Fighting the Resistance
Uncovering new strategies for when cancer overcomes a drug’s effectiveness

To Eliminate Cancer Disparities, It Takes a Center
Behind the effort to improve access to care for all patients

Pushing Boundaries
Clinical trials help advance the frontier of cancer treatment

Maintaining Momentum
Tech tools help keep patient care and support on track
and results will vary. Dana-Farber provides personalized care for each patient based on their unique needs; their experiences of actual medical results. Dana-Farber shares patient stories which may include descriptions of remission or slowed its growth fizzles out, allowing the cancer to return Dana-Farber’s work on drug resistance, when a medicine that initially put cancer into remission or slowed its growth fizzles out, allowing the cancer to return. Our work to improve access to care for all patients, particularly those dealing with breast and gynecologic cancers. How clinical trials help advance the frontiers of treatment in breast and gynecologic cancers. How virtual programs and tools helped keep care and support on track. Women stand undeterred in the face of a cancer diagnosis. Kornelia Polyak, MD, PhD, seeks new ways to tailor cancer treatment. Elizabeth Stover, MD, PhD, pursues innovations in GYN cancer therapies. Looking at our research priorities and work. Highlights of current work in the Susan F. Smith Center for Women’s Cancers. Research grants, innovative studies, promising drug therapies, and other recent highlights from the Susan F. Smith Center.

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A Message From the Directors

As cancer clinicians and scientists, we at Dana-Farber need to be as resilient as our patients. When difficulties arise – a treatment is less effective than hoped, an experiment proves inconclusive, a supply shortage occurs – it’s our job to find a workable solution and a way forward.

Dealing with the unexpected has been part of medicine, but COVID-19 tested the health-care system in unprecedented ways. When the pandemic began early last year, Dana-Farber, like many hospitals and research centers, limited the number of people in its clinics and laboratories to reduce the spread of the coronavirus. In a matter of weeks, procedures that had once been relatively routine, like scheduling patient appointments or arranging prescription pick-ups at the Institute, had to be revamped.

The changes put in place did more than enable us to continue treating patients and conducting clinical research – they taught us how to improve both of these aspects of our mission.

We learned how to integrate telehealth, which had been used only sporadically prior to the pandemic, into patient care. We learned that medicines could be shipped to local pharmacies with no loss of quality control and with added convenience for patients. And we learned that notoriously rule-bound clinical trials can be adapted to unusual circumstances. A study by Dana-Farber investigators found that even at the height of the pandemic, almost all patients enrolled in clinical trials at the Institute were able to remain on them, and that new patients continued to enroll.

The pandemic-born incentive to innovate has paid dividends for basic researchers as well. With travel bans preventing researchers from attending professional conferences in person, we developed systems for collaborating by Zoom and other web-based platforms. The ease of communicating with distant colleagues in a virtual setting has led to collaborations that may not have happened under ordinary circumstances.

The pandemic has presented a challenge, but not a setback, to cancer care and research. The determination our patients so often show in dealing with adversity has been an inspiration in an especially difficult time. Their example is our motivation.
At the Susan F. Smith Center for Women’s Cancers, cancer care, clinical research, and basic research are parts of an ongoing cycle. Research into the basic workings of cancer cells and their interactions with the rest of the body provides leads for the development of new therapies. Clinical testing explores whether such therapies are safe and effective enough to become standard care for patients. And clinical care generates information and hypotheses that can be taken back to the laboratory to devise even better treatments.

Here is a brief look at how this dynamic is guiding our work.

**Division of Breast Oncology**

Dana-Farber scientists and physicians are attacking the puzzle of breast cancer by breaking it into its component parts. Subtype by subtype, researchers are working to understand the molecular machinery driving the disease and to use that knowledge to improve diagnosis and treatment.

Some of the most encouraging advances are in the area of immunotherapy. An immunotherapy-chemotherapy combination initially tested at Dana-Farber recently received approval from the U.S. Food and Drug Administration (FDA) for patients with some forms of triple-negative breast cancer—the first time an immunotherapy treatment has been officially approved for breast cancer.

While researchers test immunotherapy drugs in new combinations, they’re also tackling the problem of drug resistance, in which drugs lose their effectiveness over time. This year, for example, Susan F. Smith Center scientists reported that in laboratory models, a well-established antibiotic selectively kills drug-resistant tumor cells marked by abnormalities in the genes BRCA1 or BRCA2. The finding has led to the launching of a clinical trial of the drug in selected patients.

Efforts to reduce the toll of breast cancer are occurring not only in the lab but in the community as well, with a focus on underserved populations. The Institute has joined a Boston-wide effort to reduce health disparities among African-American and low-income patients, and is working with other Boston hospitals to reduce obstacles to breast cancer treatment.

**Division of Gynecologic Oncology**

For virtually every type of gynecologic cancer, the outlook for patients continues to improve as a result of advances in the laboratory, the clinic, and the community.

In endometrial cancer, for example, a drug compound that blocks a key point in the cell cycle caused tumors to shrink in nearly one-third of patients with an aggressive form of endometrial cancer who participated in a clinical trial led by Dana-Farber investigators. The results prompted trial leaders to open a follow-up study in two more groups of patients.

In ovarian cancer, our researchers continue to make headway on a blood test for early detection of the disease. By scanning blood samples for 14 microRNA molecules unique to ovarian cancer, the test would identify women predisposed to develop the disease. Our scientists are also at work on new treatment approaches, including vaccines tailored specifically to each patient’s tumor.

For cervical cancer, progress is occurring on multiple fronts, including the development of a blood test for human papilloma virus, which may be used to determine how well the cancer is responding to therapy and which patients are at highest risk of a recurrence. And, building on the FDA’s recent approval of an immunotherapy agent for cervical cancer, Dana-Farber investigators have opened a clinical trial of two such agents in combination with radiation for patients with recurrent gynecologic malignancies.
The Center for Cancer Genetics and Prevention operates on the principle that knowledge is power – that knowing one has an increased risk of developing cancer is the starting point for steps to manage that risk and to make sure that if cancer does occur, it is detected at an early stage when treatment has the greatest likelihood of success.

The center offers genetic testing and counseling services to help patients learn if they have an increased risk of breast, ovarian, or a range of other cancers and to develop a plan to manage that risk with surveillance and risk-reduction strategies. The center is also home to an array of research studies examining cancer-prevention strategies and early detection measures.

In breast cancer, for example, the PROMISE trial is examining whether the drug Duavee can lower the risk of invasive breast cancer in patients diagnosed with ductal carcinoma in situ, a condition that predisposes them to breast cancer development. Judy Garber, MD, MPH, is the U.S. leader of a definitive international trial asking whether the drug denosumab, usually used to treat osteoporosis (bone loss), can reduce breast cancer risk in women with an altered BRCA1 gene. Dr. Garber and her team hope that it will allow BRCA1 carriers to delay or even avoid risk-reducing surgery.

In ovarian cancer, researchers are focused on early detection, a critical need for people with inherited ovarian cancer risk. They are studying microRNAs, a potentially powerful set of molecules that have been very promising in this especially challenging space. Learn more about this research on page 8.
Remembering Larissa Lee, MD

Larissa Lee, MD, a pioneer in the treatment of patients with gynecologic cancers, died June 23 at 44.

Larissa Lee, MD, a pioneer in the treatment of patients with gynecologic cancers and director of gynecologic radiation oncology at Dana-Farber and Brigham and Women’s Hospital (BWH), died June 23, 2021, of advanced gastrointestinal cancer at age 44.

Equally respected as a researcher, clinician, teacher, mentor, and colleague, Lee was a member of the department of Radiation Oncology since 2010. Her scientific contributions over the past decade include advances in radiation treatment techniques, trials of novel immunotherapies, and studies to overcome the problem of treatment resistance. Her impact on the field of gynecologic cancers, and the example she set of compassion, scientific rigor, and collaborative spirit, are indelible, say those who knew her.

As a clinician, Lee was known for her expertise in brachytherapy, in which radioactive material sealed in small pellets is implanted in cancerous tissue to kill tumor cells. Her reputation in this field helped make the Dana-Farber/BWH Gynecologic Radiation Oncology Service the treatment center of choice for patients across New England and drew trainees from around the world.

Her research centered on improving the efficacy of radiation therapy and reducing its side effects. She led efforts to improve the use of biomarkers – bodily substances that can indicate a tumor’s aggressiveness or response to treatment – developed devices used in treatment, and she directed multiple clinical trials of potential therapies and techniques.

In the area of biomarkers, she was one of the first to show that the protein p16 can guide the treatment of vulvar cancer. Her work led to changes in how patients who test positive for p16 are counseled about their risk of cancer recurrence and how their radiation dose is selected. She also identified genomic features in tumor cells that indicate whether early-stage, low-risk endometrial cancers are likely to recur after treatment.

Lee was an inventor as well, helping design and test new tools for the treatment of gynecologic cancers. She developed a device that measures oxygen content within tumors during brachytherapy procedures. The information helps doctors identify portions of the tumor where oxygen levels are low, which tend to be less susceptible to radiation therapy. These areas can then be earmarked for additional doses. Lee also worked on a tracking device that fits inside implanted catheters and receives signals from an MRI machine, giving real-time information about the location of the catheter and ensuring it’s maneuvered into the proper place.

Lee’s clinical research included trials of novel therapies. She led one of the first trials of radiation therapy in combination with drugs known as immune checkpoint inhibitors. Participants, who have recurrent or metastatic gynecologic cancers, receive radiation to the abdomen along with two checkpoint inhibitors, a regimen that may be more effective than any of the therapies alone. To reduce toxicity, she also pioneered a treatment for patients with endometrial cancer that reduces radiation doses by 30-40% to minimize side effects.

Lee’s clinical and scientific accomplishments were complemented by a kindness that radiated to her patients and their families, colleagues, and trainees.

“Larissa devoted her career to the study of gynecologic cancers and developing better and less toxic radiation treatments for people with gynecologic cancers,” says Ursula Matulonis, MD, chief of the Division of Gynecologic Oncology. “She was a superb and compassionate clinician who cared deeply about her patients and was a wonderful collaborator and colleague. She was a treasure to all of us who had the honor of knowing her and interacting with her. She was an incredibly special person, and she will never be forgotten.”

Lee is survived by her husband, Jai Eswara, MD, their sons Ethan and Erik, and by her sister, Brittany Bychkovsky, MD, her brother, Chris Mellee, and her parents, Susan and John Lee.
Executive Council Explores Groundbreaking Work in Breast and Gynecologic Cancer

The Executive Council of the Susan F. Smith Center for Women’s Cancers at Dana-Farber sponsored a virtual event in Sept. 2020 that united more than 460 women to hear from Dana-Farber physician-researchers about recent groundbreaking science, new discoveries and novel treatments revolutionizing treatment in gynecologic and breast cancer. Led by moderators Judy Garber, MD, chief, Center for Cancer Genetics and Prevention, and Sara Tolaney, MD, associate director, Susan F. Smith Center for Women’s Cancers, the event explored details on the first personalized cancer vaccine trial in ovarian cancer, remarkable progress for patients with advanced HER2-positive breast cancer and on a novel, targeted therapy in uterine cancer.

“This is the most exciting forum I participate in,” Dr. Garber says. “It has a level of excitement that truly energizes all the researchers in the room.”

This event raised more than $150,000 for the Susan F. Smith Center. Each year, the Executive Council awards four innovation grants of $75,000 each for early-stage, high risk/high reward breast or gynecological cancer research that is not eligible for government funding.

Panelists at the forum talked about their cutting-edge science and new discoveries:

• **Ian Krop, MD**, associate chief, Breast Oncology at Dana-Farber discussed how “smart bombs” are being used to treat HER2-positive breast cancer. The FDA recently approved a new targeted drug for patients with advanced HER2-positive breast cancer, who had exhausted all standard treatment options, based on a study lead by Dana-Farber. The drug, called trastuzumab deruxtecan, kept tumors in check significantly longer than other therapeutic options for people living with this difficult form of the disease.

• **Panos Konstantinopoulos, MD**, director of the Center for BRCA and Related Genes, director of Translational Research in Gynecologic Oncology, discussed the latest clinical trial on the first personalized vaccine for ovarian cancer. The trial led by Dana-Farber is designed to test a vaccine that is tailored to spur a powerful, precise immune system attack on tumor cells in ovarian cancer patients whose disease has progressed following chemotherapy.

• **Joyce Liu, MD, MPH**, associate chief of the Division of Gynecologic Oncology, director of Clinical Research in Gynecologic Oncology, discussed a novel targeted therapy trial in uterine cancer. In a trial that represents one of the most significant breakthroughs in uterine cancer in years, Dr. Liu’s research data shows a considerable response to a new drug called a Wee1 inhibitor. This targeted therapy has great potential for patients with serous endometrial cancer, which represents fewer than 10% of uterine diagnoses and a disproportionate 45% of deaths.

New Chief of Breast Oncology

Sara Tolaney, MD, MPH, has been appointed the new chief of Breast Oncology. Dr. Tolaney joined Dana-Farber in 2008 and in 2017 was appointed associate director of the Susan F. Smith Center for Women’s Cancers. During her tenure, she has become a respected leader well experienced in clinical trials across a variety of settings. Her broad view of breast cancer research includes the integration of basic, translational, and clinical research. Her work, along with the work of her many colleagues, has contributed to bringing new treatments into clinical practice. As chief, Dr. Tolaney will lead efforts to further expand our clinical trials infrastructure and clinical research. She replaces Eric P. Winer, MD, who this year stepped down after 24 years in the role.

Dr. Tolaney earned her undergraduate degree from Princeton University and her medical degree from the University of California-San Francisco. She completed her residency in internal medicine at Johns Hopkins University and had fellowships in hematology and medical oncology at Dana-Farber. She earned her master’s degree in public health from the Harvard T.H. Chan School of Public Health.
Dr. D’Andrea Elected to National Academy of Sciences

Alan D’Andrea, MD, director of the Susan F. Smith Center for Women’s Cancers and the Center for DNA Damage and Repair at Dana-Farber, was elected in 2021 to the prestigious National Academy of Sciences (NAS). The election recognizes Dr. D’Andrea’s distinguished and continuing achievements in original scientific research. He also serves as the Fuller-American Cancer Society Professor of Radiation Oncology at Harvard Medical School.

“Election to the Academy is one of the highest honors that a scientist can receive,” said Laurie Glimcher, MD, president and CEO of Dana-Farber. “This well-deserved recognition is a testament to Alan’s landmark contributions to cancer research and his dedication to the advancement of science.”

The National Academy of Sciences is a private, nonprofit society of distinguished scholars. Established by an Act of Congress signed by President Abraham Lincoln in 1863, the NAS is charged with providing independent, objective advice to the nation on matters related to science and technology. Scientists are elected by their peers to membership in the NAS for outstanding contributions to research.

Dr. D’Andrea is internationally known for his research in DNA damage and DNA repair. His laboratory also investigates the pathogenesis of Fanconi anemia, a genetic disease characterized by a DNA repair defect, bone marrow failure, and cancer predisposition.

Dr. Winer Elected ASCO President for 2022

The American Society of Clinical Oncology (ASCO) elected Dana-Farber’s Eric P. Winer, MD, to serve as its president for the term beginning in June 2022. He took office as President-Elect during the ASCO Annual Meeting in June 2021. Dr. Winer is the chief clinical development officer, senior vice president for medical affairs, principal investigator of the Dana-Farber/Harvard Cancer Center SPORE in Breast Cancer, and the Thompson Chair in Breast Cancer Research at Dana-Farber. He is also a professor of medicine at Harvard Medical School.

“I am deeply honored to be named President-Elect of ASCO and serve our members who are committed to improving patient care around the world,” Dr. Winer said. “ASCO is as equally devoted to improving outcomes for patients as it is to supporting oncology professionals and enhancing their ability to deliver the best possible care, and I look forward to supporting the ASCO mission in this role.”

Dr. Winer has received numerous awards for breast cancer research, while also being recognized for his efforts to mentor younger clinicians and investigators.

Dr. Winer is a longtime member and volunteer of ASCO. He served on its board of directors from 2011 to 2015, and he served as chair of the ASCO Government Relations Committee, Cancer Communications Committee, and Health Services Research Committee, among numerous other volunteer roles. He is the 2017 recipient of ASCO’s Gianni Bonadonna Breast Cancer Award and Lecture. He will be the seventh Dana-Farber-affiliated physician to serve as president since ASCO was founded in 1964.
Prestigious Grant Will Accelerate Ovarian Cancer Research

Dana-Farber/Harvard Cancer Center (DF/HCC) was in late 2020 awarded a $12 million grant from the National Cancer Institute (NCI) to bring promising ovarian cancer research from the laboratory to clinical practice. The highly competitive Specialized Programs of Research Excellence (SPORE) grant will help fund three research studies on overcoming the problem of treatment resistance in ovarian cancer and enable DF/HCC-affiliated institutions to build on recent therapeutic advances in this disease. The principal investigators of the SPORE grant are Alan D’Andrea, MD, director of the Susan F. Smith Center for Women’s Cancers; Ursula Matulonis, MD, chief of the Division of Gynecologic Oncology at Dana-Farber; and David Spriggs, MD, director of Gynecologic Oncology at MGH Cancer Center.

“Through the Ovarian Cancer SPORE of the DF/HCC, several of the most urgent questions in ovarian cancer therapy will be addressed,” said Dr. D’Andrea. “We are grateful to the National Cancer Institute for recognizing the combined expertise of the DF/HCC institutions and providing the resources to further advance the significant therapeutic progress made in this disease in recent years.”

The three research projects supported by DF/HCC Ovarian Cancer SPORE seek to translate scientists’ growing understanding of treatment resistance in ovarian cancer into new therapeutic approaches.

New classes of drugs known as PARP inhibitors, which hamper cells’ ability to repair damaged DNA, are increasingly used to treat patients newly diagnosed with ovarian cancer as well as those whose disease has recurred following standard treatment. These agents have changed the standard of care for many patients with ovarian cancer and represent a major advance in the treatment of the disease. However, many patients eventually develop resistance to PARP inhibitors.

The first research project supported by the SPORE grant will include clinical trials of drug combinations designed to extend the effectiveness of PARP inhibitors.

Rebecca Porter, MD, PhD, was awarded a Career Enhancement Program grant through the SPORE to support the development and study of a novel neoantigen vaccine trial for ovarian cancer patients. The personalized vaccine will be designed to recognize cancer-specific proteins, called neoantigens, that are present on an individual’s cancer cells but not on normal cells.

Used in conjunction with immunotherapy drugs known as a checkpoint inhibitors, such a vaccine could “steer” the immune system to a direct assault on the cancer cells. Dr. Porter’s work on the study centers on identifying specific targets for the vaccine by evaluating ctDNA in individual patients.

The third project will address patients with recurrent or drug-resistant high-grade serous ovarian cancer or low-grade serous cancer. The SPORE funds will support research into novel combinations, such as a BCL inhibitor and a MEK inhibitor, and will look for biomarkers of drug activity.

“Our focus will be on new ovarian cancer therapies for which laboratory research provides evidence of their effectiveness,” said Dr. Matulonis. “Physician-researchers across the DF/HCC institutions will work collaboratively to test and develop the next generation of agents that we can deliver to our patients and ultimately improve outcomes. This is a very important collaborative grant for us.”

Gynecologic Cancer Research and Clinical Trials

Researchers in the Susan F. Smith Center’s Division of Gynecologic Oncology explore gynecologic cancers from a wide variety of scientific angles – from discoveries about the genes that cause tumors to develop and grow, to investigations of immunotherapies, to studies of ways drugs can be combined to fight recurrent cancer. Find a complete list of our latest clinical trials online at [www.dana-farber.org/clinicaltrials](http://www.dana-farber.org/clinicaltrials).
Dana-Farber Scientists Team Up to Speed Ovarian Cancer Blood Test

A partnership between researchers at Dana-Farber and University College London (UCL) may prove decisive in the quest to develop the first blood test for early-stage ovarian cancer.

Under the agreement, researchers at UCL will provide Dana-Farber scientists with thousands of blood samples from women at high risk of developing ovarian cancer, including those who carry mutations in *BRCA* genes. The researchers will work together to refine a promising early-detection test for the disease. The test, developed at Dana-Farber, has been shown to be 99.8% accurate for women from high-risk families — tantalizingly close to the 99.9% required for potential clinical use.

“The biobank at UCL has one of the world’s largest and most comprehensively curated collections of blood samples for the study of women’s cancers,” says Dipanjan Chowdhury, PhD, a co-director of Dana-Farber’s Center for *BRCA* and Related Genes. “The more than 35,000 samples that have been collected represent one of the most powerful sets available for this type of research, especially considering that women at high risk for ovarian cancer comprise a relatively small portion of the population.”

The need for an early-detection test for ovarian cancer is urgent. In more than 70% of women with the disease, it has already spread at the time of diagnosis, making it difficult to treat successfully. In these patients, the five-year survival rate is only 30%. When the cancer is diagnosed at stage 1 — before it has had a chance to invade surrounding tissue — the five-year survival rate is more than 92%.

Unlike many other cancers, ovarian cancer often doesn’t produce symptoms in its initial stages. The lack of any FDA-approved test capable of detecting the disease early on is one of the single biggest obstacles to improving survival rates.

Dr. Chowdhury and his colleague Kevin Elias, MD, of Dana-Farber and Brigham and Women’s Hospital, have developed a test that looks for certain microRNAs — small, non-coding pieces of genetic material — in blood samples to detect early-stage ovarian cancer in high-risk families. In studies, the test has proven to be exceptionally accurate, returning the correct result in 99.8% of cases.

Impressive as that rate is, it needs to be virtually 99.9% before the test can be potentially accepted for clinical use, Dr. Chowdhury explains. The reason has to do with the lack of any follow-up procedure to confirm the test’s findings. Screening for colon cancer, for example, can now be done with tests for DNA markers in blood or stool. When a test comes back positive, the next step is a colonoscopy to examine the large intestine for abnormal growths. No equivalent of a colonoscopy exists for ovarian cancer. The only follow-up to a positive test for ovarian cancer would be surgery to remove the affected ovary. Such a step would not be taken unless the results of the test were absolutely reliable.

To raise the test’s accuracy to 99.9%, researchers need to analyze large numbers of blood samples from women at risk for ovarian cancer — so the roster of microRNAs signaling the presence of the cancer can be further refined. The samples from UCL are critical in this regard. The UCL biobank has samples collected over nearly a decade from more than 200,000 women, including 4,300 from families with a high risk of developing ovarian cancer — some of whom went on to develop the disease.

“We now have serum and plasma samples from these women that were taken years before their cancer was detected by surgery,” Dr. Chowdhury says. “We’ll be analyzing these samples to see what additional information we can obtain about microRNAs that are a sign of ovarian cancer.”
New Dana-Farber Program for Triple-Negative Breast Cancer

In 2020, Dana-Farber received a $5 million gift from the Benderson Family of Sarasota, Florida, that will accelerate research in triple-negative breast cancer (TNBC) and strengthen the Institute’s capabilities for treating this disease. The gift establishes the Benderson Family Program for Triple-Negative Breast Cancer and represents the largest philanthropic donation to TNBC research at Dana-Farber. The $5 million commitment is the Benderson Family’s second major gift to Dana-Farber in support of TNBC research and treatment.

Under the direction of Eric P. Winer, MD, chief clinical development officer and principal investigator of the Dana-Farber/Harvard Cancer Center SPORE in Breast Cancer, the commitment by the Benderson Family provides the resources for Dana-Farber to expand a novel comprehensive TNBC research registry and establish a new endowed fund, the Benderson Family Endowment for Triple-Negative Breast Cancer Research. The resulting robust TNBC cohort will provide the data and samples necessary to conduct vital laboratory experiments, identify potential drug targets, and design clinical trials for the more effective treatment and improved outcomes for TNBC patients.

Triple-negative breast cancer is one of the most challenging forms of breast cancer to treat. Despite recent advances forged by physician-scientists at Dana-Farber and elsewhere, new and novel treatment approaches for TNBC patients are needed. Currently, chemotherapy remains the backbone of treatment for TNBC, but recent trials have demonstrated the value of immunotherapy in preventing disease recurrence in stage 2 and 3 disease. Ongoing clinical trials at Dana-Farber, supported by the Bendersons, are testing new forms of immunotherapy, antibody drug conjugates, and PARP inhibitors.

“Lori and I are thankful to Dr. Winer and his team for the amazing care received at Dana-Farber,” said Randy Benderson. “We truly hope that our gift will accelerate triple-negative breast cancer research and bring better treatments to other women sooner. We are confident that Dana-Farber will lead the way to a cure for this relentless disease.”

TNBC describes breast cancer cells that do not have estrogen, progesterone, or HER2 receptors. TNBC makes up approximately 10-15% of all breast cancers and is usually more aggressive than estrogen-receptor-positive breast cancer and HER2-positive breast cancer. This disease is often found in younger women (age 39 and younger) and in women of African American or Hispanic background. The disease may also be associated with having an inherited mutation in the BRCA1 gene.

“Many women diagnosed with triple negative breast cancer today will do very well with existing treatments,” said Dr. Winer. “But there are still far too many women with TNBC who urgently require new and better therapies. The incredibly generous support from the Benderson Family allows our researchers to build on recent advancements in TNBC, with the goal of delivering novel and promising treatment strategies to more patients.”

The Metastatic Breast Cancer Project

Metastatic breast cancer patients across the country are joining the metastatic breast cancer project to help advance research and treatment. Learn more by visiting www.mbcproject.org or following @MBC_Project on Twitter.
FIGHTING

FINDING NEW TACTICS WHEN A TREATMENT FAILS

For cancer cells, making mistakes is a survival strategy. Unstable and erratic, they reproduce with such abandon that bothersome details like accurately copying their DNA often get neglected. The result is a skein of genetic mutations and irregularities that can make malignant cells extraordinarily difficult to pin down, either by the body’s immune defenses or by medical interventions.
Cancer’s error-prone ways are partly responsible for the problem of drug resistance, the all-too-common situation in which a medicine that initially threw cancer into remission or slowed its growth seems to tire out, allowing the cancer to return. The fault isn’t within the drug itself, but within the cancer: as new mutations crop up, they may give tumor cells the ability to stand up to drugs that previously would have killed them.

Drug resistance constitutes one of the toughest challenges in cancer medicine, and one of the most active fields of research. If resistance didn’t occur — if cancer presented a consistent, steady target to therapy — then any agent that shrunk a tumor or kept it in check could be counted on to maintain that effectiveness over the long term. Resistance impacts the treatment of breast and gynecologic cancer in a variety of ways. About 90% of primary breast cancers and 50% of metastatic breast cancers respond to initial drug therapy, sometimes virtually vanishing. Months or years later, however, the disease can come back, usually in a drug-resistant form. Even ovarian cancer, which in most cases isn’t diagnosed until it has reached an advanced stage, generally shrinks after its first course of platinum-based chemotherapy. Unfortunately, 75-80% of patients experience a recurrence. A second round of chemotherapy often sends the disease into remission, but over time new, resistant tumors can emerge.
“When therapy of any kind doesn’t eradicate a patient’s cancer, the surviving tumor cells can set the stage for a return of the disease,” says Ursula Matulonis, MD, chief of Gynecologic Oncology at Dana-Farber. “Understanding how cells become resistant to treatment, and how we can overcome resistance, is critical to improving outcomes for our patients. At the Susan F. Smith Center, we’re working to shed light on these resistance mechanisms.”

**Shifting Gears When Tumors Return**

Tumors can foil cancer drugs in a variety of ways. If a drug targets a particular protein in a cell-growth pathway, a genetic mutation may alter that protein so it eludes the drug’s grasp. If one part of a growth pathway is shut down by a drug, a mutation may provide a detour around it, much as a stream, if dammed, may form new branches to reach its destination. Mutations can produce changes in proteins on the cell surface that prevent cancer drugs from binding there. Some tumor cells even develop the ability to pump out drugs that have breached their membranes.

Metastasis is another part of cancer’s evasive repertoire. “However cancer cells spread – via the bloodstream, the lymph system, or even through direct spread in the abdomen to areas such as the omentum [a fatty structure that drapes the intestines and is a common site for metastatic ovarian cancer] – they may grow differently depending on their environment or ‘neighborhood’ they’re in, and they also may respond differently to treatment depending on the organ or tissue they’re in,” Dr. Matulonis observes. “Even within a single patient, different sets of tumor cells may exhibit different mechanisms of resistance.”

To deal with these ploys, scientists are working on a range of countermeasures. They’re developing techniques to destroy, rather than merely block, proteins involved in drug resistance. They’re testing whether different drug doses or treatment schedules can prevent resistance or reduce its likelihood. Most promisingly, they’re working to decipher the genetic mechanisms behind resistance, looking for ways to block or circumvent them.

Today, when a patient’s tumor stops responding to a drug or combination of drugs, physicians may recommend another regimen or a clinical trial of a novel treatment. But because tumors can become resistant to multiple therapies, new approaches are urgently needed.

**A New Option When PARP Inhibitors Fail**

A recent study by Dana-Farber researchers exemplifies science’s ability to get the upper hand over cancer drug resistance.

Drugs known as PARP inhibitors have become a major part of the arsenal against cancers with mutations in the genes **BRCA1** and **BRCA2**. The drugs employ the same strategy as a trade embargo against an outlaw nation. If some of that country’s supply lines have already been disrupted, it’s likely to be desperately dependent on its remaining suppliers. Shutting down those sources would be devastating. **BRCA1** and **2** help cells repair double-stranded breaks in their DNA. When those genes are knocked out of commission by a mutation, tumor cells rely more heavily on PARP proteins, which make single-stranded DNA repairs. Blocking the PARP proteins with an inhibitor drug can create such a build-up of genetic damage that the tumor cells die.

“**BRCA** mutations are found in many breast, ovarian, prostate, and some pancreatic cancers,” says Alan D’Andrea, MD, director of Dana-Farber’s Susan F. Smith Center for Women’s Cancers and the Center for DNA Damage and Repair, who led the new study with Raphael Ceccaldi, PhD, PharmD, of the Curie Institute in Paris. “For many patients with these cancers, or cancers with other DNA-repair deficiencies, PARP inhibitors can be extremely effective.”

In nearly every case, though, tumors that were once susceptible to PARP inhibitors become resistant to them and mount a comeback, leaving patients in need of new options. Dr. D’Andrea and his team set out to find one.

At a Harvard Medical School facility, they screened thousands of molecules – approved drugs as well as experimental compounds – in **BRCA**-deficient tumors to see if they had any effect on tumor growth. The screenings were conducted in laboratory cell lines, in organoids – three-dimensional cultures of tumor tissue – and in animal models.

Of all the drugs tested, one stood out for its ability to kill the tumor cells while leaving normal cells unharmed – the antibiotic novobiocin. When they learned the identity of the protein that novobiocin targets within cells, they had a shock of recognition.

Back in 2015, Dr. D’Andrea’s team had found that tumors with poorly functioning **BRCA1** and **2** genes are overdependent for their growth and survival on an enzyme called POLH, or POLQ. Like the **BRCA** proteins, POLQ specializes in mending double-strand DNA breaks. In tumors with mutated **BRCA** genes, the...
POLQ pathway becomes all the more vital, and any drug that targets it could deliver a death blow to cells.

Now, in the new study, Dr. D’Andrea’s team had discovered that novobiocin’s protein target was none other than POLQ.

An Old Drug, Reborn to Treat Ovarian Cancer

Novobiocin is a drug whose best days were thought to be behind it. Originally developed in the 1950s and licensed for patients in the 1960s, it gradually fell into disuse as newer, more versatile antibiotics came on the market. Its primary use today is in veterinary medicine.

As Dr. D’Andrea and his colleagues searched the medical literature for reports on novobiocin, they found that this wasn’t the first time it has been studied as a potential cancer drug. Nearly 30 years ago, investigators had tested it in clinical trials for patients with hard-to-treat cancers. Most of the patients didn’t benefit from the drug, but a handful did, having their cancer stabilize or recede.

“At the time, no one knew what the drug’s target was,” Dr. D’Andrea remarks. “Now we do, and, as a result, we have an indication of which patients are likely to be helped by it.”

To see if novobiocin works as well in people as it has in the laboratory and in animal models, investigators are launching a phase 1 clinical trial of the drug in late 2021 for patients with ovarian cancer whose tumors have defects in BRCA or other genes involved in DNA repair. Geoffrey Shapiro, MD, PhD, who will lead the trial, has high hopes for its success.

“The discovery of novobiocin’s potential in BRCA-deficient cancers is an example of how research at the basic, molecular level can pave the way to better treatments for patients,” Dr. D’Andrea says. “It’s an early indication of how powerful this approach can be in solving the problem of drug resistance.”
TO ELIMINATE CANCER DISPARITIES, IT TAKES A CENTER

by Saul Wisnia

The COVID-19 pandemic may have helped raise the public’s collective attention to racial disparities in health care, but faculty and staff within Dana-Farber and its Susan F. Smith Center for Women’s Cancers needed no reminders. At the local and national level, they have long been at work addressing these problems — along with inequities due to socioeconomic status, geographic location, gender identity, age — as they exist for those dealing with breast and gynecologic cancers.

Through programs, research, and community-based outreach efforts, clinicians, scientists, and support staff are committed to improving access, delivery, and outcomes for all individuals needing care. In 2014, Dana-Farber and the Boston Public Health Commission led the formation of the Boston Breast Cancer Equity Coalition (BBCEC) in response to persistent city-wide disparities in breast cancer mortality among minority, low-income patients. The BBCEC is focused on eliminating disparities in breast cancer care and outcomes due to race, ethnicity, or financial challenges through community partnerships, educational programs, support networks, and by advocating for Boston and Massachusetts legislation relevant to breast cancer.

BBCEC initiatives include a series of Facebook Live seminars with medical experts on breast cancer protocols during COVID-19; establishment of the Pink and Black Education and Support Network, which has worked with the Pink and Black Ambassadors — a group of Black breast cancer survivors — to increase awareness, outcomes, and quality of life for Black patients and survivors around the disease; and introduction (in collaboration with Dana-Farber) of the Breast Cancer Equity and Early Detection Bill into the Massachusetts State Legislature. The bill would ensure patients can access diagnostic breast imaging with no out-of-pocket costs.

Rachel Freedman, MD, MPH, a breast oncologist in the Susan F. Smith Center, was one of the BBCEC’s founders.
Marlene Escobar (left) and Magnolia Contreras, MSW, MBA.
other clinicians to identify specific issues faced by their patients, with a focus on reaching out to individuals from Greater Boston neighborhoods with the greatest needs – Dorchester, Mattapan, Mission Hill, and Roxbury. This allows her to be the most proactive in helping patients throughout their treatment course.

“We want to be prepared to address – and anticipate – some of the needs these patients might have, such as unemployment, financial problems, and food insecurity,” says Magnolia Contreras, MSW, MBA, vice president of Community Health at Dana-Farber. “The goal is to identify a patient as early as possible, get to know the patient as early as possible, and be able to respond quickly and thoughtfully to their needs, starting with calling to help them before their first appointment.”

Navigating Care

One way to meet such goals, Dr. Freedman says, is by building on already proven initiatives. For nearly 20 years, Dana-Farber’s Patient Navigation Program has paired vulnerable patients with bilingual professionals called patient navigators who help with basic but important needs like transportation to appointments, scheduling visits, and understanding information patients get from their health care providers. Traditionally, navigators are connected with patients who have a breast or cervical cancer diagnosis or have received an abnormal finding on a breast or cervical cancer exam, such as a Pap smear.

In 2021, Marlene Escobar became the first patient navigator dedicated to one Dana-Farber treatment center: the Breast Oncology Center. Escobar works directly with Dr. Freedman and other clinicians to identify specific issues faced by their patients, with a focus on reaching out to individuals from Greater Boston neighborhoods with the greatest needs – Dorchester, Mattapan, Mission Hill, and Roxbury. This allows her to be the most proactive in helping patients throughout their treatment course.

“We want to be prepared to address – and anticipate – some of the needs these patients might have, such as unemployment, financial problems, and food insecurity,” says Magnolia Contreras, MSW, MBA, vice president of Community Health at Dana-Farber. “The goal is to identify a patient as early as possible, get to know the patient as early as possible, and be able to respond quickly and thoughtfully to their needs, starting with calling to help them before their first appointment.”

Building further on this early-outreach model, Escobar will work with partnering community health centers and other primary care practices throughout Greater Boston and Massachusetts to establish a smoother process by which they can refer patients to the Susan F. Smith Center. The eventual goal, says Contreras, is to have a patient navigation service that is community-focused.

Educational programs around cancer prevention, another vital resource in the fight against disparities, were aided by one of the few positive developments to come out of the pan-
demic: the rise of virtual events. While in-person workshops might draw 20 or so participants due to challenges including transportation and childcare, a Zoom-based prevention and education event focused primarily on gynecologic and breast cancer and led by Dana-Farber’s Community Benefits office in October 2020 drew more than 100 attendees.

“Partnering with other local organizations that have established online communities, we’ve been able to reach a number of audiences that we might not otherwise have been able to reach,” says Contreras. “There is an engagement and intimacy that occurs online, and even for smaller workshops the attendance has been strong and consistent. We know that this is where opportunities lie for us going forward, and we could not be more thrilled.”

Study and Response

A key to addressing and eventually eliminating disparities is taking the proper steps to better understand what causes them in the first place. During the past decade, Dana-Farber staff have contributed to numerous research studies probing the reasons for variances in breast and gynecological cancer incidence and mortality.

“We’ve worked very hard here and with colleagues across the country to disentangle – and document – what causes racial, ethnic, and socioeconomic disparities,” says Alexi Wright, MD, MPH, director of Gynecologic Oncology Outcomes Research at Dana-Farber. “The key now is addressing these issues head-on.”

Through efforts including establishment of a Disparities Research and Implementation Task Force at Dana-Farber/Harvard Cancer Center, Dr. Wright and colleagues are working on solutions to inequities like those uncovered by clinical gynecologic oncology fellow Stephanie Alimena, MD, and radiation oncologist Martin King, MD, PhD. In their study of more than 16,000 women in the National Cancer Database treated for cervical cancer between 2004 to 2016, they found that a primary reason Black women have the highest incidence and mortality from this disease in the United States is because they are far less likely to receive a specific type of radiation – brachytherapy – that is especially effective in treating advanced cervical cancer.

“This trend held across the country,” says Dr. Alimena. “Black women who didn’t have brachytherapy had much lower survival rates, but if they did get brachytherapy, their survival was completely equivalent to that of white women. We found that women of all races were less likely to receive brachytherapy in the southern and western United States, where there are far fewer physicians trained in brachytherapy and a paucity of radiation treatment centers. There is a higher concentration of Black women who live in the South, so that is likely a factor.”

While this research is helpful, Drs. Alimena and King know, getting Black patients access to brachytherapy is only one factor in eliminating cervical cancer disparities.

“The human papillomavirus (HPV) causes roughly 90% of cervical cancers,” says Dr. King. “While overall incidence of cervical cancer is declining because of HPV vaccination, disparities in screening and vaccinations persist. At Dana-Farber, our general cervical cancer population is much more disadvantaged than our typical endometrial or prostate cancer population. They come from different parts of the state, and a lot of them have a lot more barriers to care and are getting diagnosed later.”

Drs. King and Alimena believe that focusing more on targeted interventions, similar to what is being done in underserved communities adversely affected by the COVID-19 pandemic, could be key to lessening the cervical cancer gap.

“We did a spinoff study looking at age and race, and found Rachel Freedman, MD, MPH, helped start the Boston Breast Cancer Equity Coalition.
that younger Black women under 40 were more likely to present with higher-stage disease and have worse survival outcomes than younger non-Black women,” says Dr. Alimena. “It may be insurance barriers causing this. Younger Black women are more likely to be uninsured or underinsured than older Black women, who at age 65 have access to Medicare.” As a result, the younger women are not being diagnosed until they reach late-stage situations.

Dr. Alimena feels partnering oncologists with primary care physicians in the community, who can encourage their patients to follow-up on abnormal Pap smears with colonoscopies, may help. She is part of another proposed study that will test this theory, utilizing the help of two Dana-Farber patient navigators.

Even in those cases when a cancer is found, treated, and eliminated, Dr. Wright says, health disparities can present new problems. One example she cites is uterine cancer which often presents with vaginal bleeding. Nearly 60% of endometrial cancers are caused by being overweight or obese. If caught early, it can usually be cured with a hysterectomy. But for the predominantly Black, Latinx, and socioeconomically challenged patients who survive this type of cancer, the same factors that often lead to it – obesity and a poor diet due to a lack of access to quality foods and physical activity – remain health risks when it is gone.

“Many women with early-stage disease feel they are in the clear after surgery, but they are still in great danger of experiencing diabetes, heart disease, and other obesity-driven cancers,” says Dr. Wright. “For obesity-driven tumors, a diagnosis of uterine cancer is like a heart attack – a wake-up call demanding major lifestyle changes – but many women are not in position to do this on their own.”

As with cervical cancer, Dr. Wright believes, the answer lays in community engagement. She and colleagues are working on an initiative through which Black and Latinx uterine cancer survivors trained by Dana-Farber will serve as health coaches to fellow people of color treated for the disease, helping them adopt a healthy diet and conditioning program.

“This will be a peer-driven program in a supportive environment,” says Dr. Wright. “Survivors will be encouraged to make smart choices, get moving physically, and lose weight by people who look like them and know the challenges they have been through.”

**Saying ‘YES’ to Change**

Younger patients are also the focus of another project that hopes to improve care and lessen disparities. Young, Empow-
Noel Peters, a breast cancer survivor treated at Dana-Farber, serves on an advisory board offering advice on the design of the Young, Empowered, & Strong (YES) portal.
Clinical trials are a linchpin of modern medical research. By rigorously studying how new drugs and treatment regimens work in patients—addressing key questions about safety and effectiveness—the medical community can bring the most promising new approaches to the clinic. Such work is vital for driving progress in all areas of medicine.
Dr. Liu is the principal investigator of an international, multi-site phase 2 trial that is also underway. In addition to this trial, tumors – what specifically makes them vulnerable – will also be studied with how cells sense and respond to DNA damage. She and her team recently published the results of an investigator-initiated phase 2 trial, which showed that roughly 30% of patients with an aggressive form of uterine cancer (known as uterine serous carcinoma) saw their tumors shrink following treatment with adavosertib. All told, about half of patients’ tumors stopped growing.

Dr. Liu’s group has expanded her initial trial to include a translational research component to shed light on adavosertib’s biology and the molecular mechanisms that underlie its effectiveness in this cancer subtype. In addition to this trial, Dr. Liu is the principal investigator of an international, multi-site phase 2 trial that is also underway.

“The science behind why adavosertib works in these tumors – what specifically makes them vulnerable – will also help guide us in figuring out what other cancer subtypes might benefit from the drug,” said Liu.

Medical oncologist Elizabeth Lee, MD, is also leading a clinical trial that includes gynecological cancers, specifically those that are positive for HER2, a key protein that helps drive cancer growth. Over the last two decades, a variety of HER2-targeted therapies have been developed, including trastuzumab deruxtecan, or T-DXd, which was recently approved by the FDA for patients with advanced forms of HER-2-positive breast cancer. T-DXd consists of two molecular components: trastuzumab, an antibody, which recognizes and neutralizes HER-2, and deruxtecan, a highly potent chemotherapy drug. These elements are chemically linked together, forming a kind of smart bomb that can deliver chemotherapy directly to HER2-positive tumor cells.

Now, Dr. Lee and her colleagues are studying whether T-DXd, in combination with another molecularly targeted drug called olaparib, can benefit patients with advanced forms of HER-2-positive cancers, including breast, ovarian, and uterine cancer. The team is conducting a phase 1 trial that is sponsored by the National Cancer Institute (NCI) that will explore the safety and dosing of the drug combination.

While it is still too early to know whether these drugs will prove effective, Dr. Lee is hopeful. “The hope is that we’ll be able provide more treatment options for patients and fit into the standard of care,” said Dr. Lee. “There are a variety of gynecological cancers that express HER2, and our goal is to take advantage of that molecular vulnerability.”

Rebecca Porter, MD, PhD, another medical oncologist within the Division of Gynecologic Oncology at Dana-Farber, is leading a clinical trial that seeks to test a new molecularly targeted inhibitor against the ATR protein in certain forms of ovarian cancer. A first-generation version of this inhibitor showed promise when combined with chemotherapy in certain ovarian cancers that are resistant to standard treatment. This work, led by Panos Konstantinopoulos, MD, PhD, director of Translational Research in Gynecologic Oncology at the Susan F. Smith Center, was published in The Lancet Oncology last year and has paved the way for a phase 3 clinical trial.

Now, Dr. Porter and her colleagues are testing a selective ATR inhibitor that is designed to be more potent, which could allow chemotherapy to be used at a lower dose in the combination therapy. A phase 1 trial has been launched to evaluate safety and dosing of this new inhibitor (known as elimusertib) together with the chemotherapy drug, gemcitabine.

“For most ovarian cancers, the question is not really if they’ll recur, but unfortunately when,” said Dr. Porter. “And
when it does, the cancer becomes more of a chronic disease that we try to hold at bay with sequential, but unfortunately often less effective, therapies. So, what’s desperately needed are drugs that can either prevent recurrence or better target treatment-resistant tumor cells.”

**Overcoming Hurdles in Breast Cancer Treatment**

Historically, most clinical trials in breast cancer have excluded patients whose disease has spread to the brain yet included patients whose tumors have advanced to other sites, like the liver. The concern is that patients with worsening disease in the brain represent a very challenging group when it comes to treatment, and their inclusion might impact the trial’s results. Consequently, there are few, if any, treatment options for patients with breast cancer that has progressed to the brain.

“This is a real problem, particularly for breast cancer patients with HER2-positive disease,” said Nancy Lin, MD, a breast oncologist and the associate chief of the Division of Breast Oncology at the Susan F. Smith Center. “Half of these patients will eventually develop brain metastases over their lifetime. So, if we exclude them, we aren’t really testing the drug in a population that is truly representative of the disease.”

Dr. Lin is one of the trailblazers solving this problem. She has helped create a roadmap for researchers on how to formulate clinical trials that include patients with brain metastases. In addition, she’s driving innovation in treatment through a variety of clinical trials that test whether novel drugs and drug combinations are effective in breast cancer patients with brain metastases.

Over the last several years, Dr. Lin and her colleagues, including breast oncologist Rachel Freedman, MD, MPH, have shown that different HER2 inhibitors – first lapatinib and later neratinib – can cause brain tumors to shrink in patients with advanced HER2-positive breast cancer when combined with an oral chemotherapy drug. “That was really the starting point for a proof-of-concept that systemic, targeted therapies can work in the brains of breast cancer patients,” said Dr. Lin.

A pillar of the team’s work is their close collaboration with research scientists, especially Dana-Farber investigator Jean Zhao, PhD, whose lab specializes in developing mouse models that more closely resemble human breast cancers and can reliably predict whether or not drugs will be active in the brain in humans.

Motivated by studies in Zhao’s animal models that showed the effectiveness of neratinib, in combination with another HER2-targeted drug called T-DM1, Dr. Freedman is now leading a phase 2 clinical trial of this drug pair in breast cancer patients with brain metastases. She and her colleagues hope to have results next year.

“Women are living longer with metastatic breast cancer, which means brain metastases could become more common,” says Dr. Freedman. “So, figuring out ways to help this group of patients is really critical.”

Most recently, Dr. Lin’s group has helped analyze the effects of a new HER2-blocking drug, called tucatinib, in combination with Herceptin, the first HER2 inhibitor to be developed, together with chemotherapy. Known as the HER2CLIMB trial, this effort led to the FDA approval of tucatinib in April 2020 for certain patients with advanced HER2-positive breast cancer. Importantly, the trial showed that the triplet therapy could not only shrink tumors in the brain and delay progression, but also significantly improve survival.

“These are patients who for many years have essentially been written off because they have a poor prognosis,” says Dr. Lin. “We’ve shown that it is possible to develop therapies that significantly extend the survival of these patients. Now, we as a community must do it.”

Together with Dr. Zhao and other collaborators, Dr. Lin is already leading the charge. Her team is now testing a new drug, called GDC-084, that targets two key cell signaling pathways at once, in combination with Herceptin. They are also launching a clinical trial of the HER2 smart bomb T-DXd, (the same drug Dr. Lee is studying in combination with olaparib). They will examine how well the drug works in breast tumors that have spread to the brain.

While metastatic disease poses treatment challenges, so too does ensuring that cancers do not return once they have been eradicated. This is especially true in some inherited forms of breast cancer caused by mutations in the BRCA1 and BRCA2 genes. But breast oncologist Judy Garber, MD, MPH, is searching for new options to help protect these patients from cancer recurrence.

Dr. Garber and her colleagues recently published the results of an international phase 3 clinical trial that examined the use of the PARP inhibitor olaparib as an adjuvant therapy in patients with early-stage breast cancer caused by the BRCA genes. (Adjuvant therapy is typically administered after the surgical removal of the tumor.) Known as the OlympiA trial, it involved more than 1,800 patients from 420 centers across 23 countries and showed that olaparib can significantly improve disease-free survival when administered to patients for a full year following standard treatment.

“We are delighted to be able to show that the PARP inhibitor had an important effect in patients around the world with breast cancers because of their BRCA1 or BRCA2 gene mutations,” said Garber, who is chief of Cancer Genetics and Prevention and a medical oncologist in the Breast Oncology Center.
Nancy Lin, MD, (left) and Judy Garber, MD, MPH, seek new strategies for improving breast cancer treatment.

at Dana-Farber. “It also means we now have a reason to genetically test more patients when they are diagnosed with breast cancer, so we can determine who might benefit from this treatment.”

Improving Early Cancer Detection and Prevention

While finding new treatments is a major focus of the Susan F. Smith Center, there is also a deep commitment to discovering ways to find tumors earlier — and even prevent them altogether.

Early detection often means better outcomes for patients, particularly those who are at high risk of developing cancer due to the genes they carry. Dana-Farber’s Dipanjan Chowdhury, PhD, is leading a clinical study that seeks to develop an early diagnostic test for ovarian cancer. Known as the MiDE study (MicroRNA Detection study), Dr. Chowdhury and his colleagues are collecting blood from individuals who carry genes, including $BRCA1$ and $BRCA2$, that increase their risk of ovarian cancer. They analyze these blood samples with a specific focus on a subset of small molecules called microRNAs. Dr. Chowdhury’s team discovered and validated a specific microRNA pattern that is associated with a high risk of ovarian cancer. Now, they are testing whether this molecular pattern can help predict whether a woman with a high genetic risk of ovarian cancer will go on to develop the disease.

“Removing the ovaries has a major impact not just on fertility, but also on overall health risk, so the anxiety that many of these patients live with day-to-day is just extraordinary,” says Dr. Chowdhury, who is chief of Radiation and Genome Stability and co-director of Dana-Farber’s Center for $BRCA1$ and Related Genes. “A test that can reliably tell women if they are going to develop ovarian cancer would be an enormous benefit.”

At the same time, Dr. Garber and her colleagues are examining the role of denosumab, a drug that blocks a protein called RANK ligand. Early research showed that blocking this protein in mice with mutations in $BRCA1$ can prevent the animals from developing breast cancer. Now, Garber and her colleagues are launching an international phase 3 trial to test denosumab in patients who carry mutations in the $BRCA1$ gene.

“At this time, we can only reduce cancer risk with surgery,” said Dr. Garber. “This clinical trial is a major undertaking that will help us understand if a medication can reduce breast cancer risk in women at very high genetic risk, and perhaps allow them to at least delay preventive surgery.”

The trial, which will run in seven countries, including the U.S., seeks to enroll over 2,900 patients. Denosumab is an FDA-approved drug already used by doctors to treat osteoporosis and prevent bone metastases in cancer patients.

“A common thread that unites these studies is finding more personalized treatments that are tailored to patients’ own disease biology,” said Ian Krop, MD, PhD, associate division chief of the breast oncology program in the Susan F. Smith Center. “When we can tailor therapy better, patients do better — and that’s really what our work is all about.”
Maintaining Momentum: Online Tools Keep Care and Support on Target

by Anna Fiorentino

An ovarian cancer survivor in a clinical trial at Dana-Farber went from using a cane to walking freely – during the pandemic, no less. “It was amazing to see how much better many women felt with relatively modest increases in physical activity,” says Alexi Wright, MD, MPH, principal investigator and director of Gynecologic Oncology Outcomes Research at Dana-Farber. “Other women felt like the study helped them begin to trust their bodies again – that muscle pain signified strength rather than disease recurrence.”

Wright’s initial pilot study, Stepping Into Survivorship, used a Fitbit activity monitor paired with a game to study the effect of exercise on outcomes, and adds to growing evidence that digital tools and online data collection can accelerate research. Wright and her colleagues are now studying this in a randomized trial called Step Into Support for Endurance and Strength (SISTERS). Dr. Wright’s study is timely. It comes at a time when the pandemic has emphasized the importance of digital data collection and enrollment, and remote delivery of tools to facilitate clinical trials.

According to the Journal of the American Medical Association, remote patient interactions across the country increased dramatically in the early months of the COVID-19 pandemic – jumping from 9% just before the pandemic hit in January 2020 to 58% in May 2020. Cancer care and survivorship was no exception.

“Many people didn’t even know the word Zoom before the pandemic,” says Ann Partridge, MD, MPH, founder and director of the Susan F. Smith Center’s Program for Young Adults with Breast Cancer. “And in the pandemic, all of our research related to young adults with breast cancer that had been taking place via mail transitioned to electronic surveying.”

The key to making research progress in the early days of COVID was a willingness to pivot and adapt. “When the pandemic first started, we knew so little about how COVID-19 was transmitted, how to treat it, who would survive,” says Dr. Wright. “It’s hard to imagine now because we’ve come so far, but at that time every human interaction seemed risky, particularly at hospitals and medical centers.”

Patients, particularly those who were immunocompromised, needed an alternative to an office visit or a healthcare provider entering their home. “They worried that having someone into their home increased their risk of contracting COVID-19 – and it may have,” says Dr. Wright. “We found that patients and their caregivers were most interested in online interventions – particularly an intervention that used telehealth to help patients manage their symptoms when they were transitioning home from the hospital.”

As the online research experiment proved successful, a new standard is now being set for the use of digital technology. At Dana-Farber, Dr. Wright, Dr. Partridge, and Huma Rana, MD, MPH, clinical director of Cancer Genetics and Prevention are helping pave the way.

Online Exercise Tools for Ovarian Cancer Survivors

Patients with gynecologic cancer diagnoses were able to enroll in Dr. Wright’s Stepping Into Survivorship study, even while hospitals limited capacity, activities moved outdoors, and people moved their workouts from the gym to the home treadmill.

Dr. Wright knew that patients with ovarian cancer could become deconditioned to their disease while undergoing intense treatment, including surgery and chemotherapy. According to previous research, ovarian cancer survivors are three times more likely to experience lower-body functional limitations.
compared with survivors of other cancers, and as a result half of ovarian cancer survivors become sedentary, and 25% become inactive. While evidence had shown that increasing physical activity could reduce the risk of cancer recurrence and mortality, reduce symptoms, and improve physical functioning and mental health, Wright was able to test physical activity interventions specifically in sedentary or older ovarian cancer survivors.

Participants in Dr. Wright’s study selected a partner and each member received a Fitbit, and set goals to increase their steps. Each week, teams received points based on progress toward their activity goals. The points had no monetary value, but many participants found them motivating because of the powerful principle of loss aversion – the concept that losing things is more salient than gaining things. Focusing on team-based activity also provided increased social support for patients transitioning away from treatment.

“Many women report that one of the toughest times is right after treatment ends,” says Dr. Wright. “Everyone expects them to be better, but many women are still exhausted, scared about the disease recurring, and may feel alone in their experience.” Preliminary results of the study show, however, that their health still improved in the pandemic.

New Tools to Overcome PARP Inhibitor Fatigue

Dr. Wright and colleagues from outside of Dana-Farber, psychologists Hanneke Poort, PhD, and Joanna Arch, PhD, also made progress last year in a clinical trial for patients with ovarian cancer who reported fatigue while being treated with PARP inhibitors, a class of drugs that have revolutionized treatment for patients with ovarian cancer. Her multi-site clinical trial called REVITALIZE provides support, knowledge, and skills to patients to reduce fatigue, psychological distress, and fear of cancer recurrence. Before long, patients in the trial like Karen Maloney saw daily fatigue disappear.

“The one-on-one sessions were very helpful in giving me new perspectives on my fatigue and new ways to lessen its grip on me,” Maloney says. “Learning new attitudes and skills to manage fatigue completely improved my quality of life.”

Maloney is among nearly 70% of women who experience fatigue while taking PARP inhibitors. “And 10-20% of those will stop the drugs early because of side effects,” says Dr Wright. “We’re trying to help women continue on these life-saving medications by tackling some of the worst side effects to make them more tolerable.”

Ann Partridge, MD, MPH

Alexi Wright, MD, MPH
the study is ongoing, several patients have noted to investigators that Acceptance and Commitment Therapy (ACT) strategies have reduced their fatigue and helped them to realign their activities with what matters most to them.

By leveraging digital tools for exercise during the COVID outbreak, Dr. Wright is closer to potentially dramatically changing the treatment landscape for patients with an advanced form of the disease. With positive preliminary results, she and her colleagues are performing a pilot randomized trial to see whether participants’ fatigue is significantly reduced by the intervention.

Online Support for Breast Cancer Patients

When the COVID lockdown started, Dr. Partridge had been on the verge of launching Young, Empowered, & Strong (YES), a five-year study using a web-based portal to track the progress of young, newly diagnosed or metastatic breast cancer patients, and to help them manage minor physical complaints and psychosocial concerns.

“Unlike a lot of people who had to just shut their research down, we were able to hit the ground running because we were already planning to go virtual,” says Dr. Partridge.

Dr. Partridge had planned to recruit patients during visits in the clinic, but that went remote, too, after the pandemic started. Once the online recruitment and consent process was in place, Dr. Partridge launched the trial in September 2020 and the mostly online study was an instant success. Designed for access by smartphone, tablet, or laptop/desktop, the portal allows patients to monitor the frequency and degree of variation in cancer-related issues by taking online surveys and assessments, and sharing self-management progress, resources, and other research opportunities all in one place.

In the comfort of their own homes, YES provides patients dealing with the isolation of cancer — in the height of isolation of the pandemic, no less — opportunities to journal online and to form a community in chat rooms to help them cope with their new normal. The online community is starting to take off, and enrollment and survey participation is up, supported by the collection of tumor and blood specimens. Meanwhile, the overall Young and Strong Program that supports the YES portal, in some cases saw enrollment double, virtual support grew, and webinars were well attended.

While clinical data on the acute effects of cancer treatments has been widely circulated, through YES Dr. Partridge is able to track less severe symptoms of young patients, as well as support self-management and survivorship, health behaviors, psychosocial concerns, and informational needs throughout their care.

“It’s great to be able to avoid coming into the clinic when you’re a survivor looking for supportive care,” says Dr. Partridge, adding that for the right kind of research going digital is “way more efficient.” Each patient’s progress is automatically computed into the portal, resulting in less paperwork for the study team.

Next, Dr. Partridge plans to launch a similar multicenter online YES portal study for survivors of breast cancer within three years of diagnosis.

Video and Chatbot Patient Education

Huma Rana, MD, MPH, is leading a two-armed, two-year study called OPTimizing Treatment Focused Genetic Testing IN Cancer (OPT-IN), to examine the impact of education for germline genetic testing education. The trial is looking to pre-test video versus chatbot education to help researchers gain a better understanding of patient preferences.

After successfully accruing patients throughout the pandemic, the study’s first arm focused on breast and ovarian cancer patients, while the second arm is open to any patient with any type of stage 3 or 4 cancer. “Patients in both arms of the trial were able to participate remotely from their homes, so it was a win for patient-centered care,” Dr. Rana says.

Virtual Visits for Genetic Counseling

Patients were able to access genetic counseling and testing through telemedicine and videoconferencing. Often, patient specimens for genetic testing were obtained through at-home saliva tests sent through the mail. This remote model resulted in 20% growth in the number of cancer genetics patients evaluated by care providers in Dana-Farber’s Center for Cancer Genetics and Prevention.

“Patients found it easier to be able to join remotely without having to travel into Dana-Farber,” says Dr. Rana. “Our patients tell us they are really happy to receive their care via telehealth or videoconferencing.” And, importantly, she says, improving access to timely genetic testing is a key factor in achieving better outcomes for patients. Dr. Rana expects discussions to continue around ways researchers and genetics providers can better care for patients and high-risk families, including remotely.
Surgical Nurse Stays on Shift During Treatment

As a nurse, Nadege Vilnaigre has devoted her professional life to helping those facing serious medical challenges. Her determination to stay on the job hasn’t waned – even in the face of her own experience with cancer.

Vilnaigre was treated at Dana-Farber for inflammatory breast cancer, which she was diagnosed with in 2019, but she was largely able to keep working at her medical surgical unit, treating patients whose issues range from respiratory and cardiac problems to cancer. It was only when her unit was temporarily converted to treat COVID-19 patients in early 2020 that she had to stay away, and with the OK of her doctors she was back by early summer. She did it all for the patients who needed her, she says.

“When I would get tired, I’d just keep saying to myself, ‘I’m not going to let this diagnosis take over my life and keep me from making a difference in the lives of others,’” Vilnaigre says.

Growing up in Haiti, Vilnaigre says she was drawn early to her future vocation.

“There was no big hospital near our village, so a lot of people tried to care for themselves at home,” she explains. “My stepmother was a nurse, so she was an early role model for me.”

After moving to the Boston area at age 13, Vilnaigre went into nursing, married, and raised twin daughters Kalina and Katrina with her husband, Karson. Then, just as the couple was preparing to celebrate their 20th anniversary with a renewal of vows, she noticed that her right breast was reddened and enlarged. Because these signs of inflammatory breast cancer are often confused with infection, and because she did not have a breast lump, Vilnaigre was prescribed seven days of antibiotics.

Later, after the renewal ceremony and a honeymoon cruise, Vilnaigre went to the doctor for a mammogram. The radiologist noticed a buildup of fluid in Vilnaigre’s right breast, which was the cause of the swelling and is another symptom of inflammatory breast cancer. In September, her diagnosis was confirmed and she was referred to Dana-Farber, where she had five months of chemotherapy, a mastectomy, and then six weeks of daily radiation treatments.

Vilnaigre calls her coworkers, family, and friends her village of support. Coworkers switched their shifts with her when she was battling side effects from chemotherapy, her husband and daughters drove her to and from appointments, and her mother had healthy dinners waiting every night. Her sister Yoldy, a nurse practitioner specializing in oncology at Johns Hopkins Hospital in Baltimore, became a regular long-distance consultant.

“Colleagues gave me comfort baskets, and greeted me with smiles, encouragement, words of wisdom, alternative thoughts and foods, salves for my battered fingers, and prayers,” she says.

“My family, well, there are no words to express how they gave me every ounce of understanding.”

It took her mastectomy, and then the COVID-19 pandemic, for Vilnaigre to finally take some time off. Her unit was treating COVID-19 patients, and because her cancer therapy left her immunocompromised, she was at higher risk for coronavirus. But as soon as her doctors deemed it safe to return to work, she did.

Even if most of her patients are unaware of her own health status, Vilnaigre says the past year has changed how she understands and interacts with them.

“I believe I’ve always been a compassionate nurse, but now I see myself as a different person because of what I’ve been through,” says Vilnaigre.
Uterine Cancer Patient Stays Optimistic With Help From Her Care Team

Stephanie Davis is a master adapter. When she was initially diagnosed with serous uterine cancer, she found a way to continue working around surgery, radiation, and chemotherapy. Today, she is still adapting – moving from one treatment plan to another as her cancer changes – and is in consultation with her care team to keep it at bay.

Rather than focus on the fact that she has a hard-to-treat form of this cancer, Davis, 68, is thankful for her close access to the Susan F. Smith Center for Women’s Cancers and the latest clinical trials in its Gynecologic Oncology Program.

“Life is about dealing with what comes your way,” says Davis. “The important thing is to have a good team helping you.”

Everything started for Davis in May 2017. She was feeling overly fatigued and her primary care physician could not determine the cause. But when Davis began experiencing post-menopausal vaginal bleeding – an early sign of cancer in some people – her gynecologist ordered more tests that led to her diagnosis.

Her initial treatment included a hysterectomy, radiation, chemotherapy, and brachytherapy. Davis responded well, and the tumor growth was controlled, so she returned to her job as an elementary school teacher.

Then, in late 2018, Davis learned the cancer was growing again – and had spread to her stomach. Standard treatments were no longer an option; she needed to go on a clinical trial. The best fit for Davis was a trial of the drug adavosertib, which was enrolling patients at Dana-Farber.

“As soon as I met my new team, I knew I was in good hands,” says Davis. “The transition to Dana-Farber was so easy, because the staff is so open to working with other people. They put the patients first, they are always available, and they know how to calm you if problems arise.”

Davis spent a year on the adavosertib (or AZD1775) trial, a combination of daily oral treatments at home and infusions each three weeks in the Susan F. Smith Center. Initially she had a 70% reduction in her tumor progression, but eventually the cancer began growing again. When the time came that a change in treatment was indicated, Davis was eager to enroll in another clinical trial.

She qualified for a study using the drugs mirvetuximab and pembrolizumab (Keytruda) that targets a different genetic expression than adavosertib. She started on this combination in August 2020, and stayed on it until early 2021. She is currently on another multidrug regimen of pembrolizumab and the oral drug lenvatinib.

“Stephanie has participated in trials that are quite unique, such as the first time a WEE1 inhibitor has been used to treat uterine serous cancers,” says her oncologist Ursula Matulonis, MD, chief of the Division of Gynecologic Oncology. “The last trial she was on combined an antibody drug conjugate and an immune checkpoint inhibitor focused specifically to this cancer.”

If and when the time comes, Davis says she will be ready for yet another trial. She feels a close connection with her care team, as well as a deep commitment to the clinical trial process. And when she had to retire from teaching due to the demands of the clinical trials, her care team was right there for support.

“If I can help other people by being on a trial, and hopefully myself too, I want to do so,” says Davis.
Kornelia Polyak, MD, PhD, likens tumors to a bucket of different colored balls, with each ball having different colors and properties. And treating cancer is like “trying to hit the red balls and then some of them will turn green. Then you try to hit the green, and you kill some of them, but then others turn yellow,” she said.

That’s heterogeneity – the makeup of cells within each tumor – and these differences in cancer cells and their microenvironments mark the progression of breast cancer “from early to later stages but also the therapeutic resistance that is an issue in all types of breast cancer tissue,” said Dr. Polyak, a breast cancer researcher in the Susan F. Smith Center for Women’s Cancers at Dana-Farber. She says that heterogeneity is a “looking glass” for a particular cancer, which can reveal information to researchers about its past, and from which they can predict its future.

Dr. Polyak studies the heterogeneity of breast cancer cells and microenvironments, and how they change over the course of cancer and treatment, to create models that predict which patients will respond to current treatment options, and to help clinicians tailor treatments to a specific tumor in a specific patient in that specific tumor’s specific microenvironment.

“At the time of diagnosis, we want to look at the tumor and its cells and see if they can be treated with a targeted therapy,” Dr. Polyak said. “You have to assess heterogeneity at the time of diagnosis, and in non-responders, you have to assess it after treatment to change treatment accordingly.”

Much of her recent work has focused on HER2-positive breast cancer, which tends to be a more aggressive type of breast cancer that is more likely to recur. But these cancers can also respond to a treatment combination of monoclonal antibodies that bind to HER2 receptors, plus chemotherapy. It’s those HER2-positive breast cancer tumors that don’t respond to therapy, and those that become resistant to it, that she wants to know more about in the hopes of finding better, more effective treatments for that particular person at that stage of cancer.

Since 2012, Dr. Polyak has been working with Susan F. Smith Center colleagues Otto Metzger, MD, and Ian E. Krop, MD, PhD, on how heterogeneity of HER2-positive breast cancers and their microenvironments affect treatment. They are currently in a phase II clinical trial looking at the effectiveness of treating early stage, pre-operative HER2+ cancers with trastuzumab emtansine (TDM-1) and pertuzumab, both monoclonal antibodies. Research from the trial, published in June 2021 in JCI Insight and Cancer Discovery, found that the frequency of cells without HER2 was a better predictor of response to HER2-targeted treatment than intratumor heterogeneity.

“If you’re just trying to treat a patient with HER2-targeting agents and the tumor is mostly HER2-negative cells, they’re not going to respond,” Dr. Polyak said. “They’re going to continue to grow and spread. That patient needs to be treated differently.”

Dr. Polyak, who joined Dana-Farber in 1998, wants her basic science work to “have a clinical impact. I want people to be treated better, or even prevent breast cancer,” she said. In an ideal future, every patient will have personalized breast cancer therapy, and while not every single combination of drugs can be tested, computational biology could look at tumor heterogeneity and predict the evolution of the tumor and its likely response to different types of therapies.

Dr. Polyak aspires to day when “We could use computational biology to help us design what rational combination would be the best for that particular patient, which is personalized and changes during the course of treatment as the cancer responds.”
Creating New Treatments to Trigger Cell Death in Chemotherapy-Resistant Ovarian Cancer

High-grade serous ovarian cancer (HGSOC) can be difficult to treat. It’s often diagnosed at an advanced stage, and while many patients initially respond to platinum and paclitaxel chemotherapy, most of their cancers come back – and are resistant to treatment.

Elizabeth Stover, MD, PhD, a medical oncologist in the Division of Gynecologic Oncology at Dana-Farber, was recently awarded the Mentored Clinical Scientists Research Center Development Award (K08), to study a better path to triggering cell death in these difficult-to-treat cancers. The award, which is given by the National Cancer Institute (NCI), funds the research of postdoctoral and non-tenured junior faculty level clinician-scientists who are also interested in research.

“We still need new therapies for women with gynecologic cancer, especially those who have recurrences after initial treatment,” Dr. Stover said. “We’ve had a lot of exciting new developments in our field, but we still don’t have curative therapies for a lot of patients.”

In previous research with Matthew Myerson, MD, PhD, Dr. Stover identified genes that affect ovarian cancer cell survival after treatment. She found that several proteins encoded by these genes inhibit cell death (apoptosis) signaling pathways associated with drug resistance, thus pointing to their role in keeping cancer cells alive. They also showed that inhibitors of anti-apoptotic proteins, like drugs that block the proteins that protect cancer cells from cell death, can collaborate with chemotherapy to increase the destruction of cancer cells.

Can drugs that modulate apoptosis be put to work together with chemotherapy to form an effective therapy for treatment-resistant HGSOC? That’s what the grant-funded project aims to find out. The team is also applying a method called BH3 profiling, developed by Dr. Anthony Letai’s lab at Dana-Farber, which helps identify the specific anti-apoptotic proteins that are most critical for survival in each individual tumor, and thus potential targets for treatment.

Dr. Stover may be a young investigator, but she’s a familiar face at Dana-Farber. She received her MD and PhD from Harvard Medical School and was a hematology/oncology fellow at Dana-Farber and Massachusetts General Hospital starting in 2011. “It was during my fellowship that I became interested in gynecologic cancer,” she said.

She is also working within her clinical group to develop a new program for research and clinical care of rare gynecologic cancers, like subtypes of ovarian cancer, endometrial cancer, and vaginal and vulvar cancer.

“I hope that through contributing to translational and clinical research, we can offer these patients more options that are effective against their cancers.”
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1 Susan F. Smith Center for Women’s Cancers Presidential Symposium

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### Susan F. Smith Center for Women’s Cancers Executive Council

The Executive Council is an essential philanthropy network for the Susan F. Smith Center for Women’s Cancers. The group has raised more than $19 million for the center from its inception in 2002. These funds go toward the Smith Center Innovation Fund, which provides support for the Smith Center to pursue cutting-edge, lifesaving research in breast and gynecologic cancer.

The Smith Center Innovation Fund was established to support early stage and novel research in breast and gynecologic cancer that otherwise would not receive government funding. The Fund has supported nearly 30 research projects, many resulting in clinical trials and novel treatments that have saved or prolonged lives.

To learn more about the Executive Council, email Maryann Zschau at maryann_zschau@dfci.harvard.edu.

### A Legacy of Support

Thanks to the ongoing generosity of our donors, the Susan F. Smith Center for Women’s Cancers at Dana-Farber has raised more than $260 million over the past 22 years, and nearly $26 million in fiscal year 2020 alone. To learn more about how you can strengthen our ongoing work against gynecologic and breast cancer cancers, contact Suzanne Kouri at 617-632-4055 or suzanne_kouri@dfci.harvard.edu.

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