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Bringing Artificial Intelligence into Personalized Cancer Care

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DEAR READERS

Ordinarily during March and April, we’d be preparing to share with you this in-depth look at our research and clinical advancements. But those ordinary times were quickly swept away and, understandably, our focus at the Institute turned to confronting the COVID-19 pandemic.

Our staff has responded admirably to the unprecedented challenges posed by this public health crisis. Their talent, tenacity, and dedication to keep our patients safe and supported has been nothing short of heroic. Certainly, we recognize that our patients’ cancers will not slow or wait for this pandemic to pass. And we have taken every possible measure to continue to be a steady source of hope and healing to our patients and families during this difficult time.

I also recognize that despite the extraordinary circumstances and uncertainty that surrounds the outbreak, this remains a revolutionary time for cancer care and scientific discovery, and we can ill afford to lose any progress. By taking the appropriate safety measures to limit the number of staff working on site and transitioning many to remote work, we are moving forward with our bold research mission, and continuing to see patients, both in person at the Institute, and virtually through expanded telemedicine options. This allows us to see thousands of new people each week, signaling to cancer patients everywhere that, as always, and especially in a time of crisis, we are here for them.

The articles in this issue of Paths of Progress shed more light on the progress that we continue to make in spite of these extraordinary obstacles. It covers work that began long before the onset of COVID-19 and will continue long after it recedes. For as daunting this experience has been for all of us, I need not look any further than our own patients as a constant reminder of why our work and mission remain critically important. The coronavirus poses its own risks and challenges to patients facing cancer. And they look to us for relief, support, and hope. I look forward to the day when this crisis is behind us and we can focus singularly on the limitless possibilities to find new cures and new hope for our patients, as we have throughout Dana-Farber’s long history.

“Our staff has responded admirably to the unprecedented challenges posed by this public health crisis. Their talent, tenacity, and dedication to keep our patients safe and supported has been nothing short of heroic.”

– Laurie H. Glimcher, MD

Laurie H. Glimcher, MD
President and CEO, Dana-Farber Cancer Institute
Saverin Family Gift Provides $20 Million for Metastatic Breast Cancer Research

A $20 million gift to Dana-Farber from the Saverin Family last year established the new Saverin Breast Cancer Research Fund under the direction of Eric Winer, MD, senior vice president for medical affairs, chief of Breast Oncology in the Susan F. Smith Center for Women’s Cancers, and the Thompson Chair in Breast Cancer Research at Dana-Farber. The commitment is the largest individual gift for breast cancer research in Dana-Farber’s history.

The sole purpose of the Saverin Family’s gift is to support research relating to treatment and eventual cures of advanced or stage IV metastatic breast cancer. Metastatic breast cancer is cancer that has spread outside of the breast and to other parts of the body, such as the bones, brain, liver, or lungs. It is a treatable but currently an incurable form of breast cancer.

A world-renowned leader in the breast cancer field, Winer has made seminal contributions to improve the treatment of this disease, with a focus on the aspects of breast cancer that remain the most challenging.

“The Saverin Family’s foresight will allow us to tackle the unsolved challenges by building on the advances we have already forged, and to develop entirely new strategies,” said Winer. “Their exceptional generosity provides resources we need to further metastatic breast cancer research that is underway, and, more importantly, to open bold avenues of investigation.”

Dana-Farber Establishes Riney Family Multiple Myeloma Initiative

Dana-Farber this year started the Riney Family Multiple Myeloma Initiative to help improve outcomes and accelerate understanding of the underlying biology for the most challenging types of myelomas, cancers that form in a type of white blood cell called a plasma cell. The initiative is being established with a $16.5 million gift from Paula and Rodger Riney of St. Louis, Missouri.

The gift from the couple’s foundation, the Paula and Rodger Riney Foundation, is the largest single gift from a family to support multiple myeloma cancer research and care in Dana-Farber’s history. The Riney Family Multiple Myeloma Initiative at Dana-Farber will add to their legacy of multiple myeloma support, and will improve outcomes for myeloma patients everywhere.

“We are deeply grateful to the Riney Family for this inspired gift that will quickly advance our knowledge of multiple myeloma,” said Laurie H. Glimcher, MD, president and CEO, Dana-Farber. “While we have made significant strides in treating multiple myeloma, this initiative provides an opportunity to accelerate the most promising strategies and meaningfully extend remissions.”

Rodger Riney was diagnosed with multiple myeloma in 2015 and treated at the Washington University School of Medicine and Siteman Cancer Center at Barnes-Jewish Hospital. In 2018, Ken Anderson, MD, program director at Dana-Farber’s Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics and Kraft Family Professor of Medicine at Harvard Medical School, joined as an advisor to Riney’s care team.

“As a myeloma patient, you are very aware of the groundbreaking work being done at Dana-Farber in multiple myeloma,” said Riney. “Dana-Farber is an institution we want to invest in given its impressive track record in improving myeloma treatment. Our hope is that this gift will inspire others to support Dana-Farber’s researchers and clinicians to extend survivorship, and ultimately find a cure.”
Largest-Ever Gift for Glioblastoma Research Aims to Address Obstacles

Dana-Farber/Brigham and Women’s Cancer Center (DF/BWCC) announced in 2019 a groundbreaking gift from Oppenheimer Generations Foundation to create The Jennifer Oppenheimer Cancer Research Initiative. This translational research initiative will address key obstacles across the continuum of care facing patients with glioblastoma — including surgery, new drug development, and palliative care.

Jonathan Oppenheimer made the gift in memory of his late wife, Jennifer Oppenheimer, who passed away from glioblastoma in May 2017. During her illness, Jennifer was treated by David Reardon, MD, clinical director of the Center for Neuro-Oncology, James Tulsky, MD, chair of the department of Psychosocial Oncology and Palliative Care, and Alexandra Golby, MD, director of image-guided neurosurgery.

“My family and I are grateful for the kind and expert care Jennifer received at DF/BWCC during the most challenging and difficult time of our lives,” says Jonathan. “Jennifer was a powerful and vibrant force for good who touched the lives of thousands through her extensive advocacy for civil society organizations. This gift is a way to give back to the physicians who took care of her while also honoring and carrying forth her work to help others.”

The Jennifer Oppenheimer Cancer Research Initiative is the Oppenheimer family’s first major gift to DF/BWCC and is the largest individual gift to glioblastoma research in DF/BWCC’s history.

Dana-Farber has been given another tool in the fight against pancreatic cancer. Thanks to a $5 million grant from the Lustgarten Foundation, the Institute established a new pancreatic cancer research laboratory in the Hale Family Research Center. The dedicated lab is one of two new facilities funded by the Lustgarten Foundation — the second is located at MIT.

Dana-Farber’s Lustgarten Foundation Pancreatic Cancer Research Laboratory is led by Brian Wolpin, MD, MPH, director of the Hale Family Research Center and the Robert T. and Judith B. Hale Chair in Pancreatic Cancer, whose research focuses on personalizing therapy and identifying new ways to detect pancreatic tumors earlier.

“You need individuals and institutions who will support your work and push you to be better,” said Wolpin during a ribbon-cutting ceremony in September 2018. “Thanks to the funding from the Lustgarten Foundation, we will have additional support to make a difference for patients with pancreatic cancer.”

In the last 20 years, the Lustgarten Foundation has given more than $10 million to Dana-Farber for pancreatic cancer research.

Brian Wolpin, MD, MPH
AROUND THE INSTITUTE

Dana-Farber Establishes Chen-Huang Center for EGFR Mutant Lung Cancers

Dana-Farber in 2020 created the Chen-Huang Center for EGFR (epidermal growth factor receptor) Mutant Lung Cancers to stimulate research, promote clinical trials, and strengthen the Institute’s capabilities for studying and treating lung cancers driven by EGFR gene mutations. The Chen-Huang Center was established with a $5 million gift from Winston Chen, PhD, and his wife, Phyllis Huang, of Silicon Valley.

For many years, the couple’s family foundation, the Paramitas Foundation, had focused on supporting higher education. Their recent funding has shifted to health care projects, specifically lung cancer care and research led by Pasi Jänne, MD, PhD, director of the Carole M. and Philip L. Lowe Center for Thoracic Oncology, and director of the Robert and Renée Belfer Center for Applied Cancer Science at Dana-Farber.

“Phyllis and I hope our gift will bring much needed attention to lung cancer and illustrate how vital financial support is for making discoveries,” said Chen. “We support Dr. Jänne and Dana-Farber because of their impressive centers, research facilities, and the discoveries they are making every day.”

Gift Creates the Edward P. Evans Center for Myelodysplastic Syndromes

A $5 million gift to Dana-Farber from the Edward P. Evans Foundation enabled the creation of the Edward P. Evans Center for Myelodysplastic Syndromes (MDS). The gift will help Dana-Farber in transformative collaborative research aimed at treating, preventing, and ultimately curing MDS.

MDS are a group of diseases in which the bone marrow makes too few healthy blood cells. Patients with MDS often suffer from debilitating fatigue and may require regular blood transfusions. Some patients with MDS are also at risk for infection or bleeding due to low white blood cell count or platelet count, and at least 20% of patients with MDS will develop acute myeloid leukemia (AML). The only current cure for MDS is a stem cell (bone marrow) transplant from a healthy donor, but currently fewer than 10% of patients with MDS are able to undergo transplant due to advanced age or other medical problems.

“The Edward P. Evans Center for MDS at Dana-Farber will be a nexus for discoveries in MDS and improvements in patient care that will help reduce the global burden of MDS,” said Laurie H. Glimcher, MD, president and CEO of Dana-Farber. “We are deeply grateful and encouraged by the support from the Edward P. Evans Foundation and are thrilled to provide a platform to support investigators at every level.”

Pasi Jänne, MD, PhD

More than 200,000 people in the U.S. and more than one million worldwide were diagnosed with lung cancer in 2019. Lung cancer remains the most common cause of cancer-related deaths for both men and women in the U.S. EGFR mutations are found in 15% of patients in the U.S. and European Union, and 50% of lung cancer patients in Asia.

“This generous gift will allow us to further push the boundaries of knowledge in this area to eventually develop new and better therapies,” said Laurie H. Glimcher, MD, president and CEO, Dana-Farber. “We are very grateful to Winston Chen and Phyllis Huang for their support to create this new center.”
Volunteers Support Patients and Staff from Home

Caitlin Geaney loved her first few months volunteering with Dana-Farber’s Ambassador Program, guiding patients and other Yawkey Center visitors to appointments and resources. But the COVID-19 crisis left her unable to provide such assistance in-person, so Geaney found other ways to show the Dana-Farber community that she and other volunteers are thinking of them.

A 21-year-old student at the Massachusetts College of Pharmacy and Health Sciences, Geaney spearheaded the Gratitude Project — a photo collage of volunteers holding messages of support and thanks. She hatched the idea when COVID-19 forced her to step away from her volunteer shifts and she saw similar efforts on social media.

“Volunteering is something I always look forward to. I saw it as a time when I could make a difference,” says Geaney. “This [project] was a way to do that from home.”

Many of her colleagues felt the same way. Dozens of volunteers, most of whom she’d never met, sent Geaney photos of themselves holding signs. Geaney designed a collage with the photos and added a message of thanks. The finished poster was shared with Dana-Farber patients and staff via email and social media.

“It shows the level of dedication people have for their volunteer roles,” says Pat Stahl, senior manager of Volunteer Services and Programs at Dana-Farber. “They’ve kept our community together.”

Dana-Farber has nearly 500 volunteers in a variety of roles. While restricted from visiting campus during the COVID-19 crisis, they continued to help remotely. Volunteers helped patients learn to use video-conferencing apps for telehealth appointments, ran online workshops, and even formed an online book club.

“It is incredible how fast our volunteers have adapted,” says Maritza Nassif, program coordinator for Patient and Family Services. “They have made it clear they want to stay involved.”

Keeping the Jimmy Fund Clinic a Place to Smile

Dana-Farber’s Jimmy Fund Clinic in April 2020 looked completely different than it did just a few weeks before, with events postponed, fewer visitors, and all staff required to wear masks – making it impossible to see the smiles that usually greet patients entering the clinics. But behind each mask is still the friendly face of someone available to talk through a difficult time or break out an impromptu dance party just to make a patient grin. That’s important, because despite the unprecedented challenges of COVID-19, the Jimmy Fund Clinic is still providing treatment to patients who need to undergo weekly, or even daily therapy.

“We’re still acting silly and crazy,” says Shea. “It’s all about staying positive, taking it one day at a time, and focusing on what the patient needs at that moment.”
Saluting our Staff During the COVID-19 Pandemic
the COVID-19 Pandemic
A CASE FOR
A CASE FOR CURIOSITY

BY ROBERT LEVY
n a pragmatic, goal-oriented age, the notion of curiosity as the driving force behind research might seem out of fashion. But in the long run, it may be curiosity – unimpeded and open-minded – that cures cancer.

For evidence, one need look no further than the 2019 Nobel Prize in Physiology or Medicine, awarded to Dana-Farber’s William Kaelin Jr., MD, Sir Peter Ratcliffe of the University of Oxford, and Gregg Semenza, MD, PhD, of Johns Hopkins University. At the outset, it was far from obvious that Kaelin’s work would contribute to a pivotal discovery about how cells adapt to changes in oxygen levels. But because it sprang from a desire to answer a fundamental biological question, and a willingness to follow a course of research wherever it led, it would be unwise to bet against its potential.

Long before the morning he learned he had co-won medicine’s highest award, Kaelin, the Sidney Farber Professor of Medicine at Dana-Farber and Harvard Medical School, senior physician in Medicine at Brigham and Women’s Hospital, and Howard Hughes Medical Institute investigator, has been making the case for curiosity-driven research and its potential to transform the treatment of disease.

“The beauty, as well as the challenge, of basic science is that you can’t always predict what the outcome of the work is going to be,” he says. “You’re investing in the creation of new knowledge, and the only thing you can be sure of is that the more you invest in basic science, the more new knowledge you will generate. And the more knowledge we have, hopefully, the more improvement we will have in the quality of our lives.”

The Right Spot

Choosing an area of research is, Kaelin likes to say, like fishing: It’s ultimately guesswork, but guesswork informed by experience and a sense of where the greatest promise lies. As a budding laboratory scientist in the early 1990s, he was looking for something that was interesting not only in itself but as a source of clues into a variety of cancers – something where research could be informative as well as impactful.

The answer came in 1993 when
he read a report in *Science* magazine about the cloning of a gene called *VHL*. “The moment I saw the paper I said, this is perfect, this is what I should work on,” Kaelin relates.

The gene met Kaelin’s criteria for a subject at the hub of multiple questions in cancer. People with a mutated, or abnormal, *VHL* gene are at high risk of developing a rare disorder called von Hippel-Lindau (VHL) syndrome in which tumors and cysts form in multiple organs and tissues. Although some of these growths are benign, they can be harmful if they press on or interfere with neighboring tissues. Some of the tumors, such as kidney cancers, are malignant and can spread to other parts of the body. Research into the disorder offered a way to help patients and, Kaelin intuited, generate broader insights. Scientists quickly determined that the *VHL* gene also plays a critical role in non-hereditary kidney cancer. Kaelin thought that studying the *VHL* gene might provide important insights into the common form of cancer.

Because tumors associated with *VHL* disease are often rich in blood vessels, studying them could also help explain how tumors reroute the bloodstream for nourishment. And because people with VHL tumors can develop a sharp increase in red blood cell production – normally a sign that tissues aren’t getting enough oxygen – VHL research could shed light on how cells sense and respond to changes in oxygen levels.

It was the last of these possibilities that would yield discoveries deserving of a Nobel Prize.

### A Monopoly on Oxygen

At first, it might seem that questions about cells’ capacity for adjusting to changes in oxygen have more to do with mountain-climbing than malignancy. In virtually all animals, oxygen is needed to convert food energy into a useful form. When the demand for oxygen exceeds the available supply – at high elevations, for example, or during exercise – the body responds by ramping up production of red blood cells (which carry oxygen by binding it to hemoglobin), building new blood vessels (to channel more blood cells to tissue), and activating glycolysis (a series of reactions that extract energy from blood sugar). A variety of diseases can prompt the body to take these steps, known as the hypoxia response, even though environmental levels of oxygen are normal – stroke, heart disease, anemia, infection, and, perhaps surprisingly, cancer. Cancer cells are hoarders at the bloodstream’s banquet of nutrients. To fuel their breakneck-growth, they demand an extra helping of oxygen. To get it, they send out distress signals that spur the formation of red blood cells and blood vessels. Understanding how cancer cells hijack the hypoxia response would be a first step toward blocking it – and potentially starving the cells of a fuel they need to survive.

By the late 1990s, several lines of research were zeroing in on cells’ machinery for gauging changes in oxygen levels and adjusting to them. Kaelin’s group had theorized that the *VHL* gene was involved in oxygen sensing:

> “The beauty, as well as the challenge, of basic science is that you can’t always predict what the outcome of the work is going to be.”

– Willam Kaelin Jr., MD

The fact that VHL tumors are laced with blood vessels and laden with red blood cells suggested that when the gene is mutated, the sensing mechanism is broken. To test the theory, they created human kidney cancer cell lines that were identical except that one had a normal version of the *VHL* gene and the other didn’t. They grew them in either a high- or low-oxygen environment and looked for the presence of RNAs that normally are produced only when environmental levels of oxygen are low. A variety of diseases can prompt the body to take these steps, known as the hypoxia response, even though environmental levels of oxygen are normal – stroke, heart disease, anemia, infection, and, perhaps surprisingly, cancer. Cancer cells are hoarders at the bloodstream’s banquet of nutrients. To fuel their breakneck-growth, they demand an extra helping of oxygen. To get it, they send out distress signals that spur the formation of red blood cells and blood vessels. Understanding how cancer cells hijack the hypoxia response would be a first step toward blocking it – and potentially starving the cells of a fuel they need to survive.

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“My jaw dropped when I saw the results,” Kaelin recalls. “We found that cells without the normal *VHL* gene overproduced those RNAs whether oxygen was present or not. It confirmed
“Now that we’ve mapped the molecular pathway behind the hypoxia response, we have clues about where to intervene to make the pathway more or less active.”

– William Kaelin Jr., MD

that the gene was required for oxygen-sensing.”

This finding, from 1996, was a major advance, but researchers didn’t know precisely how changes in oxygen flipped this molecular switch. Semenza had found that when oxygen levels are high, a protein complex called HIF-1 is steadily eroded, but when they’re low, HIF-1 builds up. The discovery quickly converged with Kaelin’s work. In 2001, Kaelin and Ratcliffe independently showed that under normal oxygen conditions, cells place a chemical tag on HIF-1, prompting the VHL protein to destroy it. When VHL is missing or deformed because of a genetic mutation, HIF-1 doesn’t get degraded, causing the cell to act as though oxygen levels are low.

The sense of curiosity that drove the researchers had brought them to a molecular mechanism that was itself a rather curious bit of cellular operations. The HIF-1 complex functions, in a way, like a reverse thermometer: when oxygen levels are adequate, HIF-1 recedes; when the levels drop, HIF-1 rises, ordering delivery of a kind of oxygen mask to cells gasping for air.

Coming to the Clinic

Following the 2001 breakthrough, Kaelin, Semenza, and Ratcliffe uncovered more details of the oxygen-response system and showed that malfunctions in
the system can play a role in cancer and other diseases. Kaelin, for example, found that a defect in HIF-2 – a close kin of HIF-1 – propels the growth of certain kidney cancers and that triple-negative breast cancers often make use of HIF-1.

Researchers are also working on practical applications of their discoveries. “Now that we’ve mapped the molecular pathway behind the hypoxia response, we have clues about where to intervene to make the pathway more or less active,” Kaelin remarks. “For example, we now have drugs that prevent HIF-1 from deteriorating, which might be useful for diseases like anemia, heart attack, and stroke, where oxygen delivery is problem. Conversely, blocking the pathway, with HIF-2 inhibitors, for example, looks like a promising way to treat kidney cancer. I’m also hopeful that HIF-1 inhibitors might be useful for certain cancers.”

The Nobel Prize win has amplified Kaelin’s challenge to those who believe curiosity-based research is too unreliable to undertake or invest in. From experience, Kaelin knows that science doesn’t exist to satisfy curiosity but to perpetuate it – that discoveries are not goals as much as they are incentives to pursue more research. At the most basic level, curiosity-driven research is an expression of confidence in the mind’s ability to make connections, perceive promise, and inspire others.

“Some people might think it risky to have talented scientists follow only their curiosity, because we won’t necessarily be able to predict where the road will take them and we won’t be able to predict what the fruits of their labors will be,” Kaelin asserts. “But we know, over and over, that’s how real progress happens.”

Kaelin and British scientist Peter Ratcliffe independently uncover a critical piece of cells’ oxygen-sensing mechanism, showing how cells “know” whether oxygen is available.

Named co-recipient of the Nobel Prize in Physiology or Medicine, together with Ratcliffe and Greg Semenza, for discovering how cells sense and adapt to changes in oxygen.
Unexpected Benefits from Targeted Therapy

How CDK4/6 and PARP inhibitors work together in targeting disease

BY ROBERT LEVY

Serendipity is rarely sweeter than when it occurs in cancer research. In a field where progress is hard-won, where success often comes in increments rather than wholesale leaps, it’s particularly rare for a new treatment to not only work as intended but also to possess powers that developers hadn’t expected.

Yet that is precisely what Dana-Farber researchers recently discovered about two of the most effective types of targeted therapies – CDK4/6 inhibitors and PARP inhibitors – to arrive in recent years. The twin findings, announced within months of each other, show that in addition to having their known effects in tumor cells, the agents also can stimulate the immune system to fight cancer. The findings suggest that, effective as the drugs are on their own, they could be even more potent when combined with agents that release barriers to the immune response.

Together, the discoveries suggest that many targeted therapies – usually thought to wage a narrow-gauge attack on cancer cells – may do double duty as immunotherapies.

Alternate Tracks

PARP inhibitors and CDK4/6 inhibitors target cancer cells by two very different routes.

CDK4/6 inhibitors, which have a long pedigree in Dana-Farber research, deprive cancer cells of their most notorious characteristic: their ability to divide endlessly. They work by blocking enzymes needed to pass from one phase of the cell cycle to the next. The result is something very un-cancer-like – a tumor cell that simply vegetates, that survives without growing or proliferating.

The drugs showed promise from the time they entered clinical trials. They were first approved by the Food and Drug Administration (FDA) in 2015 for patients with the most common subtype of breast cancer (hormone receptor-positive breast cancer) and are currently being tested, with encouraging results, in a variety of other cancers. “In early trials of these drugs, we noticed that in some breast cancer patients the tumors didn’t just remain the same size – as would be expected with drugs that interfere with cell division – but began to recede, sometimes quite dramatically,” said Dana-Farber’s Shom Goel, MD, PhD.

The reason for the shrinkage, scientists at Dana-Farber and Brigham and Women’s Hospital...
(BWH) found, lay outside the cell-division machinery itself, in the cancer’s always delicate relationship with the immune system. Leading the research with Goel were Hye-Jung Kim, PhD, working the laboratory of Jean Zhao, PhD, of Dana-Farber and the Broad Institute of MIT and Harvard, and Molly DeCristo, a Harvard Medical School graduate student in the laboratory of Sandra McAllister, PhD, at BWH.

To understand why the tumors sometimes shrank, the investigators examined how the CDK4/6 inhibitor abemaciclib acted in animal models of breast or other solid tumors. They found it not only stalled the tumor cycle but also caused the immune system to mount an attack on the tumors – a finding they confirmed by analyzing tissue samples from women in a clinical trial of a CDK4/6 inhibitor for breast cancer.

The drugs trigger an anti-tumor immune response in two ways, the researchers reported in Nature. They prompt tumor cells to reveal their malignant nature by decking themselves in abnormal proteins called neoantigens. The immune system, incited by this display, responds by attacking the tumor cells. At the same time, the drugs cause the number of “T regulatory cells,” or Tregs, to diminish. These cells, the

“In early trials of these drugs, we noticed that in some breast cancer patients the tumors didn’t just remain the same size – as would be expected with drugs that interfere with cell division – but began to recede, sometimes quite dramatically.”

– Shom Goel, MD, PhD
“We’ve shown that in the case of ovarian cancer, another factor is at play – the effects of the drugs on the interaction of tumor cells with the immune system.”

– Jean Zhao, PhD

Both CDK4/6 inhibitors and PARP inhibitors stimulate an immune system attack on cancer cells

Mutations or other genetic abnormalities can disable proteins involved in making such repairs. As the damage mounts, the cell’s ability to function – dependent on the instructions encoded in its DNA – diminishes, potentially to the point where it can no longer sustain itself.

PARP inhibitors take advantage of this weakness by administering a finishing blow to cancer cells. Cells with mutations in the *BRCA* genes, for example, have trouble repairing breaks that occur in both strands of the DNA molecule. They compensate, in part, by relying on genes that mend breaks in one strand. PARP inhibitors work by crippling some of those single-strand specialists. Already coping with the loss of two-strand repair genes, the cells are ready prey for drugs that shut down the single-strand repair machinery.

PARP inhibitors have been approved for patients with breast or ovarian cancer who have inherited mutations in the *BRCA* genes, as well as for some patients with recurrent ovarian, fallopian tube, or peritoneal cancer that responds to platinum-based chemotherapy, and are...
Ian Krop, MD (left), Jean Zhao, PhD (middle), and Shom Goel, MD, PhD (right), in the lab.

mainly viewed as a response to the die-off of tumor cells triggered by PARP inhibitors. Zhao and her colleagues wanted to determine if that was truly the case.

To assist in this effort, Liya Ding, PhD, a research fellow in Zhao’s lab, created animal models of high-grade serous ovarian cancer (HGSOC), the most common form of ovarian cancer, that closely resembled HGSOC in humans. One set of models had a normal complement of the BRCA1 gene, the other lacked the gene.

In the models without normal BRCA1, researchers found that PARP inhibitors sparked an immune response that inundated the tumors with T cells and other immune system agents. “We then asked whether the immune response was meaningful. That is, does it actively contribute to inhibiting tumor growth or is it primarily a passive response to the death of tumor cells?” Zhao remarks.

In a series of experiments, they demonstrated that it is overwhelmingly the former. In one, they disabled T cells known as CD8+ T cells – which directly attack tumor cells – after the animals had been treated with a PARP inhibitor. The result was a regrowth of the ovarian tumors – evidence that CD8+ T cells were active participants in the assault on cancer cells. This finding, coupled with further research, provided convincing evidence that the immune response to PARP inhibitors is more than just a mop-up crew for dead cancer cells but a partner in causing their death.

Because BRCA1-deficient HGSOC tumors tend to wear a thicker coat of PD-L1 proteins after treatment with a PARP inhibitor, Zhao’s team theorized that pairing the drugs with checkpoint inhibitors would be even more effective. Experimental results bore that out: investigators found that mice treated with a PARP inhibitor-checkpoint inhibitor combination lived longer than those treated with the PARP inhibitor alone.

“These findings have important implications for the treatment of ovarian cancer,” said Ursula Matulonis, MD, director of Gynecologic Oncology in the Susan F. Smith Center for Women’s Cancers at Dana-Farber and a co-leader of the research. “When used in conjunction with other agents such as PD-1 inhibitors, PARP inhibitors can have enhanced anti-cancer activity, and we now know why. The findings add new impetus to clinical trials testing this combination.”

Many researchers believe that PARP inhibitors and CDK4/6 inhibitors are not the only agents to have a pleasant immunological surprise. Future studies will reveal if there are others.
Shapeshifters
Glioblastoma is the worst of the worst. A form of brain cancer that affects adults and children, it is both aggressive and difficult to treat. Tragically, most patients die within two years of diagnosis. But new research is cracking open the biology of the disease, helping explain the tumor’s tenacity even when faced with targeted therapies. And those insights are at last giving scientists a critical toehold in the hunt for new, more effective glioblastoma treatments.

In a study published last summer, a team from Dana-Farber, Boston Children’s Hospital, and other leading research organizations used single-cell techniques, which can examine the genetic information within individual cells, one at a time. The researchers scrutinized more than 23,000 cells from both pediatric and adult tumors. They uncovered some surprising similarities among the cells that drive these cancers, insights that could help spur new drugs aimed at glioblastoma.

“We’ve kind of come full circle in how we think about adult and pediatric glioblastoma,” said Mari ella Filbin, a lead author of the recent paper, which appeared in Cell, and a pediatric neuro-oncologist at Dana-Farber/Boston Children’s Cancer and Blood Disorders Center. “Up until about a decade ago, we thought they were essentially the same, so we treated them that way. But more recently, studies of the tumors’ genomes revealed distinct genetic mutations — and that got us thinking that glioblastoma in children is quite different than in adults.”
Now, Filbin and her colleagues are finding that the two cancers may actually be more alike than not. They determined that the cells that drive both adult and pediatric glioblastoma exist in four distinct states, which are defined by the constellation of genes that are switched on or off—a kind of molecular signature. These signatures closely resemble those seen in the assortment of normal cell types that make up the developing brain. Importantly, Filbin and her team revealed that these driver cells are not static and can readily switch from one state to another, like a game of whack-a-mole. That discovery helps explain a sobering clinical reality: why existing, single-target drugs for glioblastoma fail to curb the cancer’s growth.

Opening Brain Cancer’s Bag of Tricks

Like other forms of brain cancer, glioblastoma is alarming because of where it originates. As the epicenter of the mind and body, the brain can endure only a limited amount of surgery and radiation. It is also separated from the bloodstream by a special structure, the blood-brain barrier, which restricts the flow of drugs and other chemicals to brain tissue, further complicating treatment.

Yet glioblastoma also has other tricks up its sleeve. The tumor becomes interwoven into the fabric of the brain, mingling with normal structures and making itself inseparable from them.

“It’s actually like trying to remove a virus with surgery,” said Keith Ligon, one of Filbin’s collaborators and a neuropathologist at Dana-Farber/Boston Children’s.

Although Filbin understood this dismal picture, she initially set out to study a different cancer, a rare brain tumor called diffuse intrinsic pontine glioma (DIPG), which affects mostly young children and, sadly, also has a grim prognosis.

She was struck by the power of new single-cell technologies, specifically single-cell RNA sequencing, which provides a cell-by-cell snapshot of which genes are active and which are not—the so-called “transcriptome.” That view goes beyond what can be gleaned simply by looking at the cells’ DNA, which only reveals which genes are missing or broken, not how those changes impact cell function. Because these techniques are painstakingly applied to individual cells, they can reveal subtle differences within a tumor that may be missed by cruder, bulk profiling methods.

“DIPG was the very first cancer I wanted to look at because these kids have such poor survival rates,” said Filbin. “We need to do better and we need to do something different to understand that disease.”

So she and her colleagues harnessed single-cell RNA sequencing to examine nearly 2,500 cells from six DIPG patients. In a paper published in Science in 2018, they revealed that the majority of tumor cells are developmentally stuck—instead of growing up and becoming more specialized, as normal cells do, DIPG cells are trapped in an immature, stem-cell-like state.

Filbin and her team also noticed something else. Prior to any treatment, a small fraction of tumor cells can overcome this developmental roadblock. They simply grow up or “differentiate”—and, at the same time, lose their tumor-forming potential.

“That is super exciting,” said Filbin. “We now have the first evidence that a pediatric brain cancer can differentiate on its own.”

She and her colleagues are now exploring whether they can exploit this capability therapeutically. Can a drug be identified that coaxes more tumor cells to differentiate, thereby rendering the cancer harmless? This concept, known as differentiation therapy, has been around for decades in pediatric oncology and currently forms the basis for treating a form of pediatric leukemia as well as another pediatric tumor called neuroblastoma.

A Cell-By-Cell View of Glioblastoma

Filbin was so impressed with the idea of differentiation therapy
for pediatric brain cancers, she wondered if it might apply to other aggressive forms, like glioblastoma. Her colleagues at Massachusetts General Hospital were already using single-cell techniques to study adult forms of the disease, so the researchers banded together to conduct a broader analysis of pediatric as well as adult tumors. They examined tumors from 20 adult and eight pediatric patients.

Prior to the advent of single-cell methods, scientists delved into the molecular makeup of patients’ tumors using a bundled approach. They would isolate a chunk of tumor tissue, grind it up, and perform experiments on that cellular “soup” – effectively averaging across all of the cells present in the mix. And yet tumors don’t grow, spread, or die as an average unit. They do so cell by cell.

“A good analogy here is your friendships,” said Ligon. “If you averaged all of your friends’ personalities, that won’t really tell you anything about what each person is like.”

With single-cell technologies, Filbin, Ligon, and their colleagues were able to glimpse for the first time a detailed picture of glioblastoma on a scale that matches its biology.

The team discovered that tumor growth is fueled by four distinct cell types or “states,” which exist at varying degrees in all glioblastoma patients, both children and adults. These states resemble different cells normally found in the developing brain, including astrocytes and oligodendrocyte progenitor cells, both types of support cells called glia; neural progenitors, which can give rise to both neurons and glia; and mesenchymal cells, which give rise to connective tissue.

These glioblastoma cell states are highly plastic and can readily shift from one to another. When Filbin and her colleagues injected just one of the four cell types into mice, tumors formed that contained all four types, helping to explain why existing single-target therapies fail to curtail glioblastoma growth.

Unfortunately, the data do not give credence to differentiation therapy as an effective treatment for glioblastoma, though, as Filbin’s earlier work indicates, it remains a promising approach for DIPG. Nevertheless, Filbin and her team believe their findings offer a roadmap for identifying new glioblastoma therapies, and they have launched early-stage research projects to pursue them.

“In every glioblastoma we looked at, whether it was from a kid or an adult, it had only those four cell types, regardless of its genetic makeup,” said Filbin. “That gives us hope that if we can find a way to block all four at the same time, we can kill the tumor.”

Such a four-pronged attack would signify a groundbreaking approach to glioblastoma treatment – one that could deliver long awaited hope to patients.

“We now have the first evidence that a pediatric brain cancer can differentiate on its own.”

– Mariella Filbin, MD, PhD
BRINGING AI TOWARD PERSONALIZED CANCER CARE

Machine language technology brings new power to study each individual’s risks and best treatment options.
Ask your cellphone a question today, and it probably understands you well enough to provide a fairly reasonable answer. That’s new. Ten years ago, such ubiquitous and even expected speech recognition didn’t exist anywhere on the planet. Now it’s on billions of mobile phones.

Much of your phone’s smarts are based on a rapidly advancing form of artificial intelligence called machine learning, in which the computer basically trains itself to find patterns within massive amounts of data. Machine learning technologies are being applied in many fields, and we’re just starting to see the impact they may have in medical research.
Researchers at Dana-Farber are bringing machine language technology to many tough puzzles in cancer. One pioneering project is gathering information on treatment outcomes in lung cancer, and a second one aims to better identify people who are at most risk to develop pancreatic cancer.

Understanding Outcomes in Lung Cancer

Dana-Farber conducts a genomic analysis on tumors from patients who give their consent. That genomic information can be essential to best understand an individual cancer and, in many instances, can help guide how to treat it. This genomic treasure trove can be combined with a wealth of other patient information, such as data from imaging, to offer an enormously valuable resource for cancer scientists.

But there’s a chokepoint for research that taps into this resource: It’s surprisingly difficult to capture how well patients are responding to treatment by analyzing routine clinical records. “As straightforward as one might expect that process to be, it can be a substantial challenge,” says Dana-Farber oncologist Kenneth Kehl, MD, MPH. He explains that information about the patient outcomes shown in a CT scan, for example, may be routinely recorded only in the unstructured text of a radiologist’s report. Tracking these outcomes requires trained staff to read and annotate such records, which can be slow and expensive.

Kehl and his colleagues turned to machine-learning tools to automate this painstaking process, in a project funded by the National Cancer Institute, the Claude...
“Labeling is a fundamental prerequisite for machine learning – we have to teach machines from a high-quality curriculum if we want to get output we can trust to inform clinical decisions."

– Deborah Schrag, MD, MPH
ware’s outcome measurements in this group predicted survival about as well as the human assessments of outcomes among the patients whose CT records were manually reviewed.

The team is now working to demonstrate that the patient outcomes gathered by software do indeed reflect known associations between tumor genomic features and outcomes in lung cancer, says Kehl. Once that’s done, he, Schrag, and their coworkers will start to ask new research questions about connections between treatments and outcomes. The researchers also will consider ways to incorporate such models into clinical care delivery, such as finding best ways to manage symptoms. And they plan to check out how well the models perform with other types of cancer.

“Moving some of this AI work into the clinic is important and complex and challenging,” Kehl says. “But it’s an important direction to take. It’s where the field will have to go.”

Who Gets Pancreatic Cancer?

When pancreatic cancer is detected before it spreads, 37% of patients survive five years. Unfortunately, that’s the best-case scenario. The survival rate plummets to 10% if the tumor is found at a later stage, which happens in about 90% of cases. That’s one main reason that pancreatic cancer is expected to become the second-most-deadly type of cancer in the United States by 2030.

The disease often can be detected at an early stage by imaging with CT, MRI, or endoscopic ultrasound. Currently, such screening is performed only for a very small group of people thought to be at high risk of the disease, either through family history or the presence of certain worrisome genetic mutations. But pancreatic cancer is far too rare for such procedures to be practical for the population at large.

Researchers know that pancreatic cancer also is linked to other factors including obesity, smoking history, alcohol history, and late-onset diabetes with weight loss and age. But there are no guidelines for integrating all these factors to provide sufficiently reliable predictions of disease risk to allow effective
screening to catch the cancer as early as possible.

Producing such guidelines through machine learning is the goal of a project co-headed by computational biologist Chris Sander, PhD, director of the cBio Center in Dana-Farber’s department of Data Sciences, and MIT computer scientist Regina Barzilay, an expert on machine learning in medicine. Medical oncologist Brian Wolpin, MD, MPH, and radiology physician-scientist Michael Rosenthal, MD, PhD, of Dana-Farber; epidemiologist Peter Kraft of the Harvard T. H. Chan School of Public Health; and disease system biologist Søren Brunak, PhD, of the University of Copenhagen are collaborating on the effort, which is funded by Stand Up to Cancer.

Their work has begun with a highly informative dataset that includes complete clinical records for about 2.5 million patients in the Danish National Patient Registry, about 20,000 of whom have had pancreatic cancer, Sander says. To meet stringent Danish privacy requirements, researchers actually must make repeated trips to Copenhagen for access to the Danish computing resources. The project also will extract risk profiles from the Henry Ford Health System in Detroit and Partners HealthCare in Boston.

In building machine-language algorithms, “we’re not going in with preconceived notions of what are the deciding factors for risk,” Sander says. “We take a snapshot of a personal’s clinical records, and starting with this raw data, we challenge the artificial intelligence engine to learn, ‘What’s the probability that this person will get pancreatic cancer in the next few years?’”

Within their stockpiles of clinical data, the team will look at unstructured doctor notes (extracted with natural-language processing techniques similar to those in the lung cancer project above), disease codes and treatment codes, blood tests, and images. “So far, we have the first results from the disease codes, and we’re getting pretty good results already,” Sander says.

The two-year project aims to produce sufficiently accurate risk guidelines for a clinical trial screening for early signs of cancer. Scientists also hope their algorithms will shed light on the roles various risk factors have in predicting (and maybe even causing) the disease and how these could be used in prevention programs.

To enter standard clinical care, the guidelines will have to deliver very high accuracy. “You can have less than 100 percent accuracy for a clinical trial,” Sander notes. “But if you want to apply the risk assessment AI tool in clinical practice, then your accuracy has to be very high to minimize the chance of unnecessary treatment.”

Truly effective screening programs also will demand more effective screening techniques. Hundreds of labs around the world are studying new methods of imaging or blood analyses for early detection of solid tumors such as pancreatic cancers. “There’s huge interest in that research,” Sander says. If better guidelines can be combined with better screening, he and his colleagues hope for real progress against this fearsome form of cancer.

“Our clinicians at Dana-Farber do a lot of work on curing cancer when it’s very advanced, which is where the suffering is and where we really need to beat the cancer,” he adds. “But it’s also important to try to catch cancer at the early stages, avoiding all the suffering along the way and bringing down the total cost of treatment, and that’s one of our top priorities.”
Cancers found in early stages are more likely to be successfully treated or cured. Unfortunately, there are few accurate, widely applicable tests for early detection of major cancers: All too often, patients are diagnosed only after they develop symptoms – when their tumors are larger and harder to treat.

However, scientists are making rapid strides in detecting early signs of cancer in a blood sample, potentially opening a new era of non-invasive cancer screening that could save many lives.

These tests, known as liquid biopsies, leverage the fact that cancers shed bits of DNA into the bloodstream, where they can be measured using increasingly sensitive and powerful technologies. This form of cancer detection needs further development and validation before it can be used routinely, but some clinical trials have yielded impressive results. One such liquid biopsy test demonstrated that it could spot more than 50 types of cancer and identify the tumors’ location in the body with high accuracy. In addition, it gave “false positive” readings in less than 1% of cases.

Consequently, there is growing optimism that liquid biopsies may have an important role in early cancer detection, as well as helping guide therapy.

“The goal is to make cancer screening more efficient, ideally with one-stop shopping, to identify clinically important cancers at a curable stage, while at the same time minimizing the risks of over-testing, over-diagnosis, and anxiety,” says Deborah Schrag, MD, MPH, chief of Dana-Farber’s Division of Population Sciences.

**A Revolution in Precision Oncology?**

The gold standard of cancer diagnosis has long been the traditional tumor biopsy. In these procedures, cells or tissues are removed from the body and examined by pathologists to confirm the presence of cancer, characterize the types of cells in the tumor, and sometimes identify alterations such as mutations that can be used to guide therapy. These biopsies usually require an invasive procedure, can be uncomfortable, and may involve hard-to-access areas of the body, such as the brain or deep in the abdomen.

There are many potential advantages to liquid biopsies, which take advantage of tumor-derived DNA that is shed into the bloodstream or other body fluids. Instead of a surgical biopsy, a liquid biopsy is much easier on the patient – a simple blood draw. Because they aren’t invasive or painful, liquid biopsies can be repeated frequently – for example, to determine how well a treatment is working, or to monitor the patient for cancer recurrences, or to look for changes in the makeup of the cancer.
“It’s a new way to look at how tumor genomics are changing over time,” says Brian Crompton, MD, a pediatric oncologist at Dana-Farber/Boston Children’s Cancer and Blood Disorders Center. “You could do a blood draw as often as necessary” in a child, rather than needing to repeat an invasive tumor biopsy. Crompton has shown that tumor DNA from five common pediatric solid tumors can be measured in the blood. He says the findings of liquid biopsies potentially could be used to predict which patients will respond well to treatments and tailor therapies to these findings.

New studies suggest that liquid biopsies could improve on current methods for detecting recurrences of cancer in patients who have completed treatment. Researchers at Dana-Farber and the Broad Institute of MIT and Harvard designed custom blood biopsy tests for breast cancer patients based on the DNA sequence of the person’s tumor. They then looked for tumor DNA in stored samples of blood from the patients, in a retrospective analysis going back 13 years. The scientists detected cancer DNA in the blood samples an average of 18 months – and as long as three years – before a metastatic recurrence of the cancer was diagnosed by standard monitoring.

“In the future, if we can find those patients with residual cancer early enough, determine whether they would benefit from another course of therapy, and give them an effective additional treatment, we could potentially change the course of their disease,” said Heather Parsons, MD, MPH, a physician-scientist in breast oncology at Dana-Farber. Studies also suggest liquid biopsies have potential to detect when a tumor is becoming resistant to treatment. They’re also being investigated as a way to determine which cancers are susceptible to immunotherapy treatment, and ones that probably are not.

Liquid biopsies can be carried out remotely – by sending a blood draw kit to individuals across the country, as is being done in a Dana-Farber study called PROMISE. In addition, compared with a surgical biopsy that samples only a particular piece of tumor tissue, liquid biopsies collect DNA fragments from tumors throughout the body.

Currently, liquid biopsies are used in specific situations to guide therapy. According to Geoffrey Oxnard, MD, Dana-Farber oncologist and liquid biopsy researcher,
these blood tests are now standard for patients with advanced lung cancer to determine if the tumor contains a particular mutation that can be targeted by a precision drug.

Oxnard says, “We’re using these tests more and more often in addition to tumor analysis to look for mutations we can effectively target.” Now the question is, “can we next apply these technologies for early cancer detection?” To do so, a test would have to be able to spot tell-tale DNA from many types of tumors – some of which are more likely to shed tumor DNA than others – and not yield false positives.

Two studies using liquid biopsies are in progress at Dana-Farber. One, PROMISE, is enrolling individuals to determine if they have precursor blood conditions, such as monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma, that can progress to multiple myeloma. Dana-Farber’s Center for the Prevention of Progression (CPOP) is studying potential interventions to block the transformation of precursor conditions into myeloma. Individuals in the PROMISE study will be followed with serial liquid biopsies which the scientists will examine only for research purposes for signs of the precursor state morphing into multiple myeloma. The patients in the study will be monitored by their own oncologists who will diagnose any change in their status.

Catherine Marinac, PhD, an investigator on the PROMISE study, says the trial is enrolling individuals who self-identify as being Black or African-American, who have a higher risk of multiple myeloma, as well as individuals who have a first-degree relative with a plasma cell disorder such as multiple myeloma or its precursor conditions. So far, she says, the study has screened more than 1,329 individuals and found 164 who tested positive for a precursor disorder to multiple myeloma.

The other clinical trial, called Pathfinder, is sponsored by GRAIL, Inc. It is testing an early detection liquid biopsy method which has shown that it can detect more than 50 types of cancer in a blood sample, across various stages. Results from prior studies suggest the test is particularly good at detecting high mortality cancers and cancers types not covered by current cancer screening approaches.

The test is being offered to patients age 50 and older at Dana-Farber and hospitals in the Partners HealthCare network who are asymptomatic and otherwise presumed to be cancer-free, but have a slightly higher risk of a positive result. This includes individuals who have a history of smoking, an inherited cancer risk, or a personal history of cancer, with definitive treatment more than three years ago. Patients who test positive in this study will be informed and recommended to undergo standard diagnostic workups to determine whether cancer is present or if the initial result was a “false positive,” says Marinac, who is collaborating with Oxnard, the principal investigator of the study.

Oxnard said the test “is not finding every cancer, but it may have the ability to find the dangerous cancers that urgently need treatment.”

The GRAIL test is not available outside the clinical trial, which is being offered at several centers around the country and aims to enroll about 6,200 participants. “To some extent, this is a feasibility study to understand the risks and benefits of this novel technology,” says Oxnard.

Hunting Cancer Signals in a Blood Sample

Although it’s long been known that blood and other body fluids contain free-floating cells and DNA from tumors, only in the past few years have methods become
powerful enough to detect them in minuscule amounts and separate them from normal cells and DNA. GRAIL's method is based on targeted methylation sequencing. Methylation is a chemical change that applies tiny tags to DNA to regulate whether genes are turned on or off. Methods that determine the methylation state of genes in a fragment of DNA can reveal whether it comes from a tumor—and even where the tumor is probably located.

Development of this test required a massive study and the use of artificial intelligence algorithms to create the cancer signatures detected in the blood sample. In Fall 2019, Oxnard reported encouraging results from a GRAIL analysis of 2,301 patients with and without cancer. Oxnard said the liquid biopsy technique was able to “detect the majority of cancers, especially high-risk cancers” with a false positive rate of less than 1%—meaning that just one person in 100 would be falsely informed that cancer was present. The sensitivity ranged from 59% to 86%, depending on cancer type, and the test could specify the tissue of origin (where the cancer developed) in 90% of cases. The test was able to detect only 34% of stage I cancers—the earliest stage—but that increased to 88% in stage II, 84% in stage III, and 92% in stage IV. “It’s not finding every cancer,” says Oxnard. “But it is finding the dangerous cancers.”

A more recent report in early 2020 on a subset of the GRAIL study focused on gastrointestinal cancers (cancers of the esophagus, stomach, pancreas, gallbladder, liver, bile duct, colon, and rectum) which were projected to account for 26% of cancer deaths in 2019. Brian Wolpin, MD, MPH, director of Dana-Farber’s Gastrointestinal Cancer Center, reported that more than 80% of those cancers at all stages were detected with a false-positive rate of less than 1%, and the location was predicted with approximately 90% accuracy. “In patients with early stage gastrointestinal cancers (stages I, II, and III), we could detect 71% with the liquid biopsy test,” Wolpin says. “These are particularly important cancers to identify, as prompt intervention has the potential to treat them most effectively.”

Dealing with Positive and Negative Test Results

A key question is how doctors and patients will follow up if a positive test is reported. “Diagnostic tests are generally different for different malignancies,” Wolpin said. “Thus, we will need to learn the most efficient ways to evaluate for cancer in our patients if a liquid biopsy test is reported as positive.”

This point raises a host of issues that go along with the fast pace of progress in liquid biopsy research, says J. Leonard Lichtenfeld, MD, MACP, deputy chief medical officer for the American Cancer Society. “We run the risk of having an available test that people use without it being meaningful,” he says. “Does it tell us anything? Does it make a difference?”

Lichtenfeld notes that not all cancers are aggressive; some are so slow-growing they would never need treatment. “We don’t know yet whether screenings with liquid biopsy could help doctors learn how aggressive a cancer is,” he says. “One of the keys in this discovery process is not only to find the cancer cell or the mutated DNA fragment circulating in the blood, but also to find out whether that particular person’s cancer is going to be a problem. To me, that’s going to be an even bigger challenge.”

Schrag agrees that significant issues abound. “We don’t want to create a population of worried, anxious people getting blood tests every five minutes” to look for cancer. On the other hand, she notes, a negative result of a liquid biopsy screening test doesn’t mean cancer is not present, and such results “shouldn’t lead people to skip” the standard screening tests that are recommended for different population groups, like colonoscopies or mammograms.

While these dilemmas exist, the fact remains that in just the past few years, advances in detecting and understanding the significance of tumor DNA in the blood have opened the way for a revolution in cancer diagnosis, prediction, and treatment.
Paths of Progress 2020 Dana-Farber Cancer Institute

conferences and in the healthcare environment, however, communities and particularly traditionally marginalized communities, aren’t always hearing about it,” adds Gonzalez. “We need to be intentional about sharing what we do, showing that everyone belongs here, and that we’re already treating your friend or family member.”

Another ongoing effort is to diversify the Institute’s workforce from the top down, while continuing to build an inclusive work environment. Gonzalez and his team have helped Dana-Farber introduce new guidelines for search firms, requiring diverse candidates for leadership roles, and adding key performance indicators around organizational inclusion, diversity, and equity. To further cement its commitment, Dana-Farber’s executive team decided to tie these outcomes to executive compensation – something Gonzalez says is not common in the Boston market.

Gonzalez and his team are also working to expand Dana-Farber’s efforts to attract diverse applicants, through efforts such as its Workforce Development Student Training Program (which provides Boston public school students with professional experience in health care), its summer administrative internship program, and collaborations with community-based organizations. The aim is to engage minority students and pipeline them into careers here.

“We can’t be bystanders and just wait for applicants to apply,” Gonzalez points out. “We need to meet applicants where they are. It’s not just about the numbers, it’s about strengthening our capabilities by adding the perspectives of individuals who can actively engage and help us care for and grow within non-traditional markets.”

All of these efforts are aimed at helping Dana-Farber grow, and to continue to bring cancer care to more people. While there is still work to be done, Gonzalez says he’s confident the Institute will continue to meet these challenges.

“I see opportunities each day for this work, and the ultimate goal is to make sure our diversity, inclusion, and equity plan speaks to every aspect of our business strategy,” Gonzalez says.
Social media is a huge change. You can now recruit online for research studies and disseminate surveys electronically to huge, targeted groups of respondents. This gives you large-scale representation, but you can also lose control over data integrity with less opportunity to properly screen respondents. In observational studies under the terms infodemiology and infoveillance, individuals will not even know they are part of a research study. In targeted studies with large groups of people still not online – often due to socioeconomic factors – you could be missing those individuals who could most influence or benefit from your study. It’s important to find that balance.

We partner closely with Boston-area colleges of nursing, inviting their undergraduate, graduate, and doctoral students to engage in projects and dissertation theses with our researchers focused on their fields of study. We are also involved with the Continuing Umbrella of Research Experiences program at Dana-Farber/Harvard Cancer Center, through which Massachusetts high school and college students from underrepresented populations are introduced to oncology research settings at area institutions – including the Cantor Center. As these students plan their futures, we are giving them hands-on experience into this growing, enriching profession.

Exposure to toxins in the environment, poor nutrition, lack of physical activity and exercise, and alcohol/tobacco/drug abuse are all large determinants of cancer. By showing the connection between these factors and cancer, our nurse scientists strive to educate the public and make an impact.

How does epigenetics play a role in cancer research?
Epigenetics – alterations in gene expression – has major implications for cancer. Bad habits like smoking, poor diet, and a sedentary lifestyle can raise an individual’s risk for epigenomic alterations, leading to an increased risk for cancer and other comorbid conditions like cardiovascular disease and diabetes.

As more people live longer with cancer, what new challenges are emerging?
Among the many challenges with long-term survivorship are an increased risk of recurrence and secondary cancers. We also study financial toxicity, or how large expenses associated with treatment can burden a family and lead to stress – resulting in a whole cycle of adverse physiological effects. By engaging in symptom science and related areas of research, we work to identify those at greatest risk.
Dana-Farber Cancer Institute

Founded in 1947 by Sidney Farber, MD, Dana-Farber Cancer Institute (www.dana-farber.org) is world renowned for its unique blend of basic and clinical research and for using its discoveries to improve treatments for cancer and related diseases. Consistently ranked one of the top cancer centers in the country by U.S. News & World Report, Dana-Farber is a founding member of the Dana-Farber/Harvard Cancer Center, which is one of 51 nationally designated Comprehensive Cancer Centers. As a teaching affiliate of Harvard Medical School, Dana-Farber has earned “Magnet” status for excellence in nursing and is a QOPI® Certified Practice.

Dana-Farber partners with Brigham and Women’s Hospital to deliver care for adults with cancer through Dana-Farber/Brigham and Women’s Cancer Center. It also has a long-standing alliance with Boston Children’s Hospital to care for pediatric cancer patients through Dana-Farber/Boston Children’s Cancer and Blood Disorders Center. These partnerships bring together the strengths of three world-class institutions, each of which provide an exceptional level of care for patients and their families.

The Jimmy Fund

The Jimmy Fund (www.JimmyFund.org) solely supports Dana-Farber, raising funds for adult and pediatric cancer care and research to improve the chances of survival for cancer patients around the world. It is the official charity of the Massachusetts Chiefs of Police Association, the Pan-Massachusetts Challenge, and the Variety Children’s Charity of New England. Since 1948, the generosity of millions of people has helped the Jimmy Fund save countless lives and reduce the burden of cancer for patients and families worldwide. Follow the Jimmy Fund on Facebook (www.facebook.com/thejimmyfund) and Twitter (@TheJimmyFund).

10% of all designated gifts supports our Faculty Research Fund to advance Dana-Farber’s research mission.

If you have any comments or would like to be removed from the mailing list, please contact:

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Dana-Farber shares patient stories which may include descriptions of actual medical results. Dana-Farber provides personalized care for each patient based on their unique needs; their experiences and results will vary.
A Message from Chief Financial Officer Michael Reney

The Institute ended fiscal year 2019 with consolidated operating income of $30.6 million, or a 1.6% operating margin. The positive results represent the second consecutive year of strong profitability following the financial challenges experienced during fiscal year 2017.

Revenues grew in all areas and investments generated strong returns despite market volatility during the first quarter of the fiscal year. Non-operating revenue was positively affected by overall conditions in the investment markets, returning 6% for the fiscal year which resulted in an excess of revenues over expenses of $54.1 million.

Patient-care revenue increased by 12% across the Institute, including its main Longwood campus in Boston, its regional satellite centers, and its physician practice offices, continuing the trend of the last several years. Research revenues increased by 18% during fiscal year 2019, with growth coming from federal, non-government foundations, commercial and clinical trial sponsors, as well as from the increased use of gifts. And, thanks to the generosity of our many donors, it was another outstanding year for philanthropy, which saw a 6% increase in unrestricted giving.

Management, faculty, and staff throughout Dana-Farber – guided by the oversight of several committees of the Board of Trustees – worked diligently to achieve these results in fiscal year 2019. We are grateful to them and to the many donors and friends of Dana-Farber who continue to demonstrate their commitment to the organization with their valuable knowledge and vital ongoing support.
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<td>With Donor Restrictions</td>
<td>975,733</td>
<td>908,509</td>
</tr>
<tr>
<td><strong>Total Liabilities and Net Assets</strong></td>
<td>$3,089,240</td>
<td>$2,861,303</td>
</tr>
</tbody>
</table>

**Summary Statistical Information**
(unless otherwise noted, includes adult and pediatric patients)

<table>
<thead>
<tr>
<th></th>
<th>2019</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion Treatments</td>
<td>187,664</td>
<td>176,630</td>
</tr>
<tr>
<td>Outpatient MD Visits</td>
<td>359,519</td>
<td>346,805</td>
</tr>
<tr>
<td>Number of Licensed Beds</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Adult Inpatient Discharges</td>
<td>1,568</td>
<td>1,304</td>
</tr>
</tbody>
</table>

*Subsidiaries include Dana-Farber Inc., Dana-Farber Cancer Care Network, and Dana-Farber Trust.*
## CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS AND CHANGES IN NET ASSETS

For the Fiscal Year Ended Sept. 30  

(Dollars in thousands)

<table>
<thead>
<tr>
<th>Revenues</th>
<th>2019</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Service, net</td>
<td>$1,302,991</td>
<td>$1,166,614</td>
</tr>
<tr>
<td>Research</td>
<td>542,805</td>
<td>457,967</td>
</tr>
<tr>
<td>Unrestricted Contributions and Bequests</td>
<td>82,696</td>
<td>77,711</td>
</tr>
<tr>
<td>Other Operating</td>
<td>31,554</td>
<td>31,094</td>
</tr>
<tr>
<td><strong>Total Operating Revenues</strong></td>
<td>$1,960,046</td>
<td>$1,733,386</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Expenses</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct Patient Care</td>
<td>966,702</td>
<td>862,378</td>
</tr>
<tr>
<td>Depreciation/Interest</td>
<td>49,671</td>
<td>49,642</td>
</tr>
<tr>
<td><strong>Total Patient Service Expenses</strong></td>
<td>$1,016,373</td>
<td>$912,020</td>
</tr>
<tr>
<td>Research</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct Research/Restricted Gifts</td>
<td>446,932</td>
<td>373,255</td>
</tr>
<tr>
<td>Institute Supported Research</td>
<td>29,941</td>
<td>33,361</td>
</tr>
<tr>
<td>Depreciation/Interest</td>
<td>50,868</td>
<td>51,322</td>
</tr>
<tr>
<td><strong>Total Research Expenses</strong></td>
<td>527,741</td>
<td>457,938</td>
</tr>
<tr>
<td>General/Administrative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General and Administrative</td>
<td>376,094</td>
<td>326,697</td>
</tr>
<tr>
<td>Depreciation/Interest</td>
<td>9,196</td>
<td>8,874</td>
</tr>
<tr>
<td><strong>Total General/Administrative Expenses</strong></td>
<td>385,290</td>
<td>335,571</td>
</tr>
</tbody>
</table>

| **Total Operating Expenses**          | $1,929,404 | $1,705,529 |

| Operating Income                      | 30,642    | 27,857   |
| Investment Gains, Net                 | 30,591    | 47,250   |
| Loss On Extinguishment of Long Term Debt | (211)   | _       |
| Royalty Income, Net                   | 23,588    | _       |
| Gain on Sale                          | _       | 23,802   |
| Interest Rate Swap Agreements         |         |         |
| Net Interest Paid                     | (3,328)   | (3,973)  |
| Change in Fair Value                  | (27,192)  | 11,797   |
| **Excess of Revenues Over Expenses**  | 54,090    | 106,733  |

| Increase in Net Assets Without Donor Restrictions | 113,433 | 114,229 |
| Increase in Net Assets With Donor Restrictions  | 67,224  | 102,684 |
| **Increase in Net Assets**                 | 180,657 | 216,913 |

| **Net Assets at Beginning of the Year**   | 1,725,548 | 1,508,635 |
| **Net Assets at End of the Year**         | $1,906,205 | $1,725,548 |

The preceding selected consolidated financial data as of Sept. 30, 2019, and 2018 (except for the summary statistical data) have been derived from the consolidated financial statements of Dana-Farber Cancer Institute Inc., Dana-Farber Inc., Dana-Farber Cancer Care Network, and Dana-Farber Trust. These have been audited by KPMG, LLP, independent auditors.

In FY 2019, the Institute raised $323 million in new gifts and new pledges through its Division of Philanthropy and the Jimmy Fund, and through the Friends of Dana-Farber Cancer Institute. For accounting purposes, the financial charts reflect new gifts and new pledges calculated at present value, excluding commitments the Institute could not record due to conditionality.
<table>
<thead>
<tr>
<th>BOARD COMMITTEES AND CHAIRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Audit and Compliance Committee</td>
</tr>
<tr>
<td>Amy L. Kyle, Esq.</td>
</tr>
<tr>
<td>Communications Committee</td>
</tr>
<tr>
<td>Nancy Q. Gibson</td>
</tr>
<tr>
<td>Community Programs Committee</td>
</tr>
<tr>
<td>Sandra Stratford, MD, MSc</td>
</tr>
<tr>
<td>Tracey L. McCain, Esq.</td>
</tr>
<tr>
<td>Compensation Committee</td>
</tr>
<tr>
<td>Joshua Bekenstein</td>
</tr>
<tr>
<td>Executive Committee</td>
</tr>
<tr>
<td>Joshua Bekenstein</td>
</tr>
<tr>
<td>Facilities Committee</td>
</tr>
<tr>
<td>Peter Palandjian</td>
</tr>
<tr>
<td>Finance Committee</td>
</tr>
<tr>
<td>John J. O’Connor</td>
</tr>
<tr>
<td>Governance Committee</td>
</tr>
<tr>
<td>Beth F. Terrana</td>
</tr>
<tr>
<td>Mary Ann Tocio</td>
</tr>
<tr>
<td>Investment Committee</td>
</tr>
<tr>
<td>Christopher J. Hadley</td>
</tr>
<tr>
<td>Medical Staff Appointments Committee</td>
</tr>
<tr>
<td>Bradley A. Lucas</td>
</tr>
<tr>
<td>Committee on Quality Improvement and Risk Management</td>
</tr>
<tr>
<td>Brian J. Knez</td>
</tr>
<tr>
<td>Trustee Science Committee</td>
</tr>
<tr>
<td>Phillip T. Gross</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BOARD PHILANTHROPY COMMITTEES AND CHAIRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philanthropy Committee</td>
</tr>
<tr>
<td>Lawrence Lucchino</td>
</tr>
<tr>
<td>Gift Planning Committee</td>
</tr>
<tr>
<td>Barbara L. Sadowsky</td>
</tr>
<tr>
<td>James P. Sadowsky</td>
</tr>
<tr>
<td>Trustee Annual Fund Committee</td>
</tr>
<tr>
<td>Jennifer Perini</td>
</tr>
</tbody>
</table>

The governance listings in this annual report are current as of Jan. 1, 2020.
The governance listings in this annual report are current as of Jan. 1, 2020.
## EXECUTIVE LEADERSHIP

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laurie H. Glimcher, MD</td>
<td>President and Chief Executive Officer</td>
</tr>
<tr>
<td>Richard S. Boskey, Esq.</td>
<td>Senior Vice President; General Counsel; and Chief Governance Officer</td>
</tr>
<tr>
<td>Craig A. Bunnell, MD, MPH, MBA</td>
<td>Chief Medical Officer</td>
</tr>
<tr>
<td>George D. Demetri, MD</td>
<td>Senior Vice President, Experimental Therapeutics</td>
</tr>
<tr>
<td>Lisa R. Diller, MD</td>
<td>Chief Medical Officer, Dana-Farber/Boston Children’s Cancer and Blood Disorders Center</td>
</tr>
<tr>
<td>Melany N. Duval</td>
<td>Senior Vice President, Chief Philanthropy Officer</td>
</tr>
<tr>
<td>Anne H. Gross, PhD, RN</td>
<td>Chief Nursing Officer and Senior Vice President, Patient Care Services</td>
</tr>
<tr>
<td>William C. Hahn, MD, PhD</td>
<td>Chief Scientific Officer and Chair, Executive Committee for Research</td>
</tr>
<tr>
<td>Kevin M. Haigis, PhD</td>
<td>Chief Research Officer</td>
</tr>
<tr>
<td>Bruce E. Johnson, MD</td>
<td>Chief Clinical Research Officer</td>
</tr>
<tr>
<td>Elizabeth A. Liebow, MS, BA</td>
<td>Senior Vice President, Chief Strategy Officer</td>
</tr>
<tr>
<td>Kathleen McDaniel, BS</td>
<td>Senior Vice President, Chief People Officer</td>
</tr>
<tr>
<td>Maria Megdal</td>
<td>Senior Vice President, Operations</td>
</tr>
<tr>
<td>Michael L. Reney, MBA</td>
<td>Senior Vice President, Chief Financial Officer, and Assistant Treasurer</td>
</tr>
<tr>
<td>Barrett J. Rollins, MD, PhD</td>
<td>Linde Family Professor of Medicine and Senior Advisor to the President &amp; CEO</td>
</tr>
<tr>
<td>Steven R. Singer, MPA</td>
<td>Senior Vice President, Chief Communications Officer</td>
</tr>
<tr>
<td>Robert J. Soiffer, MD</td>
<td>Chair, Executive Committee for Clinical Programs</td>
</tr>
<tr>
<td>Lesley Solomon, MBA</td>
<td>Senior Vice President, Chief Innovation Officer</td>
</tr>
<tr>
<td>Chief Innovation Officer</td>
<td>Mary-Ellen Taplin, MD Chair, Executive Committee for Clinical Research</td>
</tr>
<tr>
<td>James Terwilliger, MPH</td>
<td>Executive Vice President and Chief Operating Officer</td>
</tr>
<tr>
<td>Eric P. Winer, MD</td>
<td>Senior Vice President, Medical Affairs and Faculty Advancement</td>
</tr>
</tbody>
</table>

## DEPARTMENT CHAIRS

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott A. Armstrong, MD</td>
<td>Chair, Pediatric Oncology</td>
</tr>
<tr>
<td>Kathleen Burns, MD, PhD</td>
<td>Chair, Oncologic Pathology</td>
</tr>
<tr>
<td>Benjamin Ebert, MD, PhD</td>
<td>Chair, Medical Oncology</td>
</tr>
<tr>
<td>Daphne A. Haas-Kogan, MD</td>
<td>Chair, Radiation Oncology</td>
</tr>
<tr>
<td>Rafael A. Irizarry, PhD</td>
<td>Chair, Data Sciences</td>
</tr>
<tr>
<td>Moritz F. Kircher, MD, PhD</td>
<td>Chair, Imaging and Radiology</td>
</tr>
<tr>
<td>Thomas Roberts, PhD</td>
<td>Chair, Cancer Biology</td>
</tr>
<tr>
<td>James A. Tulsky, MD</td>
<td>Chair, Psychosocial Oncology and Palliative Care</td>
</tr>
<tr>
<td>Kai W. Wucherpfennig, MD, PhD</td>
<td>Chair, Cancer Immunology and Virology</td>
</tr>
<tr>
<td>Gerard M. Doherty, MD</td>
<td>Chair, Surgery</td>
</tr>
</tbody>
</table>

The governance listings on this page are current as of Jan. 1, 2020.
FRIENDS OF DANA-FARBER CANCER INSTITUTE

Co-Presidents
Gabrielle Baron
Lucy Santos

Executive Committee
Heather Gelchion, Treasurer & Clerk
Jen Cunningham Butler* and Carrie Wilson, Vice Presidents of Patient Services
Kathleen Cook and Seth Andrea McCoy, Vice Presidents of Membership
Suzanne Chapman* and Gina Morda, Vice Presidents of Fundraising

Executive Committee
Heather Gelchion, Treasurer & Clerk
Jen Cunningham Butler* and Carrie Wilson, Vice Presidents of Patient Services
Kathleen Cook and Seth Andrea McCoy, Vice Presidents of Membership
Suzanne Chapman* and Gina Morda, Vice Presidents of Fundraising

Governors Directors
Suzanne Fisher Bloomberg
Sarah Bowler
Betsy Cohen
Melanie Conroy
Trudi Feinstein
Anita Fink
MaryBeth Finn
Lauren Frei*
Jayne Bennett Friedberg*
Susan Mendoza Friedman
Micki Hirsch
Jane M. Holt*
Julie Kae
Amye Kurson-Collins
Eileen MacElroy
Debbie Maltzman*
JoAnne Marshall
Jane B. Mayer
Judith O’Karma McCaffrey
Jane R. Moss
Marcì Noller*
Tobey Oresman
Leeann To Quimet
Jean F. Pearlstein*
Lesley Prowda
Jane Savas
Alexandra Slote
Elaine Zouzas Thibault
Dana Gerson Unger

Directors-at-Large
Helen Lin
Jamie Monovoukas
Jill Papagni
Andrea Segel

Honorary Directors
Jean Speare Canellos*
Barbara Lapp
Louise S. Shivek**
Susan F. Smith**
Marilyn N. Wolman

Founding President
Sheila Driscoll Cunningham**
* Past President
** Deceased

TRUSTEE CHAIRS AND CO-CHAIRS, PRESIDENTIAL VISITING COMMITTEES

Visiting Committee for Discovery Science
Harvey J. Berger, MD

Visiting Committee for the Gastrointestinal Cancer Center
Winnie. W. Wong, PhD

Visiting Committee for Hematologic Oncology
Marc A. Cohen
Theodore T. Pasqurello

Visiting Committee for Institute Initiatives
Nancy Q. Gibson
Jennifer Perini

Visiting Committee for Pediatric Oncology
Alison Poorvu Jaffe
T. Conrad Wetterau

Visiting Committee for the Lowe Center for Thoracic Oncology
Alice Cutler
William M. Gillen

Visiting Committee for the Susan F. Smith Center for Women’s Cancers
Jane Brock-Wilson
Jane P. Jamieson

DANA-FARBER INSTITUTE INC.

CORPORATE OFFICERS
Joshua Bekenstein
Chair
Laurie H. Glimcher, MD
President and Chief Executive Officer
John J. O’Connor
Treasurer and Vice Chair
Michael L. Reney
Assistant Treasurer
Monica Chandra
Secretary
Richard S. Boskey, Esq.
Assistant Secretary
Sharon Herrick, Esq.
Assistant Secretary

TRUSTEES
Joshua Bekenstein
Laurie H. Glimcher, MD
Christopher J. Hadley
John J. O’Connor

Dana-Farber Inc. manages the investments of Dana-Farber Cancer Institute Inc.

The governance listings in this annual report are current as of Jan. 1, 2020.
Music therapy at the Jimmy Fund Clinic at Dana-Farber/Boston Children’s Cancer and Blood Disorders Center brings a smile to a young patient.