RESEARCH *Matters*

Spring 2024

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

McLaren

RESEARCH AROUND McLAREN

ANCHOR ASTHMA CLINICAL TRIAL

McLaren Health Care is excited to announce our health system is the first of three health systems in the nation to be selected to participate in a new clinical trial called ANCHOR: Assessment of Combination Short-Acting BroNchodilator and Inhaled Corticosteroid Rescue Therapy on Health Outcomes in Routine Care. The ANCHOR study is a prospective, Phase IV, single-arm, open label study to assess the effectiveness of AIRSUPRA on reducing asthma exacerbation, healthcare resource utilization and cost.

John Youssef, MD

In January 2023, AstraZeneca's AIRSUPRA Inhaler became the first and only rescue medication approved in the US for as-needed use to reduce risk of asthma exacerbations. This medication is designed to both routinely treat asthma symptoms and help prevent severe sudden breathing problems, "asthma attacks." AIRSUPRA is a first-in-class, pressurized metered-dose inhaler (pMDI) fixed-dose combination rescue medication containing albuterol and budesonide. A recent series of real-world observational studies have shown that prescription or possession of three or more short acting beta agonist (SABA) canisters per year has consistently been associated with increased exacerbation and mortality risk, and asthma-related health care resource utilization and costs. The ANCHOR study aims to add real-world evidence to the existing set of randomized clinical trial outcomes around inhaled corticosteroid/SABA combination asthma rescue therapy.

Dr. John Youssef, pulmonologist from McLaren Flint, will be serving as the Principal Investigator for the ANCHOR Study at McLaren Health Care. Enrollment is not limited to Flint. This study will include potential candidates from any McLaren provider across the system. "We are thrilled to offer study participation across the entire health system, this is a first for McLaren, and something we've been growing toward for many years," states Chandan Gupte, VP of Clinical Excellence and Research.

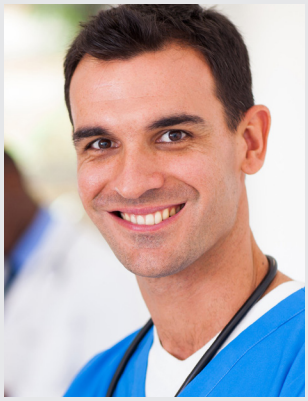
The ANCHOR study is not only unique in its wide-spread availability, but that the entirety of the patient's participation is performed virtually. Patients will not have to commit to additional travel for clinic visits or research specific testing as all study interactions will be via phone or email. According to Pam Wills-Mertz, Director of Corporate Research Administration, "Remote access to clinical trials is becoming more and more prevalent, McLaren is ready with the staffing and technology necessary to accommodate patients and sponsors in this accessible and convenient research experience."

AIRSUPRA®
(albuterol 90 mcg/budesonide 80 mcg)
Inhalation Aerosol

Eligible patients who consent to participate in the ANCHOR study will receive a prescription card that will allow them to fill their AIRSUPRA at no cost during the 12-month participation period. The study team will reach out to patients every three months via phone to gather study-related information. For clinics that have interest in offering this trial to their patients, a study specific liaison can come to their clinic and provide study material for clinicians and patients as well as answer questions about AIRSUPRA.

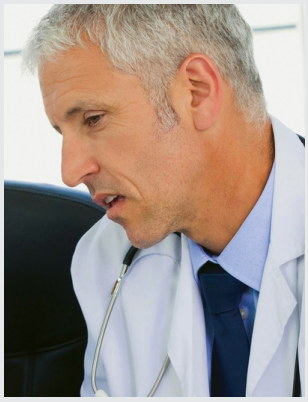
Clinicians can get more information or refer patients to the study team by calling **1-844-ANCHOR-0**, calling or texting **(248) 748-9971**, or emailing **ANCHOR@mclaren.org**.

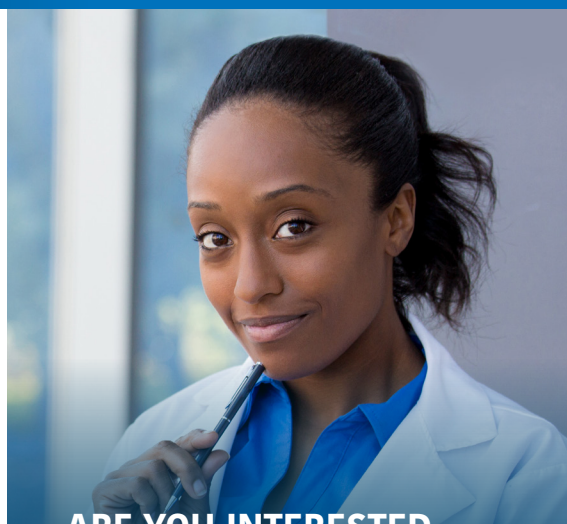
DO YOU HAVE A RESEARCH PROJECT THAT NEEDS FUNDING?



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 1, April 1, July 1, and October 1 of each year.

The application process can be accessed at **mclaren.org/fundingapplication**. Required information for the application includes a detailed description of the research project, as well as a proposed budget.





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

McLAREN NEUROSCIENCE RESEARCH UPDATE

Neuroscience has been a rapidly expanding research therapeutic area in recent years. Our investigators have been honored to participate in many pivotal clinical trials. Three of those trials have released results that we wish to share with the research community.

Aniel Majjhoo, MD and Marci Roberts

Recently, the *Journal of the American Medical Association* (JAMA) featured an article that outlines the results of one of these studies. The ARCADIA randomized clinical trial studied whether anticoagulation (apixaban) is superior to antiplatelet therapy (aspirin) in preventing recurrent strokes in patients with cryptogenic stroke and evidence of atrial cardiopathy. The results of this study show no significant decline in the rate of stroke between the patients receiving anticoagulation and those receiving antiplatelet therapy. Despite not producing a positive result, this trial answered an important question and solidified the standard of care for cryptogenic stroke patients. The ARCADIA trial was open at McLaren Flint under the direction of Dr. Aniel Majjhoo, at McLaren Macomb under the direction of Dr. Mahmoud Rayes, and at McLaren Northern Michigan under the direction of Dr. Karl Meisel. To read more about the trial results, please visit **https://jamanetwork.com/journals/jama/fullarticle/2814933**.

An additional study that produced recent results was MOST. This was a randomized trial that tested the efficacy of tPA alone, tPA with argatroban and tPA with eptifibatide in improving outcomes in acute ischemic stroke patients. This was a complex trial that required a great deal of excellent timing and teamwork as the study drug was required to be administered within 3 hours of stroke onset and one hour of initiation of tPA. This trial was open at McLaren Flint under the direction of Dr. Majjhoo. Unfortunately, there was no increase

Neuroscience has been a rapidly expanding research therapeutic area in recent years. Our investigators have been honored to participate in many pivotal clinical trials.

in outcomes in study participants. According to Dr. Majjhoo, "500 patients were enrolled in the study and there was only a 0.2% chance of argatroban and 0.9% chance of eptifibatide improving outcomes. On a positive note, McLaren was recognized as an honorable mention for our strong enrollment in this valuable trial."

Finally, the EMBOLISE trial has released results from one arm of the trial at the International Stroke Conference. EMBOLISE is open and enrolling at McLaren Flint under the direction of Dr. Majjhoo. This study is designed to determine if use of the ONYX™ Liquid Embolic System to embolize the middle meningeal artery (MMA) with or without surgical intervention or surgical intervention alone improves outcomes in patients with subdural hematoma. Surgical interventions include both burr hole evacuation and craniotomy. MMA embolization with ONYX ™ led to a three-fold reduction in recurrences requiring surgical drainage compared to surgery alone. These results are considered a "game-changer" according to Dr. Majjhoo. To read more about these findings, please visit **https://www.tctmd.com/news/landmark-moment-middle-meningeal-artery-embolization-subdural-hematoma**.

We look forward to continuing to bring pivotal neuroscience research to our patients at McLaren. If you are interested in learning more, please email **MCRI@mclaren.org**.

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

RESEARCH AROUND McLAREN

$1.4 MILLION AWARDED TO KARMANOS

WSU RESEARCHER TO EXPAND FINDINGS SURROUNDING PROSTATE CANCER

A team of researchers at the Barbara Ann Karmanos Cancer Institute and Wayne State University (WSU) were awarded a $1.4 million, three-year grant from the U.S. Department of Defense for the study, "Cytochrome c acetylation drives prostate cancer aggressiveness and Warburg effect."

Maik Hüttemann, PhD

The study, led by Maik Hüttemann, PhD, Tumor Biology and Microenvironment (TBM) Research Program member at Karmanos, professor of Molecular Medicine and Genetics, and Biochemistry, Microbiology and Immunology at WSU's School of Medicine, aims to establish the role of the protein cytochrome c, which the team proposes is central in two hallmarks of cancer: switching from aerobic to glycolytic metabolism – also known as the Warburg effect – and evasion of apoptosis.

In the past decade, diagnoses of prostate cancer increased from 3.9% to 8.2%, with African American men having the highest incidence and mortality rates of the disease compared to White, Hispanic and Asian men. Cytochrome c was previously suggested to be a molecular determinant of prostate cancer health disparities, and this study will further explore that hypothesis. The research team proposes that cytochrome c transitions from a non-acetylated form in a normal prostate to a K53-acetylated cytochrome c in cancer.

"What we are proposing is that this transition causes switching from aerobic metabolism to Warburg metabolism because the modification renders cytochrome c less effective in transferring electrons in the electron transport chain, and at the same time making it incapable of triggering apoptosis," Dr. Hüttemann said. "Warburg and evasion of apoptosis are two key features of cancer cells. This funding from the Department of Defense will allow us to develop an antibody as a prognostic and diagnostic tool and to mechanistically study the pathways leading to the acetylation of cytochrome c, with the ultimate goal of identifying novel therapeutic targets that could result in developing a drug to overcome treatment resistance as a stand-alone or combination therapy."

Additional Karmanos research members collaborating on this project include Izabela Podgorski, PhD, TBM Research Program member, professor of Pharmacology; Elisabeth Heath, MD, FACP, medical oncologist, Genitourinary Oncology Multidisciplinary Team leader, associate center director of Translational Science, TBM Research Program member at Karmanos and professor of Oncology; and Seongho Kim, PhD, Molecular Therapeutics Research Program member at Karmanos and professor of Oncology. (The grant number for this U.S. Department of Defense grant is HT94252410073.)

Originally published at Today@Wayne.

STUDY INVESTIGATING BIOLOGICAL AGE AS FACTOR FOR CANCER TREATMENT THERAPY DECISIONS

RECEIVES $400K FROM U CAN-CER VIVE FOUNDATION

Suresh Balasubramanian, MD, and his team of investigators at the Barbara Ann Karmanos Cancer Institute have received a significant gift from the U CAN-CER-VIVE Foundation. The organization awarded the team a $405,315 grant for their continued research, titled "Biological Aging and Mutational/Immunological Signatures as Prognostic and Predictive Biomarkers for Treatment of Hematological Malignancies."

Suresh Balasubramanian, MD

"Receiving such generous backing from the U CAN-CER VIVE foundation is truly significant," said Dr. Balasubramanian, hematologist, medical oncologist, member of the Hematology Oncology and Multiple Myeloma and Amyloidosis Multidisciplinary Teams, and Molecular Therapeutics (MT) Research Program member at Karmanos. "This grant will enable us to employ the latest scientific techniques to finetune and validate a new biomarker in different clinical settings, which has the potential to transform the care of our patients."

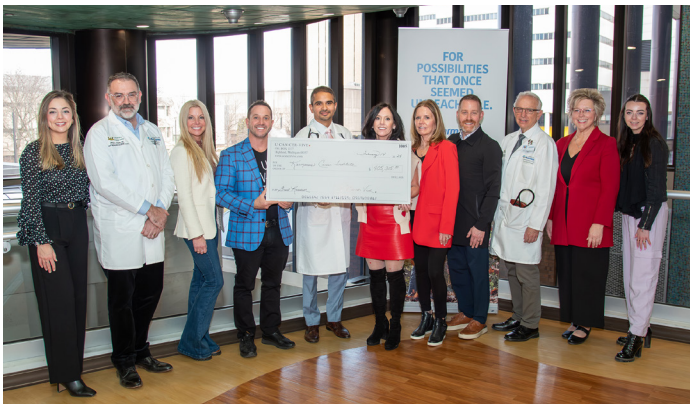
Dr. Balasubramanian and his team of investigators are exploring the idea of estimating biological age as a better surrogate to determine treatment decisions for certain cancers as opposed to chronological age. Chronological age takes into account the number of birthdays a patient has, whereas biological age would help consider various changes that happen in a patient's body at the tiny level of cells and their parts.

"Changes at the cellular level can be DNA damage, cells getting old and stopping to divide, adjustments to how genes work that don't involve changes in the actual DNA code, cells losing their ability to produce energy efficiently, and changes in how our immune system works and how our body handles energy and nutrition as we get older. Many of these changes can make a person susceptible to cancer," explained Dr. Balasubramanian.

His team is specifically looking at DNA methylation, which is a small chemical modification that occurs in DNA. According to Dr. Balasubramanian, these changes are predictable as we age and can be measured using advanced machine-learning tools to estimate their biological age.

"We plan to study this biological age and epigenetic age acceleration further in unique clinical settings, like how biological age would influence the outcomes in allogenic transplant recipient patients and various myeloid malignancies and be used as a biomarker for response in a multiple myeloma clinical trial. Additionally, we are also looking at whether biological age has any role in the racial disparity of cancer outcomes," said Dr. Balasubramanian.

"We also envision incorporating biological age as a standard of care for cancer treatment. In the future, we expect to expand the input into the machine learning tool to include additional aspects of cellular aging, not limited to just DNA methylation, to estimate the biological age."



Dr. Balasubramanian is collaborating on this research with co-investigators Joseph Uberti, MD, PhD, hematologist and medical oncologist, Bone Marrow and Stem Cell Transplant MDT leader, and Tumor Biology and Microenvironment Research Program member, and Jeffrey Zonder, MD, hematologist, Multiple Myeloma and Amyloidosis MDT leader, Hematology Oncology MDT member and the MT Research Program member.

ALSO READ:
Precision Medicine Research at Karmanos
Comparing Biomarker Predictions for African American, Middle Eastern Breast Cancer Patients Receives $16K Boost at **karmanos.org/hcp**.

RESEARCH AROUND McLAREN

NEW WSU RESEARCH PROGRAM LED BY KARMANOS RESEARCHER

ADDRESSING DIVERSE DISEASES, INCLUDING TREATMENT-RESISTANT CANCERS

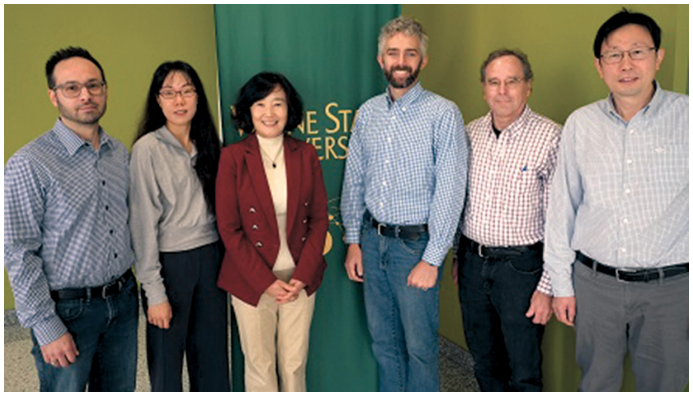
A Karmanos Cancer Institute researcher is leading cancer studies funded by a new program.

The Barber Integrative Metabolic Research Program was established at Wayne State University (WSU) School of Medicine thanks to an initial funding commitment of $1 million from the Barber Research Fund. The program is built on groundbreaking research that has identified a novel molecular target for treating metabolic diseases and treatment-resistant cancers.

The research, led by James Granneman, PhD, member of the Tumor Biology and Microenvironment (TBM) Research Program at Karmanos, professor of Molecular Medicine and Genetics in the Center for Molecular Medicine and Genetics, and of Internal Medicine in the WSU School of Medicine, and Christopher Kelly, PhD, associate professor of Physics and Astronomy in the College of Liberal Arts and Sciences, focuses on understanding the intricacies of cellular lipid metabolism. Imbalances in lipid metabolism are linked to the progression of catastrophic diseases, including diabetes, fatty liver disease and cancer.

The team has discovered that a key regulator of lipid metabolism, the protein ABHD5, can be targeted by natural and synthetic chemicals to regulate metabolism. Through medicinal chemistry, the team has developed a panel of potent ABHD5 activators and inhibitors that will be used to unravel the fundamental mechanisms of lipid metabolic control, including pathways that contribute to metabolic diseases and cancer. The project's long-term goal is to develop new therapeutic entities for treatment-resistant diseases.

The program comprises three integrated arms, each led by distinguished researchers, including Dr. Granneman and Emilio Mottillo, PhD, associate scientist, Henry Ford Health, who will investigate cellular responses to



synthetic activators and inhibitors in liver and fat cells; Karmanos TBM Research members Hyeong-Reh Kim, PhD, professor of Pathology, and Jian Wang, PhD, associate professor of Pathology, who aim to develop ABHD5 ligands into new therapeutic entities for treating fatty liver disease and treatment-resistant cancers; and Dr. Kelly and Y. Mindy Huang, PhD, assistant professor of Physics and Astronomy, who will focus on the structural and biophysical bases of ABHD5 action.

"The Barber Integrative Metabolic Research Program is currently supported by two NIH and DoD grants, and the additional funding from the Barber Research Fund will further enhance critical integration within the team," Dr. Granneman noted. "This collaborative effort is poised to make significant strides in metabolic research and advance innovative treatments for associated diseases."

"This program integrates researchers from across our campus to develop solutions to serious problems faced by many," said Timothy Stemmler, PhD. "Faculty from Wayne State University's College of Liberal Arts and Sciences, School of Medicine, the Division of Research… will assemble in our Integrative Biosciences Building (IBio) as a demonstration of the importance of interdisciplinary collaboration. The goal of IBio is to coordinate research teams and programmatic initiatives to tackle critical urban challenges across a spectrum of disciplines, and this research is an excellent example of how our researchers are coming together to make a significant impact locally and globally."

Originally published at Today@Wayne.

ALSO READ:
More Than $3 Million Granted to Karmanos Researcher's Lab to Combat Therapy-resistant Cancers at **karmanos.org/hcp**.

DETROIT RESEARCH TEAM TO DEVELOP NOVEL STRATEGIES TO IDENTIFY GENETIC CONTRIBUTIONS TO CANCER RISK

OVERCOMING BARRIERS TO GENETIC TESTING FOR AFRICAN AMERICANS

A team of researchers from the Barbara Ann Karmanos Cancer Institute and Wayne State University has received a five-year, $9.6 million grant from the National Cancer Institute of the National Institutes of Health for the study "Genetic Variation in Cancer Risk and Outcomes in African Americans." This is a Program Project Grant that includes three large studies. The team will work to improve the identification and clinical management of hereditary and multiple primary cancers in African Americans, a population that is currently underrepresented in genetic research.

Ann Schwartz, PhD

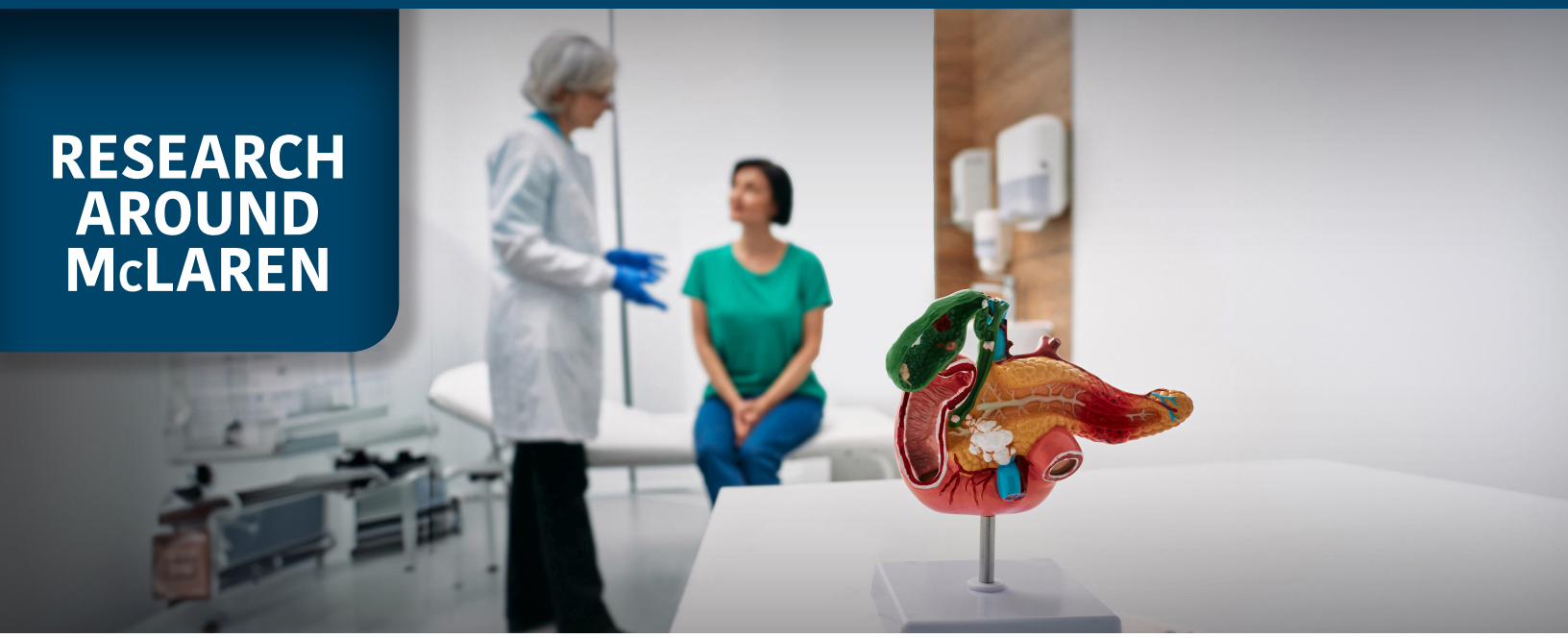
According to Ann Schwartz, PhD, principal investigator of the project, vice president and deputy director of Research and Academic Affairs at Karmanos Cancer Institute, and professor and associate chair of Oncology at the Wayne State University (WSU) School of Medicine, genetic testing has identified high-risk populations for targeted prevention and screening, identified targets for new treatment strategies, and has led to some of the most significant inroads in reducing cancer burden. Jennifer Beebe-Dimmer, PhD, MPH, is the co-principal investigator on this award and is the scientific director of the Epidemiology Research Core, leader of the Population Studies and Disparities Research Program at Karmanos, and a professor of oncology at WSU School of Medicine.

CONTINUED ON PAGE 11

The team will work to improve the identification and clinical management of hereditary and multiple primary cancers in African Americans.

ALSO READ:
Research Program Leader, Mentee Receive Supplement Award to Explore Financial Toxicity Burden of Black Adolescent, Young Adult Cancer Patients Compared to White at **karmanos.org/hcp**.

RESEARCH AROUND McLAREN



LATEST CUTTING-EDGE TECHNOLOGY, DIGITAL SPATIAL PROFILING

HELPING KARMANOS INVESTIGATORS UNDERSTAND SELINEXOR'S MECHANISM OF ACTION FOR PANCREATIC CANCER

A recently published study led by researchers at the Barbara Ann Karmanos Cancer Institute investigates the molecular mechanism of action of Selinexor in pancreatic ductal adenocarcinoma and the tumor's surrounding microenvironment. Asfar Azmi, PhD, Molecular Therapeutics (MT) Research Program Leader and Pancreas Cancer Research Director at Karmanos, guided this study titled "Molecular analysis of XPO1 inhibitor and gemcitabine-nab-paclitaxel combination in KPC pancreatic cancer mouse model," published in Clinical and Translational Medicine in December 2023. Md. Hafiz Uddin, PhD, MT Research Program member, was the first author.

Asfar Azmi, PhD

Pancreatic cancer can be deadly because the tumor and the microenvironment work collectively to maintain growth and promote drug resistance, meaning most patients experience disease progression. Researchers at Karmanos have been studying the drug Selinexor for quite some time. Earlier studies from Dr. Azmi's group showed that pancreatic cancer cells have excessive protein export signaling, causing the tumor suppressor proteins to mislocate leading to uncontrolled cell growth. Selinexor blocks nuclear protein transport to retain good proteins in the correct compartment of cancer cells, thus killing tumor cells.

"Our team used spatial transcriptomics and spatial proteomics to investigate anti-tumor changes by Selinexor in pancreatic cancer cells and stromal cells using the gold standard, KRAS-p53-Cre (KPC) model," explained Dr. Uddin. "The KPC mice model replicates the human disease with the same amount of high stroma surrounding the tumors. In return, we learned that Selinexor causes a broad penetration in the pancreatic tumor and stroma supporting pathway in KPC tumors."

Karmanos investigators identified a key molecule called Chitinase-3 like-protein-1 (CHIL3), which was downregulated in both cancer and stromal cells. The publication also includes other traditional techniques, such as single nuclear RNA sequencing.

Md. Hafiz Uddin, PhD

"Digital spatial profiling is a powerful new technology that gives us much deeper insight into the molecular changes happening

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DETROIT RESEARCH TEAM

CONTINUED FROM PAGE 9

"We have assembled one of the largest populations of African American cancer survivors to date in a study called Detroit Research on Cancer Survivors – or ROCS – to now study genetic susceptibility and genetic testing in this population," said Dr. Schwartz. "Our overall goal for this new project is to improve the identification and clinical management of hereditary and multiple primary cancers in African Americans."

Jennifer Beebe-Dimmer, PhD

While genetic testing to date has made a great impact on identifying high-risk populations for targeted prevention, screening and treatment strategies, there is still much to learn about the role of inherited genetic susceptibility and cancer, especially in underrepresented populations. To date, most genetic studies have been conducted in largely non-Hispanic White populations with uncertain applicability to minority populations, limiting strides in early diagnosis and treatment that can result in increasing disparities in cancer incidence and mortality.

"While a number of penetrant cancer-susceptibility genes have been identified in African Americans, there is still a need to expand clinical testing in minority populations," said Dr. Schwartz.

Kristen Purrington, PhD, MPH, Karmanos and WSU, and Elena Stoffel, MD, MPH, University of Michigan, are leading a project to better understand contributions from variants of uncertain clinical significance that occur in the high-risk African American population.

Dr. Beebe-Dimmer and Kathleen Cooney, MD, Duke University, are leading a project to identify risk factors for multiple primary cancers.

According to Dr. Beebe-Dimmer, "If we can identify potentially modifiable risk factors that can partially mitigate genetic risk related to highly penetrant variants and understand their relationship to more common variants of low-penetrance, we may provide a pathway to improve cancer screening and prevention."

While the current genetic knowledge has improved over time, there are still significant barriers to accessing genetic counseling and testing services among African Americans. The third project, led by Felicity Harper, PhD, and Hayley Thompson, PhD, both at Karmanos and WSU, will lead to novel strategies to improve genetic testing in this population. (The grant number for this National Cancer Institute of the National Institutes of Health grant is NCI P01CA272239.)

"We have assembled one of the largest populations of African American cancer survivors to date in a study called Detroit Research on Cancer Survivors – or ROCS – to now study genetic susceptibility and genetic testing in this population."

– Ann Schwartz, PhD

RESEARCH AROUND McLAREN

KARMANOS RESEARCHERS REVEAL INSIGHTS INTO HUMAN DEVELOPMENT AND CANCER THROUGH TERATOMA-BASED EPIGENETIC MAPPING

Investigators from the Barbara Ann Karmanos Cancer Institute and Wayne State University (WSU) School of Medicine have advanced our understanding of human developmental processes by studying teratomas, tumors capable of mimicking various stages of human development.

Benjamin Kidder, PhD

This study, "Decoding the universal human chromatin landscape through teratoma-based profiling," published in Nucleic Acids Research in January 2024, leverages teratomas to explore the epigenetic and gene expression dynamics that underpin human development. Benjamin Kidder, PhD, the senior author and a member of the Tumor Biology and Microenvironment Research Program at Karmanos, has utilized the teratoma model to investigate developmental processes necessary to understand human cellular diversity. There are practical and ethical limitations to studying human development, so scientists always look for better models and methods.

"Employing teratomas to investigate human development and cancer biology can significantly enhance our understanding of cell fate decisions and tumor dynamics," said Dr. Kidder, who is also an assistant professor in the Department of Oncology at WSU School of Medicine.

"Employing teratomas to investigate human development and cancer biology can significantly enhance our understanding of cell fate decisions and tumor dynamics."

– Benjamin Kidder, PhD

Dr. Kidder's research focuses on epigenetic mechanisms of stem cell self-renewal and differentiation, transcriptional networks, genome stability and cancer epigenetics, and reprogramming and transdifferentiation.

The findings from the study are pivotal for understanding the mechanisms of cell differentiation and the formation of various cell types, which are essential for understanding and combating cancer. The study provides valuable resources for examining the relationships between histone modification patterns and gene activity, enhancing our understanding of epigenetic mechanisms that shape human development. This investigation is further enriched by including a single-cell multiome atlas, which combines gene expression and chromatin accessibility analyses. This research is particularly relevant to cancer studies, as it offers a deeper understanding of how teratomas, which can be benign or malignant, differentiate into a wide array of cell types. This differentiation mirrors the complexity of human tissues and provides a model for exploring the underlying causes of cancer development and progression.

"The insights from this study offer valuable tools for understanding how epigenetic changes influence gene activity, both at specific genes and across the entire genome," explained Dr. Kidder.

The promise of this research not only advances our knowledge of human developmental biology using teratomas but also significantly contributes to cancer research. Additionally, this study opens new avenues for understanding cancer development and identifying potential therapeutic targets.

"The results from this study create opportunities for cancer researchers and developmental biologists to better understand cell behavior in tissues and tumors, as well as gene regulation, offering insights that could lead to breakthroughs in how we approach cancer treatment and understand human development," concluded Dr. Kidder.

UPCOMING RESEARCH EDUCATION

MHC Research Integrity Brown Bag Session
The Intersection of Emerging Technologies and Research Ethics: Challenges and Opportunities
Tuesday, June 4, 2024
12:00 pm - 1:00 pm

Speaker:
Dr. Michael Zimmer
Professor & Vice Chair, Department of Computer Science
Marquette University

ACRP
ACRP 2024 is Where Clinical Researchers go for Inspiration, Education, and Connection.
Anaheim Marriott
May 3 - May 6, 2024

To register follow the link:
https://2024.acrpnet.org/

The Future of Home Health Care in Clinical Trials
May 22, 2024
12:00 pm - 1:00 pm

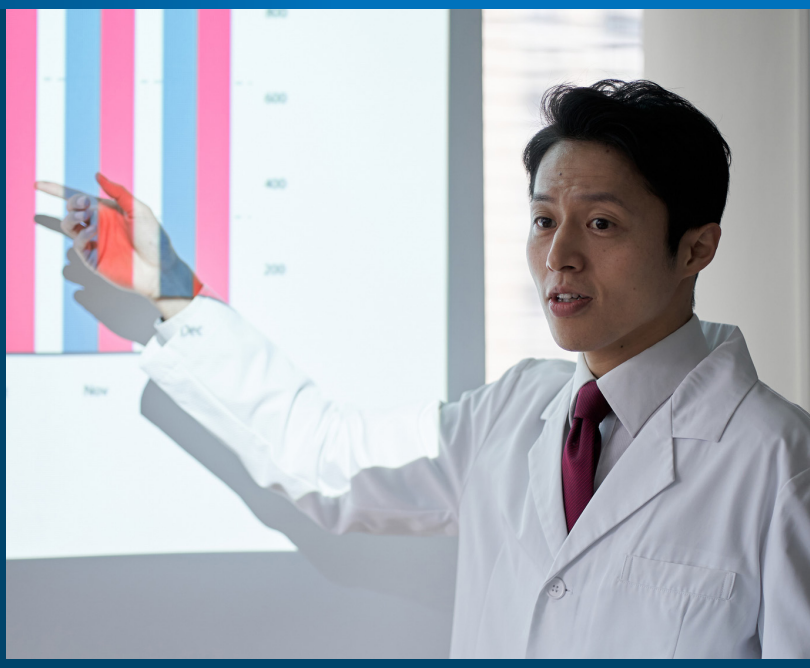
To register follow the link:
https://acrpnet.org/courses/the-future-of-home-health-care-in-clinical-trials/

From Conflict to Collaboration: Enhancing Site and Sponsor/CRO Relationships
June 12, 2024
12:00 pm - 1:00 pm

To register follow the link:
https://acrpnet.org/courses/from-conflict-to-collaboration-enhancing-site-and-sponsor-cro-relationships/

OHRP
Curating Connection Objectives:
Research Community Forum with University of Miami
April 10, 2024 - April 11, 2024
Coral Gables, FL

To register follow the link:
https://web.cvent.com/event/bfa81286-5b7f-45ec-8cb8-d8d83f9f0878/summary?i=VyFfJei_i0SVPkpBqjg9Lw&locale=en-US



SOCRA
17th Annual Device Research & Regulatory Conference
May 1 - 3, 2024
Nashville, TN

To register follow the link:
https://www.socra.org/conferences-and-education/training-conferences-workshops-courses/device-conference/program-information/

Protecting Human Research Participants: Legal, Ethical, and Practical Considerations
May 16 - 17, 2024
Scottsdale, AZ

To register follow the link:
https://www.socra.org/conferences-and-education/training-conferences-workshops-courses/protecting-human-research-participants-legal-ethical-and-practical-considerations/program-information/

PRIM&R
IRBs and Expanded Access: Ethical Considerations and Implementing FDA Guidance
Tuesday, June 18, 2024
1:00 pm - 2:30 pm

To register follow the link:
https://primr.org/programs/webinars/irbs-and-expanded-access

AAHRPP
2024 AAHRPP Annual Conference:
Science and Standards in San Diego
May 21 - 23, 2024
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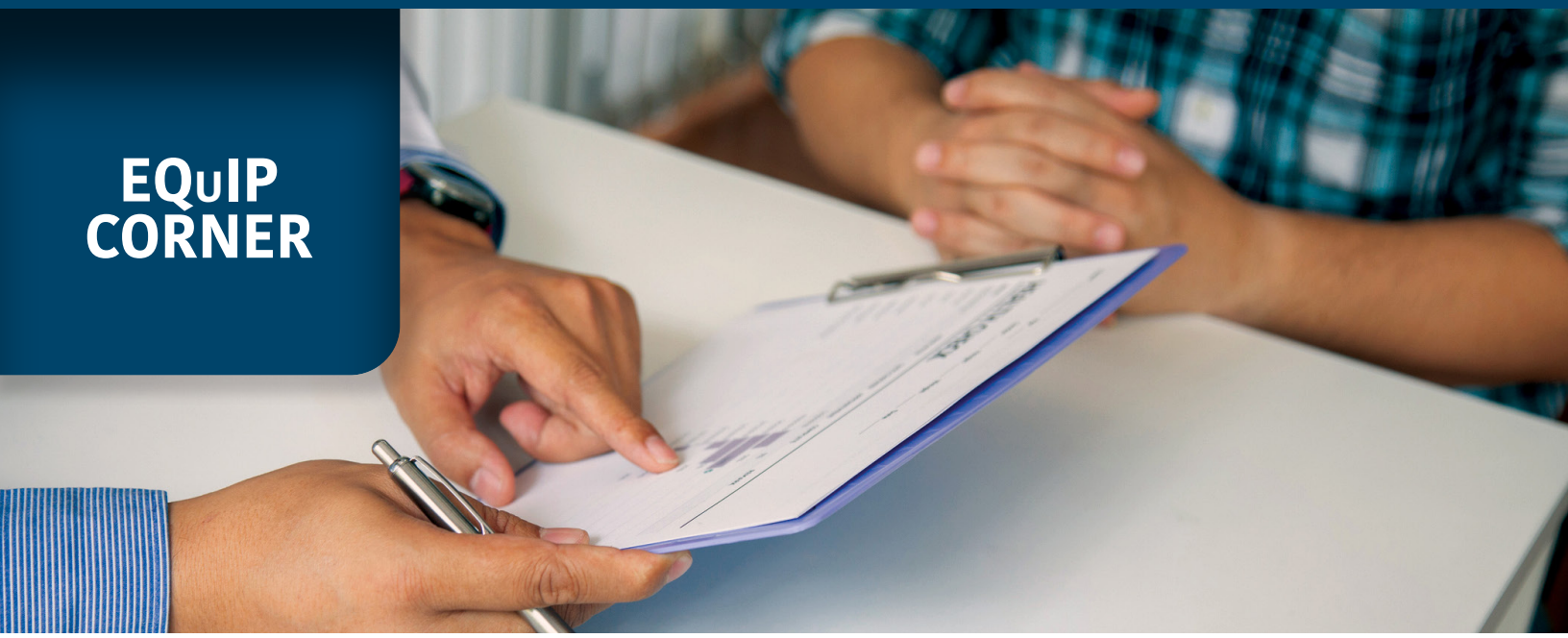

INFORMED CONSENT PROCESS

ENHANCING PARTICIPANT UNDERSTANDING

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

Introduction

The cornerstone of ethical clinical research is Informed Consent. Informed Consent is a process in which the prospective research participant must receive and comprehend information appropriately to make an autonomous decision. It is the principal investigator and study team member's ethical responsibility to disclose information to research participants and to ensure that the person has the capacity to reach a decision based on the information provided. Challenges affecting comprehension during the informed consent process can occur from a variety of factors including but not limited to the complexity of research, length of the consent form, cognitive ability, literacy, state of health, etc. The purpose of this article is to explore strategies to enhance understanding including more effective communication and assessing understanding.

Susmita Jain, MS

The process of informed consent can be challenging for a variety of reasons. These reasons may be related to the researcher, the prospective participant, or consent the document itself.

What makes an informed consent process meaningful?[1]

Meaningful informed consent includes the following four criteria: information disclosure, competence, comprehension, and voluntariness. If these criteria are met, the process can be described as complete, valid and meaningful.

- **Information disclosure** involves participants receiving all relevant information about the research, including purpose, benefits, risks, available alternatives, etc.
- **Comprehension** implies that participants understand all information provided to them.
- **Competence** refers to the participant's ability to make an informed decision regarding participation.
- **Voluntariness** means a participant's decision to participate in clinical trials without undue influence or coercion.

What can cause participants to fail to understand consent information?

The process of informed consent can be challenging for a variety of reasons. These reasons may be related to the researcher, the prospective participant, or the consent document itself. Any of which can lead to failure of comprehension. Examples are:

- Lack of time to go over the consent form.

- Lack of training of the research team on how to facilitate an effective informed consent discussion.
- Ineffective researcher-participant communication may result in not believing the person providing information.
- Participants feeling overwhelmed and anxious with the information provided.
- An individual's ability to understand information may change from one day to the next depending on their state of mind.
- Communication of highly technical and complex clinical trial information to participants with limited literacy, diverse sociocultural backgrounds, and diminished autonomy is challenging for clinical researchers.

METHODS TO ENHANCE PARTICIPANT UNDERSTANDING:

Communicate effectively

Effective communication helps participants receive clear information relevant to their specific learning needs and encourages informed decision-making during the consent process.

As per FDA guidelines, the use of simple language (eighth grade standard reading levels) for English language consent documents or translation to local languages, which are easy to understand is recommended. Simplified information appeals to patients, decreases their anxiety, and assists in a better understanding of medical terms and concepts.

In today's world, reading and learning habits have evolved. The informed consent document alone is not always sufficient and should be tailored to social changes that facilitate understanding.

Providing printed brochures, use of illustrations, and information sheets about the clinical trial can appeal to the participants. This may engage the participant to read the entire message and help patients with poor literacy to better understand.

Using multimedia, and audio-visual tools may help to save a physician's time during the consent process and enable immediate verbal reinforcement of written information, which aids in effective comprehension and recall.

Another approach is to encourage extended discussions after the actual consent process between the research team member and trial participant for better understanding and retention of trial information by study participants.

Training for the researchers and research staff

- Provide a formal training program to research members on effective researcher-participant communication and shared decision-making and the impact on informed consent and patient safety.
- Develop and implement policies and procedures for consenting patients with limited health literacy, limited English proficiency, and visual or hearing impairments.
- Provide communication models and ways to evaluate patient understanding with follow-up conversations to address miscommunications.

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

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ENHANCING PARTICIPANT UNDERSTANDING

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Informed consent document

- Provide guidance materials to help simplify the content, length, and language of informed consent documents and patient education materials.

Role of the IRB

The IRB reviews the informed consent form to ensure that the required study information is communicated in language that is readily understandable to the person who may volunteer to be a research subject.

It may be found that PIs submit to the IRB, overly long and complicated forms and that PIs may underemphasize the risks and overemphasize the potential benefits of research. IRBs may wrestle with how to strike a balance, wanting to neither eliminate hope nor oversell a treatment; but doing so can be challenging.

IRBs also struggle to take into consideration subjects' vulnerability which may be because of ongoing illness or sudden illness, such as Emergency Department visits. In such circumstances, patients may simply not be able to concentrate on lengthy documents.

IRBs have also been criticized for focusing more on the informed consent form and not the actual "process" because of its inherent limitations and lack of resources to ensure that consent is more of a process (i.e., monitoring the process itself). But review processes are evolving. More IRBs are performing onsite audits of the actual consent process to ensure its validity.

Assessing participant's understanding – Teach-Back Method

Regardless of a research participant's literacy level, researchers must ensure that participation in the study is truly voluntary, and the participants must understand the information that has been given to them and what they are agreeing to. Participants should not feel rushed or pressured.

It is well-known that in research 'informed consent is not just a form, it is a process,' but there are PIs who are obtaining research consent that have never been trained on how to have an effective research consent discussion. An effective process needs to include

an assessment of understanding. This often includes questions such as "Do you understand?" or "Do you have any questions?" are asked. This is not enough of a discussion to ensure the participant has a true understanding of the research study.

So, what can be a better process that results in valid consent? One of the ways to assess the participant's comprehension is using the Teach-Back Method. What is the Teach-Back Method?

- It is a strategy to improve the researcher's ability to explain the consent form content clearly.
- It assures that the participant is provided with sufficient opportunity to discuss the information provided to them and to consider whether to participate in the research.
- It also helps identify weaknesses in the consent process. For example, if multiple participants misunderstand the same piece of information, the consent form or process needs to be modified.
- It involves asking potential research participants to demonstrate understanding using their own words, what the research study is about and what they will be expected to do if they choose to participate. If the participant is unable to teach back the information correctly, then they require further and possible different explanations. A signature is obtained only if the participant has demonstrated an adequate understanding of the study.
- It uses open-ended or non-directive questions for example:
  - In your own words, could you please tell me what you will be doing during this study?

- Can you tell me the purpose of this study?
- Can you tell me what will happen if you agree to take part in this study?
- What would you do if you wanted to leave the study?
- What are the consequences if you withdraw from the study?
- What more would you like to know?

Asking questions can further the discussion, prompt questions from the participant, provoke the participant to think more carefully about the study, and help the researcher decide whether the person has adequately understood the study.

What if the participant cannot successfully explain the research study components?

If a person is unable to reiterate the information back to us, we can say something like: "Let me see if I can do a better job explaining that to you."

Be creative about how you present the information and use different strategies. Perhaps someone is a visual learner so drawing a diagram might help. This process is repeated until the person shows understanding and if several attempts do not work, you will not be able to get valid consent and should not enroll the patient.

Conclusion

Informed consent is a continuous process during clinical trials. Knowledge assimilated by the trial participant greatly impacts the performance, compliance, and retention of the participant in a clinical trial. The informed consent process must be viewed as a unique opportunity to build a communication channel and trust with participants. It is therefore important for all stakeholders in clinical research to have collaborative efforts and employ innovative strategies to overcome those challenges and promote conducting a valid, meaningful, and complete informed consent process.

REFERENCES

1 Informed consent process: A step further towards making it meaningful, Rashmi Ashish Kadam, Perspectives in Clinical Research, v.8(3); July-Sep 2017

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DIGITAL SPATIAL PROFILING

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simultaneously in the entire tumor and surrounding stromal tissue. We anticipate that these findings will help the enhanced use of Selinexor in tumors beyond pancreatic cancer, especially in cancers with dense stroma," concluded Dr. Azmi.

Additional Karmanos and Wayne State University authors of the study include Najeeb Al-Hallak, MD, MS, Husain Yar Khan, PhD, Amro Aboukameel, MS, Yiwei Li, MD, Sahar Bannoura, MS, Gregory Dyson, PhD, Seongho Kim, PhD, Yosef Mazannar, Ibrahim Azar, MD, Steve Kim, MD, FACS, Rafic Beydoun, MD, Ramzi Mohammad, PhD, and Anthony Shields, MD, PhD.

FACULTY, FELLOWS & RESIDENTS

SCHOLARLY ACTIVITY NEWS

McLAREN DIVISION OF SCHOLARLY INQUIRY – WORKSHOP ATTESTATION FORM

By Carlos F. Rios-Bedoya, ScD, MPH

Carlos F. Rios-Bedoya, ScD

The Graduate Medical Education's Division of Scholarly Inquiry at McLaren Health Care in coordination with other MHC departments and divisions has established procedures and guidelines to assure compliance with internal as well as external regulations related to scholarly activity. During the current academic year, we have encountered several residents submitting incorrect forms for pre-determination and for SARC review and approval. Additionally, we have even had residents asking for authorization to submit abstracts, posters, and manuscripts without having gone through the established procedures.

Despite plenty of available resources, such as at least one PhD assigned to each residency training program at each hospital, a scholarly activity website, the infographic shown on next page*, and a series of four mandatory quarterly workshops; there seems to be some barrier in recognizing and understanding the required procedures and forms needed for review and approval of ALL residents' scholarly activity projects. One potential explanation is that some residents are quite selective in what information, emails, and communications they read and are missing important scholarly activity information sent their way. Given this situation, the Division of Scholarly Inquiry will immediately implement a Scholarly Activity Attestation Form during the fourth quarterly workshop required for first-year residents (PGY-1s).

The main purpose of this attestation form is to raise awareness among PGY-1s that there are a series of required procedures and forms that should be followed before implementing any kind of scholarly activity. These procedures and forms are presented and discussed during the required fourth quarterly workshop. In addition, it should remind them that there are plenty of resources available that they can and should use during the review and approval of their scholarly activity; none as important as contacting the PhD assigned to their training program. Furthermore, it should provide an additional accountability mechanism regarding awareness and knowledge of the required established procedures for review and approval of residents' scholarly activity.

The Division of Scholarly Inquiry is committed to supporting and facilitating scholarly activity for McLaren residents, fellows, and faculty.

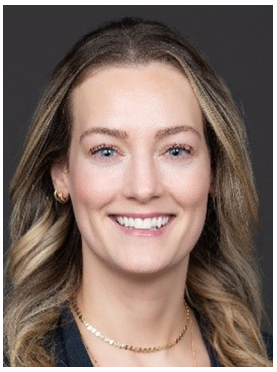
For additional information contact Dr. Carlos F. Ríos-Bedoya at **carlos.rios@mclaren.org**.

** Infographic not applicable to case reports or case series*

ANNOUNCEMENTS AND WHAT'S NEW

Elizabeth Cunningham

Congratulations to **Elizabeth Cunningham**, MS, CCRP, on her new appointment as the Interim Vice President of the Karmanos Cancer Institute Clinical Trials Office (CTO). Elizabeth is a University of Michigan alumna, and she received her master's in psychology from Duquesne University. She is a certified clinical research professional (CCRP) recognized by the Society of Clinical Research Associates (SoCRA). With a distinguished nine-year tenure at Karmanos, Elizabeth worked as a clinical research coordinator before advancing to managerial positions overseeing CTO quality assurance and education efforts. We are enthusiastic about the future of the CTO under Elizabeth's leadership as Karmanos Cancer Institute strives to broaden our clinical trial research initiatives.



Kasha Donahue

Karmanos Cancer Institute Clinical Trials Office (CTO) is happy to announce the promotion of **Kasha Donahue** to Director, Regulatory and Clinical Research Operations. In her new role, Kasha will oversee the CTO regulatory team and the specialized coordinators that support Karmanos Cancer Institute CTO operations. Kasha is a certified clinical research professional (CCRP) recognized by the Society of Clinical Research Associates (SoCRA) and brings years of experience and knowledge in regulatory activities, Cancer Center Support Grant related activities and overall operations. Kasha has been a pivotal leader in numerous process improvement initiatives. Congratulations, Kasha!

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ANNOUNCEMENTS AND WHAT'S NEW

Jaclyn Dominello

Karmanos Cancer Institute Clinical Trials Office (CTO) is happy to announce the promotion of **Jaclyn Dominello** to Director, Study Coordination and Research Nursing. Jaclyn will oversee and support all CTO study coordination personnel and services, as well as the Detroit and Farmington Hills research nursing team. Jaclyn has a Bachelor of Science in Global Public Health and Epidemiology from Michigan State University and is a certified clinical research professional (CCRP) recognized by the Society of Clinical Research Associates (SoCRA). Jaclyn has 10 years of progressive clinical research study coordination experience and has demonstrated a commitment to enhancing processes and collaboration with all members of the research team. Congratulations, Jaclyn!

Mackenzie Thrower

We are pleased to announce **Mackenzie "Mac" Thrower**, MA, EMT-P, has joined the McLaren Center for Research and Innovation from McLaren Lapeer Region where he was the Emergency Preparedness Coordinator. He has a varied skillset with experience as a Paramedic and Police Officer with the Genesee County Sheriff's Office, SNAP-Ed Program Manager with the Crim Fitness Foundation and AmeriCorps Service. Mac received his bachelor's degree in Spanish and International Studies and master's in Social Science from the University of Michigan-Flint. He joins the MCRI team at McLaren Flint. Welcome, Mac!

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