Proceedings of the FH Foundation’s inaugural
Familial Hypercholesterolemia Summit:
Awareness to Action
Annapolis, Maryland — September 18th & 19th, 2013

The first global FH Summit: Awareness to Action was conceived and organized by the FH Foundation to: 1. Raise awareness of FH as a public health concern and 2. To formulate actionable recommendations to help embed FH in a strong public health movement, bringing attention to this common but underdiagnosed and undertreated disease.

The meeting was co-chaired* by Dr. Muin Khoury (CDC, Office of Public Health Genomics) and Dr. Dan Rader (University of Pennsylvania). With the help of a very active and well-respected steering committee** including lipidologists, public health experts, geneticists and patients, the FH Foundation brought together world-renowned experts from 11 countries. These included the United States, Canada, England, Wales, Spain, the Netherlands, Japan, Brazil, Australia, South Africa, and China, representing not only the medical and scientific community but also governmental organizations (NHLBI, CDC, several State Departments of public health), professional organizations (NLA, ASPC, PCNA, WomenHeart) healthcare organizations (Kaiser Permanente), pharmaceutical companies, diagnostic testing companies and payers. In addition there was active participation of individuals with FH representing the patient perspective throughout the meeting.

The Summit’s participants were asked to address the following issues:

• Review existing diagnostic criteria with the goal of determining those with the greatest potential for public health impact and recommend simple tools for increasing rates of early detection and management of FH.
• Define approaches for population-wide cascade screening programs in the United States.
• Evaluate the role of genetic testing in enhancing cascade screening efforts.
• Share opportunities for harmonization of FH disease registries in different regions, to maximize their potential to improve public health, patient outcomes and research.
• Discuss ways to measure progress and recommendations for future research.

Through short (but dynamic) didactic presentations from international experts as well as facilitated panel discussions the group exchanged information on evidence-based best practices for early identification, genetic screening, and treatment of patients with FH. The coalescence of these groups led to concrete plans of action enumerated below. The
Summit culminated in the launch of the FH Foundation’s national patient registry (CASCADE FH) when the first FH patient enrolled on site during the meeting.

**Specific Action Items and Takeaways included:**

- Organize and lobby for a public health awareness campaign [*in progress through the FH Foundation*]
- Increase FH awareness with the public and healthcare professions [*in progress through the FH Foundation*]
- Establish a public-health “friendly” case definition for familial hypercholesterolemia [*commenced by The FH Foundation with domestic and international leaders*]
- Strong lobbying effort for a specific ICD-10 coding [*in progress through an FH Foundation collaboration with the NLA*]
- Encourage systematic searches of EMRs across the country and work to have FH included in HEDIS measures [*in progress through The FH Foundation*]
- Encourage the inclusion of cascade screening in AAP/NHLBI pediatric lipid guidelines
- Add FH to the WHO screening criteria
- Development of pilot projects to demonstrate effectiveness and cost effectiveness
- Initiate multi-faceted outreach campaign to encourage patient and provider recruitment in CASCADE FH Registry [*in progress through the FH Foundation*]

*This report is a full summary of the program of presentations and panel discussions that took place at the 2013 FH Summit. The complete agenda included five sessions, each followed by a moderated panel discussion:*

**Opening Remarks**

- Muin Khoury, MD, PhD and Daniel Rader, MD

**I. The Role of FH in Public Health Efforts to Reduce the Burden of Cardiovascular Disease**

*Moderator: Laurence Sperling, MD*

- David Gordon, MD - Opening Remarks From NHLBI Perspective
- Yuling Hong, PhD - Current Public Health Efforts to Reduce the Burden of Cardiovascular Disease
- Eric Sijbrands, MD – Example Of The Dutch Experience
- Facilitated Panel Discussion
  
  Henry Ginsberg, MD (EAS), Stacey Lane, JD (Individual with FH)

**II. What Diagnostic Criteria for FH Would Have the Greatest Public Health Impact?**

*Moderator: Daniel Rader, MD*
- Katrina Goddard, PhD – Systematic Review Of Criteria And Their Impact: Evaluation Of Genomic Applications In Practice And Prevention (EGAPP), Knowledge Synthesis Center
- Raul Santos, MD – Comparing Sensitivity/Specificity Of The Simon Broome, MEDPED, and Dutch Lipid Clinic Network Criteria in Brazil
- Facilitated Panel Discussion
  - Paul Hopkins, MD, MSPH (United States, MEDPED), Anthony Wierzbicki, MD (United Kingdom, Simon Broome), Patrick Moriarty, MD (FH Foundation Scientific Advisory Board)

III. Enhancing FH Screening Efforts: Finding the Index FH Case

Moderator: Debra Duquette, MS, CGC
- William Neal, MD – Successful Implementation of a Universal Screening Program
- Samuel Gidding, MD – Pediatric Screening
- Peter Wilson, MD – Use of Electronic Medical Records for FH Finding (VA)
- Facilitated Panel Discussion
  - Peter Kwiterovich, MD (Johns Hopkins), Lisa Hudgins, MD (FH Foundation Scientific Advisory Board), Ronald Scott, MD (Kaiser), Joyce Ross, CRNP (Board Member, FH Foundation)

IV. Strategies for Implementing Systematic Cascade Screening

Moderator: Muin Khoury, MD, PhD
- Fernando Civeira, PhD – Spain
- Frederick Raal, MD, PhD - South Africa
- Amy Sturm, MS, CGC – The challenges of Implementing Genetic Testing Into Cascade Screening Efforts In The United States
- Dev Datta, MD - Wales
- Facilitated Panel Discussion
  - Joep Defesche, PhD (Netherlands), Mariko Harada-Shiba, MD, PhD (Japan), Gerald Watts, MD (Australia), Jie Lin, MD, PhD (China)

V. Can National Registries Improve Population-based FH Surveillance and Outcomes?

Moderator: Daniel Rader, MD
- Jacques Genest, MD – Overview Of Current FH Registry Efforts Worldwide
- Muin Khoury, MD, PhD - Developing National Surveillance Indicators-Healthy people 2020
- Matthew Roe, MD – Success of Registries
- Joshua Knowles, MD, PhD – Unveiling The Familial Hypercholesterolemia Foundation CASCADE FH Registry
- Facilitated Panel Discussion
  Dev Datta, MD (Wales), Katherine Wilemon (Founder & President, FH Foundation)

Wrap-up and Takeaways

Moderators: Muin Khoury, MD, PhD and Daniel Rader, MD

* The Summit was hosted by the FH Foundation’s Chief Medical Officer, Joshua Knowles, MD, PhD, of the Stanford Center for Inherited Cardiovascular Disease, and by its President and Founder, Katherine Wilemon, whose own diagnosis of FH led her to be an active advocate for early detection and treatment of the disorder.

Serving as co-chairs for the Summit were Muin Khoury, MD, PhD, Director of the Office of Public Health Genomics (OPHG)— Centers for Disease Control and Prevention (CDC), and Daniel Rader, MD, Chief of the Division of Translational Medicine & Human Genetics at the University of Pennsylvania.

** The Summit Steering Committee consisted of Catherine Davis Ahmed, MBA (FH Advocate, Arlington, VA), Debra Duquette, MS (Michigan Department of Community Health, Lansing, MI), Jacques Genest, MD (McGill University, Montreal, Canada), Stacey R. Lane, JD (FH Advocate, New York, NY), and Laurence Sperling, MD (Emory University School of Medicine, Atlanta, GA).
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Opening Session

INTRODUCTION TO THE INAUGURAL FAMILIAL HYPERCHOLESTEROLEMIA SUMMIT

In the Summit’s opening session on the evening of September 18, Founder and President of the FH Foundation, Katherine Wilemon, described her own experiences living with undetected FH, and her impetus for creating the Foundation. She first learned at age 15 that her blood cholesterol was very high, but as her high cholesterol was accompanied by joint swelling and pain, she was referred to a rheumatologist rather than a cardiologist. Her elevated total and LDL-cholesterol had been “just a lab finding” over the years. When as a young adult she presented multiple times with shortness of breath and even chest pain, physicians repeatedly told her that she was too young and healthy to have heart disease. After suffering a near-fatal myocardial infarction (MI) at age 39, she underwent genetic testing and learned that she and her five-year-old daughter both had heterozygous FH (HeFH). Ms. Wilemon’s experience led her to found the FH Foundation in 2011. The Foundation is a patient-centered nonprofit organization dedicated to raising FH awareness through education, advocacy, and research. Ms. Wilemon discussed some of the challenges faced by those affected by or concerned about FH. Why have so few people heard of this relatively common disease? The lack of an ICD code and paucity of data are key; both these issues will be extensively discussed by our expert participants during the Summit.

President Wilemon’s introduction was followed by comments of Matthew Roe, MD, MHS (Director, Global Outcomes/Megatrials, Duke Clinical Research Institute [DCRI]; Associate Professor of Cardiology, Duke University School of Medicine). First, Dr. Roe identified the critical need for FH to be assigned an International Classification of Diseases (ICD-10) code, one of several Summit participants who would do so. Dr. Roe told the audience that the FH Foundation is sponsoring the first patient-centered familial hypercholesterolemia registry in the US, with data to be collected from multiple sources, that is, not only from clinicians but also directly from their patients who have FH and from people who access the registry because they suspect they may have FH. By gathering longitudinal data from persons with FH, the registry will provide insight into the natural history of the disease, the patients’ long-term outcomes and health-related quality of life, the clinical and genetic features of the disorder, and how best to identify people with FH and offer them treatment in the US.

Matthew Ito, PharmD, FCCP, CLS, FNLA (Professor, Pharmacy Practice; Director, Cardiovascular Pharmacodynamics Laboratory, Oregon State University) was diagnosed with FH when he was 10 years old and has been closely monitored ever since. In early 2013, with no warning and only weeks after a negative stress test, he experienced his own near-fatal MI while bicycling with friends in the mountains of Oregon, miles from the highway. With crushing chest pain, he rode as far as he could to meet the ambulance before collapsing. In the hospital, he was found to have multi-vessel disease and required triple bypass grafting. Dr. Ito noted that his experience exemplifies the severity of subclinical disease among FH patients compared to the general population.
The evening session was closed by Joshua Knowles, MD, PhD (Chief Medical Officer of the FH Foundation, who expressed the hope that the ideas and knowledge exchanged during the Summit would lead to major progress in addressing FH as a public health priority.
Opening Remarks by the FH Summit Co-Chairs

The Summit was opened on the second day with remarks by its two co-chairs, Dr. Muin Khoury and Dr. Daniel Rader.

Daniel Rader, MD – Division of Translational Medicine and Human Genetics, University of Pennsylvania

Dr. Rader thanked the FH Foundation and its corporate sponsors for convening the first FH Summit, and asked that the clinicians, epidemiologists, and geneticists in attendance take a hard look at the issue of FH from a public health standpoint. Specific issues to be addressed include how to increase awareness of FH, identify more people with FH, make use of cascade screening to identify their affected family members, and save lives with appropriate treatment.

Muin Khoury, MD, PhD – CDC Office of Public Health Genomics

Dr. Khoury outlined the elements of a public health approach to genetics and genomics with a focus on FH. He noted that 2013 includes two important anniversaries — those of the 1953 discovery of the molecular structure of DNA, and of the 2003 completion of sequencing of the human genome — making this an auspicious time to build on public health programs featuring evidence-based genomic testing.

Dr. Khoury defined public health genomics as a multidisciplinary field concerned with effective and responsible translation of genome-based knowledge and technologies gained from individuals to the improvement of population health. He quoted CDC Director Dr. Thomas Frieden, who, speaking to reporters in early September 2013, said that “Nothing is more important than lowering the rate of heart disease and stroke. One preventable death is a tragedy...because we’re talking about hundreds of thousands of deaths that don’t have to happen.”

Dr. Khoury related that the CDC’s Office of Public Health Genomics was founded in 1998; its goals were to implement evidence-based genomic testing and family health history applications into public health programs; to evaluate genomic tests to find opportunities to improve health and transform healthcare; and to develop communications of all types for providers, policymakers, and consumers. Dr. Khoury praised the accomplishments of the late Dr. Roger R. Williams, founder of MEDPED (Make Early Diagnosis to Prevent Early Death) and of the University of Utah’s Cardiovascular Genetics Research Clinic. Dr. Williams had long worked to screen Utah school children and their families for inherited high cholesterol. He designed MEDPED as a global health program intended to combine new genetic discoveries and computerized genealogical tools to trace the pedigrees of FH-affected families. The project that he began serves that mission to the present.

Dr. Khoury also discussed the work of the US Department of Health and Human Services’ (DHHS) initiative, EGAPP – Evaluation of Genomic Applications in Practice and Prevention. EGAPP is an independent, multidisciplinary, non-federal panel established by the CDC in 2004 to assess the validity
and utility of genomic tests and the application of data gathered from family health histories. These will include evaluation of newly available tests, including next generation sequencing (NGS) and stratified screening — determining which individuals to screen based on such factors as polygenic risk and family history. EGAPP has already issued recommendations for genomic applications for Lynch Syndrome, Hereditary Breast/Ovarian Cancer Syndrome, and other diseases, and is currently working to arrive at a statement of recommendations for FH. EGAPP is also working to set an agenda of translational research needed to address major gaps in the knowledge around FH.

Dr. Khoury went on to note that, based on evidence-based recommendations for FH released in 2008 by the United Kingdom (UK)’s National Institute for Health and Care Excellence (NICE) 2008, the CDC considers FH to qualify as a Tier 1 indication for clinical use of genomic testing and family history to identify relatives at risk. He noted that the CDC defines a Tier 1 indication for genomic testing as “recommended for clinical use by evidence-based panels, based on systematic review of evidence of validity and utility.” (http://www.cdc.gov/genomics/gtesting/tier.htm), and that such Tier 1 indications as FH, Lynch syndrome, and Hereditary Breast/Ovarian Cancer Syndrome share the following characteristics:

- They are autosomal dominant disorders
- They are relatively common
- Most cases are not ascertained or managed by the health care system
- There are effective interventions that reduce morbidity and mortality
- Recommendations for testing and management are evidence-based
- Ideally, dealing with the disorders requires taking of family history and cascading interventions
- Genomic testing can be integrated into existing public health programs
- A genomic testing program can serve as a model for similar genomic applications
- The known incidence is only the tip of the iceberg – many more cases not identified.

Dr. Khoury pointed out that the public health approach for solving health care problems requires the contributions of employers and business, the media, academia, the governmental public health infrastructure, communities, and the health care delivery system. He noted that there are three components to the solution of every public health problem: (1) data assessment, to see who is affected by the condition and who can benefit from the services; (2) development of policies, working with the professional groups for guidelines, and with government agencies to develop programs and to address coverage and reimbursement; and (3) working to assure that the right people are connected with the necessary services.

Dr. Khoury displayed the pyramid model of interventions and their related impact on public health, borrowed from CDC Director Tom Frieden. He noted that widespread positive changes in socioeconomic factors, such as more education and less poverty, form the base of the pyramid because have a huge impact, but such changes are difficult. The next level in the pyramid entails changing the context of health-related decisions — for example, by giving women folic acid to prevent birth defects, enacting laws that ban smoking in public places, or raising taxes on tobacco. Dr. Khoury
asked the participants to consider whether it was possible to address the issue of FH in the US with a similar change in context. He noted that the third level deals with long-lasting protective interventions such as immunizations; smoking cessation; and screening colonoscopies. Near the top of the health impact pyramid, noted Dr. Khoury, clinical interventions such as drug treatment of high cholesterol or diabetes, and individual counseling and education have potential to have an impact if followed by large numbers, but since both treatment and education programs rely on long-term individual behavioral change, the public health impact may be very low. He pointed out that it is unreasonable to expect individuals to behave differently than their peers.

Dr. Khoury concluded by summarizing the work to be done at the Summit: first, how to define what is and is not FH; how best to find the cases on a public health scale; and how to advance the science by making use of the information gained from FH registries.
Session I
THE ROLE OF FH IN PUBLIC HEALTH EFFORTS TO REDUCE THE BURDEN OF CARDIOVASCULAR DISEASE

In Session I, speakers addressed the potential impact of appropriate diagnosis and management of FH in the context of past and current public health efforts to reduce the burden of cardiovascular disease (CVD).

In his introduction, moderator Laurence Sperling, MD (Professor of Medicine – Cardiology; Founder and Director of Preventive Cardiology; Co-Director, Cardiovascular Disease Fellowship Program, Emory University School of Medicine; FH Foundation Steering Committee), noted that the session was designed to help understand the opportunities, but also the challenges to be faced, in raising FH awareness in the US.

1 Session I — David Gordon, MD, PhD, MPH
Opening Remarks from the NHLBI Perspective

David Gordon, MD, PhD, MPH (Special Assistant and Acting Associate Director, NHLBI Division of Cardiovascular Sciences) stated that the history of FH research and the National Heart, Lung, and Blood Institute (NHLBI) have been intertwined from the Institute’s founding in 1948. He characterized the study of FH as “a cornerstone of the current understanding of cholesterol in atherosclerotic cardiovascular disease and in the practical prevention and treatment of the disease.” Dr. Gordon noted that the Nobel prize-winning discovery of the LDL receptor (LDLR) by Drs. Michael Brown and Joseph Goldstein and their elucidation of FH as due to a genetic deficiency in that receptor were supported by NHLBI funds. He affirmed that the NHLBI looks forward to learning the newest developments in the understanding and treatment of this still devastating disease.

2 Session I – Yuling Hong, PhD
Current Public Health Efforts to Reduce the Burden of Cardiovascular Disease

Yuling Hong, PhD (Associate Director of Science, Division for Heart Disease and Stroke Prevention, CDC; Adjunct Professor, Emory University), provided a summary of the CDC’s public health efforts to reduce the burden of CVD in four domains: 1) epidemiology and surveillance – the recognition that supportive data are key for the CDC; 2) environmental approaches to better health; 3) community-clinical linkages for prevention and management of chronic diseases; and 4) health system interventions to improve access, delivery, and usage of preventive services. Dr. Hong described examples of public health initiatives in which the CDC is a partner, such as the State Public Health Actions (SPHA) to Prevent and Control Diabetes, Heart Disease, Obesity and Associated Risk Factors and Promote School Health Program; the Racial and Ethnic Approaches to Community Health Initiative (REACH), and the Million Hearts Initiative, a public-private sector partnership to reduce the number of people who develop CVD and to optimize care for people with CVD.
3 Session I – Eric Sijbrands, MD
Example of the Dutch Experience

Eric Sijbrands, MD (Professor, Internal Medicine; Department of Cardiovascular Genetics at Erasmus MC/University Medical Center in Rotterdam) discussed the knowledge gained from the program of FH screening and treatment in the Netherlands, which has been in operation for nearly two decades. Instituted in 1994, the Dutch nationwide screening program for FH maintains a registry, but more importantly provides a proven mechanism to accomplish widespread screening, identify probands and their relatives, and assure that effective cholesterol-lowering treatment is available to individuals with FH. As of 2013, the Dutch program had accomplished the identification on a molecular (genetic) level of 75% of FH patients estimated to live in the Netherlands, as well as the implementation of cascade screening of the blood relatives of index cases as an accepted routine. The Dutch program continues to increase the understanding of the complications of FH and its management, and provides ongoing monitoring of the efficacy of statin treatment, not only for people identified by FH screening, but also for individuals found to have FH only after a lifelong burden of elevated cholesterol resulting in CV events or symptoms that brought them to the attention of the lipid clinics.

In order for an FH registry and screening program to succeed on a large scale in the US, Dr. Sijbrands emphasized the need for physician education. Physicians—primary care providers and specialists alike — must be trained to recognize that inherited syndromes are not rare and should be considered in the differential diagnosis of all patients with elevated LDL cholesterol (LDL-C), along with acquired secondary hypercholesterolemia. Physicians must recognize the implications of xanthomas and, in patients less than 45 years of age, of corneal arcus; and they must also be trained to understand that if a patient is identified with FH, there is a possibility of premature CVD in other members of the family.

Dr. Sijbrands recommended that a US FH screening program make use of a scoring system to rate the probability of the patient’s having FH and allow evaluation of the screening program’s yield. He gave the example of the Dutch Lipid Clinic Network (DLCN) criteria, by which an individual is rated as possibly, probably, or definitely having FH based on their family history, clinical, and molecular criteria.5 By DLCN criteria, the probability score of FH increases if the patient has a first-degree relative with premature CVD, LDL-C greater than the 95th percentile for age and gender, and/or tendon xanthomas or corneal arcus (< 45 years). Points are added to the score if the patient has a personal history of premature CVD (men <55, women < 60), premature coronary vascular accident (CVA) or peripheral vascular disease (PVD, < 60 years), or has either tendon xanthomas or corneal arcus. Higher scores are assigned for each incremental level of LDL-C, with levels of 6.5 – 8.4 mmol/L (251– 329 mg/dL) scored as probable FH (DLCN=6–8); and LDL-C > 8.5 mmol/L (> 330 mg/dL) as definite FH (DLCN > 8), regardless of family or patient history.

The DLCN criteria also consider molecular diagnosis of FH, and detection of a functional mutation in the LDLR gene is considered definitive for FH. In the Dutch program, Dr. Sijbrands explained, any screened patient with a score of 6 or greater by clinical criteria is tested for mutations in the LDLR and APOB

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genes, which in the Netherlands account for approximately 95% and 4%, respectively, of FH cases. Mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9) are also tested, although Dr. Sijbrands noted that the frequency of PCSK9 mutations is very low among people with FH in the Netherlands. At several local centers, additional testing, such as for APOE, ABCG5/ABCG8, and LDLRAP1 mutations, is performed to detect the rarer genetic dyslipidemias.

In the Dutch program, if the index case undergoes genetic testing based on clinical suspicion and has an FH-causing mutation, cascade screening is initiated, with the first degree relatives tested for the same specific mutation. Dr. Sijbrands noted that if a molecular diagnosis is not confirmed, the patient’s family is still screened for elevated LDL-C or other lipid disorders and for evidence of CVD.

Routine genetic cascade screening within the Dutch program — that is, identifying the mutation that has resulted in FH in the index patient, and screening family members for the same mutation — was shown even 10 years ago to be cost-effective in terms of cost per life year saved. Dr. Sijbrands noted that while new cost data are pending, it is very likely that cost effectiveness has only improved, given the lower price of the statins and steady improvements in DNA screening.

Dr. Sijbrands showed the annual screening results from 2006 to 2010: every year, 4000 to 5000 people underwent genetic testing for FH and an additional 1600 to 2200 people were found to have an LDLR, APOE, or PCSK9 mutation. By the end of 2013, the DLCN will have identified 75% of the program’s initial goal of patients identified on a molecular basis. Because of the increasing difficulty of finding the remaining 25% of FH patients, there are ongoing discussions as to whether the Dutch screening program will continue at its present level of government funding beyond the coming year.

Dr. Sijbrands observed that moving from discovery of the index patient and his or her causative mutation to locating and screening of first- and second-degree relatives should perhaps be termed “opportunistic” screening, rather than cascade screening. He noted that trying to find family links among different small pedigrees that share a common mutation, although work-intensive, has occasionally helped to identify additional family branches that included new FH cases.

While molecular diagnosis by genetic testing is intrinsic to the Dutch screening program, the LDL-C level alone is highly diagnostic in certain patient groups. Based on a Dutch study of over 26,000 people who underwent family screening for FH, the sensitivity and specificity of diagnosing FH based on the LDL-C level alone is influenced by the degree of LDL-C overlap between FH patients and their unaffected relatives, which in turn depends on the severity of the LDL-receptor mutation. A diagnosis based on the level of LDL-C was most accurate when the FH-causing mutation was a null allele mutation, resulting in no residual LDLR function and thus, extremely high LDL-C in the affected vs. unaffected family members. Dr. Sijbrands noted that, in an area with a high prevalence of the null mutation, due to a founder effect, LDL-C levels alone could be used to diagnose FH with nearly 100 per cent accuracy.

Dr. Sijbrands emphasized that in children, the level of LDL-C alone can be used to screen for FH with a post-test probability of 98%, much better accuracy than among adults, and he provided examples of diagnostic algorithms that can be used based on a child’s LDL-C. For example, a child with elevated LDL-C
(≥ 135mg/dL) and one parent with definite FH has a post-test probability of FH equal to 0.98 (95% CI: 0.96-0.99). A child whose LDL-C is at the 95th percentile for age and sex, but who is lean and has a normal level of thyroid stimulating hormone (TSH) has a post-test probability of having an autosomal dominant mutation for FH equal to 0.95 (95% CI: 0.96-0.99).12

Dr. Sijbrands explained that the Dutch screening program includes DNA analysis for all patients who meet clinical and family history criteria, because DLCN investigators have determined that, for adults in the Dutch general population, diagnosing FH by cholesterol levels alone risks unacceptably low specificity and sensitivity.13 A Receiver Operating Characteristic (ROC) curve was based on total cholesterol levels from 278 FH patients who were confirmed carriers of LDLR gene mutations. Based on the ROC, the best available cutoff point of total cholesterol to diagnose FH in relatives of the carriers was the age- and sex-specific 90th percentile. However, given the cholesterol levels measured from 2039 LDLR mutation carriers and 3403 non-carriers who participated in the screening program over a five-year period (1994 to 1999), using the 90th percentile total cholesterol as a cutoff for screening the relatives would have missed the diagnosis in 18% of FH carriers whose levels of LDL-C were less than the 90th percentile (false negatives), and would have wrongly diagnosed FH in 18% of non-carriers (false positives) whose levels of LDL-C were greater than the 90th percentile.13

For people to agree to participate in screening, they have to understand that FH is a serious disease. In the large pedigrees delineated by the DLCN, a family analysis showed a coronary artery disease (CAD) hazard ratio of 8.54 in FH vs. non-FH relatives.14 Dr. Sijbrands noted that this level of risk is similar worldwide, although in Japan, the hazard ratio is as high as 11, for reasons not yet explained.

Dr. Sijbrands presented a large multi-generational Dutch pedigree whose family members included known and suspected FH carriers traced to a single pair of ancestors born in the eighteenth century.15 Noting the longevity of some of the FH carriers in the family, even long before the statin era, he said that it helps illustrate that approximately 40% of untreated patients with FH reach an advanced age of 70 years or more, a fact of vital importance when trying to persuade insurers to offer affordable insurance premiums to people with FH. From this Dutch pedigree, Dr. Sijbrands reported, all-cause mortality was estimated among the individuals in each generation who had FH and who were untreated and non-selected for CVD.15 The standardized mortality ratio for FH carriers in the pedigree was close to normal (that is, a ratio equal to 1.0 when compared with non-carrier family members) or even less than 1.0 during the 19th century. It is thought that in the pre-antibiotic era, FH mutations may have conferred protection against infection or some other causes of early mortality. The mortality ratio for FH carriers then rose to a peak in the 1930s to 1960s. Significant variability in the risk of death attributable to FH was found over time and across the three branches of the pedigree, suggesting that an FH carrier’s risk of CVD-related morbidity and mortality is influenced by a strong interaction between genetic and environmental factors.

Dr. Sijbrands emphasized that environmental factors — male gender, smoking, hypertension, diabetes mellitus, low HDL cholesterol and lipoprotein(a) levels —have proven to be important risk factors for
CVD in FH patients. In addition to statin therapy, controlling the risk factors needs special attention in the management of FH.

The Dutch pedigrees also show that FH patients did not immediately receive statin treatment when these drugs became available, around 1989. Dr. Sijbrands observed that this delay in instituting proven treatment highlights the need to assure that FH patients will be started on statins right away, and he noted that lifestyle intervention must happen as well.

Given the proven effectiveness of statins in lowering cardiovascular risk in the general population, it was not ethically feasible for the Dutch investigators to assess statin treatment of FH patients with a placebo-controlled trial. However, they were able to mimic a controlled trial by means of a time-dependent cohort analysis of 2146 lipid clinic patients with FH who had no coronary heart disease before January 1990 (when the first statin became available in the Netherlands). Over a mean follow-up of 8.5 years, the risk for MI among FH patients treated with statins was no longer significantly different from that of the Dutch population in general. In addition, statin doses lower than currently advised reduced the risk of CHD to a greater extent than anticipated in patients with FH. Among untreated FH patients (that is, patients who delayed statin treatment), the hazard ratio for MI of 8.69 (p<0.001) was essentially the same as the hazard ratio for CAD in untreated FH vs non-FH relatives (HR=8.54) found in large multi-generational Dutch pedigrees constructed by the DLCN.

To evaluate the Dutch program’s success at appropriately treating FH patients once they were identified, the total 1062 subjects (aged 18-65 years) diagnosed in 2006 were sent a questionnaire about their use of cholesterol lowering medication (CLM) two years after the diagnosis. The questionnaire was completed by 781 (74%). Among the 781 respondents, the number of subjects using CLM increased from 397 (51%) at baseline to 636 (81%) after genetic testing and FH diagnosis. Mean LDL-C decreased from 4.1 mmol/L (232 mg/dL) at baseline to 3.2 mmol/L (124 mg/dL) on treatment, although only 22% of respondents had reached the LDL-C target of <=2.5mg mol/L (97 mg/dL). Dr. Sijbrands noted that this was a slightly better rate than in his outpatient clinic, where only 18% of the FH patients are at the target LDL-C level.

Dr. Sijbrands next spoke of the problem of FH patients who are not captured in the screening program but present to the lipid clinic as older adults. He noted that such patients comprise the upper percentile of risk among those with FH, because even if asymptomatic, their long exposure to elevated LDL-C has done significant cardiovascular damage. He cited a single-center (Erasmus Medical Center/Rotterdam) study, in which computed tomographic (CT) coronary calcium score and plaque burden were assessed in 101 consecutive asymptomatic patients with FH (mean age 53 ± 7 years; 62 men) and in a control group of 126 patients with non-anginal chest pain (mean age 56 ± 7 years; 80 men). The median total calcium score was significantly higher for the patients with FH (Agatston score = 87, IQR 5-367) when compared to the patients with non-anginal chest pain (Agatston score = 7, IQR 0-125; p < 0.001). The overall coronary plaque burden was significantly higher in patients with FH (p < 0.01). Although all patients with FH had received statins (mean duration, 10 ± 8 years before CT), the only FH patients protected from plaque burden were males with LDL-C levels below 3.0 mmol/L (116 mg/dL). Dr. Sijbrands
showed dramatically that waiting for FH patients to present at clinic finds them too late: in CT images from two 64-year-old men, he contrasted the very clear coronary arteries of a patient who had diabetes but no mutation for FH, with the calcified and badly obstructed arteries of a man with FH who had no other risk factors for heart disease. Dr. Sijbrands concluded by saying that the DLCN program of cascade screening has identified 75% of patients with FH, but that a huge implementation gap persists. Three things are necessary to optimize the prognosis for an individual with FH: timely identification, early treatment, and getting more patients to the target level of LDL-C. **There is a need to educate doctors about the seriousness of the disease and convince them to refer their patients and their families for screening at a young age.** Although, he said, it still isn’t known what the optimal age is for starting a child with FH on statins, people with FH should at least start treatment as young adults. Better medication is needed, so that more patients attain the target level.

**Session I – Panel Discussion**

**Moderator:** Laurence S. Sperling, MD, FACC, FAHA, FACP (Emory University School of Medicine; FH Foundation Steering Committee)

**Speakers:** David Gordon, MD, PhD (NHLBI); Yuling Hong, PhD (CDC); Eric Sijbrands (DLCN)

**Panelists:** Henry Ginsberg, MD (Columbia University, European Atherosclerosis Society [EAS]); Stacey Lane, JD (FH Foundation Steering Committee)

The panel’s moderator, Dr. Laurence Sperling (Emory University School of Medicine) began by asking the panel to give the audience a sense of the importance of the FH initiative in terms of public health, and further, in terms of a US public health perspective, what would the potential impact of a successful program be?

In response, Dr. Gordon (NHLBI) observed that the study of FH has had a large impact on the overall burden of CVD, leading as it has to better understanding of the link between hyperlipidemias and atherosclerosis and to the development of effective drug treatment. He emphasized the continuing importance of research in the area of FH as a way not only to help patients with FH, but to lower the prevalence of CVD in general.

In his turn, Dr. Henry Ginsberg (Columbia University, and representing the European Atherosclerosis Society at the FH Summit) observed that just coming to the Summit had given him a better awareness of FH as a public health issue not yet addressed in the US. He said that like most of the physicians and health care professionals in attendance, he specializes in the care of patients with lipid disorders. As a result, when FH patients are referred to him, perhaps with triglycerides over 600 mg/dL or statin intolerance, he does not always think of the problem of how to identify patients with FH, because the FH patients are being sent to him; they are in front of him. He said he didn’t know how many he had seen, and he hadn’t thought about how many were *not* being sent to him.
Dr. Ginsberg said that it is possible that a greater proportion of people in the US are being treated with statins for hypercholesterolemia than in the Netherlands or other European countries, because people are very aware of the cardiac problems related to high cholesterol, and checking LDL-C and knowing that total cholesterol over 200 is high has been taken up by the entire US population. He said that the US takes care of people with FH, but only when their symptoms are apparent later in adult life, and then everyone gets the mid-range dose of a statin, because physicians and patients see the statin achieve a certain level of LDL-C reduction and are satisfied with that. Dr. Ginsberg said that he suspects that there are not many people with FH in the US who do not receive treatment if they have access to health care and can have their cholesterol measured. However, he said, there are certainly FH patients being treated inadequately and/or too late. Dr. Ginsberg stated that a national campaign to increase awareness and to focus on FH as a different kind of hypercholesterolemia is clearly needed.

Dr. Sijbrands agreed that many of the people in the US with FH probably are being treated, but that the US data to be gained from the registry and from screening are needed to confirm that they are being treated, and treated adequately.

Stacey Lane, JD, of New York is an attorney and an FH patient advocate whose FH was identified when she was very young. She spoke of her good fortune in receiving early diagnosis and successful treatment and said that she would hope that the same could be extended to other people with FH. She noted the need to let people know that FH is different from acquired hypercholesterolemia, and that there are life-saving treatments available.

Dr. Sperling next asked Dr. Sijbrands to discuss the criteria for predicting FH in children, and the appropriate ages to screen and to initiate treatment in the pediatric population. He asked in particular whether the NHLBI guideline, to check lipids in children at age 10, is appropriate.

Dr. Sijbrands responded that the criterion of LDL-C ≥3.5 mmol/L (135 mg/dL) for diagnosing FH in a child who had one parent with definite FH was based on 1034 children with FH parent(s) who were brought to the Pediatric Lipid Clinic. Their ages ranged from 2 to 19 years. Although, he said, genetic screening for FH could certainly be part of newborn screening, or performed during visits for routine immunizations, the problem was that neither efficacy nor safety data for treating children are complete. He called for a worldwide registry for children being treated, to learn whether such treatment is really safe for children. Dr. Sijbrands noted that there are two possible approaches, in deciding how early to begin treatment for pediatric FH patients: There are lipidologists who begin treating children with FH at age eight, and there are some trials that support that. The other approach is to wait until the child is 18, and then only treat those from very high-risk families. If the first approach is taken, treating all affected children from age eight, then screening as part of an immunization program may be convenient because it is early but not too early.

Dr. Ginsberg asked Dr. Hong of the CDC and Dr. Gordon of the NHLBI to comment on how best to engage their respective organizations’ support of a national FH initiative. Dr. Gordon noted that, although in a challenging fiscal environment, the NHLBI is working to leverage its investment by
collaborating with the activities of foundations (like the FH Foundation) and others. The Institute also wants to support embedding clinical trials in population studies such as the new Cascade FH registry.

Dr. Gordon spoke of the difficulty of developing treatments for patients with HoFH, because of its rarity, but noted that, in the case of HeFH, the potential is rich for clinical trials – not only with surrogate endpoints – based on the FH patients who can be screened and identified in the registry.

Dr. Hong observed that, whereas the NIH is focused on knowledge discovery, the CDC is more concerned with health knowledge dissemination, intended to educate the public and policy makers.

Asked by Dr. Ginsberg if there is a way to connect the FH public health initiative to the Million Hearts Initiative (MHI)\(^1\), Dr. Hong pointed to the MHI’s use of publications, press releases, and various social media, suggesting that FH could be featured in the MHI educational campaign as an example of a different type of hypercholesterolemia.

Dr. Sperling referred to Dr. Sijbrands’ mention of the need to train physicians and asked him to explain. Dr. Sijbrands observed that there was no need to train such experts as those gathered at the Summit, but that primary care providers do need to be educated about FH. To illustrate his point, he related the experience of one of his longstanding FH patients, who had presented at his outpatient clinic a few weeks earlier. Because her lipid levels had been on target for 10 years with only a 40 mg dose of simvastatin, he had told her that going forward, her general practitioner (GP) could manage her treatment, and he shook her hand goodbye. Yet she very soon returned to Dr. Sijbrand’s clinic to tell him that her GP wanted to stop the statin treatment because (the GP informed her) she had been “treated long enough and he considered me cured.” Dr. Sijbrands stated that there must be websites, books, and symposia, not for the lipidologists but for the GPs and other physicians who are likely to be the first point of care for people with FH.

Noting that in the Dutch national program, 75% of people with FH had been identified in 10 years, Dr. Sperling asked Dr. Sijbrands if there was a way to cut that time in half in the US. Dr. Sijbrands responded that successful screening will come down to obtaining funding and reimbursement of the cost, and he praised the FH Foundation which is taking some of the first steps toward achieving those goals.

Dr. Sijbrands strongly emphasized the need for US data, noting that the FH Foundation must obtain funding for simple research, which will establish the prevalence of FH and also help to elucidate how many patients are already treated with statins. He also emphasized the need for a strong lobby to convince the federal government that FH is not only a serious disease, but that continuing to do nothing results in an unnecessary economic burden, while finding and treating FH patients will lead to a large cost savings.

Dr. Gordon said that the existence of a US registry that has already identified and recruited subjects with FH will be a tremendous platform for clinical trials and other hypothesis-driven research, which are the greater focus of the NHLBI. Because the registry will provide assurance that the necessary patients

\(^1\) a public-private sector initiative launched in 2011 by the Department of Health and Human Services [HHS] to increase US awareness of how to prevent heart attacks and stroke\(^1\)
can be recruited, the FH research should be well received by the NHLBI. He also noted that as researchers learn of the registry as a resource, it could become a stimulus for investigator-initiated research, which is increasingly an area of emphasis for the NHLBI.

Dr. Ginsberg spoke to the need to work with the professional associations, although he considered that it may not be necessary to take the FH message to such cardiology-based associations as the American Heart Association (AHA) or the American College of Cardiology (ACC). He recommended that to reach the family physicians and generalists who see the patients first, there should be outreach to the pediatric societies—the American Academy of Pediatrics has been very involved with the question of how to manage FH in children—and to the generalists represented by, for example, the American Medical Association and the American College of Physicians.

Dr. Ginsberg also talked about the different profiles of patients with FH, and the impact that such differences have on when and how aggressively the patient will be treated. Dr. Ginsberg noted that as a lipidologist practicing in New York City, his impression is that an FH patient with an LDL of 300 mg/dL, even if FH is not identified, will receive medical attention and treatment with at least one drug. He voiced more concern for people who present at age 40 or 45 with LDL-C levels of 160 - 200 mg/dL and a various risk factors that could account for the elevated cholesterol level, regardless of FH. His sense is that such patients, even when it is discovered that they have FH, are likely to receive only one drug, achieving a 35%-45% reduction in LDL-C that pleases the physician and the patient; however, treatment to that level fails to take into account the cumulative effect of the patient’s lifelong burden of cholesterol. Dr. Ginsberg noted that identifying FH in this group and then treating them to attain a target LDL-C of less than 100 mg/dL will probably have the greatest benefit over the next 20 years, in terms of MIs prevented.

Dr. Sperling’s last question for the Session I panelists was, what are going to be the challenges, specific to the US, of conducting such a registry and program of screening and treatment; and secondly, what are the opportunities to make a difference?

Dr. Gordon of the NHLBI noted that there would be challenges getting complete registration of patients with the US system of healthcare compared with the Netherlands and some other European countries. Dr. Hong of the CDC agreed, having spent some years in Europe including in Rotterdam, that an FH program in the US will be challenged by the variable nature of its health care systems. He is hopeful that the development of a national health record will improve the access to data that helps to find and treat FH patients.

Session I – References

8. State Public Health Actions to Prevent and Control Diabetes, Heart Disease, Obesity and Associated Risk Factors and Promote School Health. Center for Disease Control and Prevention (CDC). (Accessed October 22, 2013,
Session II
WHAT DIAGNOSTIC CRITERIA FOR FH WOULD HAVE THE GREATEST PUBLIC HEALTH IMPACT?

Even among the world’s leading treatment centers and most established national screening programs, the various published criteria used to diagnose FH differ in ways that can be confusing for clinicians and confounding when attempting to analyze data across studies. The objective of Session II was to consider the strengths and weaknesses of various published diagnostic criteria in order to determine which would have the greatest public health impact.

Introducing Session II, moderator Daniel Rader, MD, (Division of Translational Medicine and Human Genetics, University of Pennsylvania) noted that the point of Session II was to explore the meaning of an FH diagnosis, given the goal of identifying large numbers of people in the US who would benefit from earlier and more aggressive treatment. He asked the participants to make the session into a practical, real world discussion rather than an academic one, as they considered a critical question: Is high cholesterol enough to make the diagnosis or are other criteria necessary?

1 Session II – Katrina Goddard, PhD
EGAPP Knowledge Synthesis Center: Systematic Review of FH Diagnostic Criteria and their Impact

Katrina Goddard, PhD, (Centers for Health Research, Kaiser Permanente Northwest: the EGAPP Knowledge Synthesis Center [KSC]) noted that the KSC has worked with the EGAPP Working Group for several years, supporting the Working Group’s charge to commission and conduct extensive reviews of evidence to ensure that it is adequate to inform EGAPP’s recommendation statements.

Dr. Goddard, whose background is in genetic epidemiology, explained that she and the co-director of KSC, Dr. Evelyn Whitlock, focus on synthesis of evidence from the medical literature. She noted that her presentation at the FH Summit was the result of a joint effort by the KSC and the EGAPP Working Group.

Dr. Goddard noted that, in simple terms, the ultimate goal of an FH screening program is to differentiate between people with FH and those without, allowing interventions for patients with FH and cascade screening of their family members, in order that affected individuals achieve better health outcomes. The first step of the process, and the focus of the KSC’s work on FH, has been to determine how best to identify the people with FH in an unselected population. She said that the KSC’s early work was confounded by the lack of a case definition of FH. The varying use in the literature of clinical and molecular diagnoses meant that among different publications, not everyone in whom FH-associated genetic mutations were found had high cholesterol, and not everyone with high cholesterol levels had a mutation. With the results to date of the EGAPP/KSC systematic review, Dr. Goddard noted, it remains uncertain whether the screening program should be designed foremost to find individuals with FH-associated mutations regardless of their cholesterol levels, or to find individuals with high cholesterol, whether or not they had a known mutation.
Dr. Goddard noted that the current effort to devise a public health program in the US to identify and treat persons with FH is comparable to efforts to implement Lynch Syndrome (LS; formerly hereditary nonpolyposis colorectal cancer [HNPCC]) screening five years ago. As with FH, more than one set of clinical criteria were in use for LS, variously based on family history, age of diagnosis, gender, and tumor type and histopathology. Genetic confirmation on the basis of germline mutations in certain mismatch repair (MMR) genes had also become possible. She explained that, in screening for LS, progress was made when there was acceptance of genetic testing. The clinical case definition was redefined when molecular diagnostics were accepted and standardized by the clinical community.

With FH, said Dr. Goddard, the published criteria in common use — MEDPED\(^1\), the Simon Broome criteria,\(^2\) and the DLCN criteria\(^3\) — each require different features to make a diagnosis of FH, and they do not completely overlap. She noted that the only two criteria common to all three tools are the LDL levels and CVD history of first degree relatives. DNA mutations do figure in the Simon Broome and the DLCN criteria, but not in MEDPED, while only the MEDPED criteria include third-degree relatives. Dr. Goddard and her colleagues in the KSC were able to create some hypothetical cases and found that they got a different answer as to whether the patient had FH or not, depending on which criteria were used: a person might be defined as having FH by one of the three sets of criteria, but not by another. Dr. Goddard cited the following as potential consequences of screening without a standard case definition:

- At the clinical level, uncertainty among medical professionals leads to lack of action
- At the evidence level, disparate studies cannot be compared to determine which components of screening will result in best outcomes
- At the system level, early implementation of a screening program not supported by good evidence may result in poor identification of cases at high cost, and early cancellation of the program.

As an evidence-based means of identifying the best FH screening tool, Dr. Goddard and her colleagues are conducting a systematic review. The value of a systematic review—that is, synthesizing the results of several studies that meet pre-specified criteria—is that the process is transparent and can be replicated, and that it is designed to minimize bias.

Even with their search carefully focused on studies of FH criteria and case definition, the KSC group reviewed abstracts for more than 2400 records found from databases and other sources, which they narrowed down to 33 studies with direct relevance to any of three pre-specified questions:

1. How well does molecular diagnosis predict LDL cholesterol level in an unselected population and also in first degree relatives of FH cases? (10 relevant studies were found.)

2. How well does each set of diagnostic criteria for FH predict patient-relevant health outcomes? (15 relevant studies were found.)

3. What is the concordance among the different criteria of FH diagnosis, in FH index cases and in first degree relatives of FH cases? How common is it to get different answers for the same
patient, depending on which criteria are used? Or did the criteria give the identical answer? (10 relevant studies were found.)

Regarding Question (1), Dr. Goddard noted that geneticists have come to recognize that an individual with a phenotype such as high cholesterol or a cardiovascular event may represent an extreme subset of mutation carriers, or may simply fit within the distribution of hypercholesterolemia and/or CV events in an unselected population. Part of the KSC’s systematic review is to examine the theoretical distribution of LDL-C in an unselected population and to assess the utility of a molecular diagnosis in predicting LDL-C levels in a population of mutation carriers vs. non-carriers; in a population of known relatives of FH index cases; and in a population of unselected mutation carriers. As of Dr. Goddard’s presentation on September 19, 2013, the systematic review had found nine studies with data on the distribution of cholesterol levels in first degree relatives; five of the nine were excluded because they included patients already in treatment. Only one study of LDL-C distribution in an unselected population had been found; however, it did not address the most common LDLR or ApoB mutations. **There remained only four studies that may be useful in addressing the distribution of cholesterol levels among first degree relatives of FH index cases.**\(^9,11,22,23\)

Dr. Goddard warned of a potential source of selection bias in that most of the studies that met systematic review criteria excluded patients already receiving cholesterol-lowering treatment, possibly resulting in patients with the highest pre-treatment LDL-C being missed in determining the distribution.

Regarding Question (2), studies that looked at how criteria predicted patient outcomes were difficult to combine because they looked at different outcomes. **Dr. Goddard and her colleagues have found direct evidence correlating only two criteria with various cardiovascular-related outcomes** (e.g., all-cause mortality, CVD mortality, MI, CVD, CHD, revascularization, number of coronary arteries with $\geq$ 50% stenosis, angioplasty). Four studies examined outcomes by genetic mutation (molecular diagnosis).\(^15,24-26\) Three other studies examined outcomes by patient scores on the Simon Broome criteria.\(^20,27,28\) She noted that the evidence from these studies is limited due to the relatively small sample sizes of most of the studies, and due to the difficulty of combining results across studies reporting so many different outcomes.

Another category of evidence was that of studies that used diagnostic criteria other than MEDPED, DLCN, or Simon Broome. So far, Dr. Goddard noted, it has been possible to map the “other” FH definitions back to at least the **clinical criteria** from one or more of the three named definitions, and the KSC has found many other studies like these that may help answer the question of how the various criteria differ in terms of predicting outcomes.

Regarding Question (3), Dr. Goddard stated that she and her colleagues have found **no direct comparisons relevant to the question of concordance among the different FH diagnostic criteria.** However, she noted, there are many studies that look at correlations between the clinical criteria and a molecular diagnosis, and the KSC’s planned analysis of these should provide some evidence to inform the level of concordance among the various FH criteria.
In summing up, Dr. Goddard spoke again to the value of a systematic, evidence-based approach to support clinical translation. Citing the limited evidence with which to compare the various FH clinical diagnostic criteria, she reiterated her view that a standardized case definition, subjected to the same level of assessment as criteria published earlier, is the necessary first step in a successful screening program for the US.

In closing, Dr. Goddard observed that, given the different context presented by the US healthcare system compared with national systems in the UK, Spain, or the Netherlands, a “one size fits all” approach to FH screening — attempting to use the same screening program that worked in, for example, the Netherlands — may not work in the US.

### 2 Session II – Raul D. Santos, MD, PhD
#### Comparing sensitivity and specificity of the Simon Broome and DLCN criteria in Brazil

**Dr. Raul D. Santos** (Director, Lipid Clinic, Heart Institute (InCor), University of São Paulo Medical School Hospital, Brazil) addressed the FH Summit on behalf of researchers at InCor who are evaluating the performance of the DLCN, Simon Broome, and MEDPED criteria in identifying Brazilians with or without FH causing mutations. As the analysis of their MEDPED data is pending, he explained that his presentation would be limited to the assessment in a Brazilian population of the DLCN and Simon Broome criteria.

An FH screening program has been in operation at InCor since 2010, and there are FH treatment guidelines, educational programs, and supportive family organizations in place.²⁹ Dr. Santos spoke of the challenge of finding all of the estimated 350,000-400,000 FH cases among the entire population of Brazil, but he expressed hope that the screening program, a campaign to improve FH awareness, and more readily available statins at lower costs will offer help to many more Brazilians with FH in future.

Dr. Santos reported that, as no clinical criteria have yet been validated to diagnose FH in a Brazilian population, researchers at InCor are evaluating the performance of the DLCN and Simon Broome criteria in the identification of Brazilian subjects with FH causing mutations versus those without such mutations. He noted that a total of 250 suspected FH index cases and 377 relatives were evaluated and FH mutations (LDLR, ApoB, or PCSK9) were found in 50.8% of index cases and 59% of relatives.

Dr. Santos reported that from January 2010 – August 2013, approximately 1500 patients were screened at InCor. Among those screened, 601 index cases and 963 relatives were identified. Of the 963 relatives, 477 (46.4%) had FH mutations and 466 (48.4%) had no mutations. Currently, he noted, a total of 155 families are being screened, and 76 mutations have been found.

Dr. Santos and his colleagues at InCor are cooperating with the SAFEHEART program in Spain,³⁰ systematically obtaining the same demographic information and clinical characteristics, and administering the same questionnaires about lifestyle, diet, and cardiac risk factors to all subjects.
screened for FH. By so doing, they will be able to share data between the Spanish FH cohort and the cohort of subjects identified in Brazil (the HIPERCOL Brasil population). The information gathered from each person screened is also adequate to allow calculation of the subject’s respective FH scores based on MEDPED, Simon Broome, and DLCN criteria.

At the time of Dr. Santos’s presentation, the InCor team had evidence available from 250 suspected FH index cases, all of whom had been genotyped. Testing was for mutations in LDLR, ApoB, and PCSK9. Of the suspected index cases, 127 (50.8%) were found to have mutations. Of 76 different mutations found in this first dataset, most were of the LDL receptor. Dr. Santos estimated that there were three or four patients with ApoB mutations, and two or three with PCSK9 mutations. Publication of information from this first dataset, which was closed a few months before the Summit, is pending.

From the first dataset of the HIPERCOL Brasil population, Dr. Santos showed preliminary data on the clinical and laboratory characteristics of index cases with mutations (n=127) and without mutations (n=123). He noted that females comprised 61% and 69%, respectively, of the group with and the group without FH mutations; perhaps this is due to greater concern among women about health issues.

There appeared to be little difference between the subjects with and those without FH mutations, with regard to the average BMI or the percentage of subjects who had hypertension, diabetes, or early CHD. Dr. Santos pointed out that the average LDL cholesterol levels for those who had mutations and those with no mutations were 328 mg/dL and 224 mg/dL, respectively, for subjects not taking medications; and 190 mg/dL and 150 mg/dL, respectively, for subjects who were taking medications.

In Dr. Santos's preliminary data, the average total cholesterol and LDL-C were significantly higher, and mean HDL-C was significantly lower, among the subjects found to have FH mutations than among those with no FH mutation found; the relative differences in TC, LDL-C, and HDL-C remained true when the subjects were stratified according to whether they were on treatment for high cholesterol or not.

As Dr. Santos pointed out, it would be ideal to have only subjects who are naïve to cholesterol lowering medications when considering the different criteria. He noted, however, that the reality is that undiagnosed FH patients often do have a diagnosis of hypercholesterolemia and are treated for it, which, if the doctor does not suspect FH and does not think of checking the patient's family, is a problem in Brazil and probably everywhere else.

Dr. Santos noted that the first dataset revealed a lower prevalence of smokers among the subjects who were found to have mutations — about 5.6% vs. 15.4% of the subjects with no mutations. Only 8.5% of the subjects with FH mutations and none (0) of the subjects without mutations had tendinous xanthomas. Given the low prevalence of xanthomas in this group, Dr. Santos observed, an FH score that includes a criterion relating to presence of xanthomas in the index case or the families may have the effect of making the diagnosis more difficult. One other interesting finding was that the percentage of subjects with CHD was nearly twice as high among those with no mutation (23.6%) as among those with a mutation (12.6%).
In looking at the performance of different FH criteria in scoring subjects from the HIPERCOL Brasil population, Dr. Santos emphasized that the data he was presenting at the Summit were preliminary and represented a very small segment of Brazil’s population. Of the 250 suspected index case subjects, a fairly large proportion did not complete the questionnaires, roughly 30% of those with, and 26% of those without a mutation. He explained that early results based on performance of the Simon Broome and DLNC criteria were available, and that the test of MEDPED criteria would require data from many more patients.

Dr. Santos looked first at analysis of DLNC scores for the sample of 250 suspected index cases from the HIPERCOL Brasil population. Among the 127 subjects found to have a mutation, the early data have shown that that with each incremental range of DLNC scores, the percentage of mutation-positive subjects appears also to increase: approximately 13% of mutation-positive subjects scored in the range of 3 – 5 points (possible FH); 24% scored 6 – 7 points (probable FH); and 39% scored 8 or more points (definitive FH). He noted an inverse trend among the 123 subjects with no mutation: the higher the range of DLNC scores, the fewer mutation-negative subjects with a score in that range.

Dr. Santos pointed out that the one DLNC category with notable overlap between the two cohorts was in the range of 6 – 7 points (probable FH), which accounted for the scores of 24% and 23%, respectively, of the mutation-positive and –negative subjects.

In applying the Simon Broome criteria to derive scores for the 250 subjects, the preliminary data suggest high specificity but lower sensitivity. Just 6.3% of the mutation-positive subjects had scores classified as definite FH, in comparison with none (0) of the mutation-negative subjects. As with the DLNC scores, the two cohorts’ Simon Broome scores showed notable overlap in the category of probable FH, which accounted for the scores of 47% and 45%, respectively, of the mutation-positive and –negative subjects. He noted that the high specificity of the Simon Broome criteria was also suggested by the high percentages scored as no FH — 11% even among the subjects with a known mutation, and 48% of mutation-negative subjects.

Based on the subjects’ DLCN scores, Dr. Santos and his colleagues are finding that as the number of points increase and the scores move from one category of FH probability to the next, specificity increases but sensitivity is reduced. In their preliminary data, definite FH using the DLCN criteria had a sensitivity of only 0.43 and a specificity of 0.87. For the Simon Broome criteria, the category of definite FH had excellent specificity (1.0), but very low sensitivity (0.097).

Dr. Santos noted that their analysis was complicated by the low number of subjects scored in the definite category of Simon Broome, and that the results will possibly change with greater numbers. But considering the DLCN criteria’s better tradeoff between sensitivity and specificity, especially for subjects with scores in the category of probable FH, he observed that the DLCN score performed a little better.

Dr. Santos listed the following as important points to consider in weighing the early results of the HIPERCOL Brasil test of DLCN and Simon Broome:
Only suspected index cases were evaluated
Not all information was available for all patients (30% of mutation positive and 26% of mutation negative individuals did not respond)
They used the highest recorded cholesterol level to calculate the score
61% of the HIPERCOL Brasil sample were already taking statins, which reduced the power to test the performance of the different criteria

Dr. Santos noted that their index cases’ family members must still be tested, and that much more data are needed, especially to test the performance of the MEDPED criteria in Brazil. He suggested that the great strength of MEDPED may be that it can be used to identify many more people with FH, more simply, being based on lipid levels easily measured by GPs and other non-specialists.

He pointed out that while the HIPERCOL Brasil screening program is probably the largest in South America, the vast size of Brazil requires that screening occur in other regions, in order to accurately estimate FH prevalence there. Although he is not aware of founder effects in Brazil, Dr. Santos observed that they could exist, for example, in isolated communities, another reason to expand the search for patients to other regions.

Even with the small sample size, Dr. Santos was able to report that, to date, both the DLCN and Simon Broome criteria seemed to result in scores for the HIPERCOL Brasil suspected index cases that are similar to those reported for populations in the UK, Norway, and The Netherlands. He concluded that both the DLCN and Simon Broome scores perform and can be used to diagnose FH in Brazilian populations.

However, he thinks the DLCN criteria performed somewhat better, based on their apparent greater sensitivity in the sample of Brazilian cases. The idea is to find more patients, Dr. Santos said, and it is better to diagnose more people and over treat, than to undertreat.

Session II – Panel Discussion

Moderator: Daniel Rader, MD, PhD
Faculty: Kristina Goddard, PhD (EGAPP Knowledge Synthesis Center); Raul D. Santos, MD PhD (InCor, Brazil)
Panelists: Paul Hopkins, MD, MSPH (US, MEDPED), Patrick M. Moriarty, MD (University of Kansas, FH Foundation Scientific Advisory Board); Anthony Wierzbicki, MD (UK, Chair of the Lipid Modification Guideline Development Group at NICE -- UK, Simon Broome)

The panel’s moderator, Dr. Daniel Rader, began by asking the panel members’ thoughts on whether sensitivity or specificity should be maximized in a case definition to be used for FH screening in the US.

Dr. Katrina Goddard suggested that the answer depends on whether the goal is to treat patients, in which case finding the people with the clinical characteristics is paramount, or to do cascade screening of relatives, in which case, she said, a molecular diagnosis is necessary.
Dr. Anthony Wierzbicki observed that when the National Institute for Health and Care Excellence (NICE) performs systematic review of guidelines, there is always a tradeoff between sensitivity and specificity. He pointed out further that if an optimal point is chosen on the basis of a ROC curve, that curve is based on a given population, and the question becomes how that point will vary by country or by region. Dr. Wierzbicki noted that with FH, it is the LDL-C that determines the patient’s phenotype, and the phenotype that drives the atherosclerotic risk. While acknowledging the value of being able to perform genetically-based cascade screening, he pointed out that it is also possible to cascade on the basis of lipids. The Simon Broome and NICE criteria, as well as the European systems, said Dr. Wierzbicki, recommend both approaches, because the group with a genetic mutation may have a higher risk of future events, but there still remains an excess cardiovascular risk in the non-monogenic group.

Dr. Paul Hopkins (MEDPED) noted that the MEDPED criteria consider DNA when available, in addition to the lipid cut points summarized in the American Journal of Cardiology. He noted that the MEDPED score, as published by the World Health Organization in 1998, includes definitions for definite, probable, and possible FH, and by those definitions, the presence of a genetic mutation constitutes a definite case.

While he was addressing the Summit and panelists, Dr. Hopkins added, he wished to express his strong wish for automated, patient-oriented, and possibly web-based systems that could allow patients themselves to get a reliable preliminary diagnosis.

Dr. Rader next asked the panel to discuss whether, in moving forward with a US screening program, the case definition should include stratifications of definite, probable, and possible FH.

Speaking for experts such as those present at the Summit, Dr. Patrick Moriarty pointed out that, “We know it when we see it,” and he voiced his concern that stratification of the diagnosis would benefit neither patients with possible FH nor the new US-based registry. In order for the registry to capture patients through self-enrollment, said Dr. Moriarty, the criteria must be as simple and clear as possible, so that people can determine whether or not they might have FH.

Dr. Goddard noted that diagnostic stratification would be important, if patients are to receive different advice depending on their levels of FH certainty, but if treatment and the extent of cascade screening is to be the same for all patients who meet any diagnostic criteria, then stratification is unnecessary.

Regarding the issue of patient self-diagnosis, Dr. Wierzbicki noted the experience of the British (Simon Broome) and Dutch programs that, while large numbers of cases are identified when patients present at lipid clinics, cardiology services, or primary care, many people either resist screening or are missed completely. He stressed the importance of asking about personal or family history of early onset CHD as a means of persuading people to have their lipids checked. He also pointed out that clinicians should be taught to lower the cut off of LDL-C for
suspected FH by an average of 40 mg/dL, when the patient or a first-degree relative has had a premature cardiovascular event.

**Dr. Hopkins** agreed, noting that the MEDPED criteria use the same approach. He recommended a recently published update regarding ideal LDL-C cut points for the British population,22 saying that given the changing US population, MEDPED should be updated as well. With regard to diagnostic stratification, Dr. Hopkins noted that, absent such “hard” findings as tendinous xanthoma or a DNA diagnosis, clinicians can probably not do better than a diagnosis of probable FH.

**Dr. Rader** asked whether some positive family history is absolutely required for the diagnosis of FH.

**Dr. Santos** responded that, although family history may facilitate the diagnosis, it may not occur to the patient or doctor whose concern is focused on a measurement showing high cholesterol. Or the patient may be adopted, or estranged from the family, or just not privy to health-related information about family members.

Dr. Santos directed a question about diagnosis of FH in patients with very early subclinical CVD and lipid levels as the only risk factors, to Dr. Wierzbicki

**Dr. Wierzbicki** responded that the stratification of FH scores by LDL-C level is an important strength of the Dutch criteria. He explained that if the patient’s LDL-C is in the top quartile (LDL-C >330 mg/dl [8.5 mmol/L]), the chance of finding a DNA mutation is greater than 50 percent, even with no other clinical or historic criteria. Further, he said, the chance of a mutation remains fairly high in the next lower quartile (LDL-C 250-329 mg/dl [6.5 – 8.5 mmol/L]), so that an LDL-C measurement within the top two levels predicts very high yield from genetic testing, which provides a definitive diagnosis. He concluded that very high LDLS should prompt screening for FH irrespective of any other criteria, adding that family history contributes more to the diagnosis at the lower levels of LDL-C.

Dr. Wierzbicki also spoke briefly about the diagnostic contribution of imaging evidence of atheroma, saying that it is currently a research tool and not yet ready for clinical use.

**Dr. Paul Hopkins** noted that only the MEDPED criteria incorporate lipid data from the patient’s family members, to make the determination of FH in that patient. He noted that the estimated probability of FH for one person who has TC of 280 mg/dL is greater when the individual has a family member with TC of 240 mg/dL, versus when all the individual’s relatives have very low cholesterol. In the latter case, Dr. Hopkins said, the question of FH in the first person becomes complex, and tools are needed to automate the calculation.

Dr. Rader turned to the question of applying the published FH criteria to children.

The panel members agreed that relevant data are sparse. **Dr. Hopkins** said he is aware of a publication based on the members ages 1 to 25 years of a single Finnish pedigree concentrated
in an area with high FH prevalence. DNA verification was used to show that MEDPED LDL-C cut offs alone would have resulted in sensitivity of 93% and specificity of 98%.31

**Dr. Wierzbicki** emphasized that the LDL cut points, in terms of diagnosing FH in children less than 16 years of age, should be approximately 50 mg/dL lower than for adults. He noted that researchers have looked closely at the peak sensitivity for screening children,32,33 and have demonstrated that, if there is to be a child-based screening policy, then screening at age six of lipid levels alone will provide a yield equal to using any of the published criteria.

**Dr. Rader** asked the panel to consider the practical importance of having a diagnosis of FH; that is, in terms of getting the patient appropriately treated and screening the family, what is the importance of telling the patient “you have FH” versus “you have high cholesterol and need treatment?”

**Dr. Moriarty** said that explaining to his patients that they had FH seemed to help them, because often the FH patients led a healthy lifestyle and were confused about needing treatment for high cholesterol. Learning that there was a genetic component to their disease allowed them to move ahead with managing it.

**Dr. Wierznecki** added that informing patients of their diagnosis provides the ability to screen the rest of their relatives. He noted that patients find it very empowering to learn that they can help family members receive early diagnosis and treatment. He also noted that the patients personally benefit, because with the certainty of their diagnosis, their adherence to treatment improves: they are more likely to receive the appropriate intensity of treatment; and they may also gain access to additional medications not available for general use in some health systems.

**Dr. Goddard** commented that providing the patient with a diagnosis of FH, even if it does not have an impact on the treatment of the particular patient, is very important from a population perspective, because it allows cascade screening and early treatment and disease prevention for the family members.

Panel members concurred with Dr. Rader that they would like to see more PCPs actually say to the patient, “you have FH.” He expressed concern that if a case definition is implemented that is too complex, physicians are less likely to use it or to provide patients that diagnosis.

Dr. Rader next asked the panel what the possibilities were of having an ICD code assigned for FH.

**Dr. Moriarty** noted that an ICD10 code would probably be related to lipids or to the LDL-C level rather than to the combination of clinical features, etc., so that, he said, the question becomes what the defining LDL level will be.

**Dr. Hopkins** pointed out that depending on the LDL-C level chosen, patients would either be missed who have the disease, or would be diagnosed with FH wrongly. He noted further that physicians in a clinical setting are not in a position, nor do they have time, to obtain family data.
Rather, he said, the patients are the ones who, once having received the diagnosis, will approach their family members and bring them in for screening.

**Dr. Rader** rejoined that, in terms of helping the most people, it may not matter if a group of people are diagnosed as having FH based on LDL-C, even if they do not have an identifiable mutation. **He added that many people have clinical FH, in whom a mutation has not been found.**

**Dr. Peter Kwiterovich** (Johns Hopkins) asked that the audience consider the large body of evidence in support of screening children of school age, and also NIH criteria based on data showing general screening greatly increases the chance of identifying children with FH. He expressed the need to take an aggressive approach to screening children, providing the earliest opportunity to treat them.

### Session II – References

5. Leren TP, Finborud TH, Manshaus TE, Ose I, Berge KE. Diagnosis of familial hypercholesterolemia in general practice using clinical diagnostic criteria or genetic testing as part of cascade genetic screening. Community Genet 2008;11:26-35.
Session III

ENHANCING FH SCREENING EFFORTS: FINDING THE INDEX CASE

Presenters and panelists in Session III discussed the most appropriate and cost effective FH screening models, considering whether protocols are justified or not depending on the sample population’s demographic profile, the means of identification, and the likelihood of pre-selection on the basis of medical history, treatment, or healthcare provider.

Moderator Debra Duquette, MS, CGC (Michigan Department of Community Health, Lansing) introduced the session by noting that the CDC’s classification of FH as a Tier 1 application led to the Michigan Department of Community Health beginning to address FH in her state. She said further that in light of the 2011 NHLBI/American Academy of Pediatrics (AAP) integrated guidelines for cardiovascular risk reduction in children, policy has been drafted that will mandate dyslipidemia screening of all children ages 9 – 11 years who are Michigan Medicaid recipients.

1 Session III – William A. Neal, MD

Successful Implementation of a Universal Screening Program

Dr. William Neal (Professor, Pediatric Cardiology, R.C. Byrd Health Sciences Center, West Virginia University; CARDIAC) opened his presentation by crediting the CDC with recognizing FH as a public health issue many years ago. He explained that a modest ($50,000 per year for two years) Prevention Research Center (PRC) grant awarded by the CDC in 1998 (“Familial Hypercholesterolemia – a Model Program for States”) enabled the initiation of the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Program at West Virginia University. Fifteen years later, CARDIAC continues as a state government-sponsored program of screening, with simultaneous referral and intervention efforts, conducted at public schools in every county of West Virginia; they have screened more than 81,000 children ages 10 – 12 years for cardiovascular and diabetes risk factors.

According to Dr. Neal, the initial goal of CARDIAC was to reduce CVD in West Virginia through research intervention in children. As the researchers realized the extent and implications of the obesity epidemic in Appalachia, the CARDIAC program was broadened to include screening for diabetes and other chronic illnesses. CARDIAC was piloted in three counties where individual healthcare providers agreed to be “champions” working for local acceptance of the program. By 2005, all of the state’s 55 counties were participating. He noted that the CARDIAC program now offers cardiovascular screening to all of the state’s fifth grade students, approximately 20,000 children per year, ages 9 to 11.

Dr. Neal described the operation of a typical CARDIAC school visit: At each visit, a team of healthcare providers and local volunteers measures each child’s height and weight (privately) to determine body mass index, blood pressure, blood cholesterol, glucose, and insulin. They examine the back of the neck for Acanthosis nigricans, calculating a homeostatic model assessment (HOMA) if the pigmentation is present. Screening results are sent home to the parents with recommendations for lifestyle changes or, if warranted, referral to a children’s lipid clinic. If the parents have provided permission, a report is also
sent to the child’s primary care provider. The parents of screened children are also eligible for free screening; as they rarely can be present at the school visit, they are offered a voucher to have labs drawn at a local LabCorp site, any time within the following month.

Dr. Neal noted that the CARDIAC program is highly dependent on the logistical support of school nurses and local area coordinators. When CARDIAC was started, health science students in the West Virginia Rural Health Education Program (RHEP) were required to complete several months of rural rotations, and so were often in place to assess the children and draw samples at the school visits. Since RHEP is now defunct, CARDIAC trains volunteers from the local community to serve as phlebotomists when none are available from the program’s staff.

Between 1998 and 2013, the CARDIAC program has screened 86,622 children. Dr. Neal noted that 28.3% of the CARDIAC participants were above the 95th percentile for BMI, versus the current national average of approximately 20%; and another 18.8% were in the 85th to 95th percentile. Noting that the total — 47% of children overweight or obese — has remained consistent over the 15 years that CARDIAC has been in operation, Dr. Neal added that the 23.2% prevalence of hypertension in the children has been almost invariably related to obesity. Of the 5.1% of children found to have Acanthosis nigricans, 38% had insulin resistance based on glucose and insulin or HOMA index.

Turning to the lipid data from 15 years of children screened in the CARDIAC program, Dr. Neal reported that 17.9% of the children have had HDL less than 40 mg/dL, and 7.5% have had LDL-C greater than 130 mg/dL. He added that for children above the 95th percentile for weight versus children of normal weight, the odds ratio for elevated total or LDL cholesterol was approximately two-fold, the odds ratio for low HDL cholesterol was greater than 5.0, and the odds ratio for hypertension was between two- and three-fold.

Citing a study of cardiovascular risk factor clustering in children assessed in the CARDIAC program between 1997 and 2006 (n=26,436), Dr. Neal noted that the percentage of children with elevated LDL-C was approximately the same across increasing weight categories of “overweight” (LDL-C elevated in 10.2% of children), “obese” (LDL-C elevated in 13.3% of children), and “morbidly obese” (LDL-C elevated in 11.4% of children), compared with LDL-C elevated in only 5.9% of children who were of normal weight or underweight. The data, he said, suggest that the impact of lifestyle or obesity on elevated cholesterol may “max out” past a certain degree of overweight, in contrast to continuous increase in prevalence of insulin resistance and pre-diabetic state with increasing obesity. The evidence, said Dr. Neal, leads him to believe that markedly elevated cholesterol is primarily due to genetic disease, and that while lifestyle has an impact, it is not a dramatic one. He added that the media have a tendency to talk about addressing the obesity epidemic as a whole with statins, which he called highly inappropriate.

Given the evidence that BMI and lifestyle alone are not reliable filters for screening children for dyslipidemia, Dr. Neal and colleagues at the CARDIAC program conducted a retrospective analysis comparing universal lipid screening of children versus targeted screening as recommended by the National Cholesterol Education Program (NCEP), that is, limited to children with a family history of
premature CHD or at least one parent with total cholesterol (TC) ≥ 240 mg/dL. The records of 20, 266 fifth-grade students whose family history was available and who had a fasting lipid profile were reviewed; 14, 468 (71.4%) of the children fulfilled the NCEP criteria, of whom 1204 (8.3%) were considered to have at least moderate dyslipidemia (LDL-C >130 mg/dL). Importantly, of the 5798 children who did not meet NCEP criteria for screening, 98 children had cholesterol levels above 160 mg/dL, the cut-off for consideration of cholesterol lowering medication in a child.

Dr. Neal reported that, **had the CARDIAC program relied on NCEP recommendations for targeted screening of children based on family history, many children who had moderate dyslipidemia would have been missed, as well as 37% of children with more severe dyslipidemias requiring pharmacologic treatment.** Another drawback to targeted screening is that the available family history is often inadequate to assess the NCEP criteria. In the CARDIAC program, he explained, the child’s family history is elicited from the parents or guardians via the consent form, which includes specific questions such as whether a parent or grandparent had had a heart attack that required hospitalization, bypass procedures, angioplasty, etc., and also asks whether anyone in the family has high cholesterol and if so, how high. However, Dr. Neal noted, many responders did not know whether there was hypercholesterolemia in the family, and often do not know their own or other relatives’ cholesterol levels, making it difficult to assess which children fulfill the criteria for family risk. Family history, he added, is often difficult to obtain due to high rates of divorce and single parenting; and the parents and grandparents of 10-year-old children may still be quite young and may not yet have had a cardiovascular event, even in a family with FH.

Dr. Neal and colleagues conduct monthly Children’s Lipid Clinics in four locations around the state. They follow the AAP 2009 guidelines and consider treatment if a child is at least eight years of age, has an LDL greater than 160 with a positive family history of premature heart disease (before age 55) or an LDL greater than 190. Some of these children are adopted, he noted, so it is not possible to assess the family history; in other cases there are additional risk factors such as obesity or pre-diabetes.

Over the years since starting the CARDIAC program, **the non-HDL cholesterol level in their subjects has decreased steadily and significantly, as is true for the US in general.** Dr. Neal acknowledged that it’s unclear whether this is due to the elimination of trans fats or some other factor or combination of factors, but it is a positive sign.

Dr. Neal presented data on pharmacologic therapy in their clinics from 1998 – 2013. He and his colleagues are currently following 76 children who have made 849 visits. The indications for treatment were non-success of 3 – 6 months of recommended lifestyle modification and an LDL-C > 190 mg/dL or > 160 mg/dL with comorbidity. **The target level of LDL-C <130 mg/dL was achieved in approximately 83% of cases. Failure to achieve this goal was usually due to non-compliance.**

Dr. Neal reported that partners from the Children’s Lipid Clinic, Adult Cardiology Clinics, and School of Pharmacy at West Virginia University have recently begun a program of cascade screening, enabled by internal funding through the WVU Clinical and Translational Science Institute. He said that the first cases
chosen for the cascade screening program — which received both grant and IRB approval just the week before the FH Summit — were 75 children from the Children’s Lipid Clinic who met the phenotypic diagnosis.

For the cascade screening program, Dr. Neal explained, the CARDIAC database was filtered for all children who had levels based on fasting lipid profiles (FLPs), excluding those from the early years of CARDIAC who had the less reliable finger sticks. Of the 52,293 children with FLPs, **111 children were identified with LDL-C > 190 mg/dL; 584 with LDL-C >160 mg/dL; and 4,011 with LDL-C >130 mg/dL.** Information is being sent to the families of these children in batches of only 50 letters at a time to allow efficient follow up with each family that responds.

Dr. Neal pointed out that many of the children with LDL-C > 130 mg/dL exhibit only mild elevations (135 – 140 mg/dL), and can be treated via lifestyle modification alone. The more immediate priority for the cascade screening program, he said, is to identify the children with extremely high levels, and then locate and screen their families. Dr. Neal concluded by noting that the cascade screening program has an excellent infrastructure comprising a research nurse and seven area coordinators. The coordinators are strategically located around the state where they can go into communities and reach the families, often at local hospitals or at a time and place convenient for the families, including on weekends if necessary.

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**2 Session III – Samuel Gidding, MD**

**Identifying Children and Adolescents with FH**

Dr. Samuel Gidding (*Division Head – Pediatric Cardiology, Nemours Cardiac Center, A.I. Dupont Hospital for Children; Professor, Pediatrics, Thomas Jefferson University*) presented the World Health Organization (WHO) criteria for disease screening:

- The condition should be an important health problem.
- There should be a treatment for the condition.
- Facilities for diagnosis and treatment should be available.
- There should be a latent stage of the disease.
- There should be a test or examination for the condition.
- The test should be acceptable to the population.
- The natural history of the disease should be adequately understood.
- There should be an agreed policy on whom to treat.
- The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
- Case-finding should be a continuous process, not just a "once and for all" project.
Dr. Gidding considered how well, in the case of FH, each WHO criterion is met. He argued that its latency period is probably one of the most compelling reasons to identify FH. There has been intense debate about which is the most appropriate test, but clearly, a test that can identify FH is available. There has been important discussion about the natural history of the disease, he noted, but by and large, this has been established. About 95–98% of the time, physicians caring for patients with FH are in agreement about which patients to treat, although there may be some disagreement about the age when treatment should start and what intensity of treatment is appropriate.

**Treating an individual with FH is extraordinarily cost-effective**, Dr. Gidding noted, but issues regarding the cost of identifying the cases have to be resolved.

Why screen children? Dr. Gidding described a study in which the Dutch FH group used ultrasound to compare age-adjusted carotid intima-media thickness (cIMT), an indirect measure of atherosclerosis, between 196 children with FH and 64 of their unaffected siblings.\(^{38}\) Clearly by age 11 or 12, he reported, the FH-affected children had significantly higher mean cIMT than the unaffected ones, indicating that in people with FH, atherosclerosis begins at a very young age. Dr. Gidding emphasized that an adult who has had an LDL of 170 or 180 mg/dL for a lifetime has a much higher risk of an adverse event than another adult whose LDL-C gradually reached the same level secondary to many years of poor diet or other lifestyle factors.

Noting the three screening options for FH — selective, universal, and cascade screening — Dr. Gidding explained that his focus would be on the first two options and how they relate to the NHLBI guidelines for cardiovascular risk reduction in children and adolescents, published in 2011,\(^{34}\) and also to the 2011 NLA guidelines.\(^{39}\)

Citing an NIH study of the distribution of LDL-C levels among children who had one parent with FH by Dr. Peter Kwitterovich and colleagues, Dr. Gidding noted that the results had shown a very clear bimodal distribution of LDL-C, with minimal overlap of levels, between FH-affected and non-affected children. **He noted that about half of the children with an FH carrier parent were also affected with FH, providing a very clear rationale for assessing any child with an affected parent.**

To investigate whether otherwise healthy children with high TC tend to have parents with TC exceeding acceptable levels established by the NCEP, Dr. Giddings and colleagues stratified 263 children ages 3–10 years into three groups — one group in which both the child’s parents had TC <200 mg/dL, one in which the parent with the higher value had TC = 200 – 239 mg/dL, and a third group, in which both parents had TC > 240 mg/dL. It was demonstrated that average TC among the three groups of children separated very cleanly in parallel with the three TC-based groups of the parents.

Dr. Gidding stressed that there are barriers associated with a model for screening that depends on accurate assessment of parental cholesterol and extrapolation to the children. Citing the inadequacy of preventive care in the US, he reported that in one study, half of the parents did not know their own cholesterol levels, making it even less likely that the children will be screened based on a parent’s high cholesterol. A further problem, he noted, arises because 40–45% of children in the US are born out of wedlock, and the parent with FH may not be in contact with the child.
Dr. Gidding expressed concern over recommendations to screen children for dyslipidemia based on family history, which he feels will miss children at risk. He pointed to a study conducted in the 1990’s in which researchers elicited family histories for children in a general pediatric practice, measured LDL-C in all of the children, and then stratified results by positive or negative family history of early onset-CVD. He noted that many children with no family history of CVD had elevated LDL-C, often as high as expected by age in FH, confirming that in a program of lipid screening limited to children with positive family history, several children with significantly elevated LDL-C would have been missed. Similar studies, Dr. Gidding said, ranging from those using large population-based databases to those conducted in individual lipid clinics, show almost exactly the same result, that 25–35% of affected children are missed by using family history criteria alone.

Dr. Gidding noted that the inadequacy of screening only children with positive family history was one factor leading to the 2011 NHLBI guidelines for children and adolescents. Using a model that combines recommendations from the NHLBI and NLA guidelines (both published in 2011), he urged that every child age 9 – 11 years should get either a fasting lipid profile or a non-HDL cholesterol. Within this age range, said Dr. Gidding, most children see a health care provider at least once; by this age, children with FH will begin to develop advanced atherosclerosis; and an LDL-C level > 160 mg/dL is consistent (for age) with FH. These guidelines have a “selective screening” component because they suggest screening any children age two or older if the child has a positive family history or other risk factor.

The NHLBI report considered LDL-C > 130 mg/dL to be high, which, Dr. Gidding observed, is still consistent with potential identification of FH. Not all children at that level will turn out to be affected, he noted; however, a subset would have FH, and using a 130 mg/dL cut-off to screen children for FH would have the advantage of being highly sensitive.

Dr. Gidding cited a meta-analysis done by Wald and colleagues to determine which parameter, TC or LDL-C, best discriminated between people with and without FH, and at what age. The meta-analysis comprised 1,907 FH cases and 16, 221 controls from 13 published studies, with subjects grouped in 10-year ranges from newborn to greater than 60 years. The results demonstrated (1) that the detection rate (sensitivity) was greatest in children age 1-9 years, with significantly lower rates of detection in both newborns and young adults, and (2) that LDL-C alone can readily be used to screen children for FH. Moreover, the authors concluded that once an affected child was identified, cholesterol measurement alone would detect about 96% of parents with FH, using the simple rule that the parent with the higher cholesterol was the affected parent. Dr. Gidding explained that the pediatric dataset in the meta-analysis generally comprised children with FH and their non-affected siblings. He suspected that, in the general population, estimates would be even more precise given the larger denominator for the assessment.

Dr. Gidding expressed his conviction that the best time to screen for FH is during childhood, and compared FH screening with colonoscopy in terms of addressing preventable morbidity and mortality.

Dr. Gidding presented results from a study of the impact of day-to-day variability on the ability to use a single lipid measurement to assess cardiovascular risk according to 1987 NCEP guidelines. Dr. Giddings and colleagues measured lipid panels three times in a week — Monday, Wednesday, and Friday — in 51 adult volunteers (hospital employees). There was significant day-to-day analytic variability, particularly in HDL-C and calculated LDL-C. Using confidence intervals constructed around the
NCEP cutoff points (in the 1987 guideline, <130 mg/dL was “desirable” and >160 mg/dL was “high”), suggested that classifying an individual’s risk from a single measurement of LDL-C was only accurate at levels < 116 mg/dL or > 174 mg/dL. The authors concluded that patients with borderline “good” or “high” levels, that is, near the NCEP cutoff points, may require repeated measurements to accurately assign risk.

As an aside, Dr. Gidding pointed out that as early as the 1992 NCEP guideline, the desirable level of LDL-C for children was established as being 110 mg/dL or less — something, he noted, that took adult medicine more than 15 years to figure out.

Dr. Gidding went on to say that, in general, it is difficult to classify someone’s CVD risk based on a single measurement of LDL-C, but a patient with a value above 174 mg/dL on one occasion is unlikely to have LDL-C < 160 mg/dL on repeat measurement soon after. He acknowledged that in patients with “borderline” high LDL-C, it is good to perform two measures to ensure that the concentration is accurate and consistently above 160 mg/dL. However, he emphasized, patients with extreme levels are easy to classify.

Dr. Gidding observed that, because the US Preventive Services Task Force (USPSTF) takes a very exacting approach to evidence evaluation, it is important to understand their procedure, which requires an accounting of possible adverse events of screening itself. Proponents of FH screening in the US must make sure, he stressed, especially with regard to children, that there are no significant adverse effects. Although there is significant discussion about possible consequences of cholesterol screening, said Dr. Gidding, since the selective screening program was introduced in 1992, there has not been a single article on the adverse effects of measuring an individual’s cholesterol.

Dr. Gidding noted that with the progress being made in more effectively defining FH in children, there is an ethical mandate to diagnose and treat. There is clear evidence of the incremental benefit to initiating treatment at age 10 vs. age 20, in terms of the duration of exposure to hypercholesterolemia. He added that there are no data demonstrating any long term side effects of statins that would outweigh the benefit of morbidity and mortality averted. He went on to remind the audience of the Tuskegee experiments, and emphasized that there are adverse effects of not treating to be considered. Dr. Gidding acknowledged that the cost of screening is much more significant than the cost of treatment, and that US-based cost/benefit analyses are needed.

With regard to screening cholesterol in children vs. young adults, Dr. Gidding referred to the recommendation in the NCEP Adult Treatment Panel III (ATP III) that everyone age 20 years or older should know their fasting LDL-C, and he asked if there might not be an incremental benefit to knowing the level at age 10 years versus 20? Dr. Gidding laughed, saying he was certain, even with no evidence, that 10-year-olds go to the doctor and 20-year-olds don’t, making 10 years of age an opportune age at which to test.

Dr. Gidding listed some of the barriers to implementing cholesterol screening for physicians, families, and society:

- For the general public, a great deal needs to be done to increase FH awareness.
- Physicians in primary care may not have the time or possess the skills necessary to handle
patients with FH.

- Reimbursement is an issue. Families face competing health priorities that, being more proximate, are perceived as more important than long-term risk for heart disease.

- Messages need to be developed that are health literate and available to people at all educational levels.

- Cost-related issues, such as cost of drugs and cost recovery in the health care system, are also important.

- Privacy issues associated with genetic testing need to be resolved.

- Societal concerns include weighing the relative importance of FH against other priorities and supporting the guidelines as a public health issue. In this regard, Dr. Gidding noted, the NIH and CDC need to endorse the evidence-based guideline on testing cholesterol in children.

Dr. Gidding acknowledged that a major limitation of the 2011 NHLBI guidelines for cardiovascular risk reduction in children is that they do not address cascade screening of relatives. He used this example to illustrate that, as new evidence evolves, the guidelines need to be constantly updated based on feedback and reevaluation of the evidence. He stressed that the NHLBI and other US agencies need to support this process.

3 Session III – Peter WF Wilson, MD
FAMILIAL HYPERCHOLESTEROLEMIA: DATABASE DIAGNOSIS

Dr. Peter Wilson (Professor of Medicine, Cardiology, Emory University School of Medicine, Professor of Public Health, Global Health, Epidemiology, Rollins School of Public Health, Emory; Director, Epidemiology and Genomic Medicine, Atlanta VA Medical Center) noted that his talk on using electronic medical records (EMRs) for FH case finding would have a qualitative focus. He recalled that when he was a resident, the family members of an individual with an MI and very high cholesterol were rarely offered screening. It is still the case, Dr. Wilson noted, that almost all patients who have heterozygous FH (HeFH) are not identified until they present with CVD in their 30s and 40s. The diagnosis is being missed, he noted, even among people with high health literacy.

Dr. Wilson noted that even very large US-based screening studies have not been done well enough to resolve questions about FH. For example, he said, even in the MRFIT program of 360,000 US men, which was seminal in establishing the association of CHD deaths with elevated cholesterol and the need for intensive treatment, no information was collected about the presence in subjects’ families of high cholesterol or high blood pressure. The MRFIT study, said Dr. Wilson, also neglected to measure height and weight for calculation of body mass index (BMI).
To avoid similar oversights, Dr. Wilson urged the FH Foundation and others hoping to move forward with FH as a public health agenda to think carefully about what gets measured, how to do it well, and how to keep it simple. He pointed out that all of the major FH efforts to date have been conducted by large national groups, and further, with the internet and iPhone, clinicians and patients in large numbers are now empowered to learn about and diagnose FH.

Based on the MRFIT curve for six-year coronary heart disease (CHD) deaths by increasing serum cholesterol,\textsuperscript{44} Dr. Wilson pointed out that for a patient with a serum cholesterol level typical of untreated FH, the risk of CHD death is 16-fold that of someone with a cholesterol of 160 mg/dL. An even better estimate, he noted, may be the 35-fold increased risk of myocardial infarction (MI) in FH patients, published by Goldstein et al in 1973.\textsuperscript{45-47}

**The prevalence population-attributable risk is also a consideration, Dr. Wilson noted, with FH probably accounting for approximately 5% of the MI burden in the US.**\textsuperscript{48} The ability in the US to track down family members with FH is not good, he said, and although the lipid clinics make every effort to find and screen the relatives of FH patients, such screening is not progressing beyond the medical setting, at least not in adult medicine.

Dr. Wilson discussed some of the challenges associated with the ongoing use of three well-accepted but different sets of criteria. Because using one set of criteria to “screen” a database that was built on a different set of criteria may fail to capture patients with FH, he noted, finding the individuals with suspected FH may necessitate reading charts.

Using the Simon Broome criteria for FH,\textsuperscript{49} Dr. Wilson observed that the xanthoma yes/no check box is not useful, because xanthomas are never mentioned, even to a person in a lipid clinic. Further, he said, it has been documented that patients are uniformly unable to report whether their parent or other first degree relative had tendinous xanthomas or what the relative’s cholesterol level was.\textsuperscript{50} He suggested that showing people clinical pictures and asking, “Do you think your father had this?” would be a more productive screening method than asking about terms such as “tendinous xanthoma.”

Dr. Wilson showed a graph from the Simon Broome website that stratifies the FH risk among relatives of index cases into “likely,” “gray zone,” and “unlikely” groups, based on LDL-C threshold levels. Although deciding what to do for all the relatives who fall into the “gray zone” is a difficult and unresolved issue, he noted, the lipidologists will agree that the “gray zone” relatives, many of whom are in pediatric age groups, should certainly receive work-up and possible treatment.

Dr. Wilson pointed out that the existing large FH datasets are mostly composed of white, middle class people of Western European origin. There are not adequate data for African Americans, for Asian Americans, and none for China, he noted, and these groups may differ in important ways, perhaps exhibiting a higher prevalence of FH or carrying different mutations. Dr. Wilson pointed out that it may not be possible, when screening for FH in the US, to extrapolate and use the same criteria for all racial/ethnic groups: for example, Asian-Americans on average have a different diet and lower cholesterol levels, which could be critical in screening different databases for FH.
Dr. Wilson reported that a project is being initiated by Emory University and the Atlanta VA to screen for FH in a database maintained since 1997 of all US veterans using VA facilities. The database comprises information from about seven million people, Dr. Wilson said, so the investigators anticipate that they will easily find a million subjects with adequate data for evaluation. He said that tens of thousands of these subjects are likely to have secondary dyslipidemias, a factor which will affect the size of “gray zones,” that is, the patients in whom the diagnosis of FH is not certain based on lipid levels alone.

Dr. Wilson emphasized that a screening program must take into account — as lipid clinics do for individual patients — the many secondary factors that may increase serum LDL-C, such as hypothyroidism, nephrotic syndrome, cholestasis, and drugs such as the thiazide diuretics, cyclosporine, or carbamazepine. He noted that there are also conditions that may lower LDL-C levels, such as severe liver disease, malnutrition, and niacin toxicity, and so result in FH cases being missed if databases are screened based on lipid levels only.

Dr. Wilson cautioned that screening for FH will often be confounded when triglycerides are recorded in the chart, but not LDL-C. A recurring problem in screening a database, he said, will be knowing how to categorize a patient with triglycerides over 400 and cholesterol “not calculated.”

Dr. Wilson reported that most EMR-based databases include digitized information including lipid levels in the fasting state, occurrence of cardiovascular events such as myocardial infarction, and the person’s date of birth. Filters can be constructed to search for affected individuals based on those features and can serve as a starting point for chart review and other forms of screening. He listed the following key data elements that must be captured, at least to the extent of coding for “yes/no/maybe” and for a rating of severity, in order to screen effectively for FH:

- Age
- Arcus corneae
- Xanthomas
- Xanthelasma
- Cholesterol level (LDL-C, Apo B) for age
- Early onset coronary artery disease
- Premature unexplained death
- Medications that lower/raise LDL-C

Dr. Wilson added that the list should probably include sex, male/female, as well, as there was not information about differences by gender in adults. He noted that there are certainly gender differences in cholesterol at the ages when young women go through puberty, and data to allow analysis at the different stages should be collected.

In addition to information about whether the individual takes lipid-lowering medications, said Dr. Wilson, the database should take account of the growing list of medications taken for psychiatric diagnoses, many of which affect triglyceride levels.
There is still debate as to which molecule should be the basis for cholesterol screening, Dr. Wilson noted, with basic science lipidologists tending to favor non-HDL (total cholesterol minus HDL), over LDL-C. Although, he concurred, non-HDL might be a more robust test, he was not aware of an analysis showing that conclusively. Controversy also continues, Dr. Wilson said, as to whether Apo-B should be measured and recorded in charts, and whether it should be captured in the database.

Dr. Wilson noted that, with regard to family history of early onset CVD or premature unexplained death, information in charts and databases will often either be missing, wrong, or inadequate. He reported that for some of his patients at the NIH lipid clinic, there was no father from whom a history could be taken; often, the mother was there with the HeFH children, because the father had died at age 35 due to an FH-related event. Databases, said Dr. Wilson, should be built to capture such information about the family.

Dr. Wilson stressed that the screening program for FH should also play a critical role in identifying patients whose cholesterol level is in the “gray zone” — meaning that the level does not rule FH in or out — and provide them with much needed further evaluation, whether it turns out that they have FH or not.

In the lipid clinics, he said, if a patient presents with very high cholesterol and normal triglycerides, the standard practice is to act as if the patient does have FH. However, said Dr. Wilson, the lipid clinics are also concerned about patients with LDL-C in the gray zone, or even low LDL-C, who may have elevated triglycerides or mixed dyslipidemia; these individuals also need to be identifiable by the screening program, so that they can be evaluated. Further, he noted, if the family of such a patient is screened, they all may have high triglycerides; this would be a family with inherited mixed dyslipidemia.

Dr. Wilson urged that a program of screening for FH in the US will require careful thought and planning to avoid excluding the people with LDL-C in the “gray zone,” whether they have mixed dyslipidemia, or obesity and diabetes, or other secondary lipid abnormalities. When screening captures people who have familial dyslipidemia and not FH, he said, there must still be a plan for informing the affected individuals and for helping their families address this and other disorders that screening will bring to light.

In closing, Dr. Wilson stressed the need to learn more about the genetics of mixed dyslipidemia, as its prevalence is probably 5 – 15% of the population as compared to 1/500 for FH. In the context of screening for FH, mixed dyslipidemia may be misleading, he noted, because in some families it may result in just one family member with high cholesterol, while the others may have triglyceride or other abnormalities.

Session III – Panel Discussion

Moderator: Debra Duquette, MS, CGC (Michigan Department of Community Health)
Faculty: William Neal, MD (CARDIAC, West Virginia University); Samuel Gidding, MD, PhD (Nemours Cardiac Center, Thomas Jefferson University); Peter Wilson (Emory University; Atlanta VA Medical Center).

Panelists: Lisa Hudgins, MD (The Rogosin Institute, FH Foundation Scientific Advisory Board); Peter Kwiterovich, Jr., MD (Johns Hopkins School of Medicine); Joyce Ross, MSN, CRNP, CLS (Board Member, FH Foundation ); Ronald Scott, MD (Kaiser Permanente Southern California)

In opening the Session III panel discussion, Moderator Debra Duquette said that her first question was directed to Lisa Hudgins, MD and Joyce Ross, CRNP: How can diverse populations be prepared for universal screening of 9-11 year-olds?

Dr. Hudgins noted that the presenters at the FH Summit had probably addressed all the necessary components, and she emphasized the need for a multi-variable approach. Dr. Hudgins noted that the FH Foundation is focusing on patients and patient education, and she agrees that ways must be found to achieve greater FH awareness at the patient level.

Particularly after hearing about the Dutch experience, Dr. Hudgins believes that there must be significant improvement in the education of medical personnel, all the way to the medical student level. If pediatricians and subspecialists are comfortable managing more and more diabetes and pre-diabetes, she observed, then they will also be increasingly comfortable monitoring lipids and managing dyslipidemias.

Dr. Hudgins expressed puzzlement that when an adult cardiologist is faced with a 30-year-old patient with MI, the cardiologist does not automatically think of FH. After years of discussion in the medical community about early onset CVD, Dr. Hudgins suggested that perhaps there’s hesitancy based on a sense of the complexity of lipid metabolism.

Ms. Ross agreed with Dr. Hudgins’ points. She stressed the importance, also, of reaching out to health care providers who are likely to see many of the young people who missed having their lipids checked at age 20. She observed that obstetrician/gynecologists could play a large role in screening for FH, because they will have opportunities to ask mothers-to-be and their partners to have lipid screening before or during the pregnancy. If either parent has high cholesterol, the provider will know that any children born to those parents should be checked either at birth or at age two years.

Dr. Hudgins responded that for heterozygous FH at least, there are limitations to the efficacy of screening lipids at birth. There is a tremendous overlap in lipid values between FH carriers and non-carriers until about age two, as demonstrated in the past by Dr. Peter Kwiterovich. However, Dr. Hudgins noted that a child with homozygous FH could have heart disease and even, as documented in one child, an MI, as early as 18 months, and she agreed that measurement of lipids at birth is indicated when both parents have cholesterol levels in the heterozygous range.
Dr. Hudgins noted that she highly favors universal pediatric screening of lipids, and her sense is that with the growing interest in childhood obesity in recent years, pediatricians are more strongly in favor of screening, including testing blood sugar in obese children. Dr. Hudgins noted that pediatricians are increasingly comfortable with screening lipids in obese children, and by extension, are starting to become more interested in appropriate screening of lipids in all the children they see.

Dr. Hudgins stressed that it should be a goal of pediatricians to bring all children to adulthood with a normal risk profile for cardiovascular disease, which would, of course, include identifying and treating children with FH. Pediatrics is strongly focused on preventive medicine, she said, and because of the childhood obesity epidemic, finding FH in children is finally receiving much-needed attention among pediatricians and other providers who see children.

Ms Duquette directed the next question to Peter Kwiterovich, Jr., MD: Should DNA testing be part of screening all children to find index cases?

Dr. Kwiterovich observed that it is possible, in the majority of families and cases, to make a reasonable clinical diagnosis of HeFH. He said that if the child has LDL-C above 160 mg/dL; there’s a family history of heart disease; and the child is at least 10 years old — an age where there is evidence that he or she can be treated effectively with statins -- he would go ahead and treat the child.

Dr. Kwiterovich noted that it costs approximately $800 to analyze the LDL receptor gene. He acknowledged that the Dutch program has demonstrated that people with LDL-C of 135 mg/dL may have a mutation, and in a child with a borderline elevated LDL such as 135 mg/dL, the physician may want the results of a genetic test before beginning statins. However, he said, he is not certain that FH screening needs to include genetic testing for every child.

Dr. Gidding agreed that, as he has learned by applying selective genetic testing in his practice in recent years, the cost of genetic testing is a barrier. However, he noted, there is still much to be learned about genotype-phenotype correlations in FH, and with newer drug therapies being developed, there will probably be increasing opportunities for personalized treatment that will be based on the individual’s FH genotype.

Dr. Gidding went on to emphasize that he always orders genetic testing for a patient who has HoFH, because knowing the genotype can be helpful in managing that patient’s treatment and because there is a great deal to learn about the application of personalized medicine for HoFH. Also, Dr. Giddings noted, the lipid specialists often get an anomalous case and genotyping may help to determine why the patient has high cholesterol. Thus, he favors determining the FH genotype whenever possible as a tool for learning and possibly for future treatment. However, in everyday practice, he agrees completely with Dr. Kwiterovich that a child with a clear clinical diagnosis should be presumed to have FH and be treated and monitored accordingly, whether a DNA diagnosis is available or not.
Ronald Scott, MD (Kaiser Permanente Southern California) noted that his organization looks at specific health issues from a systems standpoint, that is, they look for the group of patients for whom Kaiser Permanente (KP) as a unified healthcare system can take action. He reported that, with guidelines in place for patients with elevated LDL-C, a search for such patients is finding that 1% or slightly less of the patients within the KP system have LDL-C ≥190 mg/dL. Dr. Scott described efforts that KP has begun in the past few years, educating PCPs about appropriate management of patients with elevated lipids, and encouraging the use of electronic decision support tools. Dr. Scott explained that KP uses automatic flags to alert the providers when a patient comes in who had elevated LDL-C in the past, so that even if the present visit is for something unrelated like a twisted ankle, it may be a good opportunity to re-evaluate the lipid profile; get the patient into a program of management; and educate the patient about ways to address hypercholesterolemia.

Dr. Scott noted that KP has not employed genetic testing for FH much so far, so he was attending the FH Summit to learn what its role might be within the KP system.

Ms. Duquette had the following question from someone in the audience, which she directed to Dr. Samuel Gidding and Dr. Peter Wilson: Given limited resources, if we must focus on only one screening approach, which approach should the US invest in:

- Universal screening of newborns;
- Universal screening of children age 10 years; or
- Adult screening with cascade screening of relatives?

Dr Gidding noted that the experience in the Netherlands, where it took 11 years to identify approximately 75% of estimated FH cases, shows that cascade screening will not actually identify everyone in a population who has FH. He also observed that when universal screening of children is recommended for other conditions, not only are there always opponents who criticize the cost or raise other concerns, but the reality will be that only about 10% of pediatricians will perform the screening. Dr. Gidding concluded that the way to achieve identification of every case is to advocate (1) for increased awareness among the general public as well as among healthcare providers; and (2) for ultimately identifying 100% of the FH population, so that plans can be made about how to pick up new cases as they arise. He stressed that the first priority is to have complete coverage of the cost of screening for and treating of FH.

Dr. Wilson said that he believes that universal neonatal screening for FH would not be taken up by the healthcare community, except in cases when both parents have HeFH. Earlier guidelines for adult cardiovascular risk were criticized for not addressing FH and hypercholesterolemia, he noted, but it is known that adults with FH have been considered and will be addressed in the new guidelines (released in November 2013).
Dr. Wilson suggested that an easy-to-recall, round number should be chosen as the level that alerts the physician — whether an internist, family medicine physician, lipidologist, or endocrinologist — so that patients who meet that level, perhaps LDL-C ≥ 200 mg/dL, and have a normal triglyceride level are considered as being in a special group that need to be treated differently.

**Dr. Gidding** agreed with Dr. Wilson that neonatal screening would not be the best approach, except when both parents have elevated lipids or are known FH carriers.

**Dr. Neal** said that any screening program, including cascade screening programs, must have sustainable funding. He noted that while the CARDIAC program began with a small CDC grant and has at different times had NHLBI, other CDC, and foundation funding, the program has been able to continue for 15 years because the West Virginia state legislature has appropriated money to cover the core costs of screening. This money pays for seven area coordinators, a biostatistician, a data entry person, and a LabCorp contract to run the lab tests. Dr. Neal suggested that, at least in the case of CARDIAC, state government has worked as a way to sustain screening for the long term.

Considering Dr. Neal’s suggestion and the example of CARDIAC, **Dr. Gidding** wondered whether the cost per child screened in the CARDIAC program might be much lower than it would be for children going to the doctor and being screened through an elaborate set of FH criteria. Dr. Neal responded that he was not certain; for example, for CARDIAC, the state is paying for a handful of personnel whereas a private practitioner would have to be supported through a different payment system, and might pay higher lab costs; he mentioned that Medicaid is a potential source of cost support, but it would be difficult to obtain Medicaid focus on a new program like FH screening.

Dr. Neal characterized the need for PCP education as “astronomical.” His experience with the CARDIAC screening program continues to be that many PCPs are not aware of the risk to a child, even when the cholesterol level is as high as 350 or 400 mg/dL. When CARDIAC sends letters to the PCP to alert them to such a child, the response is often one of no concern. Dr. Neal said that in such cases, he calls the physician and also the child’s family, to explain the risk, try to convince them to address the child’s hypercholesterolemia, and check the family. He has found, he said, that a point that PCPs must understand is that children with high cholesterol should be treated. It is important to spread the message that the biology of the patient from childhood to adulthood does not change at some point, but is a continuum.

**Dr. Wilson** observed that the best approach may be pediatric guidelines recommending that at the age of 10 years, all children have their lipids measured, so that the cholesterol levels are known. He said that it probably does not need to be repeated often unless the values are clearly elevated or at least borderline. For instance, he said, if the cholesterol is well within normal limits, it probably only needs to be checked again in 10 – 15 years.
Dr. Wilson also pointed out that employers increasingly are asking whether the employee uses tobacco, and if not, he or she pays less for their healthcare insurance. He noted that employers and insurers should similarly be interested in the healthcare costs to be avoided by addressing hypercholesterolemia, and suggested that it should be asked whether the employee has a cholesterol level checked at least once every five years. Dr. Neal said that with the Affordable Care Act in place, more dollars for such a prevention effort should be available, but only if the proponents of such a program, such as the FH Summit participants, follow through to make it happen.

One of the audience asked the Session III panelists whether the best approach would be to screen all children at age 10 and then screen the parents accordingly.

**Dr. Neal** suggested that representatives of the Dutch program, who have the most experience in cascade screening, would be the best ones to address cascading from a child index case to adult family members. He noted that for most physicians in adult medicine, it takes a sentinel event, such as a heart attack in a 35-year-old, to prompt the physician to check the siblings and children. However, he noted, any of the pediatricians in attendance at the FH Summit would certainly want to screen the family of a 10-year-old child with an LDL-C level of 300 mg/dL. With regard to parents’ acceptance of cascading from a child index case, Dr. Neal said that in the CARDIAC program, the parents were aware of the reasons for the child’s screening at school, because they has signed a consent; thus, he concluded, most parents would probably be willing to be screened themselves, if their child was found to have elevated cholesterol.

Speaking to the Dutch experience, **Dr. Erik Sijbrands** (the Netherlands) noted that, the majority of the time, screening was performed in adults, and then cascaded to the adult proband’s family members, including children. However, he said, when a child was referred by the PCP to a lipid clinic because of dyslipidemia, then the cascade screening would be followed from child to family members.

With regard to insurability of persons with FH, Dr. Sijbrands added that the Dutch program of cascade screening had **improved insurability of people with FH, because it showed the cost effectiveness of identifying and treating them early.** He stressed that screening programs must take steps to make certain that, if people are identified with FH, there will be no increase in the cost of their health insurance.

Dr. Neal agreed with Dr. Sijbrands’ comment on insurability. He noted that the CARDIAC program of screening is offered to all fifth-grade children in West Virginia, but only 45 – 50% of parents accept and sign consent for their child. To investigate the differences between parents who agreed to their children’s screening versus parents who did not, he and his colleagues polled some of the parents by phone and found that the parents who did not consent appeared to be slightly less likely to have a PCP for the family and were slightly less likely to have health insurance. He expressed hope that the latter problem is becoming less of a hurdle, since West
Virginia and many states have Children’s Health Insurance Programs (CHIP) for children not otherwise covered.

Dr. Gerald Watts (Australia) asked the panel whether, in a US program of screening, they would want to incorporate screening the family members of individuals who are in coronary care units.

Dr. Gidding agreed that screening the family of people in coronary care units is extremely important and is likely to yield good compliance because the request for screening comes at a time when the family is very focused on that issue. He noted that Dr. Ronald Lauer had screened children whose relatives had experienced cardiac events and had found children with high LDL-C levels, but also found many children with severe metabolic syndrome and obesity phenotype. Dr. Gidding pointed out that if children whose relatives are in coronary care are screened, the prevalence, and therefore, the yield, of metabolic syndrome would be higher than that of FH. However, he said, that made such screening a good opportunity to identify children with either or both health issues.

Speaking further to the sometimes competing demands of FH and childhood metabolic syndrome/obesity, Dr. MacRae Linton (Director, Vanderbilt Lipid Clinic; Co-director Atherosclerosis Unit; Professor of Medicine and Pharmacology, Vanderbilt University Medical Center) commented that the pediatric guidelines for childhood cholesterol screening have had a tremendous impact on the Vanderbilt Lipid Clinic, where so many children are referred that clinicians barely have enough time to see adult patients. Many of the children, he said, have metabolic syndrome, so they are sent to the lipid clinic’s dietician, with hopes that this will help. Although, Dr. Linton noted, the Vanderbilt Lipid Clinic also sees many children with FH, the real problem has become how to effectively address metabolic syndrome and obesity in children.

Dr. Hudgins acknowledged the difficulty of helping children with metabolic syndrome, saying that the problem requires more dietary and nurse practitioner staff that can provide the nutritional and lifestyle counseling needed. She noted that such teaching and support must be covered by insurance and that making any progress with obesity in children is complex and time consuming.

Ms. Ross added that it is extremely difficult to help a child with metabolic syndrome/obesity unless the family is ready to make changes in their lifestyle and diet. She noted that a team, for example a physician and nurse practitioner, need to work together to teach the parents about good nutrition and other changes for their child, without making the parent feel guilty about the child’s obesity.

Dr. Hudgins emphasized that the education and dietary counseling must be reimbursed. She noted that at her lipid clinic, they cannot bill dietician visits as such, even though the dietician’s work is essential for children with problems of metabolic syndrome/obesity.
Ms. Duquette directed another question from the audience to Dr. Hudgins: As statin treatment becomes more prevalent, how do you factor past and current statin treatment into family history?

**Dr. Hudgins** explained that the first question to address is how to define high cholesterol and positive family history in a child; for example, is high cholesterol in one parent enough? She noted that because obesity results in so many people with high cholesterol, screening LDL-C often needs to extend back to the child’s grandparents. With statin use being so widespread, Dr. Hudgins noted, making use of some theoretical correction factor may be the only way to estimate the baseline cholesterol in the family member.

Ms. Duquette directed the final question of the panel discussion to **Dr. Ronald Scott**: What are the greatest barrier and the greatest opportunity with regard to diagnosis and treatment of FH in children?

**Dr. Scott** reiterated that his organization, KP, looks carefully at their own quality metrics compared with other health care delivery systems, to improve KP’s Healthcare Effectiveness Data and Information Set (HEDIS) score. He explained that KP must report to the government, which in turn issues national reports comparing quality metrics among the different accountable care organizations. Noting that an LDL-C level of 190 mg/dL is a threshold value of long standing, if KP wanted to emphasize universal cholesterol screening in adults, they already know that among their patients with diabetes and/or coronary artery disease, approximately 96 – 98% are regularly having LDL-C measured each year, because KP has multiple systems in place to drive that performance by practitioners.

Dr. Scott went on to say that, by knowing how many people, and which ones, ever had an LDL-C level recorded in their charts, it would be possible to filter for the percentage of all patients whose latest LDL-C had been greater than or equal to 190 mg/dL. With a system as large as KP, he noted, there would be a strong incentive to get those patients enrolled into lifestyle change programs, or to get them on treatment, so that the system could show a sizeable decrease in the percentage of patients with LDL-C > 190 mg/dL. He noted that the combination of guidelines and a metric showing patient improvement will help gain the support and leadership necessary to achieve success with a new healthcare initiative.

### Session III – References

Session IV
STRATEGIES FOR IMPLEMENTING SYSTEMATIC CASCADE SCREENING

The objective of Session IV was to weigh the merits of various strategies for implementing systematic cascade screening for FH. Opening the session, moderator Muin Khoury, MD, PhD (CDC Office of Public Health Genomics) called the question of how to perform cascade screening of relatives “the hard stuff.” The presenters and panelists in Session IV also discussed the benefits and challenges of incorporating genetic testing into an FH screening program, and the ethical and cultural considerations associated with approaching relatives of an individual newly diagnosed with FH.

1 Session IV — Fernando Civeira, MD, PhD
Strategies for Implementing Systematic Screening in FH: Experience from Spain.

Fernando Civeira, MD, PhD (Chief, Lipid Clinic and Chief of Research, Molecular Laboratory – Hospital Universitario Miguel Servet; Professor of Medicine, Zaragoza School of Medicine) told the Summit participants that Spain is a country of nearly 50 million people with strong genetic connections to Mediterranean and Atlantic Europe. The country tends to be genetically homogeneous, with immigration of minorities, mainly from South America and Africa, reaching appreciable levels only in the past 10 years. In Spain, he noted, there are an estimated 100,000 patients with heterozygous FH (HeFH) and, at the time of his presentation (September 19, 2013), exactly 18 patients known to have a clinical diagnosis of homozygous FH (HoFH).

Dr. Civeira explained that the Spanish Health System integrates all public health resources into a single system that is extended to the entire population and financed publicly. He noted that while the central government decides what health services are universally available — for example, free medication for all patients with FH -- the management of those services is highly decentralized, with each region determining its own system of reimbursement for services.

Dr. Civeira related that systematic screening for FH in Spain began almost 20 years ago. Since that time, approximately 20,000 patients with HeFH have been diagnosed, most of them with genetic confirmation in the proband or in a first-degree relative (FDR). It is estimated that over 30% of the FH cases in Spain, at least those with the most severe phenotype, have been diagnosed and are being treated in specialized lipid clinics throughout the country.

Dr. Civeira cited four important factors contributing to the success of FH Screening in Spain:

1) The presence of active research groups focused on FH, leading to the early detection of most of the LDLR mutations in Spain. Screening began 20 years ago in his country, with several groups actively looking for FH mutations, which allowed analysis of the main FH mutations, particularly in the region of Zaragoza.
2) The involvement of a Spanish biotechnology company, Progenika Biopharma SA, in the FH diagnostic process, leading to the development of a microarray (LIPOchip) that included all known LDLR and APOB mutations causing FH. Progenika’s collaboration with Spain’s lipid clinics has greatly facilitated genetic analysis of FH mutations.

3) A network of 70 lipid clinics distributed throughout Spain, sharing many management procedures, and organized as a specific section within the Spanish Atherosclerosis Society (Sociedad Espanola de Arteriosclerosis, SEA).

4) The founding in Spain 10 years ago of Fundacion Hipercolesterolemia Familiar (FHF), a powerful FH patient organization with important resources from the Spanish National Health System. Primarily through patient efforts, the FHF has raised substantial money for research and even for reimbursement of medications.

Regarding the first of these factors, Dr. Civeira emphasized that it has required a research program of many years’ duration to discover so many of the pathogenic mutations that cause FH in Spain.52-56 Twenty-two different mutations were found in the first 50 patients, who were screened at a single lipid clinic in Zaragoza. The screening study was expanded to all lipid clinics participating in the SEA, and to date more than 100 FH-causing mutations have been found in 1500 patients from 68 of the 70 lipid clinics located throughout Spain.

The second factor contributing to successful FH screening in Spain has been the creation and continual up-grading of a genetic diagnostic platform for FH, a DNA chip called LIPOchip® (Progenika-Biopharma SA, Derio, Spain). When first released in 2004, LIPOchip included a microarray for detection of the first 118 FH mutations that had been detected in the Spanish screening program.57,58 Dr. Civeira explained that in Spain, when the LIPOchip result is negative for a patient with a clear FH phenotype, the LDL receptor and the binding region of Apo-B are fully sequenced. Any new mutations discovered have been incorporated into a new version of LIPOchip. Since 2004, 10 successive versions of LIPOchip have been released as new mutations were found, and the technology now incorporates over 200 different mutations for FH in LDLR, PCSK9, APO-B, and LDLRAP1. He noted that use of the LIPOchip platform to detect FH mutations has spread from Spain to include sites in Wales, the Netherlands, Germany, Italy, Japan, and for clinical research in the US.

According to Dr. Civeira, the third important factor is the existence of the network of lipid clinics with their own section in the SEA. The lipid clinics work together to obtain research funding for FH as well as for other conditions, and they have their own annual meetings. They share a common database, he said; however, within that database, each clinic enters and controls access to its own patient data. For each case of a patient with suspected FH, the clinic is able to enter laboratory measurements, family history, physical exam, analytical data, treatment, clinical diagnoses, and other information in the database -- Red Informatica de Hipercolesterolemias Autosomicas Dominantes (RIHAD). At the time of Dr. Civeira’s address to the FH Summit, more than 1000 FH patients had been entered in full into the RIHAD
database, and their data will allow better understanding of the phenotypes and clinical course of patients with FH in Spain.

The fourth important factor has been the FH Foundation in Spain. Dr. Civeira attributed the success of this group to its being built and run by patients who have their own research and education programs and their own database, into which patients are able to directly enter their data. He showed the homepage of the FHF website — http://www.colesterolfamiliar.org, a resource for study information, education, nutritional advice, and lipid clinic locations.

For beginning a large scale FH screening program in the US, Dr. Civeira stressed the importance of bringing together experts to reach agreement on diagnostic criteria that could be applied consistently by all clinicians. He noted that in Spain the involvement of representatives of the national system of healthcare and its collaboration with the FHF have been very important in the success of the country’s FH screening program.

To illustrate the development of the FH screening program in Spain, Dr. Civeira said that, beginning 10 years earlier, investigators at the lipid clinics in Aragon decided that the most important population to screen for FH was people aged 16 to 65 years. It was expected that in Aragon, this age range would comprise approximately 1800 heterozygous FH patients, from a total population of ~1.3 million. The lipid clinics worked with the local government to inform general practitioners (GPs) about the importance of identifying FH. The GPs were initially asked to look for patients who had either total cholesterol over 300 mg/dL with normal triglycerides and/or a family member who met those criteria, and to refer such patients to one of Aragon’s lipid clinics. Once at the lipid clinic, the suspected FH patients underwent further laboratory tests. Genetic testing was requested if the patient scored at least 8 points by the Dutch Lipid Clinic Network criteria. By 2008, Dr. Civeira said, it was clear that many patients did not have their family’s cholesterol information, so the criteria for lipid clinic referral were changed to focus on what was consistently available directly from the patient, that is, the patient’s age, LDL cholesterol, and personal history of xanthomas. The indication for genetic testing in a suspected FH proband was determined by LDL-Cholesterol, with the cut off LDL-C level adjusted based on the patient’s age and presence or absence of xanthomas.59,60

Dr. Civeira reported that, at the time of the FH Summit, FH screening in Aragon had identified 782 subjects with a diagnosis of HeFH based either on positive genetic testing, or, if genetic testing was negative, on a Dutch Lipid Clinic Network (DLCN) score of 9 or greater. He noted that another 356 subjects had a clinical diagnosis, with negative genetic testing and DLCN scores greater than 7 and less than 10. Based on either genetic or clinical diagnoses, the investigators estimate that they have identified 62% of the approximately 1800 people expected to have HeFH in Aragon.

Dr. Civeira said that the diagnostic rate for FH has differed among different regions of Spain over the past 10 years, noting that, for example, the diagnostic rate was slightly lower in Catalonia than in Aragon, perhaps because Catalonia’s larger area and population mean that screening for FH requires more time and greater resources.
In addition to the joint efforts of the Spanish FH Foundation and SEA, Dr. Civeira credited the ongoing success of FH screening to the fact that patients with either a clinical or genetic diagnosis in the lipid clinic receive lipid-lowering drugs for free.

Based on the first 10,000 LIPOchip results, Dr. Civeira noted, LDL receptor mutations account for over 90% of the mutations causing FH in Spain. In 6500 index cases, 210 different mutations in LDLR, 3 mutations in APOB, and 4 mutations in PCSK9 were found. He pointed out that there is a challenge posed by the high proportion of the subjects who had negative genetic test results, regardless of their DLCN score, including 84% of subjects with scores <3 (not FH), 76% of subjects with scores of 3 – 5 (possible FH); 69% of subjects with scores of 6 – 7 (probable FH); and 46% of subjects with scores of 8 or more (definite FH). These individuals having a clinical FH diagnosis but no mutation comprise not only individuals who are wrongly diagnosed as having FH, but also others whose hypercholesterolemia is caused by other genes such as LDLRAP1, by genes not yet known, or by regions of the LDLR, APOB, and PCSK9 genes that have not been studied yet.

Dr. Civeira noted that PCSK9 and LDLRAP1 testing capability has recently been added to the LIPOchip platform, and he closed his presentation with some early results. Citing a personal communication from Progenika, Dr. Civeira reported that, among the first 1000 subjects who had sequencing of the PCSK9 gene, 10 patients (1%) were found to have FH pathogenic PCSK9 mutations, 32 patients (3.2%) were found to have a total of 22 different unknown variants; and 16 subjects (1.6%) had low LDL-C and no effect-associated variants. One patient was homozygous for an FH pathogenic mutation of LDLRAP1. Dr. Civeira explained that approximately 700 of the 1000 subjects were new patients and that so far, approximately 300 had been rechecked with LIPOchip to confirm their negative results. The early results suggest, he said, that perhaps 1 to 3% of the FH cases in Spain are related to PCSK9.

2 Session IV – Fredrick Raal, MD, PhD
Founder Mutations and Cascade Screening Efforts in South Africa

Fredrick Raal, MD, PhD (Director, Carbohydrate and Lipid Metabolism Research Unit; Head of the Division of Endocrinology and Metabolism – Department of Medicine, Johannesburg Hospital; South Africa) observed that Dr. Evan Stein of the Lipid Disorders Center, Transvaal Memorial Hospital for Children in Johannesburg, first described FH and its the prevalence in SA in 1977, when she characterized the scale of the problem as “a host of hypercholesterolaemic homozygotes.” He said that in South Africa (SA), there are currently two lipid clinics, in Johannesburg and in Pretoria, that specialize in the diagnosis and treatment of familial dyslipidemias and FH in particular.

Dr. Raal reported that the last census in 2011 showed the population of SA to be about 50 million, with the vast majority being Africans, that is, of black African ancestry (~40 million). The other major demographic groups are people of mixed lineage (~ 4.4 million); Indian or Asian people (~1.3 million), and White South Africans (~4.6 million). The latter include Afrikaners – Afrikaans-speaking descendants of European ancestry, especially descended from 17th-century Dutch settlers; English-speaking
descendants of people from the British Isles; and immigrants and their descendants from the rest of Europe.

Dr. Raal noted that the prevalence of FH among Africans in SA is unknown, although he believes it is probably less than 1:500. The estimated prevalence of FH among Ashkenazi Jews in SA is 1:67, probably the highest prevalence in the world. In the Afrikaner population, the estimate is between 1:70 and 1:100.

So, he said, although the worldwide prevalence of HeFH is estimated to be one in every 300 to 500 persons, in the combined SA populations of Afrikaners, Ashkenazi Jews, and Gujarati Indians, the prevalence is about 1:80 for HeFH and 1:40,000 for HoFH. He reported that there are an estimated 120 individuals with HoFH in SA.

Dr. Raal noted that for the SA populations of Afrikaners, Ashkenazi Jews, and Indians, the high FH prevalence is likely due to founder effects.

- Afrikaners are mainly descended from a group of about 1800 white settlers sent by the Dutch East India Company, who reached the Cape of Africa in about 1652. These were later joined by settlers from France and Germany, and by 1800, the total white settlement was about 15,000, mainly of Dutch descent. In SA, there are now approximately 2.5 million Afrikaners, and ∼30,000 have HeFH.
- Between 1881 and 1910, approximately 40,000 Jews arrived in SA from Lithuania, and their strong group and religious identity encouraged marriage within the group.
- From around 1860 through the early twentieth century, approximately 150,000 Indians, mainly from Gujerat province, immigrated to SA as laborers, often on the sugar cane plantations in Natal.

Because of these founder effects, Dr. Raal said, there are five main mutations prevalent in these three populations. He said that if an Afrikaner has FH, there is an 80–90% chance that the patient will have one of three mutations. The most common of the three is FH Afrikaner 1 (c.681C>G;D206E), found in about 70% of Afrikaner FH patients, followed by FH Afrikaner 2 (c.1285Q>A;V406M) in about 20%, and FH Afrikaner 3 (c.523G>A;D154N) in about 10%.

Both FH Afrikaner 1 and FH Afrikaner 3 are defective mutations, which result in some residual LDLR activity (5-15%, and 5-20%, respectively), while FH Afrikaner 2 is a null allele (<2% LDLR activity). The mutation predominantly found in affected Ashkenazi Jews in SA — FH Lithuania (654_656del;Gly219del)— is also a null allele (<2% LDLR activity), while the mutation predominantly found in the Indian population of SA — FH Gujerat (c.2054C>T, P664L)—results in 15 – 30% of LDLR activity.

With regard to HoFH, Dr. Raal referred to a retrospective review of the records of 149 SA patients with HoFH followed over a 25-year period in either of the two SA lipid clinics. Twenty-one of the 149 were deceased or lost to follow-up. Of the remaining 128 known survivors, 70 had true homozygous FH, and 58 had compound heterozygous FH. Of the 70 surviving homozygous patients, 43 had the FH Afrikaner 1
mutation (Afrik 1/1 homozygous). In all of the 58 patients with compound HeFH, FH Afrikaner 1 was one of the pathogenic mutations present.

Dr. Raal noted that even in SA, where the majority of genetically confirmed FH cases are caused by 5 founder mutations, there is still a debate about how far to push to identify all the different mutations when there is a clinical diagnosis. Among a group of 1031 subjects attending the Cape Town lipid clinic who had a clinical diagnosis of HeFH, only 46% had a mutation identified by testing for locally prevalent mutations.69 He stressed that in SA, clinical testing is recommended to identify affected relatives of index cases with a clinical diagnosis of FH.70 Explaining the current practice in SA for suspected FH, he said that when a mutation is identified, DNA testing of relatives is considered worthwhile and should be performed; however, when no mutations are identified, screening the family according to clinical criteria and lipid levels is considered sufficient.70

To be maximally cost effective, Dr. Raal said, cascade testing for FH should be systematic, centrally coordinated in specialized centers, and carried out using a combination of clinical criteria and genetic testing. He stressed that a national, family based follow-up system to enable comprehensive identification of affected persons with FH is a priority.70

Dr. Raal informed the Summit participants that at the lipid clinic in Johannesburg, there are approximately 3000 HeFH patients from 1000 pedigrees. He personally sees 20 to 30 new FH subjects each year, and follows about 50 HoFH individuals. At the Cape Town clinic, because it is a smaller city, there are about 1500 HeFH patients.

Dr. Raal pointed out that SA does not yet have an adequate FH screening program, because FH is eclipsed by the high numbers infected with HIV (>10 million in SA), malaria, chronic hepatitis B, and tuberculosis, and because of the rising prevalence of “lifestyle diseases” like Type 2 diabetes mellitus and hypertension. He noted that, in spite of high prevalence and a large effort to increase awareness among GPs, FH remains undiagnosed and untreated in the majority of affected South Africans. Based on MedPed estimates regarding the prevalence of FH diagnosis and treatment as of 2002, in SA, <20% of FH patients are diagnosed; <10% of FH patients are on any medication; and <5% of FH patients have achieved “good” cholesterol control, defined as LDL-C < 3 mmol/L.

Dr. Raal concluded by presenting photographs of xanthomas on the wrist and ankles of a two-year-old child with HoFH. He said that the little boy had been seen by several pediatricians, none of whom measured a cholesterol level, before the child was finally referred to the lipid clinic by a dermatologist.

3 Session IV – Amy Sturm, MS, CGC
Challenges of Implementing Genetic Testing into Cascade Screening Efforts in the United States

Amy Sturm MS, CGC (Clinical Associate Professor and Certified Genetic Counselor, Division of Human Genetics; Associate Professor, Internal Medicine; Ohio State University), described for the Summit
participants the challenges faced in the United States (US) in efforts to incorporate genetic testing into a program of cascade screening for FH. She emphasized that for FH cascade screening with genetic testing to succeed, the causative mutation in the index patient must first be identified.

Ms. Sturm observed that it has been shown, based on data from other countries, that FH cascade screening – systematic family tracing – can be cost effective,\(^{71,72}\) and further, that cascade screening that combines genetic testing plus lipid testing is more cost-effective than a lipid panel alone.\(^{73}\) However, she said, while detection of pathogenic LDLR, APOB, or PCSK9 provides an unequivocal diagnosis of FH, such genetic testing has not been systematically incorporated in the US, and there are no US guidelines recommending genetic testing in FH. In the US, therefore, genetic testing is not the standard of care, even though it is considered the diagnostic gold standard.

Ms. Sturm noted that in the US, clinical genetic testing is available via multiple commercial laboratories, but these vary in clinical sensitivity, cost, and health insurance billable allowances. Physicians who want genetic testing to confirm index cases and screen family members are often deterred by the knowledge that a genetic test for FH can be ordered but not necessarily reimbursed. In addition, cardiologists and other clinicians may be confused about when to order a genetic test.

In order to systematically incorporate genetic testing into cascade screening in the US, Ms. Sturm listed three needs that must be met:

1) **Development of US-based guidelines, recommendations, and consensus statements that specifically address genetic testing**

2) **Identification of the pathogenic mutation in the index patient**

3) **Identification and contact of biological relatives to commence cascade genetic testing**

Ms. Sturm noted that the success of cascade screening programs is dependent on a high uptake of screening from the proband’s first and second-degree family members (‘contact tracing’), which in turn depends on the information being reported to those relatives by the proband.

Citing the NIH Genetic Testing Registry, Ms. Sturm noted that the clinical sensitivity is far from 100% for the available tests for FH mutations in LDLR, APOB, and PCSK9, which account for approximately 60 - 80%, 1 – 10%, and <5%, respectively, of FH cases. She noted further that the price for such testing is still high in the US, with the cost currently ranging from \(~\$400 for targeted mutation analysis of either APOB or PCSK9, to \(~\$1300 for whole gene sequencing of LDLR, while commercial labs bill payers about \$1000 to sequence a gene. However, she argued that the same issues of imperfect accuracy and high cost are faced with virtually every condition evaluated in the genetics clinic, and that, given the understanding of such limitations by the patients and providers, genetic testing can still be utilized effectively.

Ms. Sturm pointed out factors that will contain costs for FH genetic testing in the US. **She noted that once the pathogenic mutation has been identified in the index case, it becomes much cheaper to test the patient’s family members, because testing can be limited to the same single mutation.** Further,
she noted, for more than a decade, technological advances have resulted in steadily decreasing DNA sequencing costs, and since 2008, the cost per megabase of DNA sequence has fallen precipitously.74

Regarding the issue of health insurance coverage of FH genetic testing, Ms. Sturm noted that coverage for genetic testing in the index patient, in whom the diagnosis may already be known, will be the first major obstacle. From her own genetic counseling practice, she knows that, particularly for an index patient who already has a clinical diagnosis of FH, the insurance company will always ask whether genetic testing is medically necessary, and whether results will affect their medical treatment or management. She noted that the National Lipid Association (NLA) clinical guidance, by stating that “Identification of the causal mutation may provide additional motivation for some patients to implement appropriate treatment,” may help to make the case for insurers to cover FH genetic testing, even in the clinically diagnosed index case.39,75

Ms. Sturm noted that, currently, no US insurers have criteria for coverage of FH genetic testing, although many of the top US insurance companies have very specific criteria for coverage of, for example, pediatric genetic conditions, hereditary cancer syndromes, and hereditary cardiovascular conditions such as long QT syndrome and other inherited arrhythmias.

Ms. Sturm emphasized that generally, genetic testing for FH is not occurring in the US. Just prior to the FH Summit, she had been informed by Ambry Genetics (Aliso Viejo, California) that over a two-year period, the company received only approximately 100 requests for comprehensive FH panels. According to Ambry’s records, insurance coverage had varied, but at least in a few cases, genetic testing had been covered by the insurers at 100%.

Ms. Sturm also highlighted relevant guidelines from three expert groups which have taken a stance with regard to FH genetic testing:

- In 2011, the NLA Expert Panel on FH wrote that there are “…cases when genetic testing has an important role, such as when the diagnosis of FH is uncertain. The panel recommends that genetic testing should be covered by payers under those circumstances.”39,75

- In 2008 and again in 2011, the National Institute for Clinical Excellence (NICE; UK) clinical guideline recommended that a DNA test be offered to people with a clinical diagnosis of FH, and then, if a gene mutation is identified in the index case, testing for that mutation, and not LDL concentrations, should be used to identify affected relatives.76

- The Cardiac Society of Australia and New Zealand (CSANZ) Cardiovascular Genetics Working Group wrote that “genetic testing can provide certainty of diagnosis” where there are confounding factors such as borderline cholesterol levels or inconclusive family histories. The CSANZ working group recommended that patients be offered genetic counseling before consenting to genetic analysis.77
Ms. Sturm made the case that genetic FH testing in the US is far from standardized, and lags behind programs of testing for other cardiovascular genetic conditions. As an example, she pointed to the 2011 joint statement of the Heart Rhythm Society and the European Heart Rhythm Association (HRS/EHRA), in which genetic testing was designated Class I (recommended) for any patient in whom a cardiologist suspects inherited long QT syndrome (LQTS) or hypertrophic cardiomyopathy (HCM). In both cases, mutation-specific genetic testing is recommended for close family members and subsequently for other appropriate relatives, following the identification of the LQTS- or HCM-causative mutation.

Ms. Sturm observed that the identification of a pathogenic mutation in an index patient must be the impetus for targeted testing of potentially FH-affected relatives. She raised the question of whether it is better for the relatives to be contacted by the index patient or by the clinic and praised the review by Newson and Humphries about the advantages and disadvantages of each approach. The authors had noted that proband-initiated family contact is the standard practice recommendation in clinical genetics because it protects confidentiality. With proband contact, however, they felt that response rates were likely to be lower due to the following causes: information from a proband could have less impact than that from a health professional; the probands may never contact relatives if they are geographically or socially distant; or the probands could provide incorrect information to relatives. The authors acknowledged the concern that direct contact, such as a letter from an unknown medical team informing the family member of a health risk, may cause the relatives psychological harm, but they cited evidence that in fact, relatives tended to report relief rather than anger or annoyance at learning of their genetic risk. The authors also believed that the risk that relatives might face higher insurance costs after receiving genetic information directly from the medical team was negligible.

While noting the limitations posed by standards of patient confidentiality and consent, Ms. Sturm pointed out that direct contact by the clinician appears to have the higher yield, in terms of relatives tested. Contact by the clinicians also could lessen the burden on the index patient, who is dealing with implications of a new diagnosis, who may feel incapable of communicating the information, or who may not be geographically or socially close to the relatives. She noted that choosing the optimum method of contacting family members to inform them of their potential risk for FH is a major area for further research in the US.

Drawing on experience with cascade screening for Lynch syndrome, another Tier 1 genomic application, Ms. Sturm summarized a recent systematic review that examined the frequency of uptake of genetic testing by the relatives of Lynch syndrome probands. Eight studies were included in the final analysis, including three that were confined to US sites. In six of the seven studies that detailed the method of contact, contact of relatives was initiated by the proband or, after consent for contact of FDRs, via written or phone contact by the academic medical center staff. She noted that relatives’ uptake of screening was low, with only 34% to 52% of FDRs undergoing genetic testing. Only 0.2 – 3.6 relatives were tested for each proband. Uptake of genetic testing for Lynch syndrome was associated with age <50, female, parenthood, education level, employment, participation in other medical studies, lack of depression, and family history including a greater number of relatives with cancer.
Ms. Sturm provided references to expert guidelines that recommend genetic counseling for persons affected by hereditary cardiac conditions, and to evidence of clinical and psychological benefits accruing to patients when a genetic counselor is involved in their care.\textsuperscript{81-87} She pointed out that there is evidence that \textit{genetic counseling interventions for probands and their families can increase the number of at-risk relatives who present for recommended evaluations, both clinical, such as measurement of lipid levels, and genetic.}\textsuperscript{83,88} Ms. Sturm also noted that, in their recent policy statement on genetics and cardiovascular disease, the American Heart Association Advocacy Coordinating Committee wrote, “We strongly advocate the involvement of physicians and centers with expertise in cardiovascular genetics...they will provide genetic counseling.”

Ms. Sturm concluded by presenting the pedigree of an FH family that is followed by the genetic counseling clinic where she practices. While acknowledging the limitations of self-reported family history data, she explained that genetic counselors work very hard to collect such data, confirm it with medical records, enter it in the patient’s electronic medical record, and provide it to the index patient along with a request that they share information with appropriate family members.

4 Session IV – Dev Datta, MD, MRCP, FRCPath
The FH Wales Cascade Testing Service

Dev Datta, MD, MRCP, FRCPath (Medical Advisor, All Wales Familial Hypercholesterolaemia Cascade Testing Service; Spire Cardiff Hospital) noted that the FH cascade screening service in Wales is funded by the British Heart Foundation and by the Welsh government. He observed that, based on the conservative estimate that 1 in 500 people worldwide have FH, there are expected to be about 110,000 affected people in the UK, of whom 6000 will be in Wales; however, less than 20\% of that number have been diagnosed and treated.

Dr. Datta explained that the protocol for FH cascade testing in Wales, a program currently in its third year, is based on National Institute for Health and Care Excellence (NICE) clinical guideline #71 (2008). He noted that FH Wales is made up of a multidisciplinary team — lipid physicians, a pediatric nurse and pediatrician, genetic counselors, FH specialist nurses, laboratory staff, and an FH research officer — and that all must work together for the screening program to succeed.

Dr. Datta said that, contrary to his early belief that the FH Wales program would “open the floodgates” and bring in multitudes of patients for screening, it has been difficult to get primary care providers (PCPs) to understand what FH is and what it is not, and to then send their patients for genetic testing and cascade screening. The FH Wales team, he said, has devoted a great deal of time to diverse educational efforts aimed at PCPs, including via the internet and social media; they produced an educational video that physicians can view to earn appraisal points. Dr. Datta said that there is not currently a financial incentive for providers to identify FH, but that is being considered in Wales as a possibility.
Dr. Datta presented a flow chart to show the path followed by each patient who is referred to FH Wales for cascade testing. A patient with suspected FH is referred by a GP or perhaps a cardiologist to a lipid clinic for clinical and lipid assessment. If the patient receives a provisional diagnosis based on Simon Broome criteria, his or her family history is documented, and the patient is offered genotyping, as well as treatment based on the lipid profile. Patients flagged using Simon Broome criteria are also offered cascade testing of FDRs.

Dr. Datta explained that each patient who tests genotype positive meets with a genetic counselor, who explains in detail the reason for family testing and how it will be performed. The patient is referred to a regional Family Cascade Program for family registration and tracing, and the FDRs are contacted for testing. If an FDR is found who has clinical and/or genetic FH, that individual becomes a new index case and in turn, his or her family is traced and the FDRs are offered testing. Persons with FH identified in the Cascade Program are referred to their local lipid clinics for ongoing management.

Dr. Datta reported that the FH Wales Family Cascade Program uses a combination of indirect and direct contact to reach out to the relatives of FH patients. The patient is given the choice as to whether family members will be contacted directly by the FH Program, or indirectly by the patient, who is given information about the testing to pass on to family members. Dr. Datta noted that the best option for contact depends on the family: some patients don’t want certain family members contacted directly, while other patients are not concerned. He cautioned, however, that family members come in much more slowly when informed indirectly by the patient.

Only a few months prior to the FH Summit, FH Wales began to provide genetic counseling for each patient who received a genetic diagnosis of FH. The genetic counselor explains to the patient in detail the reasons for extending testing to the patient’s family members and the ways in which cascade testing will be performed. Dr. Datta noted that one reason that genetic counselors were added to the team was that they were expected to increase the yield of relatives coming in for cascade testing.

The FH Wales program has each FH family pedigree stored in a system that is accessible to all authorized personnel. As each patient’s test results are added to the system, they are automatically integrated within the pedigree, providing an overview of cascade testing for the family: who has been tested and who has not; who is positive for a mutation and who is negative.

Dr. Datta explained that FH Wales has been using “modified Dutch” criteria, not to diagnose FH but as a tool for determining whether or not to perform genotyping. The one item that differs from the DLCN criteria is that tendinous xanthoma is counted whether present in the patient or a relative, since, even if the patient is unsure about any relatives having xanthoma, such information may still be available for family members registered within the health system. The criteria also take into account the patient’s LDL-C and incorporate a subtraction for fasting triglycerides, since patients with combined hypercholesterolemia are less likely to have a genotype-positive diagnosis of FH.

The FH Service in Wales uses a modified Dutch criteria tool to decide which patients will undergo genetic testing. Dr. Datta explained that a numeric score is derived from measures of family history, clinical
signs, cardiovascular history, LDL-C, and triglyceride levels. Each criterion is weighted differently, with varying scores. And only one score can be circled from each section. Using these criteria, if a patient has a score of 6 or above, then they would be regarded as eligible for genetic testing. Patients scoring less than 6 are only eligible if there are special clinical circumstances; this allows some clinical judgement.

Dr. Datta explained how the criteria are used with the example of a theoretical patient:

1) Family history: The theoretical patient has a FDR with CHD before the age of 60, and so scores 1.
2) Physical examination: The theoretical patient is found to have tendon xanthomata, and so scores 6.
3) Clinical history: The theoretical patient had an MI at age 55, and so scores 2.
4) LDL-C: The patient is found to have a pre-treated LDL-C level equal to 7 mmol/L, and so scores 5.
5) Fasting triglycerides in this patient are slightly elevated, so 2 is subtracted from the score.

Dr. Datta explained that the modified criteria subtract points from the score if the patient has elevated triglycerides, not because the Programme is trying to completely exclude patients who appear to fit the clinical criteria for familial combined hyperlipidemia (FCH), but rather in order to differentiate between FCH and FH. Clinicians completing the scoring form for a patient are asked to record any clinical reasons the patient may have that would account for elevated triglycerides, such as poorly controlled diabetes or obesity.

The theoretical patient has a total score of 12, and therefore will be eligible for genetic testing.

Dr. Datta presented preliminary data showing the correlation between patients’ scores based on the modified Dutch criteria and the pick-up rate for pathogenic mutations. *When patients in Wales were evaluated for FH according to the modified criteria, those with a low score were unlikely to have a pathologic variant, while those with higher scores were very likely to have a pathologic variant, particularly if they had tendinous xanthoma.* Of the initial 623 index patients who were genotyped, the likelihood of finding a mutation among patients who scored 5 or less was only 4%. The percentage increased as the score increased: the chance of having a pathogenic mutation identified was 9% among patients with a score of 6; 16% among patients with a score of 7 – 8; 38% among patients with a score of 9 – 10, 51% among patients with a score of 11 – 12; and 81% among patients who scored 13 or higher. Dr. Datta said that genetic testing may not be very useful in the “query FH” case, adding that in his experience, if he finds himself wondering whether a patient has FH or not, then they probably do not.

Dr. Datta spoke about the information technology (IT) system that is utilized for the Cascade Screening Programme. He explained that, like a registry, the system incorporates all relevant demographics, the patient’s DNA report, treatment, etc. In addition, however, the system provides a system of workflow, showing the key individuals — genetic counselors, nurses, laboratory staff, physicians — who work with
the patient or their samples. The ability to map work by different clinical members of the team allows coordination of their work to cover all of Wales.

After two and a half years of gathering data, Dr. Datta said, FH Wales has genotyped approximately 1500 patients, of whom more than 900 are index cases, with the rest being relatives. Of the index cases, approximately one-third have been genotype positive, while among the relatives screened, approximately half have been genotype positive and half genotype negative. Overall, the programme in Wales had identified slightly fewer than 600 people with genotype positive FH, at the time of the FH Summit. He stressed that another important accomplishment is that the Cascade Testing Programme in Wales has been able to reassure more than 200 people in FH-affected families that they do not have FH.

Dr. Datta talked about public awareness campaigns used by FH Wales to engage both people in the community and GPs. He displayed a magazine article, “Could a letter save your life?”, describing the experience of the owner of a large dairy business in Wales who thought she was in good health, but who, because of her siblings’ early-onset CVD, asked a GP about the possibility of a genetic role in the family’s cardiovascular problems. The GP suggested that she have genetic testing for FH. She did have a positive genotype, and so had an angiogram and, within a few weeks, triple bypass surgery. Direct contact letters were sent out to all of her relatives. Those who lived in Wales came forward for testing. The Cascade Testing Programme sent letters to the patient’s relatives in Scotland, London and Australia. The son who lives in Australia took the letter to his doctor and subsequently ended up having a scan which showed extensive coronary disease and resulted in him having a bypass operation which most probably saved his life.

Dr. Datta noted that FH Wales has an active family forum, and these patients and their families have been particularly important in getting the cascade testing service funded. He stressed that a program to identify FH patients and start them on life-saving treatments will not succeed without the involvement of the patients themselves. He noted that, although he thinks he knows “a bit about FH,” when he talks with his FH patients, he always learns that he needs to know much more.

Session IV – Panel Discussion

Moderator: Muin Khoury, MD, PhD  
Faculty: Fernando Civeira, MD, PhD (Spain); Frederic Raal, MD, PhD (South Africa); Amy Sturm, MS, CGC (United States); Dev Datta, MD, PhD (Wales).  
Panelists: Joep Defesche, PhD (Netherlands), Mariko Harada-Shiba, MD, PhD (Japan), Jie Lin, MD, PhD (China), Gerald Watts, MD (Australia)

In opening the panel discussion following Session IV, moderator Muin Khoury (Office of Public Health Genomics [OPHG], CDC) observed that the Session IV speakers had made clear that the implementation of cascade screening is complicated. He commended FH Summit participant and genetic counselor Karen Greendale, MA, CGC (Consultant, McKing Corporation for OPHG), who in consultation with the OPHG
had worked for the previous year on developing the OPHG clickable map and virtual toolkit, which focus on the Tier 1 applications, all of which utilize cascade screening.

Dr. Khoury first asked the panelists to react to the information presented on cascade screening and to address the associated challenges based on their own experiences and perspectives.

Joep Defesche, PhD (Chairman, International FH Foundation; Head, DNA Diagnostic Laboratory, Department of the Netherlands) pointed to approximately 23 years of cascade screening experience in the Netherlands, saying he credits the Dutch screening program’s success at least in part to the fact that, from the beginning, genetic testing and DNA analyses have always been covered by national health insurance.

Currently, Dr. Defesche said, there is a very high rate of participation in the Dutch screening program: approximately 98% of all family members contacted are willing to participate, and the results, whether positive or negative, are often seen as “good news”. Approximately two thirds learn that they don’t have the familial mutation, will not pass a mutation on to their children, and have normal cardiovascular risk. Even for the one-third who learn that they have a mutation, the news may come as a relief: Dr. Defesche explained that there is a high level of anxiety in families with FH, who all wonder whether or not they will be affected like their relatives who have had heart disease or even have died at a young age. With cascade genetic testing, he noted, people are learning at a fairly young age, often before age 40, whether they have the familial mutation, and they learn that they can take advantage of appropriate, effective treatment.

Addressing Summit participants working toward a program of FH screening for the US, Dr. Defesche stressed that, just as in the Netherlands, Wales, or Spain, “you just have to start.” He noted that screening in his country was in the first couple of years essentially a pilot program limited to investigation of the family members of index cases and funded by the investigators’ own research funds. After the first few years, the Dutch government picked up the program because of its clinical and economic effectiveness.

Dr. Defesche recommended that cascade screening in the US begin similarly on a small, regional scale, requiring only a small group of knowledgeable physicians and one laboratory that can perform the genetic testing. Other regions, he said, will quickly follow. He noted that an initial financial investment will be necessary in the US, but that support will grow once it becomes clear that screening succeeds in relieving the cardiovascular burden on tested individuals and their families.

Regarding the state of FH screening in Japan, Mariko Harada Shiba, MD, PhD (Director, Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center, Japan) said that very few lipidologists are ordering genetic testing for their patients with lipid disorders. She noted that in her country, despite recent publication of guidelines that recommend cascade
screening for FH, genetic testing for FH is available at only two institutions, and less than 2% of the expected number of people with FH are diagnosed.

Jie Lin, MD, PhD (Professor, Department of Atherosclerosis, Department of Endocrinology; Beijing Anzhen Hospital, Capital Medical University; China) noted that FH is a big problem in China because of the large population; however, there have been no guidelines and little information specifically about FH in China until recently.

Beginning in 2005, Dr. Lin and her colleagues have collected nearly 70 pedigrees from about 300 FH patients. She said that until 2010, individuals with heterozygous mutations for FH were identified by means of denaturing high pressure liquid chromatography (DHPLC) and then with the first generation sequencing methods. Since 2010, Dr. Lin and other researchers in China have used random mutation capture technology and second generation sequencing to find additional FH mutations in Chinese patients.

Dr. Lin noted that the main problem of genetic testing is cost, especially in China, where there is limited health insurance. She wants to see more genetic testing for individuals in China with FH, so that the window of opportunity for treatment from an early age is not missed. She noted that genetic testing for FH is a critical public health issue in China.

Gerald Watts, DSc, MD, PhD, FRCP, FRACP (Chair, FH Australasia Network; Director, Metabolic Research Center & Lipid Disorders and Hypertension Clinics – Royal Perth Hospital) suggested that there are a number of necessary elements for a successful national program of cascade screening. He noted that the screening program must be integrated into patient care, so that patients who appear to be at high risk for FH are in fact screened.

Speaking from his experience, Dr. Watts emphasized that in order to secure payer and government support, proponents of a US program of cascade screening for FH must demonstrate the cost effectiveness of such a program using US-based data. He noted that success will require the support of the community, of FH family support groups, and of PCPs.

Dr. Watts noted that central coordination has been absolutely vital to the successful cascade screening program in Western Australia. He suggested that both federal and local sources of funding be explored, in particular to fund DNA testing as an integral part of the cascade screening program. He noted that in Australia, nurses with genetic counseling skills are often the ones to find and contact family members of index cases.

Dr. Watts noted that laws on the nondisclosure of health information pose significant ethical issues for cascade screening programs, definitely slowing attempts to extend FH screening to family members. He stressed that staff of the screening program have no choice but to comply with the laws that apply in the local jurisdiction.
Dr. Watts said that cascade screening has to be viewed as “opportunistic screening.” For example, he noted that getting parents to have their children tested is problematic in the screening program in Western Australia, but he is optimistic that universal screening of school children will help to resolve that problem. He provided examples of how to find the index cases, such as having local laboratories flag suspicious lipid results and alert PCPs to the possibility of FH, or by screening all personnel working in corporations, mining companies, and universities.

Dr. Khoury asked the panelists to say more about dealing with the ethical constraints of informing family members, when an index patient is found.

Dr. Civeira noted that in Spain, the duty to warn family members is in fact the driving force behind the program of cascade screening. He observed that when a cardiologist, lipidologist or internist learns that a patient has FH, the physician has a great responsibility to have family members informed and tested.

Ms. Sturm agreed that there is a duty to warn potentially affected family members, although, she said, privacy laws in the US don’t allow providers to go directly to the family without the patient’s consent. She added that in the US, there is legal precedent set, with regard to genetic disorders, that physicians could be held liable if they fail to document that they at least counseled the index patient that his or her family members could be at risk.

Dr. Khoury next asked that representatives of regions where there had been many years of cascade screening experience tell what they would do differently, if they were to set up an entirely new national program of cascade screening. He asked how they would start a program “from scratch,” given the information technology available in 2013 and the ability to make use of social media to enhance awareness in the general population.

Dr. Datta (Wales) observed that there will always be local differences, and so there can be no one way to develop such a program. He noted that the FH screening program in Wales could probably be carried out in a similar way across the UK, but due to different health care systems, programs of cascade screening in other parts of Europe and certainly in the US will probably be very different. Dr. Datta observed that the cascade screening program in Wales began two-and-a-half years ago, and that he and his colleagues have spent most of that time, far longer than they had anticipated, just trying to involve all the relevant stakeholders and get the program set up. He had initially thought that a program of FH education directed to GPs would result in the referral of large numbers of suspected FH patients and their families for screening; however, that has not been the case. What had probably been the most effective effort, Dr. Datta reported, was when nurses from the FH service visited the offices of GPs, taking with them the laboratory lipid results and showing the GP exactly which of the GP’s patients had an LDL-C >7.5 mmol/mL (~300 mg/dL). Once a GP saw that the patient could be referred to the FH
service, receive a genotype diagnosis, and, through cascade testing, have vulnerable family members tested, they quickly became supportive of the program.

Dr. Watts (Australia) noted that in retrospect, if there had been enough money, he would have concentrated more on identifying index cases to pour into the system. He said that, early on, the program’s managers were less impressed with the need to detect index cases among patients in coronary care, but five years later, they believe it to be crucial. Dr. Watts also recommended that screening be focused on FDRs, saying that more distant relatives in the extended pedigree will generally be picked up in universal screening programs or by selective screening based on their own clinical phenotype and history.

Regarding DNA testing, Dr. Watts said that he generally agrees with Dr. Datta’s results showing little need for genetic testing of a patient whose score on the Dutch criteria is less than 4 or 5. However, he stressed that sometimes criteria-based scores don’t give the correct answer, so that the doctor must rely on clinical know-how. Dr. Watts recalled that one of the first patients seen in the Australian screening program was a GP who told him that she had FH; her total cholesterol was 6.4 mmol/L (−250 mg/dL). Since the patient said that she had FH, he asked that her 72-year-old mother come in for evaluation. The mother’s Dutch lipid score was only 2, but she had corneal arcus, so Dr. Watts decided to break protocol and perform DNA testing. There was in fact a pathogenic mutation, and as a result, the entire family has been screened. He stressed that there must be protocols and criteria for DNA testing, but that, in the end, the physician has to factor in his or her “intuition” about whether the patient has FH or not.

While acknowledging the importance of education and of finding ways to have GPs think of identifying patients who might have FH, Dr. Defesche (the Netherlands) observed that most people with overt FH will be identified, so his concern is finding the people whose FH is not yet apparent. He noted that the yield of FH patients diagnosed could be greatly increased by means of “reverse cascade testing,” that is, carrying out universal screening of children as they enter school, and then going backward to screen the parents of any children found to have mutations.

Pointing to data out of the UK and the Netherlands that demonstrate the cost effectiveness of cascade FH screening, Dr. Khoury asked the panelists to consider one final question: In a time of limited resources, what kind of data will be enough to get cascade screening for FH integrated into the US health system and have it paid for?

Dr. Watts (Australia) made the point that, in the US, universal newborn screening for congenital hypothyroidism is paid for, although the prevalence, approximately 1:20,0000, is very low compared with a prevalence of 1:300 in FH, and that looking for the more prevalent disease is much more cost effective. He said that he could not understand why a child in the US could not have cholesterol testing, when so many other measurements are being done.
Dr. Datta said that there must be US data to support the cost effectiveness of the initial screening of suspected FH index cases and of cascade screening. He noted that there must be US-based data to demonstrate the worth of FH screening in terms of quality-adjusted life-years.

With regard to achieving payment for FH testing, Dr. Defesche reminded the panel of the importance of an active and powerful patient-based FH organization, which, he noted, the US fortunately now has.

Returning to the topic of newborn screening, Dr. Khoury observed that it is well organized and has gone on for 50 years, with four million births screened every year in the US in order to pick up approximately 10,000 infants who have any of the more than 30 conditions on the panel. He said that if the US similarly funded adult-based genetic screening, which could have among its components Lynch syndrome, Hereditary Breast/Ovarian Cancer, and FH, the yield would eclipse that from newborn screening, based on the prevalence of FH alone. The difference, Dr. Khoury noted, is that the case has already been made for newborn screening, but not for an adult-based screening program, which would require building consensus among different groups for different diseases with different guidelines, as well as across 50 different states.

Dr. Khoury continued that he was not advocating for screening newborns for FH, but rather for a public health/health care collaborative model to conduct universal FH screening at some evidence-based point of life, whether that was age 10 years, 20 years, or something in between. That model would identify the probands at a young age, and cascade screening could proceed through their families.

Dr. Watts added a caveat regarding reverse cascade screening when a child is the index case, noting that the stakeholders involved in the cascade screening program in Australia strongly opposed that idea, due to the potential harm of disclosing the child’s genetic or even phenotypic diagnosis of FH to a parent who may not previously have been aware of non-paternity.

Session IV – References

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Session V
CAN NATIONAL REGISTRIES IMPROVE POPULATION-BASED FH SURVEILLANCE AND OUTCOMES?

The final session of the FH Summit was focused on the potential for national registries to improve population-based surveillance for FH, and vitally, to improve patient outcomes.

1 Session V – Jacques Genest, MD, FRCP
FH Registries Overview

In his written abstract for the Program of the 2013 FH Summit, Jacques Genest, MD, FRCP (Scientific Director, Center for Innovative Medicine, McGill University Health Center; FH Foundation Steering Committee) summarized the importance of disease registries as follows:

“National registries for rare diseases are increasingly mandated by Health Authorities in order to determine the prevalence of a disease, standardize medical care, and provide therapeutic options and access to costly therapies. In the field of cardiovascular diseases, such registries provide a glimpse of current clinical practices, are used to identify care gaps and unmet needs and, by using longitudinal follow-up, allow the evaluation of temporal changes in clinical care and the impact of guidelines and novel therapies on outcomes. Importantly, registries provide a key link between patients, health care providers and payers...”

Dr. Genest opened with the observation that the Netherlands, Spain, and Wales are recognized to have a successful approach to the management of FH, and their programs have excellent FH registries. The US, Brazil, Australia, the Czech Republic, Ireland, New Zealand, Norway, the Slovak Republic, Slovenia, France, and Canada are developing FH registries, and there is much to be learned from their successes and challenges. Dr. Genest noted that there had been previous programs in the U.S., which developed FH registries; notable among these is the MEDPED program, championed by the late Dr. Roger Williams.

Dr. Genest noted that a recurrent theme across successful FH registries is that all stakeholders and partners are involved: the “champion” specialist, health care teams, health care systems, pharmaceutical and biotechnology companies, granting agencies, and the patients themselves are all extremely important factors in making the registry a success. He noted that clear practice guidelines must be provided to physicians and other providers with continuous measurement of performance indicators and feedback given to the providers. Finally, said Dr. Genest, goals regarding patient outcomes must always be kept in mind.

Dr. Genest pointed out that the success of a large registry requires more than a single source of funding. He noted that in a recent paper by Humphries, et al. on the study of an LDL-C gene score to distinguish polygenic and monogenic FH,89 the list of stakeholders included the British Heart Foundation, several
pharmaceutical companies, the NIH, the NHLBI, the John D. and Catherine T. MacArthur Foundation, and the Department of Health and Trade Industry.

Dr. Genest commended an analysis by the NICE group in the UK,\(^90\) which found that a cascade screening strategy can lead to an estimated 101 fewer cardiovascular deaths per 1000 patients with FH. He added that he is not aware of many screening strategies offering that magnitude of benefit to patients. Importantly for government, he said, the NICE group estimated cost savings on the order of £378M, for a yearly program cost of about £6.9M. Clearly, concluded Dr. Genest, the cost of cascade screening for FH would seem to be handsomely repaid, and the Summit participants must convince their colleagues and their governments that this is a worthwhile venture.

Dr. Genest next cited the European Atherosclerosis Society (EAS) consensus guideline on FH,\(^91\) focusing on the authors’ stance with regard to the contact of relatives for cascade screening. The EAS consensus is that notification of relatives [for cascade FH screening] should generally not be initiated without consent of the index case. Likewise in Canada, Dr. Genest noted, notification of relatives must be thoroughly discussed with the index patient during the informed consent process, and respect for the patient’s privacy and autonomy is extremely important. He pointed out how disconcerting it could be to receive a phone call from someone who says, “I am your brother’s doctor and I want to test you for FH,” when the siblings never talk to one another.

Dr. Genest also stressed the EAS principle that all material communicated to relatives, as well as the approach to such communication, should be comprehensible and not cause alarm, especially when dealing with young patients. He noted that pretest counseling should be offered, an important role for nurses and genetic counselors.

Dr. Genest observed that genetic testing is important in making this diagnosis, but not always obligatory. In some small communities, he noted, he may be able to make a highly accurate molecular diagnosis based only on the individual having the same surname as a family known to be affected.

With regard to the interpretation of genetic testing, Dr. Genest highlighted the following tenets of the EAS consensus:\(^91\)

1. If genetic testing detects a causative mutation, a definitive diagnosis of FH can be made in the tested individual, particularly when the phenotype also suggests FH;
2. If genetic testing does not detect a causative mutation, the diagnosis of FH can be excluded, except when the clinical phenotype is highly suggestive of FH;
3. If genetic testing detects a causative mutation but the phenotype does not suggest FH, then a definitive diagnosis of FH should not be made; however, LDL cholesterol in the individual and first-degree family members should be monitored every 2-5 years.

Dr. Genest stressed that in spite of the advanced technology now available, an absolute null diagnosis still cannot be made if a patient has very high LDL-C but no mutation. However, he said, when a causal mutation is found in the index case, it makes possible very rapid cascade screening.
Also noted in the EAS consensus is the point that genetic testing for FH may have implications for insurance coverage in certain countries, and Dr. Genest observed that in the US, genetic testing could affect insurance premiums.

Dr. Genest noted that there is a tremendous overlap, in terms of appropriate management and follow-up, between the group of patients who have causal mutations in the LDL receptor and/or PCSK9 genes and those with only a clinical diagnosis of elevated cholesterol. He pointed out that some patients with an unambiguous DNA mutation have normal cholesterol, suggesting that there may be some protective genes. Further, there is a significant minority of patients in whom no molecular diagnosis can be made despite a very high LDL-C. He said that the recommendation in this situation is to treat predominantly the LDL-C level and not the mutation.

Dr. Genest referred to data published in the EAS consensus, which showed that in FH, the increase in CVD risk ranges between eight- and 22-fold.\textsuperscript{91} He noted that in countries with a high prevalence of FH, it may be fairly easy to obtain families’ agreement to screening, because they are aware of the FH-related cardiovascular morbidity or mortality experienced by the index patient.

In Canada, Dr. Genest said, policy makers are now convinced that primary prevention of CVD can be achieved in FH patients who are identified and treated from an early age, and that such patients should have a fairly normal life expectancy. He suggested that as FH patients are treated earlier and earlier and given potent statins in adulthood, it will probably be possible to deflect the curve of morbidity, so that a patient with a diagnosis of FH, but a normal LDL cholesterol, will no longer be a concern for insurance companies. Dr. Genest noted that the EAS group illustrated these gains with a Kaplan-Meier curve showing a tremendous benefit of early treatment of FH patients, in terms of cumulative coronary heart disease event-free survival.\textsuperscript{91}

On a less positive note, Dr. Genest noted that severe under diagnosis and under treatment of FH continue, concurring with the EAS that “\textit{there is an urgent worldwide need for diagnostic screening together with early and aggressive treatment of this extremely high-risk condition.}”\textsuperscript{91} Assessing the burden of disease, he said, is complex, especially as many regions have little or no data to inform estimates of FH prevalence. In Canada, if about 68,000 FH patients are expected, then only approximately 10\% are reported to various databases. Dr. Genest cautioned that if, as SE Humphries et al have suggested recently, estimates of FH prevalence worldwide should be adjusted from 1:500 up to 1:200, then the number of undiagnosed FH carriers is astronomical, and the burden to individual countries will be proportionately high.

Dr. Genest next reported on the efforts of the Canadian Familial Hypercholesterolemia Registry/\textit{Registre Canadien d’hypercholestérolémie familiale} (FH/HF Canada), which is developing a network of 15 lipid research clinics integrating the work of lipid specialists, endocrinologists and cardiologists to treat patients with the highest standard of care and to create a collaborative research environment. Using a “hub and spoke” model, the registry will be extended in various communities to link primary care physicians (PCPs) with provincial academic centers.
Dr. Genest noted that FH/HF Canada is aided by the advice of a team of international experts, many of them, he noted, in attendance at the FH Summit. The mission of FH/HF Canada, Dr. Genest explained, is to create a multidisciplinary group of physicians and basic and clinical researchers to form a Canada-wide network of academic lipid clinics, with the ultimate goal to improve the care of patients with FH and to reduce mortality and morbidity due to CVD in this high risk population.

Dr. Genest noted that Canada is a large country divided into ten provinces and two territories, where health care is universal but is managed at the provincial level. He observed that in Canada, with a single payer for health care and a unique identifier issued to each person at birth, it is possible to track each individual’s use of medical resources, diagnoses, and mortality and morbidity. As a result, said Dr. Genest, health outcomes and health economic studies can be conducted quite well at every provincial level.

Dr. Genest noted that genetic findings can be compared, for example, between Quebec and Ontario. Quebec, he explained, has the typical founder effect - the bottleneck event in this case being the 1759 defeat of the French by the British, essentially ending the migration by the French into Canada, so that present-day French Canadians are descended from an estimated 8000 common ancestors. Dr. Genest explained that five mutations explain approximately 95% of FH cases in Quebec; of the five, one is a mild Exon 3 mutation, while a second one is a severe copy number variant (CNV) in the promoter region of the LDL receptor (LDLR) gene that results in a null allele. Because so many people in Quebec have one of the two latter mutations, he said, it has been possible to compare the severity of disease and outcome between the two affected groups.

Dr. Genest described the governance structure of the FH/HF Canada registry, emphasizing the involvement of patients, clinicians, legal and ethics representatives on the national advisory board, plus an international advisory board of FH experts. The organization includes investigators conducting biomedical, clinical, health outcomes, and health economics research.

Dr. Genest noted that the hope of FH/HF Canada is that their research will lead to the identification of novel targets, but also that the registry will improve patients’ access to expert care, clinical trials, novel therapies, consultation, and cascade screening. The anticipated benefit of FH/HF Canada for clinicians, he said, will be the opportunity to participate in investigator-initiated research in clinical trials, and to work with referral clinics in a spoke-and-hub fashion, while Industry will have immediate access to a large network of experts in Canada, hopefully leading to the identification of novel genes and targets.

FH/HF Canada is developing training and translation to the clinic of the knowledge that is gained, and in that regard, hopes to work closely with the National Lipid Association, which is well-respected worldwide.

Finally, noted Dr. Genest, FH/HF Canada wants to demonstrate benefit for the country: he and his colleagues are writing consensus practice guidelines for FH, including pediatric guidelines, but he noted
that they also hope to provide evidence on health outcomes and health economics related to FH that will assist with resource planning and allocation in Canada.

Dr. Genest described the registry processes planned by FH/HF Canada, saying that a patient with a high LDL-C will be assessed for FH criteria (in development at the time of the FH Summit). Once a patient satisfies the clinical/history criteria for FH, he or she will be entered into the registry, and consent and samples for centralized DNA biobanking obtained. With the patient’s consent, family evaluation will be conducted to the level of first degree relatives (FDR); if an FDR is found to have FH, that individual will become an index patient and be asked to enter the registry system. The registry will conduct longitudinal follow-up, Dr. Genest said, to check lipid level, medication, and vital status. He added that patients who do not satisfy FH criteria will be asked to consent for entry into the Systems and Molecular Approach in Severe Hyperlipidemia (SMASH) registry for other severe disorders of lipid metabolism.

Dr. Genest noted that access to the registry databank will be granted only after review by the appropriate scientific and ethics panels. At the local level, he said, the FH registry can be interrogated for a given patient’s data; however, because the patient will be known by name at the local clinic, such a query will be treated as private health information. Dr. Genest added that, at the provincial level, only the insurance identifier will allow the patient to be tracked, and the database for the rest of Canada will be completely anonymized.

In closing, Dr. Genest emphasized that experience in the Netherlands, UK, and Spain has shown decisively that FH registries can save lives and decrease healthcare costs. FH/HF Canada hopes to meet yearly, if only because over time and with new research, the diagnostic criteria as well as the therapeutic options may change. He described one such change that has made interpretation of the old clinical criteria for FH more difficult: based on 20 years’ data on the clinical presentation of patients with FH in Quebec, the number of new patients who present with tendinous xanthomas/xanthelasmas has decreased by 80%.

2 Session V – Muin Khoury, MD, PhD
Developing National Surveillance Indicators – Healthy People 2020

Dr. Muin Khoury (Director, Office of Public Health Genomics [OPHG], CDC) explained that his colleague Katherine Kolor, PhD (Health Scientist/Policy Officer, OPHG, CDC) was to have addressed the present topic, but was unable to attend the Summit. The idea behind his talk, he said, was to emphasize the need for data, whether from a registry or a national surveillance system. Data drives action, said Dr. Khoury, and the subtext is that what gets measured gets done. Without measurement, he pointed out, he has no way of convincing anyone at the CDC or elsewhere that FH is an important health issue that requires attention.

Dr. Khoury noted that for each of the three Tier one recommendations — BRCA-associated hereditary breast and ovarian cancer (BRCA), Lynch syndrome (LS), and FH— recently issued by the Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP), data collection can occur by
population level approaches and/or by a family-based cascading approach. Although, he said, the data collection may differ in each case, the two strategies can be combined.

In the case of FH, Dr. Khoury said, with the exception of the 2011 American Academy of pediatrics (AAP) guidelines that advocate screening all children at age 9-11, practice guidelines in the US have not changed in recent years. He noted that based on a 2008 recommendation statement, the US Preventive Services Task Force (USPSTF) advises lipid disorder screening starting at age 35 for all men and at age 45 for all women, except for persons at high risk for CVD, for whom screening is recommended to begin at age 20. Dr. Khoury observed that now recommendations would be for screening to begin earlier, especially since the US has adopted the evidence-based NICE (UK) recommendations.

Dr. Khoury asked the Summit participants to consider another example, besides FH, of a genetic disorder where data are beginning to make a difference. Lynch syndrome, he said, has moved into the implementation phase of cascade genetic screening as a result of a long history of research, data collection, and outcomes assessment, and Dr. Khoury emphasized that this progress was definitely helped by the 2009 EGAPP recommendation for LS cascading.

Dr. Khoury explained that LS cascading would be accomplished by universal screening of all cases of colon cancer. In the US, he noted there may be 150,000 cases annually of colorectal cancer (CRC), but only 3000 to 5000 of those will be due to LS. The rationale, he said, is that once the LS proband is found, cascade screening of the relatives should occur, because the FDRs are at 50% risk. For those who are found to have LS, the requirement for CRC screening is not to start at the typical age of 50 or above, but to start at age 20 or 25 with more frequent screening.

Dr. Khoury pointed out that LS cascade screening has generated a lot of debate in the US. He noted that there have been many activities to promote LS screening within both the public and private sectors, including the recent formation of a Lynch Syndrome Screening Network, co-led by Debra Duquette, MS, CGC (Michigan Department of Community Health; FH Foundation Steering Committee). Dr. Khoury noted that there have been a significant number of papers published on the LS cascading experience and results. There is always room for improvement, he said, and supporters of the effort to improve FH screening in the US need to learn from the LS example.

Dr. Khoury reported that the OPHG has canvassed what’s going on at the state level with regard to the three Tier 1 applications, and that, since 2008, the CDC has been actively funding a few states including Michigan, Oregon and recently Georgia, to pursue genomics applications in HBOC and LS. These programs, he noted, are intended to support states in (1) identifying individuals and families who should be targeted for screening, utilizing the cancer registries that every state maintains; (2) educating healthcare providers about genomic screening needs; (3) implementing model payer policies to facilitate coverage consistent with the USPSTF BRCA recommendations; and (4) developing and evaluating new data sources to monitor implementation of screening applications.

Dr. Khoury noted that, due to a lack of funding for public health genomics that is specific to heart disease, similar support has not been available for states to carry out such activities directed at FH. A
further hindrance to the implementation of FH applications, he noted, is that most states do not maintain registries for heart disease, as they do for cancers. Because new cases of any cancer are entered in a state’s cancer registry, it is possible to use a public health approach to do bidirectional reporting: each time the health care system registers a new case of CRC, Dr. Khoury explained, the genomic screening program can go back to the health care system to ask whether the new case has been tested for LS; if not, why not; and to ask how the screening program can help. He added that the CDC is trying to develop new data sources to allow similar approaches for FH screening.

In 2010, the Department of Health and Human Services’ (DHHS) Healthy People 2020 (HP2020) program introduced a new topic area to address the use of genomic testing in clinical and public health practice. Dr. Khoury observed that, as in many countries, the US has public health goals relating to every evidence-based recommendation, genomic or otherwise. He emphasized that whatever gets measured gets done, because, he noted, once a goal is set for the nation that morbidity and mortality are going to be reduced by a specified time, then resources flow from the public health sector, and sometimes from other groups, into that effort. Dr. Khoury observed that HP2020 defines public health objectives related to uptake of genetic counseling and testing for the hereditary cancer syndromes LS and HBOC, but not for FH. Unfortunately, he said, NICE is based on data collected from the UK population, and he stressed that addressing FH in the US requires American data and an American pronouncement.

Dr. Khoury observed that LS is an example where the “needle in the haystack” issue comes to mind because it accounts for only a small fraction of all cases of CRC at any age, although the lower the age of CRC onset, the greater the proportion of cases linked to LS. Similarly, he noted, less than 1% of all heart attacks at any age are related to FH, a proportion that also increases with decreasing age at the time of MI: in people who have an MI before age 65, FH accounts for approximately 3-5% of MI, but in people who have an MI before age 45, FH accounts for 10-20%. As to how to find those “needles in a haystack” and thus prevent disease, Dr. Khoury pointed out that the CDC is known for its surveillance systems in infectious disease particularly, but the CDC Divisions of Heart Disease and Stroke Prevention, Cancer Prevention and Control, and Diabetes Translation are all working to implement active surveillance state by state, sometimes providing funding and technical assistance to allow the states to do the surveillance.

Quoting CDC Director Dr. Thomas Frieden’s statement in 2010 that “The single most important thing that Public Health can do is to increase the degree to which decisions are based on good data,” Dr. Khoury noted that data will drive FH decisions as well. He observed that for any genomic application, and probably for any disease, there is a progression of indices, from defining the burden of the disease, to planning for implementation of the guidelines once they are available, to monitoring the implementation.

In the public health framework, Dr. Khoury explained, to define the burden of the disease in the targeted population, it is necessary to know how many people are affected, which in turn requires a good case definition; plus, the associated morbidity and mortality must also be characterized and quantified. To plan strategies for the implementation of widespread screening requires adoption of a set
of standardized screening criteria. He added that if the necessary data are not available from a registry or surveillance system, then it may be necessary to conduct a population-wide survey. To understand how many people in the US who have early heart attacks have FH, the target population would be all new cases of people admitted with heart attacks. The point is, concluded Dr. Khoury, those data are necessary in order to address FH on a public health level, and while the pertinent FH data are available from some countries, they have not been collected in the US, a fact that he asked the Summit participants to consider a plea for action.

Dr. Khoury next discussed preliminary results from an analysis of National Health and Nutrition Examination Survey (NHANES) data performed by his OPHG colleague Dr. Katherine Kolor. He explained that NHANES is an open access surveillance system that allows population-based estimates of health conditions, awareness, treatment and control of selected diseases, environmental exposures and nutrition status and diet behaviors in a random sample. Since 1999, the NHANES system gathers data from residents of all ages from the 50 states and the District of Columbia, but incorporates oversampling of African Americans, Hispanics, people ages 60 and older, and low income whites. Although NHANES has collected data for many years, Dr. Khoury noted, the yearly sample size of roughly 5000 is not large enough to quantify FH prevalence in the US accurately.

Individuals participating in NHANES are brought by the CDC’s National Center for Health Statistics to a trailer where in the course of a day, they undergo a physical exam, laboratory tests, and an extensive health and nutrition interview. Dr. Khoury noted that among the data collected from each subject, items with particular relevance to FH include total cholesterol, fasting LDL-C, family history of early heart disease, personal history of early heart disease, personal history of CHD, lipid screening history, lipid treatment history, and demographics.

Dr. Khoury stressed that he was presenting very preliminary findings from the NHANES FH study: The first study sample comprises 12,106 adults (20+ years) with complete data in the system on family history of early heart disease, personal history of heart disease, and fasting total cholesterol and LDL-C. The second sample comprises 4648 children (12 – 19 years) with complete data on fasting total cholesterol and LDL-C. From the two age groups, Dr. Kolor is comparing the numbers of FH affected subjects who would be identified, among the various case definitions derived from the MEDPED, Simon Broome, and Dutch diagnostic criteria for FH.

Dr. Khoury pointed out that the NHANES data— having no information on corneal arcus, tendinous xanthomas, DNA mutations, family history of high LDL-C, or early peripheral vascular or cerebrovascular disease— were inadequate for the Dutch criteria, nor did the data include all elements necessary for the Simon Broome criteria. Also, “early” heart disease, for men, is defined in the Simon Broome criteria as less than 60 years, versus less than 50 years in the NHANES system.

Dr. Khoury reported that of the 12,106 adults in the NHANES FH sample, 59 people met the MEDPED criteria for FH; and 71 people met the Simon Broome criteria, or less than 1% for both definitions. By the Dutch criteria, 413, or about 3%, met the definition for possible FH. Because there were fewer than five
adults in the sample with probable FH and fewer than five with definite FH according to the Dutch criteria, he explained, the data were censored by NCHS due to the potential for identifiability; thus, the NHANES sample had no more than eight adults total with probable or definite FH.

Dr. Khoury highlighted response data for some of the NHANES interview questions that illustrate the information and treatment gaps around FH in the US. Using the 59 subjects who met MEDPED criteria as an example, he reported that to the question “Have you ever had your cholesterol checked?” 25 of the 59 said no; thus, the NHANES intake was the first time these 25, comprising approximately 40% of the subjects who met MEDPED criteria for FH, had ever had their cholesterol checked. The remaining 34 subjects with FH per MEDPED said yes, they had had their cholesterol checked; however, only 26 had been checked within the previous five years. Further, although these subjects clearly had high cholesterol and met MEDPED criteria, 19 of the 34 whose cholesterol had been checked before NHANES reported that their doctors had never told them that they had high cholesterol. This left 15 people who had been told by their doctors (before NHANES intake) that they had high cholesterol, but only eight of these 15, Dr. Khoury reported, had been told to take treatment, and less than five of the eight were currently on prescription medication for high cholesterol at the time of the NHANES interview. Dr. Khoury noted that the results show the need for improvement at every step, from patient diagnosis, to the physician prescribing treatment, to the patient’s long term compliance with medication.

In summary, Dr. Khoury noted the following preliminary findings of the FH analysis of NHANES data:

- Prevalence estimates for FH vary widely depending on stringency of criteria, as expected.
- Prevalence estimate for MEDPED (1: 277) is similar to published prevalence estimate for FH, with consideration of false positives.
- Prevalence estimates for FH clinical criteria differ in association with age
- A minority of people identified as having FH using the MEDPED criteria, and a majority of people identified by the Simon-Broome and Dutch criteria, report having had cholesterol screening within the last five years, and having been told by their doctor that they have high cholesterol.
- Most people identified as FH screen positive by MEDPED, Simon-Broome, or Dutch criteria do not report currently taking prescription medications to control cholesterol.

Dr. Khoury reiterated that there were many limitations to the NHANES FH study, and the findings should be considered preliminarily. The data collected, he noted, were not adequate for assessment by either the Simon Broome or Dutch criteria. DNA was available, but genotyping was not done for FH. The sample size was small given the prevalence of FH, and the interview data were self-reported. Dr. Khoury noted further that there was no correction to account for use of lipid-lowering drugs, and if an individual had FH but was being treated, that subject could have been missed altogether, if they did not score as having high cholesterol. Finally, the data span only 12 years, from 1999 to 2010.

Returning to the question of public health data needs to drive decision-making for FH, Dr. Khoury asked that the current limitations be first considered. He stressed that at a minimum, lipid lab results are necessary to assess the FH criteria. Another hurdle, he said, as mentioned by several of the Summit’s
speakers, is the lack of a specific ICD9 or ICD10 code for FH. And although there are health system administrative databases and clinical research studies, Dr. Khoury said, studies are not surveillance systems or surveys because once the funding ends, there is no more study.

For FH surveillance purposes, Dr. Khoury listed the following data sources to consider:

- **Electronic health records (EHRs), which Dr. Khoury characterized as probably “one of the low-hanging fruits” in terms of data collection.**
- Health system administrative databases
- Cholesterol screening programs – some funded by CDC, others by state health departments, in addition to the CARDIAC program described by Dr. Neal of West Virginia
- Surveys and special studies, although Dr. Khoury cautioned that clinical research studies should not be regarded as a surveillance system, because once funding is depleted, the study ends.
- **National and international registries, with clear criteria for FH, following the traditional model in use for cystic fibrosis (CF) and various rare genetic diseases**

Dr. Khoury returned to the issue of the science-based objectives of HP2020. The objectives, he said, are designed to find ways to make the US healthier by encouraging collaboration, empowering individuals, and measuring the impact of prevention activities. Dr. Khoury noted that although he and his colleagues haveworked very hard over the last ten years to add genomics objectives to HP2020, only two such objectives have been added to date, for BRCA and Lynch syndrome. The criteria for new HP2020 objectives are strict, and new objectives will not be considered unless they include valid measures to track the progress achieved.

In closing, Dr. Khoury summarized the public health data that are critically needed in order to address FH in the US: standard approaches to screening and a diagnostic case definition; how many FH patients go undiagnosed using the population strategy of cholesterol screening alone; how many people with FH are untreated; how much family cascade testing is currently occurring, and both the effectiveness and cost-effectiveness of population-based and cascade screening strategies.

### 3 Session V: Matthew T. Roe, MD, MHS
**Success of Registries in Cardiovascular Disease**

In opening, **Matthew Roe, MD, MHS (Associate Professor of Medicine with Tenure, Cardiovascular Medicine, Duke University Medical Center; Director, Clinical Research Fellowship Program; Faculty Director, Global Outcomes Commercial Mega trials, Duke Clinical Research Institute)** said that he concurred with many others at the FH Summit as to the critical need for data on American patients with FH. His hope, he said, was to demonstrate how registry data can be used to change practice and greatly raise awareness of a disease, and he congratulated those maintaining successful FH registries in other countries.
Dr. Roe presented an analysis showing that, of the current American College of Cardiology (ACC)/American Heart Association (AHA) Cardiovascular Guidelines, less than 30% of recommendations meet Evidence level A,95 that is, backed up by at least two randomized clinical trials proving the benefit of a therapy. For many cardiovascular disease states, far less than 30% of recommendations met that level of evidence, and Dr. Roe observed that there will never be enough clinical trials for trial data alone to inform all the decisions in health care.

The key to conducting research with registries and using those data to improve care is standardization, said Dr. Roe. The infrastructural requirements for a registry to result in useful and meaningful results, he noted, are many and complex: the registry must enroll adequate numbers of patients, providers, and care settings that are representative of usual clinical practice for the disease being studied. The data collected in the registry must be detailed, accurate, and complete, comprising standardized data elements; the data must be analyzed using state-of-the-art methodology and thoughtful interpretation, and analysis should occur regularly to address important research questions in a timely way. The results learned from the registry must be actionable, that is, they must be disseminated back to the providers to help improve their care of patients, and also to the patients themselves, to empower them to be their own and their relatives’ health care advocates.

Dr. Roe cited a model adapted from Califf and Peterson,96 to explain the central role of clinical registries in the whole cycle of clinical therapeutics. Clinical evidence is developed through trials and other randomized approaches, and guidelines and performance indicators can be formulated, but Dr. Roe emphasized that registries are necessary to understand what is actually happening in practice and in patient outcome, and in turn, that understanding raises new questions and stimulates the development of new concepts for investigation. A good example, he said, is from an acute cardiac syndrome (ACS) registry begun years earlier: one of the elements collected was the administration of morphine to patients with chest pain in the emergency room, which was common practice. A clinical research fellow being mentored by Dr. Roe wanted to analyze those data, and although Dr. Roe had been skeptical, no matter how the data were analyzed, the morphine appeared to be harming, not helping, the patients. He related that the resulting paper was rejected by five journals before being accepted by a sixth, “…probably because the reviewers couldn’t believe the results.” In the end, said Dr. Roe, the research fellow’s look at the registry data led to a change in the guidelines.

Dr. Roe listed the ways in which registry data should be used: to evaluate current practice patterns, identify gaps in care delivery, evaluate temporal changes in care patterns (e.g., when important new treatment becomes available, what changes occur from that point forward), investigate associations related to treatment patterns, and identify new targets for quality improvement. He stressed that registries should not be used to attempt to estimate impact and safety of therapies in non-randomized fashion, promote use of therapies not recommended by practice guidelines, bolster competition among hospitals based upon quality performance, or encourage punitive measures against clinicians or hospitals based upon treatment results reported within a registry. Dr. Roe reported that in some registries, the Duke Clinical Research Institute (DCRI) has encountered the concern that hospitals would
use their treatment or patient outcome results in advertising or to try to compete with another hospital, and he stressed that these are not appropriate uses of registries.

Dr. Roe reported that the greatest body of data from heart disease-related registries relates to ACS quality improvement initiatives. Over the two-decade timeframe, five ACS registries — NRMI Registry, GRACE Registry, CRUSADE QI Registry, GWTG CAD Registry, ACTION Registry — have gathered data from roughly four million patients. The five registries collected primarily US data, he noted; only the GRACE Registry collected data from patients in the US and other countries. He summarized the purposes and scope of each registry as follows:

- **The National Registry of Myocardial Infarction (NRMI)** followed hospital treatment of more than 2.5 million acute MI patients in the US from 1990 – 2006. At its peak, 1100 hospitals participated. The NRMI provided quarterly feedback to the sites. Its initial focus was ST elevation myocardial infarction (STEMI), but this expanded to include non-ST elevation myocardial infarction (NSTEMI) with NRMI-4.

- **The CRUSADE Registry** looked at patients with unstable angina and non-ST-elevation MI (NSTEMI), to evaluate awareness of and adherence to new ACC/AHA guidelines (published in 2000) for non-ST elevation ACS (NSTEMI), among cardiologists and emergency medicine physicians; to implement quality improvement initiatives promoting the new guidelines; and to improve clinical outcomes for NSTEMI patients via early risk stratification and implementation of evidence-based care. The CRUSADE registry was maintained for four or five years, during which time there were innovations in how to feed data back to the participating centers. CRUSADE allowed comparison over time of performance, provided feedback to providers, and encouraged collaboration among providers. **With the data accrued, it was possible to document, over approximately three years, sustained, incremental improvement on a national level, in the use of therapy according to the different practice guidelines, both in acute care and at discharge.** Between early 2002 and late 2004, CRUSADE data showed that a composite score of adherence to the NSTEMI guidelines improved from 73% to 82% for acute care, and from 73% to 86% for discharge care.

- From 1999 through 2007, the **GRACE Registry** followed ~102,000 patients with unstable angina, NSTEMI, or STEMI. The registry enrolled participants in the US and other countries, and tracked acute treatment and in-hospital outcomes. Over approximately six years, between 1999 and 2005, the registry data demonstrated improvements in care, with increasing rates of use of recommended acute medications, that is, beta-blockers, statins, and angiotensin-converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARB). Dr. Roe noted that it is difficult to directly relate improvements in care to changes in patient outcome, because the mix of patient cases varies over time; however, the Grace Registry did demonstrate a decreasing percentage over time of patients with congestive heart failure or pulmonary edema (from 12% to 7.7%); while the annual percentage of patients who died, adjusted for risk, declined from 2.9% to 2.0%.
• Started in 2007, the **ACTION Registry** merges three prior US registries, CRUSADE, GWTG CAD, and NRMI. ACTION features consecutive enrollment of NSTEMI and STEMI patients at hundreds of participating hospitals across the US. ACTION comprises ~500,000 patient records, and is the platform for the AHA Mission Lifeline program. Dr. Roe presented a summary of 12-months’ data (calendar year 2012) from ACTION subjects, demonstrating how the registry data allow analyses, for example, of demographic and baseline characteristics; use by drug class of acute medications for MI; proportion of patients undergoing invasive cardiac procedures; in-hospital patient outcomes; and discharge medications prescribed. To illustrate composite measures made possible by the registry, he also showed indicators of performance by all hospitals participating in ACTION in 2012, including overall AMI performance, overall “defect free” care, STEMI performance, NSTEMI performance, and both acute and discharge AMI performance. Dr. Roe highlighted the defect-free score, measured for each patient and defined to mean that the patient is getting all recommended therapies after accounting for any medication(s) contraindications. He noted that the ACTION data revealed only a 72% rate, for 2012, of registry subjects receiving defect-free care; thus, the registry allows investigators to gauge the treatment gap in current practice.

• Started in 1997, the **NCDR Cath-PCI Registry** was the initial component of the National Cardiovascular Data Registry (NCDR) and enrolls patients at almost all centers in the US that perform percutaneous coronary intervention (PCI). Dr. Roe noted that this is the largest registry for CVD in the US, with more than 15 million patient records and currently over 1500 participating hospitals. Capturing the data for this registry, he said, is made easy because all procedural data are recorded while the patient is in the catheterization lab. In-hospital data are also collected. The NCDR Cath-PCI Registry is considered a benchmark registry for facilitation of novel data feedback mechanisms and public reporting of outcomes for cardiovascular procedures. Many state health care organizations and private insurers are requiring that hospitals participate in this registry in order to be reimbursed.

• **The ICD Registry**, for patients who received implantable cardioverter defibrillators (ICDs), is the other registry with almost universal participation of targeted patients, said Dr. Roe, because Medicare will not pay for an ICD for a patient who meets the indications for the device unless the patient’s data are entered into a registry. He commended this policy as forward-thinking in terms of how the resulting data will inform the understanding of patterns of ICD use and patient outcomes with the device.

Dr. Roe noted that many public health issues can be addressed with clinical registries, and that the vision for the CASCADE FH Registry about to be launched may include comparative effectiveness research (CER), analysis of the impact of different therapies on patients with FH, the uptake in clinical

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2 The Institute of Medicine defines comparative effectiveness research as “...the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of comparative effectiveness research is to assist
practice of different therapies, and the long-term safety of therapies after approval. He observed that the Affordable Care Act strongly endorses CER, and the Patient-Centered Outcomes Research Institute (PCORI) was authorized by Congress for this specific purpose.97 CER, Dr. Roe noted, enables us to look at the use of therapies in everyday practice and to understand how effective they are. He said that CER is more widely applicable than a focused, highly specific clinical trial, with relevance at both the patient and the population levels.

Dr. Roe expressed optimism that the design of the CASCADE FH Registry will also allow registry-clinical trial hybrids. The clinical data registry can serve as a backbone to facilitate study planning, he explained, because the registry supplies data that help to predict the likely number of events and appropriate eligibility criteria; identify appropriate sites and investigators; identify potential patients; and assess the generalizability of a study’s objectives. In addition, he noted, the registry platform allows concurrent data collection for the registry and the trial, and facilitates patient follow-up.

Dr. Roe related that the DCRI has worked with the ACC and the NHLBI to develop an organization called The National Cardiovascular Research Infrastructure (NCRI) to make use of the registry platform for post-trial surveillance efforts and to facilitate efficient and streamlined clinical trials. Dr. Roe explained that the project will enable the use of EHRs to assist in the collection of registry data, identification of patients for potential randomized studies, and development of a network of sites able to directly upload appropriate EHR data to registries. The CATH-PCI registry has been chosen as the initial platform for implementation of the NCRI project, he said, because it is the largest platform and has the most sites participating, and the proof-of-concept trial has already been completed. In the SAFE-PCI study, an important trial for understanding the preferred vascular access for PCI in women, the hypothesis was that compared with femoral access, radial access PCI would be superior with respect to bleeding and vascular complications, and non-inferior with respect to procedural failure. The subjects were all women enrolled in the CATH-PCI registry and having PCI, and the data were collected directly from the registry.

Dr. Roe told FH Summit participants that registries will present remarkable opportunities in the future, and his hope is that the Summit will stimulate creative thinking that will help develop the vision of what the FH Registry can do in future. He listed the following as important next steps toward increasing the capabilities and efficiencies of national clinical registries:

- **Perfect the techniques for the automatic download of EHR data into registry platforms.** Dr. Roe stressed the need to streamline data collection, and move beyond the expense and inefficiency of having a person key data from a paper medical record into a web-based data collection platform.

- **Encourage real time data entry and performance feedback in real time to assist providers with moving quality improvement into day-to-day practice.** There are countries, said Dr. Roe, where consumers, clinicians, purchases, and policy makers to make informed decisions that will improve health care at both the individual and population levels.” (IOM) Institute of Medicine. 2009. Initial National Priorities for Comparative Effectiveness Research. Washington, DC: The National Academies Press.
physicians performing a PCI get feedback before the patient leaves the catheterization lab; similarly, he believes, it will be possible for clinicians treating patients with FH to get real-time feedback on their diagnostic and treatment approaches while the feedback is most actionable because the patient is still in the clinic.

- **Focus upon promoting novel quality improvement targets at the hospital and provider level.**
  Dr. Roe pointed out that the registry will provide data to inform quality targets for proper treatment and follow up once the FH patient is identified, not only at the level of the provider, but across large health systems like the Veterans Administration, Kaiser Permanente, and others whose patients potentially include thousands of people with FH.

- **Creatively determine how to operationalize and conduct large, simple trials utilizing the registry infrastructure.**
  Here, Dr. Roe said, he is thinking of CER and trials of strategies to improve outcomes, but also to understand the best use of available treatments.

In closing, Dr. Roe stressed that there are many unique opportunities for research and learning from the CASCADE FH Registry. He said that the goal for the registry should be to enroll every patient in the US with potential FH.

**4 Session V – Joshua W. Knowles, MD, PhD**

**The FH Foundation: Cascade Screening for Awareness and Detection of FH**

Joshua Knowles, MD, PhD *(Attending Physician, Stanford Center for Inherited Cardiovascular Disease; Chief Medical Officer, The FH Foundation)* opened his talk by introducing patient advocate Scott, who had agreed to go to the back of the lecture hall while Dr. Knowles was speaking and become the first-ever subject to enroll in the CASCADE FH Registry. Dr. Knowles said, “Scott has a remarkable story as can be seen from his pedigree. All three of his children are affected, as is his mother. I urge those in the audience to talk to Scott about his story or see it on our [the FH Foundation] website.”

Dr. Knowles acknowledged that many of the speakers before him had made clear that FH creates a huge health care burden, is associated with high morbidity and mortality, and is vastly under diagnosed. It is estimated, he noted, that less than 20% of FH patients are treated. Yet research on FH is greatly underfunded compared with less prevalent diseases, and when the CDC announced in a recent press release that one-fourth of heart attacks and strokes in the US are preventable, FH was not mentioned as an important contributor. The omission was significant, he noted, because FH is known to cause about 20% of MIs in people younger than 45, and 5% in those younger than 60. Based on AHA statistics, he noted, people in these age groups in the US experience approximately 24,000 MIs per year, and approximately half of those 24,000 will die from their initial event. The
immediate cost of care is approximately $20,000 per MI, said Dr. Knowles, so that preventing even just one-third of those “early” MIs would represent a cost savings of $160 million, without considering costs of later, often devastating effects on the patient and family. He noted that these issues show the kinds of data that must be generated to begin to address FH in the US.

Dr. Knowles noted that in his clinic he sees patients with all kinds of inherited heart diseases, and although many genetic diseases are much rarer than FH, he finds that they are much better known by the public, a situation, he said, that needs to change. He observed that FH is the most common autosomal dominant condition, affecting more people than many much better known genetic diseases. Although historically FH was estimated to affect ~ 1: 500 of people worldwide— which would translate to 621,200 people in the US — recent large genetic studies have demonstrated a higher prevalence of approximately 1:250 people of European descent. It is important, said Dr. Knowles, for the public and health care providers to know that FH affects at least 600,000 individuals, and possibly as many as 1.2 million, in the US. He noted that there is no more than an informed guess to suggest that < 1% of Americans with FH have been diagnosed, but said “We don’t truly know what percentage of these patients are diagnosed in the US, and I think we really need to try to figure that out.”

Considering the disease’s high prevalence, FH research is vastly underfunded in the US, as Dr. Knowles recently learned from the NIH Research Portfolio Online Reporting Tools (RePORT): in 2011, he found only seven NIH grants that included “familial hypercholesterolemia” in the title of the abstract, representing a total of only $7M for research. By comparison, Dr. Knowles found that in the same year, there were 65 grants with total funding of $41M for hypertrophic cardiomyopathy (HCM), which has a prevalence of 1:500; and 395 grants for CF, which affects an estimated 30,000 people in the US. Although, he said, FH research funding has increased somewhat in the US since 2011, it remains very low in proportion to the estimated prevalence and burden of the disease.

Dr. Knowles pointed out that the US is often not good at tracking disease or measuring progress. He agreed with the other Summit speakers that the lack of an ICD9 or ICD10 code is a major hindrance in efforts to address FH. In the view of the FH Foundation, he said, other serious gaps are the lack of an active US-based disease registry for FH; the country’s fragmented health care system, which makes case identification and cascade screening difficult; the fact that the various case definitions for FH are challenging for non-experts; and a general lack of awareness of the grave public health implications of FH in the US.

Dr. Knowles stressed that if FH can be identified early, then patients can benefit from highly effective and inexpensive therapies. He noted further that the real benefit for public health will be in cascade screening.

Dr. Knowles stressed that FH is a “winnable battle,” and that it is viewed as such by the FH Foundation. To illustrate the point, he presented findings of a comparison of cumulative CHD-free survival over 15 years among Dutch subjects with HeFH, 413 of them on statin treatment, and 1537 off statin treatment, noting that with proper identification and treatment, morbidity and mortality from FH approach that of
Dr. Knowles said that he is immensely encouraged by the tremendous success of the Dutch national program of FH screening: through 2012, he noted, the Dutch program had identified 5,151 genetically positive index cases; and by cascade testing of more than 60,000 relatives, identified a total of 27,069 FH cases, that is, 36% of the family members, with a positive genetic test. Moreover, Dr. Knowles pointed out, the Dutch program is clearly cost-effective, as they have demonstrated that the cost to identify one FH patient was €1200, and the cost saved for even a single life-year was €8700.

Dr. Knowles referred to Dr. Muin Khoury’s earlier point that the CDC has identified cascade cholesterol testing among relatives of persons with FH as a Tier 1 genomic application — meaning that it is recommended for clinical use by evidence-based panels on a systemic review of analytic validity and clinical validity and utility. He pointed out that the full benefits of whole genome sequencing will not be realized until sometime in the future, but cascade screening for FH can benefit people right now, and advocates for people with FH must do what they can to make this happen.

Patient advocacy and a strong FH Foundation, Dr. Knowles emphasized, are absolutely critical if the US is to duplicate the success of the Netherlands and other countries with screening programs to identify and treat persons with FH. Pointing to the tireless effort by FH Foundation President Katherine Wilemon as an example, he cited the commitment, energy, and unquestioned legitimacy of patient stakeholders, and noted that their compelling personal stories are key for fundraising, while their social networking connects patients with other patients and helps them to assist one another.

Dr. Knowles explained that a national FH registry is essential to the mission of the FH Foundation, playing a central role in all the Foundation’s goals: identification of persons who must receive life-saving treatment, generation of data to support advocacy, education of primary caregivers and family members, proactive treatment and referral before significant damage is done, and active participation in research. The FH Registry is starting at a time when “all the stars are aligned,” said Dr. Knowles, noting that the following factors all bode well for the Registry’s success:

- The FH Registry’s sponsorship by the FH Foundation
- Support for the Registry by professional organizations such as the National Lipid Association, the Preventive Cardiovascular Nurses Association, the National Society of Genetic Counselors, and the American Society for Preventive Cardiology
- Government agencies such as the CDC and the NHLBI, and state health departments like that of Michigan
- Availability of data from large healthcare organizations like the Veterans Administration and Kaiser Permanente
- A growing number of laboratories with the ability to facilitate lipid and genetic testing on a large scale
The experience and support of an international community of experts in the identification and treatment of FH.

Dr. Knowles said that the increasing emphasis on patient empowerment and quality of care is likely to play an important role in efforts to address FH in the US. With the implementation of the Affordable Care Act, there is an increased emphasis on disease prevention, he noted, and a PCORI grant is being written for the Foundation by Emily O’Brien (PhD, DCRI). The FH Registry, by helping to identify high risk patients, is also aligned with groups in the business of managed care, such as health maintenance organizations (HMOs) and large, self-insured healthcare networks that emphasize disease prevention.

Dr. Knowles acknowledged that if maintaining an FH registry and finding and treating all the FH patients were easy, it would have been done before. The immediate challenges, he said, are not to be underestimated, including how to incentivize health care providers to recruit patients and collect longitudinal data; how to link the FH Registry with multi-national partners to facilitate collaboration; and determining what data fields to collect, so that the registry is comprehensive but not so cumbersome that participants become discouraged. With regard to data collection, Dr. Knowles added, a further issue is that patients with homozygous FH are likely to face a more complex clinical course, and so require collection of more and different data, compared with those with heterozygous FH.

With a firm commitment to helping patients and their family members participate at will, Dr. Knowles said, the CASCADE FH Registry was designed with a simple interface in order to be user-friendly for people of all levels of health literacy, and it is seamlessly integrated with the FH Foundation website. Further, he noted, the Registry was designed to comply with HIPAA policies and procedures protecting patient and practitioner privacy, and data security is ensured by regular audits and automatic backup. The CASCADE FH Registry database is scalable and will be able to import large data sets from academic centers and HMOs; and it can be used to generate custom reports to address a multitude of public health, clinical, and research questions.

Dr. Knowles explained that the builders of the CASCADE FH Registry made use of advice and best methods from successful FH registries in the Netherlands, UK, Australia, and Canada, and CASCADE FH was designed with data elements harmonized with the predecessor registries to allow future collaborations.

The MEDPED experience, said Dr. Knowles, played an absolutely crucial role in the understanding of FH, establishing a model set of diagnostic criteria, and an understanding of the natural history of FH and its response to evolving treatment options. MEDPED actively enrolled from 1988 until 2004, he noted, and in doing so, identified roughly 8000 FH patients, extending pedigrees to find and treat affected family members, and documenting improved outcomes. The lessons of MEDPED include the difficulty of building a registry without patient self-referral and the need for broad based funding to sustain such an effort.

Dr. Knowles pointed out that the CASCADE FH Registry is also learning from long-established registries such as the Cystic Fibrosis Foundation Patient Registry, which for over 40 years has collected
information from people with CF, helping to drive the development and uptake of new treatments and the delivery of optimal care. He pointed out that the average life expectancy of a person with CF has increased dramatically in the past 30 years, and that the CF registry has been central to this progress.

Living in 2013, Dr. Knowles said, “we have to recognize that technology is our friend,” helping to overcome what were impediments but no longer are. He stressed the need to succeed in a world of limited resources and attention spans, where there is increasing reliance on mobile technology and social networks. Disruptive technologies such as these can and must be leveraged to achieve worldwide awareness, he said, because FH is a worldwide problem.

Referring to the conflict between sensitivity and specificity, Dr. Knowles said that the CASCADE FH Registry had been intentionally built to be overly sensitive, but with filters that allow researchers to capture information on people who meet the MEDPED, Dutch, or Simon Broome criteria. Patients can take advantage of self-registration with simple entry criteria, he noted, and because each patient who joins the registry will sign a release of their medical records, overseers of the Registry have a way to verify participants’ information.

Dr. Knowles said that it is important to the FH Foundation to give something back to the patients and by their participation in the Registry, patients receive education and their family tree. He explained that there is a FH specific, mobile device-friendly, family tree tool being developed at Duke called “MeTree,” which prints out a pedigree for the patients indicating which of their family members may be at risk; the patients can then try to encourage those family members to take steps to find out if they have FH. Dr. Knowles noted that, although the pedigree tool was still being refined at the time of the FH Summit, he had loaded a pilot test of MeTree on his iPhone, and it was already working.

Dr. Knowles displayed the official logo of the CASCADE FH Registry, commending Katherine Wilemon for her beautiful design, and noting that it was interesting that all three countries with strong patient organizations for FH — Spain, Wales, and the US — had independently chosen a tree motif for FH, which highlights the importance of screening the families of affected individuals. He announced that the Registry was now activated, and it is easy to navigate, mobile friendly, HIPAA compliant, secure, and IRB approved. Ultimately, he said, the CASCADE FH registry will be allowed interface with electronic medical records of patients who give permission for such access.

Dr. Knowles acknowledged that the FH Foundation had chosen a very ambitious long term goal, that is, through efforts that will be greatly facilitated by the CASCADE FH Registry, 90% of FH patients in the US will be diagnosed and treated. He noted that the main objectives of the Registry are as follows:

1. Promote awareness of FH prevalence, risk factors, and optimal management through education at both the patient and provider levels.

2. Identify and enroll FH patients through a hybrid mechanism of clinic-based, community-based, and family-based screening initiatives to track therapy, patient-reported outcomes, and clinical outcomes over time.
3. Evaluate patterns of real-world clinical practice and patient experiences to contribute to the state of scientific knowledge about FH care, quality of life, and health outcomes.

The knowledge gained from the CASCADE FH Registry will be used to improve quality of care, drive regulatory change, and facilitate research design and recruitment for clinical trials, Dr. Knowles noted, and data entered into the Registry will also provide evidence-based material for further education of people with FH and their healthcare providers.

Dr. Knowles noted that the FH Foundation is first a group of FH patient advocates, extremely committed to the Foundation’s mission, who have received extensive training about FH, including media training. Next, he said, the FH Foundation includes a community of FH physicians, epitomized by the Scientific Advisory Board, whose members view a registry as being central to determining longitudinal outcomes and gaining insight into patient experience; encouraging cascade screening; reducing knowledge gaps; and ultimately, perhaps, facilitating a biobank. At this time, Dr. Knowles observed, knowledge about patient experience with FH in the US is practically non-existent.

Turning next to the study design, Dr. Knowles explained that the CASCADE FH Registry features a dual pathway for enrollment. Phase 1 is online patient self-enrollment, he noted, and the first patient, Mark, was launching Phase 1 by enrolling as Dr. Knowles spoke. Phase 2, he said, is the collection of patient data as abstracted and entered at each clinical site, and Phase 3 will be longitudinal follow-up, with each patient’s longitudinal data collected at six month intervals; the follow-up will include information on quality of life, medications changes, and clinical events.

Dr. Knowles noted that, in choosing criteria for enrollment in the CASCADE FH Registry, its designers intentionally set a low bar to encourage the maximal number of patients with FH to join. Any patient with a clinical diagnosis of FH made by a lipidologist or other physician using any set of FH criteria is eligible, he said, as well as any patient that meets the following criteria: children < 18 years old with LDL> 160 mg/dL or total cholesterol > 260 mg/dL, and adults 18 years or older with LDL> 190 mg/dL or total cholesterol > 300 mg/dL. Dr. Knowles acknowledged that the correction factors built into the Registry for treatment with statins “might be overly aggressive” but this was done so that individuals with FH would not be excluded if their LDL-C happened to be a little low compared with the level specified by the criteria utilized.

For online self-enrollment (Pathway 1), patients who access the Registry through an online patient portal will be prompted to first respond to screening questions that elicit the patient’s lipid values. If the screening questions indicate that the patient is eligible to register, the patient will sign a consent form including a medical release. If those screening questions are negative, the patient will be informed so, but will still be directed to educational information. The Registry overseers will validate some of the patient information by checking medical records.

Dr. Knowles explained that clinic-based enrollment and data collection (Pathway 2) can be accomplished either prospectively or retrospectively:
For prospective information, if a patient is known by the physician to have FH, the provider tells the patient about the registry and obtains the patient’s consent, then enters the clinical data elements and updates the patient’s panel of information after each visit. Once registered, the patient will be able to enter limited (patient survey) data regarding family history and known CVD risk factors via the patient portal.

To gather retrospective information on the clinic’s population of patients with FH, at the outset, authorized personnel at the clinical site will enter de-identified FH patient data via the clinician portal. Each individual whose data were entered in this manner will be informed about the registry at their next clinic visit. Provided the patient gives informed consent, the provider enters the individual patient’s clinical data elements and updates the patient’s panel of information after each visit. Once registered, the patient will be able to enter limited (patient survey) data regarding family history and known CVD risk factors.

With regard to validation of data entered in the CASCADE FH Registry, Dr. Knowles reported that high-volume sites will generally operate under local IRB approval, and the site clinicians will confirm all patient-entered data, adding supplemental data as appropriate. The site will complete a limited survey regarding the patient after each clinic visit. Community sites, he noted, will generally operate under central IRB approval; otherwise their validation processes will be the same as at larger sites, in that site clinician(s) will confirm all patient-entered information and will add supplemental data. If a community site with no IRB approval collects data on FH patients, they will send the data (medical records) to DCRI for abstraction and data entry into the Registry, and at one year updates, a request for a repeat record abstraction will be issued.

Dr. Knowles noted that the clinical data elements that will be collected by the Registry include limited demographic information, medical history, family and patient FH history, current medications and contraindications for medication, imaging and procedures, laboratory and genetic data, physical assessments, and the patient’s clinical trial participation. He reported that there are fewer than 90 questions, and when piloted with several FH Foundation patient advocates, the patient online survey for the Registry has taken 20 – 25 minutes to complete.

Referring first to the online portal for patient self-enrollment (Phase 1), Dr. Knowles showed Summit participants a series of screen shots to illustrate the question areas presented in the Registry.

- With regard to patient-reported past medical history, Dr. Knowles explained, the questions ask about cardiac and lipid disorders, and about cardiac procedures performed within the past five years. The registry includes photographs of xanthomas and corneal arcus, he noted, so that patients can recognize what they are. Patients answer the survey in a yes/no/unknown format, and importantly, he said, not knowing the answer to a given question does not limit patients’ ability to submit their other data.

- With regard to collection of family history, Dr. Knowles stressed that the Registry is limited...
by HIPAA to collecting non-identifying information about relatives and so cannot legally collect the names of family members. However, family history of FH, hyperlipidemia, and CVD can be collected, which allows Registry overseers to try to ascertain the number of “at risk” family members and provide that information to the patient.

• Information on each patient’s FH history and their diagnostic journey will be collected. Particularly in response to hearing so many times that patients go for months, years, or even decades without knowing that they have FH, Dr. Knowles noted, the Registry was designed to try as best as possible to capture information, including LDL-C and total cholesterol levels, from people with FH not yet diagnosed or treated. Once information is captured from such patients, he said, the Simon Broome or Dutch Lipid Clinic Network criteria can be applied, in order to determine an FH diagnosis for those individuals.

• With regard to FH treatment, Dr. Knowles reported, there will be very simple questions about the patient’s use of available therapies. Questions about non-statin therapies, he said, will mostly be limited to yes/no questions; however, the line of questioning about statins and statin dosing will be more granular, because the appropriate intensity of statin dosing is really the mainstay of therapy. Dr. Knowles noted that the Registry will also capture information on drugs only recently available as well as on any new ones that will hopefully reach the market in the next few years.

• Dr. Knowles noted that the CASCADE FH Registry is unique in its collection of patient-centric data, specifically, patient-reported quality of life. Patients are asked a limited set of questions about their quality of life, he said, focusing on the diagnostic journey: they are asked how FH has affected their life; and how it has affected their perception of their risk. The hope is that answers to these questions will not only help to learn the extent of patients’ understanding of FH, but will also enhance the patient’s experience of participating in the Registry.

Turning next to the Registry’s electronic data platform for use by clinical sites (Phase 2 and Phase 3), Dr. Knowles explained that it was designed for more detailed data collection, based on authorized site personnel’s direct access to medical records. He noted that one very important aspect of the Registry is that it will be possible to give the sites information back about their enrolled patients, informing them how their patient panel looks compared with the rest of the cohort; the purpose, he said, is to facilitate improvement of patient care overall, and not to criticize any site’s performance.

Dr. Knowles explained that the FH Foundation is working in many ways to engage patients in learning about FH and to build interest in the Registry:

• The “MeTree” FH pedigree tool is available to patients when they import their data, although it will not be fed into the Registry database because of HIPAA laws. The MeTree tool is easy to use, Dr. Knowles said, featuring a drag-and-drop mechanism for patients to use to fill out information about their parents, their children, and other relatives who might be affected; and it provides a pedigree at the end. MeTree can be built for multiple conditions with decision support tools, and as adapted for FH, he observed, should provide

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3 The Health Insurance Portability and Accountability Act of 1996
an important added value for the patients.

- Education is the other way in which the FH Foundation works to engage patients. The Foundation recently commissioned an FH awareness video done in song-and-dance, now posted on the FH Foundation website where patients can access it and other information, and forward them to relatives. The Foundation also creates printed educational material. Dr. Knowles noted that he particularly values the legitimacy of the Foundation’s materials, which use photographs of real patients and real families who are affected with FH.

- Once patients do access the online portal for the Registry, Dr. Knowles noted, they will find easy instructions for how to register online. Everything, he said, is built to make the process of enrolling as seamless as possible.

Dr. Knowles noted that careful planning also went into demonstrating the value of the FH registry to health care providers and engaging their participation. Providers will have access to data from their own patients, he said, as well as to aggregate data from the Registry. The providers will also see reports generated using key aggregated data, which can be used to compare local and national trends in therapy.

At least yearly, Dr. Knowles said, the CASCADE FH Registry overseers plan to conduct longitudinal follow-up. Patients enrolled in the Registry have ongoing access that allows them to update their data at any time, he noted, but every six months they will also receive electronic reminders by email, with a link to allow them to update their data using a brief survey that asks, for example, whether the patient has had any events since last contact; what her latest cholesterol levels are; what medication changes have been prescribed; and whether she has recommended anyone else to be tested for FH. Dr. Knowles’ hope is that the survey will not be too long or burdensome. However he noted that a program of follow-up is extremely costly and the participation of patients will help to reduce that cost. Providers will contribute to follow-up by updating each patient’s data yearly.

Dr. Knowles explained the rationale for a hybrid model registry. He noted that the patients will register themselves, and their data will be verified. Individual practitioners will be able to either register patients, he said, or simply refer the patient directly to the website to decrease the burden on clinic personnel. For medium-sized to large lipid clinics, Dr. Knowles noted, there will be a mechanism to help defer some of the cost of entering the data; this will involve partnering with academic medical centers.

Dr. Knowles asked the Summit participants to consider a small sample of preliminary data from the Stanford, Duke and VA health care systems (Dr. Knowles noted that the VA system project is a collaboration with Paul Heidenreich, MD, MS, FACC [Assistant Professor, Cardiovascular Medicine, Stanford University; Director, Echocardiography Laboratory: Palo Alto Veteran’s Health Care System]). Dr. Knowles and colleagues looked at the numbers of patients not on statins with severe elevations in LDL-C: patients below age 20 with LDL-C >190 mg/dL, patients ages 20 – 29 with LDL-C > 220 mg/dL, and patients ages 30 – 39 with LDL-C > 240 mg/dL.

Dr. Knowles reported that the VA system had data on 1,600,000 patients not on a statin who had an LDL value, of whom 1541 patients met the severely elevated criteria; this translated to prevalence in the VA group of 1:1000. Dr. Knowles pointed out that, compared with estimated FH prevalence worldwide, the VA is apparently doing a pretty good job of getting patients on statins. At Stanford, he noted, an electronic medical record (EMR) search of 73,000 patient records found 220 patients who met the
severely elevated LDL-C criteria, an estimated 1:331 patients. To quote Dr. Knowles, “I guarantee you we don’t have 220 patients in our FH clinic, and we’re sending letters to all providers of those patients to try to get them to think about this.” A similar search of roughly 52,500 records at the Duke Health System found 198 patients with severely elevated LDL-C, an estimated 1:265 patients.

In terms of oversight of the CASCADE FH Registry, Dr. Knowles commended the active executive committee that includes members of the FH Foundation, the DCRI, and potentially others in attendance at the FH Summit. He noted that patients will be involved, as well as a scientific advisory board, and said that a publications committee will evaluate collaboration opportunities. The Registry data, stressed Dr. Knowles, are meant to push the field forward, and will be made available to academic researchers through simple research requests, which will be evaluated by the registry advisory board. The Registry’s overseers are dedicated to making it as simple as possible to deliver the data needed to answer the questions asked.

Dr. Knowles concluded by thanking, on behalf of the FH Foundation, the FH patient advocates in attendance at the Summit, those patients who will be registering online, and the DCRI and collaborators for all their help. He expressed how encouraging it was to have representatives at the FH Summit from the Canadian Heart Association (CHA), the American College of Cardiology (ACC), the National Lipid Association (NALA), the Preventive Cardiovascular Nurses Association (PCNA), and multiple international collaborators. Dr. Knowles thanked the founding sponsors for the FH registry, Sanofi and Amgen Cardiovascular, and the other partners of the FH Foundation: Aegerion Pharmaceuticals, Genzyme, Regeneron, and HDL Inc.

Session V — Panel Discussion

**Moderator:** Daniel Rader, MD, PhD (University of Pennsylvania; FH Foundation Scientific Advisory Board)

**Faculty:** Jacques Genest, MD (Canada); Muin Khoury, MD, PhD (US, OPHG/CDC); Matthew Roe, MD PhD (DCRI); Joshua Knowles, MD, PhD (The FH Foundation)

**Panelists:** Dev Datta, MD (Wales); Katherine Wilemon (The FH Foundation)

Noting that Dr. Knowles, in his presentation of the CASCADE FH Registry, had alluded to means of stimulating clinician and patient recruitment and enrollment in the CASCADE FH Registry, moderator Dr. Daniel Rader asked the Session V panelists to discuss what it will take to motivate clinicians to enroll their patients, and patients to go to the website and enroll themselves.

**Dr. Knowles** said first that he is eager to have the input of the FH Summit participants. He explained that initially, the Registry’s overseers would be collaborating with a small group of larger lipid clinics, which as an incentive would receive small grants for data entry. He added that the Registry will have to depend on patients entering a lot of their own data to counter some of the prohibitively high cost of maintaining the Registry on a large scale for many years. Dr. Knowles noted that the FH Foundation plans to take advantage of the high energy that
patients demonstrate when they and their families have a stake in fighting FH, and he expressed his belief that patients will be engaged to a large extent by the education they receive when they visit the Registry website.

Dr. Datta reiterated that enrolling patients in the FH registry is somewhat different in the UK because of the structure of the health system. However, he said he had been thinking of recent efforts to set up a registry for LDL apheresis: to date, he said, it has been unsuccessful because there is no incentive for sites to complete the data entry needed for each patient, even though the group of patients is very small. Dr. Datta noted that they have been able to grow the apheresis registry only by obtaining external funding to pay for a nurse to enter the data retrospectively, something that he said would not be practicable given the large number of patients anticipated to be eligible for a US-based FH registry. He said that the idea of educating and empowering patients to enroll themselves was fascinating to him, and potentially a very powerful way of getting high quality data.

Dr. Rader next asked if Dr. Roe felt, considering his vast experience with clinical registries, that the incentive for hospitals to enter patients in large registries for cardiovascular conditions or interventions was strictly financial.

Dr. Roe responded that in some cases, as for the acute coronary syndrome (ACS) registries, the hospitals must actually pay significant participant fees, which they do because there are mandates from insurers for the hospitals to participate. However, he said, he believes that the real value to the participating sites is really in the data feedback, adding that visionary clinicians and health care systems will devote time to something that they believe will improve their practice.

Dr. Roe said that the CASCADE FH Registry will start with devoted members of the lipidology community who will devote time to enrolling the large number of FH patients that are concentrated in their practices and by so doing set the stage for wider involvement of clinicians and sites. He noted that it may be difficult for busy PCPs to enter data themselves, although each PCP would have only a small number of patients eligible for the Registry. Dr. Roe emphasized the importance of the concentrated efforts by the FH to engage and inform patients, noting that as patients network and share information, they will be motivated to enter their data for reasons of education trying to improve their care, and also altruism in terms of helping to increase the understanding of FH.

Dr. Khoury voiced his congratulations at the launching of the CASCADE FH Registry. From a public health perspective, he observed, the value of the Registry can only increase over time if its coverage of the hard-to-reach populations increases. Otherwise, he noted, the registry information will not be generalizable to the whole population. In any public health initiative to register, for example, a particular birth defect or cancer, said Dr. Khoury, the first subjects enrolled are “the coalition of the willing,” but to learn the full picture of FH in the US population,
the Registry must find ways to include the patients who are difficult to reach because they do
not have health care access. **He stressed that the Registry must leverage EHRs, as well as the
very large databases such as the VA Health System maintains, to cast the “broadest net
possible” to reach patients.**

Dr. Rader next directed two questions from the audience to Dr. Knowles, asking whether enrollment in
the CASCADE FH Registry might be too challenging for some patients, and whether there was a way for
patients to enroll that does not require them to access their own computer.

**Dr. Knowles** emphasized that in designing the CASCADE FH Registry and in particular, the
patient portal, a great deal of thought had gone into making the process as easy as possible for
patients. **Aside from the patient entering the data directly, he said, there are two other ways
to obtain the data: either the patient’s provider will enter the data, or, because every
enrollee signs a release for medical records, arrangements can be made for Registry staff to
obtain the patient’s records and abstract the data directly from them.**

Alluding to the MeTree family pedigree tool that is available to patients enrolling in the Registry, Dr.
Rader asked whether MeTree could be adapted so that health systems could generate a family tree in
each patient’s EMR. Dr. Knowles concurred with the need and agreed that they should work on that,
although warning that some EMR systems are not yet able to accommodate add-on applications.

Dr. Rader said that he understood the Registry’s initial criteria for enrollment were based on the levels
of LDL-C and TC, with no criterion specifying a certain triglyceride level. Given that, he asked
Dr. Knowles, will patients who have, for example, mixed or combined hyperlipidemia be included or
excluded from the registry?

**Dr. Knowles** confirmed that the initial entry criteria, the ones that allow patients to go on and
enter more data, are based on LDL-C and TC. However, once the patient gets into the Registry,
information on triglycerides is captured. **If someone wants to perform an analysis purely
focused on FH based on a given set of criteria, it will be possible to filter the database and
exclude individuals with elevated triglycerides.** However, he explained, the thought in
designing the Registry was that there are many people with FH who may have high triglycerides
for other reasons, and the Registry’s overseers did not want to exclude them and possibly miss
capturing members of their family with FH. He noted that if warranted in future, the Registry
could be changed to be more specific.

Noting that Dr. Knowles had cited the Cystic Fibrosis Registry as a prime example, Dr. Rader asked the
panelists whether there are other disease registries, specifically in the US, that might be considered
more closely related to FH and serve as a source of information about best practices.

When asked if the LS registry might be a better example, **Dr. Khoury** said that it was more of a
network for LS screening rather than a patient-based registry, and that it was no longer in
operation. He pointed out that there is no one correct way to do a registry: they may originate
in a Congressional mandate, or a state-based mandate such as cancer registries. On the heart disease side, Dr. Khoury noted, the magnitude of the problem is very great, and although there has been a movement to do surveillance and registration for heart disease and stroke, he was unable to speak to its success. There is no BRCA1 registry, he said, adding that the CF registry model was probably the closest example that came to mind.

A member of the audience suggested that there is a registry for alpha-1 antitrypsin, which she said may be somewhat more comparable to FH, than CF. Dr. Rader agreed that that was a good example. A second member of the audience suggested that, if a registry exists in the US for Type 1 diabetes, it may be a useful model in some respects for the FH Registry.

Dr. Rader's next question was directed to Dr. Knowles and FH Foundation President Katherine Wilemon: What will the FH Foundation consider to be success—in one year, two years, five years—in terms of numbers of patients identified and enrolled in the Registry?

Dr. Knowles said that he hoped, realistically, for enrollment to be in the hundreds of patients in the first year, and in the thousands in the second year.

Ms. Wilemon countered that the Foundation have a very committed scientific advisory board, all of whom have agreed to be initial sites for the Registry. With those 11 initial sites based at the leading lipid centers in the US, and a strong effort by everyone involved, she expressed her strong belief that the Registry can realistically enroll more than 1000 patients in the first year and more than double that number in the second year. Stressing that “...first we have to imagine it to get it done...and we don't have a choice,” Ms. Wilemon announced that her five-year goal is 25,000 patients. She then turned the question around to Dr. Rader, asking what he considered realistic, given his experience in the field.

Dr. Rader responded that the clinics will have to work out the logistics and the costs of getting people entered in the Registry in the clinic setting. With that in mind, he asked if it would be possible to have computer kiosks available at the clinics, so that patients could be entering information for the FH Registry while waiting to see their doctor.

Ms. Wilemon answered that the Foundation is considering sending one or two dedicated computer tablets to each of the initial Registry sites, which would be available for patients to enter their own information during a clinic visit, while the patient is enthused and has the free time. She noted that it should be feasible and affordable to provide tablets to the initial sites in the first phase of the Registry’s launch.

Dr. Rader said that with regard to the expected enrollment numbers, although the uptake at clinics remains to be seen, his thinking was that success will ultimately come from patient networking and use of social media, and the value that patients see in getting each other to enter. If the Registry really catches on with patients, Dr. Rader said, then he believed Ms. Wilemon’s anticipated numbers are realistic.
Dr. Knowles pointed out that a second and tremendously important measure of success will be achieved when, sometime in the near future, every physician in the US who orders a lipid panel, and every individual who has a lipid panel done, thinks about FH when they get the results back. He acknowledged that this is ambitious, and that it relates not to the number of patients in the Registry, but to the broader goal of education and raising awareness. “If we can accomplish that,” Dr. Knowles pointed out, “everything else will fall into place.”

**Dr. Khoury** had the following question for Dr. Knowles: Based on the CASCADE FH Registry’s enrolling criteria, what percentage of the US population — perhaps 1%, 2%, or 3%? — is expected to be in the Registry?

**Dr. Knowles** first explained that the percentage of people “in,” that is, enrolled in the Registry, would be very different from the percentage eligible. He noted his belief that the clinical diagnosis of FH will be the determining factor in getting patients into the Registry. The Registry was designed with clinical criteria that are not very stringent, said Dr. Knowles, because finding patients with possible FH is too important to delay until the medical and public health stakeholders reach consensus on an FH case definition. However, he noted, those criteria can be made more stringent, if those at the FH Summit believe changes are needed.

Regarding Registry entry criteria for LDL-C levels, **Dr. Rader** noted that one point raised during the Summit was the potential advantage of using an LDL-C threshold that is a round number and easier for PCPs and the public to remember, such as 200 mg/dL versus 190 mg/dL.

A member of the audience, alluding to Dr. Knowles’s announcement that the Registry would initially enroll at clinical sites represented by members of the FH Foundation Scientific Advisory Board, asked whether Registry enrollment was currently limited to those 11 sites.

**Dr. Knowles** explained that the Scientific Advisory Board had offered to pilot the Registry at their centers, so those were the only site agreements already in place at the time of the Registry launch. However, he added, the FH Foundation would gladly partner with every site that wanted to take part in the Registry immediately.

**Dr. Gerald Watts** (Australia) expressed his congratulations to the FH Foundation on the launch of the CASCADE FH Registry. Dr. Watts asked whether unaffected family members are going to be included in the registry, noting that there could still be value in terms of understanding them as controls, versus the FH cases, for the natural history of the condition.

**Dr. Knowles** replied that, after a good deal of debate, the Registry was not constructed to enroll unaffected family members. One factor in the decision, he said, was the potential for IRB issues to arise when unaffected individuals are in a registry for a disease state. Dr. Knowles noted that the inclusion of unaffected family members in the Registry is a question that may be revisited in future.
Amy Sturm, MS CGC (*Wexner Medical Center, Ohio State University*) congratulated the FH Foundation on their great accomplishment with the launch of the Registry. Pointing out that genetic counselors represent a significant source of help and education for patients dealing with, for example, CF or prenatal diagnoses, Ms. Sturm suggested that the Registry’s overseers consider making genetic counselors an intrinsic part of services available through the FH Registry. Related to Ms. Sturm’s comment, Ms. Wilemon added that the FH Foundation has applied for a PCORI grant to fund health coordinators who will work with families with FH. Although obviously not synonymous with having a genetic counselor, she acknowledged, the health coordinator would be able to offer some guidance and to encourage cascade screening of LDL-C in the family.

In closing the Session V panel discussion, Dr. Rader observed that the Registry’s success depends on the Summit participants’ embracing the concept of addressing FH in the US, and on their being champions of the Registry, talking about it to their patients and their colleagues, and showing a lot of enthusiasm.

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Conclusions to the FH Summit 2013: Wrap-up and Takeaways

In the conclusion to the Inaugural FH Summit, Co-Chairs Daniel Rader, MD and Muin Khoury, MD, PhD, summarized the five sessions and highlighted the following action items as articulated by speakers, panelists and audience members.

(1) Engage and involve major US public health organizations; FH should, for example, be incorporated into the Million Hearts Initiative

(2) Through collaborative action, organize educational activities targeting public health providers and primary care providers

(3) Launch the CASCADE FH Registry; set the bar low for entry into the Registry and focus on recruiting providers and affected individuals

(4) Put together a working group to develop a case definition for FH

(5) Lobby for an ICD-10 code for FH

(6) Conduct research measuring the impact on patients of being diagnosed with FH vs. high cholesterol

(7) Encourage the initiation and expansion of FH screening programs during childhood

(8) Work to foster collaboration between public health entities and health systems

(9) Assure sustainability of existing screening programs

(10) Decide what needs to be measured since “What gets measured gets done”

(11) Advocate for including cascade screening in generic lipid-lowering guidelines

(12) Encourage systematic searches of EMRs across the country for potential FH cases

(13) Work to include FH in HEDIS measures

(14) Broadcast simple, easy-to-understand educational messages related to FH

(15) Work with organizations such as AAP and NHLBI to update pediatric lipid guidelines to include cascade screening

(16) Consider working to add FH to the list of diseases meeting WHO screening criteria

(17) Develop guidelines specifically for the US and expand US data collection
(18) Examine the role of genetic testing in cascade screening and consider the likely impact of new technologies (such as next generation sequencing and whole genome sequencing)

(19) Conduct pilot projects to demonstrate effectiveness and cost effectiveness of cascade screening for FH, utilizing the CASCADE FH Registry and other means

(20) Launch cascade screening via an integrated health care/public health approach

The Summit was ended with these inspirational words from Katherine Wilemon: “You have to imagine it to make it happen”.