



Health Professionals Follow-Up Study NEWSLETTER

Harvard T.H. Chan School of Public Health

Winter 2019

Dear Colleagues,

Thanks to your invaluable contributions, HPFS remains the largest, detailed long-term study of men's health.

In this year's newsletter, our feature article focuses on the current and future landscape of nutritional epidemiologic research. We also highlight some of our recent findings such as the benefits of regular aspirin intake, the role of Mediterranean diet in preventing cognitive decline in later life as well as new findings on prostate cancer risk.

Lastly, we invite you to visit our website at <https://sites.sph.harvard.edu/hpfs/>. Here you can find our most recent updates and announcements as well as a list of all of the articles ever published using HPFS data.

Thank you for your tireless support over the past 33 years!

Walter C. Willett, M.D., Dr. P.H., and Lorelei A. Mucci, MPH, ScD, Principal Investigators

Current and Future Landscape of Nutritional Epidemiologic Research

Almost everyone is bombarded with claims that specific foods or diets can either confer huge health benefits or undermine our longevity. Due to confusion about diet and health in the general public and among health professionals, the editors of the *Journal of the American Medical Association (JAMA)* recently invited Drs. Frank Hu and Walter Willett of the Department of Nutrition at the Harvard T.H. Chan to comment on the current and future of research on diet and health (*JAMA* 2018; 320 (20):2073-2074). Since participants in the Health Professionals Follow-Up Study have contributed hugely to this research, we are providing a slightly modified version of this commentary.

The last half-century of nutrition research has expanded beyond traditional approaches based primarily on in vitro biochemistry, animal models, and short-term feeding studies with risk factors as the primary outcomes. Although such studies are still an integral part of nutrition research, they do not directly connect diets with long-term health and disease in humans. Dietary guidelines and recommendations, until recently, were in part based on professional opinions using extrapolations across species and experimental models, and limited human

evidence from cross-sectional or small feeding studies. Nutritional epidemiology, building on the experience of epidemiology in other fields of public health, has begun to provide important new information and has had substantial effects on diets globally.

A successful example of nutritional epidemiology affecting policy is the substantial reduction in *trans* fatty acids from partially hydrogenated oils. The combination of consistent findings from epidemiologic studies, such as the Health Professionals Follow-Up Study (HPFS) and sister study, the Nurses' Health Study (NHS), demonstrating an association between *trans* fat and coronary heart disease, along with evidence from controlled feeding trials showing adverse effects on blood lipids, provided sufficient certainty of harm to ban industrially produced *trans* fat in the United States and many other countries. Similar bodies of evidence have contributed to the substantial reduction in consumption of sugar-sweetened beverages in the United States. Over the last 60 years, heart disease mortality rates have decreased by about 70% in developed countries, which is largely attributable to improvements in lifestyle and diet-related risk factors.

Well-conducted, large prospective epidemiologic studies, such as the HPFS, have been crucial in updating dietary guidelines. While earlier US dietary guidelines that were based on limited and indirect data advised low-fat/high-carbohydrate diets, more recent epidemiologic studies, combined with controlled feeding studies, have provided robust evidence to change the guidelines to emphasize the type of fat rather than the total amount of fat in the diet. Also, without the extensive epidemiologic data on coffee and many health outcomes, the requirement in California for companies to provide warnings about cancer risk associated with coffee may have influenced individuals to give up coffee. Evidence from nutritional epidemiologic studies, including the HPFS and the NHS, led to a reversal of this requirement. With the constant onslaught of exaggerated claims and warnings about diet and aggressive marketing by food companies, nutritional epidemiology, interpreted in the context of other evidence, is essential for helping to separate myth from fact. Despite seemingly endless public debates, a strong consensus exists among nutritional researchers and clinicians about the basic elements of a healthy diet even though uncertainties about many details need resolution by further research.

Nutritional epidemiology has sometimes been criticized for inaccurate dietary assessment and reliance on observational study design. Human diet is a complex, dynamic exposure with no perfect method to quantify all aspects of dietary intakes or eating behaviors. Concerns about measurement of diet have been addressed in many studies that have compared standardized questionnaires with detailed weighing and measurement of foods and with biomarkers of intake. For most nutrients and foods, carefully designed food frequency questionnaires, such as what we use in the HPFS, work sufficiently well to detect important associations if they truly exist. Repeated measurements of diet are particularly useful in reducing random errors while representing long-term dietary habits, and statistical methods have been developed to account for systematic errors.

Objective biomarkers (such as blood levels of fatty acids and carotenoids) and digital technologies

(such as cell phone images of foods and meals) have the potential to improve the accuracy of dietary assessment and are an active area of research in nutritional epidemiology. However, considering their limitations, new biomarkers or technologies are likely to complement rather than replace self-reported dietary assessment tools. Control of confounding is at the core of robust epidemiologic studies and can be done well with careful study design and analyses. Yet differentiating among strongly correlated constituents of foods can sometimes be difficult or not possible. In many cases, analyses of whole foods or overall dietary patterns are more informative for providing practical guidance for making dietary choices, despite that the roles of specific constituents are left unknown.

Although the simplistic response to concerns about causality is to conduct a randomized trial, doing so is often infeasible because decades of follow-up are needed for outcomes like cancer, and long-term adherence to assigned diets is usually poor. In this context, the guidelines for inferring causality outlined by Bradford Hill many years ago are still relevant. Often in public health and many other areas, no single study can provide a definitive answer and no study design is without its limitations. Thus, conclusions and policy decisions need to evaluate and quantify sources of biases and to use the totality of the best available evidence, recognizing that this is an iterative process.

Diets of individuals in the United States remain far from optimal, scoring only about 50 of 110 on a scale of diet quality. Thus, translating existing nutritional knowledge into policies and public health practice remains a top research priority. Individual food choices are shaped by many factors including biology, education, socioeconomic status, and the food environment. Meaningful improvements in long-term eating habits will require policy changes including soda taxes, financial incentives for producing and purchasing healthy foods, food labeling, regulation of food marketing, and creating healthy school and work environments. No single approach is likely to be successful. Monitoring and evaluating the effects of these policies on diet quality and health outcomes will be critical. Nutrition literacy and communications are integral to improving diet quality, and health care professionals have an important responsibility to promoting healthy eating habits but often lack basic nutrition knowledge.

Nutrition education in medical school curricula is greatly needed.

Many new opportunities for nutritional epidemiologic research have been created by remarkable advances in omics technologies, including genomics, metabolomics, proteomics, and the study of the human microbiome. The integration of these technologies into nutritional epidemiology and adopting a “systems epidemiology” approach can help to understand individual variability in dietary responses, discover novel biomarkers of diet, identify high-risk populations to target for intervention, and provide molecular insights on metabolic pathways. However, these technologies all have sources of error and limitations, and unrealistically high expectations need to be tempered. The interpretation and value of these technologies could be greatly enhanced by inclusion of data on diet, which may be an upstream determinant of what is being measured or a modifier or mediator of observed effects. Whatever mix of new technologies and methods are applied, study designs need to recognize that most of the serious diseases affecting modern populations develop over many years, or decades, and may have their origins in early life. Thus, long-term studies with repeated measures of diet and other exposures are essential.

The integration of omics and digital technologies in nutrition research has heightened enthusiasm for “personalized nutrition” or “precision nutrition,” which would identify optimal diets for each individual depending on their genetics and other factors. Although this approach has shown some promise in disease management and improvement of certain metabolic conditions, there is still a long way to go before its widespread clinical application. Future research is needed to explore the combination of population-wide interventions (such as education, taxation/subsidies, and limiting the marketing of unhealthy foods) and personalized approaches in facilitating behavioral changes and improving health outcomes of individuals and populations.

In the next decade, nutrition research will need to address many societal and global challenges. First,

the food system is rapidly evolving, and gaps in diet quality between various population groups have widened. Reducing food (and health) disparities is thus an important research goal. Second, the continuing increase in obesity rates is affecting life expectancy adversely and can reverse the gains in health achieved over the last 50 years. When addressing the obesity epidemic, a shift is needed from the traditional biomedical model to a socioecological model by improving the overall food environment combined with more efficacious individualized interventions. Third, in low- and middle-income countries, nutrition and epidemiologic transitions are occurring at an unprecedented pace, while undernutrition and nutrient deficiencies continue to remain major problems. Further research is needed to address the dual burden of undernutrition and overnutrition in these populations. Fourth, the global food systems are having a major influence on environmental degradation and climate change, contributing to about a quarter of greenhouse gas production. Thus, every aspect of food production and consumption needs to be evaluated through both health and environmental lenses because human well-being ultimately depends on planetary health.

Over recent decades, the combination of a multitude of research approaches, including carefully conducted nutritional epidemiologic studies, has provided much new knowledge about the important influence of diet on human health, and this knowledge has been translated to guidelines and policies that have improved longevity and well-being. The potential for further enhancements in health through better nutrition remains large. A research agenda that incorporates a multidisciplinary approach applied across the life cycle, that leverages new technologies, and that addresses new challenges is likely to be most effective for ensuring healthy and sustainable diets in the United States and globally.

“Translating existing nutritional knowledge into policies and public health practice remains a top research priority”

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Research Highlights

Regular Aspirin Use Linked with Reduced Lethal Prostate Cancer Risk

Members of the prostate cancer epidemiology team recently published a paper on aspirin use and prostate cancer risk in *European Urology Oncology* entitled “Aspirin Use and Lethal Prostate Cancer in the Health Professionals Follow-Up Study.” Previous studies have found a slight inverse association between regular aspirin use and incident prostate cancer, but these findings are inconsistent and have relatively small sample sizes. The researchers leveraged data from 49,409 men from the Health Professionals Follow-Up Study for this study. Beginning in 1986, participants completed biennial questionnaires on their health and lifestyle.

By the end of the study period, 804 men developed lethal prostate cancer. Compared to men who had

never taken aspirin or those who had stopped taking aspirin, men who were regular users of aspirin had a significantly lower risk of developing lethal prostate cancer. Aspirin use post-diagnosis was also associated with lower lethal prostate cancer and overall mortality. The results from this study add support for adults to take a daily aspirin, but please consult with your health care provider because this is contraindicated for some people. [Downer et al., *European Urology Oncology* (2018)]. <https://doi.org/10.1016/j.euo.2018.07.002>

Downer MK, Allard CB, Preston MA, Wilson KM, Kenfield SA, Chan JM, Mucci LA, Giovannucci E, Stampfer MJ. Aspirin use and lethal prostate cancer in the Health Professionals Follow-Up Study. *European Urology Oncology*. 2018 Jul 31.

Mediterranean Diet Linked with Improved Cognitive Function in Men

Many diets have gained popularity in recent years, including paleo, keto, gluten-free, raw, vegan/vegetarian, Whole 30, Mediterranean, and intermittent fasting to name a few. Many of these diets are relatively new and have not been scientifically studied for their effectiveness. Researchers from Harvard published a paper analyzing the Mediterranean diet in the *European Journal of Epidemiology* entitled “Adherence to Mediterranean diet and subjective cognitive function in men.” This study sought to investigate how the Mediterranean diet influences subjective cognitive function (SCF) in later life.

The Mediterranean diet (MD) includes unsaturated fats, omega-3 fatty acids, fruits, vegetables, whole grains, and nuts, with limited consumption of red meat and dairy. Previous studies have linked MD with lower risk of cardiovascular disease, but there have been limited data on MD with cognitive function. The authors used the Health Professionals Follow-Up Study to study the diets and cognitive function of 27,842 men from baseline in 1986 to 2012. The researchers gave each participant a MD score of 0-9 based on adherence (0 = low, 9 = high) to the diet. The SCF score was based on 6 questions, with a low score indicating good subjective memory and a high score indicating poor subjective memory.

The results of the analyses showed that higher MD scores were significantly associated with a lower likelihood of moderate and poor SCF. This association was true for men who currently adhere to MD and those who followed a MD diet several decades earlier. This study sheds more light on the importance of diet in preventing cognitive decline in later life, and current analyses are evaluating the specific components in the MD that may be most important for maintaining a high level of cognitive function. (Bhushan et al., *European Journal of Epidemiology* (2018)). <https://doi.org/10.1007/s10654-017-0330-3>.

Bhushan A, Fondell E, Ascherio A, Yuan C, Grodstein F, Willett W. Adherence to Mediterranean diet and subjective cognitive function in men. *European Journal of Epidemiology*. 2018 Feb 1;33(2):223-34.



Family History of Breast or Prostate Cancer Linked with Increased Risk of Prostate Cancer

Prostate cancer is one of the most heritable of all cancers. Men with male relatives diagnosed with prostate cancer have a 2- to 4-fold higher risk of developing prostate cancer themselves. As a result of recent genetic testing and research into the BRCA gene mutation, prostate cancer risk has also been linked with family history of breast cancer. Researchers with the Harvard Cancer Epidemiology group recently published a paper in *Clinical Cancer Research* titled “Family history of breast or prostate cancer and prostate cancer risk” that investigates the connection between family history of breast or prostate cancer on prostate cancer risk. They leveraged 16 years of data on 37,002 men from the Health Professionals Follow-Up Study. Researchers used information from participants’ answers on family medical history as well as diagnoses during the follow-up to determine the importance of family history.

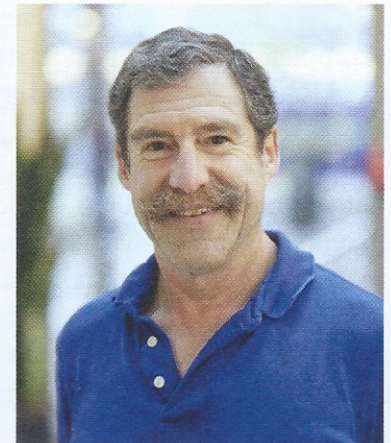
The results from the analyses showed that men with a family history of breast cancer, prostate cancer, or breast and prostate cancer had a significantly higher risk of developing prostate cancer than men with no family history of either cancer. These findings further support the link between BRCA mutations with both breast and prostate cancer. These results shed light on the importance of including family history of broader cancers in cancer screening strategies. (Barber *et al.*, *Clinical Cancer Research* (2018). doi: 10.1158/1078-0432.CCR-18-0370.

Barber LE, Gerke T, Markt SC, Peisch SF, Wilson KM, Ahearn TU, Giovannucci EL, Parmigiani G, Mucci LA. Family history of breast or prostate cancer and prostate cancer risk. *Clin Cancer Res* 2018;24:5910-5917.

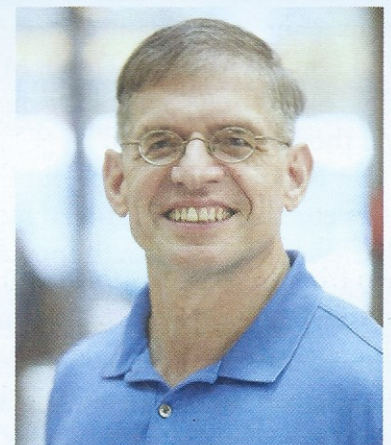
Research Team Focus: Ed Giovannucci and Meir Stampfer

Ed and Meir have been close colleagues for over 30 years, since 1986 when Ed came to Harvard School of Public Health (HSPH) as a doctoral student, after completing his BA at Harvard, and medical school training (and pathology) at University of Pittsburgh. At that time, Meir was a newly minted assistant professor, and had helped Walter Willett establish HPFS that same year. Meir did his undergraduate degree at Columbia, his MD at NYU, and his doctorate in public health at HSPH. Ed and his wife Lydia – a programmer for HPFS - live in Brookline, MA with their two children, Isabel and Michael. Meir and his wife Claire also live in Brookline; their children Sam, Eliane and Orly live in Atlanta, Salt Lake City and Seattle.

Ed and Meir have worked on many projects together. One recurring theme has been the distinction between indolent and potentially lethal prostate cancer. Prostate cancer is the second leading cause of cancer death in men in the US, but most men diagnosed with prostate cancer die of another cause, and a large proportion are treated unnecessarily. Ed and Meir, together with Lorelei Mucci and other HPFS colleagues, have identified a distinctive pattern of risk factors for potentially lethal disease that requires prompt treatment, as compared with indolent prostate cancer for which aggressive therapy is not appropriate. For example, in a series of papers from HPFS, we found that vigorous physical activity lowered the risk for potentially lethal prostate cancer, as did long term use of statins, and consumption of lycopene (from cooked tomatoes) and fish. These protective factors appeared to have little influence on indolent disease. Conversely, taller height was associated with slightly higher risk of lethal disease. These studies have changed the face of men’s health, and offer ways to lower risk of serious prostate cancer.



Meir Stampfer, M.D., Dr. P.H.



Ed Giovannucci, MD, ScD.

Interview with HPFS Participant

We were very fortunate to meet one of our participants, Dr. Howard Needleman, and talk about his experience as an HPFS participant over the past 30 years. Dr. Needleman is a pediatric dentist, who trained at Harvard and Children's Hospital in Boston. He had a career that combined research, administration, and clinical practice. In 1986 he joined the Health Professionals Follow-Up Study. Dr. Needleman recalls why he decided to participate in this study:

"I've done clinical research, I know what it is to recruit people in your study to participate and continue the participation. <...> It seemed an interesting study, it would yield valuable information to me personally, and to the greater population to understand nutrition and its effect on our health."

Dr. Needleman has been a very active participant; he completed every single questionnaire both on paper and online, participated in many sub-studies, such as Mens' Lifestyle Validation Study, and has provided multiple biological samples.

"It was hard, but I did it. I guess it talks to my personality. I am fairly compulsive. I am a committed person. If I say I'm gonna do something, I do it. Trust and commitment and follow-through are very important qualities on a personal and academic level. I never give up!" says Dr. Needleman.

We also talked about the experience of filling out the questionnaires that is, at times, rather challenging: "Most often when filling them out, I am yelling upstairs to my wife "Leslie, what kind of olive oil do we use?" or "How many ounces?" It's very challenging. And I don't prepare my food. My wife is a wonderful cook. So I found some of the questions challenging and thought-provoking."

Dr. Needleman pointed out the importance of the newsletters as a motivational factor: "When I read the newsletter, it impacts upon my behavior in terms of what I eat. I say, I did some good, the world knows that X is related to Y and it's been shown in your study fairly definitively that there is an important causal relationship between some dietary intake and some particular medical entity. So it's very motivating. So I figure it's a helpful thing for participants to be aware of and read these newsletters. That keeps me going."

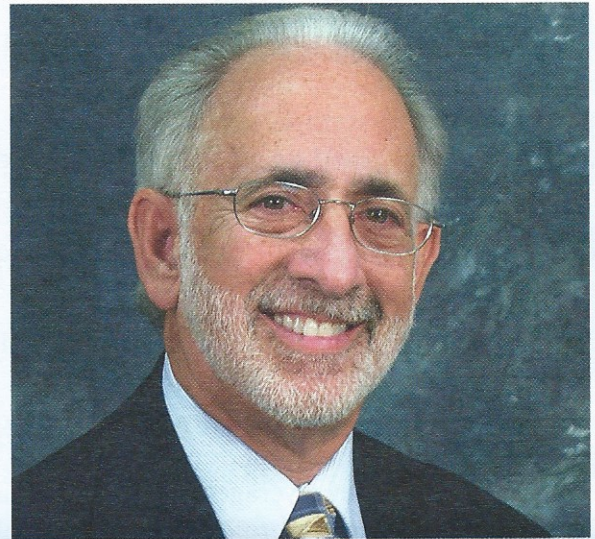


photo courtesy of Dr. H. Needleman

We also asked Dr. Needleman about some of the recommendations he would like to give us to improve the way we communicate the study's updates to the participants. Dr. Needleman suggested that we communicate our findings more often, not only every two years through our newsletter. Dr. Needleman mentioned that he found out about the study's website recently, but thought that the website was for researchers, not participants.

We inquired whether the study participation had changed his life in any way. Dr. Needleman replied: "For sure. The data that's coming from the study made me more cognizant of nutrition and health. It has changed my diet. I try to stay slim, I try to stay active. I cheat a little bit, but everything in moderation. If we find that eating vegetables is healthy, to prevent colon cancer, for example, I do it, and my wife reads these articles with me."

And as a message to all fellow HPFS participants Dr. Needleman says:

"Keep at it! We've started it, let's finish what we've started! Don't give up, it's a worthwhile study, a lot of good data that's coming helps us individually and the world in general. We are committed to do it, let's do it till the last time we're able to fill it out. Stick with it!"

We are very grateful to Dr. Howard Needleman and all other HPFS members for their valuable contributions to science, their dedication and commitment!

HPFS Website and Twitter

Where can you find information about our latest findings and topics related to nutrition and health?

Sometimes we get phone calls or letters from our participants who ask us: “I’ve been part of this study for many years, but what are the results of my participation? Where can I find the research papers that used the data we all have provided over all these years?”

We realized that many participants are not aware of available resources such as our study’s website, its Twitter page and the Harvard Chan Nutrition Source. First of all, we suggest you visit **our website** at <https://sites.sph.harvard.edu/hpfs/>. You can find the updated list of all of the articles ever published using HPFS data (abstracts are attached). This website is a great source of information for you, your family and friends. Besides the publications you can also find copies of all past questionnaires and newsletters, information about the researchers involved in the study, and more. And of course, you can update your current mailing and email address online using our website.

We also wanted to let you know that we recently launched our **Twitter page**. It’s a great way to keep up with our updates, announcements, etc. Please follow us @hpfscohort.

If you are interested in additional information on nutrition and health, we invite you to visit the website maintained by the Department of Nutrition at Harvard T.H. Chan School of Public Health called **the Nutrition Source**: www.hsph.harvard.edu/nutritionsource/. In addition to research from the HPFS, this site includes findings from other studies around the world including our cohorts of women, the Nurses’ Health Studies. The website also contains reviews on controversial topics in nutrition and helpful articles on how to put newly found knowledge into practice, such as replacing saturated fats and refined grains with polyunsaturated fats and whole grains. We also provide healthful recipes for foods served in our food service at Harvard, including those developed by the famous cookbook writer, Mollie Katzen.

Please note that much of the information would not be available without your MANY contributions as a member of HPFS. We are truly grateful for all you have provided.



Privacy

Large studies will be the key to the success of these efforts to understand the role of genes. This highlights the importance of collaboration and careful data sharing with appropriate safeguards on participant confidentiality. Indeed, the National Institutes of Health (NIH) has mandated that data from studies of DNA and disease risk be deposited in a controlled-access database. Any data sent to this database will not contain any personal identifiers (e.g., name, date of birth, address, zip code, or any trait information that could identify you).

Our participation in this NIH database will contribute to the large international effort to identify the genetic variants underlying the inherited predisposition to cancer, heart disease, diabetes, and other diseases. The goal is to develop more effective prevention and treatment strategies. However, we recognize that DNA sequence data are potentially sensitive. If you have any question about these studies (called GWAS or sequence studies), or you wish to withdraw from them in the future, please send an email to hpfs@hsph.harvard.edu or write to us at HPFS, 677 Huntington Avenue, Boston, MA 02115.

Donations

Our research relies on federal funding from the National Institutes of Health (NIH). Over the past several years, NIH funding for our work has been significantly reduced even though the HPFS has been given the highest possible rating by review committees, making the future of our research less certain. This lack of stability means we must now focus on simply keeping the core of the studies moving forward.

Many participants and their families have asked how they can support the Health Professionals Follow-Up Study beyond the wonderful and generous donations that all participants make of their time and energy. In these uncertain times, we are deeply grateful for the expressions of support and donations made to the Friends of the Health Professionals Follow-Up Study Fund. Donations and bequests help to sustain our continued work. Donations may be sent to the Harvard T.H. Chan School of Public Health. For information on how to give or to make a secure gift online, please visit www.hsph.harvard.edu/giving and indicate that the gift is in support of the Friends of the Health Professionals Follow-Up Study Fund.

To donate by mail, please make your check payable to and mail to:

Health Professionals Follow-Up Study
Harvard T.H. Chan School of Public Health
677 Huntington Ave
Boston, MA 02115

Thank you! Your support truly makes a difference!

PROMISE Study

HPFS is committed to improving men's health. Given that many blood cancers such as multiple myeloma are more common in men, we would like to mention a new study coordinated by the Dana Farber Cancer Institute titled, "Predicting Progression of Developing Myeloma in a High-Risk Screened Population (PROMISE)." The objective of the PROMISE Study is to test at-risk individuals for early warning signs of multiple myeloma, a cancer of the blood. These early warning signs, which are often called "**precursor conditions**," include monoclonal gammopathy of undetermined significance (**MGUS**) and smoldering multiple myeloma (**SMM**). The mission of the PROMISE Study is to contribute to future therapies and lifestyle interventions that will prevent myeloma from developing.

Who is eligible? Individuals between the ages of 45 and 75 who have a first-degree relative, such as a parent, a sibling, or a child, who has been diagnosed with multiple myeloma or one of the following related plasma cell conditions: MGUS, SMM, or Waldenstrom macroglobulinemia, and/or who are African-American.

What does the study involve? Participants are asked to complete a study questionnaire and go to a local clinic or lab to collect a blood sample to ship back to the PROMISE Study for analysis. The research team will analyze this blood sample to detect if participants have one of the two precursor conditions: MGUS or SMM. Participants that test positive for one of these conditions will be invited to take part in a group that will be followed on a regular basis. Participants that test negative will be invited to be re-screened every three years.

To learn more information about the PROMISE Study, please visit www.PromiseStudy.org. The staff at the PROMISE Study would be happy to answer any questions at **(617) 582-8544**, or by email at PROMISEstudy@partners.org

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To report name or address changes, please email the project coordinator at hpfs@hsph.harvard.edu or visit <https://sites.sph.harvard.edu/hpfs/>. Letters and feedback are welcome.