Familial Hypercholesterolemia: Personalized public health epitomized

Joshua W. Knowles, MD, PhD
Stanford and the FH Foundation

STANFORD CENTER FOR INHERITED CARDIOVASCULAR DISEASE

FH FOUNDATION
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CDC: One-Fourth Of Heart Attack And Stroke Deaths Preventable

by SCOTT HENSLEY

September 03, 2013 4:02 PM

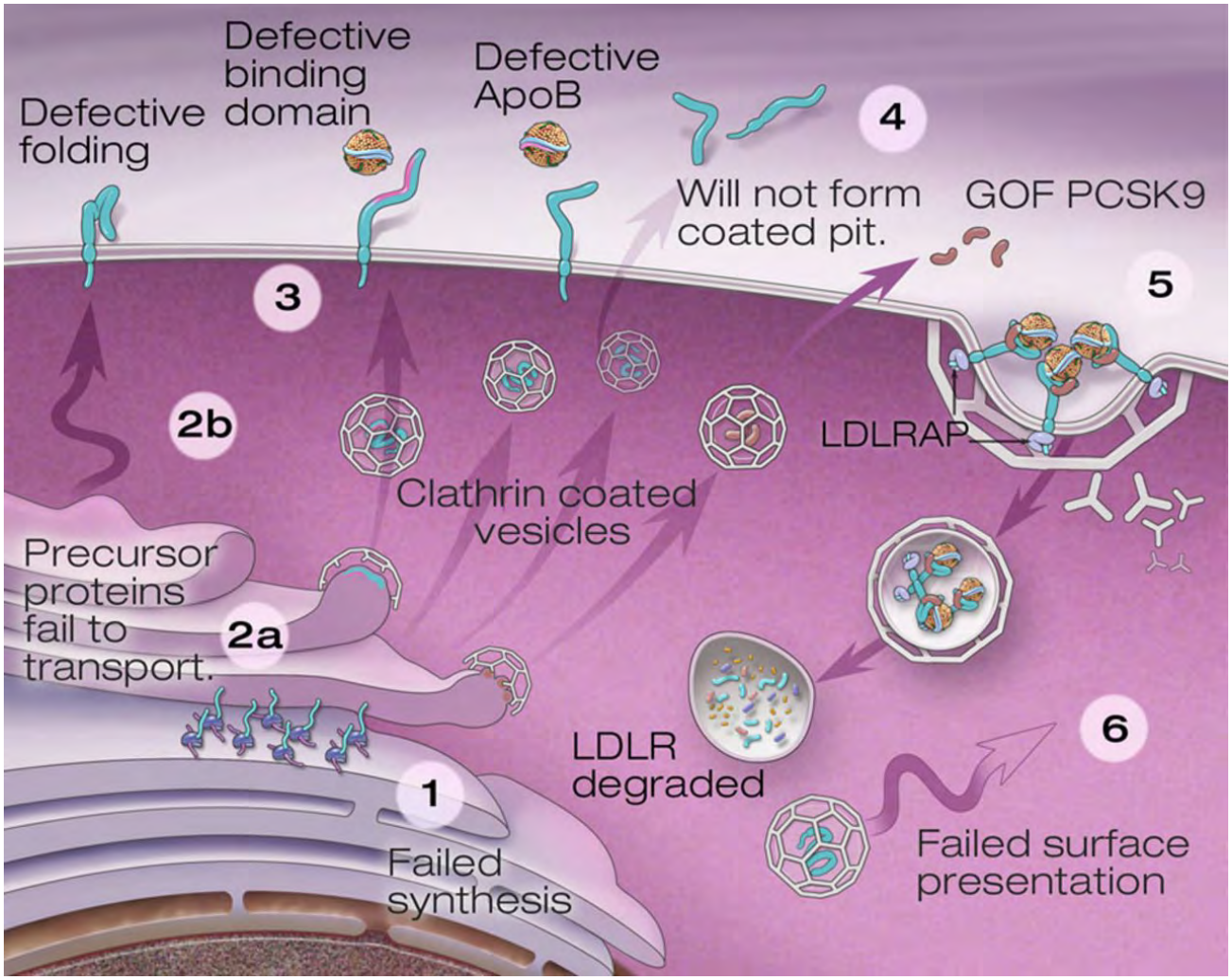
There has been more progress in lowering deaths from heart attacks and strokes among people who qualify for Medicare than those who are younger.

Trends in Acute Myocardial Infarction in Young Patients and Differences by Sex and Race, 2001 to 2010

Aakriti Gupta, MBBS,*† Yongfei Wang, MS,*‡ John A. Spertus, MD, MPH,§‖ Mary Geda, MSN,* Nancy Lorenze, DNSc, MSN,* Chileshe Nkonde-Price, MD,‡¶# Gail D'Onofrio, MD, MS,** Judith H. Lichtman, PhD, MPH,*†† Harlan M. Krumholz, MD, SM*‡‡‡§§

Our most notable finding is an absence of significant declines in hospitalization rates among young women and men across all age subgroups from 2001 to 2010. This observation is in contrast to the Medicare population studies, in which we described a >20% decline in hospitalization rates for AMI during this time period (8). One potential explanation for

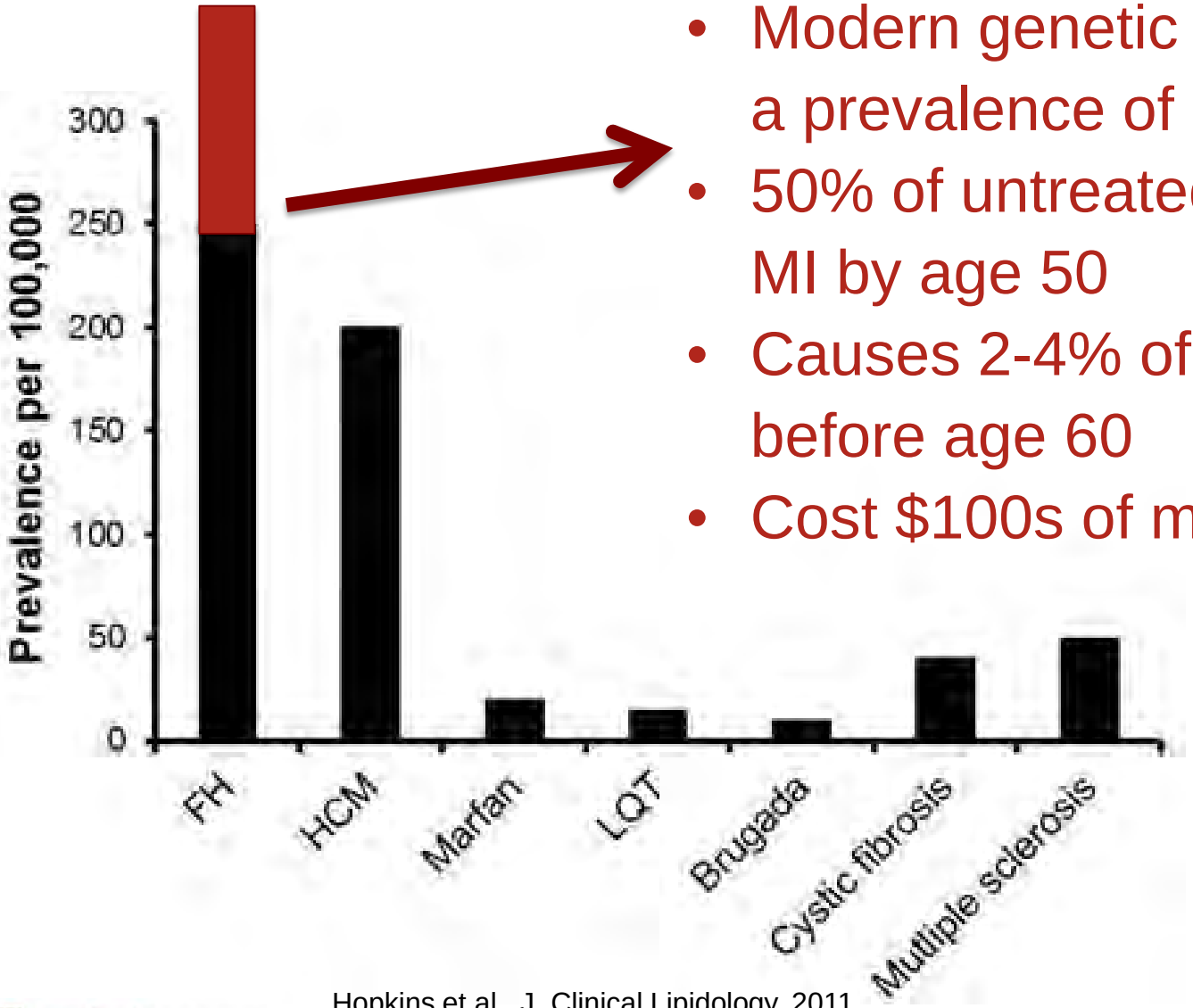
The known mechanisms causing familial hypercholesterolemia linked to low-density lipoprotein (LDL) receptor (LDLR) function.



Samuel S. Gidding et al. Circulation. 2015;132:2167-2192

American Heart Association.

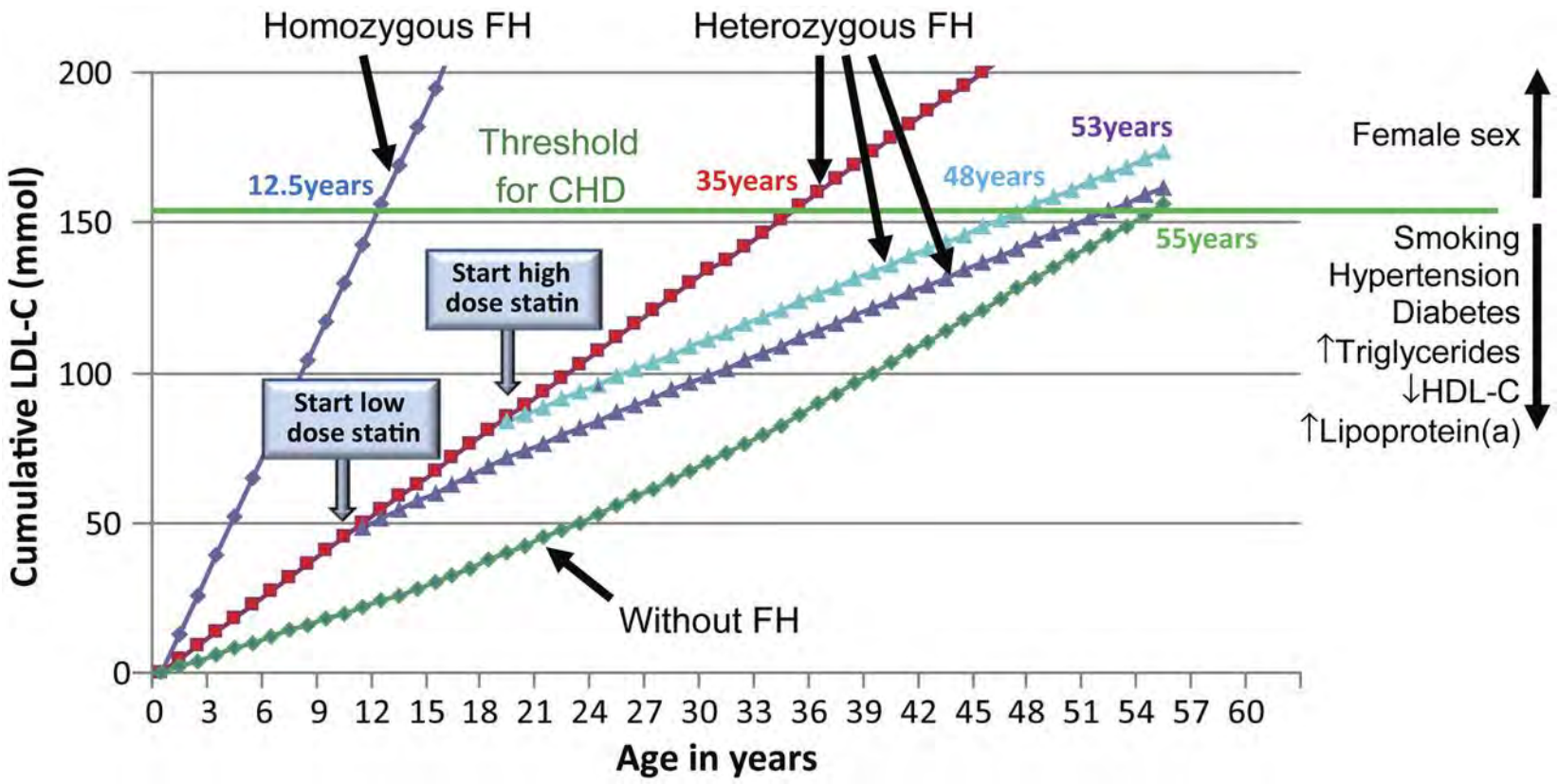
FH is common and devastating



- Modern genetic studies support a prevalence of ~1 in 250
- 50% of untreated men will have MI by age 50
- Causes 2-4% of heart attacks before age 60
- Cost $100s of millions

Hopkins et al. J. Clinical Lipidology. 2011
Goldberg et al. J. Clinical Lipidology. 2011

Lifelong exposure to high LDL causes early onset coronary disease.



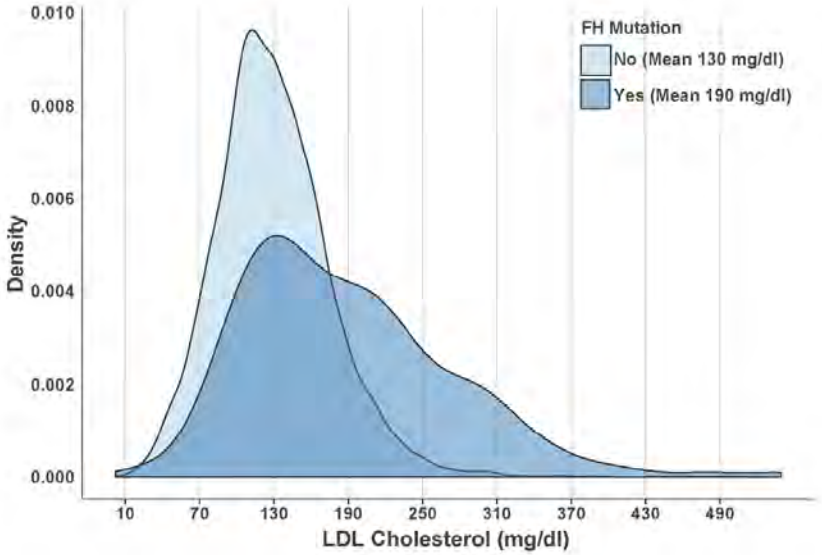
Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273

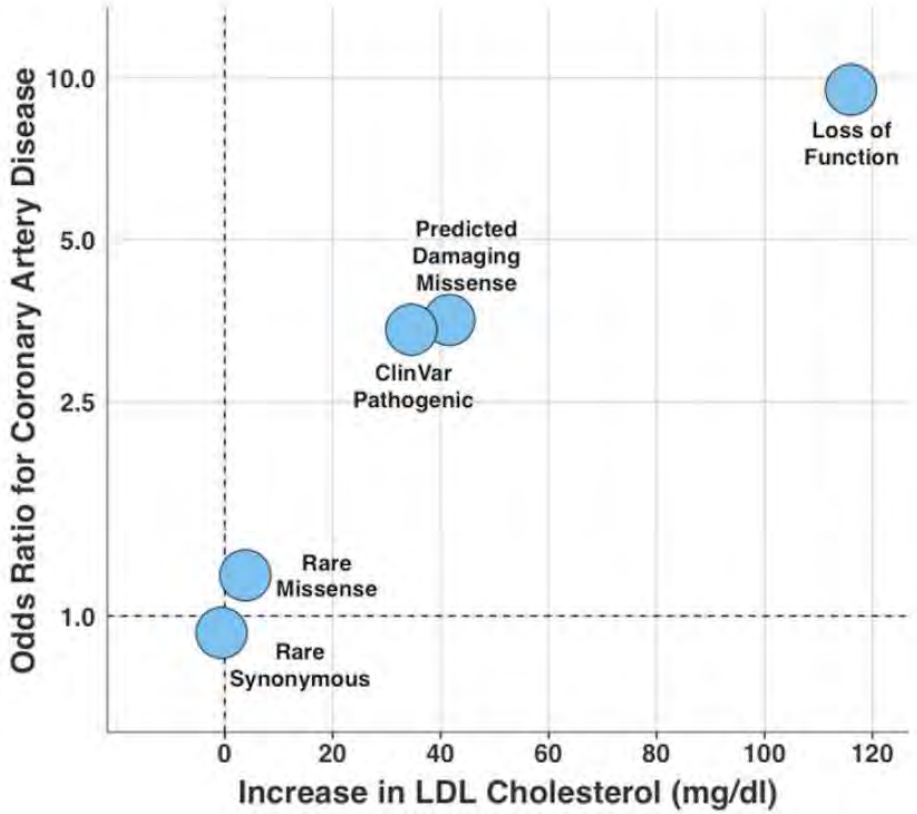
European Heart Journal

JACC

Diagnostic Yield of Sequencing Familial Hypercholesterolemia Genes in Patients with Severe Hypercholesterolemia

Amit V. Khera, MD, Hong-Hee Won, PhD, Gina M. Peloso, PhD, Kim S. Lawson, MS,





Mutation Class	N of 14,117 Individuals (% Cases / % Controls)	Increase in LDL Cholesterol (95%CI)	OR for CAD (95%CI)
FH Mutations			
Loss of Function	31 (0.5% / .05%)	+ 116 (101 – 132)	9.5 (3.6 – 33)
Predicted Damaging Missense	100 (1.3% / 0.3%)	+ 42 (33 – 50)	3.5 (2.3 – 5.7)
ClinVar Pathogenic	45 (0.5% / 0.2%)	+ 35 (22 – 47)	3.4 (1.8 – 6.9)
Any FH Mutation	164 (2.1% / 0.6%)	+ 50 (44 – 57)	3.8 (2.6 – 5.4)
Any Rare Missense	2289 (16.4% / 16.1%)	+ 3.8 (1.8 – 5.8)	1.19 (1.08 – 1.32)
Any Rare Synonymous	1965 (12% / 15%)	- 0.6 (-2.7 – 1.6)	0.93 (0.84 – 1.03)

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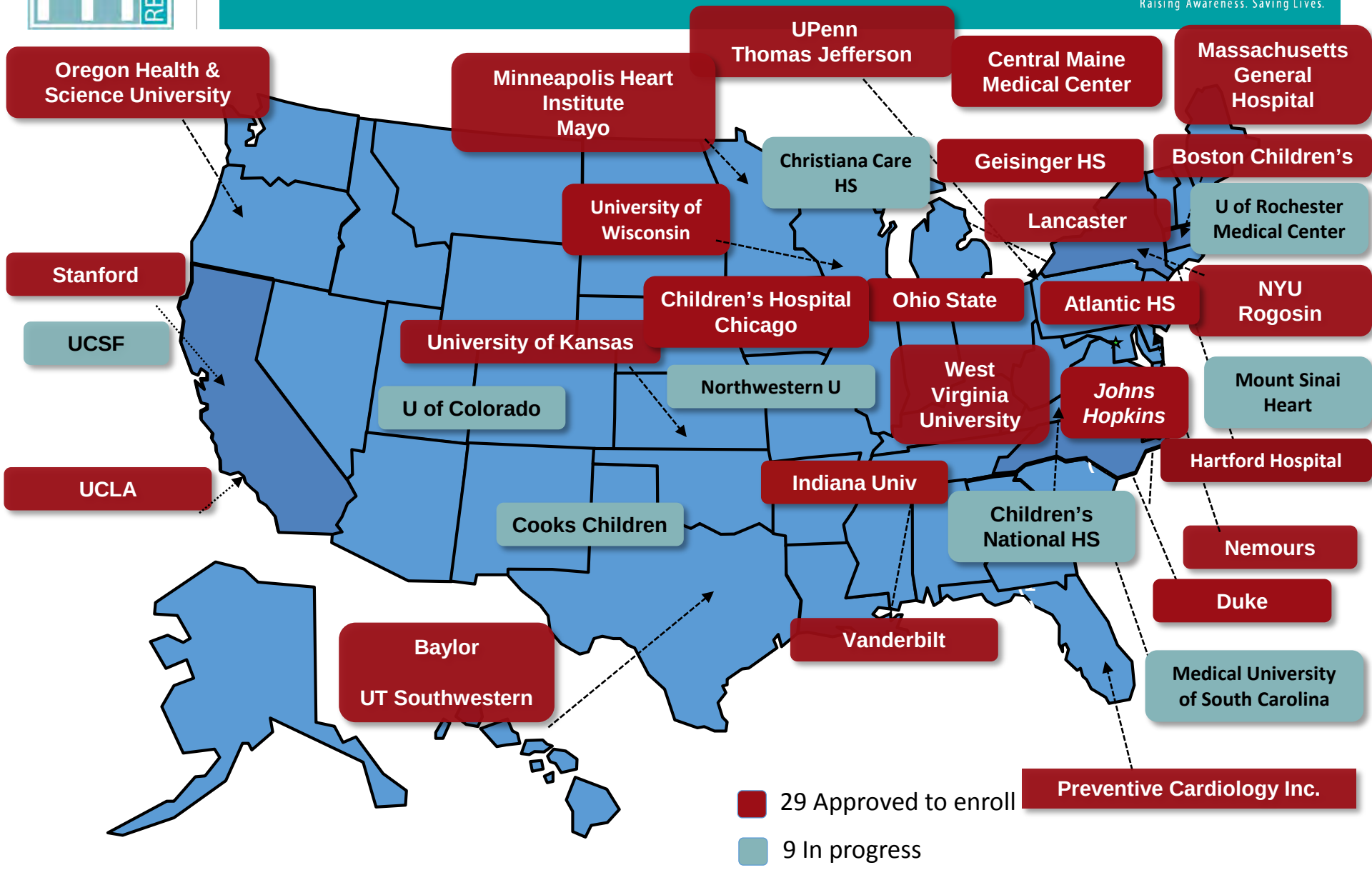
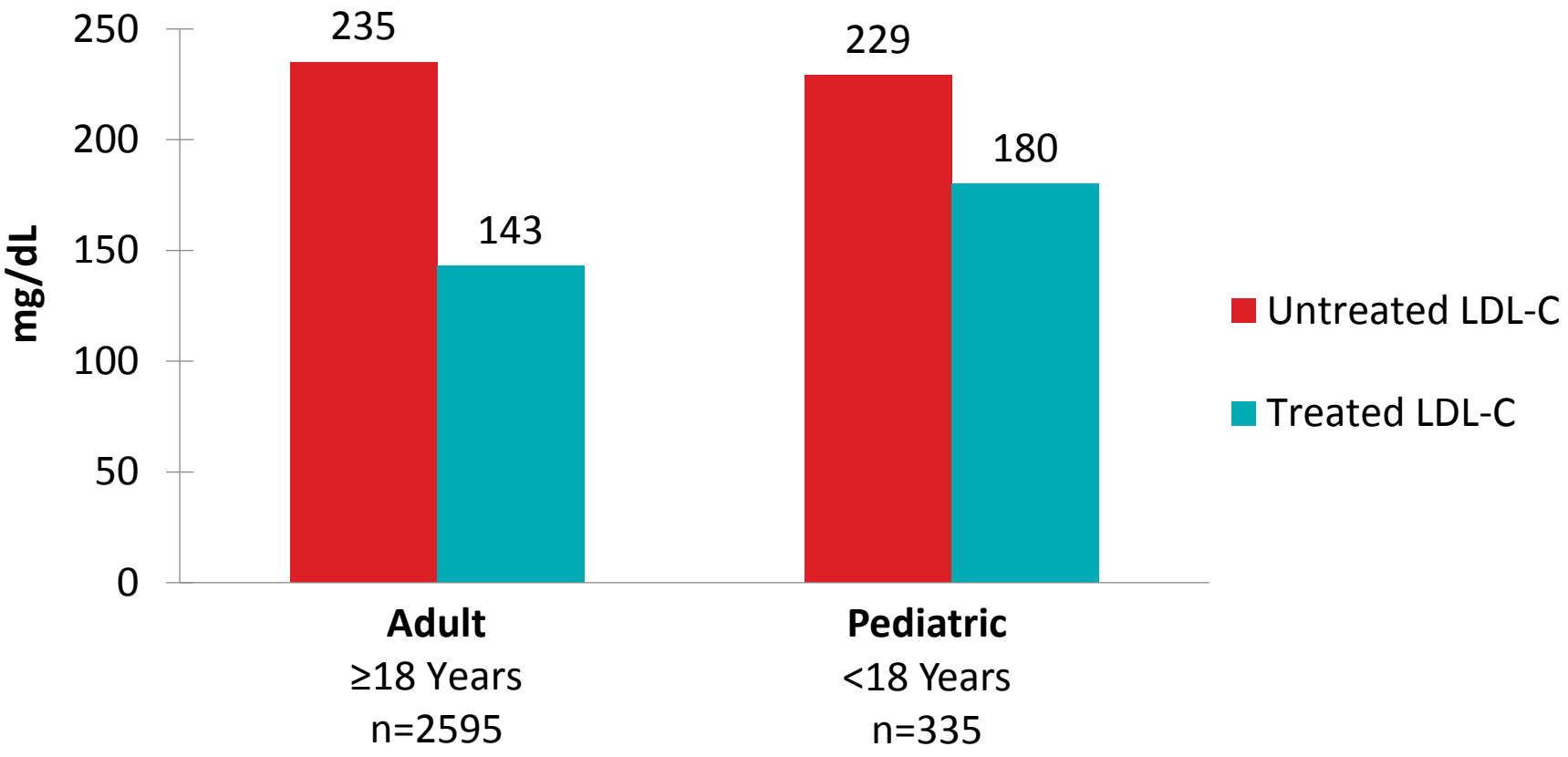
The FH Foundation

CASCADE FH™ Registry

CASCADE FH™ Registry Clinical Sites



Treated LDL-C is suboptimal (HeFH)



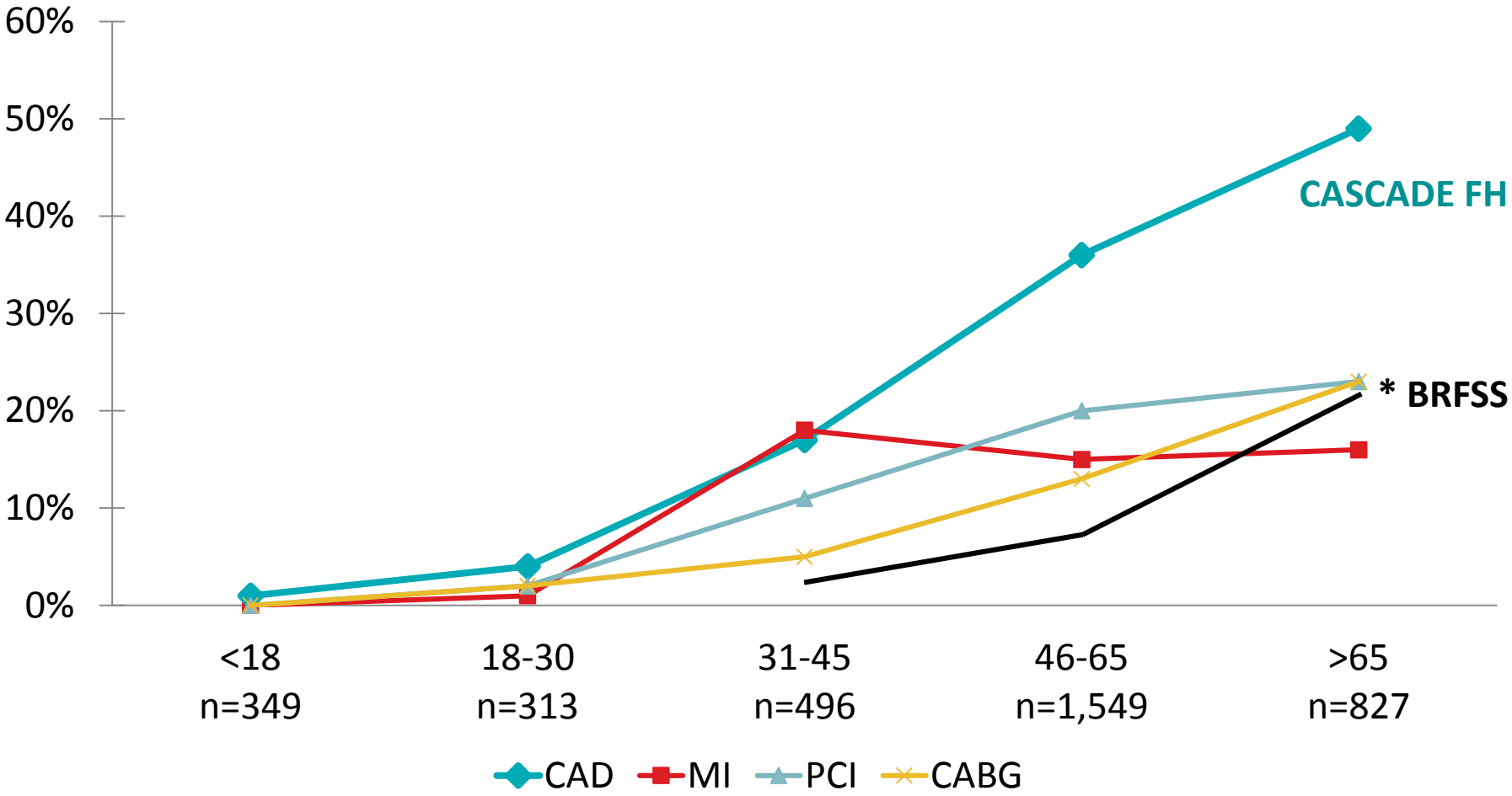
CAD more much more common in HeFH

	Female	Male
	n=2095, 41%	n=1424, 59%
Average Age	57	52
Prior CAD	**26%**	**37%**
Prior MI	8%	16%
Prior PCI	13%	21%
Prior CABG	8%	17%

5-6 fold higher than general population *

* DeGoma, E et al, Circ CV Genetics, 2016

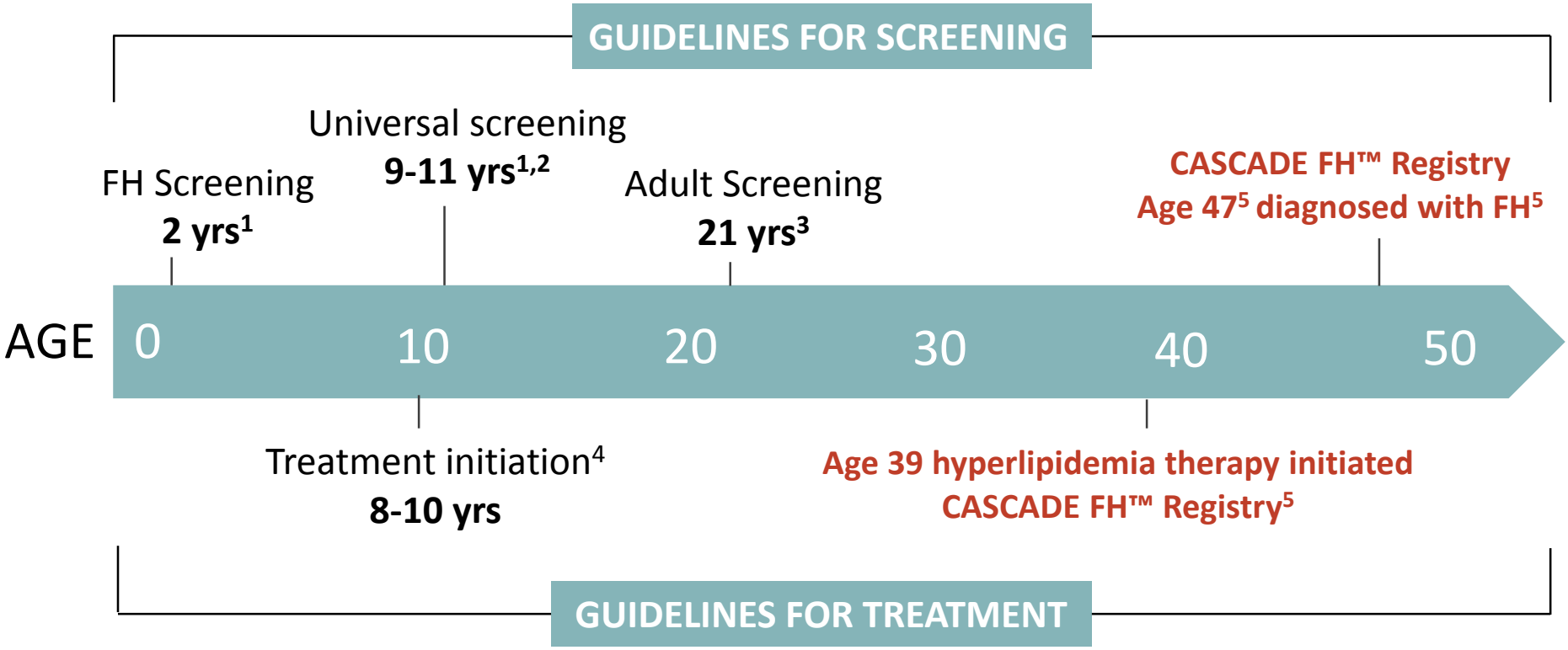
FH disproportionately affects the risk of premature CAD



Data from Behavioral Risk Factor Surveilance System (BRFSS): MMWR, October 2011. Prevalence of coronary heart disease United States 2006-2010
https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6040a1.htm

Data from the CASCADE FH™ Registry

Late Diagnosis and Treatment



[1]The AAP recommends screening for high cholesterol at age 2 if child has two parents with FH or high cholesterol; universal screening ages 9-11

[2]EAS Guidelines recommend universal screening for cholesterol ages 9-11

[3]ACC/AHA Adult Guidelines recommend universal screening of adults at age 21

[4]EAS Guidelines recommend US statin initiation for at ages 8-10 for FH

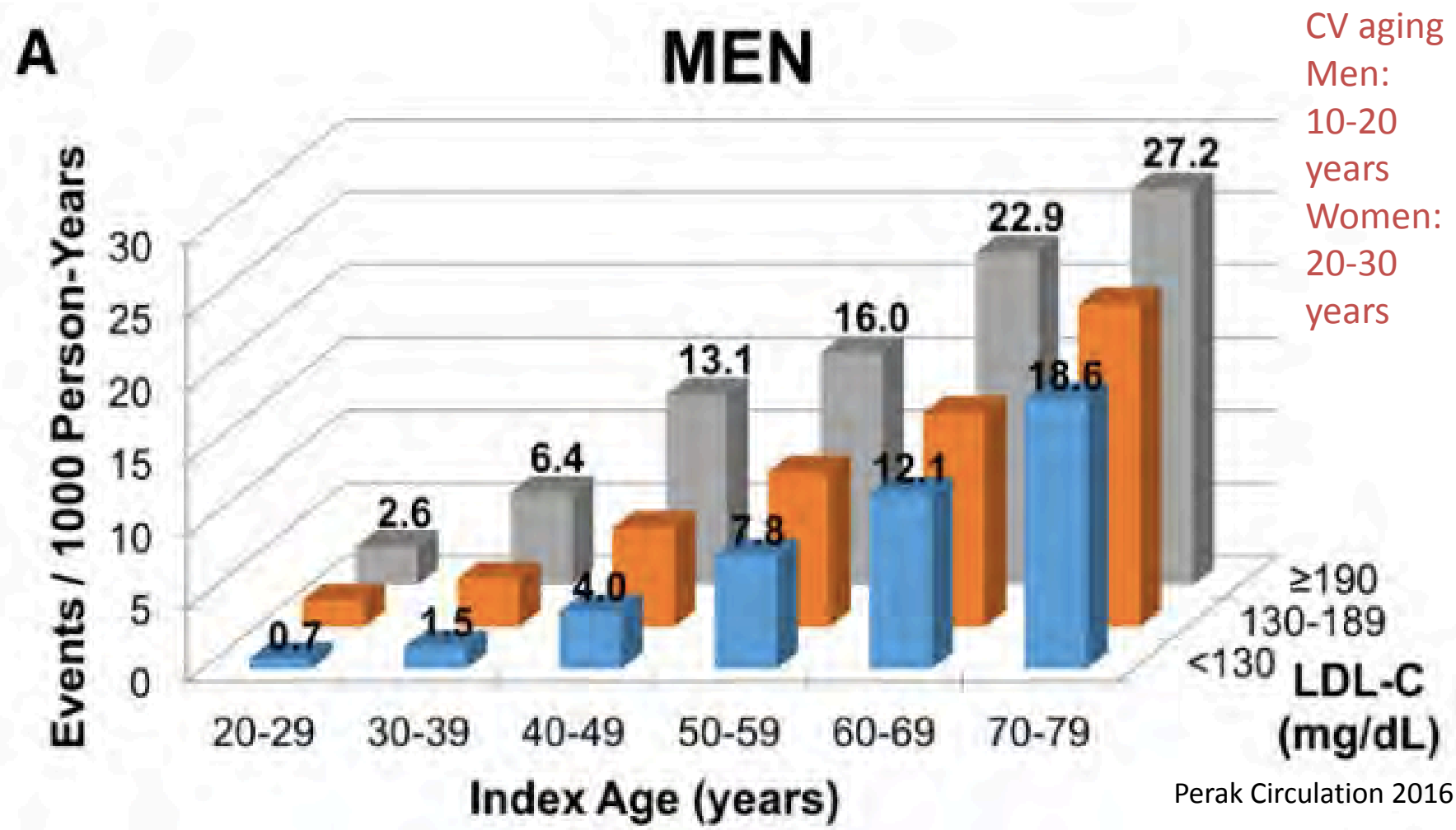
[5]CASCADE FH™ Registry participants are initiating lipid-lowering therapy at age 39 and receiving an appropriate diagnosis of FH at age 47

Estimating FH risk in the pooled cohorts

- Individual pooled data from 6 large US epidemiological cohorts
  - FHS, FHS Offspring, CARDIA, ARIC, CHS, NHANES III mortality dataset
  - 68,565 individuals with 1.2 million person-years of follow-up
- 20-79 year olds, categorized by baseline LDL level
  - FH phenotype (LDL-C ≥190 mg/dL) found in 3850 (5.6%)
  - non-FH, LDL <130 mg/dL (comparison)
- 30-year hazard of fatal and non fatal CHD
- Sensitivity analyses varying the definition of FH

Perak Circulation 2016

CHD events in the FH phenotype



CV aging
Men: 10-20 years
Women: 20-30 years

Perak Circulation 2016

and <60 years of age, respectively. Comparing this number of deaths with the leading causes of death by age group in the United States is revealing: Early-onset CHD death associated with the FH phenotype would cause more deaths in adults <60 years of age than homicide and would be comparable to road accidents (≈9000 and ≈20 000 deaths per year).

Rodriguez and Knowles, Circulation 2016
Perak et al., Circulation, 2016
Gupta et al. JACC, 2014

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Dutch national program has been spectacularly successful

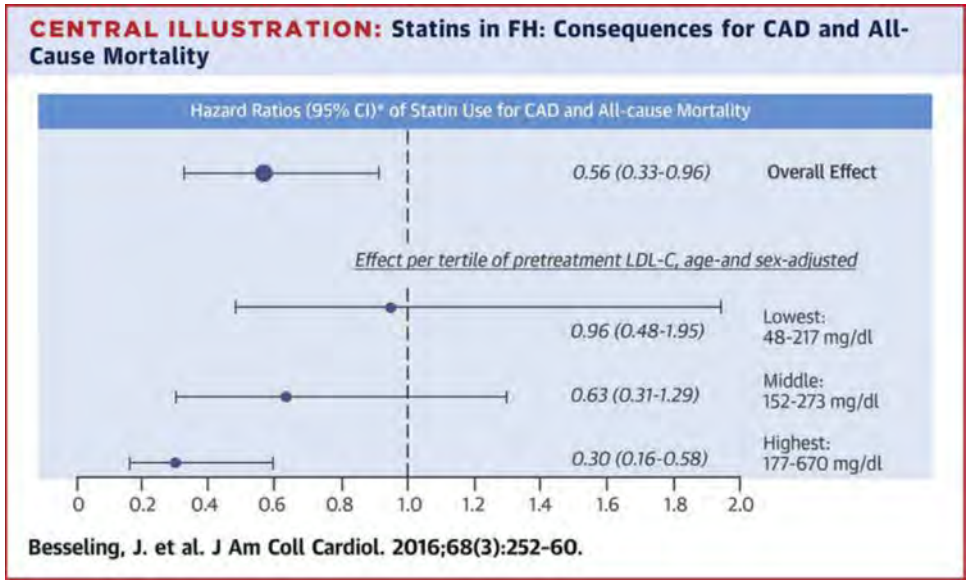
- As of 2012: 5,151 index cases of genetically positive FH identified
- Resulted in screening of 60,000 family members
- In total **27,069** FH cases identified
  - 36% of the family members had a positive genetic test.
- Costs for identifying 1 FH patient: 1200 euro
  - Test almost 3 family members to identify 1 positive FH mutation
- Costs effectiveness: costs per life year saved: 8700 Euro *

*Cost-Effectiveness Analysis of the Genetic Screening Program for Familial Hypercholesterolemia in the Netherlands David Wonderling, M.Sc., Marina A.W. Umans-Eckenhausen, M.D., Ph.D., Dalya Marks, Ph.D., Joep C. Defesche, Ph.D., John J.P. Kastelein, M.D., Ph.D., and Margaret Thorogood, Ph.D. Sem.Vasc.Med 2004:4:97

JACC Journals

From: **Statins in Familial Hypercholesterolemia: Consequences for Coronary Artery Disease and All-Cause Mortality**

J Am Coll Cardiol. 2016;68(3):252-260. doi:10.1016/j.jacc.2016.04.054



- FH patients who were statin users had a 44% RR reduction for the CAD and all-cause mortality versus those who had never used statins.
- Translates to a number needed to treat (NNT) of 222 for 1 year of statin therapy to prevent a ***death*** in FH patients.
  - Far outstrips the NNT for 1 year for primary prevention in non-FH patients (NNT: 500)
  - indeed, it is lower than the NNT for ***secondary*** prevention in non-FH patients (NNT: 350)

Cascade testing for FH has a “Tier 1” indication

- Good evidence if FH is identified early and treated aggressively, morbidity and mortality reduced 80%
- Highly cost effective
  - “We never find an individual with FH, we only find families with FH”

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Genomics
All CDC Topics

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Genetic Testing

Genomic Tests by Levels of Evidence

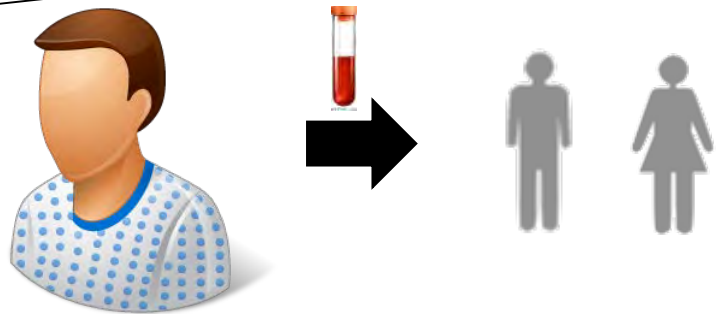
The CDC Office of Public Health Genomics provides the following list of genomic tests and applications in practice according to three levels of evidence based on the paper by Khoury et al. This list is provided only for informational purposes to researchers, providers, public health programs and others. The table was updated on August 23, 2012 to reflect the addition of emerging cancer genomic tests. For additional information on the updated list, read our accompanying blog.

Tier 1 genomic applications are recommended for clinical use by evidence-based panels on a systematic review of analytic validity, clinical validity and utility for specific clinical scenarios

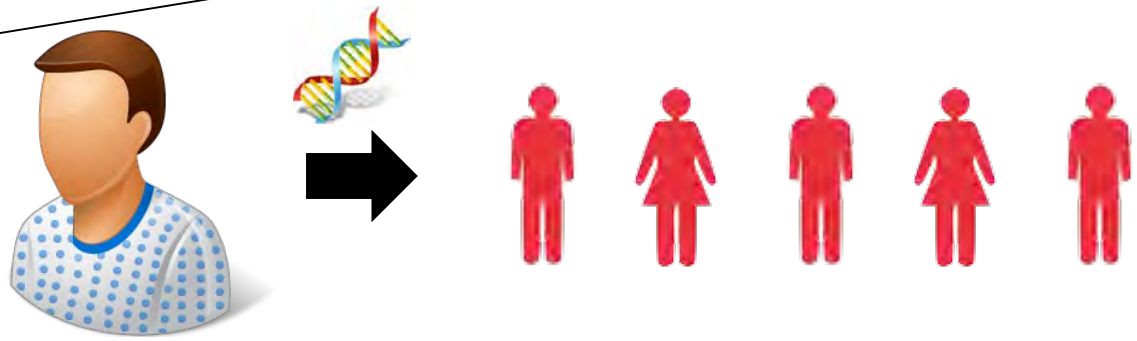
Test/Application	Scenario	Evidence-based recommendation
Newborn screening panel of 31 core conditions	Screening all newborns at birth through public health programs	Secretary's Advisory Committee on Heritable Diseases of Newborns and Children (2011)
BRCA1/2 analysis for hereditary breast and ovarian cancer	Genetic counseling of women with specific family history patterns of breast or ovarian cancer	US Preventive Services Task Force (2005) Additional Information: NCCN Guideline: Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer [PDF 615.35 KB] (2012)
Lynch syndrome testing	Screening newly diagnosed cases of colorectal cancer for Lynch syndrome and cascade testing of relatives of affected Lynch syndrome cases	Evaluation of Genomic Applications in Practice and Prevention Working Group (2009) Additional Information: NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology (2011)
Familial Hypercholesterolemia	Cascade cholesterol testing with/without DNA analysis among relatives of affected persons with familial hypercholesterolemia	NICE Guideline: Identification and management of familial hypercholesterolaemia [PDF 746.30 KB] (2008)

I FIGhT FH: Randomized Trial

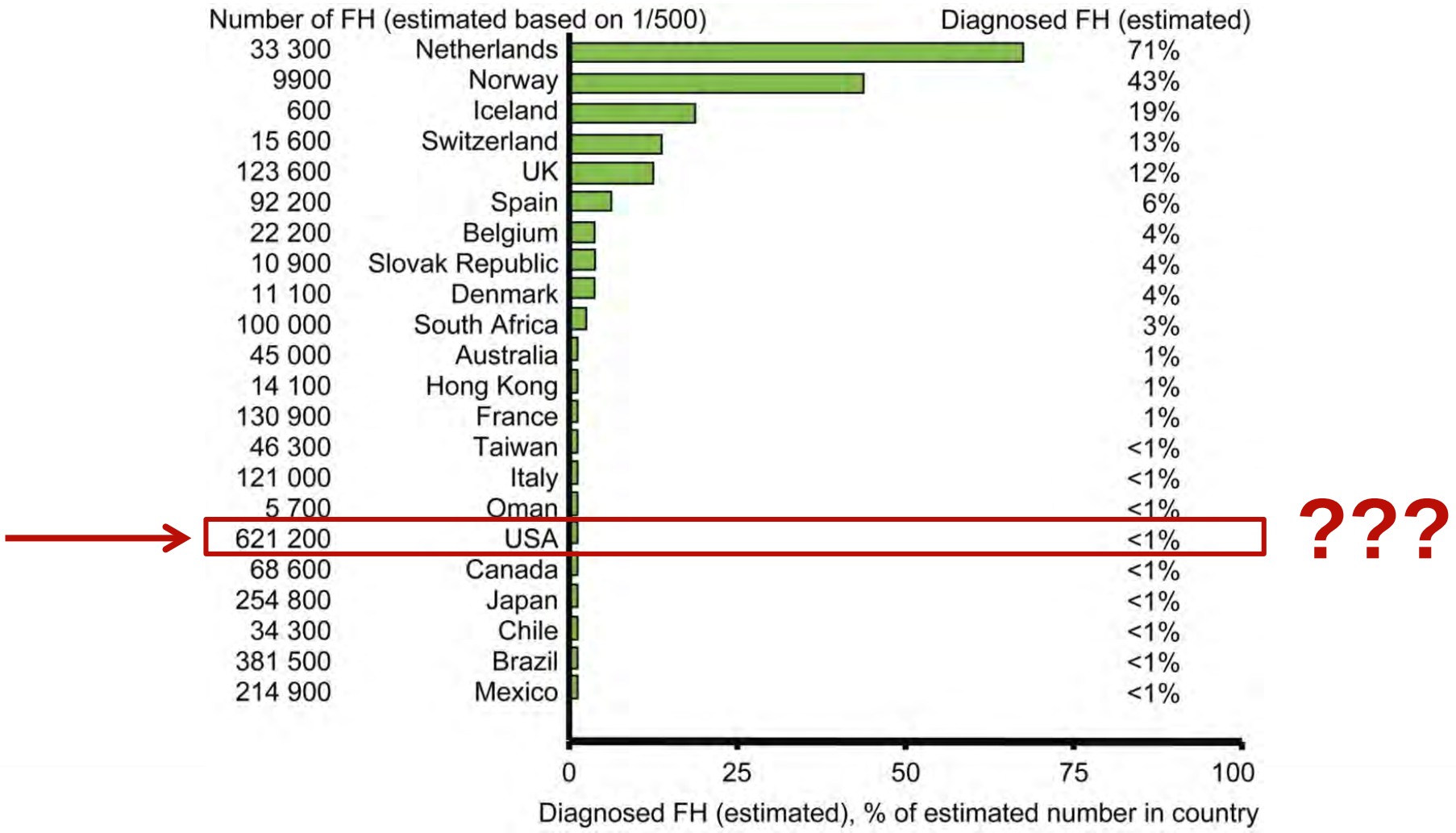
You have **high cholesterol**. It is important that your relatives get checked.



You have this particular gene mutation that is causing your high cholesterol. It is important that your relatives get checked.



In the US, FH is rarely diagnosed



???

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273

European Heart Journal

E78.01: FAMILIAL HYPERCHOLESTEROLEMIA

Z83.42: Family history of familial hypercholesterolemia

EFFECTIVE OCTOBER 1, 2016

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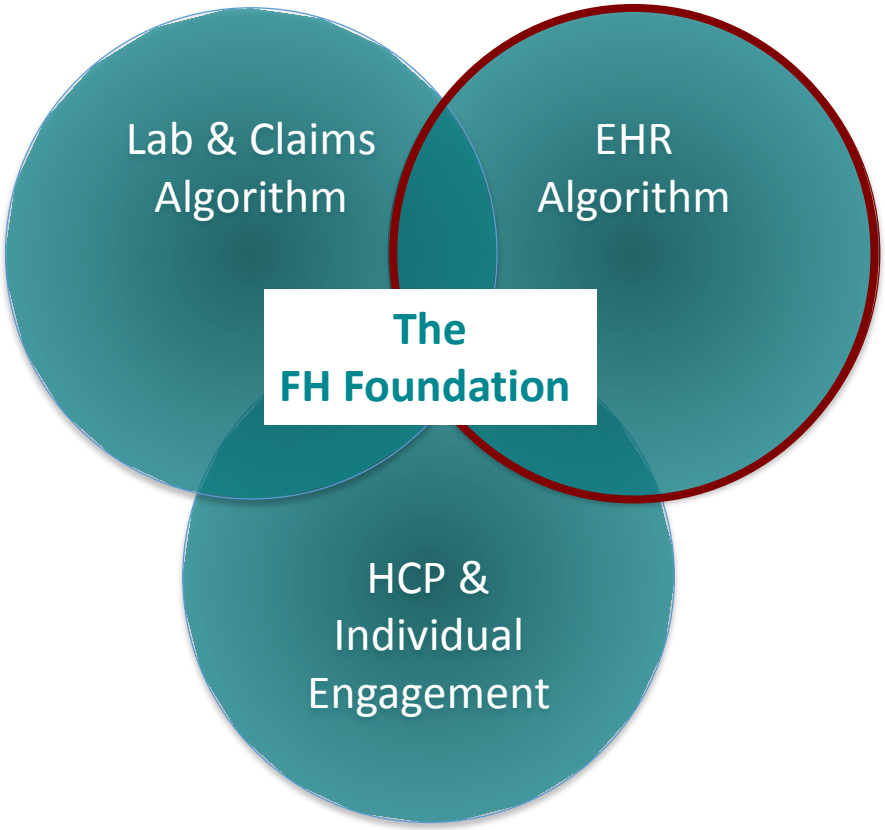
The FIND FH® Initiative

www.theFHfoundation.org

FIND FH®

A multiyear screening and engagement initiative to identify and encourage the diagnosis and treatment of FH



Lab & Claims Data Mining

- Healthcare Encounter Data on 89 Million Americans with Cardiovascular Disease
- Data from a significant majority of clinical practices

EHR Data Mining

- **Comprehensive EHR data from two academic centers**
- **Expanding to key integrated health systems**

HCP & Individual Engagement

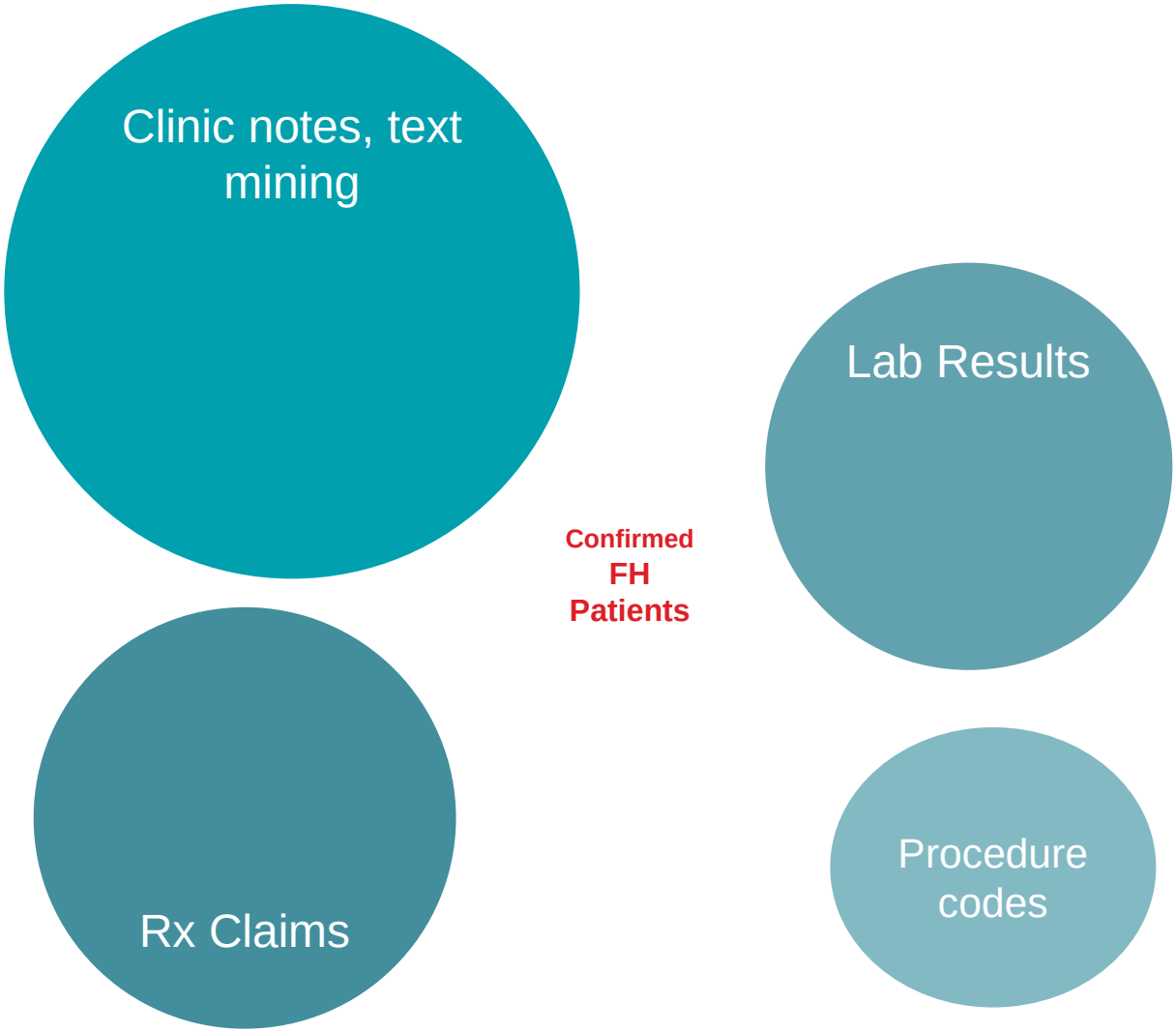
- Multichannel tools to engage health systems and individual HCPs
- Tools for clinicians and individuals with FH

FH Foundation FIND FH® Clinical Partners

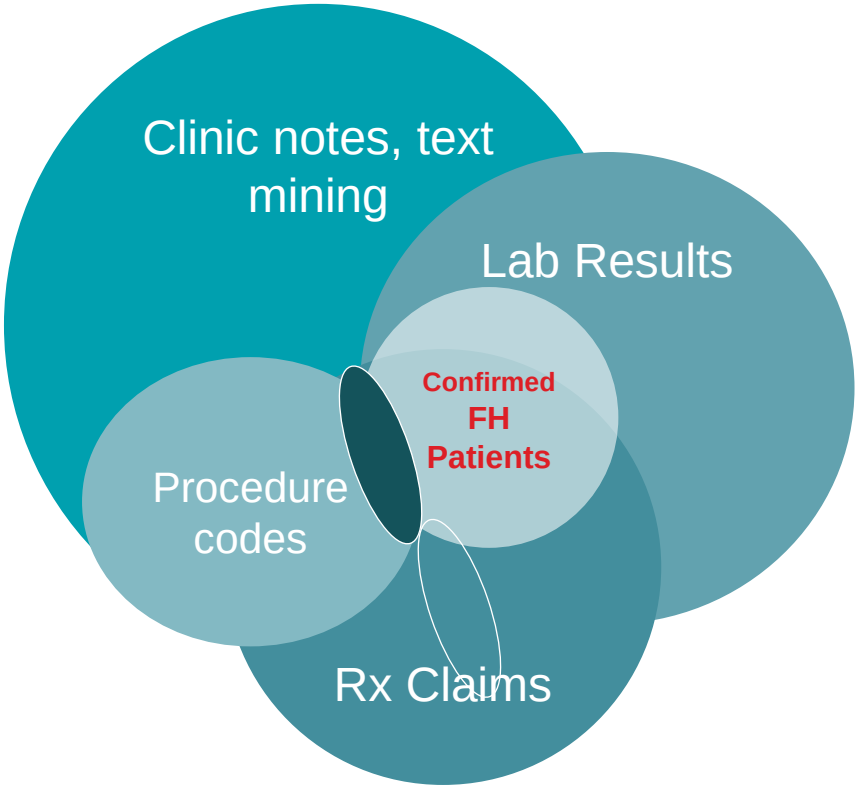
Machine Learning

- Software that learns by example.
- We show the model examples of FH and Non-FH patients.
- Patients are described to the model using features (inputs):
  - Lab Results
  - Patient Age
  - ICD9-10 & CPT codes
  - Prescription Medications
- The model learns correlation between certain features and FH rate.
- Model can classify FH in new patients using just their features.

Identifying FH patient characteristics using orthogonal data



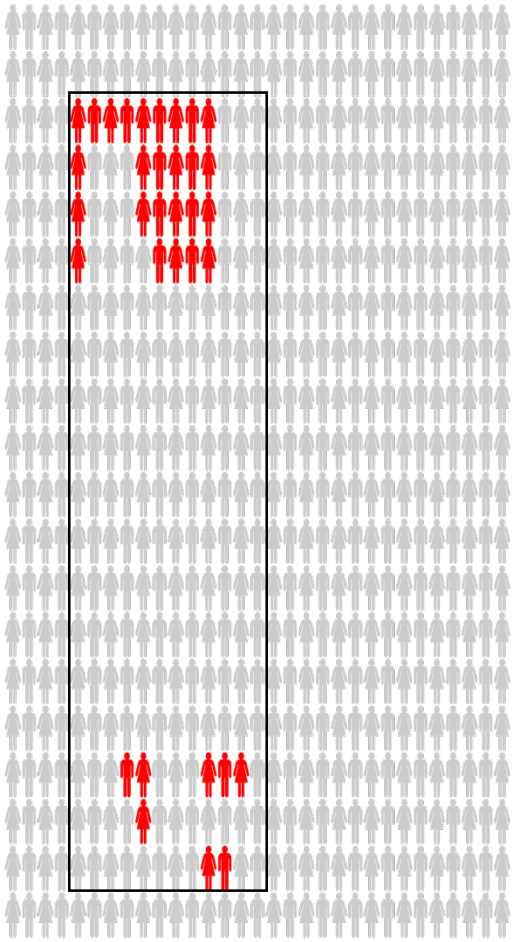
Identifying FH patient characteristics using orthogonal data



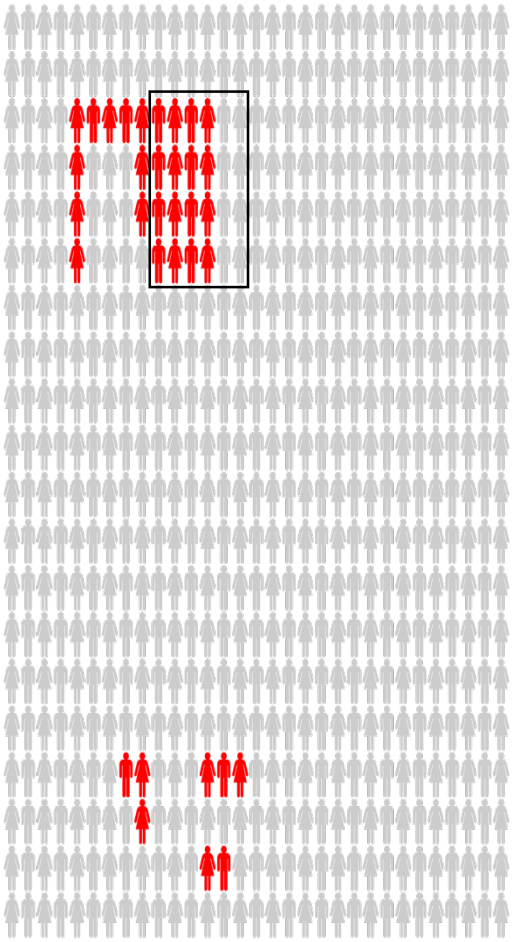
Unstructured data	**Clinic notes, dictations for key words, phrases** • **Personal medical Hx: age of cardiac event, procedure** • **Disease names: FH, hyperlipidemia,** • **Family history: premature coronary disease** • **Signs: xanthoma, xanthelasma, arcus**
Structured data	Labs: LDL-C, Total-C Procedure codes: cardiac cath, PCI, CABG, stress test Drug lists: statin and non-statin agents

Use discovered patterns in the small number of patients with the most complete data to identify other patients in the larger data set.

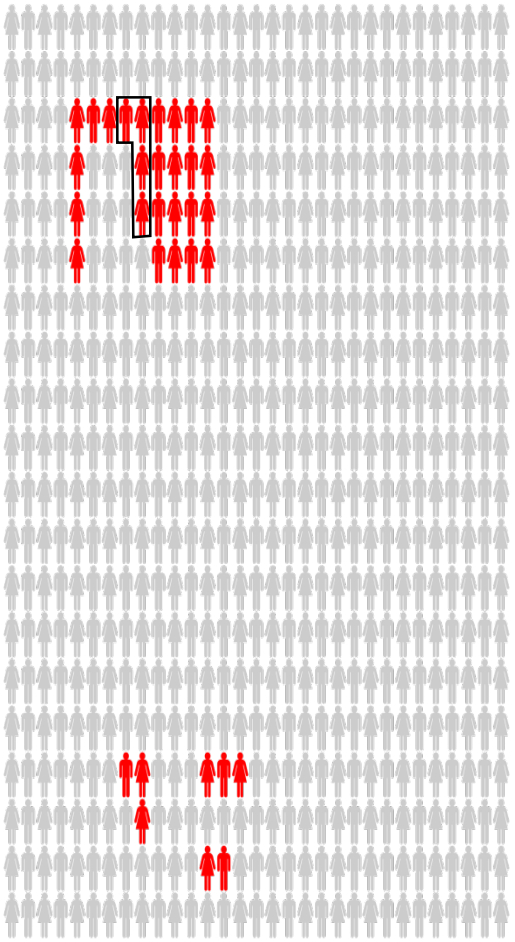
Striking a Balance Between Precision (PPV) & Recall (Sensitivity)



Perfect Recall; Low Precision

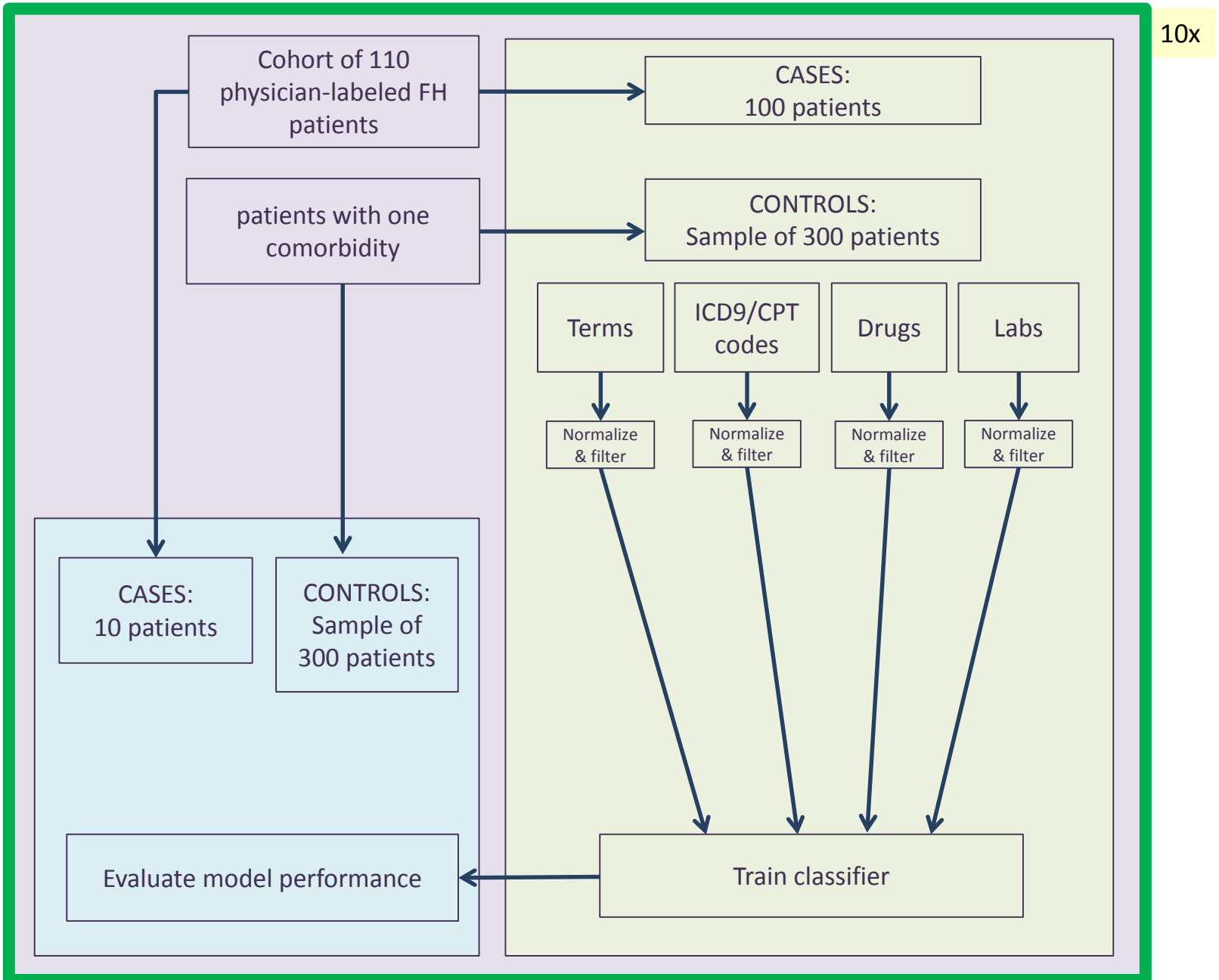


Balanced Recall and Precision

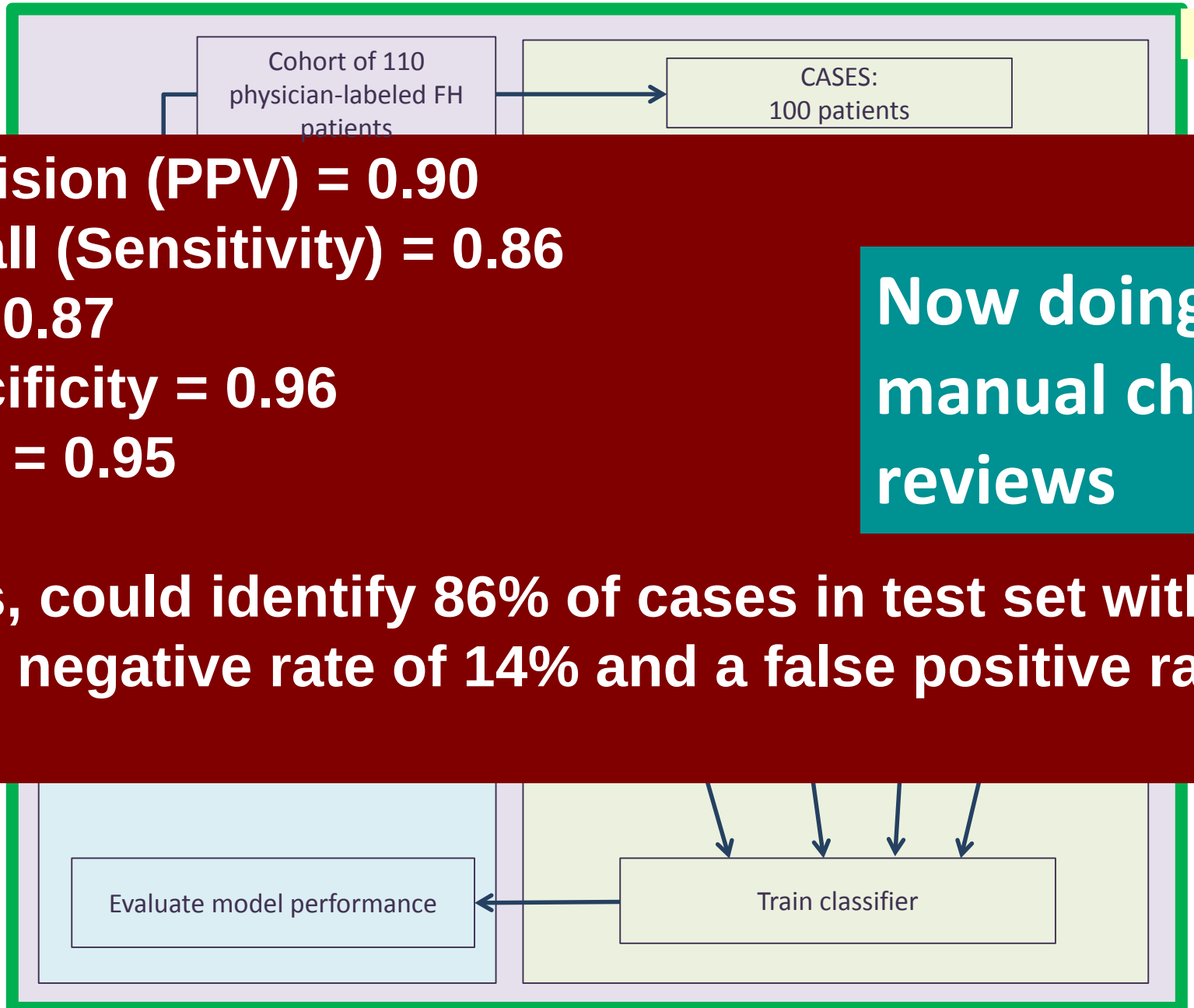


Low Recall; Perfect Precision

Workflow for Random Forest model



Workflow for Random Forest model

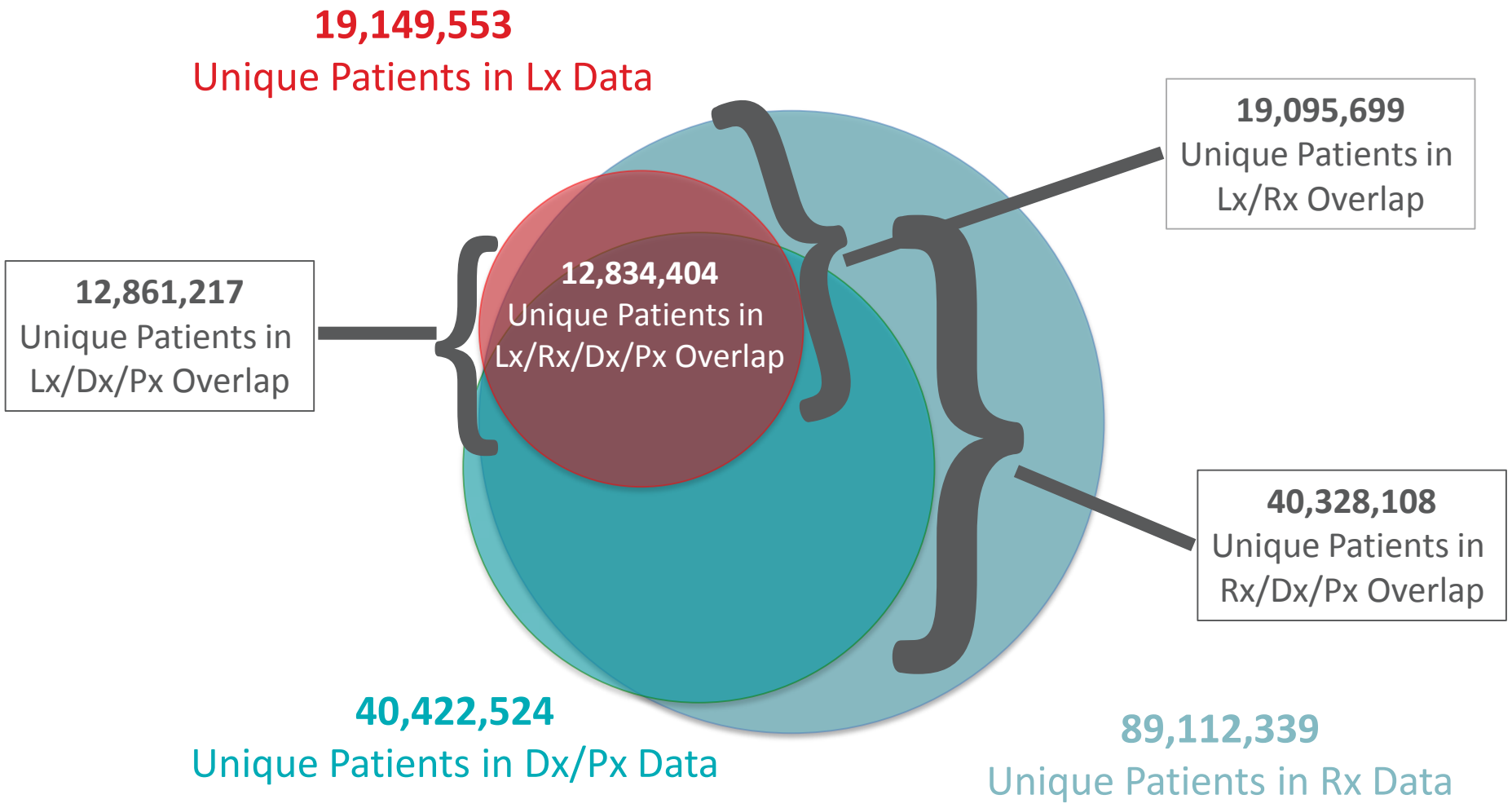


Precision (PPV) = 0.90
Recall (Sensitivity) = 0.86
F1 = 0.87
Specificity = 0.96
ROC = 0.95

Now doing manual chart reviews

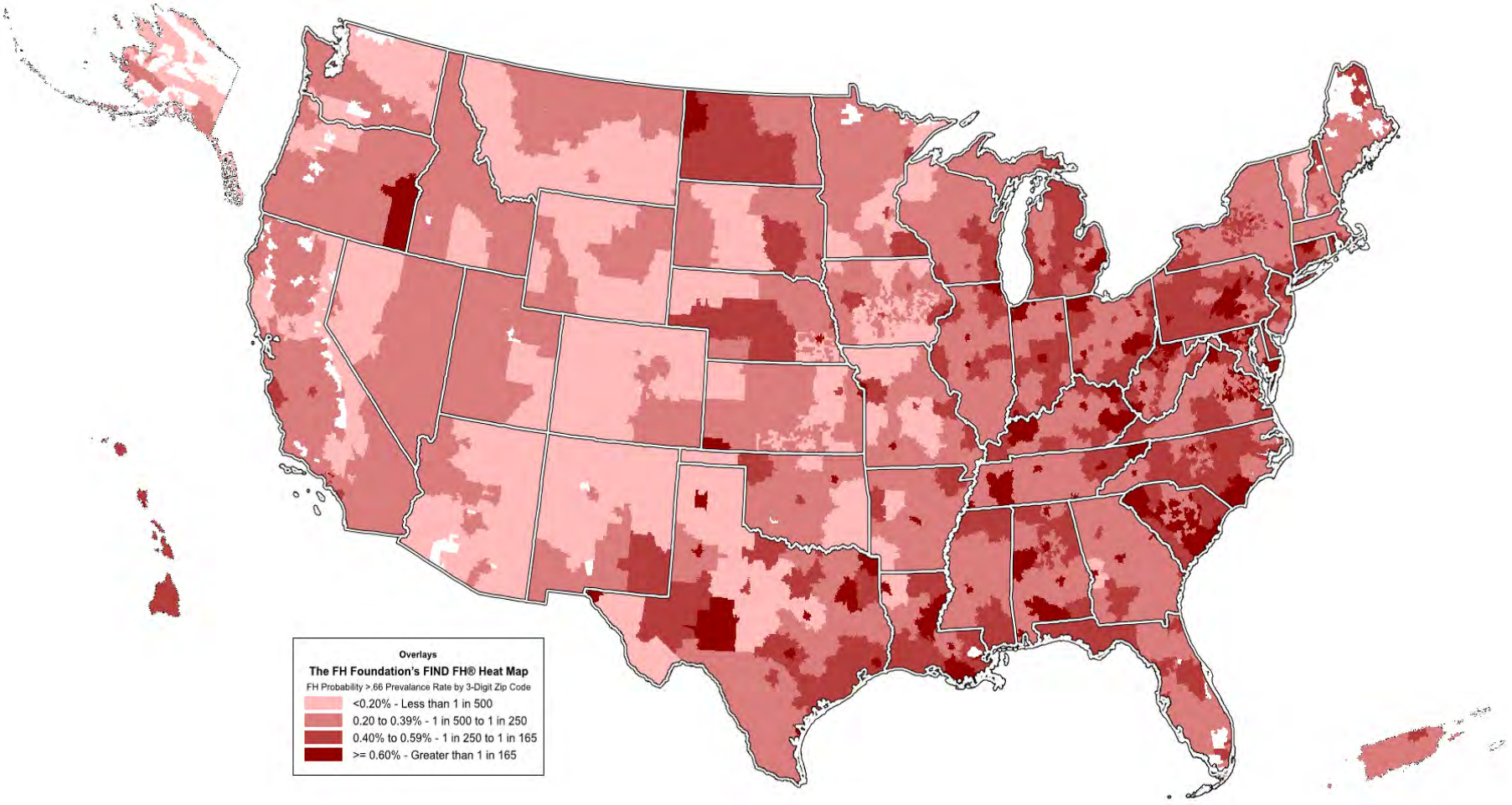
Thus, could identify 86% of cases in test set with false negative rate of 14% and a false positive rate of 10%.

FIND FH® Lab & Claims Database



FINDFH®

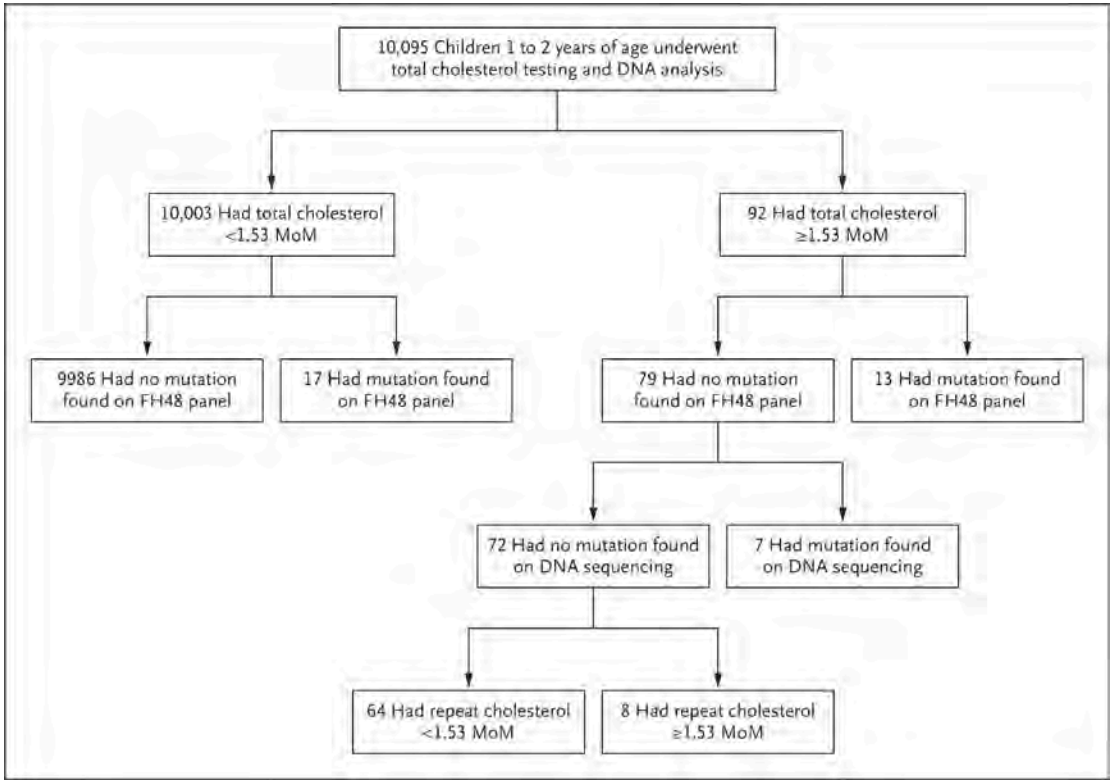
Find • Identify • Network • Deliver



FIND FH® Lab & Claims Algorithm Developed by The FH Foundation
Claims Data Source: IMS Health Real World Data: LRx longitudinal prescriptions and Dx medical claims

The case for the utility of lipid and genetic testing in childhood

Child–Parent Familial Hypercholesterolemia Screening in Primary Care



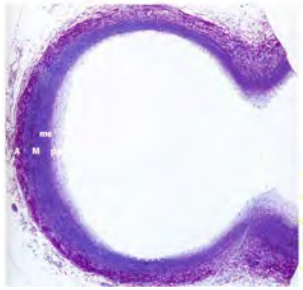
- Child–parent screening was feasible in primary care practices at routine child immunization visits.
- For every 1000 children screened, 8 persons (4 children and 4 parents) were identified with FH and were consequently at high risk for CVD.

The NEW ENGLAND JOURNAL of MEDICINE

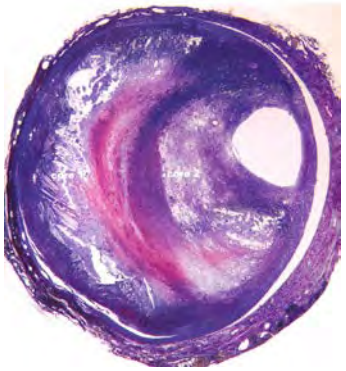
Wald DS et al. N Engl J Med 2016;375:1628-1637

For diseases like familial hypercholesterolemia (FH), the time is now.

When one base pair change (misspelling) can turn this



into this



The FIND FH® Team

The FH Foundation: Katherine Wilemon, Bill Neal, Seth Baum, Christiane Rivard, William Howard, Tim Howard, Seth Myers, Kelly Myers

Stanford: Josh Knowles, Nigam Shah, Juan Banda, Fahim Abbasi

U Penn: Dan Rader, Yuliya Borovskiy, Ezimamaka Ajufo, Brian Wells

Collaborating Institutions:

Geisinger: Mike Murray, David Ledbetter, Les Kirchner, Joe Leader, Marylyn Ritchie

Ohio State University: Kavita Sharma, Amy Sturm, Kelly Scheiderer, Marr-Zann Adams

Lancaster General Hospital: Rolf Andersen, Lars Andersen, Lisa Estrella

Sponsors:

Amgen (Founding), Sanofi/Regeneron

American Heart Association, Stanford Data Science Initiative