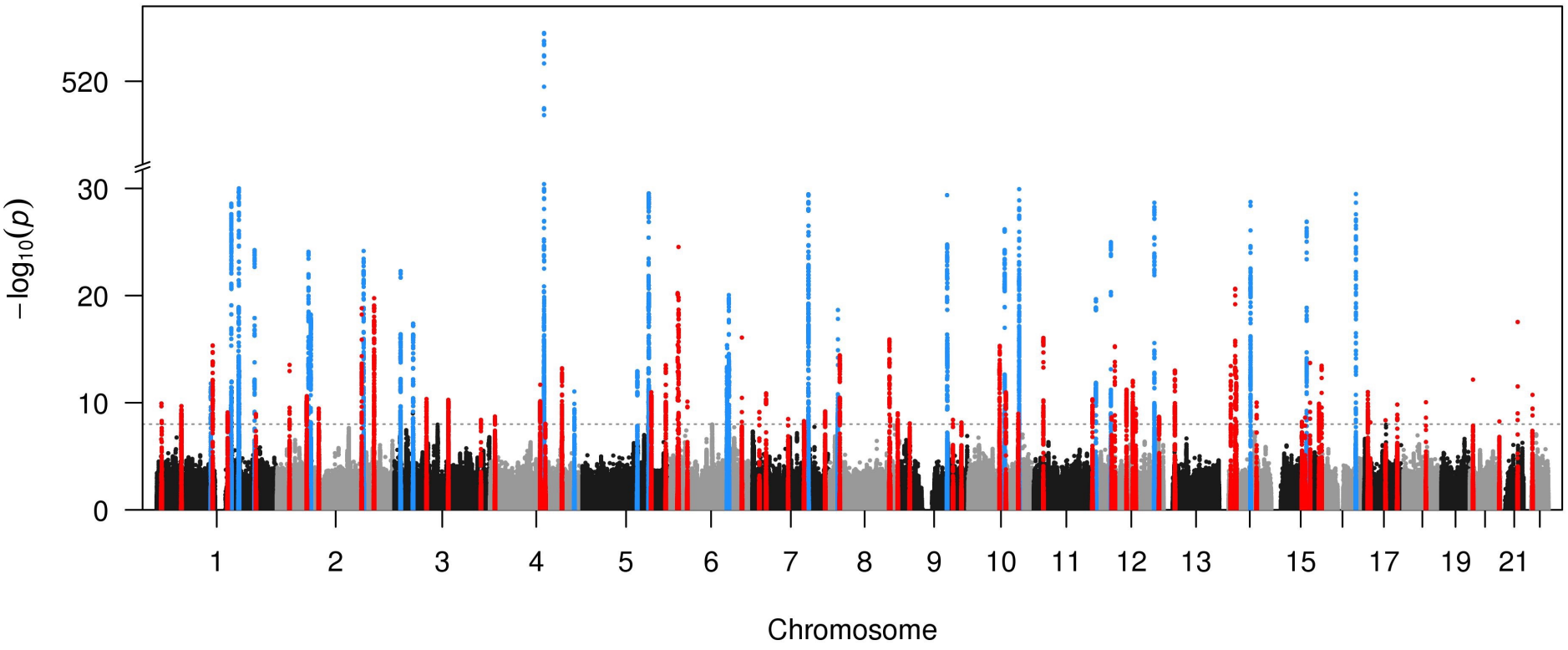
But many genes have unknown relation to AF

Challenge is linking gene to mechanism

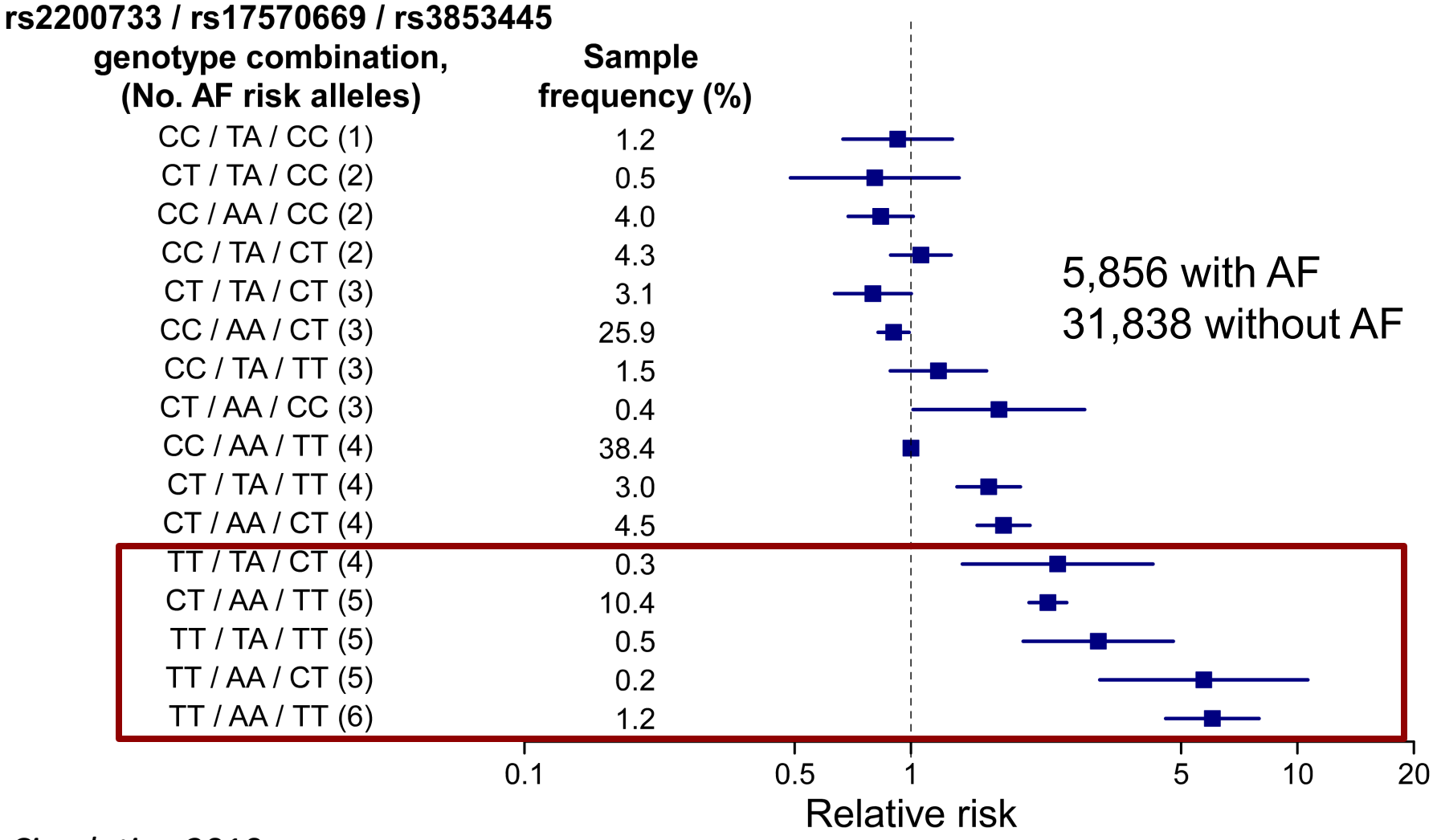
# How can we use polygenic risk of AF?

- AF risk prediction in general population
- Biomarker in high risk individuals – cryptogenic stroke
- Differential outcomes – HF, stroke, mortality
- Interaction between common and rare variation

# A dominant locus for AF at *PITX2*/4q25

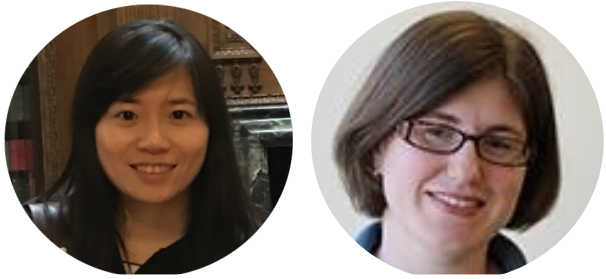


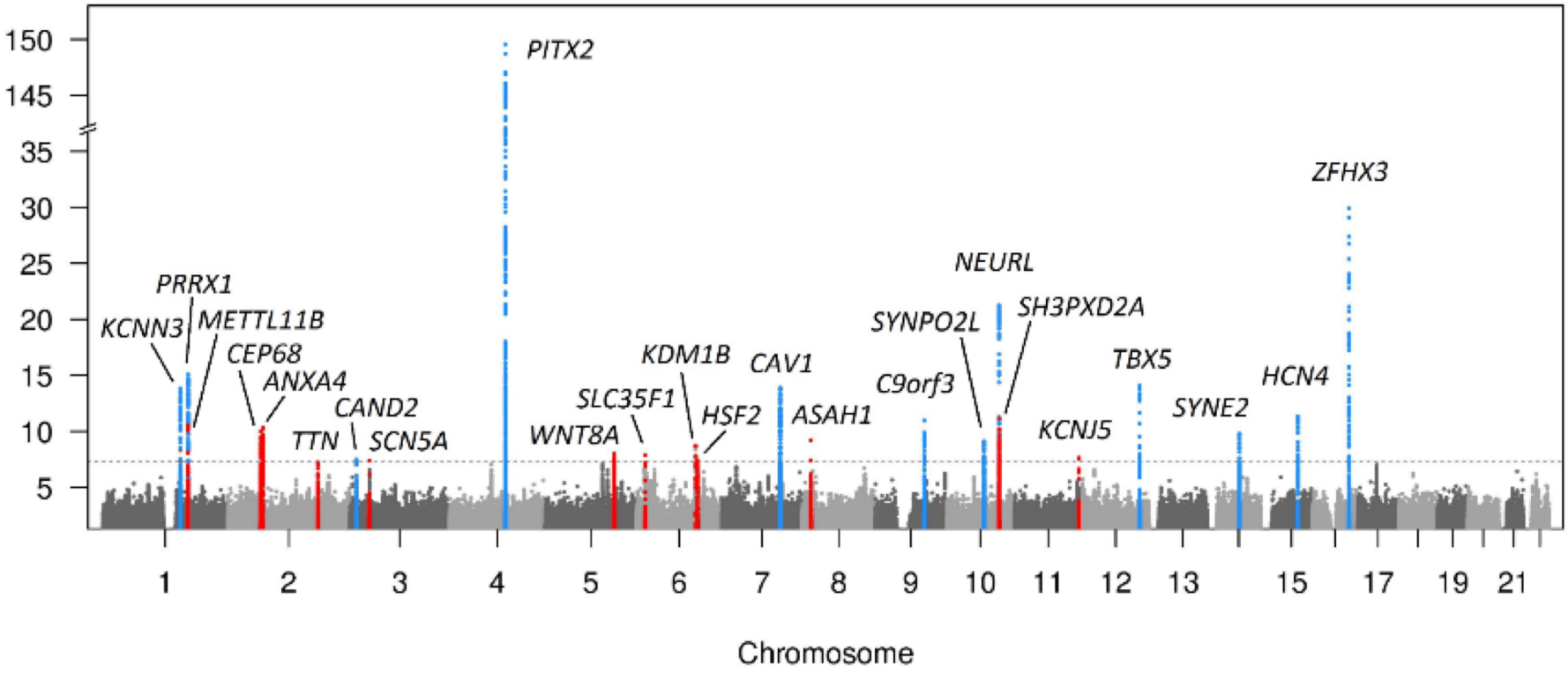
# 3 SNPs at top AF locus can identify high risk of AF




*Circulation* 2010

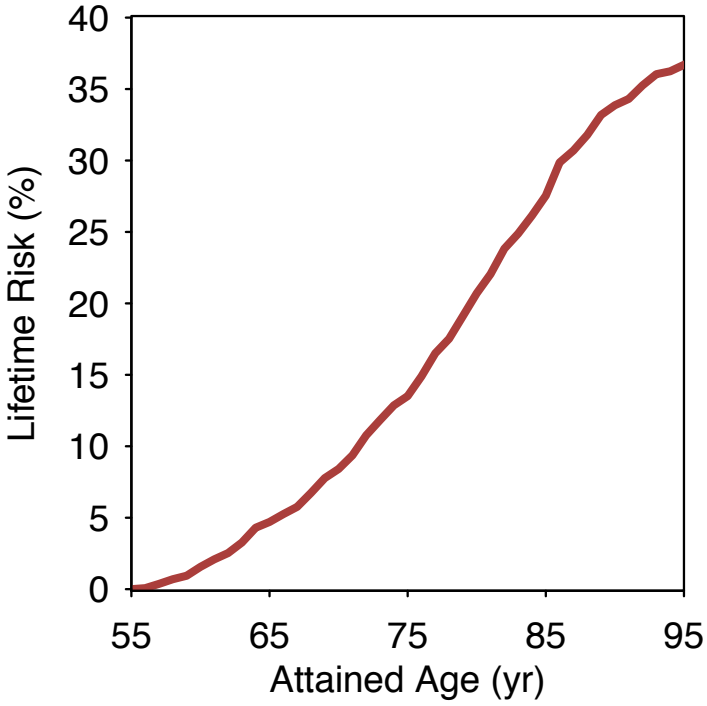
# How does genetics influence the risk of AF?

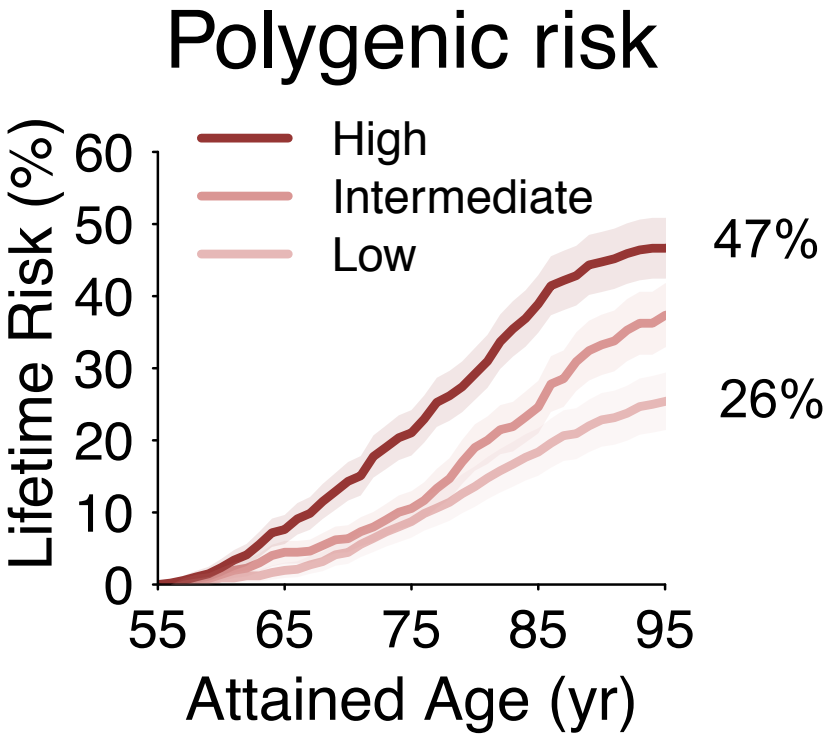




# Lifetime risk of AF is high

## Genetic risk can stratify lifetime risk of AF




Weng, Preis et al *Circulation*, 2017

# How can we use polygenic risk of AF?

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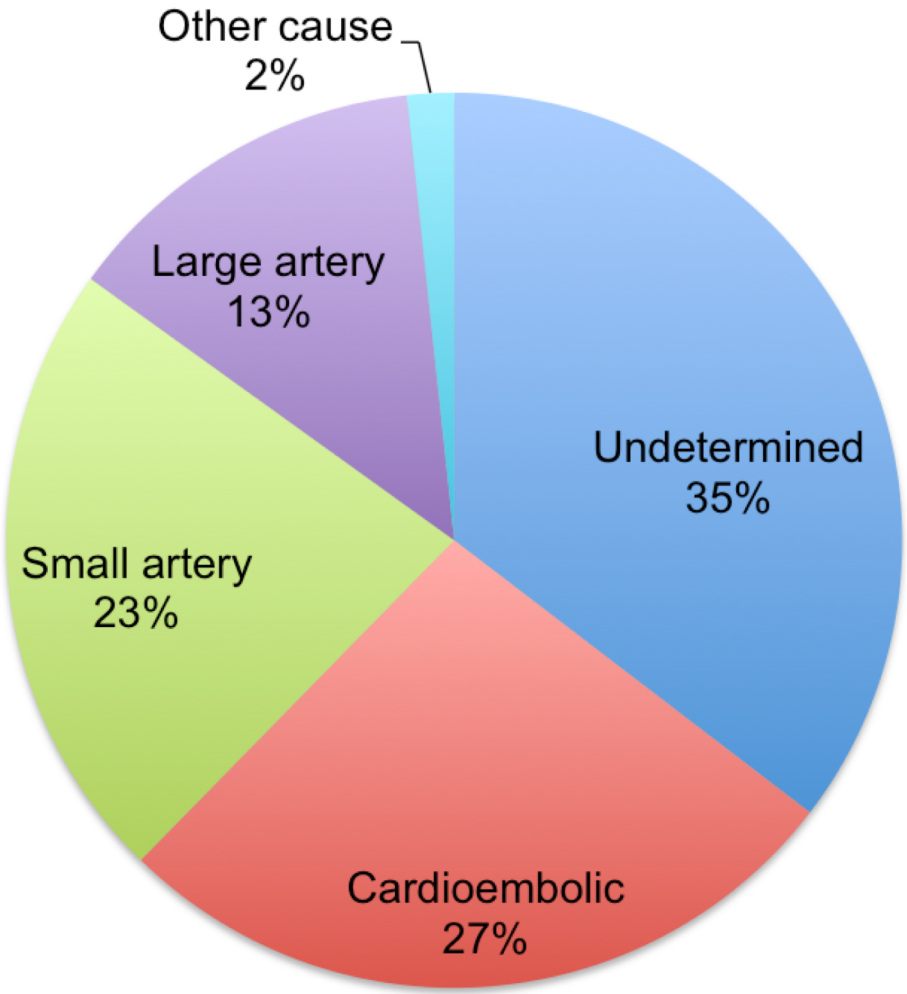
# One third of strokes are cryptogenic



# Anticoagulation in cryptogenic stroke trials has failed

| Trial | Anticoagulant | Comparator | Reduced recurrent stroke with anticoagulant |
|---|---|---|---|
| WARS 2001 | Warfarin | ASA 325 mg | No |
| NAVIGATE-ESUS 2018 | Rivaroxaban 15 mg | ASA 100 mg | No |
| RESPECT-ESUS 2018 | Dabigatran 110 mg or 150 mg BID | ASA 100 mg | No |
| ATTICUS | Apixaban 5 mg BID | ASA 100 mg | Pending |

Would genetically determined AF/cardioembolic stroke subgroups benefit from anticoagulation?

# SiGN Consortium: AF genetic risk is specific for cardioembolism

**Chris Anderson**

**Sara Pulit**

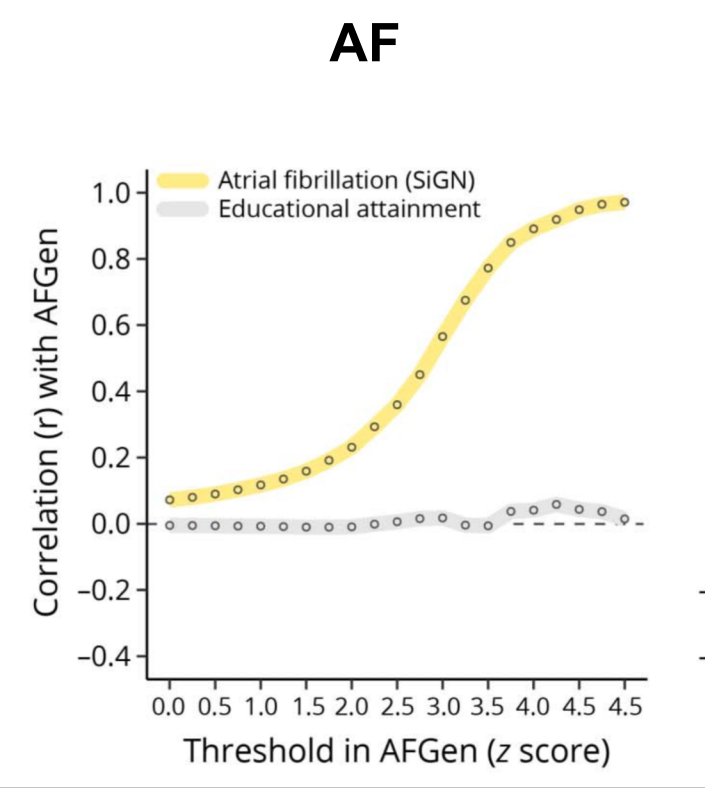
**Steve Lubitz**

13K ischemic stroke cases &
28K referents

- ~25% cardioembolic
- ~20% large artery
- ~20% small vessel
- ~25% cryptogenic

*Neurology Genetics* 2018

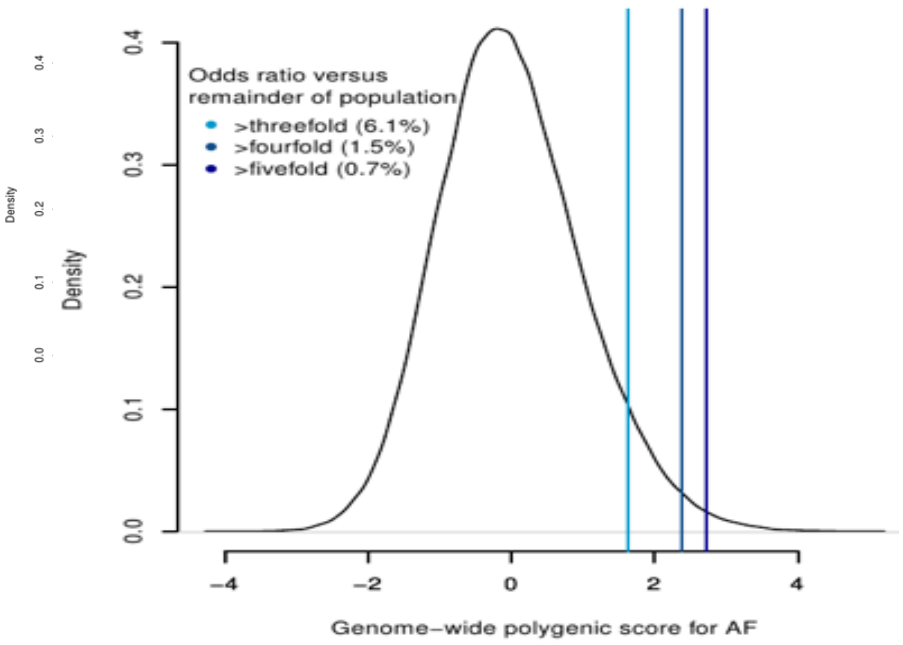
# SiGN Consortium: AF genetic risk is specific for cardioembolism




*Neurology Genetics* 2018

# Using AF GRS to identify at risk patients

**Individuals without AF, but high clinical or GRS**

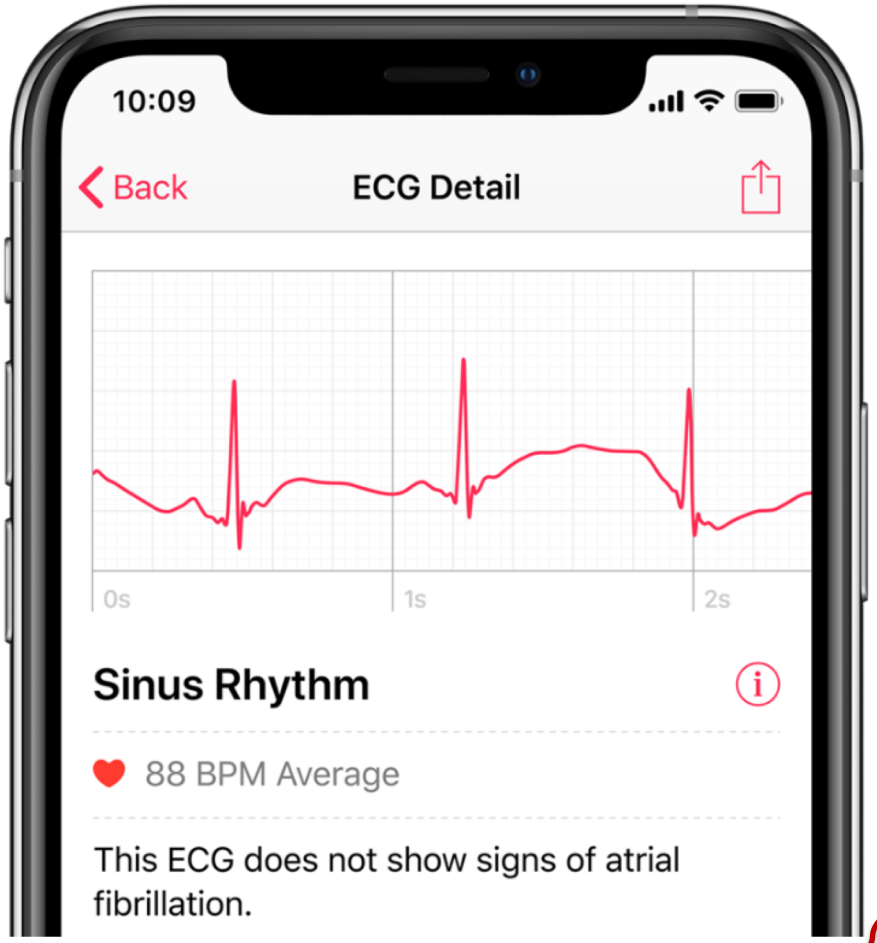



**Screening**


Khera, Chaffin et al, *Nature Genetics*, 2018

# Single lead electrocardiogram


# We will find AF, but at a cost…




yikes!

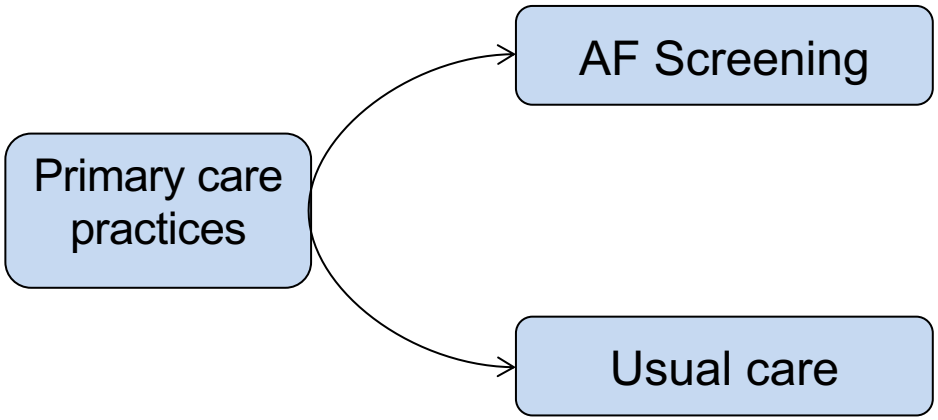
# Plenty of other technologies


Google Fit

# Large scale screening is already underway

VITAL-AF

- Cluster RCT
- N=35,000
- Age ≥ 65 years

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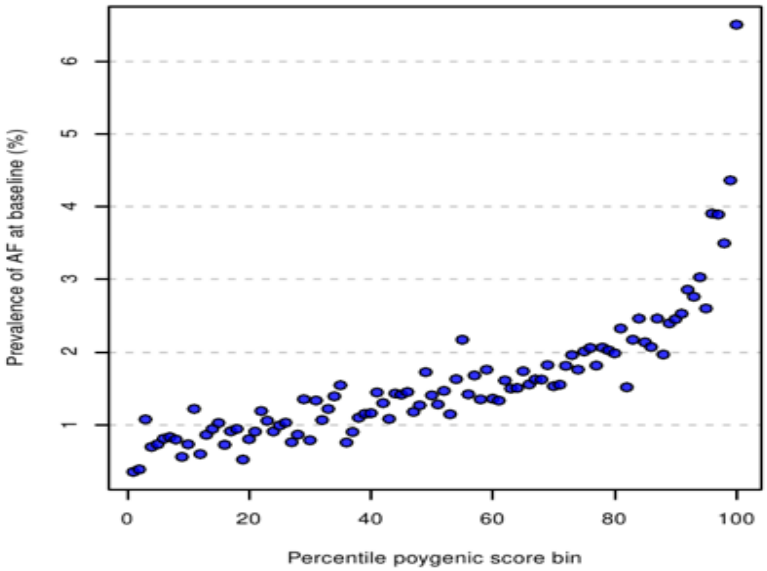
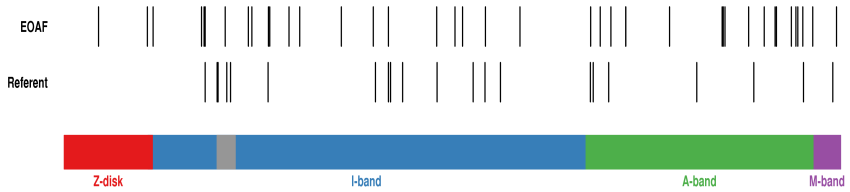
# Ongoing work to examine interaction between common and rare variation

**Polygenic risk**




**Rare variation**



# Conclusions

- Identified >130 genetic loci for AF
- Titin LOF variants in early-onset AF
- AF PRS
  - Can identify high risk individuals
  - May refine cryptogenic stroke risk
  - Should be considered with clinical RFs
- Screening of AF is increasingly widespread

# Our team

**MGH**
Mirranda Birraza, Seung Hoan Choi, Amelia Hall, Alan Hanley, William Hucker, Heather Jameson Christina Lee, Elsa Ronzier Marisa Shea, Nathan Tucker

**Precision Cardiology**
Christian Stegmann, Francois Aguet, Kristin Ardlie, Denis Amer-Akkad, Anant Chopra, Hanna Eilken, Stephen Fleming, Raj Gupta, Alex Ehrmann

**Lubitz, Milan and Kathiresan labs**

**Broad Institute**
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**AFGen Consortium**

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