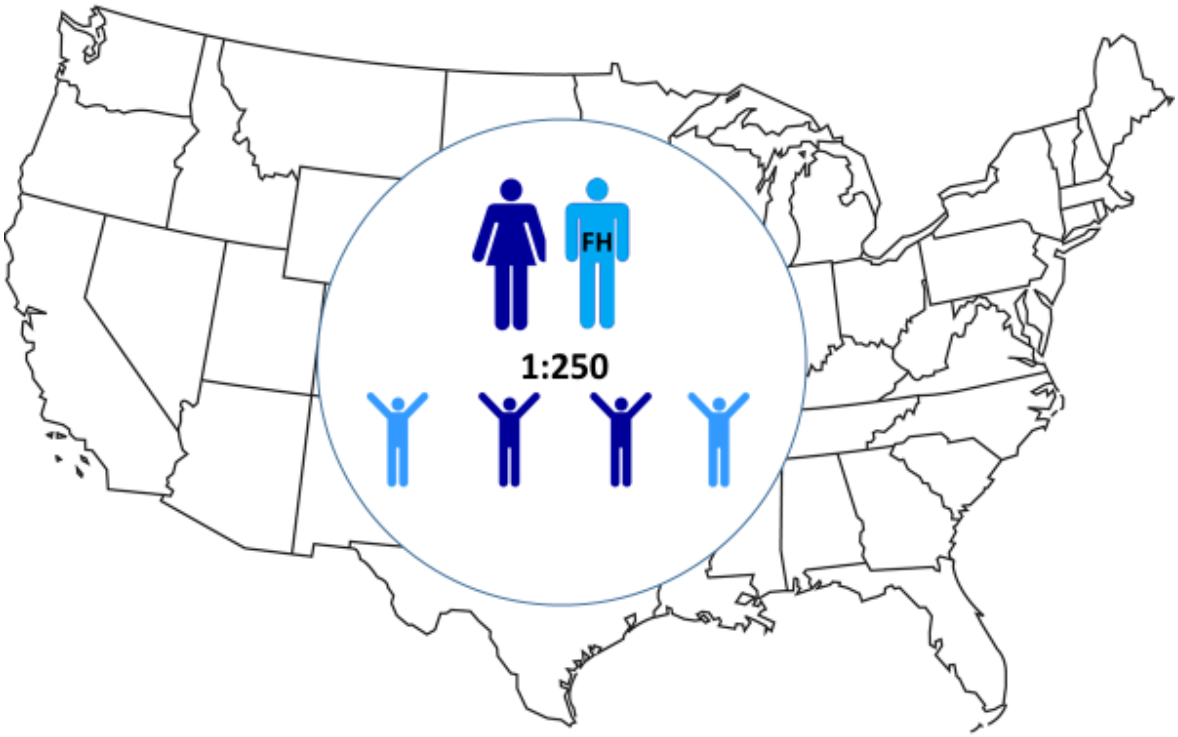
Familial Hypercholesterolemia: Improving Detection and Management



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This is to acknowledge that Dr. Khera has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. He will not be discussing off-label uses in his presentation.

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Purpose & Overview

The purpose of this presentation is to describe the biology, diagnosis, and medical therapy for Familial Hypercholesterolemia (FH), with special focus on screening strategies for identification and emerging treatment paradigms.

Familial Hypercholesterolemia is an autosomal dominant disorder that in its classic form involves defective or deficient LDL receptors, as discovered by Drs. Brown and Goldstein. The diagnosis of FH is made by applying one of the various clinical criteria. The fundamental insult is marked elevations LDL-C levels, in the range of 200-400mg/dL in the heterozygous form (the focus here), with cumulative exposure since birth. While previously thought to effect ~1:500 individuals in the U.S. and worldwide, more recent data suggest that ~1:250 individuals have FH. Cascade screening which is screening every first degree relative of a proband with FH, and repeating the cycle iterative for each newly diagnosed individual, is a very effective strategy for case identification. A few EHR based screening algorithms have been developed for large scale detection in populations. Other genetic based screening programs have been described which are reasonably effective, but have both strengths and weaknesses.

All adult patients with FH and elevated LDL-C should initiate statin therapy, and statins are approved for use in children with FH after age 8. Further, all children with a family history of dyslipidemia or premature CVD are recommended to undergo lipid screening after age 2. Most societies recommend that those with FH should target a ≥50% reduction in LDL-C and an LDL-C goal <100 and <70mg/dL for primary and secondary prevention, respectively. The majority of patients will require multiple drugs to meaningfully lower their LDL-C levels, and few actually reach these targets. The development of PCSK9 inhibitors that result in a further 50-60% LDL-C reduction is a major development in this field. Despite clinical trial evidence for their efficacy, the cost of these agents promotes the need for risk assessment tools in patients with FH to more precisely target their application.

Educational Objectives

1. Describe the molecular basis of FH.
2. Apply diagnostic criteria to identify patients with FH.
3. Understand principles of cascade screening and emerging applications of electronic health record and genetic screening programs for FH.
4. Incorporate current guideline recommendations for FH treatment targets and treatment regimens.

Familial Hypercholesterolemia: Seminal Discoveries of Drs. Brown and Goldstein

The seminal work of Drs. Michael Brown and Joseph Goldstein took root while the two were in training at the NIH and encountered a pair of siblings, ages 6 and 8, who had homozygous familial hypercholesterolemia (FH), with LDL levels >1000mg/dL and who were already experiencing coronary artery disease (**Fig 1**). Little was known about the disease at that time, and they began their study of this illness as faculty members at UT Southwestern in the early 70's. Soon thereafter, they demonstrated that skin fibroblasts from subjects with homozygous FH had defective binding of low-density lipoproteins (LDL) while fibroblasts of normal subjects had high affinity binding.[1] Further, this binding proved to be a key step in suppressing the synthesis of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, the rate limiting enzyme in cholesterol synthesis. This and subsequent work helped elucidate the role of cell surface receptors, particularly the LDL receptor, and receptor mediated endocytosis and receptor recycling. Drs. Brown and Goldstein purified the LDL receptor from cow adrenal glands in 1982 and cloned the LDL receptor gene in 1983, demonstrating along the way that subjects with homozygous FH had inherited mutations in both copies of the LDL receptor gene. For their groundbreaking discoveries, they were honored with the Nobel Prize in Medicine or Physiology in 1985 and the National Medal of Science in 1988.

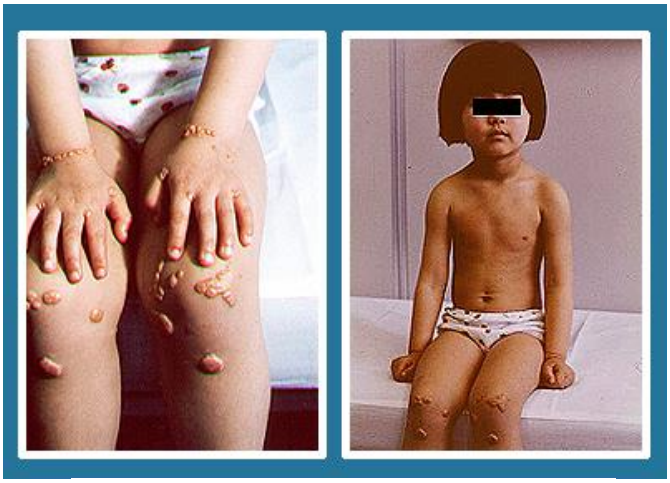

Fig 1. 6 year-old girl with homozygous FH; skin findings represent xanthomas

In addition to defining the biological underpinnings of a deadly disease, their work also lead to its treatment. They helped characterize mechanisms and key regulators of cholesterol biosynthesis, which opened the door for the development of HMG-CoA reductase inhibitors, or statin drugs. Over three decades after they defined the gene defects and mechanisms of FH and provided a pathway for screening and treatment of individuals afflicted with this disease, it remains vastly under recognized and undertreated.

Clinical Characteristics of Familial Hypercholesterolemia

While Drs. Brown and Goldstein characterized the classic form of FH involving the LDL receptor, a broader interpretation of Familial Hypercholesterolemia (as used in this protocol) includes severe *hypercholesterolemia with autosomal dominant inheritance pattern*.[2] A synonymous term is autosomal dominant hypercholesterolemia. The primary genes involved in FH include the LDL receptor (*LDLR*) reportedly in 85-90% of cases where genetic causes are uncovered, the apolipoprotein B gene (*APOB*; Arg3500Gln) in 5-10% of the cases, and *PCSK9* gain of function mutations in 5% of the cases. Homozygous FH involving inheritance of defective genes from both parents is quite rare, affecting ~1:1,000,000 individuals, resulting in LDL-C levels >400mg/dL and vascular disease and premature death starting in childhood and teenage years. Heterozygous FH, the milder form with LDL-C in the 200-400mg/dL range, is quite

common and had been reported to affect ~1:500 individuals worldwide. However, several populations such as Christian Lebanese and South African Ashkenazi Jews have a much higher frequency (~1:85 and 1:67 respectively), and several recent studies have suggested that the overall prevalence of FH is significantly higher than the 1:500 figure, as described below. As such, FH is one of the more common inherited cardiovascular disorders. The focus of this protocol will be on heterozygous FH.

The fundamental derangement in FH is elevations in LDL-C, which drives all of the adverse consequences. Reported LDL-C levels in patients with heterozygous FH have varied in the literature depending on the ethnicity and region of the population studied as well as their mode of subject ascertainment. A recent U.S. based study involving genetic screening of the Geisinger Health System population described median LDL-C levels of 202 mg/dL in those with FH genetic mutations and 133mg/dL in controls, with significant overlap in LDL-C levels between the groups.[3] Importantly, LDL-C levels varied by affected gene, with highest levels in those with *LDLR* mutations (240mg/dL), followed by those with mutations in *APOB* (178 mg/dL) and *PCSK9* (155 mg/dL). To date, more than 1200 different mutations have been described in the LDL receptor gene which can be divided into 6 different classes of receptor abnormalities.

Diagnosing Familial Hypercholesterolemia

There is no one agreed upon algorithm for the diagnosis of FH, but several clinical criteria have been proposed that variably comprise LDL-C levels, physical findings (**Fig 2**), family history, and in some cases, genetics. The three most commonly used include the Simone Broome, Dutch Lipid Clinic Network and MEDPED criteria. The original Simone Broome criteria are fairly simplistic and involve LDL-C levels as well as the presence of xanthomas and family history of myocardial infarction (MI) to determine probable or definite FH (**Table 1**).[4] The Dutch Lipid Clinic Network criteria are more specific, but less sensitive, and involve a point scoring system integrating LDL-C, physical findings and family history of vascular disease in the patient and family members, and DNA markers with a score ≥6 denoting probably FH. Finally, the US based MEDPED criteria involve thresholds of total cholesterol by age, with different cut points to use for screening in the general population or for identifying affected family members in those with known FH.

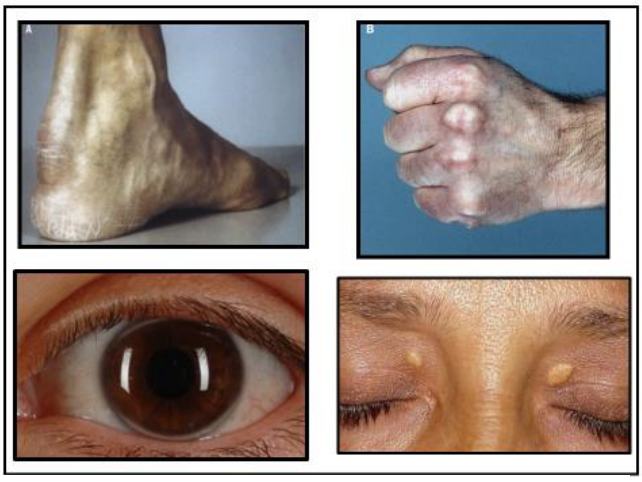

Fig 2. Physical findings with FH (clockwise) tendinous xanthomas in the Achilles and extensor tendons of the hand; xanthelasma of the eyelids; corneal arcus

Total cholesterol >290 or
<u>LDL >190 mg/dl in adult</u>,
or total cholesterol >260 or
<u>LDL>160mg/dl in child</u>
AND
<u>Definite</u>: Tendon xanthoma in patient or relative
<u>Probable</u>: Family history of premature MI, OR
Hypercholesterolemia in 1st or 2nd degree relative

Table 1. Original Simon Broome criteria for FH

Clinical Implications of Familial Hypercholesterolemia

The major consequence of FH is excess and earlier vascular disease. In a classic study by Neil Stone (who provided skin biopsies of a patient with FH for Brown and Goldstein's original studies), 116 families with FH were investigated for coronary artery disease (CAD) predilection.[5] Here, the risk of CAD death or MI was 5-fold higher in family members with FH compared to unaffected relatives. In addition, males with FH had a 50% chance of developing CAD by age 50 and females had a 30% chance by age 60. All told, FH has been reported to confer a ~5-15 fold increased CAD risk across various studies.

A critical concept in understanding the excess vascular disease risk of FH is appreciating the persistence of elevated LDL-C since birth. While two patients may have similarly elevated LDL-C in middle age, the one with FH has had a much greater *cumulative* exposure to LDL-C over his/her lifetime (**Fig 3**).[6] This concept of gram-years of LDL-C exposure is akin to the metric of pack-years of cigarette smoking, and once a critical threshold is crossed, coronary heart disease manifests.

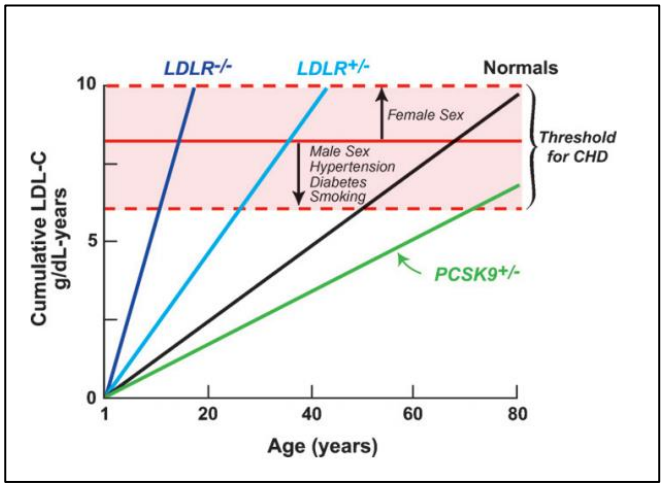

Fig 3. Conceptual model of cumulative exposure to LDL-C in gram-years in homozygous and heterozygous FH, and normals. Once a critical threshold is reached, CHD occurs.

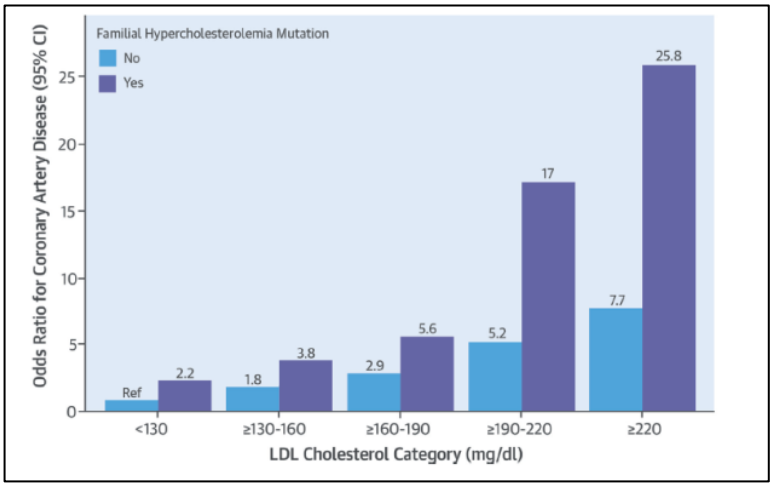

Fig 4. Interplay of LDL-C levels and FH genetic mutations. For every level of LDL-C, the presence of a mutation is associated with higher risk of coronary artery disease.

This conceptual model was confirmed in a recent study involving 38,000 subjects from a case-control cohort consortium and from a series of prospective cohort studies.[7] Participants underwent sequencing for variants deemed to be pathologic in the *LDLR*, *APOB*, and *PCSK9* genes and were then categorized by LDL-C level and the presence or absence of an FH causing mutation. At every category of LDL-C, those with a mutation had a significantly higher risk of CAD than those without, including those with LDL-C≥220 mg/dL where the risk was 3 fold higher in mutation carriers (**Fig 4**). The authors further explored the underpinnings of this observation by matching 25 mutation carriers to controls matched by the most recent LDL-C level. Tracking prior serial lipid levels in these individuals demonstrated that those with mutations had persistently higher LDL-C levels (~17 mg/dL) prior to the terminal values that were similar.

The implications of this conceptual model of cumulative LDL-C exposure are several fold. First, traditional cardiovascular risk scores such as the ASCVD risk estimator are not accurate in patients with FH. In addition, adult patients with FH and elevated LDL-C universally require lipid lowering treatment to offset the years of LDL-C exposure, regardless of other risk factor levels. Finally, since exposure begins to accumulate at birth, it is imperative to identify patients with FH in childhood to alter the natural history of their disease.

Screening for FH

Population Prevalence

Assuming a world-wide population prevalence of 1:500 individuals, FH is estimated to affect 15 million people worldwide, including 620,000 in the U.S. While the prevalence can vary widely depending on the population studied, several recent studies from Europe have suggested that the prevalence may be closer to 1:200. Prior U.S based estimates derived from select populations but estimates were recently determined using the population-based NHANES study.[8] Here, investigators applied the Dutch Lipid Clinic Network criteria to the 1999-2012 sample and determined that the estimated prevalence of probable/definite FH was 1:250, meaning that ~834,000 Americans have FH. These estimates varied by race/ethnicity including 1:249 in whites, 1:211 blacks, and 1:414 Mexican Americans. Despite being relatively common, FH is seldom recognized or diagnosed.

Cascade Screening

Given the significant cardiovascular implications of FH, there is much interest in enhancing screening for the disease. It fulfills the guidelines and principles published by the WHO for screening in that it is an important health problem with an appropriate treatment and one for which diagnostics are available in a latent phase of the disease. While there are no randomized trials for ethical reasons on statin use in patients with FH, observational data suggest that much of the adverse cardiovascular ramifications can be mitigated by statin initiation. In an observational study from the Netherlands, approximately 2000 individuals with FH and free of CVD were assessed based on the initiation of statin use after the advent of simvastatin in 1990.[9] The 87% of patients who started a statin had an almost 80% reduction in risk of coronary heart disease over 8.5 years of follow up compared to those who elected not to take a statin, after adjusting for known risk factors. Patients with FH on statins actually had a comparable rate of coronary heart disease to matched non-FH controls from the general population.

Statins are not only approved for all adults with dyslipidemia, they are also FDA approved for children with FH starting at 8 for pravastatin, and 10 for simvastatin, atorvastatin, and rosuvastatin based on data demonstrating improvement in lipids and atherosclerosis measures such as carotid intima-medial thickness, without any adverse consequences on growth, hormonal levels, and maturation. In 2011, the NHLBI published guidelines for lipid screening in children, advocating screening all children between the ages of 2-8 years with a family history of premature CVD or with dyslipidemia in their parents (**Table 2**).[10] The objective behind these controversial recommendations was to identify children with FH whereby early intervention could alter

their lifelong course. Universal lipid screening was also recommended for all children ages 9-11.

Table 2. NHLBI Guidelines for Pediatric Lipid Screening

Age	Category	Grade
2-8 years	**Parent, grandparent, aunt/uncle, or sibling with MI, angina, stroke, CABG, stent, <55 male, <65 female**	**B, Strongly recommended**
2-8 years	**Parent with TC ≥240mg/dL or known dyslipidemia**	**B, Strongly recommended**
9-11 years	**Universal**	**B, Strongly recommended**

The autosomal dominant nature of FH provides a significant advantage for detecting disease in the population in the form of cascade screening.[11] Here, identification of an initial patient with FH allows for screening of all first degree relatives, with the expectation that 50% will be affected. Upon detection of the next case, the cycle is repeated (cascaded) for all of the first degree relatives of that individual, thereby multiplying the number of cases ascertained. The diagnosis can be made using clinical or genetic criteria. Cascade screening for FH has been found to be highly effective and efficient, and has been implemented broadly in various European countries including the Netherlands where screening identified an average 8 affected relatives for each index case. In addition, cascade screening has been shown to result in earlier diagnosis and higher treatment rates, and is highly cost effective (incremental cost-effectiveness ratio ~ $2500 to $4500 per quality-adjusted life-year gained). Currently, cascade testing for FH has a “Tier 1” recommendation from the CDC. However, screening programs in the U.S. are quite nascent due to lack of adequate public health infrastructure, large geographic territory, barriers to access to care, and privacy concerns.

FH Electronic Health Record Based Screening Programs

The advent of electronic health records (EHR) and larger conglomerated health care systems provides an opportunity for coordinated and facilitated FH screening programs. Currently, there are just a few examples of such EHR-based initiatives in the published literature. The Mayo Clinic retrospectively applied an ePhenotyping algorithm in their EHR which included records from 131,000 patients receiving primary care in their Olmstead County health system from 1995-2014.[12] Using structured data fields such as ICD-9 diagnosis codes, labs, and medications, as well as unstructured data fields (xanthomas, xanthelasma, etc) abstracted from clinic notes and other records using natural language processing, they were able to apply modified Dutch Lipid Clinic Network FH criteria to this cohort. They restricted this analysis to the 5992 subjects with LDL-C≥ 190mg/dL and found definite/probable FH in 423 (1:310 of the entire cohort). These subjects had a maximal LDL-C of 246 mg/dL with only 11% initially on treatment, but increasing to 82% on treatment during the retrospective period. They

also carried a diagnosis of premature CAD in 64%, but only 22% achieved an LDL-C <70mg/dL. While there is currently and ICD-10 code specific for Familial Hypercholesterolemia, no such code exists in ICD-9 nomenclature, and only 55% of those with FH carried an ICD-9 diagnosis of hypercholesterolemia.

The FH Foundation, a prominent patient advocacy organization, similarly is developing an ePhenotyping tool called Find FH®, in partnership with the Stanford School of Medicine. This algorithm was created using machine-learning where information from patients with FH and without FH are entered into a database and the model is developed by iteratively analyzing certain characteristics of each. The algorithm entails over 350 variables from medical records and insurance claims, including diagnosis codes, procedure codes, prescription codes, lab values, gender and age. In partnership with a vendor with administrative data on over 100 million Americans, they created a heat map (**Fig 5**) of probable FH density by locale in the United States and aim to translate this algorithm into an actionable protocol to notify physicians about patients with FH in their practices.

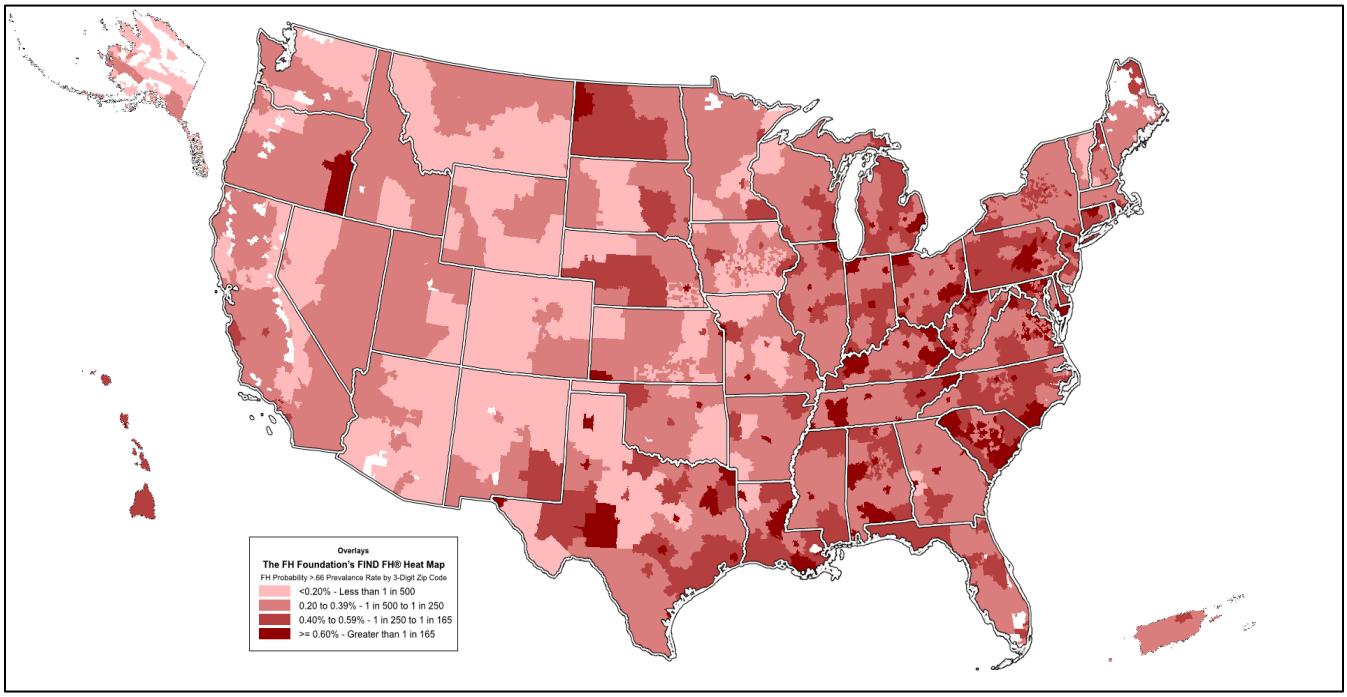

Fig 5. Find FH heat map of FH prevalence in the U.S.

Genetic Screening Programs

Genetic screening offers several potential advantages in the detection of patients with FH. First, there is variable penetrance of the disease such that many carriers may have milder forms with LDL-C that overlap with non-carrier levels. In addition, LDL-C levels can be altered by treatment and detailed knowledge of not only lipid lowering prescription, but also adherence is required to adjust LDL-C for application of clinical diagnostic criteria. Further, once the causative mutation is identified in a proband, cascade screening is fairly efficient by just assessing for that specific mutation in all first degree relatives. Genetic screening programs have been highly successful in some

countries such as the Netherlands, and more recently, they are being developed in various large health care systems in the U.S.

Geisinger Health system is a large integrated U.S. health care system which has developed the MyCode community health initiative, linking EHR and biobank data for precision medicine research. As part of this initiative, they collaborated with Regeneron Genetics to perform whole exome sequencing in 50,726 individuals. In those with prior lipid levels, they specifically evaluated for variants in *LDLR, APOB,* and *PCSK9* to determine the prevalence of FH in their population, as well as the treatment patterns and implications of this disease.[3] Of the 42,696 individuals with LDL-C data, they identified 35 known or predicted pathologic variants in these genes in 229 individuals, for a population prevalence of 1:256, which is in line with national data based on clinical criteria. Interestingly, 44% would have been categorized as unlikely to have FH by Dutch Lipid Clinic Network criteria while only 24% would be categorized as probable/definite. LDL-C levels were 69 mg/dL higher in FH mutation carriers compared to non-carriers, but there was significant overlap in the LDL-C levels between these two groups (**Fig 6**). Out of all individuals with LDL-C ≥190 mg/dL, only 2.5% were carriers of an FH variant which almost exactly the percentage seen in those with LDL-C ≥190 mg/dL in another recent FH genetic study.[7]

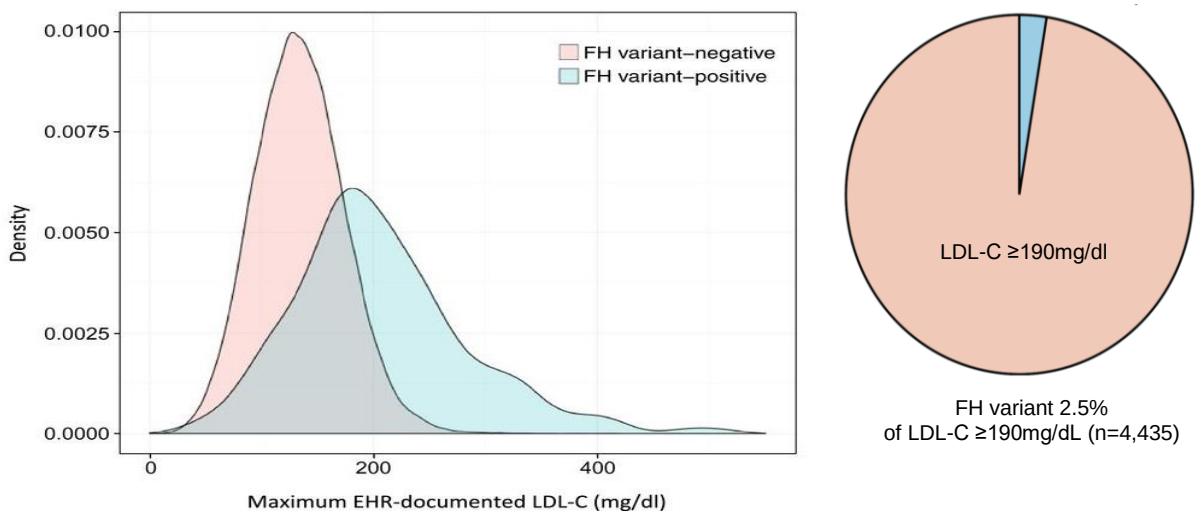

Fig 6. (Left) LDL-C levels in FH variant positive and negative individuals in Gesinger cohort. (Right) proportion of individuals with LDL-C ≥190mg/dL with FH variant (2.5%)

The diagnosis of FH by a healthcare provider was inferred using the ICD-10 diagnosis code of “pure hypercholesterolemia” or referral to lipid clinic and only 15% of FH variant carriers met these criteria. Further, only 56% were currently on statin treatment and only 46% had an LDL-C <100mg/dL.

The Geisinger data suggest that genetic screening for FH on a population or health care system level may uncover many undiagnosed individuals, including those who would have been missed by clinical criteria alone. These individuals are generally

undertreated and provide a real opportunity for prevention. However, they also demonstrate some of the challenges of a genetic screening approach. While those with FH by genetic criteria but with LDL-C <190 mg/dL may have variants with incomplete penetrance, an alternate possibility is that these variants are not actually pathologic. Whole exome sequencing often yields variants of unknown significance (VUS), and research studies such as this one use predictive programs to categorize some of the potentially pathologic variants, rather than proving pathogenesis clinically or biochemically. In addition, the fact that only a small fraction of individuals with LDL-C≥190 have FH genetic variants may mean that these individuals do not actually have FH. Alternatively, this could also signify that there are other unknown genes involved. In fact, a study by Zahid Ahmad and Abhimanyu Garg at UTSW assessed for mutations in *LDLR, APOB*, and *PCSK9* in 101 subjects meeting modified Simon Broome criteria for FH and found that 65% had "unexplained" FH. The lack of causative mutation ranged from 77% in African Americans, to 57% in non-Hispanic whites and 53% in Hispanics.[13] Novel genes may be implicated in these individuals, and a proportion likely has a polygenic form of autosomal dominant hypercholesterolemia.[14] As such, the lack of a targeted genetic mutation does not necessarily negate the possibility of FH and clinical and genetic data may be complementary for screening.

Rather than starting with adults, a recent study explored genetic and lipid based screening for FH in children at the time of vaccinations.[15] 10,095 children ages 1-2 years from 92 primary care practices in the U.K. had blood and DNA samples collected at these routine visits. Lipid levels were assessed and all children had genotyping done for the 48 most common mutations in *LDLR* (n=46), *APOB* (n=1) and *PCSK9* (n=1) found in a genetic lab of that region over a 10 year period. A total of 37 children were positive for one of these FH variants (1:276) (**Fig 7**). Of the remaining children with total cholesterol ≥99th percentile, 7 had an FH variant identified by DNA sequencing, and another 8 had repeat total cholesterol ≥99th percentile, yielding 45 children with suspected FH (1:224).

Parents of these children were also assessed for FH. The parent with the higher cholesterol levels was presumed to have FH, and 84% of them were also positive for an FH variant. Despite total cholesterol levels being higher in these individuals, none were on a statin at the time of diagnosis, but 90% elected to take a statin in follow up. A

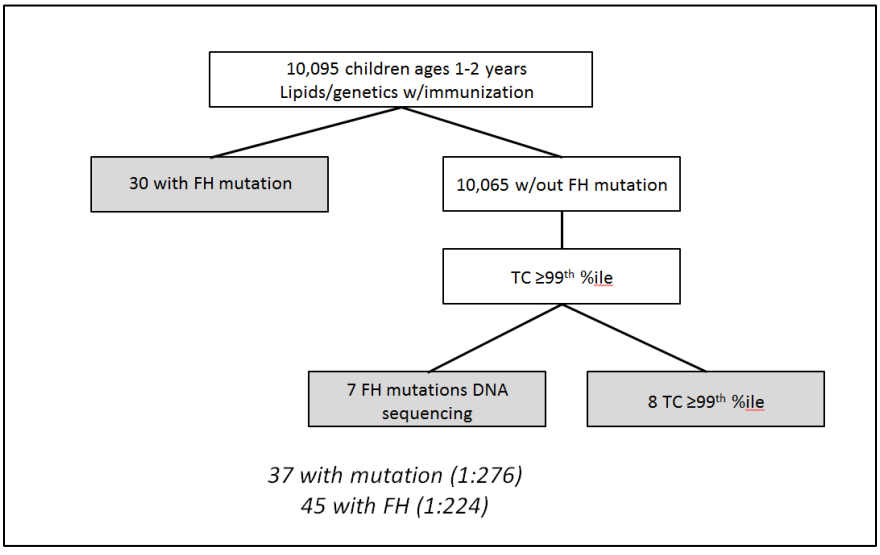

Fig 7. Algorithm for FH detection in UK child screening cohort. 37 children had FH variant and 8 had persistently high total cholesterol (≥99th percentile).

modified algorithm proposed by these investigators integrating iterative LDL-C thresholds and genotyping suggested that for every 1000 children screened, 8 individuals (4 children and 4 adults) would be diagnosed with FH. This paradigm of childhood screening is appealing in the lipid levels may better discriminate between FH and unaffected individuals in children than adults. In addition, both the children and the parents who are generally younger themselves, have an earlier opportunity for prevention.

Treatment of FH

All adults with FH have an imperative for lipid lowering upon diagnosis, starting with statin therapy. Given the marked elevations in LDL-C, many will require more than one agent for adequate LDL-C reduction. The CASCADE-FH registry of 1295 subjects with clinical FH followed in 11 lipid clinics in the U.S., including UT Southwestern, reported that 15% of these subjects were on no treatment, while 40%, 30%, and 15% were on 1, 2, and ≥3 drugs, respectively. Despite this, only 25% achieved an LDL-C <100 mg/dL, and only 41% achieved ≥50% LDL-C lowering from baseline levels.

Current recommendations

The recommended goals of therapy in patients with FH vary between different societies.[16-19](**Table 3**) Most advocate for a ≥50% LDL-C reduction from baseline in both primary and secondary prevention. The majority also recommend LDL-C goals of <70 and <100 mg/dL for primary and secondary prevention, respectively, except for the National Lipid Association which endorsed <100 and <160 mg/dL. All of these recommendations generally derive from expert consensus as there are no high quality data specifically in patients with FH to inform the appropriate treatment algorithm.

Table 3. Recommendations for FH treatment goals from various organizations

Organization	CHD/ASCVD	No CHD/ASCVD
NICE Guidelines 2008	**≥50% LDL-C reduction**	**≥50% LDL-C reduction**
National Lipid Association 2013	**≥50% LDL-C reduction and LDL-C <100mg/dL***	**≥50% LDL-C reduction and LDL-C <160 mg/dL**
European Athero Society 2013	**LDL-C <70 mg/dL****	**LDL-C <100 mg/dL**
International FH Foundation 2014	**≥50% LDL-C reduction and LDL-C <70 mg/dL**	**≥50% LDL-C reduction and LDL-C <100 mg/dL**
ACC Expert Consensus Non-Statins 2017**	**≥50% LDL-C reduction and LDL-C <70 mg/dL**	**≥50% LDL-C reduction and LDL-C <100 mg/dL**

PCSK9 inhibitors

Despite the availability of statins, ezetimibe and other agents to lower LDL-C, most patients with FH do not meet the stringent LDL-C targets advocated in various

guidelines. One of the most significant advances in the field of FH since the work of Drs. Brown and Goldstein is the advent of the novel class of LDL-C lowering agents, PCSK9 inhibitors. PCSK9 is an enzyme that affects LDL-C levels by direct binding of the protein to epidermal growth factor-like repeat A in the extracellular domain of the LDL receptor, thereby accelerating degradation of the receptor. Both gain-of- function and loss-of-function variants in the *PCSK9* gene have been described that cause higher and lower levels of LDL-C, respectively, and variants in *PCKS9* contribute to population variability in LDL-C levels

The unprecedented pace of development of PCSK9 inhibitors from the first description of family with a PCSK9 gain of function mutation in 2003 to the FDA approval of the first PCSK9 inhibitor in 2015 was propelled by the work of Drs. Helen Hobbs and Jonathan Cohen at UT Southwestern. Using the Dallas Heart Study and ARIC cohorts, they demonstrated that black individuals with loss of function mutations in PCSK9 had modest 28% lower LDL-C levels from birth that resulted in an 88% reduction in CHD in middle age.[20] Further, individuals with these mutations had no untoward adverse consequences upon careful interrogation of detailed phenotyping. These observations paved the way for development of PCSK9 inhibitor drugs after demonstrating potential reduction in CHD by targeting this pathway and a lack of concerning safety signals.

Currently, there are two FDA approved PCSK9 inibitors, alirocumab and evolocumab. Both are murine monoclonal antibodies delivered via subcutaneous injection every 2 weeks (option for every 4 weeks with evolocumab) that markedly lower LDL-C (55-65% reduction) as monotherapy or on top of statin therapy. In patients with heterozygous FH on high intensity statin therapy ± ezetimibe not achieving LDL-C <100 mg/dL or 70 mg/dL for primary and secondary prevention respectively, the addition of alirocumab resulted in achieving these LDL-C targets in >75% and >60% of subjects. The recent FOURIER randomized placebo controlled trial of 27,564 subjects with stable vascular disease and LDL-C>70mg/dL on maximal statin therapy demonstrated that evolocumab lowered LDL-C from median level of 92mg/dL to 30mg/dL in the treatment group, accompanied by an 15% relative risk reduction in CV events over a 2.2 year period.[21] (**Fig 7**)

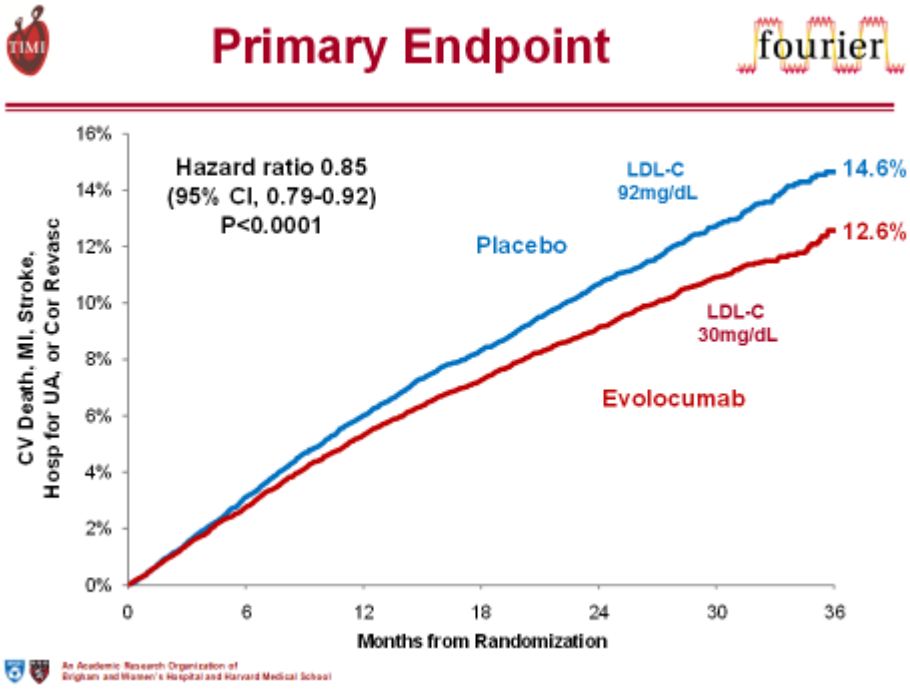

Fig 7. Primary endpoint results for FOURIER trial of evolocumab in patients with ASCVD and LDL-C >70mg/dL

There were minimal side effects with evolocumab, and importantly, no adverse cognitive effects of these very low LDL-C levels over a 2 year period in a carefully conducted companion study which interrogated cognitive endpoints.

Treatment Algorithms for FH

Despite these impressive LDL-C lowering data and clinical trial evidence for CVD risk reduction, a major limitation for PCSK9 inhibitor use in clinical practice is cost (~$14,000/year). As mentioned, most patients with FH will require multidrug treatment to achieve sufficient LDL-C lowering. Various algorithms have been proposed to sequentially allocate the various agents that include statins, ezetimibe, PCKS9 inhibitors, bile acid binding resins, and nicotinic acid. A position statement by the AHA in 2015 recommended ezetimibe as the second line agent after high-intensity statin treatment for patient with FH not achieving LDL-C goals.[22] However, a more recent update from the ACC Expert Panel on Non-statin agents included the FOURIER trial results in crafting their recommendations. Here, in patients with initial LDL-C >190mg/dL (ie: FH phenotype) with ASCVD and LDL-C ≥70mg/dL on maximally tolerated statin, ezetimbe OR PCSK9 could be chosen for second line therapy.[17] (**Fig 8**).

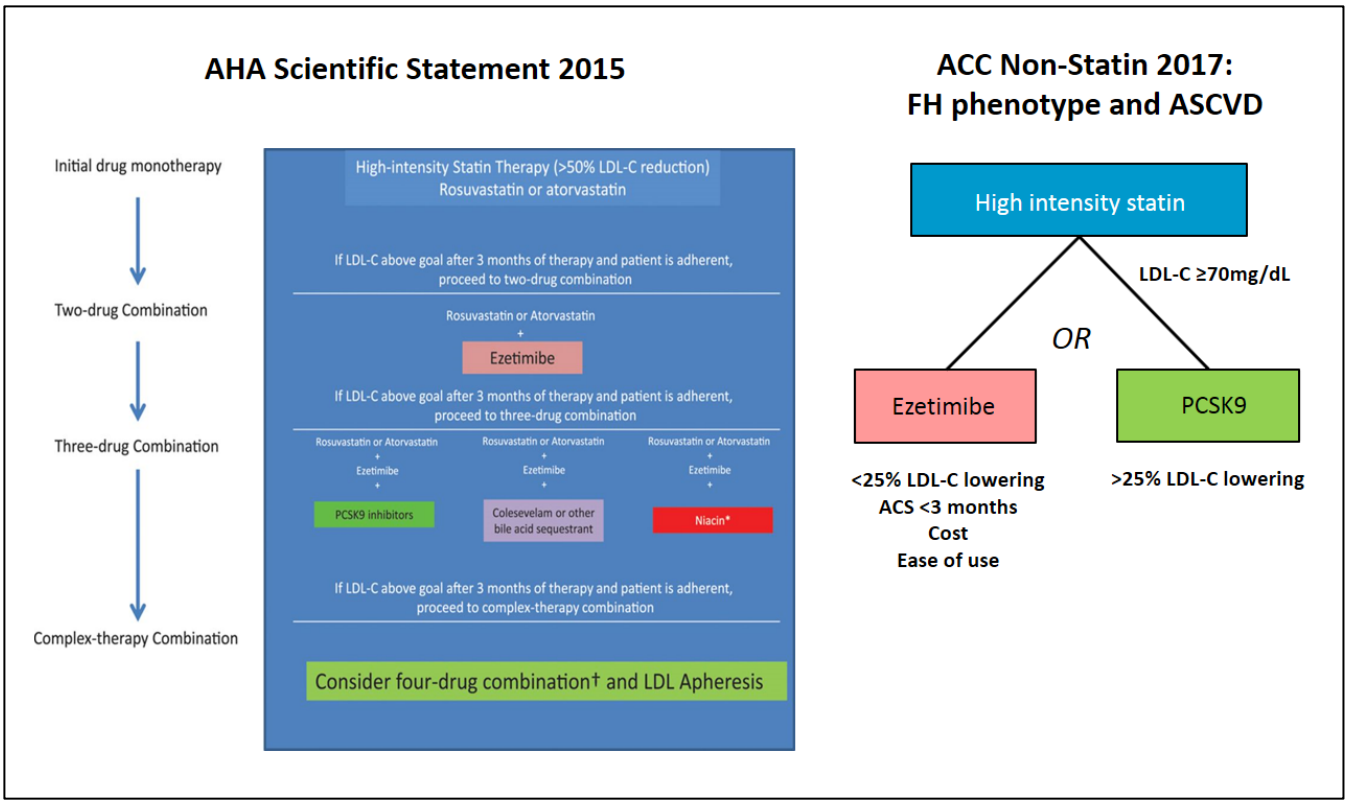

Fig 8. Treatment algorithms for LDL-C lowering in FH

Addressing Heterogeneity of Risk

Patients with FH that have had prior ASCVD are at markedly high risk for recurrent events and clearly necessitate aggressive LDL-C lowering therapy. However, the considerations for primary prevention patients with FH are a bit more complex. There is

growing appreciation that there is heterogeneity of risk amongst such patients. In the classic study by Neil Stone regarding CHD risk with FH, the converse observation can be made that 50% of men and 70% of women with FH do NOT have CHD by the ages of 50 and 60 respectively. In patients with modest residual elevations in LDL-C (100-160mg/dL) on high intensity statin therapy, the potential benefit of each sequential therapy added has to be weighed against the patient burden and cost, especially with PCSK9 therapy, given that these patients are generally younger and will require decades of treatment. Precision medicine approaches to more focused targeting of therapies in patients with FH are starting to emerge.

Unfortunately, current ASCVD risk algorithms such as the ACC/AHA ASCVD Risk Estimator are not applicable to patients with FH, as they were developed and validated in the general population. However, the SAFEHEART investigators recently developed an ASCVD risk score specifically for patients with FH. They assembled a cohort of 2404 subjects with molecularly defined heterozygous FH from a multicenter, nationwide, long-term prospective cohort study in a Spain, with 5.5 years of follow up for ASCVD events. Independent predictors of ASCVD events included age, male gender, history of previous ASCVD, high blood pressure, increased body mass index, active smoking, and LDL-C and Lp(a) levels, from which a risk equation (SAFEHEART-RE) was developed.[23] (**Fig 9**) This FH specific ASCVD risk model had excellent discrimination (area under the ROC curve for ASCVD events= 0.85), which was superior in performance to the Framingham risk equation and the ACC/AHA ASCVD Pooled Cohort Risk Equations. One limitation of this risk score, however, was lack of external validation as there are few such large cohorts of patients with FH and clinical event follow up for study.

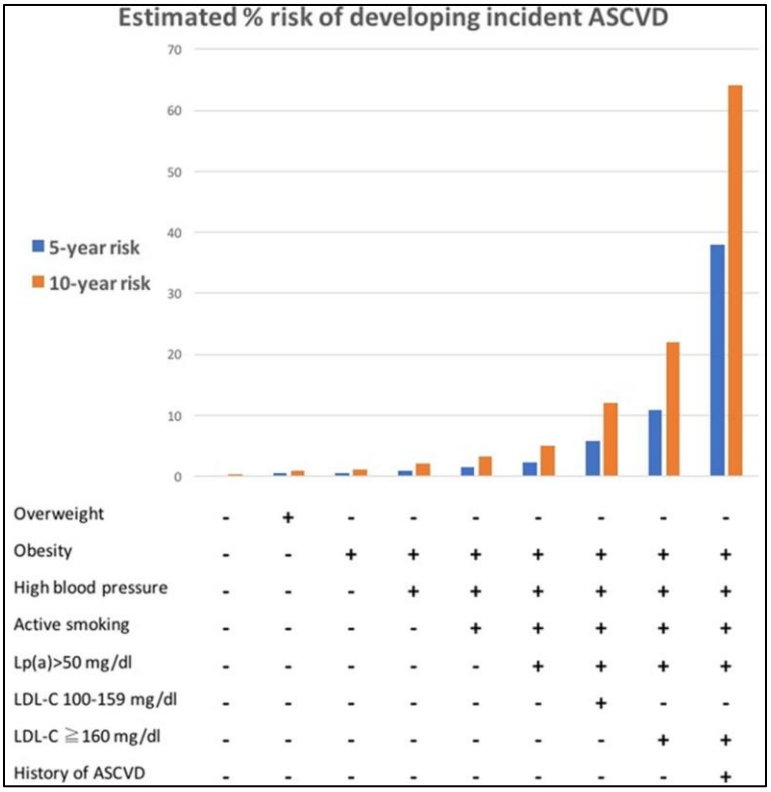

Fig 9. SAFEHEART score: risk of developing incident ASCVD for 66-year-old men with FH and LDL-C <100 mg/dL

Atherosclerosis imaging tests, and coronary artery calcium scanning in particular, are powerful novel risk assessment tools to aid in decision making for ASCVD prevention. Coronary artery calcification is synonymous with atherosclerosis and CAC scores are highly correlated with the burden of atherosclerosis. Numerous prospective studies have demonstrated that higher CAC scores are associated with a significantly greater risk of ASCVD and CHD events (~4-6 fold) and a score of 0 is associated with a fairly good prognosis. There are a handful of studies which have applied CAC scanning and

coronary CT angiography in patients with FH to better determine patterns and correlates of atherosclerotic plaques in these groups.

In one study of 102 subjects with FH and 35 controls undergoing coronary CTA, the investigators discovered that subjects with FH had a much lower probability of having a CAC score of 0 (50% vs. 90%), and were much more likely to have any coronary plaque (calcified or non-calcified) (48% vs. 14%, p=0.0005).[24] Importantly, there was a spectrum of CAC scores among the patients with FH, suggesting heterogeneity of CV risk (**Fig 10**). Amongst those with FH, 19% had obstructive coronary plaques with stenosis >50%, but none had obstructive stenosis with a CAC score of 0. The independent risk factors for any coronary plaque were age and total cholesterol. The overall predictive accuracy of risk factors and lipid levels for CAC and coronary plaque were not reported, so it remains unclear the extent to which these coronary imaging findings are potentially additive for ASCVD risk information.

One small study investigated the predictive value of coronary CTA atherosclerotic burden in 101 Japanese patients with mutation confirmed FH with a mean age of 56 years and mean LDL-C of 264 mg/dL.[25] The coronary plaque burden was determined for each coronary segment and summed for a plaque score. Those with a plaque score ≥ median value had a significantly greater risk of CV events than those with a score < median, (HR 5.4, 95% CI 1.4-21), independent of other risk factors. The study had a relative short follow up period (~2.5 years) and a small number of CV events (n=21), and did not assess for any incremental value of plaque score over LDL-C level and other clinical factors, but was proof of concept of the potential value of coronary CT imaging in patients with FH for risk stratification.

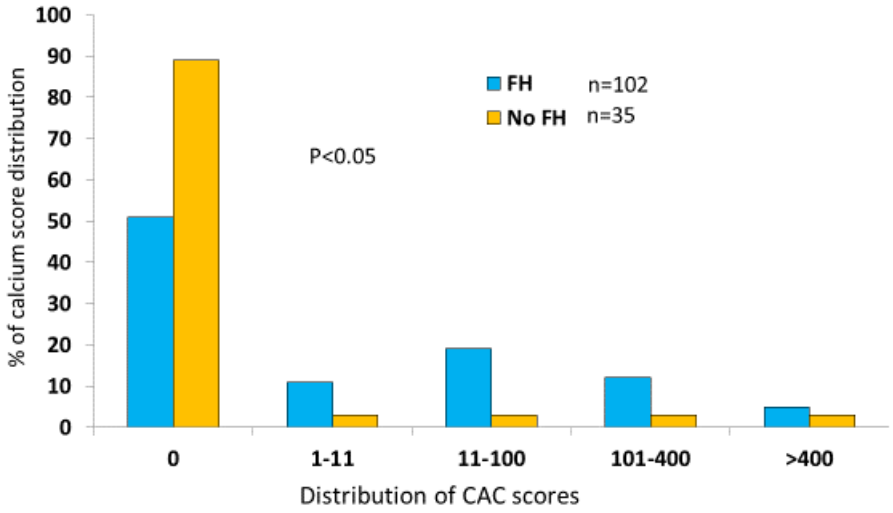

Fig 10. Distribution of coronary artery calcium scores in individuals with FH and normal controls

Conclusions

The molecular basis for Familial Hypercholesterolemia was decoded by Drs. Brown and Goldstein over three decades ago. Advances in electronic health records, high throughput genotyping, and creative approaches have facilitated the ability for large scale screening programs for FH. In parallel, new treatments have emerged, particularly PCSK9 inhibitors, that can essentially render LDL-C values to the normal range. All of these developments are converging at a time when FH has been found to be more common that previously appreciated. There is a real opportunity to identify and treat the vast majority of individuals with FH, particularly the younger ones, to change a previously morbid and mortal illness to a fairly benign one.

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