PUTTING WOMEN’S CANCER RISKS IN PERSPECTIVE
We’ve come a long way in the treatment of cancer. The first chemotherapy had its beginnings amid the horrors of World War I when a pathologist noticed that in fatal casualties of mustard gas attacks all the lymphatics seemed to disappear. This led to the birth of modern chemotherapies as my alma mater, Yale Medical School, performed the first therapy in the 1940s using a derivative of mustard gas to treat lymphoma. For the next half century, cancer research never evolved much past developing a better chemotherapy or better radiation method.

Some of these advancements have been very effective. For instance, modern chemotherapies give patients with early stages of Hodgkin’s lymphoma a five-year survival rate of 90 percent. Even late-stage survival is 65 percent. However, too many people are still dying.

Thankfully, we are now in an era that is moving beyond chemotherapies and radiation. In the last several years, three fields have emerged that give me new hope that we can make significant progress against almost all cancers.

In this issue of Forefront, you will read how one researcher is using targeted therapies to shut down one of the most common and lethal forms of lung cancer. The combination therapy inhibits a known cancer gene that helps cancer stem cells re-establish themselves after therapy.

You will read about how Mayo Clinic Cancer Center researchers and physicians are using the latest genomic information to develop a breast cancer and ovarian cancer risk assessment individualized for each woman, based on her unique genome.

And you will read about how one Mayo Clinic finding nearly two decades ago opened up the world of immunotherapies, which are harnessing the body’s ability to heal itself. Immunotherapies are giving new options to people with some of the most difficult-to-treat cancers such as lung cancer and late-stage melanoma.

These three fields are revolutionizing not only how we treat cancer but also how we think about it. This is an incredibly exciting time for cancer research. New findings are released every day with real impacts — better quality of lives and longer lives. But so much more needs to be done. As a cancer researcher, I know that the arc toward effective cancer treatments can be frustratingly slow at times. But I also know it’s always bending toward better options.

I am deeply grateful for your commitment to cancer research and the role you play in bending the arc, making a difference for patients everywhere.

Thank you, and enjoy this issue of Forefront.

Robert B. Diasio, M.D.
Director
Mayo Clinic Cancer Center
William J. and Charles H. Mayo Professor
Each Woman’s Risk
Personalizing Risk Assessment for Breast Cancer

Taking the First Step
Addressing Disparities in the Use of Minimally Invasive Surgery

Turning the Page
A New Drug With Roots at Mayo Clinic Is Saving Lives

Attack the Gap
New Immunotherapy May Help Fight Ovarian Cancer

Ever Evolving
A Look at Proton Beam’s Impact on the Future of Cancer

Better Cancer Care
Meeting the Needs of Florida Residents

Research Soars
The Fifth District Eagles Cancer Telethon

Meet the Investigator
Ex-Smokers Still at Risk for Lung Cancer

Just because you quit smoking a while back doesn’t mean you shouldn’t continue to be screened for lung cancer.

A study led by Ping Yang, M.D., Ph.D., an epidemiologist at Mayo Clinic Cancer Center in Rochester, Minnesota, found that expanding lung cancer screening to include people who quit smoking more than 15 years ago could detect more cases and further reduce associated mortality.

“The common assumption is that after a person has quit for so many years, the lung cancer rate would be so low that it wouldn’t be noticeable,” she says. “We found that assumption to be wrong.”

Dr. Yang and colleagues found that, compared with other risk categories, patients who quit smoking for 15 to 30 years accounted for the greatest percentage of patients with lung cancer who didn’t qualify for screening.

“Lung cancer rates are dropping because smoking is decreasing, but that doesn’t mean that our current screening entry criteria are good enough,” Dr. Yang says. “It is understandable because the relative importance of risk factors changes over time. We need to adjust the screening criteria periodically, so we can catch more lung cancers in a timely fashion, meaning at a curable stage.”

A New Option for Bladder Cancer

People with metastatic bladder cancer have few treatment options after failure of chemotherapy — until now.

In early May, the Food and Drug Administration (FDA) approved the immunological drug atezolizumab to treat the disease. The decision came following results of an international, multisite phase 2 clinical study published in The Lancet. Mayo Clinic’s Florida campus was one of the largest sites involved in the study.

Of 310 patients, 15 to 20 percent had significant and lasting response. Richard W. Joseph, M.D., a Mayo Clinic oncologist involved in the study, says the drug works by helping the patient’s own immune system fight cancer.

“Until now, chemotherapy has been the only option for these patients, but many people are unable to tolerate the full course of chemotherapy, due to its toxicity,” says Dr. Joseph, whose research is part of the Cancer Immunology and Immunotherapy Program within the Mayo Clinic Cancer Center. “New approaches, such as immunotherapy medications like this, are desperately needed.”

Immunotherapy drugs have also recently been approved for melanoma, kidney cancer and lung cancer.

Aspirin May Reduce Bile Duct Cancer

“Our study found that individuals who took aspirin had a more than a 2 ½- to 3 ½-fold lesser chance of developing bile duct cancer, compared to individuals who did not take aspirin,” says Lewis R. Roberts, M.B., Ch.B., Ph.D., the senior author of a study recently published in Hepatology.

Bile duct cancer is an uncommon cancer that forms in the slender tubes (bile ducts) that collect bile formed by the liver and deliver it to the intestines, where the bile aids in digestion of food. It is an aggressive type of cancer that progresses quickly and is difficult to treat.

“We know that continuous unremitting inflammation is one of the main factors that promotes cancer of the bile ducts,” says Dr. Roberts, who is the Peter and Frances Georgeson Professor of Gastroenterology Cancer Research. “Aspirin, with its anti-inflammatory properties, may reduce the risk of bile duct cancer by lessening inflammation.”

But it is not certain that aspirin is safe to use for cancer prevention. Dr. Roberts and his colleagues say additional confirmatory studies are needed before aspirin can be recommended for use in preventing bile duct cancer.
Shutting Down Stem Cells, Tumor Growth in Lung Cancer

Researchers on Mayo Clinic’s Florida campus have shut down one of the most common and lethal forms of lung cancer by combining the rheumatoid arthritis drug auranofin (Ridaura) with an experimental targeted agent.

The combination therapy worked in a laboratory study to stop lung adenocarcinoma associated with mutation of a gene (KRAS) that plays a key role in cell signaling. The study was published in the journal Cancer Cell.

“Conventional chemotherapy can effectively kill non-stem cancer cells, but cancer stem cells often survive,” says Mayo Clinic’s Alan P. Fields, Ph.D., a cancer biologist and the Monica Flynn Jacoby Professor of Cancer Research in the Department of Cancer Biology.

“Then, once therapy is stopped, these cancer stem cells can re-establish the tumor and cause a relapse.”

Dr. Fields says the current study builds on a previous report from his lab that showed the cancer-causing protein kinase Ciota (PKCi) is critical for maintaining cancer stem cells in a related form of lung cancer — squamous cell carcinoma. In the current study, Dr. Fields’ group found that PKCi also controls cancer stem cells in lung adenocarcinoma involving the KRAS oncogene.

However, he and colleagues were surprised to find that PKCi activates different pathways in each lung cancer. In lung squamous cell carcinoma, PKCi activates a pathway called hedgehog signaling. In KRAS lung adenocarcinoma, it activates Notch3 signaling.

Using this knowledge, Dr. Fields’ group found that the PKCi inhibitor auranofin can be combined with a second drug that inhibits NOTCH signaling to effectively inhibit lung adenocarcinoma cell growth.

“This research indicates that auranofin might be useful in treating two different major lung cancer types,” Dr. Fields says. “By combining auranofin with a second agent that targets the specific PKCi signaling pathway activated in that cancer subtype, we believe we can fine-tune therapy to the particular vulnerabilities of each of these very common, difficult-to-treat lung cancers.”

A Possible Breakthrough for a Rare Cancer

Each year, about 200 to 400 Americans develop pancreatic acinar cell carcinoma, a rare form of cancer that has no effective standard of care. However, a recent study from Mayo Clinic in Jacksonville, Florida, is providing new hope.

Using human pancreatic acinar cancer cells transplanted in mice, the researchers showed that the chemotherapy drug oxaliplatin (Eloxatin) stopped the growth of the tumor after only three treatments. And it didn’t come back after the treatment ceased.

Importantly, the tumor cells were found to contain a DNA repair mutation.

Oxaliplatin inserts itself into DNA, which results in the death of multiplying tumor cells — particularly if those cells carry a DNA repair mutation, that is commonly the case in this rare tumor.

“The demonstration of the activity of oxaliplatin against this tumor is consistent with the finding of frequent DNA repair mutations and for an individualized medicine approach toward treatment,” says John A. Copland III, Ph.D., study senior investigator.

The study’s co-author, oncologist Gerardo Colon-Otero, M.D., adds, “These findings point to a possible new effective treatment for this rare tumor.”
Protecting Children

Vaccine Prevents Cancer Caused by HPV

Human papillomavirus (HPV), the sexually transmitted infection that is the cause of cervical cancers as well as the majority of mouth and throat cancers, is an outlier in the cancer world — in a good way. Since 2006, vaccines have been available. They are safe and nearly 100 percent effective against the most common cancer-causing strains of the virus.

But unlike many countries, the U.S. has failed to vaccinate its population against HPV. The vaccines are routinely recommended in the U.S. for boys and girls 11 to 12 years of age, but by the time they are 13 to 17 years old, only 20 percent of boys and 40 percent of girls have completed the three-dose series.

Why does early vaccination matter? The recommendations target young adolescents to take advantage of their strong immune response and to deliver all three doses long before any exposure to the virus.

“These sexually transmitted viruses are things we don’t like to think about. And of course we want our adolescents to put off being sexually exposed for years and years, as appropriate,” says Robert M. Jacobson, M.D., a pediatrician and medical director of the Population Health Science Program in the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery.

But, he says, the HPV vaccine saves lives and helps patients avoid surgical and medical procedures. In the 10 years since the vaccine became available, the prevalence of HPV strains responsible for cervical cancer has been cut in half — and that’s despite relatively low vaccination rates in the U.S.

“We know the vaccine works, so imagine if we boosted these vaccination rates to those of other routinely recommended vaccines, such as Tdap,” the vaccine that protects against tetanus, diphtheria and pertussis (whooping cough).

“We can get even closer to wiping out these cancers once and for all,” Dr. Jacobson says.

Like several other childhood vaccines, the HPV vaccine must be administered through a series of three doses over the course of at least six months, and that can be a challenge for families of teenagers. Teens just do not have that much contact with clinicians.

So since 2006, primary care providers at Mayo Clinic in Rochester, Minnesota, have routinely recommended that patients begin the vaccine at 9 or 10 years of age instead of 11 or 12. With a large cohort of this younger patient population to study, Dr. Jacobson and a team of researchers from the center tested whether starting the vaccine series earlier was associated with higher rates of completion.

They used data from the Rochester Epidemiology Project, a unique medical records linkage system that fuels many population-based studies at Mayo Clinic.

The team’s conclusion: Starting the HPV vaccine earlier worked. Among children starting the vaccine at 9 or 10 years of age instead of 11 or 12, nearly 1 in 5 failed to complete the series. Among those between the ages of 9 and 10, it was only 1 in 50.

Based on these findings, Mayo Clinic now recommends patients at all Mayo campuses begin the HPV series at 9 to 10 years of age rather than 11 to 12 years.

“We can get even closer to wiping out these cancers once and for all.”

— Robert M. Jacobson, M.D.
‘It’s Unbelievable’

Seeing, Feeling the Tumor Before the Operation

Michael Slag is in awe. In his hands he holds an exact replica of his ribs, aorta, pulmonary artery, veins and the invasive tumor.

The growth is a type of lung cancer called a Pancoast tumor, so rare that Mayo Clinic has only seen 60 cases in the past 20 years.

“We frequently may have a plastic surgeon, an orthopedic surgeon, a vascular surgeon, and myself, all involved in a Pancoast tumor resection,” says Mayo Clinic thoracic surgeon Shanda Blackmon, M.D.

Usually the procedure requires opening the chest cavity so surgeons can see the entirety of the tumor. However, with Michael, the surgical team tried something new.

Radiologists spent hours incorporating MRI images, CT scans and sophisticated computer software to first create a virtual model of Michael’s anatomy, color-coded for each specific tissue type. The team fed all that information into a computer, which then took about 70 hours to print a 3-D model of Michael’s anatomy and tumor.

Dr. Blackmon says the model helped eliminate surprises, by showing the team exactly how Michael’s large tumor was wrapped around several critical nerves and blood vessels. The model showed the team that Michael’s lung tumor could be removed thoracoscopically, without opening his chest.

“It’s unbelievable,” Michael says. “In fact, I was walking the first night after surgery. I’m sure if my chest would have been split open I probably would have been in an ICU and probably had a whole different experience.”
Every day, Sandhya Pruthi, M.D., sees women seized with the fear of having breast cancer. She is deluged with questions: I have a family history of breast cancer; does this mean that I am at an increased risk? Does my sister have the same chance of getting breast cancer as I do? Will I get it? Can I do anything to prevent it?

Personalizing Risk Assessment for Breast Cancer
In recent years, answering these questions has become much easier. Doctors are now able to provide more viable options for prevention. For instance, studies show that the risk of contracting breast cancer can be reduced by 50 percent through a five-year course of preventive drugs, such as tamoxifen. However, women still struggle with the decision to take the medication.

“These drugs have been proven to reduce breast cancer in women with an increased risk by 50 percent if taken, but there’s a low uptake,” says Dr. Pruthi, a consulting physician in Mayo Clinic’s Breast Diagnostic Clinic. “We haven’t given our patients the tools and information from a personalized approach that they need to properly understand how high their risk is. With the right personalized information, we feel our patients are better served because we can make the right treatment decisions for each patient.”

Our DNA is the key to unlocking personalized answers.

**A Single Number**

Over the past decade, researchers have identified over 200 different regions of the genome that have been shown to influence breast cancer development. Common inherited variants in these regions contribute to a small amount of a person’s overall risk, while other variants in genes, such as BRCA1 or BRCA2, are rare and place women at a very high breast cancer risk. Combining information from these rare and common genetic mutations is necessary to accurately define a woman’s risk.

To individualize each woman’s risk, Mayo Clinic researchers Celine M. Vachon, Ph.D., and Fergus J. Couch, Ph.D., worked with an international team to combine information from 77 of these common genetic variants. This complex statistical score, called a polygenic risk score (PRS), provides a single number that can be used to better inform a woman’s breast cancer risk.

The Mayo Clinic researchers took the work a step further in a companion study that combined these genetic variants with other risk factors, including breast density, which has been shown to put women at a four- to sixfold increased risk of breast cancer.

“We can add this information to the other traditional risk factors, such as family history, lifestyle, previous biopsies and breast density,” says Dr. Couch, a molecular geneticist and pathologist at Mayo Clinic and the Zbigniew and Anna M. Scheller Professor of Medical Research in Honor of Dr. Thomas J. McDonald. “This really improves our ability to identify those women who are at a higher risk of getting breast cancer.”

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The Next Step

Dr. Pruthi believes that combining the individual polygenic risk score with current standard risk assessment tools will help women decide whether the preventive medication is right for them. In March 2016, Dr. Pruthi, along with Drs. Couch and Vachon and Daniel J. Schaid, Ph.D., a statistical geneticist and the Curtis L. Carlson Family Professor of Genomics Research, launched a clinical study at both Mayo Clinic and the CancerCare Manitoba Clinic in Canada to test this theory.

Study participants will receive their polygenic risk scores after a simple blood test. Once the report is administered, women will answer questions inquiring about the benefits of having the additional information gained from the polygenic risk score, as well as whether or not it helped them decide to take a preventive medication that has been proved to reduce breast cancer risk.

As part of the study, researchers will follow participants for two additional years, ask them to complete questionnaires on quality of life and assess if they are still taking the preventive medication. This is the first study of its kind to provide information on the polygenic risk score, to follow patients at increased risk of breast cancer, and to assess the benefits of preventive medication.

A polygenic risk score and other risk factors, including family history, lifestyle, previous biopsies and breast density, help identify those women who are at a higher risk of getting breast cancer.
Understanding the Risks

Breast and ovarian cancers hit some families harder than others. One or both arise over and over again in a single family tree, claiming the lives of an aunt, a grandma, a sister, a mother.

Understandably, these cancer diagnoses worry every woman in that family tree, leaving each with many hard-to-answer questions: Will the cancer strike me? What can I do to prevent it? What will life be like after a preventive mastectomy?

In a review article published in the New England Journal of Medicine, a pair of Mayo Clinic Cancer Center researchers provides an overview to help guide these women through their treatment options — before cancer develops.

In the article, Lynn C. Hartmann, M.D., an oncologist at Mayo Clinic’s campus in Minnesota, and Noralane M. Lindor, M.D., a medical geneticist at Mayo Clinic’s campus in Arizona, provide optimal risk assessment for these women; discuss the effectiveness of risk-reducing surgery; describe the side effects of these procedures; and list alternative strategies for cancer prevention. They also provide best practices to help with the decision-making process.

“Although these women can reduce their risk considerably through preventive mastectomies or removal of their fallopian tubes and ovaries, or both, these procedures come with their own complications and psychosocial effects,” Dr. Hartmann says.

Providing this information for women from families with breast and ovarian cancers while they are still cancer-free will enable them to make their care decisions based on data and science, and not out of fear of the unknown.

Looking to the Future

The next push with the study will be adding women with a BRCA mutation. If women have a mutation in BRCA1 or BRCA2, they are at a 67 percent lifetime risk of getting breast cancer. However, a 67 percent lifetime risk means 33 percent of women with this mutation don’t get breast cancer.

“So who gets breast cancer and who doesn’t? Or, at what age will they get it? We might be able to personalize their risk through the polygenic risk scores and answer some of these questions by using these common variants. Showing that someone thought to be at a 67 percent lifetime risk is actually only at a 25 percent lifetime risk by answering some of these questions is really beneficial,” say Dr. Couch.

Dr. Vachon agrees, pointing out the endless possibility of this research.

“As a team, we are hoping to better personalize not only treatments but also breast screening approaches based on genetics and risk factors, so patients experience personalized medicine across the spectrum — screening, prevention and treatment,” she says.

“In the future, we imagine obtaining a blood sample as a source of genetic information on each patient that can help personalize strategies for each woman, not only in breast cancer but hopefully across all diseases.”
TAKING THE FIRST STEP

Addressing Disparities in the Use of Minimally Invasive Surgery
“Would you like to try to walk?” the nurse asks. It was 7 p.m., only a few short hours after undergoing a hysterectomy to combat the patient’s shocking diagnosis — endometrial cancer.

A month before, Mary Ann Knesevich, M.D., was living in Texas as a wife, a mother of two and a practicing psychiatrist conducting clinical trials of new central nervous system medications. Dr. Knesevich never imagined she would be diagnosed with cancer, especially since no one in her family on either her mother’s or father’s side had the disease.

But here she is, lying in a hospital bed after a hysterectomy to save her life. Dr. Knesevich remembered from her days in medical school that a hysterectomy was a difficult, painful surgical procedure with a long recovery. But that was 35 years ago.

When the nurse asks her to walk, she says to herself, “Well, okay, let’s give it a go.” Accompanied by a pair of watchful nurses, Dr. Knesevich inches out of bed, stands and, to her surprise, makes two laps around the unit without difficulty or pain.

The next day, a little more than 24 hours after surgery, she leaves the hospital. A week later, Dr. Knesevich is back to work in Texas.

**Discovering a Disturbing Discrepancy**

The key to Dr. Knesevich’s quick recovery was the type of surgery her care team at Mayo Clinic used — a minimally invasive hysterectomy. At Mayo Clinic, physicians use laparoscopy or robotics to treat 90 percent of patients like Dr. Knesevich who have early-stage endometrial cancer. However, there is a significant gap in its use across the country, greatly affecting patient care and bottom lines.

But for Sean C. Dowdy, M.D., the bottom line isn’t just financial.

As a professor in the Mayo Clinic Cancer Center, he joined the leadership team for the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery to improve the quality of care patients receive, including surgery delivered to women with gynecologic cancers.

“Minimally invasive surgery results in reduced hospital stay, reduced complications, faster recovery, faster return to work and improved quality of life compared with laparotomy (open surgery),” Dr. Dowdy says. “The patient-reported outcomes are much, much better with minimally invasive surgery.”

With this in mind, Dr. Dowdy joined forces with researchers at Johns Hopkins and the University of California to answer a disturbing question: If minimally invasive surgery is recommended by the Society of Gynecologic Oncology and the Commission on Cancer for stage I-III endometrial cancer, then why don’t all surgeons employ this technique?
The team examined data from 32,560 patients treated at 1,051 hospitals between 2007 and 2013. And while they expected to see that the use of minimally invasive surgery for the treatment of endometrial cancer varies, they were shocked at what they found — surgeons across the nation only use the procedure in less than half of patients.

Dr. Dowdy and colleagues concluded that if minimally invasive surgery had been utilized in 80 percent of those patients instead of roughly 50 percent, it would have averted 2,300 complications and saved approximately $19 million.

Why Does the Disparity Exist?

Dr. Dowdy and his team are now turning their focus on the reason for this disparity. He suspects some of it is due to lack of awareness.

“We have to do a better job of educating our patients that minimally invasive surgery might be an option for them,” says Dr. Dowdy. “But not only do we need to educate our patients, we need to hold ourselves accountable. One of the biggest challenges we have today in health care is to understand how to help physicians evolve more quickly as new medical techniques become available.”

To address the urgent need for change, Dr. Dowdy recently partnered with the Society for Gynecologic Oncology to introduce minimally invasive surgery as a national quality measure for patients with endometrial cancer. He says as the Mayo Clinic Cancer Center and the Kern Center for the Science of Health Care Delivery continue to find ways to improve health care, the team’s findings could have a broader impact on implementation of minimally invasive surgery in other cancers as well.

A Bright Outlook

Back in Texas, Dr. Knesevich remembers her original diagnosis. “Of course, I immediately thought about my family and the impact this would have on them, particularly if my cancer was found to be one that would not be easily treated or that would be far advanced,” Dr. Knesevich says. “Every mother wishes to see her children grown, educated and successful in life, and I certainly wished to see that as well and hoped that this diagnosis would not deny me that wish.”

For many patients, the anxiety of a cancer diagnosis is amplified by the daunting journey associated with treatment. Chemotherapy can make your hair fall out. Radiation can make you nauseous. And surgery can knock you off your feet for weeks with pain and discomfort.

But thanks to the right procedure, a week after surgery Dr. Knesevich was back to work conducting clinical trials and presenting research projects. And most importantly, she was home, enjoying her family.
MY LAST ONE

SO happy for you! Congrats! Cornelia

Congrats! Jess

Congrats!!!

Statmir
DubDroma, Mayo

#35
The 10th floor waiting room bathes Debra Wagner in the natural light from a wall of windows. A nurse calls her name, and as she walks through a set of automatically opening doors, Svetomir N. Markovic, M.D., Ph.D., is waiting on the other side.

As usual, he looks slightly disheveled from the insanely long hours he puts in trying to help people battle melanoma — 8 a.m. to 6 p.m. seeing patients, followed by another eight to 10 hours in the lab looking for cures. Then there are the conferences, the special meetings and the funerals. Far too many funerals.

But as he sees Debra come through the doors, he doesn’t look tired. Instead, he’s beaming. “There she is,” he says loudly as he opens his arms and gives Debra a hug. “Congratulations. You did it.”

Debra pulls out a homemade placard adorned with rhinestones and flower designs. It says in all caps, “MY LAST ONE.”

Dr. Markovic signs the placard, and Debra begins to cry.

“Thank you for everything,” she says through tears.

“Oh, you’re welcome,” Dr. Markovic says quietly and hugs her again. “Don’t cry. Don’t cry.”

Debra knows she’s lucky to be alive. A few years ago, she was diagnosed with one of the deadliest cancers — metastatic melanoma.

Many people think of melanoma as a simple skin cancer that is easily treatable, as did Debra in 2012 when a mole started to grow and bleed. She was diagnosed with localized melanoma and treated with the drug interferon.

It seemed to work, but then in 2013, she noticed a fast-growing lump under her skin — the melanoma had spread.

Metastatic melanoma has no cure. It kills more than 10,000 people each year and has a five-year survival rate of about 16 percent. At first, it looked like Debra might become one of those statistics.

“I burst into tears because it had come back a second time,” Debra says as she recalls her diagnosis.

Luckily, her mother was a patient at Mayo Clinic and called her doctor there, who said, “I know somebody, the best, for your daughter. Have her come here to Mayo Clinic.”

Within a few hours, Debra got a call from a nurse and she was on her way to Mayo Clinic.

“A New Drug

Debra’s surgery was successful, and as she recovers, she is hopeful for everyone else that’s fighting this ugly beast called melanoma.”

— Debra Wagner
Relief and Hope

After performing an MRI scan, doctors at Mayo Clinic had hard news for Debra — the melanoma that started in her thigh had spread to her brain, liver and lungs.

“Oddly enough, I was actually relieved because then I finally knew,” Debra says. “The whole time, from when I was first diagnosed until I had the interferon and had to go off of it, I wasn’t sure if I was OK. Once I knew what was going on, I was relieved. From day one, Dr. Markovic and my oncology nurse, Lisa Kottschade, were so positive, especially Dr. Markovic. He puts a positive spin on everything. He just made me feel that everything was going to be OK.”

Though the cancer had metastasized, Dr. Markovic did have some good news for Debra: Mayo Clinic was hosting a phase 1 clinical trial testing a new drug to treat her disease.

The development of the drug, called MK-3475, was dependent in part on the research lab of Lieping Chen, M.D., Ph.D., while he was at Mayo Clinic. Dr. Chen discovered previously unknown molecules involved in how a form of white blood cells, lymphocytes, communicates with other cells.

One of the most insidious aspects of cancer development is how the disease evades the immune system. Dr. Chen discovered that the PD-L1 molecules put the brakes on potent, disease-fighting white blood cells called T cells, a major component of the immune system. With this knowledge, Dr. Chen and colleagues developed an antibody to block the molecule’s function.

After the findings were published, multiple pharmaceutical companies began leveraging Mayo Clinic’s discoveries to develop and win approval for a new generation of cancer-fighting drugs.

During clinical trials, MK-3475 showed such promise that the Food and Drug Administration (FDA) granted it a “breakthrough therapy designation” after completing a phase 1 trial involving 411 patients.

Usually drugs have to advance through larger phase 2 and phase 3 trials, but the FDA gave MK-3475 priority review because it showed “a significant improvement in safety or effectiveness in the treatment of a serious condition.”

In September 2014, the FDA gave the drug, now available under the brand name Keytruda, approval as a first-line treatment for advanced melanoma. It has since been approved for cancers of the breast, bladder, gastrointestinal system, head and neck, and others.

In cancer treatment, every day spent administering an ineffective drug is another day that the cancer grows and gets stronger. Too much time delivering the wrong treatment can have lethal consequences.

In the two years before Keytruda was approved, the FDA approved five other treatments for advanced melanoma, giving doctors more than half a dozen choices. Debra tried one, interferon, and it didn’t work. Was Keytruda the right one for her? Based on his prior experience and understanding of her disease, Dr. Markovic believed it was. But there was no way he could be sure.

For patients like Debra, it’s imperative to take the guesswork out of cancer care.

Recently, Mayo Clinic researchers, led by Haidong Dong, M.D., Ph.D., who helped design the experiments that led to Dr. Chen’s discovery, identified a protein biomarker whose frequency may help physicians predict how a patient with melanoma will respond to a PD-L1 blockade immunotherapy such as Keytruda.

Predicting Response

To date, Keytruda has been one of the most effective drugs ever developed to treat metastatic melanoma. However, its response rate hovers around 35 percent. That meant that when Debra started her drug regimen, nobody was sure if it would work. This unknown could have very real ramifications.
The marker, called Bim, is a protein that helps coordinate programmed cell death. Researchers at Mayo Clinic found that patients with metastatic melanoma who responded to Keytruda had more Bim and PD-1 in their blood prior to therapy than did patients who did not respond. “If I know that a patient has a very high likelihood of responding to anti-PD-1 therapy, I’m going to be more inclined to recommend that treatment and feel better about the choice,” Dr. Dronca says.

A New Life

Like almost all people with melanoma, Debra contracted the disease from tanning. When she was young, she says she believed the norm that ideal beauty meant tan and thin. But the disease helped her realize what’s really important in life.

“All that tanning — it wasn’t worth it,” she says, sitting in a Mayo Clinic treatment room with an IV tube sticking out of her arm. Debra thinks about where she was a few years ago. Her body was riddled with stage IV melanoma, and the odds said she wouldn’t live.

“Melanoma has affected every single aspect of my life,” she says.

But with Keytruda running through her veins, today Debra has new hope. She rejoiced recently when Dr. Markovic told her she was in full remission and wouldn’t need to keep coming in for treatments, which she had been doing for two years. She’ll still need regular monitoring, but she’s optimistic the treatment knocked out the cancer for good.

“It’s been a real miracle for me,” Debra says, with tears welling up. Her voice shakes as she continues. “I’m so grateful. I am so grateful to whoever had a hand in developing the drug, to everyone here at Mayo Clinic. I can’t say enough about how grateful I am. I’m hopeful that it will stick. And I’m hopeful for everyone else that’s fighting this ugly beast called melanoma.”

Doctors at Mayo Clinic are just as hopeful that their work will help more people like Debra receive the exact treatment they need when they need it.
ATTACK THE GAP

New Immunotherapy May Help the Body Fight Ovarian Cancer
It was only when Kathi Schroeder took to the bone-chilling streets of Cedar Rapids, Iowa, on her bike last January that she noticed something was not right.

“I was having trouble breathing; just taking a deep breath was difficult,” she remembers.

Kathi went to her local doctor’s office and was prescribed a round of antibiotics and steroids to address what the doctor considered a respiratory issue.

“I felt better for a little while — but then by March, I just bloated up and was having increasing difficulty breathing,” she says. “It was terrible. I just thought, something is horribly wrong.”

As the symptoms progressed, Kathi’s concern grew, and on March 18, 2015, she went in for a chest X-ray. Her doctor took one look at the X-ray and sent her directly to the emergency room for a CT scan and additional X-rays.

The news was not what she was expecting. “Right there in the emergency room, they told me, ‘We think you might have ovarian cancer.’”

A week later Kathi arrived at Mayo Clinic in Rochester, Minnesota, in search of answers. A series of biopsies on the fluid around her lungs confirmed her worst fears. “To be hit at that point with ‘You have stage IV cancer,’ you have to stop and say, ‘Where do I go from here?’”

**Attacking the Cancer**

Kathi had a general idea of the statistics. Even if she beat the cancer in the first round, upward of 80 percent of women with her diagnosis will have a recurrence of, and ultimately die of, the cancer. A main reason why is because, most of the time, ovarian cancer only presents after it has spread within the abdominal cavity. And since it is constantly bathed in abdominal fluid, the cancer tends to break off and spread before the tumor grows in size.

Unfortunately, the only approved treatments are surgery and chemotherapy.

“The standard options against ovarian cancer are maxed out,” explains Mayo Clinic oncologist Matthew S. Block, M.D., Ph.D. “We have drugs that work and surgery works, but they don’t work perfectly. They are reasonably effective when there’s a known tumor, but they’re not effective to continue throughout the remission. Unfortunately, the majority of my ovarian cancer patients still die of their cancer.”

Kathi didn’t want to accept that finality.
First of Its Kind

One of the trickiest aspects of cancer is its ability to outwit the body’s immune system. For instance, T cells are on the forefront of the immune system. It’s their job to recognize invasive cells and kill them. They do this by detecting proteins — cells with familiar proteins are left alone; cells with foreign proteins are destroyed. But as cancer cells grow, they devise ways to kill the T cells or trick them into leaving the cancer cells alone.

“The idea behind cancer vaccines is to present the tumor to the immune system in such a way that the immune system attacks it as if it were a virus or bacteria,” Dr. Block says. “Essentially, we need to tell the immune system that this is a threat, and we need to attack it.”

To help patients harness the power of their immune systems, Dr. Block and colleagues launched a clinical trial. The phase I trial targets a specific protein, folate receptor alpha, in the cancer cells. It also uses a specific type of T cell, Th17, to trigger an immune response. These T cells not only attack the tumor cells but regulate other T cells that suppress the immune system’s response.

The trial is the first of its kind.

“There are plenty of other ovarian cancer vaccines, but to my knowledge, this is the first time something has that goal of attacking T-reg cells via Th17 cells,” Dr. Block says.

When Kathi heard about the study, she knew she wanted to participate. Fortunately, she met the criteria — have stage III or IV cancer, be in remission, and have completed both surgery and chemotherapy.

“I’m always like, This is the next step, this is the next step,” she says. “That’s just my nature. This study has helped a lot because it feels like I’m doing something. It just makes you feel very powerful. I want it to work not only for me but also for other women that are out there in this situation.”

Back on the Bike

Kathi arrives at Mayo Clinic every three weeks for a series of shots and to be tested for recurrence. After the first three months, she will reach the maintenance phase — only coming in every three months for two years. “This is so easy. You get a few little shots, and you’re free to go. It’s just a wonderful study.”

And so far so good.

Kathi is back to riding her bike and is training for RAGBRAI — a nearly 500-mile, seven-day bike ride across Iowa.

“You wonder, how much of my life can I cram into the next year, two years,” she says. “The people that live past five years are what, maybe 20 percent? Where do you go with that when you have a family? You look to your bucket list and say, ‘Let’s just plan it and do it.’

“There’s not a day that goes by that I don’t think about it. I try to keep a positive attitude. I mean, in this case, it feels like I’m doing something — but you still have to live day to day. You can’t just stop living. This study is helping me with that.”
IMAGINE WATCHING your 14-year-old son play lacrosse one day and the next day he’s being helicoptered to Mayo Clinic for brain surgery. Unfortunately, this is the story of Michelle and Patrick Fisher, whose son Jackson was suddenly diagnosed with a large malignant brain tumor.

Jackson’s tumor needed to be reduced even further after chemotherapy. Surgery wasn’t an option because of the risky location — fortunately, proton beam was. Proton beam is considered the ideal radiation treatment for children because their organs are still developing.

After seven weeks of proton beam treatment, Jackson was back to his normal life, playing lacrosse and basketball, hanging out with friends, and spending time with his brother and pets.

“Proton beam therapy was available at Mayo just in time for my child.”

— Michelle Fisher (Patrick’s Mom)
To help people similar to Jackson, the Mayo Clinic Cancer Center opened its first proton beam radiation therapy facility in Rochester, Minnesota, a year ago. Since then, it has also opened a proton beam facility in Phoenix. These facilities use pencil beam scanning, the most precise form of proton beam therapy available. This allows Mayo Clinic physicians to paint each patient’s tumor with radiation while leaving surrounding tissue undamaged.

The results for people like Jackson, whose tissue is still growing, means fewer side effects and secondary cancers. However, as with any new therapy, there is a gap in scientific data to translate its potential. To close this gap, Mayo is conducting groundbreaking research and clinical trials to establish which cancers are best treated by protons and which cancers benefit from combination therapies, all while gaining a greater understanding of the disease.

“Mayo Clinic is at the forefront of proton beam therapy and cancer research, converting science into real benefits for every patient, every day,” says Sameer R. Keole, M.D., medical director of the Proton Beam Therapy Program in Phoenix. Dr. Keole understands the power of proton beam, as he treated more than 300 patients with proton beam at two other cancer centers prior to joining Mayo Clinic.

Dr. Keole and his Mayo colleagues are collaborating with proton beam programs at other cancer centers to help advance the science and expand treatment capabilities. Experts in cancer biology, genomics, physics and engineering have already begun studying ways to refine and expand the use of proton beam therapy.

Their work will ensure people similar to Jackson get the exact treatment they need, when they need it.
Key Projects

Establishing a Patient Database to Measure Outcomes
Critical to Mayo’s treatment and research efforts, a registry captures a complete summary of the history, diagnosis, treatment and disease status for registered radiation therapy patients. This registry allows researchers to compare outcomes based on the type of radiation therapy each patient received.

To date, Mayo Clinic has approached 1,577 radiation therapy patients and accrued 1,449 (over 90 percent) in its patient registry. Of these patients, 209 are proton beam patients. Using the registry data, researchers have designed and built an electronic prospective database to collect outcome data such as survival, tumor control, side effects and complications, quality of life, functional outcomes and costs for proton beam therapy from the patient’s perspective.

Mayo Clinic researchers are sharing their data with other proton beam programs at academic medical centers for the development of clinical trials.

Decreasing the Cost of Cancer Care While Improving Patient Outcomes
Studies are underway to determine the fewest number of treatments patients will require and the resulting impact on lowering the cost of cancer care. The potential benefits to patients are myriad, including a decrease of long-term health issues, fewer side effects, a lower incidence of recurrent cancer and fewer out-of-pocket expenses. The decrease in expense can be attributed to no longer needing to travel for proton beam treatment and the shorter overall treatment schedule.

Evaluating Toxicity and Efficacy of Cancer Treatment Options
Mayo Clinic researchers are performing clinical trials to determine the effectiveness of proton beam on a number of different cancer types and in combination with surgery or with other treatments such as chemotherapy, hormonal therapy, gene therapy, immunotherapy or biologically targeted therapy.

Very little is known about such combinations and how they affect patient outcomes and quality of life.

Despite all the proof available to demonstrate improved outcomes, unfortunately, there remains some debate over proton technology. As a clinical trial site that evaluates proton therapy for more-common cancers such as prostate and breast cancer, this research aims to help Mayo Clinic work with health insurance companies so future patients don’t have to overcome the same hurdles to receive coverage for this treatment.

Advancing proton science will expand treatment capabilities so more patients can benefit from proton therapy.
A Year in Review

Now offering every type of radiation treatment, Mayo Clinic provided cancer care to more patients this year than at any other time in its 150-year history.

**Year One:**
- Delivered state-of-the-art proton beam treatment to more than 225 patients; 1 out of 5 were children.
- Treated patients with ages ranging from 10 months to 85 years old.
- Obtained consent for more than 70 percent of the patients seen in Rochester to join clinical studies, an exceptional statistic given the enrollment standard is 3 percent.
- Provided hope to those patients who have previously undergone radiation and cannot receive conventional radiation a second time because they have reached their lifetime safe maximum dose. Twelve percent of patients underwent radiation for a second time, this time with proton beam.
- Surpassed the projected number of patients treated to date.
- Delivered therapy for 13 tumor sites from head to toe.
- Published 49 peer-reviewed manuscripts since project inception.

**MAYO CLINIC CANCER CENTER IN ARIZONA:**

30,000 CANCER PATIENTS A YEAR
5,000 NEW CASES A YEAR

13 MILLION CLINICAL TRIALS
150 EXTRAMURAL FUNDING
NCI-Designated Cancer Center in Arizona

The Mayo Clinic Building on the Phoenix campus opened in February. This building is home to the Mayo Clinic Cancer Center, the pencil beam scanning Proton Beam Therapy Program and other medical practices.

As part of the only National Cancer Institute comprehensive cancer center with a national footprint, this new facility integrates all cancer services from prevention to survivorship. It harnesses the efforts of over 240 Cancer Center faculty, cancer education programs and Cancer Clinical Trials Center. The Cancer Center combines personalized cancer treatment with leading-edge research to provide patients with unparalleled cancer care.

A Patient-Designed Cancer Center

Mayo Clinic designed the new facility with feedback from patients and in close collaboration with Mayo Clinic’s Center for Innovation to include:

- Waiting areas with quiet workspaces, charging outlets and places for conversation.
- An infusion center with private areas, communal areas for socialization and space for loved ones to work.
- A friends and family lounge with kitchen amenities.

The sophisticated technologies and equipment in the brand new facility have a single mission — assisting staff members in healing patients. Features of the Mayo Clinic Cancer Center in Arizona include:

- Blood and Marrow Transplant Program
- Breast Multidisciplinary Center
- Cancer Clinical Trials Program
- Cancer Diagnostic Center: Department of Laboratory
- Cancer Wellness Program
- Cancer Therapy Infusion Center
- Comprehensive Radiation Oncology Program
- Hematologic Malignancies Program
- Medicine and Pathology; Radiology — PET MRI, CT cyclotron, imaging center
- Multidisciplinary Cancer Clinics
- Palliative Medicine Program
- Patient Education Classroom
- Proton Beam Therapy Program

IN THE FIRST YEAR:

225 PATIENTS WERE TREATED
1 in 5 WERE CHILDREN

Tumor sites from head to toe: 13

Patients ranged in age from 85 years to 10 months

70% of Rochester patients join clinical studies

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70% of Rochester patients join clinical studies
A NEW WEAPON  Audra Popp has a tumor so rare that only a handful of people are diagnosed with it each year in the entire world. She’s had five craniotomies in 15 years, three regimens of chemotherapy and six weeks of radiation therapy to beat back the tumor — anaplastic pleomorphic xanthoastrocytoma (anaplastic PXA) — but it keeps coming back.

In 2014, after her fourth surgery, Audra’s surgeon suggested radiation therapy, but she was turned down.

“Across the board, the radiation oncology team at Mayo Clinic felt it was too risky and possibly too damaging given that I’d had radiation therapy seven years before,” she says.

However, after her last surgery in 2015, doctors had a new weapon — proton beam therapy.

“Brain that has previously been exposed to radiation is more sensitive to injury from a second course of radiation,” says Nadia N. Laack, M.D., Audra’s radiation oncologist at Mayo Clinic in Rochester, Minnesota. “Proton beam therapy is much more targeted than traditional radiation therapy and gives us more options for tumors in sensitive areas and in situations where minimizing radiation dose to adjacent tissue is critical.”

Given her history, Audra opted for the treatment.

“Mayo has let me be an active participant in my treatment plan, which gives me confidence,” she says. “I’m in the best hands I can be. I’ve met so many wonderful individuals along the way and learned so much. It hasn’t been the easiest path, but I am surrounded by caring, supportive people.”

“It hasn’t been the easiest path, but I am surrounded by caring, supportive people.”

— Audra Popp
Mayo Clinic recently began constructing an innovative destination medical building that will meet the needs of patients in Florida, which has the second-highest cancer burden in the nation.

More than 126,000 patients are expected to visit the first year the building opens. The new 150,000-square-foot building will initially rise four stories, with the potential for 11 more stories. It will house:

A **chemotherapy area** that offers patients privacy and comfort, as well as space for family members, a dedicated nourishment area and a patient library.

**Education enhancements** designed specifically for Mayo Clinic’s education efforts and the training of residents and fellows.

**One floor devoted exclusively to neurology and neurosurgery.**
The new building also doubles the space for the neurology and neurosurgical departments. This will support the hiring of 12 new neurologists and neurosurgeons.

**Two floors devoted exclusively to hematology and oncology care, more than doubling** the size of the Division of Hematology/Oncology. This will be complemented by a 50 percent increase in staff. The number of clinical trials and Mayo’s capacity to serve patients also will increase.

**Patient care enhancements** include an outdoor garden and meeting space for support groups.

A rendering of the destination medical building at Mayo Clinic in Florida. The building will finish construction in 2018 and significantly expand Mayo Clinic’s ability to serve cancer patients and patients with neurologic disorders.
Increased Room for Advanced Imaging
Choline C-11 Scans Target Recurrent Prostate Cancer

In addition to the destination medical building, the first phase of Mayo Clinic’s Florida campus capital expansion will include a state-of-the-art positron emission tomography (PET) radiochemistry facility for new forms of screening, including a scan for recurrent prostate cancer.

“Millions of dollars are spent each year in the U.S. on producing cancer therapies that don’t help — often because physicians and medical personnel can’t see where the cancer has spread,” says Gianrico Farrugia, M.D., CEO, Mayo Clinic in Florida. One tool he says will help address the problem is choline C-11 PET scanning. Mayo Clinic’s Rochester, Minnesota campus is the first medical center in the nation to receive Food and Drug Administration approval for choline C-11. The scans “light up” prostate cancer wherever it is found and provide targets for therapy. Locating recurrent prostate cancer sooner may enable Mayo physicians to target the cancer more quickly, before it spreads even further, allowing for more effective treatment.

The facility will house a radiochemistry laboratory and a cyclotron — a particle accelerator important in the production of radiopharmaceuticals.

“With the ability to produce choline C-11 PET scans, Mayo’s cyclotron will be unlike any other in the Southeast,” Dr. Farrugia says. “It will enhance Mayo’s clinical practice and play an important role in research.”

Answers = Hope
New Jacoby Center for Breast Health Provides Answers Patients Need

One of the big challenges people with breast conditions face is segmented and, sometimes, incomplete care. For instance, a woman who has an abnormal mammogram result might be shuffled around from one provider to the next, waiting days or weeks for another appointment, another test, the whole time enduring the heart-wrenching anxiety of the unknown.

To provide these patients hope and answers, benefactors Robert and Monica Jacoby gave Mayo Clinic a leadership-level gift to establish the Mayo Clinic Robert and Monica Jacoby Center for Breast Health at Mayo Clinic in Jacksonville, Florida. The 16,000-square-foot multidisciplinary breast center opened in January and offers patients a comprehensive array of diagnostic, treatment and after-care services for all types of breast disease, including breast cancer, in a single location.

Sarah A. McLaughlin, M.D., who leads the center, says it is designed to promote the highest level of collaboration among all providers, researchers and educators in all disciplines related to breast health — for both men and women.

“It allows for true integration and efficacy of care, as patients can now access breast health experts from virtually every related medical discipline, all in one location,” she says. “In one place patients can receive genetic counseling, breast imaging and diagnosis, oncology care, breast and plastic surgery consultations, survivorship support and discussions regarding integrative therapies. Dr. McLaughlin says it’s the most comprehensive, multidisciplinary breast health facility in the Southeast region. It boasts more than 50 team members, 11 exam rooms, seven mammography rooms and a dedicated radiology consultation suite.”
The Fifth District Eagles Cancer Telethon and its supporters are among Mayo Clinic Cancer Center’s most dedicated benefactors. Each year, hundreds of Eagles and community members volunteer thousands of hours to organize events all over southern Minnesota and northern Iowa — folk music festivals held on family farms, beanbag tournaments, ice golfing, wild game feeds and personal chef auctions.

These innovative fundraisers engage the community in fun events that are focused on helping fight one of America’s most tenacious diseases.

All of these fundraisers combined with the annual Eagles Cancer Telethon raised more than $1 million last year. This was the first time the organization had ever passed this impressive milestone, and the Eagles did it again this year.

In a single year, the Eagles Cancer Telethon Research Fund made all of the following research projects possible for Mayo Clinic Cancer Center researchers.

**GILOBLASTOMA**

Glioblastoma is one of the most aggressive brain cancer types. Unfortunately, the vast majority of patients succumb to the disease within the first five years, and the effectiveness of front-line therapies has been limited.

One of the things researchers have noticed is that certain proteins are critical to how cells respond to therapies. With the Eagles’ support, Danielle M. Burgenske, Ph.D., is testing a drug cocktail that combines traditional chemotherapy with a drug called VX-970, which prevents the function of one of these proteins.

This data may provide the foundation for a clinical trial for patients with glioblastoma.

**DETECTION**

The increased use and resolution of medical imaging techniques has led to a rise in the detection of cancerous and noncancerous lesions of the pancreas. One particular lesion — intraductal papillary mucinous neoplasm — is especially difficult to manage because, although noncancerous, it is considered premalignant. Some lesions can progress to invasive carcinoma.

Stephanie K. Carlson, M.D., is testing a new form of MRI, which can detect specific metabolic agents with accuracy 10,000 times greater than conventional MRI. Her results could provide a new monitoring tool, which is greatly needed for pancreatic cancer.
OVARIAN CANCER
The majority of women with a common and lethal type of ovarian cancer will typically die within six to 12 months of developing resistance to the most effective form of chemotherapy for this cancer — platinum therapy.

In an effort to better understand why some women with this form of ovarian cancer respond to platinum therapy and others do not, Cristina Correia, Ph.D., used the Eagles’ support to design a project that examines the disease’s metabolic structure. As part of this project, she is assessing which women will benefit from a therapeutic agent recently approved by the Food and Drug Administration.

BRAIN CANCER
In children, tumors affecting the brain result in more cancer-related deaths than any other type of tumor. Among pediatric patients, one of the most devastating brain tumor types is diffuse intrinsic pontine gliomas. It’s critical that researchers identify new therapies.

David J. Daniels, M.D., Ph.D., is following the promising lead that the majority of these cancer tumors harbor a mutation of the histone H3K27M. What’s more, researchers know that this histone needs the amino acid glutamine, a well-known promoter of cancer growth, to survive.

The Eagles’ funding of Dr. Daniels’ studies will confirm the importance of glutamine metabolism in these tumors and lay the foundation for identifying novel drug targets for this deadly disease affecting children.

BREAST CANCER
Triple-negative breast cancer is a highly aggressive breast cancer subtype that lacks effective targeted therapies. However, some promising leads are emerging.

Researchers have discovered that the process by which epithelial cells transition to mesenchymal cells — which are a kind of stem cell that contributes to healing — plays a key role in the metastatic process. Researchers have also discovered a specific protein essential to this process.

Min Deng, Ph.D., is dissecting the mechanisms of this protein to learn how it is affected by a specific enzyme. Understanding this process will reveal a new therapeutic target in metastatic breast cancer.
LYMPHOMA
Richter’s syndrome is a highly malignant condition that transforms chronic lymphocytic lymphoma, which is a manageable disease, to diffuse large B-cell lymphoma. Unfortunately, patients with Richter’s syndrome have a short survival time.

In a recent phase 1 clinical trial, Wei Ding, M.B.B.S., Ph.D., noticed that patients with Richter’s syndrome react differently to immunotherapies than patients who have relapsed B-cell lymphoma. Eagles funding is allowing her to understand why by examining biomarkers and T cell infiltration into the tumor types.

Dr. Ding’s overall goal is to identify and confirm the genomic and immune biomarkers that will predict which patients with Richter’s syndrome will benefit most from a particular immunotherapy and which will not. She predicts these biomarkers will be useful for other types of cancer as well.

CANCER GENETICS
Cancers are complex human diseases that involve “crosstalk” of myriad signaling and biochemical events that are extremely hard to decipher. They involve large numbers of abnormalities associated with gene mutations, epigenetic alterations and gene expression.

Hu Li, Ph.D., is studying how cancer develops in certain contexts and how to identify driver genes across different cancer types. His project is initially focused on breast, ovarian, pancreatic and liver cancers.

The project is expected to grow into a platform that will allow researchers from across Mayo and from across cancer types to explore the molecular causes that drive cancer progression. The end result will be the realization of individualized and precise cancer treatments.

LIVER CANCER
Bile duct cancer is the second most common cause of primary liver cancer and currently has a dismal prognosis. However, with the Eagles’ funding, Lewis R. Roberts, M.B., Ch.B., Ph.D., the Peter and Frances Georgeson Professor of Gastroenterology Cancer Research, and Ju Dong Yang, M.D., are testing new screening options that can detect the cancer and its growth through a simple blood test. The methods identify cancer cells and tiny amounts of tumor DNA that leave the bile duct and circulate throughout the circulatory system.

If successful, doctors will be able to consistently monitor the cancer and adjust treatment as soon as the cancer mutates, which is a very common challenge for all cancers.
KIDNEY CANCER
Kidney cancer is among the leading causes of cancer death in the United States. However, exciting findings reveal that genes involved in controlling when other genes are turned on and off become mutated in more than 50 percent of cases. This gives clues as to how the cancer develops.

Keith D. Robertson, Ph.D., is validating findings from an earlier study that suggests specific DNA modifications are linked to recurrence and metastasis. His work could lead to methods to control DNA dysfunction, giving patients with kidney cancer a new option.

IMMUNOTHERAPY
One of the most dangerous aspects of cancer is the way it can manipulate the body’s immune system to evade detection. Fortunately, one of the most promising areas of research to emerge in the past few years is harnessing the body’s ability to recognize and kill cancer cells.

In metastatic melanoma, immunotherapy has been shown to provide unprecedented durable clinical response rates in certain patients. Unfortunately, the majority of patients do not respond.

Yiyi Yan, Ph.D., is testing the use of two drugs — pembrolizumab and ibrutinib — to restore the immune system and support the expansion of tumor-specific T cells. Success would mean improved outcomes for patients with metastatic melanoma.

OVARIAN CANCER
Ovarian cancer is one of the most common gynecological cancers among women worldwide. And although 80 percent of patients respond to the initial platinum-based therapy, the development of resistance is far too common.

One of the ways the cancer does this is by repairing its DNA more quickly than therapies can destroy it.

The Eagles Cancer Telethon funding is allowing Jian Yuan, Ph.D., to go after the pathways that cancer cells use to accomplish this repair. Because of the Eagles, these studies will reveal a new therapeutic target that will sensitize ovarian cancer cells to drugs that can kill them.
Alex Adjei, M.D., Ph.D.

The Power of Hope

There’s a reason Mayo Clinic oncologist Alex A. Adjei, M.D., Ph.D., spends so much time in the lab testing molecular solutions to cancer — it gives his patients hope.

When Dr. Adjei started as a lung cancer specialist about 20 years ago, patients with the disease had a dismal prognosis. There was basically one treatment option, and if that didn’t work — and it usually didn’t — there was little else he could do.

“When I started in ’95, of my first 20 lung cancer patients, nobody had any tumor shrinkage,” Dr. Adjei recalls. “All they did was lose hair and lose weight. None lived a year. It was so depressing. But now I have patients with metastatic lung cancer who I’ve been taking care of since 2009 and 2010. Now the vast majority of metastatic lung cancer patients are living 2 years or more.”

Dr. Adjei recently returned to Mayo Clinic (after starting his career here, he spent 9 years at Roswell Park Cancer Institute in Buffalo) to develop even better options for people with cancer. In his new role he’ll help lead the Mayo Clinic Cancer Center’s Early Therapeutics Program.

The program involves first-in-human trials testing new cutting-edge treatments for patients with a variety of cancers for whom no life-prolonging treatments exist. This is a critical step in the development of all new promising treatments for cancer. As medical director of this program, Dr. Adjei will help build an enterprisewide cohesive program, making these promising treatments available to all Mayo patients with all type of cancers across its centers in Minnesota, Florida and Arizona.

Dr. Adjei says this kind of work gives patients hope, which changes the way they face their disease.

“You may not always change how long they will live with the disease,” he says. “But it’s amazing how people react when they are told we can try something. People feel better that they aren’t just waiting to die, but they are trying something, they are fighting. I strive to not mislead a patient but also not to take away hope. I don’t want to take away hope completely because people don’t do well in that situation.”

And he’s just as hopeful. He talks about one patient who came to him with stage IV lung cancer in 2000. He enrolled her in a clinical trial testing a new drug. The drug failed the trial and was never approved. But for her, and only her, it worked. She’s still alive today.

“That kind of situation is certainly not common,” Dr. Adjei says. “And going in, we know the chances of survival may be really, really small. But they aren’t zero. And that gives patients, and me, hope.”
Harnessing Nanotechnology to Study Cancer

When you are a driven neurosurgeon but not a morning person, sometimes it's about your socks.

“I lose no time matching,” says Mayo Clinic’s Betty Kim, M.D., Ph.D. “They’re all the same color, so I can get an extra minute of sleep.”

Yet, in her daily work, misplaced colors are critical. Dr. Kim is trained in neurosurgical oncology and engineering, and she spends her time reviewing brain scans and making sense of a cacophony of colors, shapes and patterns. All too often, a colored dot in the wrong place means a life-threatening brain tumor.

Committed to continually improving the treatment of her patients, Dr. Kim has helped pioneer novel ways to fight brain tumors on the molecular level by developing nanomaterials that can target specific cells in the body.

Nanomedicine is the art of synthesizing microscopic materials to diagnose or treat something harmful in the body. In addition to exhibiting the characteristics of the compounds from which they are made, nanomaterials can acquire new properties due to their extremely small size.

“I want to use the technology to discover safer ways to detect brain tumors earlier,” Dr. Kim says.

Her lab currently specializes in a compound called a quantum dot, a semiconductor so small that its electronic properties make it glow with great intensity when struck by light. Quantum dots are currently used in the newest television monitors to offer the best possible image quality and resolution. However, Dr. Kim and her colleagues are using the dots to study cancer.

Her team is exploring how quantum dots behave. She’s using this understanding to synthesize the dots to seek out brain tumor cells and, like a bird dog, point to their location. The quantum dots can paint tumors with different colors, allowing surgeons to shine a flashlight of sorts on the brain. The illuminated cells provide a detailed map of the disease, showing surgeons exactly which tissue needs to be removed.

But quantum dots also show promise as a therapeutic tool. Dr. Kim is finding that the dots can be loaded with different substances and serve as nanocarriers, delivering drugs to specific disease sites rather than inundating a patient’s entire body with toxic compounds.

“We envision that new nanotechnology tools will be routinely employed in clinical medicine for earlier cancer detection, enhanced drug delivery and personalized therapies,” Dr. Kim says.
On the brink of discovery, Sandra J. Gendler, Ph.D. and Peter A. Cohen, M.D., take a moment to reflect on a collaboration and friendship that began in 2008 when Dr. Cohen made the move to Mayo Clinic in Arizona.

“I recognized that this chance to work closely with Sandy offered a once-in-a-lifetime opportunity to figure out how to target cancer cells effectively through their expression of MUC1,” says Dr. Cohen.

And what has made them such a good team over the years?

“We both love music and good movies, although Peter’s movie interests are mostly confined to pre-1931,” jokes Dr. Gendler. “We’re not afraid of getting scientific results that are the opposite of what we expected because some of the biggest discoveries are first observed during ‘failed’ experiments.”

Currently the two are addressing one of the toughest challenges immunotherapists face — that even advanced cancers often remain inconspicuous in the body for months to years before causing major problems, leading the immune system to coexist rather than attack cancers.

However, the dynamic duo is reprogramming the immune system to create the next line of defense against cancer. Their partnership is the leading force behind a major clinical trial currently in progress that attempts to trick the immune system into perceiving cancer less as a chronic entity and more like a life-threatening infection.

When they started this work five years ago, there were already dozens of immunotherapy agents designed to treat cancer patients, but they proved disappointing in clinical trials. The pair of researchers hypothesized that alternative dosing schedules might unmask the therapeutic potency of the agents that seemed to have the most potential.

“We pitted such agents against the worst tumors we could find, including a notorious breast cancer tumor that metastasizes widely within minutes of being inoculated into models, as well as an equally tough-to-cure pancreatic cancer tumor,” Dr. Cohen says.

The combined drug treatment was not only more effective, but extremely well-tolerated.

“When we do this in test models, we are able to make advanced breast, colon and pancreatic cancers go away and not come back, so now we are attempting to achieve the same therapy in patients with advanced cancers,” Dr. Gendler says. —
CANCER RESEARCH PROGRAMS

**Cancer Prevention and Control**
Scott Leischow, Ph.D.
Program Co-Leader
Charles Loprinzi, M.D.
Program Co-Leader

**Cell Biology**
Panagiotis Anastasiadis, Ph.D.
Program Co-Leader
Jan van Deursen, Ph.D.
Program Co-Leader

**Developmental Therapeutics**
Scott Kaufmann, M.D., Ph.D.
Program Co-Leader
Zhenkun Lou, Ph.D.
Program Co-Leader
Alex Adjei, M.D., Ph.D.
Program Co-Leader

**Gastrointestinal Cancer**
Kenneth Wang, M.D.
Program Co-Leader
Tanios Bekaii-Saab, M.D.
Program Co-Leader
Frank Sinicrope, M.D.
Program Co-Leader

**Genetic Epidemiology and Risk Assessment**
James Cerhan, M.D., Ph.D.
Program Co-Leader
Alexander Parker, Ph.D.
Program Co-Leader

**Gene and Virus Therapy**
Evanthia Galanis, M.D.
Program Leader

**Hematologic Malignancies**
Leif Bergsagel, M.D.
Program Co-Leader
Stephen Ansell, M.D., Ph.D.
Program Co-Leader
Asher Chanan-Khan, M.D.
Program Co-Leader
Richard Vile, M.D.
Program Co-Leader
Larry Pease, Ph.D.
Program Co-Leader
Protul Shrikant, Ph.D.
Program Co-Leader

**Immunology and Immunotherapy**
Joseph Loftus, Ph.D.
Program Co-Leader
Jann Sarkaria, M.D.
Program Co-Leader
Brian O’Neill, M.D.
Program Co-Leader

**Neuro-Oncology**
Jamie Bakkum-Gamez, M.D.
Program Co-Leader

**Women’s Cancer**
Amy Degnim, M.D.
Program Co-Leader
Matthew Goetz, M.D.
Program Co-Leader

**Specialized Programs of Research Excellence (SPORES)**

**Brain Tumor**
Brian O’Neill, M.D.
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**Breast Cancer**
James Ingle, M.D.
Co-Principal Investigator
Matthew Goetz, M.D.
Co-Principal Investigator

**Lymphoma**
(Shared with the University of Iowa)
Thomas Witzig, M.D.
Co-Principal Investigator

**Solid Tumor**

**Ovarian Cancer**
Gloria Petersen, Ph.D.
Principal Investigator

**Pancreatic Cancer**
Scott Kaufmann, M.D., Ph.D.
Principal Investigator

**Ovarian Cancer**
Gloria Petersen, Ph.D.
Principal Investigator

**Prostate Cancer**
Co-Principal Investigator

**Appointments to Mayo Clinic**

**Affiliations and Collaborations**

*Academic and Community Cancer Researchers United*
Alliance for Clinical Trials in Oncology
American Cancer Society
American College of Surgeons Oncology Group
Biosdesign Institute - Arizona State University
*Breast Cancer Prevention Network*
Children’s Oncology Group
Coalition of National Cancer Cooperative Groups
Council of Scientific and Industrial Research, India
Seoul National University Bundang Hospital
Cancer Center, Korea
Eastern Cooperative Oncology Group
Experimental Therapeutics Clinical Trials Network
GLIOGENE
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Mayo Clinic Department of Development
Toll-free: 1-800-297-1185
e-mail: development@mayo.edu
www.mayoclinic.org/development

FOREFRONT

Managing Editor:
Brett C. Vermilyea

Please address comments to forefrontmagazine@mayo.edu or Forefront magazine,
Mayo Clinic
200 First Street SW
Rochester, MN 55905

cancercenter.mayo.edu
e-mail: cancerresearch@mayo.edu

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OUR MISSION:
To relieve the burdens of cancer by promoting basic and clinical research on the incidence, causes and progression of cancer and translating discoveries into improved methods for prevention, detection, diagnosis, prognosis and therapy.

OUR PRIMARY VALUE:
The needs of the patient come first.