MINUTES

Observational Study Monitoring Board
Framingham Heart Study
12/5/2012 Meeting

PARTICIPANTS:

OSMB Members Present: Russell Luepker (Chair), Pamela Douglas, Philip Greenland, James Neaton, Lewis Smith, Jennifer Van Eyk, Alexander Wilson

Investigators: Adrienne Cupples, Christopher O'Donnell, Joseph Massaro, Vasan Ramachandran, Philip Wolf

NHLBI Staff: Richard Fabsitz (Executive Secretary), Cashell Jaquish, Cheryl Jennings, Hanyu Ni, Mona Puggal, Phyliss Sholinsky, Paul Sorlie, Pothur Srinivas, Gina Wei, Elizabeth Zoller

INTRODUCTION

Dr. Fabsitz announced that there were now two vacancies on the Board as Dr. Mary Cushman and Dr. Charles Rotimi were no longer on the Board. Both were acknowledged for their valuable contributions to the Board. Dr. Fabsitz suggested that the Board consider what expertise would be particularly valuable to add to the Board given the evolving scientific focus of the Framingham Heart Study. He would solicit the Board's suggestions following the meeting.

Dr. Wei reported that the NHLBI contract for the study ends in spring of 2015. In August 2012, NHLBI convened a panel of seven outside experts to discuss possible future directions of the study. Dr. Philip Greenland chaired the panel, which provided their initial input in writing and then participated in a 2-hour conference call. The summary of the panel was shared internally within NHLBI. An initiative to renew the study is being discussed within NHLBI under a broader evaluation of all NHLBI-supported cohort studies.

STUDY DESCRIPTION

The Framingham Heart Study (FHS) is a longstanding study of the NHLBI. It was initiated by NHLBI in 1948 and currently comprises three cohorts representing three generations that have participated in multiple exams over varying lengths of time and time intervals between exams. The original cohort has been examined every two years since 1948. The Offspring cohort has been examined periodically since 1971. The third generation (Gen 3) has been examined twice since 2000. In 2009, the Omni Group 1 and Omni Group 2 cohorts, previously supported by grants, were integrated into the Framingham contract. Funding for FHS' current contract was continued in 2008 for seven years. A reexamination of all three cohorts, as well as the Omni cohorts, is part of the current contract. In 2011, the 31st exam of the original cohort and the second exam of Gen 3 and Omni Group 2 were completed. The Offspring cohort exam 9 and Omni Group 1 exam 4 started in 2011 and are anticipated to end in 2014.

STUDY PROGRESS

Scientific progress includes more than 128 publications during the last 12 months with 51 focused on genetics. The 9th exam of the Offspring cohort is ahead of schedule with nearly 2000 of 2700 participants examined. Omni Group 1 exam 4 is in progress and on schedule with over 200 of 360 participants examined.

There were 357 referrals for further medical evaluation among the 1397 participants examined between October 2011 and September 2012; they were primarily for elevated blood pressure values (>140/90 mg Hg). Among the 1215 participants seen in the clinic, there were 7 adverse events, or which 5 occurred with individual experiencing vasovagal response with the pulmonary function test (a known reaction). The other 2 adverse events were: one participant tripped when exiting an exam room due to his/her footwear (flip flops); another hit her head on an open locker in the dressing room, and ice was immediately applied to the injured area.

Dr. Ramachandran reported on mentoring fellows within the study. He explained that there were multiple avenues for research fellows entering the study. Two were funded annually by the core contract funding. Six others are from Boston University's other programs. Approximately 10 are associated with the NHLBI intramural program. Two more are international fellows. Seven come from other Boston area hospitals. Other collaborations come through the CHARGE Consortium and from various international fellows via Boston University. Many fellows go on to receive K grants and AHA fellowships. The fellows were responsible for 32 publications last year, several in high-impact journals. They also participated in the most recent FHS scientific retreat where they presented their findings and discussed approaches to improving productivity.

RESPONSES TO THE 2011 OSMB RECOMMENDATIONS

1. **Results Reporting**: Dr. Wolf and the investigators noted that the last coronary artery calcium (CAC) scan collected in FHS was 1.5 years ago. The investigators felt it was too late now to change the reporting thresholds for CAC results. They did review the CAC reporting procedures for MESA and CARDIA and noted inconsistencies between those studies as well. They stated that if CAC were collected in some future exam, the investigators would need to develop a revised plan to return results, ideally one that involves a consensus of all the cohort studies. Regarding results reporting of echocardiographic diastolic dysfunction and pulmonary hypertension, they noted that echocardiography is not being collected in the current exam. Prior echocardiography did not report such results because the protocol used was limited in evaluating diastolic dysfunction and pulmonary hypertension; in the primary care setting, there is no evidence for net benefit: risk from testing for or reporting these findings. CRP results are returned with all CAP/CLIA approved laboratory measurements. Reporting of genetic results has just started with reporting of Familial Mediterranean Fever and hemochromatosis. A genetic counselor was hired and is available for consultation when results are returned.

2. **Comparative analysis of sequencing from cell lines vs whole blood samples**: Dr. Cupples described the study design in FHS that test samples on 30 people (60 samples) and accounts for three sources of variation: de novo mutations, somatic mutations and genotype error. The design conducts exome sequencing on 10 trios to take advantage of the family relationships.

Sequencing has been completed and QC is currently underway. Analysis of the data is pending. The Board was disappointed at not seeing the results. The Board asked if there was an action plan based on the results of the analyses. That had not been addressed yet. Dr. Cupples shared that a presentation at ASHG of a similar analysis suggested there were not large differences.

3. **Data analysis of longitudinal data**: Dr. Massaro represented a list of recently published FHS papers that leveraged the rich longitudinal risk factor data collected in the study. Among them is a Dec. 2012 paper in JACC that showed early and long-term average lipid levels, as compared with contemporary measures, are more strongly associated with elevated CAC. The Board commended their efforts in expanding this research area.

4. **SABRe biomarker study.** Dr. O'Donnell presented a status report on SABRe, which includes four projects focused on 1) proteomics and metabolomics, 2) development of immunoassays of circulating proteins, 3) gene expression studies, and 4) miRNA profiling. There were multiple questions and comments regarding the SABRe Project. The Board urged more active role of the SABRe advisory board in providing expertise not only in laboratory technology but also in framing the scientific questions for investigation. The raw data should be deposited to dbGaP as is standard in this field so that other analysts may analyze results that may not have been addressed by the current investigators. Analyses require replication and assessment for clinical utility to be published, but it was unclear if that was part of the plan. Normally these activities are done on multiple small cohorts and then a larger cohort.

GENETICS/GENOMICS AND BEYOND

A major accomplishment last year was the design and conduct of the DNA comparison between whole blood and cell lines that has already been described (see Response # 2 above)..Large amounts of data continue to be deposited in dbGaP, including imputed genotypes and the Illumina OMNI5.0 chip data. Since its initial deposits in dbGaP, 202 requests for Framingham SHARe data, 85 requests for GAW16 data, and 20 requests for SHARe Social Networking data have been approved. With such data, analytic techniques have been created to estimate the genotypes of missing family members. In addition, a major accomplishment was the development of a new software package (FAMSKAT) for association tests of rare variants with family data. Imputation based on the 1,000 genomes project for 36 million variants, including indels, is planned. CHARGE produced 47 publications in the last year and 183 since inception in October 2008. In the coming year, additional sequencing data from the ESP, CHARGE-S and Exome Chip projects can be expected. Testing is expected to shift to RNA sequencing in the coming year. There is also a great deal of excitement over the NEXTGEN project to create adipocytes and hepatocytes from iPS cells to study gene expression and metabolomics. Return of results with familial Mediterranean fever and hemochromatosis variants is beginning as described above.

DISTRIBUTION OF BIOLOGICAL SAMPLES

Requests for DNA have declined since the release of SHARe data to dbGaP. Only 17 requests were received (of which 13 were approved) by the FHS DNA Committee since October 2011. The Laboratory Review Committee continues to review applications for non-genetic specimens.

Requests for biological samples continue but at a slower pace. Most requests for non-genetic specimens are from FHS investigators. In 2012, a total of 13 such proposals were received, 4 of which were disapproved primarily because they overlap with other ongoing projects.

UPDATE OF ONGOING ANCILLARY STUDIES

Multiple ancillary studies are conducted in Framingham. Some are built into the exam, others require only data or samples. The core exam is limited to four hours and the call-back ancillary studies are limited to two hours so as not to overburden the participants. There are no new ancillary studies requiring OSMB approval at the moment. Consortia participation is a large source of ancillary studies that generally do not require subject burden. Recent non-genetic participations include the Emerging Risk Factors Collaboration and NHLBI Multi-Cohort Analyses for new NHLBI guidelines. The Board questioned why NHLBI participates in international consortia when they could form their own consortium of NHLBI-funded studies with much higher visibility for NHLBI.

UPDATE ON OTHER STUDY OPERATIONS

The pulmonary function subcontract is making progress. It is focusing on GWAS analyses related to decline in lung function, and CT-based airway wall thickness, loss of pulmonary vasculature and emphysema. Data have been submitted to dbGaP. Six papers have been published in the last year. Plans include GWAS on lung density and diffusion capacity and an analysis of dietary correlates of emphysema. The Board asked if analyses of pulmonary measures were ever evaluated in the context of cardiac measures and recommended that as an approach.

The study is expanding access to CMS data. Data linking FHS and CMS are currently available on 2001-2008. Investigators plan to expand the data available to files from1991-2000 and 2009. The advantage of these data is that they will fill gaps in events follow-up and provide additional utilization data for those using fee-for-service plans.

SCIENTIFIC PRESENTATIONS

Three scientific presentations were provided. Dr. Massaro presented a study on CVD prediction and risk classification using coronary, aortic, and valvular calcification and subcutaneous/ visceral fat. Dr. Ramachandran presented on brain-derived neurotrophic factor (BDNF) as a risk factor for CVD. Levels are known to increase with exercise and decrease with higher BMI. Lower levels are associated with many outcomes including cognitive function, but this is the first analysis to show a relationship with CVD. Dr. O'Donnell presented the results of GWAS on calcification in areas other than coronary arteries. The study identified 2 GWAS associations with aortic and mitral valve calcification improves risk prediction even after adjustment for CAC. The Board was very impressed with the new findings from the study.

RECOMMENDATIONS

The Board thanked the investigators for their comprehensive report and commended their leadership in data sharing, the extraordinary fellows program, greater emphasis on longitudinal data analyses and the return of genetic results to study participants. The Board also acknowledged the passing of Dr. Larry Atwood as a loss to the study and to the profession. The Board recommended continuation of the study overall and had the following specific recommendations requiring an interim response from FHS investigators by **May 1, 2013**:

1. The Board was very disappointed at not seeing the results of analyses comparing the DNA sequencing from whole blood to those derived from cell lines; it requests the investigators to prioritize this analysis and provide results to the Board by May 1, 2013.
2. The Board requested an analysis and report on the effect of using CMS records to fill in morbidity and mortality follow-up of the FHS cohorts.
3. The Board continues to feel the SABRe Project lacks focus and would benefit from greater use of its advisory board. Limitations and strengths of its protocol should be carefully considered in the context of not only laboratory technologies but also data analysis; for example, there are still unknowns on the applicability of using mRNA and miRNA from blood vs. directly from tissues or organs. For biomarker discovery, plans should prioritize markers based on validity and clinical utility to create a minimum set for clinical use. The Board requests an analysis plan based on the above guidelines.
4. The Board requested a more detailed summary report on retention and follow-up rates relative to the originally recruited numbers and numbers of participants alive.
5. The Board requests a plan for data analyses of pulmonary function in the context of cardiac disease; analyses of lung volume and diffusion capacity should also be pursued.
6. The Board encourages greater emphasis be placed on clinical utility in future analyses and publications.

The Board also had the following recommendations for NHLBI (these should involve not only investigators from the Framingham Heart Study but also other NHLBI-funded cohorts):

- To convene a workshop to develop consensus for reporting individual study examination results to its participants, including what, how, and to whom results should be returned.
- To create an emerging risk factor consortium of NHLBI-funded studies to evaluate putative new risk factors on a larger scale to increase NHLBI visibility.

NEXT MEETING

The Board agreed to meet on Wednesday, December 11, 2013 in DC or Bethesda.

SIGNATURES

___X__ APPROVAL _____ DISAPPROVAL

Susan B. Shurin **December 21, 2012**

Deputy Director, NHLBI **Date**