Main Line Health®

LANKENAU INSTITUTE FOR MEDICAL RESEARCH

CATALYST

FALL 2023/WINTER 2024

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Lankenau Institute for Medical Research (LIMR) is a nonprofit biomedical research institute located on the campus of Lankenau Medical Center and is part of Main Line Health. Founded in 1927, LIMR's mission is to improve human health and well-being. Using its ACAPRENEURIAL™ model that integrates academic and entrepreneurial approaches, faculty and staff are devoted to advancing innovative new strategies to address formidable medical challenges including cancer, cardiovascular disease, tissue regeneration, gastrointestinal disorders and autoimmune diseases such as diabetes and arthritis. LIMR's principal investigators conduct basic, preclinical and clinical research, using their findings to explore ways to improve disease detection, diagnosis, treatment and prevention. They are committed to extending the boundaries of human health through technology transfer and training of the next generation of scientists and physicians.

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George C. Prendergast, PhD

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Lankenau Institute for Medical Research, Main Line Health

A breakthrough moment in cardiovascular research for LIMR

Attracting the best physicians relies on a strong research environment that can deliver a halo effect, enhancing the quality of the whole program. Over the last decade, Lankenau Institute for Medical Research (LIMR), part of Main Line Health, has focused much of its efforts on cardiovascular research and, just before this issue of *Catalyst* went to print, those efforts produced one of our greatest success stories.

A study organized by LIMR, with William A. Gray, MD, as senior author, led the U.S. Food and Drug Administration to rescind warnings that stents and balloons coated with a drug called paclitaxel, designed to improve treatment outcomes for peripheral artery disease, might be linked to increased mortality. Dr. Gray made the first public presentation of those results at TCT 2023, one of the leading international conferences for interventional cardiology, with the results simultaneously published by *The Lancet*, one of the world's premier medical journals.

The Lankenau Heart Institute is known for outstanding care in cardiology and cardiothoracic surgery, and as the spearhead for research, LIMR is driving important new breakthroughs through high-impact studies. Many first-in-human studies have been conducted here by Dr. Gray, and several other trials have LIMR physician-scientists as principal investigators.

This issue has a story on two LIMR trials for treatment of heart failure, which affects more than 6 million Americans. ALT-FLOW II and EMPOWER are examples of trials at LIMR that truly can lead to improvement in clinical care. This progress is building Lankenau Medical Center's reputation as a nonuniversity academic medical center, further heightening its prestige as a center for patient care.

Another story demonstrates how Main Line Health conducts the kind of cancer research and treatment thought to be reserved only for university-based academic centers. A new study with Tracey Evans, MD, as senior author indicates that simultaneously conducting a standard tumor biopsy with a liquid biopsy — a blood test that finds circulating tumor DNA — can increase the chances of detecting genetic mutations in tumors that can be treated with oral drugs. That's important because such molecular-targeted drugs may be more effective — and are certainly easier on the body — than traditional chemotherapy. Dr. Evans, along with Scott Dessain, MD, PhD, and their coauthors demonstrated in their study that the method is practical for wide usage by community hospitals.

Lastly, our cover story on a program initiated by Marisa Weiss, MD, a nationally known breast cancer radiation oncologist, discusses a promising program to address inequities in clinical trials for breast and other types of cancers by aggressively reaching out to enroll patients from races and ethnicities that are typically underrepresented in trials. Only with a representative sample of patients can we have confidence that the treatments we study work for all.

I hope you find this issue informative.

A program to 'Just ASK™' Black patients to participate in trials gains momentum

Breast cancer patient Rasheena Phinisee took part in a Lankenau Institute for Medical Research (LIMR) drug trial. Why? Because the clinical team just asked her.

Mistrust regarding clinical trials has long existed in the Black community, in part due to a legacy of past medical research abuses, including the Tuskegee experiment that ran from 1932 to 1972. This history is bound up in the nation's ongoing problems with health inequities, which were aggravated by the pandemic. "Being familiar with our history makes us reluctant to participate, but we can't dispel these ideas if we don't engage with the medical community," the West Philadelphia resident says.

Marisa Weiss, MD, director of breast radiation oncology at Lankenau Medical Center and a LIMR adjunct investigator, works to address inequities in breast cancer care. She found it challenging to recruit Black patients for a clinical trial that studied the impact of CBD on chemotherapy-induced neuropathy, a common yet difficult-to-treat side effect of chemotherapy disproportionately affecting Black patients. But with research showing that a concerted outreach effort could increase participation of underserved groups in trials, she and her clinical team followed the principles of a new program called Just ASK and … just asked. The results were dramatic: 30% of participants were Black — five to 10 times higher than usual.

"Recruiting patients, especially in underserved communities, felt impossible as people dealt with further delays in medical care and social isolation due to the pandemic," Dr. Weiss says. "But a 2021 study in the *Journal of the National Cancer Institute* indicated that regardless of race or ethnicity, if you just ask, more than half of candidates will agree to participate in a cancer trial. We queried our electronic medical records system, found eligible patients, and they responded."

Dr. Weiss initiated the effort to implement the training and principles of Just ASK, a program offered by the American Society of Clinical Oncology (ASCO) and the Association of Community Cancer Centers (ACCC), at Main Line Health (of which LIMR is part) because the need is so critical. Despite numerous advances in cancer care, Black women are not only being diagnosed younger but are 41% more likely to die of the disease than white women. "If a trial doesn't include a representative number of Black patients, then we can't know if the treatment will be effective for that population," Dr. Weiss says. "We have a responsibility to provide equitable, quality care to all our patients, not just those with easier access to studies."

Numerous barriers to overcome

Two years ago, at age 36, Phinisee was breastfeeding her baby when she found a lump. She would undergo surgery, radiation therapy and chemotherapy. She turned out to be ineligible for Dr. Weiss' neuropathy study but fared well in another LIMR trial. It evaluated targeted-therapy drugs aimed at eliminating the need for additional chemotherapy after surgery for patients with HER2-positive breast cancer.

Just being asked, of course, wasn't sufficient to sustain her participation in the trial amid 18 months of challenging cancer treatment. She needed and received critical help when her health forced her to close one of her businesses and lose sizable income. Her Lankenau Medical Center social worker, Gabrielle Bidas, and Dr. Weiss' national nonprofit, Breastcancer.org, plugged into their resources to help with rent and utilities.

"These are things that you don't think are a big deal in life, but they become a big issue when you can't afford it or can't get to the store because you're ill," Phinisee says.

Income is just one of the barriers for patients in underserved areas such as West Philadelphia, a community of 178,000 that is 71.9% Black with a median household income of $36,186. Patients deal with hunger, inability to find transportation to appointments, childcare issues and psychosocial health.

Rasheena Phinisee and Asha (l). Sister Assiah cradles Asha as a baby (r).

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Phinisee understands how those barriers can preclude community members from participating in trials, let alone obtaining basic health care. But she has become a fierce advocate for Black patients to engage with the medical community.

"The more we participate, the more effective treatments we can have," she says. "But we'll never know if we don't participate."

Addressing patient needs

The ASCO-ACCC training program is designed to attune health care providers to those issues and help them find ways to address them so the patient can participate in the trial.

"People refer to these factors as social determinants of health, but I prefer to call them social drivers of health," Dr. Weiss says. "It connotes that they're a strong force, but they can be overcome."

Dr. Marisa Weiss playing with Asha, 2, as mom Rasheena Phinisee looks on.

Implementing the initiative requires challenging conversations and buy-in throughout a health system. Dr. Weiss says she has found that support from Jack Lynch, president and CEO of Main Line Health; Lankenau Medical Center President Katie Galbraith; Bryn Mawr Hospital President John Schwarz; LIMR President and CEO George Prendergast; Deric C. Savior, MD, and Michael Walker, MD, co-directors, Main Line Health Cancer Care; Paul Gilman, MD, director of the LIMR Clinical Research Center; and others.

"The program is critical because it will help us understand and combat the biases and beliefs that too often prevent us from delivering equitable care to underrepresented populations," Dr. Savior says. "It is unacceptable for us to provide care for one patient population and not another."

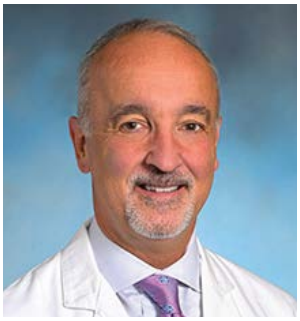
A plan to tackle diversity in clinical trials

Just ASK is just one cog in a strategic plan at Lankenau Institute for Medical Research, part of Main Line Health, to address diversity in clinical trials. The other parts under development are to:

- Collect, analyze and track data to better understand study participant demographics and the overall Main Line Health patient population
- Strengthen diversity, respect, equity and inclusion training as part of the program for new fellows in cardiology and hematology/oncology
- Implement an effective diversity plan through relationships with clinical trial sponsors
- Engage in community outreach

Rosangely Cruz-Rojas, DrPH, vice president and chief diversity & equity officer, Main Line Health, leads a discussion at Population Health Research Day on Oct. 16. The Main Line Health Center for Population Health Research at Lankenau Institute for Medical Research and Thomas Jefferson University's College of Population Health hosted the event. Main Line Health staff and members of the public collaborated on finding ways to improve health care for the community.

Study organized by LIMR reverses FDA warning on peripheral artery disease treatment



William A. Gray, MD

Four years ago, following a publication based on the limited data available, the U.S. Food and Drug Administration (FDA) warned doctors that stents and balloons coated with a drug designed to improve peripheral artery disease (PAD) treatment outcomes might be linked to increased mortality. Research organized by the Lankenau Institute for Medical Research (LIMR) has led the FDA to remove those warnings and is now being circulated worldwide.

Results of the study on devices coated with paclitaxel were presented at the TCT 2023 meeting, the world's largest interventional cardiology meeting. The study showed no increased risk of death from use of paclitaxel-coated devices and was simultaneously published on a fast-track basis by *The Lancet*. William A. Gray, MD, system chief of cardiovascular diseases, Main Line Health; co-director of the Lankenau Heart Institute; LIMR professor; Professor of Medicine, Thomas Jefferson University; and Phillip D. Robinson Chair in Cardiovascular Diseases; is the study's senior author. Based on the findings issued prepublication and the totality of other supportive data, the FDA issued a letter rescinding its warning in July.

"The study and the FDA's response restore a critical tool for treating patients with PAD, and we are extremely pleased that LIMR was able to play such a central role," Dr. Gray said.

'Lankenau approach' may be a novel method for treating atrial fibrillation

The "Lankenau approach" is showing potential to effectively, rapidly and safely restore normal heart rhythm and prevent its recurrence in patients with atrial fibrillation (AFib). AFib is highly prevalent and greatly increases one's risk of stroke.

More efficient methods of stopping AFib are needed. Alexander Burashnikov, PhD, and Charles Antzelevitch, PhD, executive director of Lankenau Institute for Medical Research's Cardiovascular Research Program, evaluated a novel approach for the management of AFib, theorizing that blocking the sodium channel current while mildly elevating serum potassium could be a more effective treatment than currently exists. Tests on mammalian hearts showed that the method was highly effective in experimental models of AFib. The authors call for clinical confirmation in specifically designed clinical studies to further assess the Lankenau approach.

$2.84M grant to fund Heber-Katz's scarless healing work

Ellen Heber-Katz, PhD, a scientist at the Lankenau Institute for Medical Research, and colleagues have been awarded a four-year, $2.84 million grant from the National Institute of Dental and Craniofacial Research for work in regenerative medicine.

The grant will fund research into new upstream targets for hypoxia-inducible factor 1 alpha (HIF-1a)-mediated regeneration in young and aged animals. HIF-1a is a central controlling gene in regeneration.

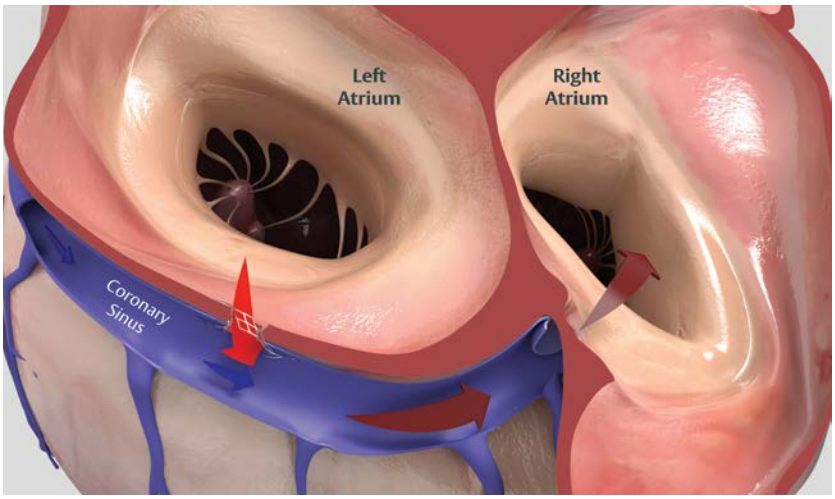
In the mid-1990s, Dr. Heber-Katz found a strain of laboratory mice that healed wounds in a way that looked as if the injury never occurred, not only sparking hope for human scarless healing but triggering headlines worldwide.

Ellen Heber-Katz, PhD

Seeking more treatment options for heart failure through clinical trials

The term heart failure doesn't mean the heart has stopped working. But it does mean it's crucial to be under medical care as the heart is no longer pumping a sufficient amount of blood to fully meet the body's needs for oxygen and nutrients.

Heart failure (also called congestive heart failure), which affects more than 6 million Americans, can cause severe shortness of breath, weakness and fatigue. Walking up the stairs, performing chores around the house and engaging in activities that once seemed effortless can suddenly seem insurmountable. Patients can also experience chest pain — often accompanied by an irregular heartbeat — persistent coughing, and swollen feet or ankles.



The experimental transcatheter shunt system being evaluated in the ALT-FLOW II trial would offload pressure from the left atrium to the right atrium via a draining vein of the heart.

"Heart failure is a serious condition, one that is not curable," says William A. Gray, MD, system chief of cardiovascular diseases at Main Line Health and co-director of the Lankenau Heart Institute. "We frequently can manage it through medication and lifestyle changes such as more exercise and a low-fat diet or, in more advanced cases, implanting a pacemaker. But when these treatments aren't enough and patients' symptoms are severe, we have to consider other options, including clinical trials."

Patients can access clinical trials through the Lankenau Heart Institute because of its connection to the Lankenau Institute for Medical Research (LIMR), the health system's research division. Dr. Gray and Basel Ramlawi, MD, system chief of cardiothoracic surgery at Main Line Health, not only are co-directors of Lankenau Heart Institute but members of LIMR's faculty.

"The intersection of clinical leadership and research has real value to our patients, including those with heart failure," Dr. Ramlawi says. "Often, we can offer treatment options through clinical trials that are unavailable elsewhere in the region."

ALT-FLOW II is one example of a trial offered regionally only by Lankenau Heart Institute/LIMR. It seeks to treat a type of heart failure where the organ is pumping enough blood, but the left lower chamber (ventricle) is unable to relax and fill with blood properly, resulting in increased blood pressure in the left ventricle and atrium (upper chamber). The trial is evaluating the safety and effectiveness of an experimental transcatheter shunt system designed to ease the pressure — and heart failure symptoms.

"The strategy is to offload the pressure in the left atrium," says Dr. Gray, who was the national principal investigator of an earlier, first-in-human ALT-FLOW study. "Subsequently, the pressure going back into the lungs is reduced and the patient has less shortness of breath. Most shunts are placed directly between the left and right atrium. This shunt goes between the left atrium and a draining vein of the heart, which eventually goes to the right atrium. It's a novel approach that we think has several advantages, including decreasing the chance of a clot moving from one atrium to the other."

Another research trial, EMPOWER, is designed for patients who have reduced heart-pumping capacity and a condition called mitral valve regurgitation, in which the valve fails to close properly and blood flows backward into the heart. For patients with these conditions, the heart becomes enlarged to try to compensate for the loss of pumping capacity and works less efficiently.

"By implanting a mechanism that addresses the problem with the valve's structure, we seek to shrink the base of the heart," Dr. Gray says. "We hope that reducing the size of the heart creates a better mechanical pumping action."

LIMR currently oversees a portfolio of more than 25 clinical trials in cardiology that seek to advance treatment options. Its trials address coronary artery disease, heart rhythm disorders, structural valve disorders and other cardiac conditions.

Combining new and standard biopsy techniques improves diagnosis and treatment of patients with advanced lung cancer

To select the correct treatment for patients with advanced lung cancer, it is essential to genetically analyze their tumors. Many lung cancers have genetic mutations that make the patient eligible for treatment with oral drugs, which have greater odds of success and fewer side effects than chemotherapy. Genetic testing can be performed using either tumor biopsy tissue or patient blood, but each test has its advantages and disadvantages, and both tests can miss an important diagnosis. As a result, there is no consensus among physicians on how these tests should be used.

A new study by Lankenau Institute for Medical Research (LIMR) researchers indicates that simultaneously conducting a liquid biopsy — a blood test that finds circulating tumor DNA — and standard tissue biopsy may be a novel way to increase the chances of detecting such mutations. And, they found, the method is practical for wide usage by hospitals.

"This is an important finding," says senior author Tracey Evans, MD, LIMR's director of thoracic oncology research. "Liquid biopsy is newer, and many oncologists are hesitant to use it. They will start with tissue-based testing and only pursue liquid biopsy if tissue fails. This approach takes time, so they start patients on chemotherapy they may not need while waiting for the results."

The study, published in *JCO® Oncology Practice*, is based on a review of cases from 2018 to 2021 at Lankenau Medical Center. Its results indicate the strategy can be used at community-based teaching hospitals like Lankenau, not just those affiliated with universities, the authors said.

The study looked at patients with metastatic (stage IV) lung cancer, finding that those with simultaneous tissue and liquid biopsy had shorter times to reach a definitive genetic-testing result than those with tissue testing only.

It found that actionable findings (genetic mutations for which a targeted therapy exists) were identified in almost half of patients in the group that had both tests compared to one-quarter of the group undergoing just tissue biopsy. Furthermore, the group receiving combined tests had an average time of 20 days to diagnosis, compared to 33 days for those undergoing only tissue biopsy. Reducing the time to come to a diagnosis is an important benefit to anxious patients and their loved ones.

"Many studies have shown that metastatic lung cancer is best treated with a type of targeted therapy using small molecules," says George Prendergast, PhD, LIMR president and CEO. "But the need to wait for genetic testing can be highly stressful for patients. We need to understand and prioritize the patient experience to fully realize the benefits of our medical research. It is no accident that this groundbreaking work was done here, where quality of care and the patient experience are the highest priorities."

Significantly, the study found, each test missed important diagnoses that were detected by the other. With 28 patients, the results for tissue and liquid biopsies matched 17 times. With the 11 other cases, there were seven instances of actionable mutations found by tissue biopsy and not liquid biopsy; in four cases, the reverse was true. That meant the simultaneous testing strategy improved the detection rate. The strategy also allowed many patients who had failed tissue testing to avoid a second biopsy.

"One obstacle is that insurances may not want to pay for both tests, but you often need both tests to be sure you have the correct diagnosis," said co-author Scott Dessain, MD, PhD. "The testing company for our study committed to not billing for unreimbursed expenses, which doesn't happen in real-world testing. We believe the ideal strategy both for medical effectiveness and financially is performing a liquid biopsy first, which only has a one- to two-week turnaround, then conducting a tissue biopsy if warranted."

Scott Dessain, MD, PhD, and Alisha Maity, MD, are among the authors of a study evaluating simultaneously conducting liquid biopsy and standard tissue biopsy.

Women's Board and Auxiliaries deliver invaluable support

PHILANTHROPY PROPELS RESEARCH INTO TREATING PANCREATIC DISEASE AND RHEUMATOID ARTHRITIS

With Lankenau Institute for Medical Research (LIMR) situated on the campus of Lankenau Medical Center, over the years they have combined to deliver a preeminent blend of health care and research. Few partners are more devoted and vital to these efforts than the Women's Board of Lankenau Medical Center and its many Auxiliaries.

The Ladies' Aid Society, which originated only two years after the 1860 establishment of the German Hospital of Philadelphia (Lankenau Medical Center's initial name), the Nurses' Alumni Association, the John B. Deaver Auxiliary and the Hamper Shop have generously contributed time, energy and philanthropic support. In the past 25 years, their energetic and passionate volunteers have contributed over $7.2 million to Lankenau Medical Center and over $1.2 million to LIMR.

"I feel very proud of the women on the Women's Board and Auxiliaries who work tirelessly year-round to support Lankenau Medical Center and LIMR," says Audrey Kese, President of the Lankenau Medical Center Women's Board. "I have been a member for 20 years and have always admired Lankenau's close-knit community and appreciated being a part of it through our efforts."

The Women's Board and Auxiliaries are of and for the community — they are driven women who have devoted countless hours toward improving the health of the community. Over the years, their philanthropy has supported basic, translational and clinical research and advanced science at every level, from research internships to career scientists. This year, the Women's Board and Auxiliaries made significant investments in several LIMR research projects. Here are just two:

- **A new approach for treatment of therapy-resistant pancreatic cancer:** Pancreatic cancer is the third-leading cause of cancer deaths in the United States. Eric Alexander, PhD, a research assistant professor working with Susan Gilmour, PhD, received a Women's Board grant to investigate use of a drug called difluoromethylornithine (DFMO) in treatment for therapy-resistant pancreatic cancer. LIMR has found that DFMO can alleviate several factors that prevent a set of immunotherapy drugs from working against pancreatic cancer. DFMO also increases T-cells and natural killer cells that can attack and kill tumor cells.
- **Uncovering the role of indoleamine 2,3-dioxygenase-2 (IDO2) in rheumatoid arthritis:** Using preclinical models, LIMR has identified the immune modulatory protein IDO2 as an important mediator of autoimmune arthritis, but exactly how IDO2 promotes autoimmunity is unknown. Lauren Merlo, PhD, working with Laura Mandik-Nayak, PhD, seeks to understand that mechanism with the goal of developing new therapeutic strategies to inhibit IDO2 and treat disease.

Kese says she is excited at the prospects of these and other projects: "I am still in awe at how much incredible research and development comes out of LIMR, and I look forward to learning of the new projects underway year after year. Seeing the progress at LIMR and Lankenau Medical Center and feeling their appreciation of our hard work make all our efforts worthwhile."

Front (l to r): Peggy Cristofalo, Linda Waddell, Renee Healy, Alice Chase, Audrey Kese, Kathleen O'Connor-Eicke, Marsha Serock, Joan Hindin. Back (l to r): Marlena Santomero, Pat Nogar, Maureen Winigrad, Sue Hirsh, Theresa Miller, Brenda Jackson, Maureen Krouse, Jill Acker, Sharon Steinberg, Barbara Evans.

Your investments in research at LIMR can have a significant impact

You can designate one of the following funds to direct your contributions and support research that is important to you.

Biotechnology Innovation Fund

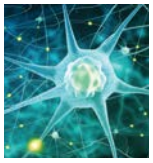
This fund supports work on biological molecules engineered by LIMR scientists that can enhance the diagnosis, prognosis and treatment of disease. Your generous contributions to this fund can help advance the work of our researchers including our studies on targeted nano-carrier therapeutics as experimental treatments for cancer and our work on cloned human antibodies as treatments for infectious disease, cancer and neurological illnesses.

Cardiovascular Breakthrough Fund

Cardiovascular disease accounts for nearly 800,000 deaths in the United States every year, or about one of every three deaths. Additionally, about 92 million American adults are living with some form of heart disease or the aftereffects of stroke. LIMR is home to world-renowned cardiovascular researchers. Your gift to this fund will further research that could benefit the lives of millions of heart disease and stroke patients.

Immunotherapy Pioneer Fund

Immunotherapy entails the prevention or treatment of disease with substances that manage the immune system's capabilities to clear disease rather than attack the disease itself. LIMR has spearheaded unique studies of disease modifier pathways that impact immunity and cancer progression, developing new drugs to target them. Your generous contributions to this fund will help us to continue to advance these innovative directions.



Regenerative Medicine Vision Fund

Regenerative medicine deals with new processes of replacing, engineering or regenerating human tissues to restore or establish normal function. LIMR is privileged to have one of the pioneers in regenerative medicine, Professor Ellen Heber-Katz, PhD, who has discovered an experimental drug approach that may eliminate a need for stem cell transfer. Your contributions to the Regenerative Medicine Vision Fund will help further her research.

LIMR Unrestricted Fund

Unrestricted gifts to LIMR enable opportunities to target your gift where our doctors and scientists believe it can have the greatest impact.

To make a donation, please use the reply envelope inserted in this publication, or donate online at limr.org (click on Giving). You may also call Katie Beddis of the Lankenau Medical Center Foundation at 484.476.8067, or email her at beddisk@mlhs.org.

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Main Line Health®

ABOUT MAIN LINE HEALTH

Main Line Health® is an integrated health system serving the Philadelphia region, with more than 2,000 physicians, one quaternary and three tertiary care hospitals, a wide network of patient care locations and community health centers, specialized facilities for rehabilitative medicine and drug and alcohol recovery, a home health service, and a biomedical research institute. Collectively, Main Line Health's physicians, care teams, health care facilities and researchers provide patients with primary through highly specialized care as well as access to clinical trials.