UCLA AGI HIRSHBERG CENTER FOR PANCREATIC DISEASES

2023 ACTIVITY REPORT

UCLA Health | David Geffen School of Medicine

OVERVIEW

In 2024, the five-year pancreatic cancer survival rate increased to 13 percent, the fourth year in a row to see an improvement. This statistic confirms that the work at the UCLA Agi Hirshberg Center for Pancreatic Diseases is having a positive effect. The need to continue that progress is evidenced in the American Cancer Society's prediction that 66,440 Americans will be diagnosed with pancreatic cancer this year — an increase of almost four percent from 2023. With pancreatic cancer remaining the third cause of cancer deaths, the partnership between UCLA and the Hirshberg Foundation takes on an ever more crucial role in enhancing translational research and holistic patient care and, ultimately, finding a cure for pancreatic cancer.

The UCLA Hirshberg Center has undergone a metamorphosis this past year and moved to its new, enhanced space on the top floor of the Vatche and Tamar Manoukian Medical Building at 100 Medical Plaza on the UCLA campus.

Timothy Donahue, M.D., Chief, UCLA Health Division of Surgical Oncology; Vice Chair, Surgical Cancer Care, Department of Surgery; and holder of the Garry Shandling Chair in Pancreatic Surgery in the David Geffen School of Medicine at UCLA, became the new director of the center in 2023. Previously the surgical director, Dr. Donahue is well-acquainted with, and committed to, the center's aims. As a professor of surgery and molecular and medical pharmacology, as well as program director of the UCLA General Surgery Residency Training Program, Dr. Donahue is dedicated to training the next generation of surgical specialists. On the national level, he serves as president of the Society of University Surgeons. As a surgeon, Dr. Donahue has some of the highest success rates in the country and is an innovative researcher, leading a National Institutes of Health (NIH)-funded laboratory.

The center's location and leadership may have changed, but its heart and vocation remain untouched, as has its reputation for excellence.

ACCOMPLISHMENTS AND RESEARCH

The center is recognized by the National Pancreas Foundation as a Clinical and Academic Center of Excellence for both pancreatitis and pancreatic cancer, awarded separately. Only 132 centers are recognized in each category for their whole-person, multidisciplinary treatment of patients.

The UCLA Hirshberg Center's clinical trial portfolio is among the strongest in the country. Trials have robust patient enrollment, with collaboration across multidisciplinary teams.

The center remains an active partner in the UC Pancreatic Cancer Consortium, intended to accelerate the progress of physician-scientists across the University of California's five National Cancer Institute-designated Comprehensive Cancer Centers. The NIH-funded study "Targeting KRAS and adenosine-mediated immunosuppression in pancreatic cancer" was initiated at the UCLA Hirshberg Center. The Hirshberg Center is also participating in the Pancreatic Cancer Early Detection (PRECEDE) Consortium, for which Dr. Donahue serves as the lead investigator at UCLA. The international, multi-institutional study investigates several aspects of early detection and prevention of pancreatic ductal adenocarcinoma (PDAC). The researchers are following individuals who have a family history of PDAC and/or carry pathogenic/likely pathogenic germline variants in genes linked to PDAC risk longitudinally.

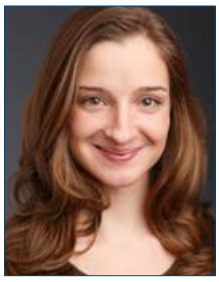
An international study led by Zev Wainberg, M.D., Co-Director, UCLA Gastrointestinal Oncology Program, and a researcher at the UCLA Health Jonsson Comprehensive Cancer Center, has led to FDA approval of a four-drug chemotherapy regimen, referred to as NALIRIFOX, for first-line treatment of metastatic pancreatic adenocarcinoma. The new therapy includes the drugs irinotecan liposome, oxaliplatin, leucovorin, and fluorouracil. The findings of the trial, called NAPOLI-3, were first presented at the 2023 American Society of Clinical Oncology Gastrointestinal Cancers Symposium annual meeting and were published in *The Lancet* this past September.

Dr. Wainberg has had promising results for a Phase I study, published in *Nature Medicine*, utilizing an off-the-shelf vaccine to treat pancreatic and colorectal cancer patients with KRAS mutations. Because the lymph node-directed vaccine is standard, rather than needing to be tailored to each patient, it can be used immediately. The immunotherapeutic, called ELI-002 2P, targets KRAS mutations, which are present in 25 percent of solid tumors and drive approximately 90 percent of pancreatic cancers, as well as 50 percent of colorectal cancers.

UCLA was selected to join the Canopy Cancer Collective, a learning health network of 14 leading cancer centers aimed at improving care coordination and clinical outcomes for patients with pancreatic cancer. As a member of the collective, UCLA was awarded a $500,000, three-year grant, funded by the 1440 Foundation. Helmed by Dr. Donahue, the grant is being used to advance comprehensive, whole-person pancreatic cancer care at UCLA, with the Hirshberg Center serving as the primary site of implementation. In 2023, the center's Canopy team made great strides in advancing initiatives in nutrition, palliative care, genetic testing, clinical trial participation, and patient education. Once refined and proven successful in the center's integrated practice unit (IPU), these efforts will be scaled to reach

patients with pancreatic cancer throughout the UCLA Health network. The goals of the collective are in concert with the tenets of the UCLA Hirshberg Center, with its focus on the IPU, which brings together various medical specialties and support services to provide comprehensive, coordinated care.

The center is now actively recruiting a patient navigator, a position essential to ensuring the delivery of integrated, coordinated care across the cancer trajectory. The patient navigator will optimize the patient experience by making sure that patients understand the next steps in their treatment process, facilitating insurance challenges, ensuring appropriate referrals, and handling any other factors that contribute to overall satisfaction for patients and their families. The patient navigator will also facilitate timely communication for patients and families, as well as for physicians and staff.



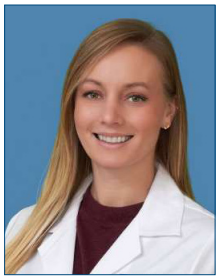
Emily Martin, M.D., M.S., FAAHPM, Associate Director, Palliative Care, and a physician informaticist at UCLA Health, leads much of the conceptualization, planning, and implementation of UCLA's Canopy efforts. She spearheads the team's strategic planning and quality improvement initiatives, including the standardized collection of patient-reported outcome and experience measures to guide clinical care.

Dr. Martin is also working to ensure that pancreatic cancer patients have equitable, timely access to specialty palliative care, which is an integral element of the Canopy plan and the center's priorities. Palliative care is focused on optimizing a patient's quality of life by preventing or treating symptoms and distress associated with a disease or its treatments and ensuring that the care plan aligns with the patient's priorities, values, and goals. A palliative care team should be formed early in a patient's treatment, regardless of stage, with its makeup based on reported patient outcomes.

Genetic testing and counseling are essential components of comprehensive pancreatic cancer care common to the Canopy initiative and the center's standards. Genetic testing is particularly important in detecting pancreatic cancer risk. Pancreatic cancer is one of four types of cancers that is FDA approved to be targeted by poly-ADP ribose polymerase (PARP) inhibitors. Therefore, if genetic testing reveals an inherited genetic alteration, precision treatment may be appropriate to target the cancer.

The UCLA Cancer Genetics Testing & Counseling program has implemented various initiatives to increase access to genetic counseling and testing. Patients with a diagnosis of pancreatic cancer no longer need to schedule a visit with a genetics expert before undergoing testing. Instead, they can watch a pre-test genetics educational video at home or in their doctor's office. If they decide they would like to pursue the recommended genetic testing, a genetic testing saliva kit can be mailed to their home, or they can complete a saliva or blood test during an oncologist appointment. Genetic counseling assistants are available to answer questions and assist those who do not feel comfortable with video education. The team is utilizing automated patient identification to overcome implicit bias and improve personalized care for each patient based on the information in their chart. A cancer genetics research registry has also been started to be able to analyze data to inform future best practices. Program leadership continuously works to incorporate quality improvement initiatives and expand the team to meet the genetics counseling needs of UCLA Health's cancer patients.

Ensuring patients have proper nutritional habits to optimize their health is essential for pancreatic cancer patients, as they have one of the highest rates of malnutrition among the cancer subtypes. In addition, pancreatic cancer patients have difficulties digesting and absorbing nutrients and also may develop pancreatogenic, or type 3c, diabetes, caused by the pancreas's inability to secrete insulin, or by surgical resection leading to endocrine pancreatic insufficiency.



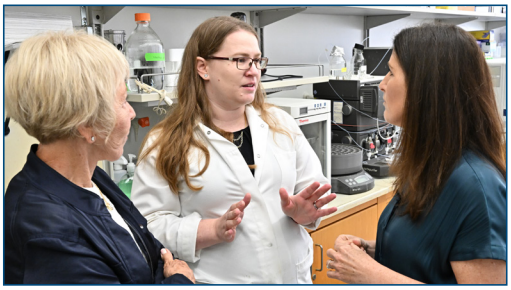
Nutrition for Safer Surgeries, part of the UCLA Health digestive diseases nutrition offerings, was originally intended to optimize nutrition for patients prior to and following surgery. Launched a year ago, it has proven to be both successful and popular. When advanced dietitian Shelby Yaceczko, M.S., R.D.N.-A.P., CNSC, CCTD, initiated the program, she saw approximately 10 to 15 patients each month, including those she saw as part of the center IPU and at her gastrointestinal practice. Yaceczko now sees approximately 120 each month. She sees patients at every phase of their cancer journey and during all types of treatment, not just preoperatively, allowing her to serve as a liaison to other supportive services. On average, Yaceczko follows up with patients every four to six weeks.

Along with the Hirshberg Foundation, Yaceczko is working on a digital flipbook on pancreas wellness. The book will include nutrition resources, such as recipes, food budgeting tips, and information on food assistance programs.

Miklos Sahin-Toth Research Fund

Miklos Sahin-Toth, M.D., Ph.D., Professor, Department of Surgery, and the Garry Shandling Chair in Pancreatic Diseases, David Geffen School of Medicine at UCLA, is a renowned expert in chronic pancreatitis and also serves as co-editor-in-chief of the journal *Pancreatology*. His laboratory works in partnership with Guido Eibl, M.D., and his Ronald S. Hirshberg Translational Pancreatic Cancer Research Laboratory, in order to better understand some of the leading risk factors for pancreatic cancer.

Dr. Sahin-Toth and his team produced a number of important papers in 2023. In an article for the January 2023 edition of *Gastroenterology*, the most prominent United States publication in the gastroenterological sciences, the researchers demonstrated that the trypsin activity produced by cathepsin B (CTSB), an enzyme, during the early phase of pancreatitis is not a driver of the disease.



Agi Hirshberg and Lisa Manheim, Executive Director, Hirshberg Foundation, discuss advances in pancreatic cancer research with Alexandra Demcsak, M.D., Ph.D.

It appears that autoactivation of trypsinogen to trypsin, rather than CTSB-induced activation, plays a unique role in the progression of pancreatitis. Dr. Sahin-Toth and his collaborators also authored two published articles in the high-impact journal *Gut* in the past year. In their February 2023 article, "Modelling chronic pancreatitis as a complex genetic disease in mice," they demonstrated that when two separate gene variants associated with chronic pancreatitis were introduced into the same scientific model, the models were highly likely to develop the disease, where they were unlikely

to develop it with a single gene variant. This study could be key in identifying potential pancreatitis patients early in the process. In "Functional predictors of pathogenicity of missense CPA1 variants in chronic pancreatitis," published in the October 2023 edition of *Gut*, Dr. Sahin-Toth's study found that surprisingly few of the 50 carboxypeptidase A1 (CPA1) mutations that his lab had categorized actually cause chronic pancreatitis.

Philanthropy from the Hirshberg Foundation is vital to Dr. Sahin-Toth's ability to support the operation of his laboratory and his team's crucial work.

Ronald S. Hirshberg Translational Pancreatic Cancer Research Laboratory

The Ronald S. Hirshberg Translational Pancreatic Cancer Research Laboratory remains under the expert leadership of Dr. Guido Eibl, Professor, Department of Surgery, David Geffen School of Medicine at UCLA. This past year, Dr. Eibl and his team completed the fourth year of a five-year Program Project Grant from the National Cancer Institute (NCI) to study the effects of obesity on pancreatic cancer growth and whether the use of statins and metformin can slow this development. While both statins and metformin are FDA-approved drugs and very widely used, a small number of patients experience significant side effects. Both drugs have been shown to reduce pancreatic cancer development when used individually in high doses, so Dr. Eibl hopes to demonstrate that the drugs used in combination at lower dosages can also inhibit pancreatic cancer, while being more tolerable for a higher number of patients. His study found that the drug combination demonstrated positive outcomes in male preclinical models, but not in the female models. This trial was published in the September 2023 edition of *Scientific Reports*.

Along with J. Enrique Rozengurt, D.V.M., Ph.D., AGAF, Ronald S. Hirshberg Chair in Translational Pancreatic Cancer Research, and Stephen J. Pandol, M.D., Director, Basic and Translational Pancreas Research, and Program Director of the Gastroenterology Fellowship Program at Cedars-Sinai Medical Center, who are also working on the same NCI Program Project Grant, Dr. Eibl and his collaborators are applying for another round of funding through the NCI, with the application due in May 2024. Their new project will focus on the dual effects of obesity and chronic stress on the development of pancreatic cancer. The link between neural signaling and cancer growth has received more attention in recent years, with studies published in high-profile journals.

Particularly timely in light of the ongoing consequences of the COVID-19 pandemic and associated lockdowns, Dr. Eibl and his team are interested in researching how social isolation produces chronic stress, and how this in turn relates to cancer development. Their preliminary findings under a two-year NCI grant showed that preclinical models that were both fed a high-fat diet and kept in isolated conditions showed accelerated rates of pancreatic cancer growth, with females experiencing more pronounced cancer development. They now hope to use these findings to secure additional long-term program funding, and Dr. Eibl is confident that their submission will be well-regarded. Funding from the Hirshberg Foundation was crucial in the researchers' ability to produce enough preliminary data to advance this project.

While the new NCI Program Project Grant submission has kept the bulk of his team busy, Dr. Eibl still found time to work on other projects. In collaboration with a group of researchers from the University of California, San Diego (UCSD), Dr. Eibl investigated the mechanisms by which pancreatic precursor lesions progress to invasive cancer through the study of a pancreatic tissue sample from a scientific model. The manuscript is now under revision with the journal *Nature Cancer*. He is also working on a second manuscript with a group from Cedars-Sinai.

UCLA researchers Yaroslav Teper, Ph.D., and Xiaoying Sun, M.D., Ph.D., continue to receive invaluable mentorship and training from Dr. Eibl, with Dr. Sun also working with Dr. Rozengurt. The support of the Hirshberg Foundation is essential to Dr. Eibl's ability to retain both Dr. Teper and Dr. Sun in the Hirshberg Laboratory. He also hopes to hire a new lab technician, although the high cost of living in West Los Angeles has made the process challenging.

Dr. Eibl remains highly appreciative of the longtime philanthropy from Agi Hirshberg and the Hirshberg Foundation.

UCLA Pancreas Tissue Bank

David Dawson, M.D., Ph.D., Professor of Pathology, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, oversees the UCLA Pancreas Tissue Bank. The bank procures and distributes human pancreas specimens to aid the basic, translational, and clinical research activities of investigators at UCLA and elsewhere. Additionally, the tissue bank provides histology and pathology services for pancreas disease investigators in support of research discovery and validation studies involving the use of human tissues and preclinical models.

The bank has continued to adapt to shifting research needs, with a current focus on providing investigators with viable cells and tissue slices derived from patient samples. The generous backing of the Hirshberg Foundation enables the UCLA Pancreas Tissue Bank to provide pathology services and tissue resources free of charge, enhancing the translational and clinical impact of research and the investigator's ability to successfully compete for research funding from the NIH and other extramural funding sources.

Beneficiaries include current and past researchers affiliated with UCLA and the UCLA Agi Hirshberg Center for Pancreatic Diseases who are working on various studies aimed at a better understanding of how diet and inflammation contribute to pancreatic cancer development. They are also studying the therapeutic potential of strategies targeting signaling pathways, metabolism, inflammation, and the immune response in pancreatic cancer.

The Pancreas Tissue Bank continues to benefit the investigations of pancreatic researchers at several institutions across the country, including UCSD; the Sanford Burnham Prebys Medical Discovery Institute; University of California, San Francisco; and the Mayo Clinic. The continued success of the Pancreas Tissue Bank is a testament to the generosity of the Hirshberg Foundation and its strategic vision to promote the banking and distribution of high-quality and clinically well-annotated patient-derived tissues and derivative materials to advance translational research and discovery.

Psychosocial Care via the Simms Mann UCLA Center for Integrative Oncology

Under the direction of Shannon La Cava, Psy.D., Director, Simms Mann UCLA Center for Integrative Oncology; and Valentina Ogaryan, Ph.D., Clinical Director, Simms Mann UCLA Center, and the Darcie Denkert Notkin Director of Psychosocial Oncology Care, the Simms Mann UCLA Center for Integrative Oncology delivers life-changing psychosocial treatment for pancreatic cancer patients and their families. Both Drs. La Cava and Ogaryan assumed their leadership roles in summer 2023, and they bring fresh perspectives and energy to the vital offerings of the center.

The Simms Mann Center now provides on-site support at more than 20 clinical locations across Southern California, including the UCLA Agi Hirshberg Center for Pancreatic Diseases, as well as a breadth of online support services, such as brief counseling sessions, group support, education, mindfulness meditation, and mind/body classes.

Katie Pool, LCSW, APHSW-C, OSW-C, is a dedicated Simms Mann clinician supporting pancreatic patients and caregivers on-site at the Tuesday IPU with Drs. Donahue and Martin. With the support of the Simms Mann Center and clinical directors, Pool is working with Dr. Martin to establish goals of care and distress screening protocols for patients diagnosed with pancreatic cancer to meet Canopy Cancer Collective best practices and implement scalable standards to enhance care for other advanced stage cancer diagnoses. Pool estimates that 30 percent of her week is spent supporting pancreatic cancer patients through the IPU, making herself available to any individuals who are in immediate distress. She considers it a privilege to serve her patients and their families as they journey through the spectrum of diagnoses, treatment, and beyond, particularly because of the unique challenges that pancreatic cancer presents.

The Simms Mann Center is proud to offer the "UCLA Health GI Cancer Program Orientation" to patients newly diagnosed with pancreatic cancer. Led by Jenny Tran, Ph.D., this program introduces patients to their supportive care teams and explains how these services address complex symptoms earlier in their treatment. Other topics include successfully communicating needs and receiving additional support. Patients are provided with resources, including such organizations as the Hirshberg Foundation. This initiative has contributed to decreased emergency department visits and intensive care unit stays, and more appropriately timed referrals to hospice care.

Dr. Tran also presented her lecture in March 2023, "Turning Down the Volume on Worry: Managing Cancer-Related Anxiety" at the Hirshberg Foundation's 17th Annual Symposium on Pancreatic Cancer, in collaboration with the UCLA Agi Hirshberg Center for Pancreatic Diseases, and moderated a panel discussion with survivors and caregivers. The Simms Mann Center team actively participates in the UC Pancreatic Cancer Consortium, with plans to create webinars for patients and caregivers in this forum.

Drs. La Cava and Ogaryan, and the entire Simms Mann Center staff are deeply thankful for the continued generosity of Agi Hirshberg and the Hirshberg Foundation. After a slight dip during the beginning of the COVID-19 pandemic, the volume of patients that the center serves has increased markedly in the past three years, and the philanthropy of the Hirshberg Foundation is central to the team's ability to benefit patients with pancreatic cancer.

Ronald S. Hirshberg Chair in Translational Pancreatic Cancer Research

Dr. Rozengurt, Distinguished Professor of Medicine; Chief of Research, Vatche and Tamar Manoukian Division of Digestive Diseases; and Director, CURE: Digestive Diseases Research Center in the David Geffen School of Medicine at UCLA, holds the Ronald S. Hirshberg Chair in Translational Pancreatic Cancer Research.

Dr. Rozengurt and his team are identifying advanced targets and strategies for the prevention and treatment of pancreatic cancer. In a series of studies that have opened up a new field of pancreatic research, Dr. Rozengurt's group has shown that metformin, an antidiabetic medication, inhibits pancreatic cancer growth in preclinical models and the proliferation of human pancreatic cancer cells in culture. A set of major publications has summarized multiple lines of evidence illustrating these anticancer effects. One of the team's hypotheses is that the pro-oncogenic protein YAP could play a key role in promoting pancreatic cancer and mediating intestinal and endothelial cell multiplication. Statins, widely used for preventing cardiovascular disease, are also implicated in the prevention of pancreatic cancer. New studies from the group — important in attracting new funding — aim to identify the mechanisms of action of these drugs in the inhibition of YAP function.

During the past year, Dr. Rozengurt and his collaborators studied the interaction between stress and obesity in pancreatic cancer development. Their project was funded by an exploratory/developmental R21 grant from the National Cancer Institute. The team's new R01 grant application to extend mechanistic studies on statins was rated "exceptional" by the National Institutes of Health Review Panel, and funding is expected. In recognition of his extensive scientific accomplishments, including his leadership of the center, Dr. Rozengurt was selected as the recipient of the 2023 VA Service Award, which recognizes how his dedication and career contributions have influenced research service and the scientific community at the VA.

Dr. Rozengurt has authored scientific papers and reviews published in significant medical periodicals, such as *The Journal of Immunology*, the *American Journal of Physiology-Cell Physiology*, *Molecular Cancer Therapeutics*, and *Gastro Hep Advances*. He also reviewed the current literature in mechanisms leading to pancreatic cancer in two articles in the journal *Cancers*. The impact of Dr. Rozengurt's work is highlighted by the number of mentions of his scientific papers by other authors. His publications have been cited more than 41,000 times with an h-index=118 (Research.com), marking him as one of the world's most important biomedical scientists.

Hirshberg Foundation Seed Grant Program

In addition to his responsibilities leading his laboratory, Dr. Sahin-Toth also completed his first year leading the Hirshberg Foundation Seed Grant Program in collaboration with the Hirshberg Scientific Advisory Board.

Three UCLA investigators benefited from Hirshberg Foundation seed grant funding this past year: Evan Abt, Ph.D.; Alexandra Demcsak, M.D., Ph.D.; and Jason Link, Ph.D. Each 2022 awardee, as well as several other past seed grant recipients, attended a small symposium in October 2023 to share updates on their invaluable research.

Dr. Abt's project sought to identify actionable immune-metabolic vulnerabilities of pancreatic cancer tumors elicited by mutant-selective KRAS inhibitors. KRAS mutations are a key feature of pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer. Though inhibiting KRAS mutations alone has produced other complications, Dr. Abt is hopeful that utilizing combination therapies will prevent the growth of PDAC cells without triggering immunosuppressive responses in the pancreas.

Dr. Demcsak, who was recently appointed an assistant professor at UCLA, works closely with Dr. Sahin-Toth, primarily researching digestive enzymes and their role in pancreas inflammation. Specifically, her project utilizing the seed grant funding has studied the role that chymotrypsin deficiency plays in the growth of PDAC cells. Dr. Demcsak hopes that her work can inform future proactive testing that helps lead to both prevention and earlier diagnosis.

Dr. Link's project studies the role that tertiary lymph structures have in combating cancer cell growth, and why a small number of long-term surviving pancreatic cancer patients seem to produce effective immune responses. Through his work, Dr. Link hopes to identify the mechanisms that support proper signaling between the tumor and the immune system, which in turn will help develop targeted therapeutics to ignite an effective immune response.

Dr. Sahin-Toth was pleased with the number of applications for seed grant funding in the last cycle, with 126 proposals submitted, including 10 applications from UCLA-based investigators. Of these 10 UCLA applications, two collaborative teams were awarded grants: Slavica Tudzarova-Trajkovska, Ph.D., and Neema Jamshidi, M.D., Ph.D.; and O. Joe Hines, M.D., William P. Longmire, Jr. Chair in Surgery, and Michael DeLong, M.D.

ON THE HORIZON

A study of the patient-caregiver dyad, funded through the generosity of the Hirshberg Foundation, is about to launch. This research effort will evaluate the ability of mindfulness interventions to alleviate the distress caregivers can experience, which can in turn affect the patient's trajectory.

Pancreatic cancer is among the first four types of cancer to be included in a prehabilitation program to prepare patients for surgery. A main component of the program, launching in April 2024, will be the Nutrition for Safer Surgeries program; other elements are physical activity, mental well-being, meditation, and breathing exercises. Educational materials including videos and care companion kits will be delivered to patients as part of the initiative. Information on prehabilitation will soon be available on the UCLA Department of Surgery website.

Work is underway toward standardizing the collection of patient-reported outcomes and experience measures and developing a dedicated pancreatic cancer clinical information system data registry and dashboard to improve care delivery.

WITH GRATITUDE AND HOPE

The UCLA Agi Hirshberg Center for Pancreatic Diseases has made tremendous progress in its fight against pancreatic cancer, assembling an ever-growing arsenal of tools to understand and mitigate the effects of the illness, and advance its quest for greater patient comfort. The valued support and partnership of the Hirshberg Foundation for Pancreatic Cancer Research have helped make these innovations possible. UCLA Health and the Hirshberg Center's faculty, administration, and patients and their families remain grateful for the visionary philanthropy of Agi Hirshberg and the Hirshberg Foundation.