CONQUEST 2020

A Report on the Maryland Cigarette Restitution Fund

This year, we start with some good news about cancer. The American Cancer Society reported the "biggest single year drop ever" in cancer deaths in the U.S.

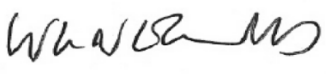
No one thing accounts for progress. It is an accumulation of efforts, including important programs like the Cigarette Restitution Fund that help launch the careers of young scientists and support promising research, that often translate into major breakthroughs.

Progress against lung cancer was a main factor in this historic decline, and CRF investigator Julie Brahmer, led several of the clinical trials that resulted in this headway.

Still, we recognize that progress is always fragile. Just as we are gaining advantages against cancer through screening, detection and treatment, factors like obesity, smoking and alcohol—all linked to cancer development and all areas of Johns Hopkins Cigarette Restitution Fund research—threaten the life expectancy of Marylanders.

As we celebrate the successes—and there are many as you will read about in this issue of Conquest—we also acknowledge that work remains.

We thank you for uniting with us in this shared mission. Many of our most monumental advances against cancer and the people who made them –from Nobel Prize-winning research to FDA approved drugs—got support from the Maryland Cigarette Restitution Fund. As you will read in the pages that follow, we could not do this without the help of the CRF.



William G. Nelson, M.D., Ph.D.
Marion I. Knott Professor and Director
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John D. Groopman, Ph.D.
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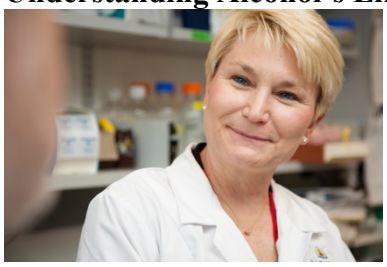
IMPACT > How the Cigarette Restitution Fund Got Its Start

In 1998, Maryland joined 46 other states in a class action lawsuit against America's cigarette manufacturers. States were seeking reimbursement for the huge costs associated with cancer and other smoking related diseases. The states prevailed and split a $53 billion settlement, known as the Master Settlement Agreement. Maryland became the national model when, in 2001, its elected officials opted to use a considerable portion of its award to fight cancer—particularly 7 CRF-targeted cancers: breast, cervical, colorectal, lung, melanoma, oral and prostate cancers—by establishing the Maryland Cigarette Restitution Fund (CRF) to fund cancer research and other projects aimed at reducing the state's cancer burden. It worked. **Maryland, which once had the highest cancer death rates in the nation, today ranks 31st.**

IMPACT > CRF in Action

Understanding Alcohol's Link to Breast Cancer



Cynthia Zahnow, Ph.D., is a cancer researcher and a breast cancer survivor, but she was surprised to learn of decades-old evidence linking alcohol consumption to breast cancer. If she didn't know, she was sure most women were unaware. "I wanted to know, as a breast cancer survivor, is it safe for me to drink alcohol," she says**. With CRF support, she began research to reveal how alcohol causes breast cancer and who may be most at risk.** In laboratory studies, she found normal breast duct cells treated twice weekly with alcohol showed epigenetic changes—alterations to chemicals and how genes are packaged in cells that can change the instruction manual that tells cells how to behave. "Cells are not happy about the alcohol," says Zahnow, who wants to find answers for herself, her daughter and all women about the risks. Zahnow says cells try to make repairs but they aren't always able to get back to normal. Her next step is to inject the alcohol-affected cells into the breast ducts of mice to see if they continue down the road to cancer. **"Prevention work is hard," says Zahnow, "and I would never have been able to do this research without CRF support. This funding is making it possible for me to begin telling this important story."**

Fitness Conquers Cancer

Catherine Handy Marshall, M.D., M.P.H., finds that the people in the best shape have the best chance of conquering cancer. **Her CRF-supported research—the first, largest and most diverse look at the impact of fitness on cancer—shows that the most fit adults have the lowest risk of developing lung cancer and colon cancer.** The physically fit also have a better chance of surviving a lung or colon cancer diagnosis than those with low fitness levels. She says her findings also seem to apply to prostate cancer and likely many other cancer types. "We think exercise and fitness work through many cellular mechanisms, and these may be different for different cancers," says Handy Marshall. Her next step is to see if improving fitness level after a cancer diagnosis helps patients. She is also designing a clinical trial of a minimally invasive weight loss procedure to see if overweight patients diagnosed with cancer benefit from losing excess pounds. The procedure was pioneered at Johns Hopkins, and this is the first time it has been studied in cancer. **"CRF support makes this type of first-of-its-kind research possible. It was part of my recruitment package, and it's one of the reasons I've stayed at Hopkins,"** she says.

Killing Prostate Cancer

Jelani Zarif, Ph.D., knows that cancer survival depends on two key factors—breaking its resistance to treatment and keeping it from spreading to other parts of the body. His research led him to particular cells within the immune system, called macrophages. In prostate cancer, he says, a specific type of these cells makes up ¼ to ½ of the tumor mass and helps the cancer avoid treatment and promotes its ability to spread. **He is testing a drug that converts the cancer-promoting type of macrophage into an immune system-alerting type of macrophage that attacks and kills prostate cancer cells**. Coupling that drug with another immunotherapy that gives the immune system an extra nudge may help patients with advanced prostate cancer. Zarif says he first dreamed of being a cancer researcher when he was in high school, and the CRF helped make that dream a reality. **"I am so grateful for the CRF support I've received," says Zarif. "My lab was completely empty except for a few chairs. My CRF grant helped me buy equipment, conduct experiments and hire a technician. It got my lab off the ground."**

IMPACT > PROGRESS NATIONALLY

CRF investigator **Otis Brawley, M.D.**, Bloomberg Distinguished Professor at Johns Hopkins, former chief medical and scientific officer for the American Cancer Society and an international authority on cancer screening and prevention, analyzed the historic decline in cancer deaths.

"Rigorous research, visionary drug regulation, and relentless public health measures have brought about tangible change," says Brawley.

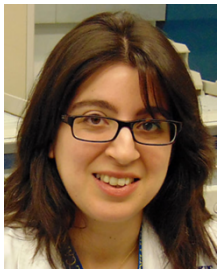
- The 2017 age-adjusted cancer death rate is 2.2% lower than the 2016 rate. This is the largest year-to-year drop since the beginning of the death rate decline.
- Declines in lung cancer deaths is the biggest driver of this trend. Immunotherapy, including breakthrough discoveries made by CRF investigators at the Johns Hopkins Bloomberg~Kimmel Institute for Cancer Immunotherapy essentially ensure this trend will continue.
- Tobacco avoidance and cessation resulted in steady improvements in cancer incidence and death rates.
- In 1991, of 300,000 Americans who died of cancer, 34% died of lung cancer. Of the 600,00 people who will die of cancer this year, 25% will die of lung cancer.

Brawley's focus at the Kimmel Cancer Center and in his CRF-supported research is on closing racial, economic and social disparities. He says, these promising statistics demand a national priority to ensure everyone benefits from the new screening methods and treatments that caused the decline in cancer death rates.

Changing the Landscape of Lung Cancer: CRF investigator **Julie Brahmer, M.D.**, Director of the Kimmel Cancer Center Thoracic Center of Excellence and Director of the Bloomberg~Kimmel Institute for Cancer Immunotherapy Lung Cancer Program led the landmark clinical trials that helped earn FDA approval for the immunotherapy drugs nivolumab and pembrolizumab in lung cancer. In some patients, these treatments ignite the body's own natural defenses to attack cancer cells, even advanced cancers that spread from the lung to other parts of the body.

- In a unique therapy developed by CRF investigator **Patrick Forde, M.B.B.Ch.**, some lung cancer patients are getting immunotherapy before surgery to decrease the cancer size and its chances of coming back after surgery, the leading cause of lung cancer death.
- Five-year overall survival quadrupled in non-small cell lung cancer treated with the immunotherapy drug nivolumab (Opdivo), compared with what we would expect from chemotherapy
- A new treatment combining immunotherapy and chemotherapy for patients with advanced small cell lung cancer received FDA approval.
- As a leader of a SU2C-LUNGevity Foundation-American Lung Association Lung Cancer Interception Dream Team, Dr. Brahmer is helping develop new ways to detect lung cancer before it progresses to an advanced stage.

Predicting Response to Immunotherapy: Immunotherapy is an exciting treatment for many tumors, but there is a great need for straight forward ways to predict which patients will respond to immunotherapy and why. CRF investigator **Valsamo "Elsa" Anagnostou, M.D., Ph.D.**, wants to know if there are specific molecular features that can help predict response.



- *Nature Cancer*, January 2020: A new approach she helped develop identifies specific molecular features that predict response to immunotherapy with immune checkpoint inhibitors, drugs that remove restraints on the immune response to cancer. She expects this approach to be incorporated into clinical practice, and believes it can change the way providers make decisions about how and when to give their patients immunotherapy.

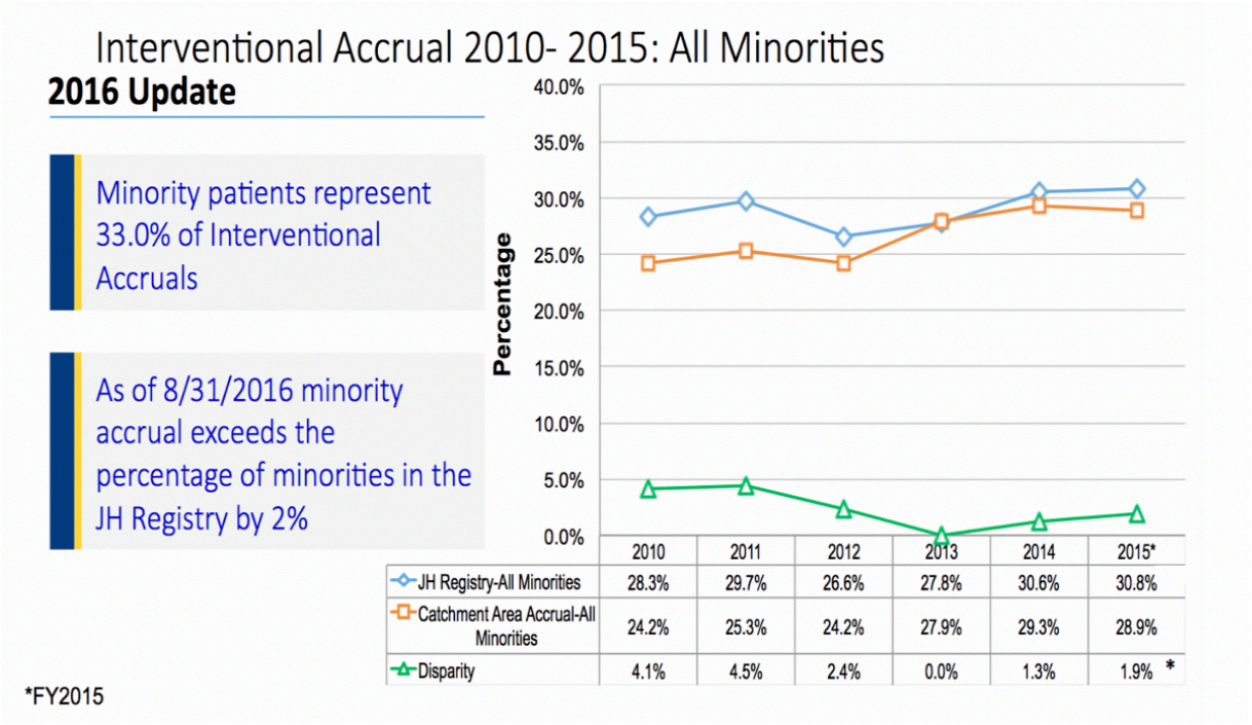
IMPACT > PROGRESS IN MARYLAND

The same approach that brought about a national change in cancer rates—research and public health changes—is also working in our state, but in Maryland and at the Kimmel Cancer Center, our investigators are required to make sure their discoveries benefit underserved Maryland residents**. Norma Kanarek, Ph.D., M.P.H.**, Executive Director of the Johns Hopkins CRF grant reports on progress:

- Maryland's age adjusted cancer mortality rate ranks 32nd (2012-2016), and 30-year cancer mortality declines outpaced other states.
- Overall cancer mortality rates declined 1.9% annually from 1990 to 2015, avoiding nearly 60,000 deaths over 3 decades.
- An enhanced focus on primary prevention is necessary to reduce incidence of several cancer types:

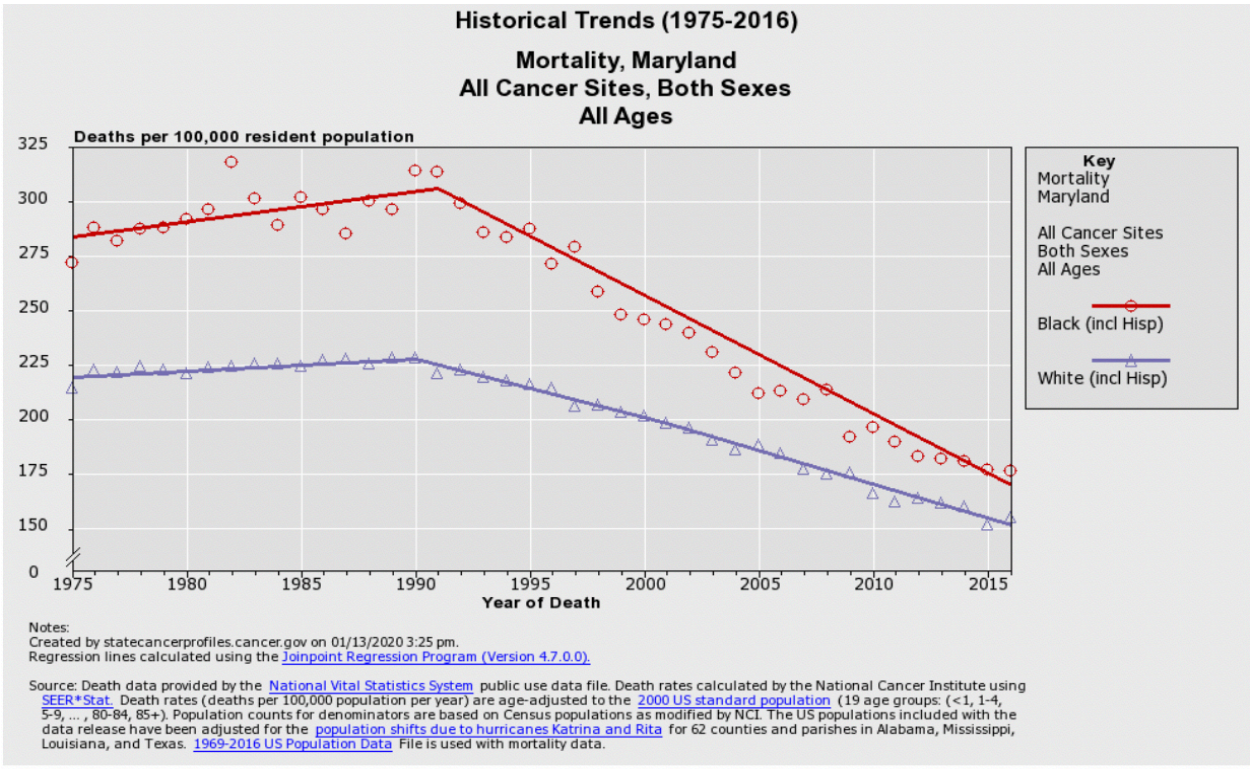
-No smoking: 12 cancers
-Moderate or no alcohol: 12 cancers.
-Overweight or obesity: 14 cancers
-Moderate or no alcohol 12 cancers
-Physical inactivity: 3 cancers
-HPV: 5 cancers

RACIAL DISPARITIES IN ACCESS TO CLINICAL TRIALS ARE BEING ELIMINATED AT THE JOHNS HOPKINS KIMMEL CANCER CENTER.

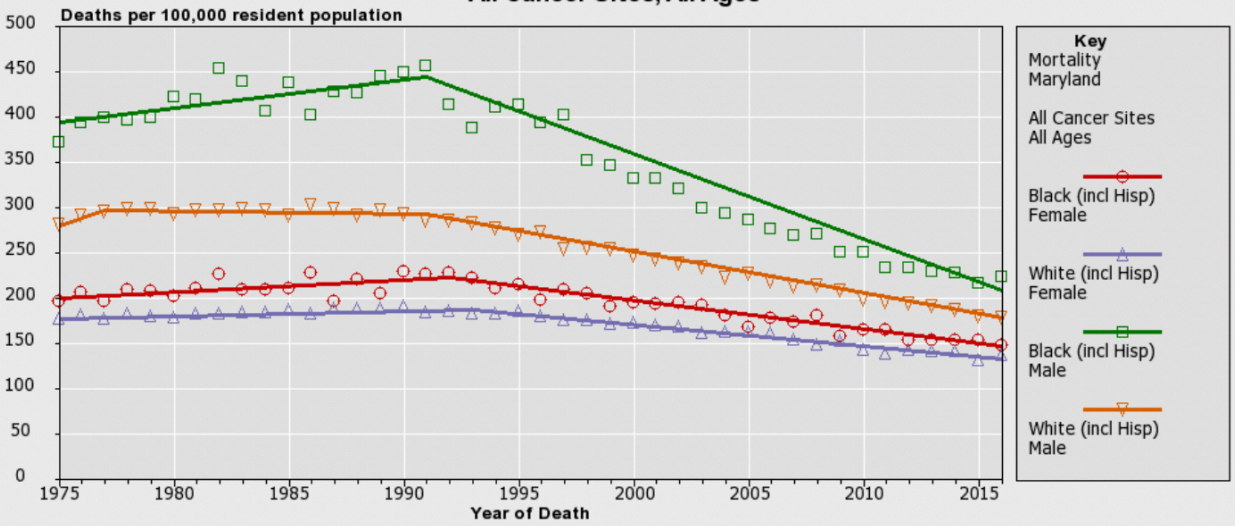


	2010	2011	2012	2013	2014	2015*
JH Registry-All Minorities	28.3%	29.7%	26.6%	27.8%	30.6%	30.8%
Catchment Area Accrual-All Minorities	24.2%	25.3%	24.2%	27.9%	29.3%	28.9%
Disparity	4.1%	4.5%	2.4%	0.0%	1.3%	1.9% *

ELIMINATING RACIAL DISPARITIES



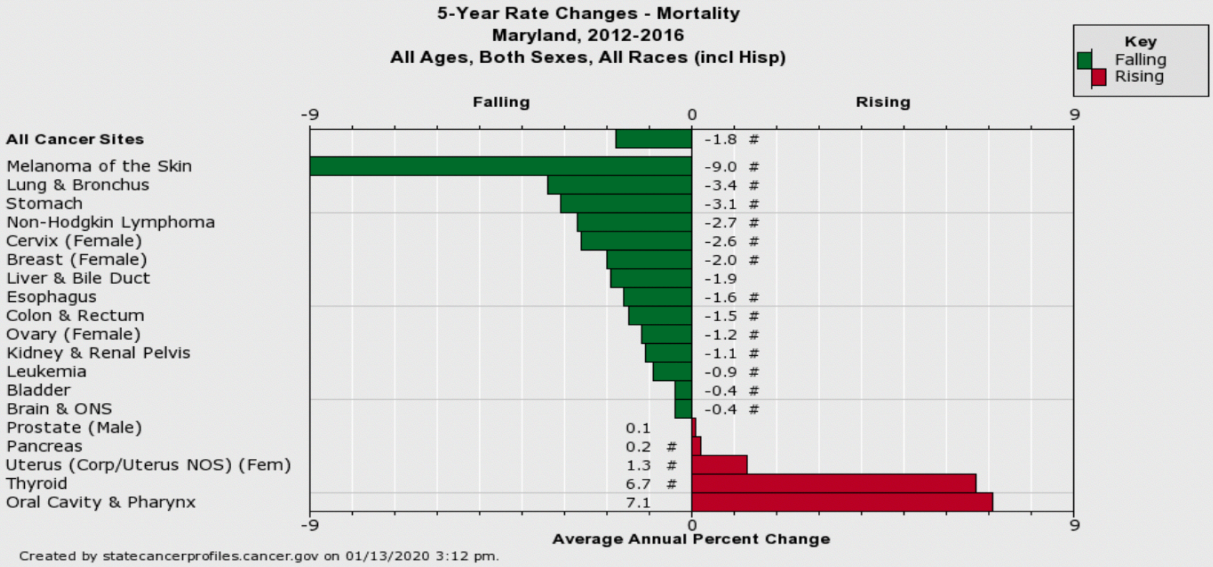
AFRICAN AMERICAN MEN AND WOMEN EXPERIENCED A GREATER REDUCTION IN CANCER MORTALITY COMPARED TO WHITES.



Notes:
Created by statecancerprofiles.cancer.gov on 01/13/2020 3:22 pm.
Regression lines calculated using the Joinpoint Regression Program (Version 4.7.0.0).

Source: Death data provided by the National Vital Statistics System public use data file. Death rates calculated by the National Cancer Institute using SEER*Stat. Death rates (deaths 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+). Population counts for denominators are based on Census populations as modified by NCI. The US populations included with the data release have been adjusted for the population shifts due to hurricanes Katrina and Rita for 62 counties and parishes in Alabama, Mississippi, Louisiana, and Texas. 1969-2016 US Population Data File is used with mortality data.

DEATH RATES FROM SIX OF SEVEN CRF-TARGETED CANCERS ARE DECLINING.



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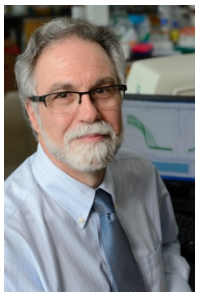
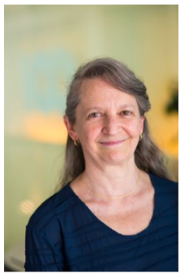
Source: Death data provided by the National Vital Statistics System public use data file. Death rates calculated by the National Cancer Institute using SEER*Stat . Death rates (deaths per 100,000 population per year) are age-adjusted to the 2000 US standard population (19 age groups: <1, 1-4, 5-9, ... , 80-84, 85+). Population counts for denominators are based on Census populations as modified by NCI. The 1969-2016 US Population Data File is used with mortality data.
Please note that the data comes from different sources. Due to different years of data availablility, most of the trends are AAPCs based on APCs but some are EAPCs calculated in SEER*Stat. Please refer to the source for each graph for additional information.

- The annual percent change is significantly different from zero (p<0.05).



Nobel Prize Winner: FY14 CRF investigator **Gregg Semenza, M.D., Ph.D.**, was co-winner of the 2019 Nobel Prize in Physiology or Medicine for his discoveries of how cells, including cancer cells, adapt to low oxygen levels. He discovered a cancer target called HIF-1-alpha that helps cancer cells acquire the oxygen and nutrients they need to survive and grow by stimulating blood vessel growth, and it also has a cancer-preventive property. It can block cell division by preventing cells from copying their DNA. FY16 CRF investigator **Danielle Gilkes, Ph.D.**, collaborated with Semenza on several published papers:

- *Nature Communications*, October 2019: Gilkes showed that cells from a primary cancer exposed to low oxygen levels have a four times greater probability of becoming viable circulating tumor cells that spread to distant tissues than those under normal oxygen conditions.
- *Oncotarget*, May 2015: Protein to protein interaction between HIF-1-alpha and TAZ revealed bidirectional crosstalk in low oxygen cells, activating changes that promote breast cancer spread.
- *Oncotarget*, December 2014: Established a molecular mechanism for induction of breast cancer stem cells characteristics in response to low oxygen.
- *Proceedings of the National Academy of Science*, May 2014: Low oxygen inside tumors recruit cells and stimulate invasion and metastasis in triple negative breast cancer cells.

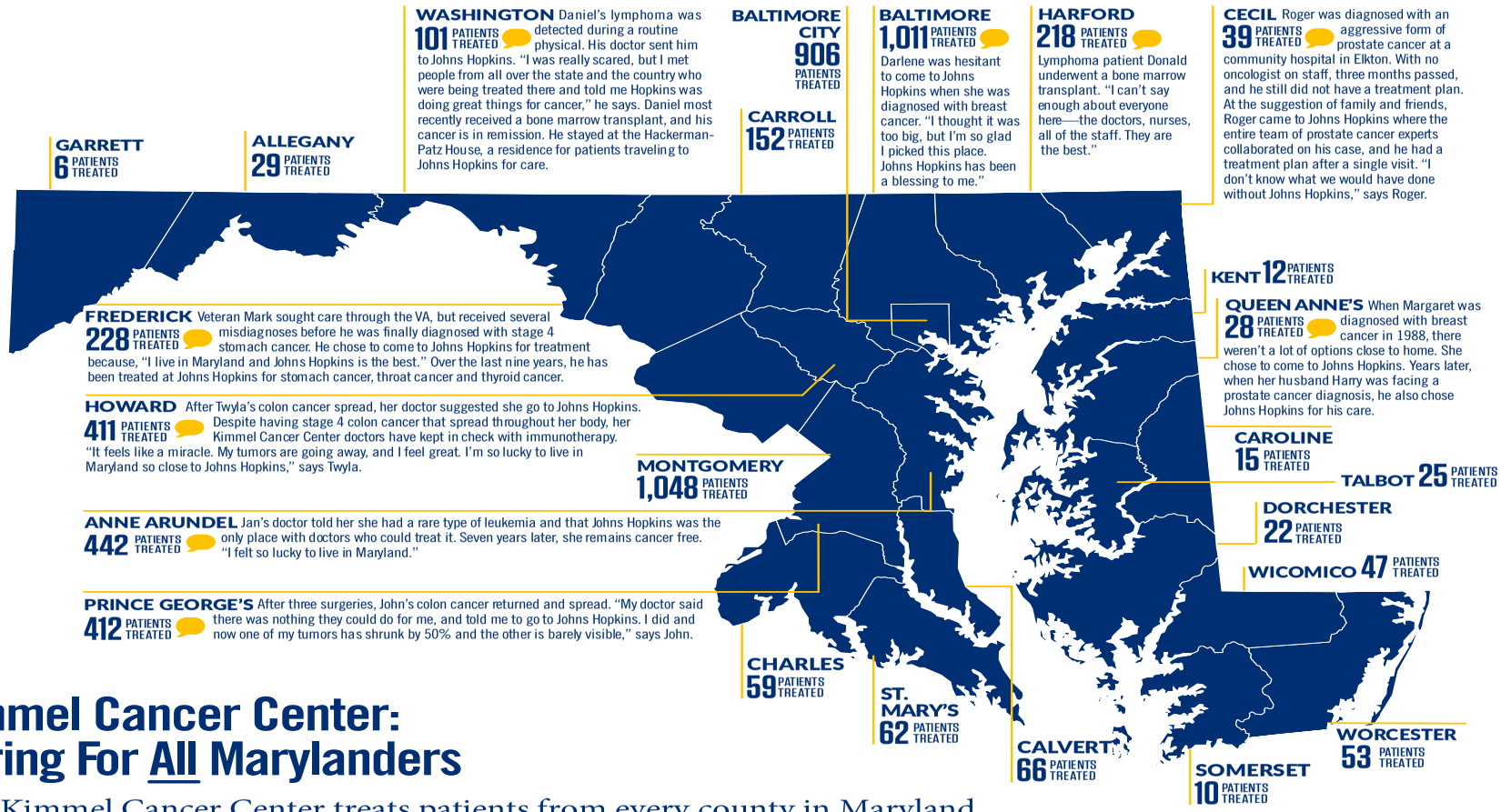


Smoke Exposure, E-Cigarettes: CRF investigator **Ana Rule, Ph.D.**, established that electronic cigarettes are important sources of metal exposure. Her research helps inform and guide smoking policies and legislation.

- *Science of the Total Environment*, February 2020: Smoke-free housing policies help reduce secondhand smoke exposure in public housing but is challenging to implement.
- *Environment International*, June 2019: Among the first studies to comprehensively characterize toxic chemicals related to waterpipe use and secondhand waterpipe exposure. Waterpipes are pipes used for smoking tobacco that draw the smoke through water to cool it. Waterpipe tobacco users and nonsmoking employees of waterpipe venues had higher urinary concentrations of several toxic metals, including manganese, cobalt and other contaminants distinctly different from cigarette smoke exposure.
- *Environmental Research*, November 2017: A study of e-cigarette users from Maryland found they were exposed to nickel and chromium from heating coils. Metal level standards called for to prevent involuntary metal exposure.

Blood Test Predicts Gastric Cancer Recurrence: FY18 CRF investigator **Victor Velculescu, M.D., Ph.D.**, developed a blood test that can predict recurrence of gastric cancer in patients following surgery.

- *Nature Communication*, January 2020: Patients who did not have mutations in the blood after surgery were all cured of cancer, while patients who had mutations in the blood typically recurred.



Kimmel Cancer Center: Caring For All Marylanders

The Kimmel Cancer Center treats patients from every county in Maryland. Approximately **65 percent** of Kimmel Cancer Center patients are from Maryland.

(Percentage of patients by region: Baltimore Metro Region 49%, the National Capital Area and Southern Maryland 31%, Eastern Shore 10%, Western Maryland 10%. Nearly 85% of patients coming from outside Maryland are from Washington, D.C. and other neighboring states.)

Patient numbers are from 2018. Patient testimonials are for care provided 2001–present.

IMPACT > FACES OF CRF PROGRESS IN MARYLAND

In 2013, then 56-year-old **Angela King**, ignored mammogram results to care for sick siblings. Today she is surviving metastatic breast cancer under the care of **Vered Stearns, M.D.** "People see me and can't believe I have breast cancer. I feel like I'm spreading joy and hope to others," says Angela. About 30% of Kimmel Cancer Center breast cancer patients have advanced cancers. "We want all women to be aware of new treatments, clinical trials and supportive care options available to them," says Dr. Stearns. "With the right care, women can live with advanced breast cancer for years and decades."

Retired school teacher **Darlene Stewart** is a two-time cancer survivor. She battled breast cancer in her 20's. Now, she is combatting advanced lung cancer under the care of CRF investigator **Joy Felciano, M.D.**, a lung cancer expert focused on breaking down barriers among populations who experience health disparities. Stewart is receiving a drug that targets a gene mutation in her cancer. The treatment has kept her cancer in check for the last six years. "I love Dr. Feliciano. It doesn't even feel like we're coming for a doctor's appointment," she says. "I feel great, and I have so much fun when I see her."

Darlene Young has a type of breast cancer known as estrogen receptor-negative and HER2 positive, that accounts for just 8% of all breast cancer. Kimmel Cancer Center experts are using PET scans as a biomarker to guide treatment. PET scans illustrate sugar uptake in cancer cells. If the PET scan still lights up two weeks after starting antibody therapy given for this type of breast cancer, doctors know the cancer is still active, and that those patients also need chemotherapy. Darlene receives the antibody alone, and her breast cancer remains in check. "Johns Hopkins has been a blessing to me," says Darlene. "The doctors and nurses have taken wonderful care of me, but there are so many others who helped me too. Social workers helped me navigate financial burdens, like the cost of driving back and forth for treatments. I'm so glad I picked this place."

IMPACT > KIMMEL IN THE COMMUNITY

Ashwani Rajput, M.D., a cancer surgeon and researcher with a special interest in health care disparities, was named director of the Kimmel Cancer Center for the Washington, D.C., region. Dr. Rajput oversees cancer services at Johns Hopkins Medicine's Sibley Memorial Hospital and Suburban Hospital, as well as Johns Hopkins' collaborative programs with Howard University and Unity Health that are designed to improve access for patients who live in Wards 7 and 8 in Washington, D.C. He also will be responsible for the expansion of cancer clinical trials offered in the D.C region, and

the development of a laboratory research enterprise — in connection with the National Cancer Institute — focusing on bringing new treatments to patients.

IMPACT > FY20 CRF AWARDS

FY20 Awards
$2,141,141

Grants:	All	New	FY Target
Translational Research	12	8	19
Faculty Recruitment	10	4	5
Faculty Retention	0	0	0
TOTAL	22	12	24

Alphabetical list of CRF grant recipients as of February 1, 2020:

Valsamo Anagnostou, M.D., Ph.D.: Evolution of neoantigen landscapes during Immunotherapy in NSCLC. **FACULTY RECRUITMENT, CONTINUED.**

Alexander Baras, M.D., Ph.D.: Leveraging clinical somatic mutation profiling of malignancies with modern electronic health records to better characterize etiologic, prognostic, and therapeutic association. **TRANSLATIONAL RESEARCH, CONTINUED**.

Anna Beavis, M.D., M.P.H., Addressing rising obesity and gynecologic cancer risks through primary prevention: a risk prediction model to guide screening for endometrial hyperplasia and cancer in obese women. **FACULTY RECRUITMENT, NEW**.

Otis Brawley, M.D.: Reduction of the cancer burden in Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins catchment area through disparities elimination. **FACULTY RECRUITMENT, CONTINUED**.

Joseph Bressler, Ph.D.: The e-cigarette sweetener ethyl maltol enhances metal transport and DNA damage. **TRANSLATIONAL RESEARCH, NEW**.

Namandje N. Bumpus, Ph.D.: Development of a novel class of Bim activators as chemotherapeutic agents. **TRANSLATIONAL RESEARCH, NEW**.

Geetanjali Chander, M.D., M.P.H., and **Heidi E. Hutton, Ph.D.**: Development of cultural adaptation and piloting of an avatar delivered smoking cessation intervention for low income smokers in Baltimore City. **TRANSLATIONAL RESEARCH, CONTINUED**.

Peter Espenshade, Ph.D.: Targeting SREBP cleavage activating protein (SCAP) in cancer. **TRANSLATIONAL RESEARCH, NEW**.

Ed Gabrielson, M.D.: Inhaled particulate matter and accelerated growth of heterotopic cancers. **TRANSLATIONAL RESEARCH, NEW**.

Mary Carol Jennings, M.D., Ph.D., and **Anne Rositch, Ph.D.**: Developing a novel geospatial database of HPV vaccine access points across Maryland and the Eastern Shore: building the evidence base to target rural disparities in cervical cancer. **TRANSLATIONAL RESEARCH, NEW**.

Norma Kanarek, M.P.H., Ph.D.: Understanding smoking behaviors in Baltimore City. **TRANSLATIONAL RESEARCH, NEW**.

Vincent Lam, M.D.: Longitudinal circulating tumor DNA profiling of resected esophageal cancer for early recurrence detection and characterization of tumor clonal evolution. **FACULTY RECRUITMENT, NEW**.

Tanguy Seiwert, M.D.: A novel model system to optimize immunotherapy for oral cancer patients using a histoculture-bioreactor system. **FACULTY RECRUITMENT, CONTINUED**.

Catherine Handy Marshall, M.D., M.P.H.: Modifiable risk factors in cancer. **FACULTY RECRUITMENT. CONTINUED**.

Elizabeth Platz, Sc.D., M.P.H.: Cancer prevention and control biostatistics core for research and proposals. **TRANSLATIONAL RESEARCH, CONTINUED.**

Karisa Schreck, M.D., Ph.D.: Determining predictors of response and resistance to RAS effector targeted therapies. **FACULTY RECRUITMENT, NEW.**

Jennifer Sheng, M.D.: An adaptive weight loss program in overweight or obese breast cancer survivors. **FACULTY RECRUITMENT, NEW.**

Claire Snyder, Ph.D.: PRO-cision Medicine: Testing to PRO system and patient-centered strategy for cancer care. **TRANSLATIONAL RESEARCH, NEW.**

Jessica Tao, M.D.: Circulating tumor DNA as a screening biomarker for aggressive breast cancer. **FACULTY RECRUITMENT, NEW.**

Jessica Yeh, Ph.D.: Behavioral lifestyle intervention in overweight or obese cancer survivors in Maryland: A dissemination and implementation study. **TRANSLATIONAL RESEARCH, CONTINUED.**

Cynthia Zahnow, Ph.D.: Alcohol exposure alters the epigenome to increase breast cancer. **TRANSLATIONAL RESEARCH, NEW.**

Jelani Zarif, M.D.: Targeting M2-tumor associated macrophages (M2-TAMs) in prostate cancer. **FACULTY RECRUITMENT, CONTINUED.**