NIH NATIONAL CANCER INSTITUTE

Li-Fraumeni Syndrome (LFS) Study *Newsletter*

July 2018

Division of Cancer Epidemiology and Genetics • Clinical Genetics Branch

MESSAGE FROM THE NCI LFS STUDY TEAM

Welcome to the latest issue of the National Cancer Institute (NCI) Li-Fraumeni Syndrome Study newsletter. Some of you have recently enrolled while others have been with the study since it first opened in 2011. The Li-Fraumeni Syndrome (LFS) clinical and scientific communities continue to make progress in understanding LFS and cancer. We share some of our latest developments in this newsletter. As a reminder, regular updates can be found on our website: **www.lfs.cancer.gov**.

FINDINGS FROM OUR CANCER SCREENING STUDY

Between June 1, 2012, and July 30, 2016, 116 individuals enrolled in our cancer screening cohort. We found that multimodal screening at baseline was successful/effective. Cancer was detected in eight individuals—two lung adenocarcinomas, one osteosarcoma, one sarcoma, one astrocytoma, one low-grade glioma, and two pre-invasive breast cancers [ductal carcinoma in situ]. All but one required surgical resection alone for definitive treatment. All cancers were diagnosed by whole body (WBMRI) or brain MRI. An additional 32 participants had findings that were incidental or benign on further evaluation, resulting in a false-positive rate of about 30%. This study describes the establishment and feasibility of an intensive cancer surveillance protocol for individuals with LFS. Further details can be found in the August 2017 issue of *JAMA Oncology*.[1]

A parallel effort at multiple global centers through the Li-Fraumeni Exploration Research Consortium, (including the NCI), confirmed the feasibility and success of whole body MRI as a screening technique in detecting early cancers.[2] This larger study of 578 individuals with LFS reported a similar cancer detection rate.

Links to all the papers listed below can be found on our website: **www.lfs.cancer.gov.** Please contact our study nurses if you are not able to access the paper and would like a hard copy.

1. Mai PL, Khincha PP, Loud JT, et al. Prevalence of cancer at baseline screening in the national cancer institute li-fraumeni syndrome cohort. *JAMA Oncology*. 2017.
2. Ballinger ML, Best A, Mai PL, et al. Baseline surveillance in li-fraumeni syndrome using whole-body magnetic resonance imaging: A meta-analysis. *JAMA Oncology*. 2017.

Additional publications since last newsletter

3. Formiga MNDC, de Andrade KC, Kowalski LP, Achatz MI. Frequency of Thyroid Carcinoma in Brazilian TP53 p.R337H Carriers With Li Fraumeni Syndrome. *JAMA Oncology*. 2017.
4. de Andrade KC, Mirabello L, Stewart DR, Karlins E, Koster R, Wang M, Gapstur SM, Gaudet MM, Freedman ND, Landi MT, Lemonnier N, Hainaut P, Savage SA, Achatz MI. Higher-than-expected population prevalence of potentially pathogenic germline TP53 variants in individuals unselected for cancer history. *Human Mutation*. 2017.

IN THIS ISSUE

NCI LFS STUDY TEAM AT THE LI-FRAUMENI SYNDROME ASSOCIATION (LFSA) SYMPOSIUM

In April 2018, 11 members of the NCI LFS Study team attended the 4th International LFSA Symposium, held in Toronto, Canada. Drs. Khincha, Savage, and Young presented to over 300 international LFS investigators and families during the four-day workshop. Dr. Kelvin de Andrade, Dr. Oba, Ms. Frone, and Ms. Bremer presented posters as well. The team was especially pleased to be joined by Dr. Joseph F. Fraumeni, Jr., and Dr. Elaine Shiang, the wife of the late Dr. Frederick P. Li, who participated in the meeting. Our website has additional details on the topics and results presented: **www.lfs.cancer.gov**.

Dr. Fraumeni (center) with NCI LFS Study Team

Invited Speakers:

Dr. Payal Khincha - Reproductive factors & breast cancer risk in women with LFS: the NCI cohort

Dr. Sharon Savage - Findings at baseline cancer surveillance in LFS and follow-up

Dr. Jennifer Young - Couples living together with LFS: Coping styles and partner roles

OUR ONGOING COMMITMENT TO VARIANT CURATION

Determining whether a specific change or variant in an individual's DNA causes a specific disease is very challenging. Doctors and scientists carefully evaluate each variant before designating its classification into one of the following categories: pathogenic, benign, or variant of unknown significance. Shifts in determinations of specific variants can happen as new evidence accumulates. These variants are usually classified based on multiple sources of evidence, such as the scientific literature, laboratory studies, reports of other patients with the same variant, and/or computational methods inferring the possible consequences of the variant on protein function.

There are many efforts – some of which the NCI team are involved in – to streamline specific *TP53* variant interpretation and facilitate consistent reports across centers and specialists. We are committed to keeping our study participants informed about the most recent information related to their family-specific LFS variant. Please do not hesitate to reach out to us if you have questions.

Poster Session Presentations:

Psychosocial Functioning in Research Participants at Enrollment in the NCI Li-Fraumeni Syndrome Study. Bremer RC, Young JL, Khincha PP, Peters JA, Achatz MI, Savage SA, Loud JT.

Insights from the International LFS Provider Survey for the optimization of service delivery of surveillance whole body MRI in the genetics clinic. Frone MN, Perry J.

Differences in germline *TP53* variant classifications affect the estimates of population prevalence of Li-Fraumeni syndrome: a gnomAD-based analysis. de Andrade KC, Frone MN, Wegman-Ostroski T, Khincha PP, Kim J, Amadou A, Santiago KM, Fortes FP, Lemonnier N, Mirabello L, Stewart DR, Hainaut P, Kowalski LP, Savage SA, Achatz MI.

UPDATES FROM THE NCI LFS STUDY

PHYSICAL ACTIVITY

We have developed a new study exploring the effects of exercise and physical activity on individuals with LFS. The benefits of exercise, including reduced risk of cancer, have been well established in the general population. However, these benefits have not been clearly evaluated in individuals with a genetic predisposition to develop cancer, such as individuals with LFS.

Adults, 18-years and older, with LFS and their unaffected adult family members are invited to participate in this study by filling out the one-page questionnaire included with this newsletter. It should take no more than 3-5 minutes of your time. Your participation is critical to advance our understanding of whether exercise and physical activity have any bearing on cancer risk in LFS. Participation in the physical activity study is completely voluntary and will have no effect on your participation in the NCI LFS Study whatsoever. If you have any questions or concerns, please contact Renée Bremer at 240-276-7266 or renee.bremer@nih.gov.

LFS INTERACTIVE FAMILY INTERVIEW STUDY

Over the past five years of the study, we have conducted over 60 in-depth family interviews with various combinations of parents, children, siblings, and intimate partners. Dr. Jennifer Young presented some of the emerging themes in family coping mechanisms at the recent LFS Symposium in Toronto. She and her collaborators are preparing manuscripts on couples' coping styles and on lessons from living with LFS that parents pass on to their children.

LFS STUDY TEAM - PERSONNEL CHANGES

We would like to highlight several changes to the NCI LFS Study team since the last newsletter.

Payal P. Khincha, MD, MSHS, a pediatric hematologist-oncologist with training in clinical and translational research was recently appointed as the Principal Investigator of the LFS Study. Dr. Khincha was previously the Lead Associate Investigator of this study and has taken over the new role from Dr. Achatz. Dr. Sharon Savage continues to be the Lead Medical Advisor for the study.

As thrilled as we were to welcome **Maria Isabel Achatz, MD, PhD**, into the LFS study team as the Principal Investigator, we are equally saddened to report that she has returned to her native Brazil. Fortunately for all of us, Dr. Achatz will continue to work with the study on a number of research projects and is still available as an LFS clinical expert.

Megan Frone, MS, CGC, is a board-certified genetic counselor with special interest and expertise in inherited predisposition to cancer and gene-variant annotation and classification. Ms. Frone's clinical background is in general pediatric genetics, inborn errors of metabolism, and pediatric and adult cancer genetics. She joined our team last year as the lead genetic counselor.

June Peters, MS, CGC, genetic counselor on the NCI LFS Study, retired after a highly productive career in clinical cancer genetics. Patients in the clinical cohort may have completed their Colored EcoGenetic Relationship Maps (CEGRMs) with June during their visit to the NIH Clinical Center. CEGRMs will continue to be administered by our new genetic counselor, Megan Frone, and our epidemiology program analyst Renée Bremer.

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CHANGES TO THE STUDY

As of April 1, 2018, over 800 individuals have joined the study and over 130 individuals are enrolled in the screening portion of the study. A heartfelt thank you to all of the participants who have taken the time to find out about this study and to enroll. Your dedication and commitment have helped us to learn more about LFS and to make progress in understanding the impact of early detection in individuals with LFS.

We recently ended the cancer screening blood draws for participants enrolled in the screening study (this was done every four months). Based on the data collected over the past five years, bloodwork every four months did not lead to the diagnosis of early leukemia or lymphoma in children or adults. Similarly, hormonal blood tests every four months in children under the age of 17 did not lead to early cancer detection. For those participants enrolled in the screening study, we will continue to collect blood at the time of your annual screening visit to the NIH Clinical Center; this will include complete blood counts (CBC) with differential, lactate dehydrogenase (LDH) and erythrocyte sedimentation rate (ESR).

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Jennifer Young, PhD, a marriage and family therapist who has conducted the family interviews for the screening cohort over the past three years. After her successful thesis defense, Dr. Young will be leaving the NCI at the end of the summer to take a post-doctoral position at Stanford University.

Mary Lou McMaster, MD, an adult oncologist with training in cellular biology and clinical genetics, has begun assisting with clinical evaluations of adult study participants who come to the NIH for screening.

Leatrisse Oba, MD, is a pediatrician who earned her M.D. from the University of Brasilia, Brazil. Dr. Oba has worked in clinical research for four years and is currently working with the LFS team on a consortium effort to understand the effects of cancer treatment on risk of subsequent cancers in LFS.

DID YOU RETURN YOUR FOLLOW-UP FORMS?

In 2016, we sent a follow-up questionnaire and consent form. If you already completed these forms, thank you for your time. If you have not yet done so, please return them as soon as possible to **Renée Bremer** (**240-276-7266** or **renee.bremer@nih.gov**); she can also send a new copy, if needed. If you enrolled after April 2017 and did not receive these forms, please let Renée know.

MEET THE NCI LFS STUDY TEAM

Back row from left: Janet Bracci, Mary Lou McMaster, Jennifer Loud, Renée Bremer, Kelvin de Andrade, & Kathy Nichols;
Front row from left: Maureen Risch, Nicole Dupree, Megan Frone, Payal Khincha, Sharon Savage, Jessica Bayer, Leatrisse Oba, & Debbie Flamish
Not pictured: Talia Wegman-Ostrosky & Katie Beebe

Clinicians: Sharon Savage, Payal Khincha, Jennifer Loud, Mary Lou McMaster
Research Nurses: Janet Bracci, Kathy Nichols, Maureen Risch, Debbie Flamish
CGB Epidemiology Program Analyst: Renée Bremer
Genetic Counselor: Megan Frone
Data Manager and Research assistants: Katie Beebe, Nicole Dupree
Research Fellows: Kelvin de Andrade, Talia Wegman-Ostrosky, Leatrisse Oba

Please visit the NCI LFS website (www.lfs.cancer.gov) to find out more about the key staff members and their roles on the study.