MEDICAL COLLEGE OF WISCONSIN
DECEMBER 1, 2022

CANCER RESEARCH STATE INCOME TAX CHECK-OFF PROGRAM
REPORTING PERIOD JULY 1, 2021 - JUNE 30, 2022

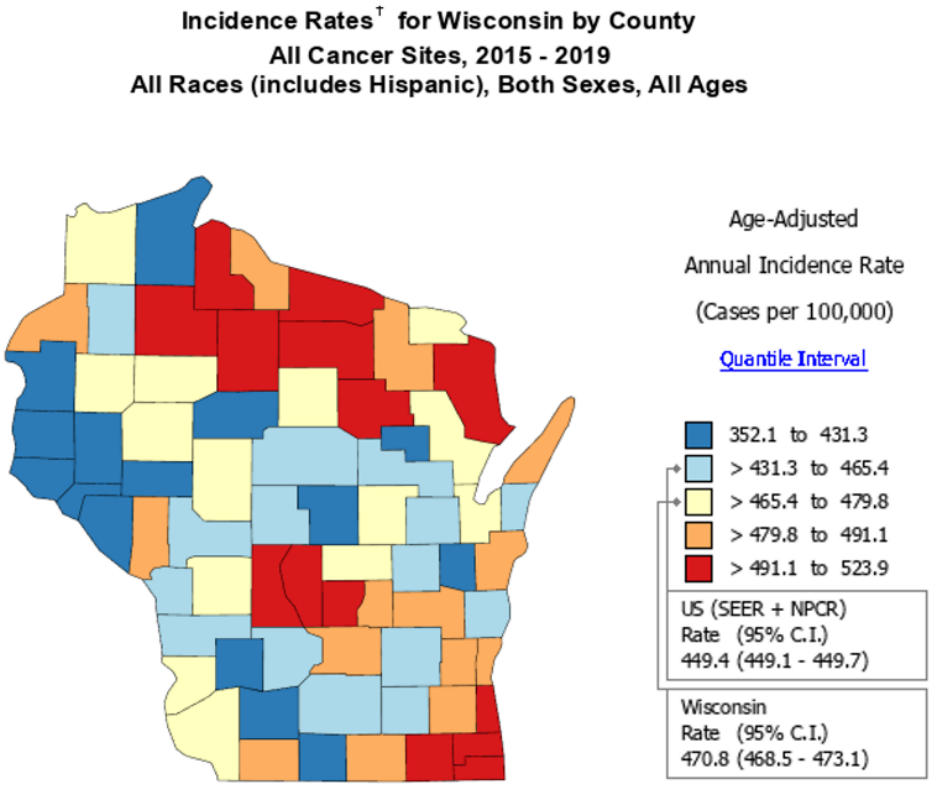
A. *BACKGROUND: CANCER STATISTICS*

Although meaningful progress continues, cancer remains among the leading causes of death in the United States and persists as a prominent public health challenge especially among specific groups of the U.S. population who experience a disproportionate burden of cancer. COVID-19, newly added as a cause of death in 2020, became the 3rd leading cause of death.[1] Additionally, the pandemic produced a vast burden for medical research and health care, including cancer research and patient care. A Kaiser Family Foundation survey, conducted at the beginning of the pandemic, concluded that 48% of US adults or their family members had foregone medical care due to the outbreak.[2]

The American Cancer Society estimates that in 2022, an estimated 1.9 million new cancer cases will be diagnosed, and 609,360 cancer deaths will occur in the United States, which is about 1,670 deaths per day. In the US, an estimated 40 out of 100 men and 39 out of 100 women will develop cancer during their lifetime.[3] Furthermore, in 2022 it is estimated that there will be 37,320 new cancer cases in Wisconsin and over 11,570 cancer-related deaths.[4] The age-adjusted incidence rate for cancer in Wisconsin is 471/100,000 population (Figure 1[5]). The four cancers in Wisconsin with the highest incidence are prostate (5,590), breast -female (5,380), Lung/bronchus (4,500), and colorectal (2,680).[4]

Like overall U.S. data, heart disease and cancer remain the leading causes of death in Wisconsin. In 2020, heart disease deaths exceeded cancer deaths by 1,396 cases: together they account for close to 40% of Wisconsin deaths. The leading cause of death varies by age group. Cancer is the leading cause for those ages 45-65 and the second leading cause of death for those ages 5-14, 35-45 and those over 65 years of age.

Figure 1



[1] Murphy SL, K. K. (2021). Mortality in the United States, 2020. Retrieved from Centers for Disease Control and Prevention: https://www.cdc.gov/nchs/products/databriefs/db427.htm
[2] Kaiser Family Foundation. KFF Health Tracking Poll – May 2020 – Health and Economic Impacts [updated 2020, May 27; cited 2021 Nov 27]. Available from: https://www.kff.org/report-section/kff-health-tracking-poll-may-2020-health-and-economic-impacts/
[3] American Cancer Society – Cancer Facts and Figures 2022. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html
[4] American Cancer Society. Cancer Statistics Center. http://cancerstatisticscenter.cancer.org. Accessed November 14,2022.
[5] State Cancer Profiles NCI/CDC http://statecancerprofiles.cancer.gov/quick-profiles/index.php?statename=wisconsin

B. *CANCER BURDEN IN EASTERN WISCONSIN*

The catchment area of the Medical College of Wisconsin Cancer Center (MCWCC) includes 29 counties that span the eastern portion of Wisconsin (Figure 2). Its 3.36M residents are 58% of Wisconsin's total population (5.8M). It includes: 7 of the 10 most populous counties, including Milwaukee (1st), Waukesha (3rd), Brown (4th) and Racine (5th); 16 of the 20 most populous cities; and 74.7% of the state's total minority population, with 85.4% and 74% of the state's African American and Hispanic populations, respectively. The following ethnic minorities account for a large proportion of the population in several counties in the catchment area: African American (Milwaukee 27.6%, Racine 12.2%, Kenosha 7.6%); Hispanics/Latinos (Milwaukee 16.4%, Racine 14.8%, Kenosha 14.4%); and Native Americans (Forest 14.7%, Vilas 10.5%) (United States Census Bureau, 2022).[6] These populations have significant disparities in cancer incidence and outcomes (United States Census Bureau, 2022).[6] Wisconsin has one of the largest racial disparities in poverty, ranking 49th (out of 50 states) on the gap in poverty rates between African American and White groups. While 11% of Whites are living in poverty in Wisconsin, 39% of African Americans and 28% of Hispanic & Latinos are living in poverty (UW - Madison, 2022).[7] While 10.8% of Wisconsin residents are below the poverty line, the rate is higher in Milwaukee County (17.5%) and much higher for Hispanics (18.5%) and African Americans (30.3%) (Smeeding & Thornton).[8] In particular, African Americans in our area have a higher incidence of, and worse outcomes for lung, colorectal, breast, prostate and pancreatic cancer (Tables 1 and 2). MCWCC is the primary academic provider of cancer care to Wisconsin's ethnic minorities. The cancer centers in Madison and Chicago (80 and 92 miles away, respectively) do not reach this population. For example, <1% of all cancer patients in our catchment area are ever seen in Madison or Chicago and even less for African American cancer patients.

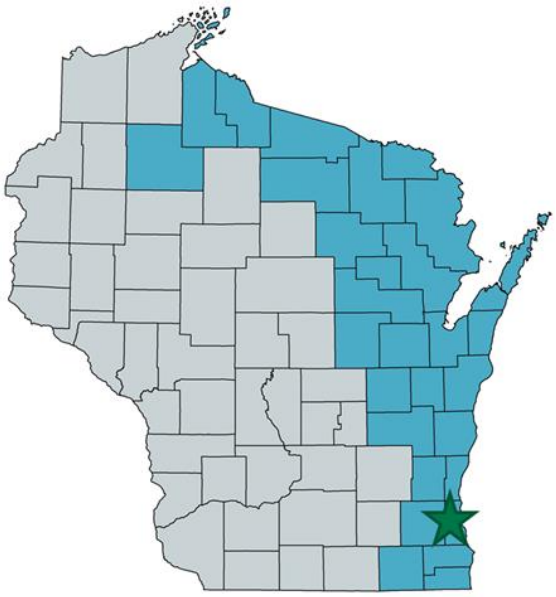


Figure 2. Counties where most of cancer patients receive care at MCW are highlighted in blue.

MCWCC's catchment area faces the socioeconomic challenges of health care access, segregation, poverty, lack of affordable housing, troubled public schools, high unemployment and incarceration. Reaching this community requires an academic cancer center in close proximity. The heart of the catchment area, Milwaukee, is the most segregated metropolitan area in the United States and, as noted, includes the majority of the state's African American population. In addition, statewide cancer disparities by race/ethnicity are evident throughout the MCWCC Eastern Wisconsin catchment area.

Table 1. Age-Adjusted Cancer Incidence Rates per 100,000 by Race (2015-2019)

Cancer	U.S. All Races	Wisconsin All Races	Wisconsin African Americans
All	**449.4**	**470.8**	**561.5**
Lung	56.3	58.6	89.9
Colorectal	37.7	36.3	51
Breast*	128.1	135.1	141.1
Prostate	109.9	118.3	196.3
Pancreas	13.2	13.8	19.9

*Excluding *in situ*
Source: NCI State Cancer Profiles, statecancerprofiles.cancer.gov

Table 2. Age-Adjusted Cancer Death Rates per 100,000 by Race (2016-2020)

Cancer	U.S. All Races	Wisconsin All Races	Wisconsin African Americans
All	**149.4**	**152.5**	**219.5**
Lung	35	35.6	54.9
Colorectal	13.1	12.1	19.7
Breast	19.6	18.4	26
Prostate	18.8	20.8	41
Pancreas	11.1	11.7	16.3

Source: NCI State Cancer Profiles, statecancerprofiles.cancer.gov

[6] United States Census Bureau. https://www.census.gov/quickfacts/fact/table/vilascountywisconsin,forestcountywisconsin,kenoshacountywisconsin,racinecountywisconsin,milwaukeecountywisconsin/PST045221

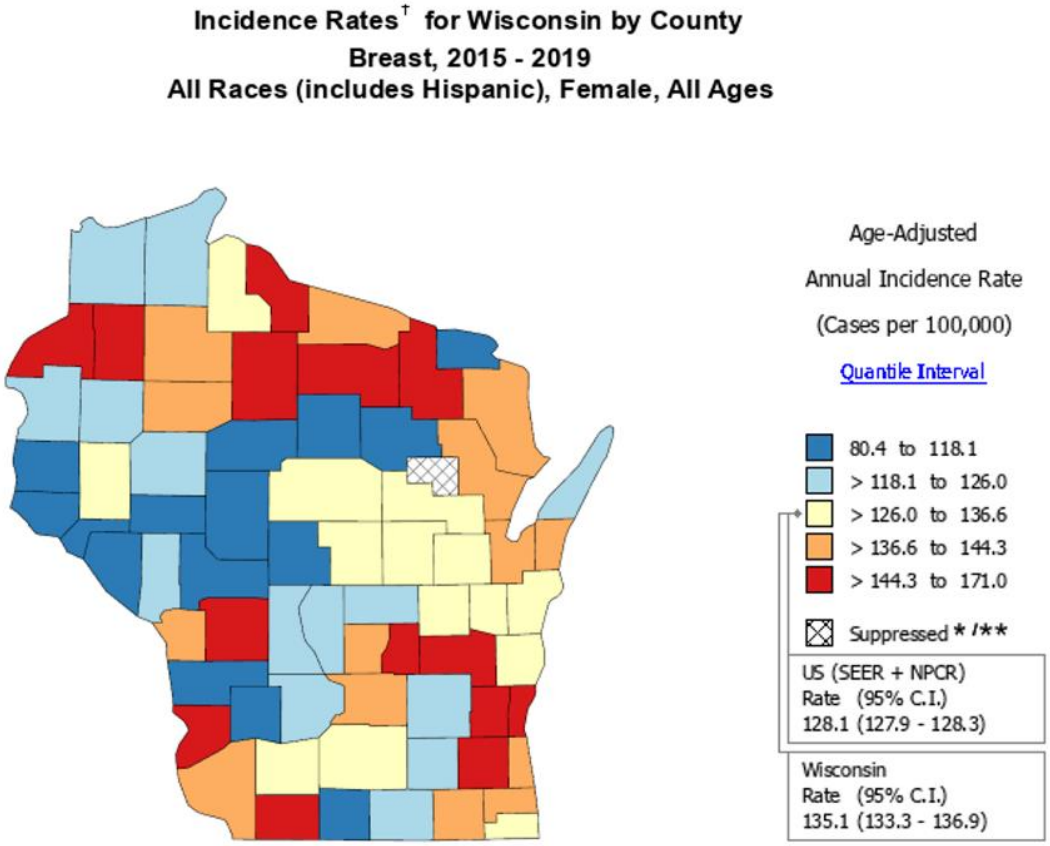
[7] UW Madison – Department of Community and Environmental Sociology. Significant Changes in Wisconsin Poverty. Accessed November 29, 2022. https://apl.wisc.edu/data-briefs/acs-poverty-15#:~:text=In%20our%20state%2C%2039%25%20of,observed%20at%20the%20national%20level

[8] Smeeding, T.M., & Thornton, K. (2018) POVERTY, INCOMES, RACE AND ETHNICITY IN WISCONSIN AND MILWAUKEE. Retrieved from UW-Madison – Institute for Research on Poverty: https://www.irp.wisc.edu/research/poverty-measurement

C. *MOST COMMON CANCERS IN EASTERN WISCONSIN*

Breast cancer remains the most diagnosed cancer among women in the United States and the second leading cause of death from cancer after lung cancer. [9] The average risk of a woman in the United States developing breast cancer sometime in her life is about 13% which translates to a 1 in 8 chance she will develop breast cancer. In Wisconsin, breast cancer is the most common cancer among women, regardless of race, and represents nearly one-third of all cancers diagnosed among women.[10] It is estimated that there will be 5,380 new diagnoses in Wisconsin in 2022 and 720 deaths.

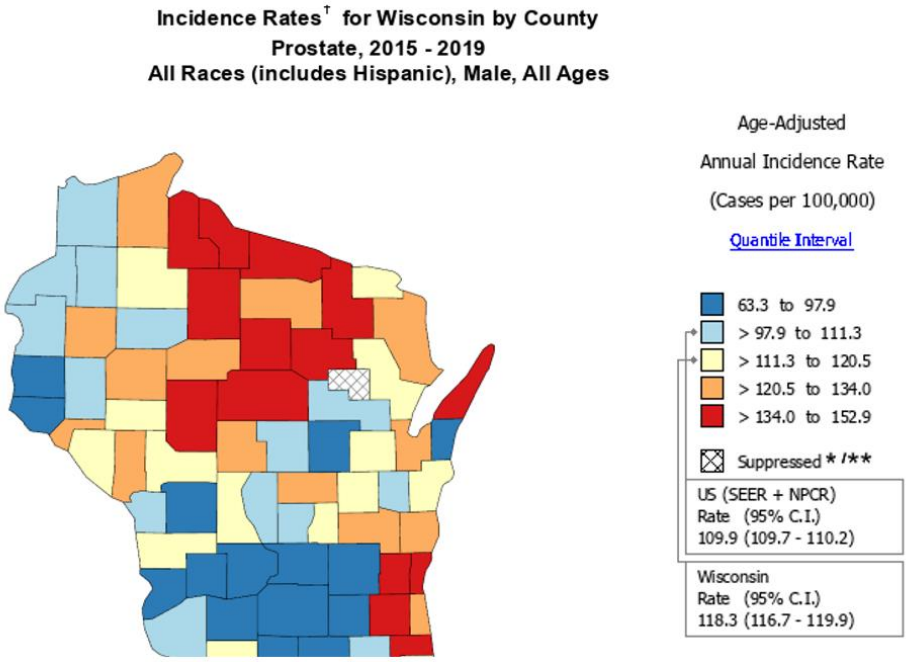
Figure 3



[9] American Cancer Society – Key Statistics for Breast Cancer. https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html
[10] American Cancer Society – Facts and Figures: Breast Cancer in Wisconsin. https://wicancer.org/wp-content/uploads/2021/11/Breast_2020-update-FINAL.pdf

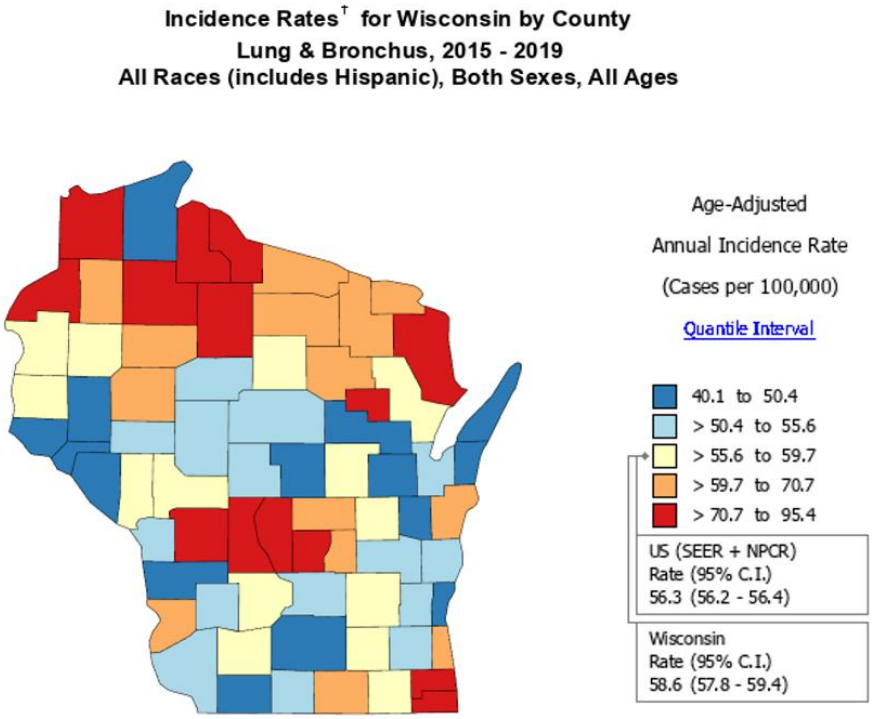
Prostate cancer is the second most common type of cancer among men in the United States and is more likely to develop in older men and in non-Hispanic African American men. The incidence rate of prostate cancer in Wisconsin is higher than the national rate and is the most frequently diagnosed cancer among Wisconsin males, representing 25% of all newly diagnosed cancers in men.[3] In 2018, approximately 4,100 men in Wisconsin were diagnosed with prostate cancer, and nearly 640 died from the disease. The American Cancer Society predicts that there will be almost 5,600 new cases and almost 1,000 deaths from prostate cancer in 2022.[4] Prostate cancer is a critical public health issue for the state, and our region, with recent data showing that prostate cancer incidence rates in the MCW catchment area are some of the highest in the nation (Figure 4).[5]

Figure 4



Lung/bronchus cancer remains the leading cause of cancer deaths among both men and women in the United States. Wisconsin, while ranking 10th in the nation for screening and early diagnosis, remains only 28th in the nation for rate of new lung cancer cases is 59/100,000 population (Figure 5). Among African Americans in Wisconsin, the rate of new lung cancer cases is 90/100,000 – substantially higher that national rates for African Americans (59) and significantly higher than the rate for whites (58/100,000) and Hispanics/Latinos (33/100,000) in Wisconsin.[11] Estimates for new lung/bronchus cancer cases in Wisconsin will exceed 4500 in 2022 and the anticipated mortality is 2500 individuals.[4]

Figure 5

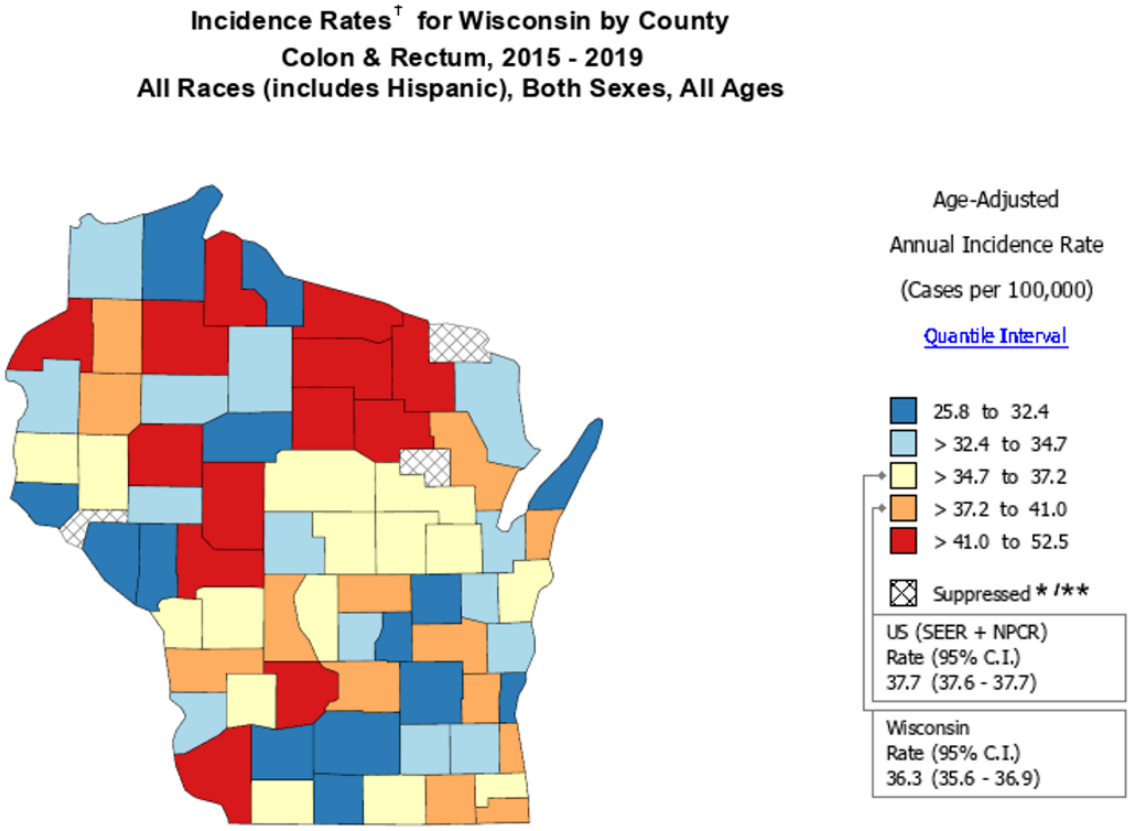


[11] American Lung Association, https://www.lung.org/research/state-of-lung-cancer/states/wisconsin

Colorectal cancer is the fourth most common cancer in Wisconsin with an incidence rate of 36.3/100,000 population (Figure 6) and is the second leading cause of cancer related deaths. In 2022, it is estimated that Wisconsin will have 2,700 new cases of and 900 deaths from colorectal cancer. The burden of colorectal cancer varies considerably by race and ethnicity. African Americans have the highest incidence and mortality of all racial and ethnic groups.

The top five counties with the highest mortality are in the MCW catchment area (Langlade, Oneida, Ashland, Sawyer, and Vilas).[12] The Milwaukee Metropolitan Area accounts for 26% of all colorectal cancer deaths, with Milwaukee leading the way at 16%.

Figure 6



Map Notes:

State Cancer Registries may provide more current or more local data.
Data presented on the State Cancer Profiles Web Site may differ from statistics reported by the State Cancer Registries (for more information).
[1] Incidence rates (cases per 100,000 population per year) are age-adjusted to the 2000 US standard population (19 age groups: <1, 1-4, 5-9, ..., 80-84, 85+). Rates are for invasive cancer only (except for bladder which is invasive and in situ) or unless otherwise specified. Rates calculated using SEER *Stat Population counts for denominators are based on Census populations as modified by NCI. The US Population Data File is used for SEER and NPCR incidence rates.
Rates are computed using cancers classified as malignant based on ICD-O-3. For more information see malignant.html
¥ Data have been suppressed to ensure confidentiality and stability of rate estimates. Data is currently being suppressed if there are fewer than 16 counts for the time period.
® Data not available for this combination of geography, statistic, age and race/ethnicity.
Data for the United States does not include data from Puerto Rico.

[12] State Cancer Profiles NCI/CDC: https://statecancerprofiles.cancer.gov/incidencerates/index.php?stateFIPS=55&areatype=county&cancer=020&stage=999&race=00&sex=0&age=001&year=0&type=incd&sortVariableName=rate&sortOrder=desc#results

D. WISCONSIN STATE CANCER RESEARCH TAX CHECK-OFF PROGRAM

The State of Wisconsin established a Breast Cancer Research State Income Tax Check-Off Program under 2003 Wisconsin Act 176, and a Prostate Cancer Research Program with creation of 2005 Wisconsin Act 460. Under these Acts, every individual filing a Wisconsin income tax return could make an additional payment or donate any portion of their refund to the breast and/or prostate cancer research programs. Following the enactment of 2011 Wisconsin Act 222, individuals filing a Wisconsin tax return could make additional payment or donation of their tax refund for research on any cancer, not just breast or prostate cancer.

After administrative expenses, the amounts received under the State Income Tax Check-Off program are divided evenly between the Medical College of Wisconsin (MCW) Cancer Center and the University of Wisconsin Carbone Cancer Center. The law requires both entities to use the funding for cancer research and to report annually on the research projects conducted during the previous year. These funds may not be used to supplant funds available from other sources.

E. RESEARCH PROJECTS SELECTION PROCESS

To ensure that the highest quality research is funded, the Medical College of Wisconsin cancer related research pilot grant applications are selected using a peer-review process that draws upon both standing and *ad hoc* Cancer Center Research Grant Committees. The MCW faculty selected to serve on these committees represent basic and translational science departments, clinical departments, and the other disciplines involved in cancer research at the College, such as biostatistics. This past year we have added three external reviewers who are national experts in their fields to add additional rigor to our review process.

Proposals are reviewed and scored in the manner of a National Institutes of Health (NIH) study section. Each assigned reviewer reports their merit scores, followed by an introduction of each application by an appointed primary reviewer. Additional comments are provided by secondary reviewers. After comments from the assigned reviewers, each application is opened for general discussion by the Committee. After discussion is completed, the two assigned reviewers report their revised merit scores to establish a voting range and each reviewer at the meeting votes a confidential merit score using the NIH-style scale of 1 (highest priority) to 9 (lowest priority). The scores are averaged to generate the relative ranking.

After applications are prioritized based on scientific merit as described above, the recommendations for funding are submitted to the Cancer Center's Director's Council. The Director's Council of the Cancer Center is responsible to the Provost of the Medical College for appropriate allocation of funds from the State of Wisconsin Cancer Research State Income Tax Check-Off Program.

Final award decisions are made after ensuring that the recommended applications comply with State requirements and that the funding is non-supplanting. The Principal Investigator must also sign a non-supplanting attestation form.

In addition to the selection process, the MCW Cancer Center has been working diligently to mentor young faculty to continually increase the number and quality of applications. As a result, the Cancer Center has established required mentorship committees, biostatistical consultations in study design and data analysis, a seven-week course on clinical cancer trial design development, and has also restructured the review summary to include strategies for applicants to improve applications and increase opportunities to obtain future funding.

F. RESEARCH PROJECTS FUNDED IN FY2022

Title of Research Project: *Soluble Urokinase-type Plasminogen Activator as a Biomarker of Stage 3 Acute Kidney Injury in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation (HCT)*
Principal Investigator: Saber Wael, MD, MS, Professor, Department of Medicine, Division of Hematology and Oncology, Medical College of Wisconsin
Co-Investigator: NA
Amount Awarded: $50,000
Period of Award: Two years (6/1/2022 – 5/31/2024)

Lay Abstract:
Acute Kidney Injury (AKI) is a frequent problem after allogeneic hematopoietic cell transplantation (HCT). Biomarkers are distinct compounds in blood that can be measured and evaluated to predict the occurrence of AKI following HCT. Biomarkers have been studied in AKI in the general population, but this has not been studied in post-HCT. suPAR is a novel biomarker that has shown promise in AKI in different clinical situations. The proposed study will evaluate the role of blood levels of suPAR to predict post-HCT AKI. The study will also compare the performance of suPAR to two well established biomarkers.

Title of Research Project: *Biochemical Modifications of ISCU Regulated by ERK1/2*
Principal Investigator: Jong-In Park, PhD, Professor, Department of Biochemistry, Medical College of Wisconsin
Co-Investigator: Susan Tsai, MD, Professor, Department of Surgery, Division of Surgical Oncology, Medical College of Wisconsin
Amount Awarded: $50,000
Period of Award: One year (5/1/2022 – 4/30/2023)

Lay Abstract:
Iron-sulfur cluster (ISC) is a key cofactor necessary for fundamental cellular processes, including bioenergetics, metabolism, gene regulation, and stress response. Accordingly, cellular processes involved in ISC production might be altered in tumor cells for their tumorigenic cell proliferation and survival. Nevertheless, our current understanding of this possibility is very limited despite its potential to be exploited for the design of a novel therapeutic strategy. The goal of our project is to provide substantial insights into how the MEK/ERK pathway, one of the most frequently deregulated pathways in cancer, regulates ISC biogenesis and how this regulation impacts tumor cell growth and survival. The biogenesis of ISC requires a scaffold protein called IscU. In preliminary observations, we have discovered that the MEK/ERK pathway mediates a series of biochemical modifications of IscU. We hypothesize that these modifications determine the function of IscU for ISC biogenesis, and hence they are a key mechanism that the MEK/ERK pathway regulate to control proliferation and survival of tumor cells, especially those that harbor mutated BRAF or KRAS. The present project aims to generate monoclonal antibodies that can specifically detect the MEK/ERK-induced IscU phosphorylation and to catalogue the secondary IscU modifications that occur in response to this phosphorylation.

G. PROGRESS REPORTS FROM PROJECTS AWARDED OR ACTIVE DURING THE PREVIOUS TWO YEARS (7/1/20 – 6/30/22)

Cancer related research grants have been awarded since the inception of the State of Wisconsin Cancer Research State Income Tax Check-Off Programs. We track the progress and scholarly output of grants for two years after their completion. The previously awarded and/or active State of Wisconsin Income Tax Cancer Research Grants from the last two academic years are listed below. An updated progress report is appended to this report (see Appendix II).

Title of Research Project:	*Characterizing the Functional Mutational Landscape in KRAS*
Principal Investigator:	Michael Zimmermann, PhD, Assistant Professor, Clinical and Translational Science Institute, Medical College of Wisconsin
Co-Investigator:	Raul Urrutia, MD, Gwen Lomberk, PhD, Brian Volkman, PhD
Amount Awarded:	$49,490
Period of Award:	One year (November 2020 – October 2021) (1-Year no cost extension to October 2022 granted to allow for completion of the goals of the project)

Appendix 1 – Research Projects Funded (FY22)

State Income Tax Check-Off Program Awards

FY2022

"Soluble Urokinase-type Plasminogen Activator as a Biomarker of Stage 3 Acute Kidney Injury in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation (HCT)"
Bhavna Bhasin-Chhabra original
Saber Wael (Current) (**6/1/2022 – 5/31/2024**) **$50,000**
Professor
Department of Medicine
FP22531

"*Biochemical modifications of ISCU regulated by ERK1/2*"
Jong-In Park, PhD (**5/1/2022 – 4/30/2023**) **$50,000**
Professor
Department of Biochemistry
FP22237

Appendix 2 – Progress Reports from Project Active During the Fiscal Years FY21-22

State Income Tax Check-Off Program Awards

FY2021

"Characterizing the Functional Mutational Landscape in KRAS"
Michael Zimmermann, PhD (**11/09/2020 – 10/31/2021 NCE through 10/31/2022**)
Assistant Professor
Clinical and Translational Science Institute
FP19178

PILOT GRANT PROGRESS REPORT
(Submitted on Date: 2022-11-29)

Amount of Award: $49490 **Award Period:** **from** 2020-11-09 **to** 2021-10-31 FP19178

Investigator (Name, Title, Department) and Co-Investigators (if any):

Investigator:
Michael T. Zimmermann, PhD
Director, Bioinformatics Research and Development Laboratory
Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine
CTSI and the Department of Biochemistry

Co-Investigators:
Raul Urrutia, MD
Director and Professor
Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine
Department of Surgery

Gwen Lomberk, PhD
Professor and Chief, Division of Research
Director Basic Science Research, Department of Surgery

Brian Volkman, PhD
Professor and Director, Program in Chemical Biology
Department of Biochemistry

Project Title:
Characterizing the Functional Mutational Landscape in Kras

Results: State the hypothesis and specific aims and summarize work to date. Use additional space or pages as necessary.

Hypothesis and Specific Aims:

This study is focused on KRAS, which is a proto-oncogene and critically important enzyme in cancer. The central hypothesis of this grant application is that *both hotspot and non-hotspot mutations disrupt the biophysical and biochemical behavior of KRAS, identifying groups of mutations that each contribute differently to known pathobiological mechanisms*. Our first Aim will use protein biophysical experimental assays for 25 selected KRAS mutations to establish the effects of each variant on the enzyme. Our second Aim is to develop and test a systematic computational biophysics-based scoring system for *KRAS* genetic variants. We will deliver the first uniform assessment of hotspot variants as well as the first characterization of non-hotspot variants.

Progress to Date:

We have advanced in both Aims of this proposal and beyond. The COVID-related shipping delays that we reported in the previous period were resolved. The primary assays described in our proposal have been completed. Using other funds we have been able to augment the data derived from this pilot award to add critical context to the data. Because KRAS has been studied for many years, and there have been recent publications that present findings relevant to the current pilot award, our collaborative team decided to generate two additional datasets to augment the current study and provide greater novelty and research value. Cell lines generated for Aim 1 of the current proposal were used in the generation of these additional data.

The enzymatic functional work that in the previous reporting period we were setup to do, but had not completed due to shipping delays, have returned data and are being analyzed. We identified a process stage that was leading to high variability across replicates and are approaching completion of a second round of the same enzymatic function assays with a protocol improvement that is yielding more consistent data. Once complete, the data will be combined with our currently complete datasets to generate new knowledge, which we intend to share through an additional publication (see below). Thus, I anticipate the return on investment for MCW and the CC, will be high.

I presented our current findings and progress at the recent CC Pilot Award Seminar.

Return on Investment Please include grants submitted and awarded, publications accepted, presentations and/or posters:

One manuscript related to Aim 2 is published: “Enhanced Interpretation of 935 Hotspot and Non-Hotspot RAS Variants using Evidence-Based Structural Bioinformatics,” Comput Struct Biotechnol Journal 2021 Dec 11;20:117-127. doi: 10.1016/j.csbj.2021.12.007. PMID: 34976316; PMCID: PMC8688876. The manuscript was refined using information gained through the analysis of Aim 2. We enhance interpretation of additional experimental data from the literature, considering preliminary data generated in pursuit of Aim 1 of this proposal.

Combining the data generated from this proposal, with additional data from our labs, I am actively preparing two additional manuscripts that are both nearing completion, with full manuscript drafts now circulating to co-authors.

I have submitted or contributed to nine grant applications that have either directly used the data generated by this pilot award or used the concepts that emerged from the pilot award. Specifically:

- PI and Directly Emerging from Grant
    - Characterizing the Functional Mutational Landscape in KRAS (NCI)
    - 3D Methodology for Interpreting Disease-Associated Genomic Variation (NIGMS)
    - 3D Methodology for Interpreting Disease-Associated Genomic Variation in Epigenetic Complexes (NHGRI)
- PI and Concepts Emerging from Grant
    - 3D and Systems Methodology for Interpreting Rett Syndrome Genomic Variation (NINDS, Rett Foundation)
    - Genomic Data Interpretation for Epigenetic Regulators: New Methods to Assess Changes to the SWI/SNF Protein Complex (NIGMS)
    - Genomic Data Interpretation for Epigenetic Regulators: New Methods to Assess Changes to the SWI/SNF Protein Complex (NCI)
- Co-I and Concepts Emerging from Grant
    - Methylosome Adaptation in Pancreatic Cancer (NCI)
    - Targeting Epigenomic Regulators at the Replication Fork in PDAC (NCI)
    - Genetic and pathophysiology mechanisms of Granulomatous and Lymphocytic Interstitial Lung Disease (NIAID)

NOTE: Not for use with American Cancer Society or Advancing a Healthier Wisconsin awards.