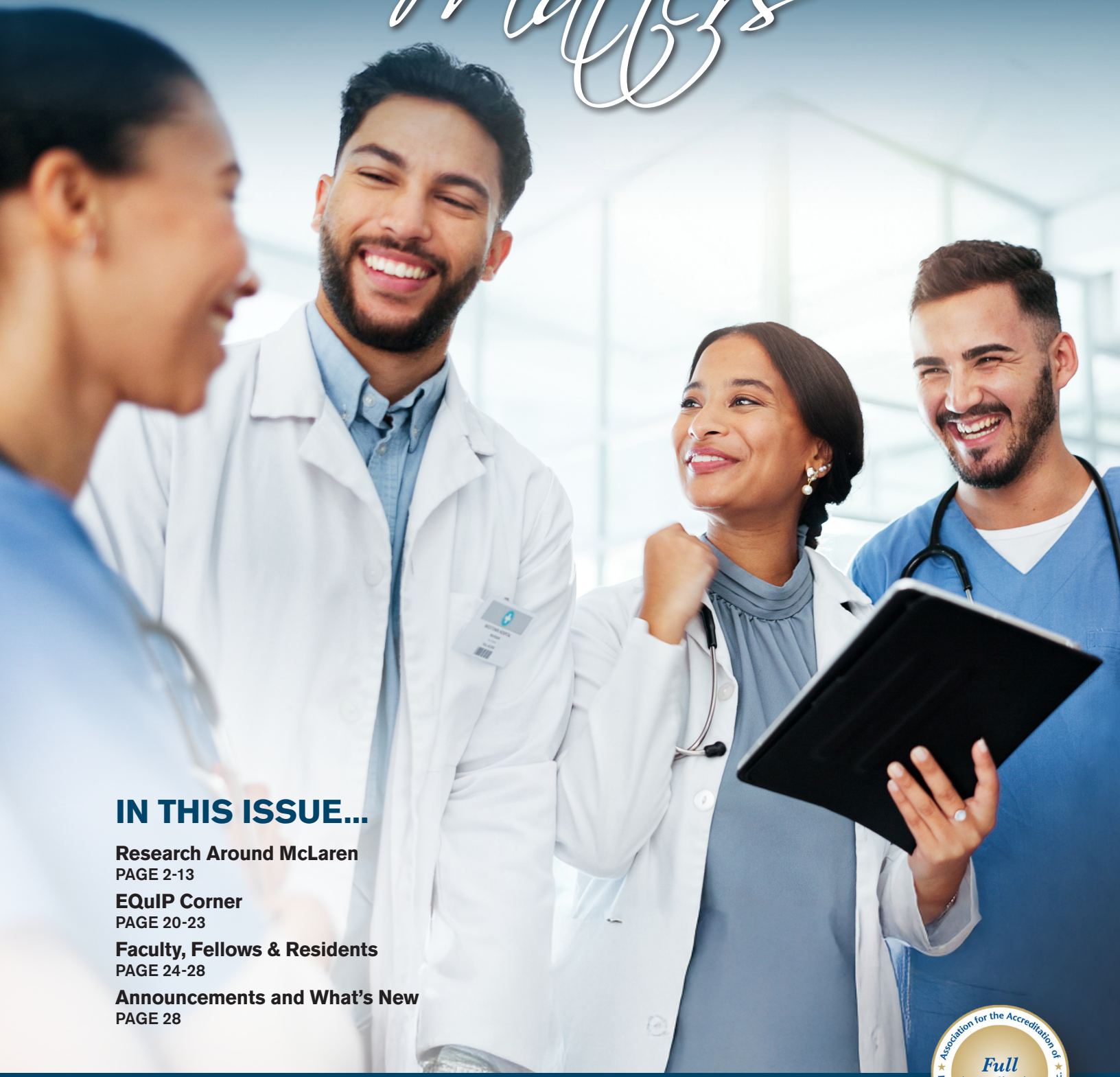
RESEARCH Matters

Fall 2024



IN THIS ISSUE...

Association for the Accreditation of Human Research Protection Programs, Inc.
Full Accreditation

McLaren

RESEARCH AROUND McLAREN

STROKE PATIENT GRATEFUL FOR CARE AND RESEARCH OPPORTUNITY

Roger Parr was shocked to learn the dizziness he experienced while standing and walking over the course of a week were signs of Transient Ischemic Attacks. “I’d had a couple of heart attacks before, and I knew that wasn’t what was going on, but I sure didn’t think it could be a stroke,” Roger said.

A trip to the emergency room in his hometown of Sault Ste. Marie led to testing, consultation between physicians, and then his family. This resulted in the decision to transfer him to McLaren Flint for further workup and symptom management by the McLaren Stroke Network.

It may be surprising to some, but patients from Northern Lower Michigan and even the Upper Peninsula are receiving advanced stroke care hundreds of miles away at McLaren Flint. The hospital is part of the McLaren Stroke Network, and its reach is due to the specialized care clinicians provide under the guidelines of a comprehensive stroke center, a designation given by the Joint Commission.

Mahmoud Rayes, MD

Upon arrival at McLaren Flint, Roger’s workup included an MRI that identified strokes involving his brain stem. The source of his strokes appeared to be due to a diseased Basilar artery.

“The risks of fixing his Basilar artery were significant,” said Dr. Mahmoud Rayes, interventional neurologist and principal investigator at McLaren Flint. “He was closely monitored, and when it was safe to do so, he was placed on anticoagulants to improve the blood flow in his arteries.”

“When Roger recovered from his stroke, I spoke with him about a national clinical trial our stroke program is a part of and asked him to consider participating in it.”

The CAPTIVA clinical research trial involves studying how stroke patients recover while taking one of three different anticoagulants along with specific doses of aspirin over the course of a year. The participants also receive intensive risk factor education and lifestyle coaching to live healthier lives. Participants are evaluated at one month, four months, eight months, and one year. Roger was receptive to the opportunity and enrolled in the CAPTIVA clinical trial.

“It is an excellent opportunity for patients to contribute to medical science, while enhancing their own care.”

– Pam Wills-Mertz
Director of Research Administration and the Human Research Protection Program

“I was so impressed with both Dr. Rayes and the team and how they worked together,” said Roger. “I can’t believe the care I received from all my doctors, nurse practitioners, nurses, and therapists; they were all great. They all listened to me, keeping me in the loop and on track. When they asked if I wanted to participate in the clinical trial, I did it because of the care I received. Plus, I thought the more people checking on me, the better. If I can help someone else, why not.”

Pam Wills-Mertz, Director of Research Administration and the Human Research Protection Program, relates that patients have an additional layer of care while participating in clinical trials. “These patients are monitored closer than the standard of care. It is an excellent opportunity for patients to contribute to medical science, while enhancing their own care. We are thrilled with Roger’s recovery and thank him for his participation.”

STUDY START-UP AT MCRI

New study opportunities come to McLaren through a variety of avenues. Sometimes you as the investigator may be approached by a colleague at a conference, a representative in the cath lab, or receive an email directly from a drug or device manufacturer, asking if you would be interested in participating in a clinical trial. Other times, study opportunities get funneled in through the staff at the sites, the management staff in the Administration Office or even cold calls to our general research line. Whichever way a study gets to us, McLaren Center for Research and Innovation has a systematic study start up management plan.

As soon as a new opportunity comes to our attention, it gets sent directly to the Corporate Research Manager, who manages the study pipeline. The study is entered into to a tracking system, then the work begins. The manager reaches out to the sponsor, telling them who we are, what we have to offer and why they should choose McLaren as a research site. From this, we often get a Confidentiality Disclosure Agreement (CDA) from the sponsor. The CDA is executed on behalf of McLaren Health Care so our whole team can receive confidential study information. Once we have a CDA, the sponsor will provide us with a study synopsis, or brief description of the trial opportunity.

The manager sends this information out to the research coordinators at all active McLaren research locations: Macomb, Flint, Bay Region, Greater Lansing and Northern Michigan. The site staff review it and see if any of their local physicians would have a particular interest in conducting the trial. Once we identify interested investigators, the manager works with the sponsor and sites to get initial feasibility questionnaires completed. The sponsor often wants to do an on-site qualification visit to each site to complete their evaluation of our institution's capabilities. The sponsor will then use this information to determine if we are a suitable site for their study.

CONTINUED ON PAGE 5

ARE YOU INTERESTED IN BECOMING A RESEARCH PARTICIPANT?

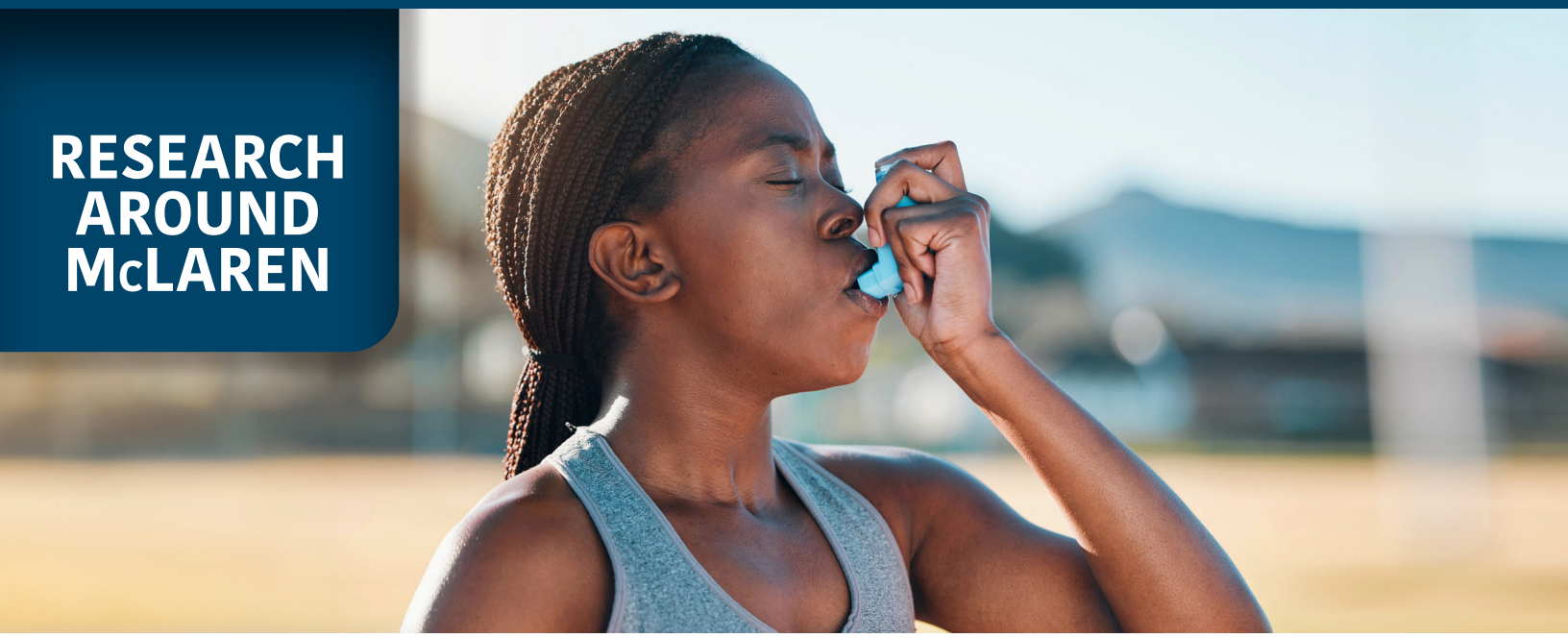
For information on enrolling in a clinical trial please visit **mclaren.org/main/clinical-research-trials**. Here you will find a list of open enrolling studies at McLaren, including which hospital the research is being done at and contact information for each study.

We have enrolling studies for the following conditions (not a complete list):

- Diabetes
- Orthopedic Surgery
- COVID-19
- High Blood Pressure (Hypertension)
- Stroke
- Heart Attacks / Heart Failure / Heart Disease
- Kidney Diseases
- Lung Diseases
- Peripheral Artery Disease
- Carotid Artery Disease
- Mastectomy
- Various Cancers
  - Breast
  - Lung
  - Prostate
  - Multiple Myeloma
- Patients who underwent intracranial aneurysm coiling
- Drug study for patients with recent acute coronary syndrome

For a complete list of conditions, please visit our website listed above.

RESEARCH AROUND McLAREN



ANCHOR ASTHMA CLINICAL TRIAL

INFORMATION FOR PROVIDERS

STUDY REVIEW

Primary Objective: Describe and compare asthma exacerbation rates in the 12 months pre-period to the 12 months post-period among participants switching from SABA only rescue inhaler (e.g., albuterol or levalbuterol) to AIRSUPRA. The patient will receive an RxStudy card that allows them to fill their AIRSUPRA at no cost during the 12-month participation period. The ANCHOR Study team will reach out to the patient every 3 months to gather study-related information.

AIRSUPRA Overview

AIRSUPRA is a combination of albuterol, a beta-2 adrenergic agonist, and budesonide, an inhaled corticosteroid, indicated for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older.

In a phase III randomized, double-blind study of patients with moderate to severe asthma comparing AIRSUPRA with Albuterol, AIRSUPRA achieved a statistically significant 28% reduction in the risk of severe asthma exacerbations among adult patients ($p<0.001$).[1]

In another phase III, randomized, double-blind, active-comparator and placebo-controlled lung function study of patients with mild to moderate asthma. The onset of bronchodilation with AIRSUPRA was as fast as albuterol.[2]

Eligible patients should be referred to the study team at **(248) 748-9971** or **ANCHOR@mclaren.org**

Referring Provider Role

- Screen patients for eligibility
- Prescribe AIRSUPRA and send electronic script to the patient's preferred pharmacy
- Report any adverse events and serious adverse events
- All other study contact and consenting will be handled by the ANCHOR team

Inclusion Criteria

- 18 years of age or older
- At least 1 visit with primary or secondary diagnosis of asthma within 12 months before or on enrollment date
- At least 1 filled prescription of SABA only rescue inhaler e.g. albuterol or levalbuterol within 12 months before enrollment date
- At least 1 asthma exacerbation within 12 months before enrollment date
- Had both medical and pharmacy insurance coverage (e.g., Medicare, Medicaid, commercial) for at least 12 months before enrollment date and without foreseeable plans to change or discontinue

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STUDY START-UP AT MCRI

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Once we are selected by the sponsor, we receive a draft contract and budget and the clock on our "study start up timeline" begins. MCRI's goal timeline is 90 days from contract receipt to IRB approval. Study sponsors expect a tight timeline to get studies enrolling as this process can be costly for them. McLaren's legal team begins reviewing the contract and the Research Administration team works with Advarra, our partnering vendor for Medicare Coverage Analysis and budget negotiations. Meanwhile, the Feasibility Review Committee, chaired by Chandan Gupte, VP of Clinical Excellence and Research, gets to work with the site staff to tease out the operational details of the protocol. FRC exists to ensure that each site has the manpower, equipment, space and local hospital resources to adequately conduct the study. The study is also evaluated for financial impact to the institution. If any feasibility issues or financial concerns are identified, the Research Administration team may schedule time to discuss with the PI and sponsor. Whenever possible, we take time to troubleshoot the issues. Occasionally we run into issues that could prevent our team from being successful and meeting our enrollment goals. In these cases, often times the best course of action is declining participation. Being open and honest with our sponsor partners about our capabilities and shortcomings is vital to maintaining the trust they have in McLaren.

After approval by the Feasibility Review Committee, MCRI's regulatory specialists begin working to get staff and investigator training documentation, regulatory documents, consents and other related material drafted and reviewed for final execution and IRB submission. Our research informatics team and research finance teams are also on high alert during this time to prepare our Clinical Trials Management System and patient payment system for the new study.

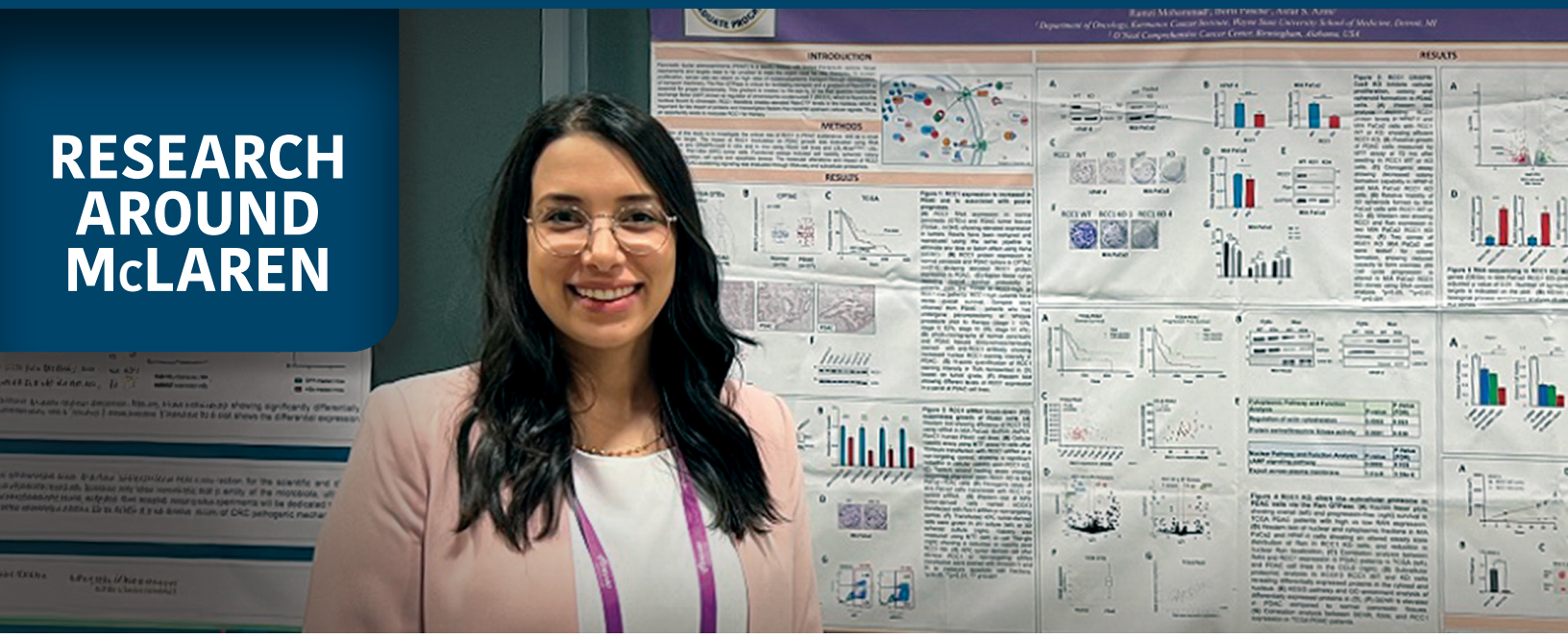
The final step before IRB submission is Protocol Review Committee. PRC, as chaired by Mark Zainea, MD, reviews research protocols for scientific merit. This committee is charged with ensuring McLaren embarks on research that has value to the scientific community and can be of potential value to our patients. The committee is made up of primarily McLaren physicians who conduct peer reviews of research protocols. This is a wonderful forum for scientific discussion and research related collaboration.

After PRC approval, the study can be released for IRB submission. Typically, once submitted, we can anticipate about 3 weeks to approval. Once the study is IRB approved, each participating site will have a Site Initiation Visit with the sponsor to ensure they are ready to begin enrollment. The SIV is conducted in-person or remotely and includes detailed training on the study protocol, FDA regulations and responsibilities of the investigator and research team. This is also when study drug, devices or other study supplies will be shipped out to the study sites. Once the sponsor gives us the go ahead, we can begin the enrollment phase of the study.

The study start-up process is vital to the success of research at McLaren. Selecting studies that match our abilities and interests provides us a strong foundation to conduct valuable scientific inquiry and provide sponsors with high quality data.

The study start-up process is vital to the success of research at McLaren. Selecting studies that match our abilities and interests provides us a strong foundation to conduct valuable scientific inquiry and provide sponsors with high quality data. When we meet our contractual obligation with these high -profile industry leaders, they value McLaren as a partner in research and come back with future contracts. If MCRI continues to refine and improve our study start-up process, we can provide McLaren opportunity to grow research at our institution in ways we have yet to imagine.

RESEARCH AROUND McLAREN



CANCER BIOLOGY GRADUATE STUDENT SECURES COVETED F99 TRANSITION AWARD FROM NATIONAL CANCER INSTITUTE

Sahar Bannoura, a doctoral candidate in her fifth year in the Cancer Biology Graduate Program at the Wayne State University School of Medicine and the Barbara Ann Karmanos Cancer Institute, has been awarded a F99/K00 Predoctoral-to-Postdoctoral Fellow Transition Award from the National Cancer Institute of the National Institutes of Health. An international student from Bethlehem, Palestine, Bannoura is mentored by Asfar Azmi, PhD.

Each institution is allowed to submit one application for the award annually, and this must be endorsed by its graduate school. Her project, "The role of guanine exchange factors in pancreatic ductal adenocarcinoma," will focus on how a specific nuclear cytoplasmic trafficking process contributes to cancer development and progression.

Pancreatic cancer is one of the deadliest cancers. By the time most patients are diagnosed, the disease is often in an advanced stage, making treatment difficult and ineffective.

"The goal of doing research in pancreatic cancer is to ultimately improve the survival of patients with this diagnosis," Bannoura said.

"I am very honored to receive this fellowship, and I am very excited to have this unique opportunity to further pursue my research interests at WSU, and as a postdoc in the future. I am very grateful for the support of my mentor, Dr. Asfar Azmi... I also want to thank the members of the research team in our lab... I am also grateful to the Cancer Biology Graduate program for its support and the unique opportunities it has provided me."

The award supports outstanding doctoral candidates in completing their dissertation research training (F99 phase) and transition in a timely manner to mentored, cancer-focused postdoctoral career development research positions (K00 phase).

Dr. Azmi, leader of the the Molecular Therapeutics (MT) Research Program, director of Pancreas Cancer Research at Karmanos, and professor of Oncology, said to his knowledge, the F99 is the first ever at WSU.

"Given its rarity, I feel incredibly honored and excited as a mentor to see one of my students receive this fellowship. It reflects her unique qualifications, exceptional research proposal and the outstanding potential she brings to the field of pancreatic cancer," Dr. Azmi said. "This award not only underscores Sahar's commitment to advancing scientific knowledge, but it also elevates the entire research team's profile. It's a proud moment to witness Sahar's hard work and talent being recognized in such a significant way, and I believe this will open new doors for her future endeavors and contribute greatly to our collective research goals."

Originally published at Today@Wayne.

ANCHOR ASTHMA CLINICAL TRIAL

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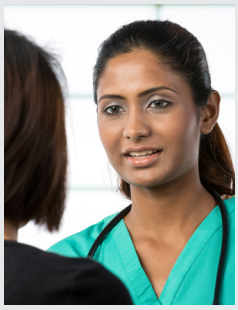
Exclusion Criteria

- Patients with major respiratory diagnoses including chronic obstructive pulmonary disease (COPD), cystic fibrosis,bronchiectasis, respiratory tract and/or lung cancer,interstitial lung disease (including pulmonary fibrosis, bronchopulmonary dysplasia and sarcoidosis), pulmonary hypertension and tuberculosis within 12 months before enrollment date
- Inpatient admission, emergency department or urgent care visit due to asthma within 10 days before enrollment date,or self-reported use of systemic corticosteroid for the treatment of asthma within 10 days before enrollment date
- Chronic use of oral corticosteroids (for any condition) within3 months before enrollment date
- History of AIRSUPRA use within 12 months before enrollment date.
- Any history of malignancy (except malignant neoplasm of skin) within 12 months before enrollment date
- For women only: Pregnant, breastfeeding or lactating women at the time of enrollment or planning to become pregnant in the year following the enrollment date

1. *AIRSUPRA® (albuterol/budesonide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023.*
2. *Chipps BE, Israel E, Beasley R, et al. Albuterol-budesonide pressurized metered dose inhaler in patients with mild-to-moderate asthma: results of the DENALI double-blind randomized controlled trial. Chest. 2023;164(3):585-595. doi:10.1016/j.chest.2023.03.035.*

DO YOU HAVE A RESEARCH PROJECT THAT NEEDS FUNDING?



McLaren Health Care has formed a corporate level Research Funding Committee. This committee has been created to establish a system-wide strategic plan and process for awarding research funding to investigators. One goal of this committee is to support and strengthen investigator-initiated research within the corporation. Awards of up to $5,000 will be awarded to individuals involved in Graduate Medical Education Research (Residents and Fellows). Awards of up to $20,000 will be awarded to non-GME individuals interested in pursuing Investigator-Initiated research. Non-GME awards are open to all McLaren employees or affiliated providers. These funds are to be used for the conduct of the observational or interventional research study and will be awarded on a quarterly basis. Due dates for application submissions are January 1st, April 1st, July 1st, and October 1st of each year. The application process can be accessed at: **www.McLaren.org/FundingApplication**. Required information for the application includes a detailed description of the research project, as well as a proposed budget.

INVESTIGATOR RESOURCES

McLaren Research Administration and Research Integrity
mclaren.org/main/research

CITI Training, Biomedical, GCP
citiprogram.org

SOCRA
socra.org

ACRP
acrp.org

Health and Human Services
hhs.gov/programs/research

FDA Guidance for Industry: Investigator Responsibilities
fda.gov/media/77765/download

FDA Guidance for Sponsor-Investigators
fda.gov/media/92604/download

GCP Regulations
fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials

Code of Federal Regulations
ecfr.gov/current/title-21

- 21 CFR 312 – Investigational New Drug Application
- 21 CFR 812 – Investigational Device Exemptions
- 45 CFR 46 – Protection of Human Subjects

Clinical Trials.gov
clinicaltrials.gov

IRB Consultations
https://www.mclaren.org/main/irb-consultations

RESEARCH AROUND McLAREN

FREE FITNESS CLASSES AVAILABLE TO CANCER SURVIVORS

KARMANOS, WSU CAPABLE PROGRAM CONTINUES IN 2025

The Barbara Ann Karmanos Cancer Institute and Wayne State University (WSU) School of Medicine are preparing for another successful year of the Cross-Training and Physical Activity: A Better Life Experience (CAPABLE) classes, free to cancer survivors. Participants do not need previous exercise experience.

What is CAPABLE?
Why Should Your Patients Participate?

CAPABLE is a 12-week physical education program that contains three sessions a week. In the sessions, cancer survivors are introduced to the sport of CrossFit.

C.A.P.A.B.L.E.
CROSS TRAINING AND PHYSICAL ACTIVITY: A BETTER LIFE EXPERIENCE

The American Cancer Society recommends cancer survivors avoid inactivity and resume their regular physical activities after a diagnosis as soon as their doctor deems it safe. They also recommend survivors exercise for 150-300 minutes weekly, including strength training. CAPABLE was designed to help survivors learn how to meet these exercise and strength-training recommendations and to teach fitness skills they can use well beyond the classes. The strength and conditioning workouts are simple movements performed at scalable levels for each participant.

Who Can Enroll?

Participants must be adults, 18 years or older, and be a cancer survivor, no matter what type of cancer they were diagnosed with. Patients who had a widely metastatic diagnosis to the brain or bones are excluded from participating in the program for precautionary reasons. Participants must have reliable transportation to travel to the sessions. All participants also must receive a medical clearance from their oncologist or primary care provider to participate.

The CAPABLE Study

In June 2023, Jennifer Beebe-Dimmer, PhD, MPH, principal investigator of the CAPABLE study, leader of the Population Studies and Disparities Research (PSDR) Program, scientific director of the Epidemiology Research Core at Karmanos, and professor of Oncology at WSU, and her research team published "The Impact of High Intensity Interval Training in a Diverse Group of Cancer Survivors: CAPABLE, A Pilot Study," in Preventative Medicine. This study featured 48 metro Detroit cancer survivors who participated in CAPABLE. Participants were mostly breast and prostate cancer survivors, which are two of the most commonly diagnosed cancers in metro Detroit. Karmanos and WSU researchers found that participants tolerated the CAPABLE format of physical education and strength training well during the 12 weeks. Benefits included weight loss, a better quality of life, and improved HbA1c levels among participants.

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MD-PhD STUDENT WINS NATIONAL CANCER INSTITUTE TRAINING GRANT

The National Cancer Institute has awarded Jugmohit Toor, a third-year student at the Wayne State University School of Medicine and the Barbara Ann Karmanos Cancer Institute, the Ruth L. Kirschstein National Research Service Award for Individual MD-PhD fellows.

Toor is an MD-PhD student in the Cancer Biology Graduate Program. This NCI grant will support his research. His dissertation project is entitled "Investigating the MAIT cell – Microbiome Relationship in Pancreatic Cancer Liver Metastasis."

"I have always taken an interest in how T cells work and how we can use them to combat cancer. With this project, I have the opportunity to figure out how this unique subset of T cells, MAIT cells, interacts in the tumor environment and how we can target them to reduce the tumor. Aside from my personal interests, this work may one day make real impacts on how patients with pancreatic cancer liver metastasis are treated," Toor said.

The competitive award combines medical school and predoctoral support, including an annual stipend and funds for tuition and fees.

Toor's dissertation advisor is Qing-Sheng Mi, MD, PhD, member of the Tumor Biology and Microenvironment (TBM) Research Program at Karmanos, and an adjunct professor in the Department of Oncology and in the Department of Biochemistry, Microbiology and Immunology. Toor joined Dr. Mi's lab in 2021.

"Jugmohit's achievement is a testament to his dedication, hard work and passion for research. Receiving this prestigious NCI grant is a significant milestone in his academic career, and it reflects the high caliber of his work and the potential impact of his research," Dr. Mi said. "I am incredibly proud of him and confident that his contributions will advance our understanding in his research field and inspire his peers."

Originally published at Today@Wayne.

"Jugmohit's achievement is a testament to his dedication, hard work and passion for research. Receiving this prestigious NCI grant is a significant milestone in his academic career, and it reflects the high caliber of his work and the potential impact of his research."

– Qing-Sheng Mi, MD, PhD

RESEARCH AROUND McLAREN

DOCTORAL CANDIDATE WINS FIRST PLACE AT INTERNATIONAL CONFERENCE IN MONTREAL

FOR RESEARCH STUDYING PROSTATE CANCER PROGRESSION IN BONE

Alexis Wilson, fifth-year doctoral student in the Wayne State University (WSU) School of Medicine and the Barbara Ann Karmanos Cancer Institute's Cancer Biology Graduate Program, received the Best Oral Presentation Award at the Eighth International Bone Marrow Adiposity Conference, held Sept. 24-26 in Montreal.

Alexis Wilson

The title of her presentation was "Tumor adaptive response to adipocyte-induced stress in bone metastatic niche: the functional interplay between Stearoyl -CoA desaturase and ATF4."

"I was very surprised when my name was called. It was unexpected and I was extremely grateful. This was a very specialized group of scientists, and I was already honored to have been selected to present my work to them in an oral presentation form," Wilson said.

Wilson's travel to the conference was supported by the Mary Lou Zieve Award for Professional Development, which she received from the Cancer Biology Graduate Program in February. The award is offered annually to a senior Cancer Biology student to attend a specialized training opportunity or scientific conference that will significantly impact their research.

Wilson's research received additional accolades at three meetings this year. She received a first-place poster award at the Jackson Laboratory Short Course on Experimental Models of Human Cancer in 2023, a fourth-place poster award at the Prostate Cancer Specialized Program of Research Excellence Meeting in March, and a first-place oral presentation award at WSU's annual Cancer Biology Symposium, in February.

She is mentored by Izabela Podgorski, PhD, co-leader of the Prostate Cancer Research Team and a member of the Tumor Biology and Microenvironment Research Program at Karmanos, as well as professor of pharmacology at WSU. Dr. Podgorski's lab focuses on the interaction between prostate cancer cells that have metastasized to bone and bone marrow fat cells.

Izabela Podgorski, PhD

"We study this interaction to understand the mechanisms in which bone marrow fat cells contribute to prostate cancer progression in bone. The objective of my project and the work I presented is to investigate the mechanisms underlying lipid-induced stress during adipocyte-cancer cell crosstalk and determine its functional relationship to cancer progression in bone," Wilson said.

Her presentation showcased that bone marrow adipocytes induce an enzyme named stearoyl -CoA desaturase, or SCD, in prostate cancer cells, an important regulator of stress, and allows prostate cancer cells to survive in bone by regulating DNA damage and lipid peroxidation levels.

"We also found that SCD works together with a very important transcription factor named ATF4, which is also involved in regulating stress," she said. "Our findings lead us to believe that bone marrow fat cells induce SCD in prostate cancer cells, to shield cancer cells from stress through crosstalk with ATF4 to foster cancer cell survival in bone. These insights enhance our understanding of how prostate cancer cells survive and thrive in the bone environment and reveal potential drug targets for bone metastatic prostate cancer."

The work is part of her doctoral thesis, funded by an F31 Ruth L. Kirschstein National Research Service Award for Individual Predoctoral Fellowship from the National Cancer Institute. This program enables promising predoctoral students to develop into productive independent research scientists to obtain mentored research training while conducting dissertation research.

"I am very proud of Alexis. This award is yet another testament to her impressive accomplishments as a PhD student in the Cancer Biology Program," Dr. Podgorski said. "The Bone Marrow Adiposity Society is an international organization composed of basic and clinical scientists dedicated to understanding the role of bone marrow adipose tissue in health and disease. Being selected for a podium presentation at this specialized conference is already a significant honor but winning the sole award for a podium presentation truly recognizes Alexis's excellence and potential as a rising young scientist."

Originally published at Today@Wayne.

"I am very proud of Alexis. This award is yet another testament to her impressive accomplishments as a PhD student in the Cancer Biology Program."

– Izabela Podgorski, PhD

CAPABLE PROGRAM CONTINUES

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Plus, this study emphasizes community building and social support among cancer survivors and strengthens the ability to do functional movements required for everyday living.

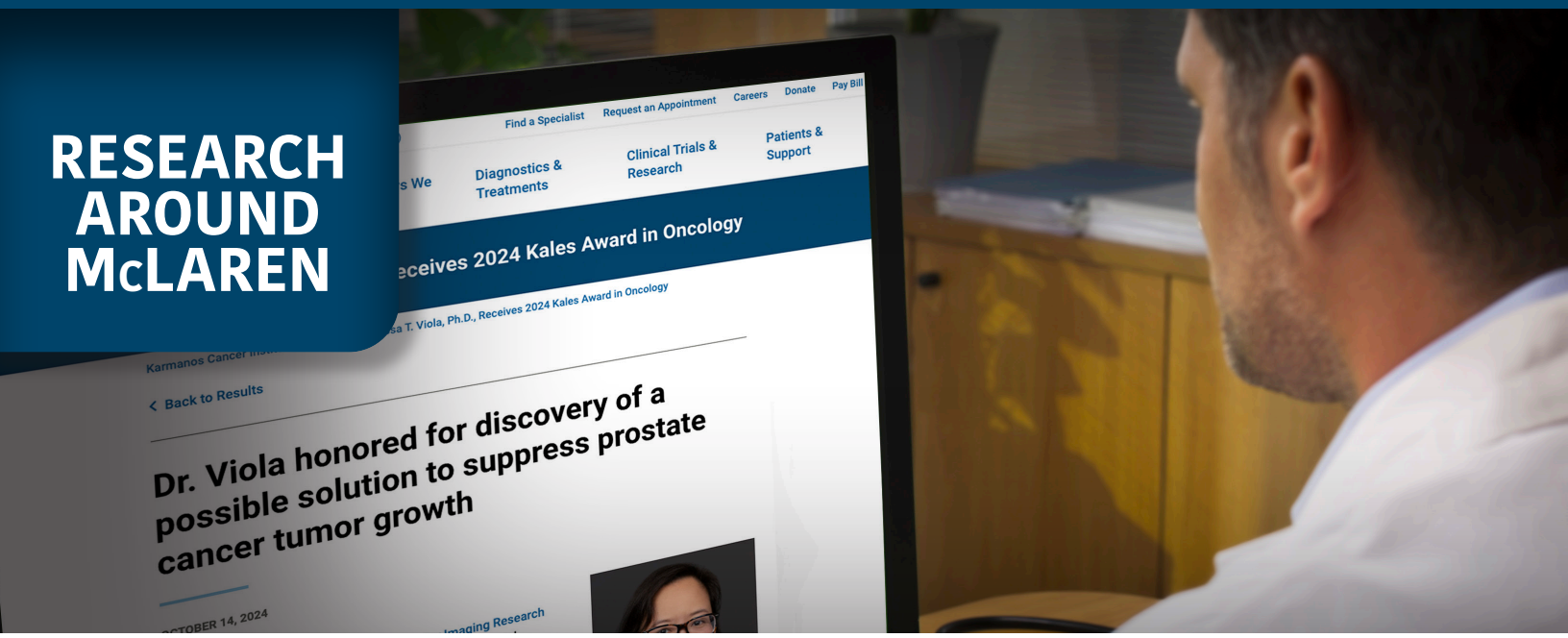
As part of the program, researchers will continue to examine the benefits of CrossFit training on cancer survivors, including how it impacts functional performance, cardiovascular endurance, metabolic health, and "everything from physical fitness and body composition to sleep health and quality of life," said Dr. Beebe-Dimmer.

Where is CAPABLE Offered?

Karmanos and WSU have partnerships with seven CrossFit gyms across Michigan. These include programs in Commerce Township, Dearborn Heights, Farmington Hills, Mount Clemens, Northville, Petoskey, and two locations in Detroit, plus plans to partner with another gym in Rochester Hills in 2025. Sessions begin at various times throughout the year.

Get More Information and Have Your Patients Sign Up

For more information about CAPABLE, contact Tara Baird, program coordinator, at **bairdt@wayne.edu** or **(313) 578-4246**. Patients may sign up by filling out the form at **karmanos.org/CAPABLE** or by emailing **CAPABLE@wayne.edu**.



NERISSA T. VIOLA, PhD, RECEIVES 2024 KALES AWARD IN ONCOLOGY

HONORED FOR DISCOVERY OF A POSSIBLE SOLUTION TO SUPPRESS PROSTATE CANCER TUMOR GROWTH

Nerissa T. Viola, PhD, leader of the Molecular Imaging Research Program at the Barbara Ann Karmanos Cancer Institute and associate professor at Wayne State University (WSU) School of Medicine, has won the 2024 Drs. Anthony and Joyce Danielski Kales Endowment Faculty Award for Innovative Cancer Research. Dr. Viola received this award for her role as the principal investigator in a collaborative preclinical study that succeeded in finding a way to potentially suppress tumor growth for prostate cancer patients.

Nerissa T. Viola, PhD

Dr. Viola's research, "Selective ablation of TRA-1-60+ pluripotent stem cells suppresses tumor growth of prostate cancer," was published in 2023 in Volume 13, Issue 7 of *Theranostics* (Impact Factor: 11.6). Co-authors include Karmanos and WSU investigators Jordan White, Nicholas Ramos, Allen-Dexter Saliganan, Jacob Lindquist, Kayla Conner, Steve Patrick, Seongho Kim, and Elisabeth Heath; National Cancer Institute and National Institutes of Health researchers Jooh-Young Chung, Meghan Bell, Freddy Escorcia; Michael Schopperle from Corewell Health and Wendy Wiesend with Curemeta, LLC.

"This award underscores the promising field of radiotheranostics as an emerging cancer treatment. Radiotheranostics uses the same drug that can detect and treat tumors by merely switching the radioisotope attached to it. Developing this agent is a significant undertaking, requiring multidisciplinary expertise of multiple collaborators. I am extremely grateful to the co-authors for their time and effort, especially to Dr. Elisabeth Heath who was instrumental in introducing this project years ago," said Dr. Viola.

This research also helped Dr. Viola answer an intellectual curiosity and made it a reality. Since becoming a postdoc, she had wondered if it was possible to detect and ablate cancer cells.

"The study demonstrates that by using radiopharmaceutical therapy targeting the biomarker TRA-1-60 (TRA), selective ablation of pluripotent cancer stem cells suppressed prostate cancer progression. We have also further shown that these TRA+ cells are culprits of tumor regrowth and require targeted treatment to prevent relapse and metastasis," explained Dr. Viola.

The team used an antibody specific to TRA, radiolabeled with zirconium-89, an isotope for positron emission tomography (PET) imaging to detect these cells within the prostate tumors. After detection, they substituted the isotope with Lutetium-177, an isotope

that emits beta particles that cause single and double-strand DNA breaks. The team injected this drug in mice with prostate cancer cells following the guidelines established by Wayne State University's Institutional Animal Care and Use Committee. They then subsequently looked at tumor growth delay over time.

"Preclinical studies using rodents, such as mice, allow us to test the efficacy of drugs like TRA-targeted RPT (radiopharmaceutical therapy). Once we validate and confirm the potency of the drugs, we can move forward to clinical trials in prostate cancer patients," said Dr. Viola.

From the experiments, researchers came to three conclusions: there is a clinical significance of TRA expression in prostate cancer, engineered and tested radiotheranostic agents can image and treat TRA+ prostate cancer stem cells, and the ablation of the TRA+ cancer stem cells did suppress the growth of prostate cancer. Their findings lead to the potential for future studies in other cancers with TRA expression, such as pancreatic, gastric, and ovarian cancers.

"The next step would be to look at targeted drug combinations with TRA RPT that will not only suppress growth but completely eradicate the tumor and prevent relapse," concluded Dr. Viola.

Dr. Viola was honored for her research at a special seminar on Friday, Oct. 18, 2024, as part of the Karmanos Cancer Institute Seminar Series. During the conference, she presented her research specific to the publication and received a plaque honoring her achievements. Additional publications highlighting Dr. Viola's research are displayed at the Elliman Clinical Research Building on the School of Medicine's campus and the Hudson-Webber Cancer Research Center on the Karmanos campus.

Boris Pasche, MD, PhD, FACP, president and CEO of Karmanos, and Nerissa T. Viola, PhD, 2024 Kales Award recipient.

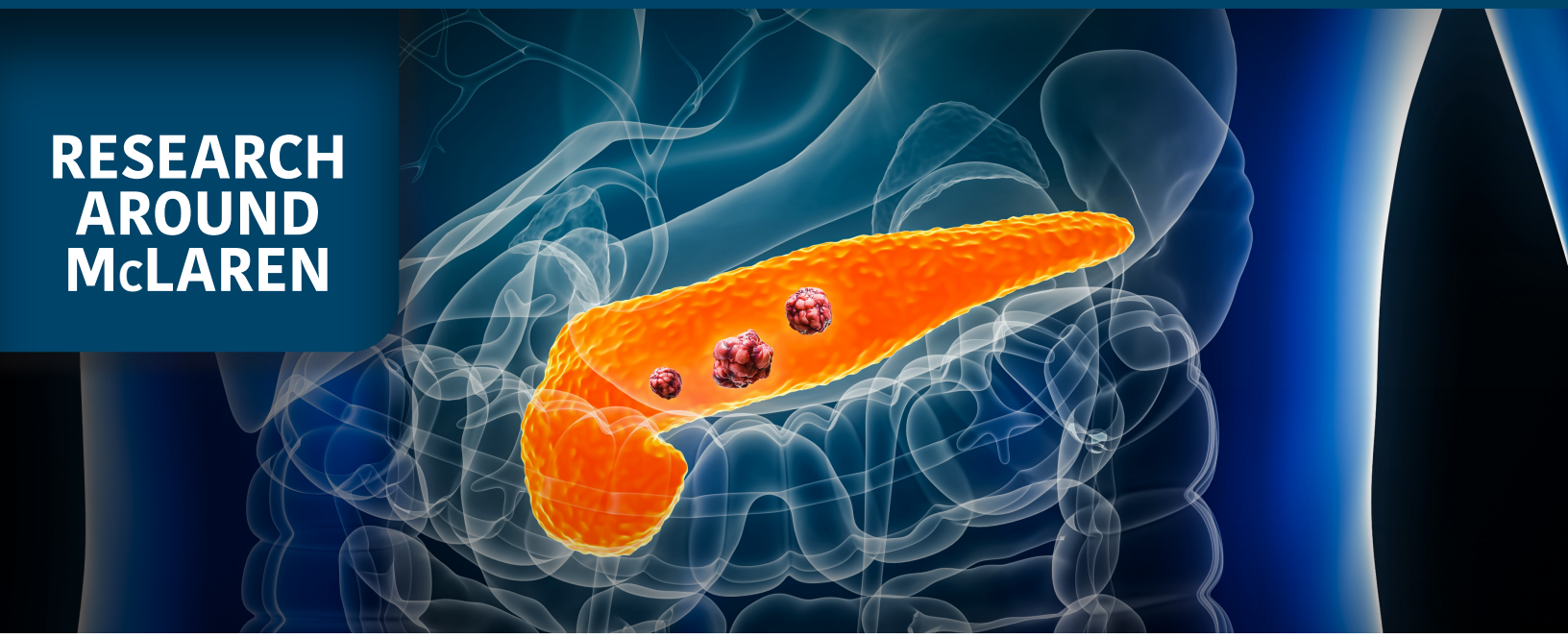
About the Kales Award in Oncology

The Kales Award in Oncology was created in 2012 at the WSU School of Medicine to recognize exemplary and innovative cancer research. Drs. Anthony and Joyce Danielski Kales established the award in memory of their brother and brother-in-law, Nicholas Kales, who died from lung cancer. The award is given to a WSU faculty member who is also a Barbara Ann Karmanos Cancer Institute researcher. Selection is based on a comprehensive review of published articles within the previous year.

Drs. Anthony and Joyce Danielski Kales are both graduates of the WSU School of Medicine, and each received the Distinguished Alumnus Award from the School of Medicine. Dr. Anthony Kales authored or co-authored more than 300 scientific publications and six books. He is internationally recognized as a founder and leader in modern sleep research and was one of a handful of founders worldwide in sleep disorders medicine. In 2007, he was awarded an Honorary Doctorate from the University of Athens School of Medicine in Greece. Under the leadership of Drs. Anthony and Joyce Kales, the Central Pennsylvania Psychiatric Institute (CPPI) was established in 1984 at the Penn State College of Medicine to provide mental health training programs in child mental health, geriatric mental health, serious and persistent mental illness, and drug and alcohol abuse.

Dr. Anthony Kales passed away in December 2023, leaving a legacy of philanthropy, mentorship, scholarship, and a commitment to human connection.

RESEARCH AROUND McLAREN



STUDY REVEALS PROMISING APPROACH

PREVENTING OR TREATING EARLY-STAGE PANCREATIC CANCER

Results from a new study focused on fighting the cancer, often called "the silent killer," show that targeting a specific protein in the body may slow or prevent the progression of the invasive disease.

Kay-Uwe Wagner, PhD, leader of the Tumor Biology and Microenvironment Research Program at the Barbara Ann Karmanos Cancer Institute and professor of oncology at Wayne State University School of Medicine, is the principal investigator of "The Janus kinase 1 is critical for pancreatic cancer initiation and progression," published in the open access journal Cell Reports.

Kay-Uwe Wagner, PhD

"Pancreatic ductal adenocarcinoma is a particularly serious type of cancer. It's often referred to as 'the silent killer' because it can progress rapidly without noticeable symptoms in its early stages," Dr. Wagner said.

Pancreatic ductal adenocarcinoma is the most common form of pancreatic cancer, making up more than 80% of cases, according to the National Cancer Institute and the Cancer Genome Atlas Program. The disease begins in the cells of the pancreas that produce and transport juices containing digestive enzymes into the small intestine.

"While the prognosis for patients with resectable pancreatic cancer is more favorable, the vast majority of cases are diagnosed in patients after the cancer cell had spread to other organs, which leads to very dismal outcomes using standard chemotherapies," Dr. Wagner added.

"Our research focused on how IL-6-class inflammatory cytokines can contribute to the development of this disease," Dr. Wagner said. "We found that a protein called Janus kinase 1 is required to relay the signals of inflammatory cytokines within pancreatic cells and how JAK1 activates STAT3 and C/EBP, two other proteins involved in tumor development."

Blocking the cancer-promoting effects of inflammatory cytokines through inhibition of the Janus kinase 1 prevents the formation of high-grade preneoplastic lesions and pancreatic tumors.

The main findings suggest that targeting JAK1 might be a promising approach for preventing or treating early-stage pancreatic cancer on its path to becoming one of the deadliest forms of cancer. Targeting JAK1 may slow or prevent the progression of operable disease in patients with pancreatic tumors at risk of recurrence.

"Understanding its role in the disease can help other researchers develop new and more effective treatment options," Dr. Wagner added.

Dr. Wagner is also the leader of the Lloyd and Marilyn Smith Chair for Breast Cancer Research at the Karmanos. His collaborators on the Cell Reports

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LAUREN M. HAMEL, PhD

APPOINTED VISITING INNOVATION FACULTY MEMBER AT THE PENN CENTER FOR CANCER CARE INNOVATION

Lauren Hamel, PhD, co-leader of the Population Studies and Disparities Research Program at the Barbara Ann Karmanos Cancer Institute, has been appointed a visiting innovation faculty member at the Penn Center for Cancer Care Innovation (PC3I) at the University of Pennsylvania, Abramson Cancer Center. This role complements her current position as an associate professor of oncology at the Wayne State University (WSU) School of Medicine.

Founded at the Abramson Cancer Center at the University of Pennsylvania in 2018, the Penn Center for Cancer Care Innovation (PC3I) is the nation's first center working at the nexus of research and practice to create, test, and scale solutions to transform cancer care delivery.

Lauren Hamel, PhD

Dr. Hamel, who has been with Karmanos since 2013, brings a wealth of experience to this new opportunity. Her research focuses on clinical communication and organizational behavior to identify and mitigate disparities as we move toward cancer health equity.

David Dougherty, MD, MBA, a close collaborator of Dr. Hamel, is a faculty member at the University of Pennsylvania and the Penn Center for Cancer Care Innovation. Given their joint goal of innovating in their shared research, he suggested the visiting faculty member position to Dr. Hamel as an opportunity to enhance that work and potentially build other collaborations.

"I'm very fortunate to be joining an incredibly accomplished group of investigators in a prestigious center of scholarship," said Dr. Hamel. She hopes this role at the University of Pennsylvania will be an opportunity to elevate the research her team has done so far at Karmanos and WSU and allow them to expand their reach throughout the country.

"Our work serves at the nexus of research and care delivery, which aligns well with the mission and vision of PC3I. What we really need now are partners to help us do that effectively and help us expand our impact, which I anticipate this role will do in new and unique ways," said Dr. Hamel.

This new opportunity at the University of Pennsylvania will allow her to address different health care disparities and improve patient-provider communication in a new environment that allows for the cross-pollination of ideas.

"It's very easy to become focused on one's immediate environment, and sometimes that can hinder research from improving, enhancing, and

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PC3I
University of Pennsylvania

"I'm very fortunate to be joining an incredibly accomplished group of investigators in a prestigious center of scholarship."

– Lauren Hamel, PhD

RESEARCH AROUND McLAREN

INVESTIGATORS: ADVANCED LUNG CANCER DEATHS DROPPED SIGNIFICANTLY SINCE IMMUNOTHERAPY BECAME STANDARD-OF-CARE

THE LARGEST POPULATION-BASED STUDY TO DATE SUPPORTS THE SURVIVAL BENEFITS OF IMMUNOTHERAPY FOR PEOPLE WITH METASTATIC NON-SMALL CELL LUNG CANCER

Since the first immunotherapy drug to boost the body's immune response against advanced lung cancer was introduced in the U.S. in 2015, survival rates of patients with the disease have improved significantly. That's the conclusion of a recent real-world study published by Wiley online in CANCER, a peer-reviewed journal of the American Cancer Society.

Dipesh Uprety, MD, FACP

A team led by Dipesh Uprety, MD, FACP, of the Barbara Ann Karmanos Cancer Institute and the Wayne State University School of Medicine, published "Survival Trends Among Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) Before and After the Approval of Immunotherapy in the United States: A Surveillance, Epidemiology, and End Results (SEER) Database-Based Study." Lead author, Yating Wang, MD, from Ascension Providence Hospital, analyzed data from the National Cancer Institute Surveillance, Epidemiology, and End Results database, which compiles cancer-related data covering approximately 48% of the US population. The investigators' analysis focused on non-small cell lung cancer (NSCLC), which accounts for up to 90% of all cases of lung cancer and is the leading cause of cancer-related death among both men and women in the United States.

In a comparison of 100,995 patients with metastatic NSCLC treated in 2015–2020 (after immunotherapy was deemed the standard of care) with 90,807 patients with metastatic NSCLC in the pre-immunotherapy era of 2010–2014, patients in the immunotherapy era were less likely to die from any cause. The overall survival rates at one, three, and five years were 40.1% versus 33.5%, 17.8% versus 11.7%, and 10.7% versus 6.8%. The median overall survival was eight months in patients in the immunotherapy era and seven months in those in the pre-immunotherapy era.

Similarly, patients treated after immunotherapy was available were less likely to die specifically from cancer than those treated before immunotherapy. The one-, three-, and five- year cancer-specific survival rates were 44% versus 36.8%, 21.7% versus 14.4%, and 14.3% versus 9%, with a median survival of 10 months versus eight months.

Survival rates remained significantly better in the immunotherapy era even after accounting for factors including age, sex, race, income, and geographical area.

"By utilizing a large national database, our study provided real-world evidence of the positive impact of immunotherapy in patients with lung cancer," said Dr. Uprety, medical oncologist, member of the Phase I Clinical Trials and Thoracic Oncology Multidisciplinary Teams, and member of the Molecular Therapeutics Research Program at Karmanos.

The investigators stressed that additional studies are needed, however.

"Immunotherapy provides long-term benefits. Since the durable benefits of immunotherapy are limited to a small subset of patients, future research should aim to optimize immunotherapy with new agents that can benefit a broader population," Dr. Wang concluded.

Along with Drs. Uprety and Wang, collaborators on this research study included Kyle Kondrat, DO, fellow with the Barbara Ann Karmanos Cancer Institute and Wayne State University; Janak Adhikari, MD, of Northern Light Eastern Maine Medical Center; Quynh Nguyen, MD, of Logan Regional Medical Center; and Qian Yu, MD, of the University of Chicago Medical Center.

Similarly, patients treated after immunotherapy was available were less likely to die specifically from cancer than those treated before immunotherapy.

EARLY-STAGE PANCREATIC CANCER

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study include WSU Professor and Chair of Pathology Rafic Beydoun, MD, member of the Molecular Therapeutics Research Program at Karmanos and professor and chair of pathology at WSU, Dr. Wagner's lab members, and senior investigators at the National Cancer Institute, Thomas Jefferson University, and the German Cancer Research Center.

Originally published at Today@Wayne.

PENN CENTER FOR CANCER CARE INNOVATION

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innovating. PC3I is well known for advancing significant innovation in cancer care," Dr. Hamel said. "Having a role focused on sharing my work and learning from others in that kind of environment is an incredible opportunity to scale up and innovate what we are currently doing and get new ideas for areas of expansion."

Dr. Hamel holds a bachelor's, master's, and doctor of philosophy in communication science from Michigan State University and has completed two significant postdoctoral research fellowships—one in organizational behavior at the Business School of Dublin City University in Dublin, Ireland, in 2013 and one in communication and behavioral oncology at Wayne State University School of Medicine and Karmanos Cancer Institute in 2015.

RESEARCH AROUND McLAREN

KARMANOS, WSU RESEARCHER FINDS BLOCKING SPECIFIC TYPE OF T CELL IMPAIRS TUMOR GROWTH

A Barbara Ann Karmanos Cancer Institute and Wayne State University (WSU) School of Medicine researcher has discovered that blocking the production of a specific type of T cell safely impairs tumor growth in prostate cancer and melanoma. The finding identifies a viable target to safely enhance anti-cancer immunity.

Eric Sebzda, PhD

"Peripheral-derived regulatory T cells contribute to tumor-mediated immune suppression in a non-redundant manner," was published in August 2024 in the *Proceedings of the National Academy of Sciences*, a peer-reviewed journal of the National Academy of Sciences. Eric Sebzda, PhD, associate professor of Biochemistry, Microbiology and Immunology, and member of the Tumor Biology and Microenvironment (TBM) Research Program at Karmanos, and his colleagues detailed findings in the report that demonstrates blocking the production of peripheral Tregs, a type of T cell, safely inhibits tumor growth in preclinical models of these two cancers.

The design of new cancer therapies hinges upon the identification of tumor-mediated mechanisms that impair immunity, Dr. Sebzda said. Regulatory T cells, or Tregs, are a key component of cancer-derived immune suppression, but these cells are necessary to prevent systemic autoimmunity, so direct targeting of Tregs is not a clinical option for cancer patients. However, eliminating the production of pTregs, a subset of Tregs necessary for melanoma and prostate cancer progression, safely prevented malignancy in animal models.

"Our results indicate that tumor-specific pTregs are critical for early stages of cancer progression and blocking the generation of these inhibitory lymphocytes safely delays or prevents malignancy in preclinical models of melanoma and prostate cancer," Dr. Sebzda said. "Importantly, pTreg function is maintained between mice and humans, which strongly suggests that pTregs perform a similarly deleterious role in cancer patients."

The elimination of pTregs, he noted, does not lead to overt pathology associated with autoimmunity. In fact, blocking the generation of pTregs in preclinical animal models actually improved immune responses correlated with positive cancer patient outcomes.

Researchers involved in this discovery include the following from Karmanos and WSU: Md Moazzem Hossain, research assistant; Paul King, research assistant; Justin Hackett, medical student; Herve Gerard, research assistant; Rajmund Niwinski, medical student; and TBM Research Program members Gregory Dyson, Ph.D., professor, and Heather Gibson, Ph.D., assistant professor. Additionally, Lan Wu, M.D., and Luc Van Kaer, Ph.D., of Vanderbilt University Medical Center;

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NEW STUDY SEEKS TO DEVELOP NEW TREATMENT STRATEGY TO PREVENT OR DELAY RELAPSE OF MYELOID LEUKEMIA ASSOCIATED WITH DOWN SYNDROME

A four-year, $1.2 million grant from the National Cancer Institute of the National Institutes of Health may help researchers find new clues to the interplay between Down syndrome (DS) and myeloid leukemia (ML).

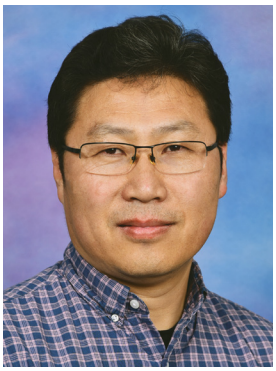
Jeffrey Taub, MD

Jeffrey Taub, MD, professor of pediatrics at Wayne State University (WSU) School of Medicine, and Yubin Ge, PhD, professor of oncology, and both members of the Molecular Therapeutics Research Program at the Barbara Ann Karmanos Cancer Institute, will use this funding to develop a novel strategy to enhance the antileukemic activity of the chemotherapy drug cytarabine against myeloid leukemia associated with DS.

Children with DS are known to have a significantly higher risk of developing acute leukemias than children without it. This study aims to identify a novel treatment strategy for enhancing cytarabine treatment to improve patient outcomes further and prevent or reduce relapses in ML-DS patients.

"There are some very unusual findings in children with DS who have leukemia," said Dr. Taub. "Why is it when children get this, it is usually highly curable, but there are other patients, including children, who are difficult to cure and whose leukemia can often relapse? We want to know why it can be so resistant to treatment in certain patients."

"There is an emphasis on this as a team collaboration," said Dr. Ge. "Dr. Taub is a physician who works with patients, and I am a basic scientist who directs the lab work. The team aspect of this is very important. I am extremely grateful for the hard work of other members of our research team, Dr. Lisa Polin, Dr. Sijana Dzinic, Dr. Wei Chen, Holly Pitman, Jianlei Zhao, Jenna Thibodeau, Jay Kushner, and Kathryn White, which was critical for the success of securing this award. I am also grateful for the institutional support from the Department of Oncology, the Karmanos Cancer Institute, and the Wayne State University School of Medicine, especially Ms. Valerie Wade, who helped with the submission, as well as the pre-award process."



Yubin Ge, PhD

Drs. Taub and Ge will test different drug treatments on ML-DS cells to identify new therapies that prevent or

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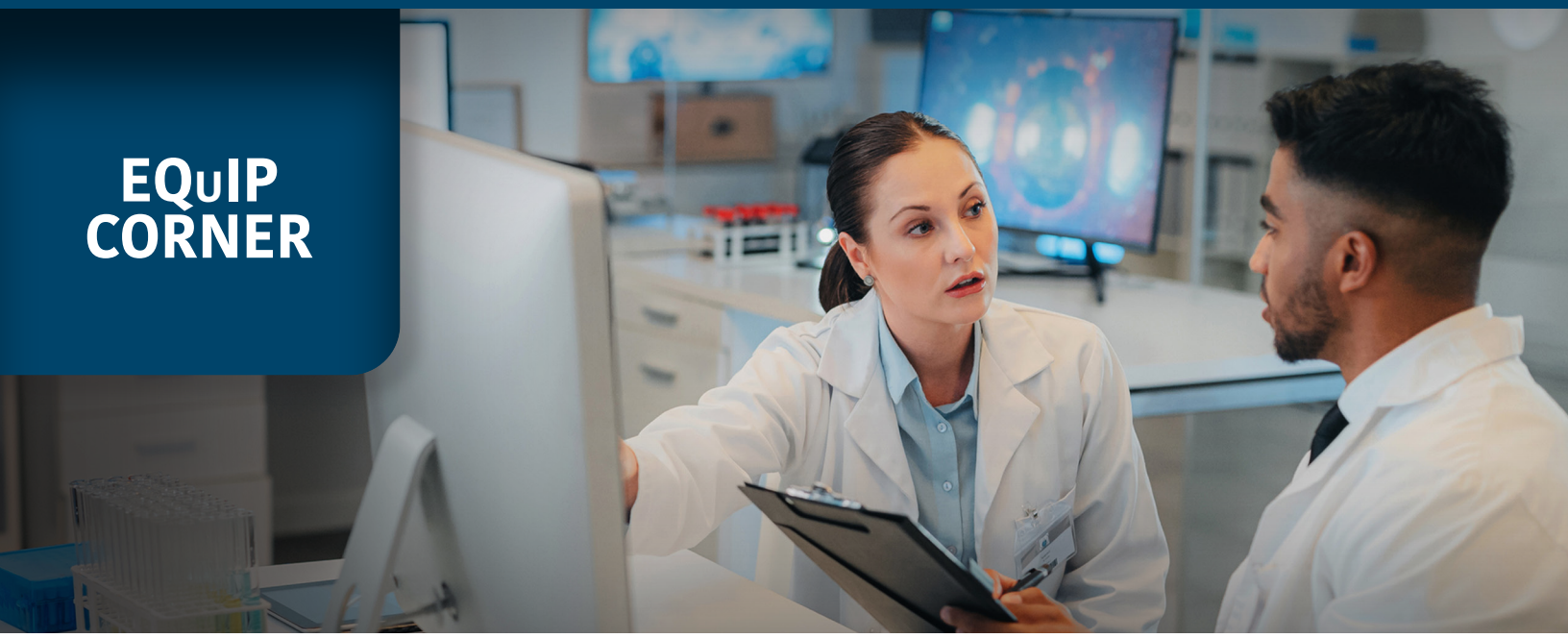

KEY TO SUCCESSFUL IRB SUBMISSION AND IMPROVING TURNAROUND TIME

By Susmita Jain, MS, Research QI and Education Specialist, McLaren Health Care

Introduction

The Institutional Review Board (IRB) reviews research involving human subjects to ensure that it meets ethical and regulatory standards, protects participants, and complies with institutional policies. Though investigators understand the value and regulatory imperative of human research protection measures, they wish for faster IRB review/approval times and note the need for a better process. The IRB turnaround time is lower when reviewing those submissions that are complete and accurate, and which arrive in the IRB office as "review ready".

Susmita Jain, MS

The IRB utilizes an IRB analyst pre-review process for all submissions regardless of the review process. A checklist guides this review and assists in identifying information that needs to be changed, modified, or corrected. This review helps identify any deficiencies to meet the criteria for approval under federal regulations and compliance with institutional policies. This article discusses the most obvious reasons for delays and describes several measures that investigators and study staff can take to ensure a timelier review of IRB submissions.

Understand the reason for the delay

Several issues slow down the IRB approval process like incomplete applications or failure to respond promptly to IRB requests (stipulations) for additional information needed for review. A key factor in slow IRB turnaround is when protocols must go back and forth multiple times between the IRB and investigators. The IRB analysts spend much time providing detailed advice and lengthy responses to investigators who have submitted incomplete applications that were not "review ready." In many cases, the IRB staff will recommend that the investigators consult* with the Research Integrity Office for assistance with completing their IRB applications. Understanding the IRB's needs and knowing how to meet their requirements can improve overall turnaround time.

Tips for completing the Research Protocol/ Application

Below are some ways to ensure that the IRB has the information it needs to review the study.

Keep in mind that the IRB is reviewing the study to determine that it meets the criteria for approval. The more information the IRB has, the easier it can be to make the required determination.

1. Review the document "Overview for Submitting a New Application to the MHC IRB**
2. **Read carefully and follow instructions!**

3. Become familiar with research policies, regulations, and templates found at https://www.mclaren.org/main/research-integrity
4. IRB applications are submitted via an electronic platform called iRIS. See iRIS application access instructions and training at https://www.mclaren.org/main/iris-research
5. **Ensure all key study personnel have their required CITI training.**
   All study staff must meet the institutional requirements for human subject protection training certification and recertification. Depending on the nature of your research, additional courses may be required. It is the responsibility of the Principal Investigators to verify the training status of all their study staff before submitting internal study personnel changes and new protocols to the IRB. Failing to do this causes processing delays. met. Please review these training requirements on the Research Integrity web page https://www.mclaren.org/main/required-training-citi
6. **Avoid the Most Common Mistakes in Completing IRB Application Form**
   - Identify the appropriate level of IRB review or exempt determination for your study before you prepare your application. Submitting your application for the wrong level of review can waste valuable time. Consider **consultation with MHC IRB** office staff to discuss the process.
   - Be sure to answer all questions on the form and provide clear and consistent responses throughout the submission. It is imperative to check for consistency throughout your written narrative and all appendices before submitting your application to the IRB. Common areas of inconsistencies include but are not limited to study duration, study end date, number of subjects, compensation amounts etc.
   - Be realistic with your enrollment size, feasibility of study, resources (financial, staffing, physical space, materials needed, etc), amount of time the study will take, use of vulnerable populations, etc.
   - Proofread your submission thoroughly for spelling errors, clarity, grammatical errors, and missing details. If possible, have someone else proofread your submission.
   - **Do not forget** to include any required appendices with your submission. These may include recruitment materials, flyers, consent forms, required department approval letters, any waiver request documents, letters of Support from external institutions/departments, all data collection instruments, surveys and questionnaires, etc.
   - The Data Confidentiality sections of both the narrative and the consent form(s) often receive the most comments requiring revisions. Be specific about your plans for data collection, storage, maintenance, and destruction, and convey this information consistently throughout the application.
   - Recruitment materials that will be read/received by participants should be written concisely with relevant information that anyone can understand (10th Grade level) and should be tailored to your targeted research population (i.e., this language will read differently for adults with full capacity to consent vs. vulnerable populations; etc.).

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Several issues slow down the IRB approval process like incomplete applications or failure to respond promptly to IRB requests (stipulations) for additional information needed for review. A key factor in slow IRB turnaround is when protocols must go back and forth multiple times between the IRB and investigators.

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GATEKEEPERS WORKING TOGETHER

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– All informed consent documents must follow the format provided in the **Informed Consent templates on the IRIS website**. Applications with informed consent that do not follow this format will be returned to the PI. Ask colleagues to share recently IRB-approved consent forms as a reference for your forms.

– Write using simple lay language and well-described concepts. Be sure to define scientific and clinical terminology. Separate research procedures from routine clinical care. Use the "Background and Purpose" section to provide the clinical context for your study.

– Know the submission deadlines for the next IRB meeting.

– Student applicants should work closely with their Academic advisor while preparing their IRB submission. Please be sure to have your Academic advisor review your final application before submitting it to the IRB.

– New Researchers - The IRB recommends that PI's who are new to the IRB submission process at McLaren Healthcare reach out to someone in their field who is familiar with the process for review of their application before submission. New researchers are also encouraged to reach out to IRB consultants for assistance while preparing their applications.

Finally, IRB is Your Ally, not a Roadblock!

Foster a constructive relationship and communication between an Institutional Review Board (IRB) and the Research Team

– Develop positive relationships with IRB staff and board members.

– Demonstrate expertise by showing confidence and knowledge about the research by describing relevant experiences in written materials and in-person interactions.

– Follow the IRB's rules and make the process as smooth as possible for IRB staff and board members.

– Seek IRB advice! Call the IRB with questions. It's faster to have a phone conversation with the IRB about application questions than to respond to requests for clarification later. Link: **https://www.mclaren.org/main/irb-consultations**

Resources

***IRB Consultations**

New to MHC? First time submitter to the MHC IRB via iRIS? Have a question? The Research Integrity/ Office of Research Protections offers consultations with researchers. Consultations provide an opportunity for researchers to meet on Microsoft Teams with an experienced IRB staff reviewer. The purpose is to provide education and guidance to research teams prior to submission of IRB applications, or before making major changes to IRB-approved studies. Getting help pre-submission may shorten review time and spare you unnecessary confusion. Consultations are available upon request for any type of study, but we especially recommend them for:

- Researchers new to the IRB review process who would like additional guidance before submitting their first IRB application.
- Study teams planning multi-site or complex projects.
- Study teams considering making major changes to IRB-approved studies.

Submit a Consultation Request Form

https://www.mclaren.org/main/irb-consultations

****Submitting a New Application**

https://www.mclaren.org/main/research-guidance-documents

BLOCKING SPECIFIC TYPE OF T CELL IMPAIRS TUMOR GROWTH

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and Alexander Borowsky, M.D., of the University of California UC Davis also contributed to the research.

This study was supported by NIH NCI T32 grant CA009531 (Justin Hackett), the Elsa U. Pardee Foundation (Heather Gibson), the Center for Genomic Pathology at UC Davis (Alexander Borowsky), NCI U01CA196406 (Alexander Borowsky), DOD PCRP grant PC140122 (Eric Sebzda, Luc Van Kaer), NCI P30-CA022453 (Gregory Dyson, Eric Sebzda) and American Cancer Society grant DBG-23-103670-01-IBCD (Eric Sebzda). The Microscopy, Imaging and Cytometric Resources Core is supported by National Institutes of Health Center grants P30 CA22453 and R50 CA251068-01.

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NEW STUDY SEEKS TO DEVELOP NEW TREATMENT STRATEGY

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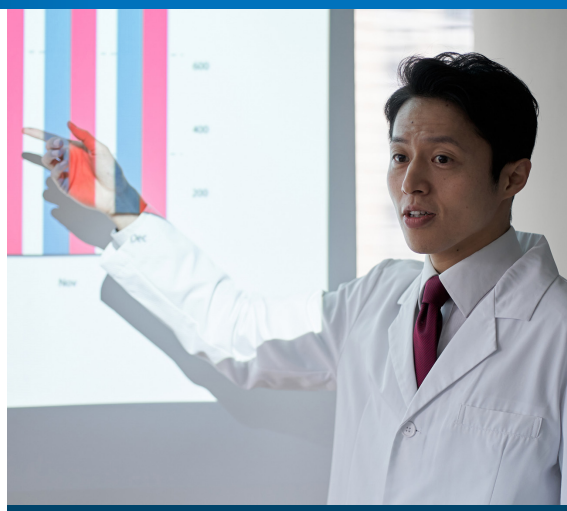
delay ML-DS relapse, which should prolong ML-DS patient survival.

“There are very few people looking at children with DS and leukemia,” said Dr. Taub. “From a pharmacology standpoint, some of our work has focused on asking what it is about DS –where these individuals who have three copies instead of two copies of chromosome 21 – that might be affecting how leukemia functions in their bodies. We are seeing if proteins are being produced as a result of how that gene is being expressed at higher levels. We want to continue to find out why some patients respond well to treatment and to see if there are any new interventions we can perform in the subset of patients who tend to relapse in their leukemia. Are there new strategies we can try from the very beginning that could prevent that relapsing or stop patients who are currently relapsing?”

“DS people are a vulnerable population,” said Dr. Ge. “What we are doing is focusing on children with DS who have myeloid leukemia. Children with DS have a significant chance of contracting the disease, but they also have higher chances of beating it. Some among them have a higher chance of the myeloid leukemia relapsing. Once it relapses, it is often too late to get the patient back into remission. We want to prevent or delay the reoccurrence of the disease.”

The award number for this grant from the National Cancer Institute of the National Institutes of Health is 1R01CA290480.

Originally Published at Today@Wayne.



UPCOMING RESEARCH EDUCATION

MHC Research Integrity Brown Bag session
Test your knowledge! (Research Jeopardy)
Thursday, November 21, 2024
12:00 pm - 1:00 pm

Speaker:
Susmita Jain, MS
Research Compliance and Education Specialist
at McLaren Health Care

To register email:
susmita.jain@mclaren.org

AAHRPP
Resources for Engaging Community Research Partners:
The Certification Training Program
November 12, 2024
1:00 pm - 2:30 pm

To register follow the link:
https://web.cvent.com/event/6e767030-1b73-47ef-86fb-60e0fa51fac5/regProcessStep1

Ask AAHRPP December 2024 Webinar
Maintaining Accreditation
December 10, 2024
3:00 pm

To register follow the link:
https://us06web.zoom.us/webinar/register/WN_Z2DbyDYOQ0yhAUBIXccjXQ#/registration

FACULTY, FELLOWS & RESIDENTS

SCHOLARLY ACTIVITY NEWS

USMLE STEP 3:

BIOSTATISTICS AND EPIDEMIOLOGY/POPULATION HEALTH AND INTERPRETATION OF THE MEDICAL LITERATURE (REVISITED)

By Carlos F. Rios-Bedoya, ScD, MPH

Carlos F. Rios-Bedoya, ScD

The United States Medical Licensing Examination (USMLE) Step 3 has come back to the forefront of discussions and conversations during Graduate Medical Education Committee meetings. Currently, McLaren requires that residents must pass Step 3 no later than December of the second year of residency training. One content area that most residents are not expecting is the Biostatistics & Epidemiology/Population Health & Interpretation of the Medical Literature and the format of its questions. Some McLaren residents who have taken Step 3 have made comments regarding how "horrible" and how many of these questions the exam had (20%-29% per USMLE website) which could make the difference between passing or not the exam. Given that this knowledge area is not a clinical one, not only most residents are unused to the content of the questions but also their format. In this edition of *Research Matters*, I will provide examples of three different types of questions commonly found in Step 3 about these topics using information from a publicly available practice exam found in the USMLE website. The objective is for residents to become familiar with these types of questions, and their format, and decrease the chances of getting blindsided by them.

The first type of question is about epidemiology/ biostatistics and follows a usual format.

A study is being conducted to assess mesothelioma in shipyard workers. A large shipyard firm has provided asbestos exposure records of all employees during the past 50 years. The health insurer for the workers has provided claims data that documents all chest x-rays and diagnoses of mesothelioma among current workers and retirees. The study enrolled shipyard workers who were diagnosed with mesothelioma and shipyard workers who were not diagnosed with mesothelioma. All subjects in the study had to have chest x-rays. Which of the following is the best rationale for selecting a comparison group that had chest x-rays?

A. Address confounding
B. Demonstrate causality
C. Minimize ascertainment bias
D. Reduce recall bias

There is not much unusual but the subject matter. Knowledge and understanding of these concepts are needed to correctly choose the right answer (C).

The next type of question deals with the interpretation of the medical literature. For this purpose, the USMLE provides an abstract of a published article follow by 2-3 questions about the abstract.

Question

In patients with cirrhosis and acute bleeding esophageal varices, how do endoscopic sclerotherapy and emergency portacaval shunt compare for control of bleeding and survival?

Methods

Design: Randomized controlled trial (San Diego Bleeding Esophageal Varices Study). ClinicalTrials.gov NCT00690027.

Allocation: Concealed.

Blinding: Blinded (gastroenterologist who evaluated patients for portal-systemic encephalopathy).

Follow-up period: Up to 17 years.

Setting: University of California San Diego Medical Center.

Patients: 211 patients (mean age 49 years, 77% men) with acute bleeding esophageal varices resulting from cirrhosis, who required a transfusion of ≥ 2 units of blood and, for patients transferred from other hospitals, observation of upper gastrointestinal bleeding within 48 hours of transfer. Exclusion criterion was > 1 previous session of endoscopic sclerotherapy.

Intervention: Endoscopic sclerotherapy (n = 106) or emergency portacaval shunt (n = 105). Emergency portacaval shunt comprised a direct side-to-side or direct end-to-side portacaval shunt done within 8 hours of initial contact.

Outcomes: Control of bleeding at > 30 days, survival, readmissions for variceal or nonvariceal bleeding requiring transfusion of packed red blood cells, and recurrent portal-systemic encephalopathy.

Patient follow-up: 100% (minimum follow-up until death or 9.4 years).

Main results: 15-year survival was lower with endoscopic sclerotherapy than with emergency portacaval shunt (10/106 vs 48/105, relative benefit reduction 79%, 95% CI 62 to 89; number needed to harm 3, CI 2 to 4). Other main results are shown in the Table.

Conclusion: In patients with cirrhosis and acute bleeding esophageal varices, emergency portacaval shunt was better than endoscopic sclerotherapy for control of bleeding, recurrent encephalopathy, and survival.

Endoscopic sclerotherapy (EST) vs. emergency portacaval shunt (EPCS) in patients with cirrhosis and acute bleeding esophageal varices

Outcomes	Child-Pugh Risk Class	EST	EPCS	P Value
Control of bleeding at > 30 days*		20%	100%	<.001
Median survival (years)	A	4.62	10.43	.003
	B	2.61	6.19	<.001
	C	0.58	5.30	.005
Mean number of readmissions for variceal bleeding requiring packed red blood cell transfusion		6.8	0.4	<.001
Recurrent portal-systemic encephalopathy†		35%	15%	.001

** Excluding indeterminate deaths at 14 days from nonbleeding causes.*
† In patients who survived 30 days and left hospital

A 52-year-old man with hepatic cirrhosis comes to the emergency department because of a 3-hour history of vomiting blood. Esophagogastroduodenoscopy confirms actively bleeding esophageal varices. Based on the abstract shown, the physician is considering an emergency portacaval shunt (EPCS) procedure rather than endoscopic sclerotherapy (EST). According to the results in the abstract, approximately how many patients must be treated with EPCS rather than EST to prevent one case of recurrent portal-systemic encephalopathy?

A. 1
B. 3
C. 5
D. 10
E. 16

Which of the following most strongly limits the generalizability of this study's findings?

A. The allocation was concealed
B. EPCS is available only at specialty centers
C. The follow-0up period was too short
D. The patients were not blinded
E. Unmeasured confounders were not controlled by the study design

Which of the following conclusions is most appropriate based on the results presented in the table?

A. The 95% confidence interval for the difference in survival between EPCS and EST for Child-Pugh class A patients includes 0 years
B. EPCS is more effective than EST in decreasing hospital readmissions for variceal bleeding requiring transfusion
C. The median survival after EPCS is statistically significantly less for Child-Pugh class C than for Child-Pugh class B
D. The randomization procedure was ineffective in decreasing bias in this study

This type of question requires you to read the abstract very quickly and answer the three questions that followed. The first question needs to calculate the number needed to treat. The second question deals with generalizability issues in the abstract. Finally, the third question asks for interpretation of data in the table.

The third type of question commonly found in Step 3 is pharmaceutical ads and clinical and research inferences that can be made based on the information presented in the ad.

An example of a pharma ad is presented next, followed by two questions related to the pharma ad. The pharma ad contains indications, dosage, warnings, side effects, contraindications, and research results. The first question asks about whether the medication should be prescribed to the patient described in the vignette. The second question asks to evaluate and interpret the graph in the ad showing the findings of a randomized control trial for the drug. Again, in this type of question, it is needed to read an "external" source of information before proceeding to answer the actual question. In addition, clinical and non-clinical knowledge is evaluated through these pharma ads. In summary, these different types of questions are trying to evaluate from exam takers their higher-level thinking process in a way residents might not be used to.

CONTINUED ON PAGE 28

Well-Tolerated at All Doses with Low Rate of Side Effects

Percentage of Adverse Events by Dose, Occurring More Frequently in Essepro™ than Placebo Patients, and in ≤1% of Patients

Adverse Event	Placebo n = 208 %	Essepro 1 mg n = 451 %	Essepro 2.5 mg n = 464 %	Essepro 5 mg n = 622 %
Dizziness	2	6	5	8
Headache	1	5	7	6
Fatigue	1	2	3	3
Nausea	1	0	2	2
Dyspnea	0	1	1	1
Chest Pain	1	0	2	1
Peripheral Edema	1	1	0	2
Bradycardia	0	2	0	1
Rash	0	0	1	1

Pooled date from three US and European phase II, 2-month, randomized, double-blind, placebo-controlled studies of Essepro in the treatment of mild to moderate hypertension (N = 2043, n = 1052).

Most side effects were mild and did not require discontinuation of Essepro[1]

- Most adverse events were assessed as mild by investigators and treatment was continued[1]
- Few patients discontinued treatment due to adverse events. 2.0% for Essepro vs. 2.1% for placebo[1]

No significant interactions with commonly used medications were observed[1]

- No significant interactions with hydro_____
- No significant interactions with hydro_____
- No significant interactions with hydro_____.

Important Safety Information

Patients treated with Essepro should be advised against sudden discontinuation of therapy. When discontinuing therapy, dosage should be gradually tapered over 2 weeks.

Essepro is contraindicated in patients with bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, severe hepatic impairment, and in patients who are hypersensitive to any component of this product.

Essepro should be used with caution in patients with peripheral vascular disease, renal impairment or thyrotoxicosis. Caution should be used in diabetics, as beta blockers may mask some manifestations of hypoglycemia.

In general, patients with bronchospastic disease should not receive beta blockers.

The Division of Scholarly Inquiry's goal of providing the best possible training and education experience is available to hold virtual training sessions on practicing for Step 3. For more information or to schedule a training session contact Dr. Carlos F. Ríos-Bedoya at **carlos.rios@mclaren.org**.

A 65-year-old woman comes to the office for blood pressure medication management. Medical history is significant for poorly controlled hypertension, psoriasis, and psoriatic arthritis previously treated with methotrexate. Additional medical history is significant for alcohol use disorder and elevated liver function tests. Medications include enalapril, spironolactone, and topical corticosteroids. Vital signs are normal except for a blood pressure of 160/104 mmHG. Physical examination discloses thick, scaly plaques on the scalp, buttocks, and upper and lower extremities. There are several spider antiomata on the chest and abdomen. The abdomen is distended and a fluid wave is noted. She has 2+ lower extremity edema. The patient says she would like to try a new drug called Essepro to treat her hypertension because she can get a 3-month supply of the medication for free.

Which of the following is the most appropriate response to the patient's request for the medication?

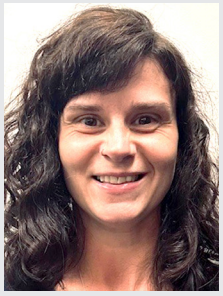
A. Essepro should be prescribed because she can get it for free
B. Essepro should not be prescribed because it can worsen her psoriasis
C. Essepro should not be prescribed because it is similar to her other medications
D. Essepro should not be prescribed because the patient has severe liver disease
E. Essepro should only be used for hypertensive emergencies

Which of the following interpretations can be made correctly from the graph on blood pressure reduction in the advertisement?

A. Blood pressure reduction from the three doses of Essepro cannot be compared to reduction with placebo because the number of patients on active drugs are higher than the number of patients on placebo
B. Doubling the highest dose of Essepro will decrease diastolic pressure from baseline by at least 15 mmHg.
C. The highest dose of Essepro should be used because it offers the greatest benefit
D. There is no clinically important difference in blood pressure reduction between the three dose groups
E. The significance of drug effect vs. placebo cannot be determined because of the low P value

ANNOUNCEMENTS AND WHAT'S NEW

We are pleased to announce **Janelle Haggerty**, Clinical Research Nurse, joined the Karmanos Cancer Institute Clinical Trials Office on July 29, 2024. Janelle obtained an Associate of Applied Science in Nursing from Kirtland Community College and a Bachelor of Science in Nursing from Chamberlain University. Janelle is providing clinical research support at Karmanos Cancer Institute at McLaren Northern Michigan. Welcome Janelle!



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