Unlocking the mysteries of healthy aging

A large study of aspirin use generates genetic data with potential for insights into human health

Introduction

Dr. Paul Lacaze from Monash University, Australia, discusses how genomics is being used in conjunction with the ASPREE (ASPirin in Reducing Events in the Elderly) study—a major, international clinical trial that is helping determine the effects of daily low-dose aspirin on health outcomes. Lacaze explains how the use of Applied Biosystems™ microarray technology is helping provide genetic data from study participants, offering a broad range of possibilities for the study of health and aging.

Thermo Fisher: Can you tell us about the ASPREE study?

Lacaze: ASPREE started in 2010 and has 19,114 participants. It took several years to recruit them—to be enrolled, they had to be located in Australia and healthy beyond the age of 70. The objective was to determine whether taking daily low-dose aspirin was beneficial in preventing a range of outcomes among the elderly, including death, disability, dementia, cancers, and cardiovascular events.

Participants were randomized to receive either an aspirin or a placebo tablet, to be taken every day for an average of five years, without knowing what they were taking—so it's a double-blind, randomized trial. It was a massive undertaking, requiring a huge team of people, including investigators in both the US and Australia. The study was funded through the United States National Institute of Health (NIH) as well as various sources of Australian funding. Early on in the study, for example, we sought and received funding from the Australian government's Commonwealth Scientific and Industrial Research Organization (CSIRO) to help establish the study's biobank. That meant that at the beginning of the trial, when people were coming into the study, we could ask them to provide a blood sample, which would go into the biobank and be used for research purposes for many years to come. This research included different types of biomarker studies as well as genetic studies.

Dr. Paul Lacaze has been Head of the Public Health Genomics Program at Monash University, Australia, since 2015, where he studies the role of human genetic data in public and population health. The program operates within the Monash School of Public Health and Preventive Medicine and is centered around genetic analyses of large-scale cohort studies, biobanks, clinical trials, and clinical registries.

At Monash University, Dr. Lacaze provides scientific leadership on significant genomic opportunities associated with the ASPREE study, ASPREE Healthy Aging Biobank, and clinical registries. This involves the integration of human genetic sequence data with longitudinal phenotype and medical-outcome data across thousands of individuals in the quest for a better understanding of human health and disease.

"We're fortunate enough to have collected samples from so many of the trial participants that we can look at their underlying genetic makeup and potentially stratify the population by their genotype. This can help us see where the benefit or harm may be in some populations within the study cohort versus others."

ThermoFisher SCIENTIFIC

Each participant got a 30 mL blood draw taken, which was then fractionated into different types of white blood cells, red cells, serum, and plasma. There were also urine and some saliva samples collected. The samples were then split into a series of aliquots and placed into freezers at –20°C or into large liquid nitrogen tanks at around –200°C in order to maintain them for many, many years in a very stable state.

We managed to collect biospecimens from over 12,000 of the study participants. And then, thanks to additional funding provided by the United States National Cancer Institute, we were able to collect samples again three years into the trial—a follow-up in which we managed to collect samples from over 10,000 participants. Throughout the course of the study, we have also collected deep and extensive medical and phenotypical information from the participants, as well as lifestyle and occupational information through an in-depth questionnaire.

When something happens to people in the participant community, whether it's hospitalization, a cancer diagnosis, or even a death, we have a variety of ways to capture that information and put it into our database.

"The aspirin trial provided such a big cohort, with so much meaningful data, that it's in fact a powerful study of health and aging. It goes beyond aspirin. We're looking at all kinds of genetic and environmental contributions to not only diseases that occur when people get older, but also which factors might help prevent disease or help people bounce back from adverse events."

Thermo Fisher: What have you been learning from the study?

Lacaze: Recently, the medication period of the study was completed, and we were able to analyze events that happened to participants over the five years to determine whether taking aspirin was beneficial in preventing adverse outcomes. The conclusion of the study, revealed in three publications in a single edition of the *New England Journal of Medicine*, was that taking aspirin daily, if you're elderly and healthy, wasn't seen to have an overall benefit versus the potential harm that we saw, which included gastrointestinal bleeding and other types of reactions to the drug.

That was, in some ways, a surprising finding, and potentially may have a very high impact since there are tens of millions of people across the world taking aspirin in their later years under the assumption that it provides a benefit, where it actually may not. Of course, we know that for some people, aspirin may be a very effective drug—for example, if they have a history of cardiovascular issues, or after they've had a stroke, or even possibly in helping prevent certain types of cancers. So, it's not a simple story. Understanding who might benefit from aspirin and who might not will require more discovering and unpacking. It's not necessarily a one-size-fits-all model—and that's where the genetic studies come in.

Thermo Fisher: Can you tell us about this genetic aspect?

Lacaze: We're fortunate enough to have collected samples from so many of the trial participants that we can look at their underlying genetic makeup and potentially stratify the population by their genotype. This can help us see where the benefit or harm may be in some populations within the study cohort versus others. That's one of the major goals of the study moving forward, and one of the reasons why we're excited about getting genotype data from all of these samples—we can do a stratified analysis of the outcomes we've looked at in the context of aspirin, but more broadly in aging.

The aspirin trial provided such a big cohort, with so much meaningful data, that it's in fact a powerful study of health and aging. It goes beyond aspirin. We're looking at all kinds of genetic and environmental contributions to not only diseases that occur when people get older, but also which factors might help prevent disease or help people bounce back from adverse events. The genetic analysis component is exciting because it's helping us study the process of healthy aging in general.

Thermo Fisher: It sounds really exciting. Can we ask you a bit about the technology that you've chosen to use for the study? There were a number of options you could've chosen to do the genotyping. Why did you choose the Applied Biosystems™ Axiom™ Precision Medicine Diversity Array (PMDA) platform?

Lacaze: The microarray, or SNP, genotyping approach really provides a backbone of information about an individual's genetic makeup. This information is the gold-standard data type for cohort studies and studies of the genetics of human populations. The data set from ASPREE will be made available to people working on so many different aspects of the study. From the pharmacogenomics of aspirin to the risks of dementia and Alzheimer's disease; from cardiovascular disease, stroke, and cancer to even things like depression or personality traits. It's a broadly applicable data source, and it also allows us to combine our findings with the findings from other studies that have used that same technology to measure genetic variation.

"We feel that measuring common SNPs and common variants using the microarray platform is very complementary to sequencing. It allows us to do all kinds of additional studies into common disease-risk complex traits and provides compatibility that enables us to join other cohorts and consortia around the world."

We actually started with a DNA sequencing approach, which gives us a deeper coverage of coding regions to pick up rare variants that might have high penetrance and be clinically significant. That's one of our major focuses for genetic studies: to look at the frequency and medical relevance and penetrance of clinically significant rare variants measured by DNA sequencing.

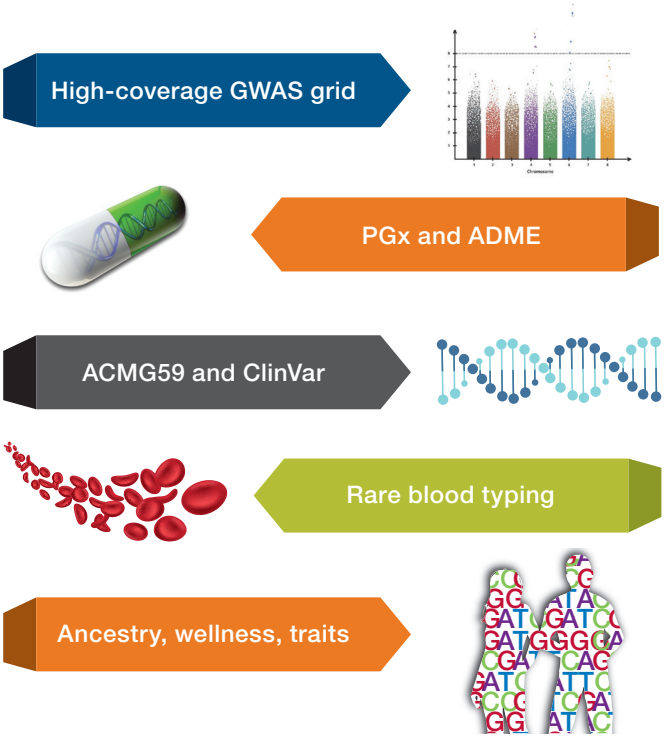
But we feel that measuring common SNPs and common variants using the microarray platform is very complementary to sequencing. It allows us to do all kinds of additional studies into common disease-risk complex traits and provides compatibility that enables us to join other cohorts and consortia around the world.

Thermo Fisher: So, if you think about large cohort studies such as these, how do you say the data are playing out in guiding therapeutic selection in the short term and also in the long term?

Lacaze: With pharmacogenomics, it's hard. There are a lot of barriers, and the science is still very much evolving. It's rarely a black-and-white problem in terms of finding a genetic variant that predicts a drug reaction—that is, an effect that could be used to guide clinical decisions. It's improving, but there's still a lot of work to be done. In our study, there are opportunities to do pharmacogenomics research, but it's a challenge because it's a study of the elderly, and a lot of people are taking many prescription drugs at this age. Polypharmacy is a big issue with the elderly.

We've also got a very high rate of antidepressant use, which is one of the categories of drugs that has a high amount of pharmacogenomic variation. So, there's a big opportunity for us to look at people's underlying pharmacogenotypes and correlate that with the prescription drug information that we've collected on people every year for up to seven years as they get prescribed new drugs. Potentially as they have adverse drug reactions, we can correlate those together to look at the frequency of meaningful or actionable pharmacogenetic variation alongside real drug prescription data.

We're excited about doing that type of analysis, and we will be looking more at the pharmacogenetics of aspirin. Some variants have been reported to have a potential effect or impact on the efficacy, toxicity, or risk of bleeding with aspirin, but none of those variants have made it to the level yet where they're considered clinical guidelines, where they would be printed on the label of a drug, or where you would measure that SNP before you prescribed a drug.



applied
biosystems

However, more and more evidence is starting to emerge about some candidate genes and candidate SNPs that might impact the way you react to metabolized aspirin, or may have a benefit in cancer prevention for some people and not others, or may be correlated to certain types of tumors and not others, particularly colorectal tumors. So, there are emerging opportunities for us to use the array data to do a very detailed analysis of aspirin pharmacogenomics.

To do that, we need to bring together studies from around the world that have been focused on aspirin, to pull out data to form an aspirin pharmacogenomics consortium where we could try to get the sample sizes and the statistics that are going to be required to either validate candidate variations or find new associations. One of the challenges this collaboration could address is defining the phenotype of the SNP as either a benefit or a harm, because there's quite a lot of heterogeneity there. Things are moving quickly, but we still have a lot of work to do in pharmacogenomics.

Thermo Fisher: So, at the moment, focusing on aspirin: who has been approaching you and asking to access this precious resource for other studies?

Lacaze: We currently have about 12 to 15 substudies funded by Australia's National Health and Medical Research Council that are looking at all kinds of issues, from sleep apnea, to falls and fractures, to brain imaging and depression. Some of them are utilizing the biobank samples, and others are recruiting subcohorts within the population for specific substudies. We now have a process in place where any investigator from Australia or around the world can request access to the ASPREE biospecimen material, to conduct any type of study that they want to. That could involve measuring a new type of biomarker, or gene, or a variety of project types. We assess those on a case-to-case basis, and the number of requests is growing every week. As funding becomes available, we're starting to see studies in areas like lipidomics and proteomics, inflammatory cytokines, and others.

We also have a similar process for providing access to the clinical and phenotypic data set, and soon the genetic data set will be available for an open and collaborative approach to research—investigators from Australia, the US, and the rest of the world will be able to apply for access to both the samples and all of the data.

Thermo Fisher: Thank you very much.

For Research Use Only. Not for use in diagnostic procedures. © 2019 Thermo Fisher Scientific Inc. All rights reserved.
All trademarks are the property of Thermo Fisher Scientific and its subsidiaries unless otherwise specified. **COL18790 0419**