Director’s Message
One Goal: Doing What is Best for Patients

An Unwavering Vision
for Proton Beam Therapy

Proton Beam Treatment Leads to a Bright Future
Anika’s Story
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Racing to Beat the Odds

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Meet the Investigator
I’ve heard people say that we live at the best time in the history of man. That certainly holds true if you look at the field of medicine. Advances in lifesaving technologies and the pace of those advances are breathtaking. But in some cases, technology has advanced so quickly that it has outpaced our ability to fully comprehend its value.

Consider the fact that in the 1930s many physicians initially doubted whether x-rays provided as good a representation of the human body as a physical exam. While no one questions the value of x-rays today, it took researchers time to demonstrate the most advantageous and appropriate use of the new technology. I believe a similar situation exists today for proton beam therapy, the topic of our cover story.

In June 2015, Mayo Clinic Cancer Center will open its first proton beam therapy center in Rochester, Minn. We will open a second center in Phoenix, Ariz. in early 2016. The opening of these centers may come amid some controversy because, despite the enormous potential of this new technology, more work needs to be done to demonstrate its best and most cost-effective use.

At Mayo Clinic, we have a tradition of pioneering new treatments that benefit patients and advance science. Our proton beam therapy program builds on that tradition.

Scientists know that proton beams can be much more finely controlled, in both width and depth, allowing for higher doses of radiation to be more safely applied to tumors located in or near sensitive areas of the body such as the brain, eye and spinal cord. The question is: How do outcomes and costs compare to traditional radiation therapy?

Our research on outcomes from other centers has already found that proton beam therapy significantly improved disease-free survival and tumor control for patients with advanced head and neck cancers of the skull base when compared to intensity modulated radiation therapy.

When our centers open, all patients will be placed on an institutional review board–approved registry and their outcomes will be collected prospectively. We will conduct research at our two facilities as a single unified program. And we will participate in a research consortium composed of Massachusetts General Hospital, the University of Pennsylvania and MD Anderson Cancer Center that is developing and conducting phase III clinical trials to compare proton beam therapy to conventional radiation therapy.

The goal of our proton beam therapy program is to do what is right for our patients. As Dr. William J. Mayo told the graduating class of Rush Medical College in 1910, “the best interest of the patient is the only interest to be considered ... It has become necessary to develop medicine as a cooperative science; the clinician, the specialist, and the laboratory workers uniting for the good of the patient, each assisting in elucidation of the problem at hand, and each dependent upon the other for support.”

Robert B. Diasio, M.D.
Director
Mayo Clinic Cancer Center
William J. and Charles H. Mayo Professor
The synchrotron is 55 feet in circumference and accelerates protons to nearly two-thirds the speed of light.
More than a decade has passed since Robert Foote, M.D., chair of radiation oncology at Mayo Clinic, became convinced about what the future of radiation therapy could look like.

For over a century, his field has provided an excellent and often curative tool in the form of radiation therapy — using high-energy radiation to kill cancer cells by damaging their DNA. “But we often face a delicate balance,” Dr. Foote says, “delivering the highest possible dose of x-rays to a tumor without causing damage to the surrounding healthy tissue. Sometimes we have to hold back on the dose, so we don’t cause harm.”
At a medical conference in 2002, there was a buzz about a new therapy using proton beams instead of conventional radiation as a more precise way to destroy tumors. A treatment that’s been in limited use around the country since the 1970s, proton beam therapy can be meticulously directed, and the beams stop when they reach their target. “I felt when I evaluated it ten years ago this was the opportunity we were hoping for. We could get a higher dose of radiation to a tumor, to eradicate it, while delivering a lower, safer dose to normal organs,” Dr. Foote recalls. But even though the approach could potentially become a game-changer, Dr. Foote and others at Mayo Clinic thought it wise to wait before investing in a still-evolving and expensive technology. “We wanted to approach a decision very carefully and thoughtfully,” he says.

As a result, Dr. Foote and his colleagues kept tabs on proton beam therapy for a decade, and they watched the technology come into its own (and determinedly invested in the approach in 2011).

The great care Mayo took in developing a plan involved not only watching the field, but also carefully researching. For a decade, Dr. Foote’s team used computer simulations to compare standard radiation treatment being given to patients with a model of proton beam therapy. “It was clear for a number of different types of cancers the proton beam could give a higher dose to the tumor and a safer dose to the surrounding normal organs,” he says. Meanwhile, an extensive body of medical literature was showing the approach to be highly effective. “At that point,” he said, “we said this is something Mayo needs to be able to offer to our patients.”

Precise Treatment
In proton beam therapy, a particle accelerator generates a highly charged beam consisting of the positively charged parts of an atomic nucleus. The approximately 5 millimeter beam can be finely controlled, in its width, height and depth, so that it’s concentrated within the three-dimensional contours of a tumor. Unlike the photons used in conventional radiation, the beam doesn’t exit through the body, so other tissues are spared. The therapy is highly useful, for instance, for melanomas that arise in the retina, head and neck cancers that are in the skull base, near the brainstem or cranial nerves, or within the nose and sinuses. Sameer Keole, M.D., who worked with proton beam therapy throughout his career and in the treatment of more than 700 patients, finds that patients tolerate it better than conventional radiation and feel fewer side effects.
It’s a particularly useful approach for treating cancers in children. Because of its focused radiation, proton beam therapy offers fewer long-term side effects and complications than conventional treatment. “Now that many pediatric cancers have significant cure rates, some as high as 85 percent,” says Dr. Keole, “we want to do everything we can to reduce the risk of chronic health problems that may arise from radiation exposure.”

**Fewer Side Effects**

Having been used in more than 100,000 patients over the last 40 years, doctors are noting that proton therapy is both effective and eliminates certain problems in treating tumors. In men with prostate cancer, Dr. Keole notes that proton beam therapy appears to cause less loss of erectile function, with less risk of bowel injury as well. It’s also becoming a tool for treating what was considered inoperable lung cancer. When it comes to breast cancer, he says, “proton beam therapy eliminates the dose to the heart.” Ultimately, women are spared a long-term consequence of radiation therapy. “In a cost effectiveness analysis of women with left-sided breast cancers, proton beam therapy reduced the risk and cost of heart of treating heart disease,” he says.

Dr. Foote notes that, along with the benefits of the treatment, the economics of proton beam therapy have been part of discussions all along. Even though the initial expense of investing in proton beam therapy is large, the reduction of long-term health issues means the treatment will help reduce overall health care costs. In the short term, studies are being performed in some types of cancer to see if proton beam therapy can require as few as five sessions, as opposed to 30 or more required for conventional radiation therapy. And over years, patients have been found to have fewer radiation-caused cancers.

In summer 2015, the Mayo Clinic Cancer Center will open its first proton beam treatment facility in Rochester, and nine months later, a foot-by-foot identical facility will open at Mayo Clinic in Phoenix.

The new technology doesn’t replace conventional radiation, as radiation oncologist Dr. Keole, medical director of the Phoenix proton beam facility, explains, but broadens the opportunities for treatment. “We’re now able to offer this therapy as another treatment option for certain cancers and for patients who would benefit most from it,” he says.

Mayo took care to pay for the two facilities with institutional funds and contributions from generous donors — including a $100 million gift from Richard O. Jacobson and a $10 million gift from Lawrence W. and Marilyn W. Matteson — not from venture capitalists, Dr. Foote points out. “We didn’t get into this to generate revenue from the technology,” he says. “We’re under no pressure to pay back an investment.” Mayo also worked
closely with a vendor to develop affordable, power-efficient machinery, and made an institutional decision to charge exactly the same amount for each session of proton beam therapy as it does for conventional therapy. “We didn’t want cost to be an issue at all for the patient, insurance companies, or Medicare. We wanted the costs to be the same in order to be able to choose the best treatment based on an individual patient’s case.”

When both sites are up and running, the facilities will have eight treatment rooms and the capacity to treat 2,400 patients annually, including about 250 children.
In the fall of 2005, Anika Chesak was diagnosed as having a rhabdomyosarcoma — a type of tumor that wraps itself around soft tissue — at age 5.

She complained of headaches, according to her mother, Sherry Chesak, Ph.D., a program director in Education and Professional Development at Mayo Clinic in Rochester.

Anika had seen her family physician at Mayo Clinic Health System in Austin, but Anika’s weight loss concerned Dr. Chesak and her husband.

“Anika was squinting and closing one of her eyes,” says Dr. Chesak. Their physician directed them to the Rochester campus.

A CT scan revealed a questionable spot, and an MRI showed a tumor behind Anika’s right eye.

The rhabdomyosarcoma was wrapped around the carotid artery, which supplies blood to the brain. “We thought it was a death sentence,” says Dr. Chesak

After the Chesaks met with the pediatric oncologist, they felt more hopeful. Anika had a good prognosis with chemotherapy and radiation treatments.

Dr. Chesak knew the treatment could affect Anika’s pituitary gland — a gland that controls hormone production — and could potentially stunt Anika’s growth. “We started researching immediately,” says Dr. Chesak. They found that proton beam therapy could better pinpoint the tumor.

As Mayo didn’t have its Proton Beam Therapy Program at that time, the Chesaks chose the M.D. Anderson Cancer Center in Houston, Tex.

Mayo Clinic physicians worked with M.D. Anderson to transition Anika’s treatment plan from Mayo.

The family noticed progress with the proton beam therapy almost immediately, as Anika’s right eye opened a little more after each treatment.

MRIs have shown no change, and Anika has been cancer-free for about five years now. Though Anika lost sight in her right eye, there were no other side effects.

“We learned quite a bit about faith,” says Dr. Chesak.
In 2007, Linda Wortman was enjoying her 34th year of working for, then, Northwest Airlines, as a flight attendant. Flying had given Linda many fond memories, including meeting her husband, Jerry, on her third flight in 1973. Together, they travelled the world and were known as the “Flying Wortmans.”

However, Linda began to develop respiratory issues, and, concerned with the recent outbreak of SARS, she decided to get examined at a local clinic. She was prescribed a Z-pack for a respiratory infection.

Linda continued to fly, unphased by these respiratory difficulties, until her annual physical at Mayo Clinic in December of 2007. The routine physical lasted three days instead of one. Then, on January 11, 2008, Linda was diagnosed with stage one, non-small cell adenocarcinoma. Linda was in a state of shock. “You have the wrong person. I’ve never smoked. I can’t have lung cancer,” Linda told her doctor.

She immediately underwent surgery to have her upper left lobe removed, where a three-centimeter tumor had taken residence. Following the operation, Linda didn’t know where her next breath would come from. “When they take your lung out it hurts. You can’t move and you can’t get a full breath, so I asked my husband to tell me to breathe, every breath, and he did,” Linda says.

After months of rest and recuperation, Linda and Jerry decided to return to the skies and travel. One of the many trips led the pair to a blues festival in Clarksdale, Miss. While attending the festival, Linda saw a sign promoting a 5K run/walk in honor of a little girl with cancer. The morning of the race, Linda decided to register for the event. She finished second in her age group, even without wearing proper running shoes.

At first, Linda participated in races to test her endurance. However, running quickly shifted to a means of competing in races around the world.
“It’s important to raise awareness because lung cancer can affect anybody, at any age, anywhere in the world, smoker or non-smoker.”

— Linda Wortman

for her to raise awareness of lung cancer. Linda pledged to run one 5K in all 50 states within two years for this cause. On Mother’s Day 2014, Linda completed her goal.

The love of running also inspired Linda to start her foundation, the Wortman Lung Cancer Foundation, with the purpose of educating and raising funds for further lung cancer research. “It’s important to raise awareness because lung cancer can affect anybody, at any age, anywhere in the world, smoker or non-smoker,” explains Linda.

Linda has been cancer free for about six years. In celebration, her next goal is to run a 5K in every province of Canada, as well as a 10K on every continent, including Antarctica. Linda’s story of determination and willpower has served as an inspiration to many.
For decades, physicians have gone after cancer with chemotherapy drugs to kill cancerous cells. Unfortunately, this is often done at the expense of damaging healthy cells. While this approach has improved the survival of thousands of patients with cancer, some still strike out.

Today, researchers are taking a definitive approach to beat cancer by scouting a cancer cell’s profile for unique genetic abnormalities or weaknesses that set that particular cancer apart from others. Their goal is to find drugs that will selectively target those weaknesses — molecular changes that result from the genetic abnormalities. This approach gives new hope to patients for whom more traditional therapies of the past have fallen short.

Leading this effort are two Mayo Clinic trials working to uncover and test targeted therapies for breast cancer and prostate cancer. In both studies, researchers are sequencing tumor biopsies to develop customized treatments based on the molecular makeup of each patient’s individual cancer. They are also implanting cells from patient tumors into mice to create personalized teams of “mouse avatars” to test whether or not these customized drug treatments are likely to work in the patient herself.
**Scouting the talent**

“Chemotherapy drugs can actually be considered a form of targeted therapy because they target processes like replication and cell division,” says Matthew P. Goetz, M.D., a Mayo Clinic oncologist. “However, that approach can lead to substantial toxicities based on the drug’s effects on normal cells — you may be successful, but you will hit a lot of bystanders in the process. We have seen a shift in oncology drug development away from chemotherapeutic agents that target general mechanisms employed by both cancerous and healthy cells toward therapeutics that hit molecular targets that specifically fuel the growth of cancer.”

The lineage of targeted therapies can be traced as far back as the 1800s, when a British physician discovered that removing the ovaries of a premenopausal breast cancer patient sent her into remission. This finding gave oncologists their first direct target, estrogen, leading — over seventy years later — to the blockbuster drug, tamoxifen, for women with estrogen receptor–positive tumors. Next, trastuzumab was discovered as a targeted therapy for patients whose tumors overexpress the HER2 protein. Despite successes, resistance to these therapies is common, and chemotherapy remains the only option for a highly aggressive form of breast cancer that expresses neither the estrogen receptor nor HER2 (termed “triple negative” breast cancer).

“What we are left with are the highest risk patients, who harbor tumors that still survive even after being treated with chemotherapy” says Mayo Clinic surgical oncologist Judy C. Boughey, M.D. “There is a significant need for better, more targeted drugs that can improve care for these patients and generate less side effects.”
Since it began in March 2012, the BEAUTY trial has enrolled 140 women from Mayo Clinic sites in Minnesota, Florida and Arizona. Each time a patient’s cancer has recurred, researchers have turned to their tumor genomes to uncover a specific set of drugs to try next. Because the process is so laborious and time-consuming, researchers often feel like they are racing against the clock to find the right drug for each patient.

Time is not the only challenge. Sometimes the researchers discover a genetic alteration in the tumors that they would like to target, but there aren’t any drugs available to do the job. Dr. Goetz says they have already begun basic science studies on one such attractive target in the hopes of passing it off to a company for further development. In many cases, the BEAUTY project has been able to successfully steer patients toward new targeted therapies. However, treating patients after the disease has recurred is not optimal. The next phase of the trial will evaluate the impact of these personalized treatments prior to the spread of disease.
Pitching to the strike zone

A separate trial at Mayo Clinic is also taking on another tough opponent. Like BEAUTY, the Prostate Cancer Medically Optimized Genome-Enhanced Therapy (PROMOTE) study combines advanced genomic sequencing with personalized teams of tumor-modeling mouse avatars. But rather than adding new tools to the anti-cancer lineup, this study is identifying which of the recently approved targeted therapies for prostate cancer will be the most effective strategy against each person’s disease.

Until five years ago, oncologists had few options once their patients stopped responding to hormone treatment, an unfortunate milestone that earns the label of castration-resistant prostate cancer. Then a spate of breakthroughs brought FDA approval of approximately six new targeted therapies for treating this progressive and incurable form of the disease.

“Now we are faced with a bounty of plenty, which makes it confusing for us to decide which drug to give to which individual,” says Manish Kohli, M.D., a Mayo Clinic oncologist who is co-principal investigator of the PROMOTE trial. “Just like with any chemotherapy or hormonal treatment, not everyone will respond. When the cancer is rampantly going forward, the window of opportunity is small and we can’t afford to make the wrong choice. That is where trials like PROMOTE come in.”

PROMOTE is taking biopsies from 150 to 200 patients, before and after treatment with a targeted therapy called abiraterone acetate. They are then looking for signals in the DNA or RNA of patient biopsies that correspond to the patient’s response to the therapy, as assessed by scans, patient diaries and PSA levels. Finally, they are confirming their results in mini-cancer models created by Dr. Wang, who is also co-PI of PROMOTE.
When baseball legend Babe Ruth made a pointing gesture to the center-field bleachers while at-bat in Game 3 of the 1932 World Series, he allegedly declared that he would hit a home run to that part of Chicago’s Wrigley Field. On the next pitch, Ruth hit a home run to center field. Ruth’s bravado and skill is remarkably similar to the confidence and skill being demonstrated at Mayo Clinic, where cancer researchers are not simply hitting for contact, but going for the targeted home run. If you would like to make a tax-deductible gift to support cutting edge cancer research at Mayo Clinic all 1-855-852-8129 tool-free or visit http://philanthropy.mayclinic.org/donate.

The researchers, who began the trial in June 2013, are currently combing sequencing data for signatures predictive of response or resistance to the drug. They have already modeled many of their patients’ tumors in mice, and are in talks with a number of pharmaceutical companies interested in using the mouse avatars to “fill an empty void” in the discovery and development of new targeted therapies.

Though the PROMOTE and BEAUTY studies are just beginning to tap into the power of personalized miniature murine teams in customizing care for their patients, the investigators are already looking forward to a day when this high-tech approach becomes the standard of care.

“My dream down the road is for patients to walk in the door, get their tumors biopsied and sequenced, and know right away which treatment will work best for them,” says Dr. Boughey.
Charles Loprinzi, M.D., oncologist at Mayo Clinic Cancer Center and the Regis Professor of Breast Cancer Research
Chemo Side Effects Inspire

A Quest for Justice

When a treatment for cancer means that patients can’t work because of burning pain in the hands and feet, or can’t wear everyday shoes, or are unable to sleep well because they can’t stand the weight of sheets touching their skin, it skews their whole outlook on life.

These physical injustices are just some of the symptoms of chemotherapy-induced peripheral neuropathy (CIPN). CIPN occurs in 30 to 40 percent of patients receiving chemotherapy and can be so debilitating that some patients opt out of further treatment.
CIPN is a prominent, unsolved problem in a long list of chemotherapy-induced symptoms that Charles Loprinzi, M.D., an oncologist at Mayo Clinic Cancer Center and the Regis Professor of Breast Cancer Research, has dedicated his career to solve.

Since 1985, when he joined the staff at Mayo Clinic, Dr. Loprinzi’s research has helped alleviate many of those symptoms and busted many myths of favored yet ineffective treatments for patients undergoing chemotherapy.

**Seeking the truth for cancer patients**
The American Society of Clinical Oncology (ASCO) recognized the importance of one of Dr. Loprinzi’s recent studies when it included the findings in its 2013 report of advances made in cancer therapy.

The study, published in *The Journal of Clinical Oncology*, refuted a 2004 study that suggested infusions of calcium and magnesium reduced oxaliplatin-induced sensory neuropathy in patients with colorectal cancer. Oxaliplatin chemotherapy is commonly used in adjuvant and palliative treatment regimens for colorectal cancer.

Oxaliplatin and paclitaxel, commonly used in therapies for colon and breast cancers, respectively, are responsible for 80 percent of CIPN symptoms — symptoms that can partially or completely resolve in some patients, but can last for years in others, causing long-term disability.

The 2004 study prompted intravenous calcium and magnesium to be commonly prescribed for patients receiving chemotherapy. Dr. Loprinzi, among others, however, recognized that the initial trial was not conclusive, and that more definitive studies were needed to resolve the debate. This led to several labs developing additional scientific trials to determine whether this was an effective way to prevent CIPN. Dr. Loprinzi led a group of researchers that conducted the largest, most definitive trial and proved that intravenous calcium and magnesium were not helpful.

“It is important to convince physicians not to prescribe ineffective therapies,” says Dr. Loprinzi. “Not only are they a waste of their patients’ valuable time, they drain resources and increase costs and some may interfere with other drugs or add toxicities.”
Fellow oncologist and Chair of the Department of Medical Oncology, Jan Buckner, M.D., acknowledges there are many trends in therapy that have little basis in science. “Some therapies owe their popularity to marketing,” says Dr. Buckner. “Many take off after poorly conducted research. Dr. Loprinzi’s emphasis is to conduct randomized, placebo-controlled, double-blind studies that eliminate subjective interpretations.”

Randomized means that study participants are allocated by chance, such as by a flip of a coin, to receive one or the other of the alternative treatments under study. Placebo-controlled means that a separate control group receives a fake treatment that is specifically designed to have no real effect. It looks exactly like the experimental treatment, and is administered in the same way, so that neither the participants nor the researchers or caregivers know which participants belong to the control group and which to the test group. That’s what makes it “double-blind.”

A long career testing comfort levels
Dr. Loprinzi credits his mentor Charles Moertel, M.D. the first director of the National Cancer Institute designated Mayo Clinic Cancer Center, for much of his success. In 1977, Dr. Moertel provided the impetus for the creation of the North Central Cancer Treatment Group (NCCTG) — a network of institutions that conduct cancer clinical trials to bring high-quality cancer care and research to community clinics. Importantly, patients who came under the NCCTG umbrella provided sufficient participant representation for scientifically valid studies.

“Dr. Moertel fostered my interest in symptom control research and was a great support in securing grants,” says Dr. Loprinzi. “He insisted on rigorous study design for high quality, evidence-based science.”

The NCCTG (which recently has combined with two other cancer research groups to form another research group called the Alliance) achieved remarkable success in almost three decades of clinical trials testing therapies to alleviate symptoms related to cancer and/or cancer therapy under Dr. Loprinzi’s leadership. He has been instrumental in the wealth of knowledge that has led to considerable improvements in patient comfort level. “Dr. Loprinzi has been the program leader of our nationally-recognized Cancer Prevention and Control Research Program within Mayo’s NCI-designated Cancer Center’s since its inception. Many of his ideas were generated at Mayo under his guidance and then later exported to the cooperative group setting,” noted Dr. Robert Diasio, current Director of the Mayo Clinic Cancer Center.

Dr. Loprinzi’s clinical trials have included multiple therapies to treat symptoms such as radiation-induced diarrhea and skin toxicity, fatigue, insomnia, nausea, loss of appetite, hot flashes, bone loss, anemia, vaginal dryness, cognitive dysfunction, pain and lymphedema following mastectomy and CIPN.

“We have tested many therapies for prevention of CIPN since 1993 but an effective solution remains elusive,” says Dr. Loprinzi.

Dr. Loprinzi recently co-chaired an ASCO expert panel that led to the release of a clinical practice guideline on prevention and management of CIPN in April, 2014.

After review of relevant medical literature, the panel identified a handful of drugs that may be helpful in diminishing the symptoms of CIPN (duloxetine, tricyclic antidepressants, gabapentin, and a topical gel containing baclofen, amitriptyline and ketamine) but did not recommend any agents for prevention of CIPN, as none have been shown to be effective. The panel also listed
agents that it specifically recommended not to offer to patients for prevention of CIPN (acetyl-L-carnitine, amifostine, amitriptyline, CaMg, dietyldithio-carbamate, glutathione, nimodipine, Org 2766, all-trans retinoic acid, rhuLIF and vitamin E).

**Continuing the quest**
The lack of success in finding an agent that definitively prevents the symptoms of CIPN is making Dr. Loprinzi try even harder to resolve this problem for patients.

One possibility is to compare DNA from patients who are being treated with oxaliplatin or paclitaxel who subsequently develop CIPN with the DNA of those who did not develop symptoms, despite receiving the oxaliplatin or paclitaxel. A better understanding of the natural history of CIPN and the establishment of a patient’s genetic predisposition could lead to early recognition, avoidance of permanent nerve damage and new therapies.

“If we know that an individual’s chance of getting CIPN is one percent versus 20 percent, that feeds into the risk-benefit decision,” says Dr. Loprinzi. “If the risk is high, it may be worth considering alternative drugs.”

Dr. Loprinzi is upbeat about a novel approach called Scrambler therapy, which treats pain through electrostimulation of the skin.

“Our pilot trial, presented on June 1, 2014, at the ASCO annual meeting, produced preliminary data that supports successful reduction of pain and numbness with no substantial adverse effects,” says Dr. Loprinzi. “Scrambler therapy appears to be effective for the treatment of CIPN and we look forward to testing it on a greater number of patients in a placebo-controlled clinical trial.”

“Dr. Loprinzi’s emphasis is to conduct randomized, placebo-controlled, doule-blind studies that eliminate subjective interpretations.”

— Jan Buckner, M.D.
Researchers Discover New Form of Cancer

By themselves, the genes PAX3 and MAML3 don’t cause problems. However, when combined during an abnormal but recurring chromosomal mismatch, they can be dangerous.

The result is a chimera — a gene that is half of each and that causes biphenotypic sinonasal sarcoma. The tumor usually begins in the nose and may infiltrate the rest of the face, requiring life-saving but disfiguring surgery.

Mayo Clinic pathology researchers have now described the molecular makeup of this rare tumor, opening up the possibility for several existing cancer drugs to be targeted against it. The findings were published in the journal Nature Genetics.

The story of this dangerous gene combination actually began long ago — in fact, longer ago than researchers today initially realized.

It was in 2004 that Mayo Clinic Cancer Center pathologists Andre Oliveira, M.D., Ph.D. and Jean Lewis, M.D. first noticed something unusual about a tumor sample they were analyzing under the microscope. By 2009, they had seen the same pathology several times and had begun collecting data.

In 2012, with a team of Mayo Clinic collaborators, Drs. Oliveira and Lewis published their discovery and defined a new class of tumor not previously described. Now, less than two years later, they are informing the medical community of the genetic structure and molecular signature of biphenotypic sinonasal sarcoma, a malignant tumor found more commonly in women than in men.

As it turns out, Mayo Clinic discovered this cancer decades ago. After the 2009 findings, Dr. Oliveira searched years of computerized medical records to see if there was more information about biphenotypic sinonasal sarcoma. He was surprised to find physician notes on a patient from 1956 that described a virtually identical but unnamed tumor.

Dr. Oliveira located the patient’s original tumor samples, which were stored all those years in a Mayo Clinic biorepository. His analysis of the samples confirmed that the tumor had the same genetic chimera — biphenotypic sinonasal sarcoma.

The researchers were able to identify and characterize the tumor because Mayo Clinic is one of the world’s largest referral centers for sarcoma diagnosis and treatment.

Significance of the Discovery

Other than the increased knowledge about this rare cancer, its mechanisms and the potential for a treatment drug, researchers also are interested in the discovery because of its potential as a disease model.

“The PAX3-MAML3 chimera we identified in this cancer has some similarities to a unique protein found in alveolar rhabdomyosarcoma, a common cancer found in children,” says Mayo Clinic molecular biologist and co-author Jennifer Westendorf, Ph.D. “Our findings may also lead to a better understanding of this pediatric disease for which, unfortunately, there is no specific treatment.”

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First Seen Nearly 60 Years Earlier
While the cancer wasn’t formally identified until 2009, a subsequent search of Mayo Clinic’s medical records showed that a Mayo patient had the cancer in 1956. The identical description was found in physician notes within Mayo’s computerized database and confirmed with careful microscopic analysis. Dr. Oliveira took his investigation one step further and located the patient’s original tumor samples, kept all those years in Mayo’s bio repositories. His analysis confirmed that the tumor possessed this same genetic chimera. In a way, Mayo Clinic had discovered the same rare cancer twice. The notes from the original physician added to the findings of the more recent discovery. For Dr. Oliveira, it was a surprising but not unheard of “collaboration” with a Mayo colleague from two generations ago.

Study Shows Virotherapy May be Promising Treatment Against Multiple Myeloma

In a proof-of-principle clinical trial, Mayo Clinic researchers have demonstrated that virotherapy — destroying cancer with a virus that infects and kills cancer cells but spares normal tissues — can be effective against the deadly cancer multiple myeloma. The findings appear in the journal Mayo Clinic Proceedings.

Two patients in the study received a single intravenous dose of an engineered measles virus (MV-NIS) that is selectively toxic to myeloma plasma cells. Both patients responded, showing reduction of both bone marrow cancer and myeloma protein. One patient, a 49-year-old woman, experienced complete remission of myeloma and has been clear of the disease for over six months.

“This is the first study to establish the feasibility of systemic oncolytic virotherapy for disseminated cancer,” says Stephen Russell, M.D., Ph.D., a Mayo Clinic hematologist, first author of the paper and co-developer of the therapy. “These patients were not responsive to other therapies and had experienced several recurrences of their disease.”

Multiple myeloma is a cancer of plasma cells in the bone marrow, which also causes skeletal or soft tissue tumors. This cancer usually responds to immune system-stimulating drugs, but eventually overcomes them and is rarely cured.

In their article, researchers explain they were reporting on these two patients because they were the first two studied at the highest possible dose, had limited previous exposure to measles, and therefore fewer antibodies to the virus, and essentially had no remaining treatment options.

Oncolytic virotherapy — using re-engineered viruses to fight cancer — has a history dating back to the 1950s. Thousands of cancer patients have been treated with oncolytic viruses from many different virus families (herpesviruses, poxviruses, common cold viruses, etc.). However, this study provides the first well-documented case of a patient with disseminated cancer having a complete remission at all disease sites after virus administration.

The second patient in the paper, whose cancer did not respond as well to the virus treatment, was equally remarkable because her imaging studies provided clear proof that the intravenously administered virus specifically targeted the sites of tumor growth. This was done using high-tech imaging studies, which were possible only because the virus had been engineered with a “snitch gene”— an easily identifiable marker — so researchers could accurately determine its location in the body.

More of the MV-NIS therapy is being manufactured for a larger, phase two clinical trial. Researchers also want to test the effectiveness of the virotherapy in combination with radioactive therapy (iodine-131) in a future study.
Endoscope with an Oxygen Sensor Detects Pancreatic Cancer

An optical blood-oxygen sensor attached to an endoscope is able to identify pancreatic cancer in patients via a simple endoscopic procedure, according to researchers at Mayo Clinic in Florida.

The study, published in the journal, *Gastrointestinal Endoscopy*, shows that the device, which acts like the well-known clothespin-type finger clip used to measure blood oxygen in patients, has a sensitivity of 92 percent and a specificity of 86 percent.

That means, of 100 patients with pancreatic cancer, this sensor would detect 92 of them, based on the findings. And of 100 patients who don’t have pancreatic cancer, the test would correctly identify them 86 percent of the time.

The device measures changes in blood flow in the tissues that are in proximity to the pancreas, under the theory that tumors change the flow of blood in surrounding tissues because the tumors need oxygen to grow. The endoscope is passed into the stomach and the duodenum, where measurements are taken. The pancreas lies just outside the duodenum.

“Although this is a small pilot study, the outcome is very promising. There is no test now available that can accurately identify pancreatic cancer at an early stage, short of removing some of the organ,” says the study’s senior investigator and gastroenterologist, Michael Wallace, M.D., M.P.H. “We need new ways to detect pancreatic cancer effectively, and simply, as early as possible.”

Now, more than 90 percent of pancreatic cancers are discovered at an advanced or metastatic stage, with no effective therapy available. That explains why pancreatic cancer is the fourth most common cause of cancer deaths in the U.S., although it ranks 10th in occurrence.

“We are now confirming our findings in a much larger study, involving institutions in the U.S. and in Europe,” Dr. Wallace says.

“The technique is a very different way of looking at cancer detection.”

“What is quite unusual is that we were trying to sense changes that are not in the tumor itself but are in the nearby, normal-appearing tissues,” he says. “It relies on a principle, now being increasingly acknowledged, called a cancer field effect. Instead of looking for the needle in the haystack, we now look at the haystack to see how it is different when there’s a needle inside.”

“The general concept is that cancers cause surrounding tissue to undergo changes in the flow of oxygen that are detectable, not visually or even under the microscope, but by this kind of sensor,” Dr. Wallace says.

To test the ability of the sensor to recognize pancreatic cancer, researchers studied two groups — one in which 14 patients were already diagnosed with the cancer, and another made up of 10 cancer-free patients.

Dr. Wallace says the blood sensor endoscope is also being tested in colon and esophageal cancers.
Alyx Porter, M.D., of Mayo Clinic Scottsdale recently cleaned out her childhood bedroom at her parents’ home. She found elementary school keepsakes, including a certificate recognizing her early storytelling skills and a fourth-grade paper in which she expressed her desire to be a doctor.

Today, she is a neuro-oncologist who diagnoses and treats primary brain tumors, benign and malignant. She’s also part of a national clinical trial aimed at reducing fatigue and improving cognition in patients with glioblastoma and a co-author of a book meant to help patients “find where they are in their journey” after learning they have brain cancer.

“I always wanted to be a doctor,” Dr. Porter says. “I don’t remember ever desiring any other career.”

While attending Scottsdale’s Horizon High School, barely 3.5 miles from Mayo Clinic Hospital, where she now works, she says her father arranged for her to shadow Holly Underwood, M.D., then a Mayo Clinic internist. Before meeting the African American doctor, her first mentor, she laughingly said, the only black doctor she had known was comedian Bill Cosby as Dr. Huxtable on television.

Dr. Porter majored in English at Georgia’s Spelman College, where she loved African-American literature, before heading to Temple University School of Medicine in Philadelphia, Pa. “I loved studying literature, but it’s not what I wanted my career to be,” she says. “I think a big part of medicine is an art, and I enjoy that.”

While a medical student, she discovered neurology during a program for under-represented minorities at Mayo Clinic in Rochester. She later returned to Mayo Clinic for residencies in internal medicine and neurology.

Joining Mayo Clinic Scottsdale in 2007 was easy. “My family is here. This was the place where I wanted to be. All of my mentors have been through Mayo.” She and her husband, a Mayo-trained physician in private practice, have two young children.

Her greatest professional accomplishment to date, she says, involves her writing skills, referring to the 2012 book “Navigating Life with a Brain Tumor” that was co-written with Tufts University neuro-oncologist Lynn Taylor, M.D., and radio producer-writer Diane Richard.

“It’s a supplemental resource to office visits for patients and their family members who have experienced brain cancer or even a benign brain tumor,” she says. “We recognized that less than half of what is said in the office is understood at that time, and it’s in an almost totally different language. So we wanted to ease the burden.”

The book encourages patients and families to “take a deep breath” and follows with easy-to-digest information about their situation and what lies ahead, from potential treatments to financial considerations.

Rather than reading from cover to cover, Dr. Porter says, families can browse the table of contents to find what information is pertinent to them.
As a boy in Pakistan, Asher Chanan-Khan, M.D., of Mayo Clinic Jacksonville had a cow named after him. Today he often mimics the voice of a naughty meerkat when reading to his son. On the job, he is a cancer researcher.

His enemies are chronic lymphocytic leukemia, multiple myeloma and Waldenström’s macroglobulinemia. He fights each with experimental but scientifically based approaches.

“The diseases that I work in are incurable,” says Dr. Chanan-Khan, chair of Mayo’s Division of Hematology/Oncology. “Standard treatments, by default, means that you know you will not cure the patient. Each patient I see gets individualized care, not only for the treatment but also for the patient’s social, spousal and family needs.”

His team developed one of the best first research models for Waldenström’s macroglobulinemia, a rare form of non-Hodgkin lymphoma, using tumors from a woman in her 40s who had wanted her case to be useful. Her tumors, put in mice immediately after her death, led to a cell line now used globally to study and fight the disease.

That work was done at the Roswell Park Cancer Institute in New York, where Dr. Chanan-Khan built his first laboratory after a residency at Columbia University’s teaching hospital in Harlem and a fellowship at the New York University School of Medicine. His team of four physicians and three researchers followed him to Mayo Clinic in 2011.

His team recently reported on the key ingredient in neem leaves that halted leukemia in a patient. Dr. Chanan-Khan had agreed, at the insistence of the patient’s wife, to try herbs before chemotherapy. When the cancer went into remission, the herb mix provided by the patient’s wife was discontinued. When the cancer returned, the herbs were resumed individually to find which one worked.

As a child, Dr. Chanan-Khan watched his paternal grandmother, in her 80s, care for rural villagers following her retirement as a government physician. She named a cow she had received as payment in her honor. “I had an amazing sense of the respect she garnered from people,” he says. “My father put enormous pressure on me to become a diplomat, but I was never inclined to do that.”

He grew up at military bases in a Christian family devoted to military or government service in a Muslim-dominated nation. At age 16, he wrote in an English paper declaring that, in the year 2000, he would be a hospital-based cancer researcher. In 2000, he was one at NYU.

Dr. Chanan-Khan earned his medical degree in 1993 from the University of Punjab. When his father retired as an Air Force colonel, the family, with Chanan-Khan’s just-issued medical degree, moved to New York City.

Dr. Chanan-Khan’s wife is a pediatrician. Their son, Matthew, is 5. “My whole world after my work is built around him. He makes me laugh and smile,” Chanan-Khan says. He reads a lot to his son, he says, taking on the voices of animals.
Jeff Sloan, Ph.D.

Come follow the path

Jeff Sloan, Ph.D. the youngest of three children in a working-class Winnipeg family, emerged as a math whiz in junior high. Later, while massaging theorems as a graduate student at the University of Manitoba, a nursing student’s call for help dialed him into a medical career.

Dr. Sloan, now a researcher in the Department of Health Sciences Research at Mayo Clinic Rochester, said he “felt quite out of place initially” when he entered a labor-and-delivery unit. Ultimately, however, he helped the nursing student devise a coding system for every interaction between birthing mothers and nurses. The study led to improved care during the birthing process.

Jenniece Larsen, dean of the university’s nursing faculty, asked Dr. Sloan to help other nurses as a part-time consultant while he finished his doctorate in biostatistics. The nurses engaged Dr. Sloan’s statistical expertise for studies in child and maternal health, psychiatry, cancer and geriatrics.

“It was an amazing education for a biostatistician,” he said. “Dean Larsen changed my life. The nurses I worked with ‘corrupted’ me by accepting me as an equal partner and showing me how rigorous scientific mathematical theory could make an impact in the real world.”

Dr. Sloan joined Mayo Clinic in 1995 after meeting Judith O’Fallon, Ph.D., director of the Cancer Center Statistics Unit, at a conference. “She urged me to apply for an opening in her department,” Sloan recalled. “She called me a quality-of-life researcher. I’d never heard the term before.”

Today, when a doctor asks how a patient feels, the reply is scored on a 10-point scale that Dr. Sloan developed. A score of 5 or less, he said, doubles the risk of death in cancer patients. Such questions are now routine at Mayo Clinic, enabling patients to provide information not seen in routine lab results.

An example is a farmer whose lab tests showed that he was cancer free for the eighth consecutive year, but when asked how he was feeling by his oncologist, a colleague of Dr. Sloan’s, the farmer scored a 2. The patient then reported being dogged by sleep-disrupting suicidal thoughts. After psychiatric treatment for depression, the farmer scored a 7 at his next checkup.

“When I was told the story,” Dr. Sloan said, “I felt we had accomplished something special. That little, simple question that we had come up with really had helped somebody in a profound way.”

Dr. Sloan is now part of an international, interdisciplinary effort to identify genetic influences related to patients’ quality of life. In 2009, he cofounded the Genetic Quality of Life Consortium, an initiative of Mayo Clinic and the University of Amsterdam.

“You can have two patients with the same disease and characteristics, yet one flies through chemotherapy without any problems and the other has a miserable time,” Dr. Sloan said. “Why is that? We are finding genetic predispositions that help or hamper our response to stress. It speaks to our resilience.”
Cancer Center Earns “Exceptional” Rating, Wins NCI Grant Renewal

The Mayo Clinic Cancer Center received an overall “exceptional” score on the competitive renewal of its National Cancer Institute (NCI) Cancer Center Support Grant (CCSG). The grant award will provide $28.6 million in funding over five years, providing essential support for the Cancer Center’s 10 research programs and 13 shared resources through 2018.

The Mayo Clinic Cancer Center’s NCI designation as a comprehensive cancer center was also renewed. To earn the comprehensive cancer center designation, an institution must participate in multidisciplinary laboratory, clinical and population-based research and educate the community it serves about research advances. The Cancer Center is one of 41 comprehensive cancer centers across the country.

“Exceptional” is the highest rating given by the NCI. Fewer than 10 percent of NCI-designated cancer centers receive “exceptional” scores.

“This rating reflects the level of science being conducted by our researchers and the high quality of our staff,” said Cancer Center director, Robert Diasio, M.D.

The NCI CCSG has provided more than $150 million to the Mayo Clinic Cancer Center over the past 40 years. The NCI first designated the Cancer Center an NCI Cancer Center in 1973. The Cancer Center has had continuous funding from the NCI since that time.

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ACCRU brings together investigators from leading academic medical centers and community oncology practices to collaborate with industry partners in the development of new cancer therapies. More than 85 member institutions, each with extensive experience in cancer clinical research, share in ACCRU’s mission of conducting clinical trials to improve cancer care. Established in 2004, ACCRU research operations are based at Mayo Clinic, yet their collaborations extend to include leading cancer researchers throughout the United States and Canada.

“Our network capabilities position us as a leader for future cancer research efforts,” says Axel Grothey, M.D., ACCRU chair and a medical oncologist at Mayo Clinic. “We are able to conduct large, randomized trials that will use molecular biomarkers to screen patients and individualize therapy so that each patient receives the best treatment for their type of cancer.”

Dr. Grothey says ACCRU’s capabilities are especially important given the limited funding resources for cancer research and the need to develop clinical trials to identify and test new therapies that have the potential to improve cancer care. He points out that more than 50 percent of ACCRU trials are investigator-written, enabling investigators both within Mayo Clinic and other institutions to turn study concepts into clinical trials that would not otherwise be developed.

In February, ACCRU launched the BOLD303 trial, a randomized phase III trial of eribulin compared to standard paclitaxel for first- or second-line treatment of locally recurrent or metastatic breast cancer. The study was developed by Minetta Liu, M.D., an ACCRU principal investigator and medical oncologist at Mayo Clinic. Sponsorship is provided by Eisai, Inc.

“This trial is the result of a true collaborative partnership between investigators, industry sponsors and our network members,” says Dr. Grothey. “In addition, this trial showcases ACCRU’s capabilities to conduct a large, multicenter trial that includes well-designed translational research that will provide important information for all physicians selecting treatments for patients with metastatic breast cancer.”

ACCRU has a broad scientific portfolio of cancer treatment and symptom management trials across many types of cancer. For more information about ACCRU and the BOLD303 trial, visit:

- ACCRU website
- ACCRU YouTube channel

MCCC Joins NCCN

The Mayo Clinic Cancer Center (MCCC) has been elected to institutional membership in the National Comprehensive Cancer Network® (NCCN®), a not-for-profit alliance of leading cancer centers dedicated to improving the quality, effectiveness, and efficiency of care for cancer patients.

“NCCN membership provides us with the opportunity to work with leadership and clinical professionals at other NCCN member institutions to create clinical practice guidelines appropriate for use by patients, clinicians and other health care decision-makers,” says Robert Diasio, M.D., MCCC director. “NCCN and the Mayo Clinic Cancer Center share a mission to better the lives of cancer patients and are excited to work with other NCCN member institutions to save lives and improve quality of life for cancer patients across the nation.”

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are used by clinicians and payers as the standard for clinical policy in oncology. The NCCN Guidelines® are developed through explicit review of evidence integrated with expert medical judgment and recommendations by multidisciplinary panels from NCCN Member Institutions.
SPECIALIZED PROGRAMS OF RESEARCH EXCELLENCE (SPOREs)

**Brain Tumor SPORE**
- Brian Patrick O’Neill, M.D. - Principal Investigator
- Robert Jenkins, M.D., Ph.D. - Co-Principal Investigator

**Breast Cancer SPORE**
- James Ingle, M.D. - Principal Investigator
- Matthew P. Goetz M.D. - Co-Principal Investigator

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

**Ovarian Cancer SPORE**
- Scott Kaufmann, M.D., Ph.D. - Principal Investigator

**Pancreatic Cancer SPORE**
- Gloria Petersen, Ph.D. - Principal Investigator

AFFILIATIONS AND COLLABORATIONS
- *Academic and Community Cancer Researchers United*
- Alliance for Clinical Trials in Oncology
- American Cancer Society
- American College of Surgeons Oncology Group
- Biodesign Institute - Arizona State University
- *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
- GLOIOGENE
- Gynecologic Oncology Group
- Hormel Institute - University of Minnesota
- Indian Health Service
- Karolinska Institute
- Minnesota Partnership for Biotechnology and Medical Genomics
- Native Programs
- National Cancer Institute
- National Comprehensive Cancer Network
- National Clinical Trials Network
- NRG Oncology
- Ontario Institute for Cancer Research
- Pancreatic Cancer Genetic Epidemiology
- Pharmacogenetics Research Network
- *Phase I Program*
- *Phase II Consortium*
- Peking Union Medical College Cancer Hospital, Beijing
- Translational Genomics Research Institute (TGen)
- *Based at Mayo Clinic*

Mayo Clinic Department of Development
Toll-free: 1-800-297-1185
e-mail: development@mayo.edu
www.mayoclinic.org/development
Mayo Clinic Cancer Center locations: Rochester, Minnesota, Jacksonville, Florida and Phoenix, Arizona.

Number dollars (in millions) of funding Mayo Clinic Cancer Center will receive over five years from the National Cancer Institute through the NCI Cancer Center Support Grant (CCSG).

U.S. states from which Mayo Clinic Cancer Center patients hail.

The year the National Cancer Institute first designated the Mayo Clinic Cancer Center as an NCI Cancer Center.