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About the cover
Young woman benefits from a circle of care. See page 10.
Priority Areas Illustrate Expertise

With a breadth that addresses all types of breast and gynecologic cancers – from the common to the obscure, the early-stage to the advanced – the Susan F. Smith Center for Women’s Cancers at Dana-Farber is propelling the science and fine-tuning patient care for women (and in a few cases, men) of all ages.

The center’s research and care expertise is growing in four major areas where patients find themselves in particular need of assistance: breast surgery, metastatic breast cancer, breast cancer in young women, and recurrent ovarian cancer.

Breast Surgery

Colleen Sullivan was prepared to follow a typical plan for her breast cancer: a lumpectomy followed by radiation. When she learned a genetic defect was causing her cancer, however, she opted for a mastectomy to decrease the odds of developing a second breast cancer.

Many breast cancer patients face such decisions, and the Susan F. Smith Center is well-prepared to guide them. Surgeons offer minimal and maximum approaches, aiming for the best outcome while adjusting for each woman’s type of tumor, unique situation, and preferences.

From shrinking tumors with drugs before surgery, to combining mastectomy and reconstruction procedures to give women the best cosmetic outcomes, surgeons continually hone their skills and work within the full picture of a patient’s life, using advanced techniques such as testing lymph nodes during surgery and viewing real-time images as surgery progresses.

Read about Sullivan’s circle of care on page 10.

Metastatic Breast Cancer

It is hard enough for a woman of any age to learn she has breast cancer. But when she finds out her cancer has spread beyond the breast, the challenges and worries multiply.

Today, women with metastatic breast cancer can live well for many years. In fact, Susan F. Smith Center scientists conduct such a wealth of research in these types of advanced cancers that some women transfer their care here when their cancer reaches this stage. Susan F. Smith Center oncologists work closely with oncologists at other centers to provide optimal care, even for women who do not live near Boston. Dana-Farber is currently conducting more than 30 clinical trials to study the effects of new, targeted drugs on metastatic breast cancer. Much of this research has resulted in treatment breakthroughs and new standards of care for these patients.

These are special circumstances, where the best that science has to offer is very important. Physician-scientists not only study targeted therapies and test various combinations, but also offer resources and support to this unique group of women.
Pat Hastings continues to live a full life with metastatic cancer, caring for purebred horses on a farm in Vermont and traveling to Dana-Farber every three weeks for experimental treatment (see page 24).

Young Women with Breast Cancer

Although a cancer diagnosis occurs less frequently in women in their early 40s or younger, sometimes the ripple effect on a patient and her family and friends can be greater. A young woman may be raising children, starting a career, or dating. She might be concerned about fertility, or have extra anxiety about both the cosmetic and medical challenges she faces. Feeling “young and strong” becomes very important to her.

Young and Strong: A Program for Young Women with Breast Cancer helps patients and providers address concerns about fertility and reproductive options, genetics, psychosocial matters, and other treatment and survivorship issues facing young women. The program’s physician-scientists are focused on improving surgical decision-making, studying the way genetics in young women might differ from that of older women, and exploring options for preserving fertility.

Established in 2005, the program is the first of its kind in New England and one of the only such programs in the U.S. Since its inception, the program has shepherded more than a thousand young women on their journey through and beyond cancer. A recent grant will expand the program to include women at Dana-Farber’s satellite centers and community network locations, in Massachusetts, New Hampshire, and Connecticut.

Recurrent Ovarian Cancer

Ovarian cancer differs from breast cancer in one obvious way: it cannot be easily detected at the early stages. Therefore, it is often diagnosed after it reaches an advanced stage, and even after successful treatment, it often returns. Donna Gregory (see page 14) found herself in just this situation.

While chemotherapy drugs that contain platinum are often very effective for ovarian cancer patients, in some cases, the cancer begins to reject the platinum. Today, several clinical trials testing drugs known as PARP inhibitors, which work by blocking one of the pathways by which tumor cells repair their damaged DNA (see page 4), are under way for patients whose tumors initially responded to platinum-based chemotherapy agents but then began to grow again.

Increasingly, Susan F. Smith Center investigators are testing drugs and drug combinations that are not chemotherapy at all. In one study, cediranib, an antiangiogenesis inhibitor that hampers cancer cells’ growth by interfering with their blood supply, combined with olaparib, a PARP inhibitor, improved outcomes in a recent study (see page 12). Olaparib has recently become the first PARP inhibitor approved by the U.S. Food and Drug Administration.

Investigators are testing other types of combination therapies for recurrent ovarian cancer as well as the effectiveness of immunotherapies (such as ipilimumab) to unleash the body’s own immune response against cancer.

Get Involved

You can support the Susan F. Smith Center for Women’s Cancers at Dana-Farber. Join an event, make a donation, attend a conference, or volunteer. To learn how, call Emily Horsford at 617-632-8832 or email emilyc_horsford@dfci.harvard.edu.
Precision Medicine:
Blood Samples Bolster Search for Targeted Therapies

The Susan F. Smith Center for Women’s Cancers at Dana-Farber has expanded the Institute’s landmark research project, Profile, to include blood samples as well as tumor tissue from cancer patients. Like the tumor tissues, the blood samples will be analyzed to learn more about the genetic mutations that cause cancer.

Analysis of the blood samples can identify germ-line molecular defects that were genetically inherited. (Tissue sample analysis largely identifies defects that are somatic, meaning they developed in the cancer cells.) Each patient’s tumor behaves in its own unique way. Research, including breakthrough discoveries at Dana-Farber, has revealed why: There are differences in the molecular defects that drive tumor growth. Ovarian cancer patients, for example, may respond to the same drug in different ways because their tumors have their own molecular defects. An additional challenge is that these molecular changes often evolve over time, making tumors resist therapies that once worked.

But while not all tumors are alike, they tend to share one important characteristic. “Many tumors have an Achilles’ heel – a molecular vulnerability that, if precisely targeted, can halt tumor growth,” says Judy Garber, MD, MPH, a breast oncologist and director of the Center for Cancer Genetics and Prevention in the Susan F. Smith Center for Women’s Cancers.

This is known as precision medicine: Identifying the specific molecular defect that is driving a cancer, and taking aim with an appropriate agent to block that gene or its pathway.

The approach is proving effective in many cancers, such as estrogen-receptor-positive and HER2-positive breast cancers, chronic myelogenous leukemia, and gastrointestinal stromal tumors. Researchers hope the method will be a game changer in the treatment of other cancers as well.

While researchers have made major strides in linking specific molecular defects with responses to certain drugs, the current challenge is to find in every tumor, in every patient, the exact molecular driver that is spurring the cancer’s growth.

The goal of analyzing a tumor tissue sample is to determine what molecular driver should be targeted, and adding the blood sample analysis is helpful for several reasons, says Dr. Garber. “First, it can identify cancer susceptibility genes such as BRCA1 and BRCA2. Second, comparing the genes in the tumor to the genes in the blood can reveal which genes in the tumor have mutations that are limited to the tumor only and therefore more likely to be driving the biology. This helps us focus our search for the right treatment target.”

“Because we can now understand the biology of tumors and characterize molecular changes, we can offer clinical trials much earlier than before to patients with metastatic disease,” Dr. Garber adds. “In that way, it’s a revolution in thinking.”
What are PARP inhibitors, and how do they play a role in treating ovarian cancer?

PARP inhibitors are relatively new “smart drugs” that target the DNA-repair pathways of cancer cells, potentially killing them off. Used to treat advanced and recurrent ovarian cancer in women with BRCA gene mutations as well as in women with high-grade serous tumors, PARP inhibitors might hold promise for treating other types of cancers as well, including some breast cancers.

Like healthy cells, cancer cells strive to correct DNA damage to stay alive, according to Ursula Matulonis, MD, medical director of the Gynecologic Oncology Program at the Susan F. Smith Center for Women’s Cancers at Dana-Farber. If the DNA can’t be repaired, the cells can die – which, in the case of cancer cells, is precisely the goal.

PARP (poly [ADP-ribose] polymerase) inhibitors work by blocking the repair of DNA breaks in some cancer cells. Some of the most vulnerable cells seem to be those in patients with BRCA1 or BRCA2 mutations, which hinder DNA repair. PARP inhibitors further impede the repair process.

Until recently, PARP inhibitor therapy was available only through clinical trials, including several at Dana-Farber, Dr. Matulonis explains. But in December 2014, the U.S. Food and Drug Administration approved the first PARP inhibitor, olaparib, for use in the treatment of advanced and recurrent ovarian cancer in women with BRCA gene mutations who had already received three or more courses of chemotherapy. Overall, the response of patients in studies of olaparib is considered to be an improvement over other therapies.

Olaparib (or Lynparza, as it’s called commercially) is produced in pill form. Other PARP inhibitors are in the development pipeline, with extensive involvement of Susan F. Smith Center researchers. Dana-Farber patients have access to clinical trials involving PARP inhibitors, other targeted therapies, and various combinations of drugs (see page 18).
What advice would you give someone newly diagnosed with metastatic breast cancer?

Learning that your breast cancer has spread to distant organs is an understandably jolting experience. While metastatic (also called advanced, or stage IV) breast cancer is treatable, it is not yet curable. For most women, the diagnosis of a life-threatening disease presents steep emotional challenges as well as physical ones.

Though individual situations vary, it’s not unusual for patients to live for years with metastatic breast cancer. “Increasingly, we are trying to manage metastatic breast cancer in ways people might associate with a chronic illness,” says Eric P. Winer, MD, director of the Breast Oncology Program at the Susan F. Smith Center for Women’s Cancers at Dana-Farber.

One of the first steps is to make sure you find the right health care providers. “You’re going to have a pretty in-depth relationship with your doctors, nurses, and social workers, so find a team you’re comfortable with,” says Dr. Winer.

While managing side effects can be a challenge, women often tolerate chemotherapy for metastatic breast cancer better than chemotherapy for earlier stage cancer. “It’s a little kinder and gentler,” says Dr. Winer. Some drugs cause hair loss or low blood counts, but others do not. “Talk to your doctor about what treatment might be the most effective, and what side effects would be most tolerable,” he says.

Feelings of fatigue and depression can also arise. It’s important to rule out physical causes for fatigue, such as low thyroid function. Rather than immediately recommending medications for fatigue, Dr. Winer suggests trying light or moderate activity. “You’ve got to know when to push yourself and when to back off,” he says. “Nothing makes people more tired than sitting around all the time.”

As for depression, it’s important to remember that emotional well-being is connected to physical well-being, so you might at times feel melancholy. “We don’t have a mind and body that live in two separate states,” says Dr. Winer. “The symptoms we have affect our emotions and psyche.” In some cases, antidepressants can help. If you have concerns, talk with your oncologist.

If you are eligible for a clinical trial, consider taking part, Dr. Winer recommends, and remain optimistic. “The longer you live, the greater the chance there’s going to be a new treatment for you,” says Dr. Winer. “And that new treatment could be a game changer.”

Eric Winer, MD, and his colleagues are helping women like Patricia Kartiganer live well with metastatic breast cancer.
Breast Cancer Experts Unite Across Continents

The vigorous spirit of cooperation that exists within the Susan F. Smith Center for Women’s Cancers at Dana-Farber extends far beyond its walls. A new collaboration with Oncolínicas do Brasil unites dozens of physicians from the U.S. and Brazil in an effort to exchange perspectives and enhance care for breast care patients.

Many of the organization’s 160 physicians connect regularly with Boston-based oncologists to discuss advances in breast cancer research and treatment. Each week, they participate online in educational programs led by physicians at Dana-Farber/Brigham and Women’s Cancer Center (DF/BWCC). Additionally, oncologists on both continents present challenging clinical scenarios and discuss treatment options through biweekly video conferences.

“This arrangement allows experts in both countries to learn from one another,” says Otto Metzger, MD, a medical oncologist at the Susan F. Smith Center and a leading force behind the program.

Two Brazilian oncologists in training spend several months at DF/BWCC, sharing the knowledge they gained here when they return to Brazil. Other Brazilian physicians visit as well, with highly experienced breast cancer surgeons spending a one-month stint in Boston in the summer.

The collaboration also gives DF/BWCC physicians the chance to travel to Brazil several times a year to lend their perspectives and learn new approaches. Teams of Boston-based medical oncologists, radiation oncologists, surgeons, and pathologists have presented symposia in Sao Paulo for their Brazilian counterparts, and plan to host similar events in Belo Horizonte.

This inaugural arrangement with a foreign practice is designed as a model for future international alliances. “We want to continue this active alliance as long as possible,” says Dr. Metzger. “Our goal is to improve breast cancer care for all patients – here at DF/BWCC and beyond.”

Online Registry Speeds Research in Inherited Cancer Risk

Patients and families who carry genetic variations that may be linked to an increased risk for cancer can now join an online registry designed to speed research and improve care. The Prospective Registry of MultiPlex Testing (PROMPT), which Dana-Farber helped establish, aims to help researchers track how newly identified mutations in cancer-causing genes may affect cancer risk. It should also help scientists better determine which cancer prevention and treatment strategies are likely to work best for people who inherit those mutations.

PROMPT is made possible in part by a newer form of genetic testing, called multi-gene panels, which can look for alterations in several different genes that may increase the risk of cancer. These genes include: ATM, BARD1, BRIP1, CDH1, CHEK2, PALB2, PTEN, RAD51C, RAD51D, STK11, and TP53.
Dr. Ligibel Sharpens Focus on Integrative Care

Jennifer Ligibel, MD, knows better than most the importance of a comprehensive approach to treating cancer. A medical oncologist in the Breast Oncology Program at the Susan F. Smith Center for Women’s Cancers at Dana-Farber, she has focused her research on developing and testing the benefits of exercise, nutrition, and other lifestyle interventions on quality of life in cancer survivors. Now, as director of Dana-Farber’s Leonard P. Zakim Center for Integrative Therapies, she is furthering this work by supporting clinical research and expanding the role of integrative therapies.

“Together with traditional medicine, integrative therapies can help cancer patients feel better during treatment, and have been shown to reduce side effects such as nausea, fatigue, and treatment-related anxiety,” says Dr. Ligibel. “It’s important that patients are aware how these services can help.”

The Zakim Center focuses on improving quality of life for adult and pediatric cancer patients through movement, meditation, creative arts, and individual therapies. Its experts work with Dana-Farber patients and their medical teams to design integrative therapy plans that match patients’ treatment schedules and individual preferences. Therapies include group programs in tai chi, qigong, and yoga, and individual therapies such as acupuncture, massage, and reiki.

Though she’s taking on a new role, Dr. Ligibel will continue treating patients in the Susan F. Smith Center for Women’s Cancers, and maintain her research on the connection between exercise, quality of life, and cancer control.

“PROMPT provides an exciting and novel way for individuals, families, researchers, and laboratories to work together,” said PROMPT co-founder Judy Garber, MD, MPH, director of the Center for Cancer Genetics and Prevention in the Susan F. Smith Center for Women’s Cancers at Dana-Farber. The registry is the result of collaboration with several academic research institutions and commercial laboratories.

If you carry a genetic mutation that may increase your risk for cancer, consider joining PROMPT today. To learn more, visit www.promptstudy.info.
Combined Therapy May Reduce Chance of HER2+ Breast Tumor Recurrence

Women with small (stage I), HER2-positive breast tumors who received a combination of lower-intensity chemotherapy and a targeted drug following surgery were highly unlikely to have the cancer recur within three years of treatment, investigators at Dana-Farber and other institutions reported in a recent study. The findings of the phase 2 clinical trial may help establish the therapy – which combines the chemotherapy agent paclitaxel and the targeted drug trastuzumab (Herceptin) – as the first standard treatment approach for this group of patients.

Breast cancers are classified as HER2-positive if their cells have surplus human epidermal growth factor receptors on their surface, making them extra-sensitive to signals to grow and divide.

“Women with small, HER-2 positive breast tumors with no sign of spread to adjacent lymph nodes have a low, but still significant, risk of recurrence of their disease,” said Eric Winer, MD, director of the Breast Oncology Program at the Susan F. Smith Center for Women’s Cancers at Dana-Farber, who led the study with colleague Sara Tolaney, MD, MPH. “This study demonstrates that a combination of lower-intensity chemotherapy and trastuzumab – which is associated with fewer side effects than traditional chemotherapy regimens – is an appealing standard of care for this group of patients.”

Eileen Duffey-Lind, RN, MSN, with a photo of her sister, Maureen.
‘Avatars’ Provide New Window into Cancer Biology

For a long time, cancer researchers relied on cultured cell lines as a primary window into the biology of the disease. These cell lines had been cultivated from tumor samples taken long ago – decades, in some cases – and have been studied in petri dishes ever since. Then scientists learned that these old cell lines look very different molecularly from those in actual patients. They don’t have the same active signaling pathways or genetic profiles, so they aren’t the best models for studying the molecular drivers of the disease.

“It was a real eye opener,” says Dana-Farber gynecologic oncologist Joyce Liu, MD, MPH.

In recent years, patient-derived xenograft tumor models, also called mouse avatars, have been developed to more closely mimic a patient’s disease. For instance, Dr. Liu developed a model of ovarian cancer that involves grafting tumor samples collected from patients onto mice, where they grow in an environment that is more true-to-life than a laboratory dish.

Since then, Dana-Farber scientists have developed avatars representing 15 distinct forms of ovarian cancer. These avatars can reliably track cancer cell growth using fluorescent imaging, enabling researchers to better understand which drugs work in which tumors, and why. “Now that we have the models, we can start doing the science,” says Ursula Matulonis, MD, medical director of Gynecologic Oncology at the Susan F. Smith Center for Women’s Cancers at Dana-Farber.

Jean Zhao, PhD, a Dana-Farber cancer biologist, is also developing mouse avatars for breast cancer, including models of the tumors that occur when the cancer spreads. For instance, over the past few years she has developed 15 mouse avatars with brain metastases. Using these models, Dr. Zhao recently identified a promising, though not yet published, drug combination for the treatment of breast cancer that has spread to the brain.

Other breast cancer avatars in Dr. Zhao’s collection model HER2-positive and triple-negative primary breast tumors, and liver and lung metastases. “We want to continue to model more advanced or metastatic cancers that are resistant to therapy,” she says.

How to Support Basic Science

In order for new drugs and drug combinations to be tested on patients, they must first be tested in the lab, which is called “basic science.” You can help make it possible for basic scientists at the Susan F. Smith Center for Women’s Cancers find the most effective, targeted treatments that will one day translate to patient care. To learn more or make a donation, contact Emily Horsford at 617-632-8832 or emilyc_horsford@dfci.harvard.edu.
Harold Burstein, MD, PhD, with patient Colleen Sullivan
Diagnosed at age 39 with stage II breast cancer, Colleen Sullivan quickly realized that “care” is a collective noun at the Susan F. Smith Center for Women’s Cancers at Dana-Farber.

Over the course of six months last year, her care team at Dana-Farber/Brigham and Women’s Cancer Center (DF/BWCC) would include not only her breast oncologist, Harold Burstein, MD, PhD, but also a cancer surgeon, radiation oncologist, reconstructive surgeon, chemotherapy infusion nurse, a nurse
practitioner, clinical assistants and facilitators, and a range of other professionals in the foreground and background. Had she been on a clinical trial of a new treatment, her team would have also included the investigator leading the trial, as well as other team members.

“Because I was diagnosed at a young age and had certain receptors on my tumor cells, Dr. Burstein recommended that I see a genetic counselor,” says Sullivan, a schoolteacher and mother of three young daughters. “I met with one at DF/BWCC, had my blood tested, and sure enough, it tested positive for a BRCA mutation,” an inherited abnormality that can dramatically increase one’s risk for breast cancer. Learning that she carried the mutation, Sullivan decided to have a double mastectomy – rather than a lumpectomy followed by radiation, as she had originally planned.

Now finished with her treatment, Sullivan remarks on the “many helping hands who guided me through this journey with cancer.” She was particularly struck by the level of communication among those on her care team. “No matter which physician I saw, he or she had already been in touch with my other doctors,” she says. “It felt as if we were one unit.”

Dr. Burstein describes the care team concept in terms of concentric circles. The inner ring includes those with the greatest contact with patients. Radiating outward are rings of other specialists – in everything from pathology to the pharmacy to nutritional counseling – who play critical, supportive roles.

“Our patients are surrounded by a team of providers to care for them,” Dr. Burstein says. “One thing that makes DF/BWCC a special place is that we are all here, working side-by-side, on a daily basis. Our clinics are arranged so that we constantly connect and interact in person – experts in every medical discipline, nurses, and laboratory scientists. Our patients feel the touch of having their medical team work together because it’s real.”

“It felt as if we were one unit.”

Colleen Sullivan, patient
Like Colleen Sullivan, women diagnosed with breast cancer at a young age (45 or younger) face a unique set of challenges. Many are parenting young children or thinking about becoming parents. They may also be working to advance their careers and forming important relationships. For women at this time of life, cancer can pose a formidable physical and emotional burden.

About 11 percent of breast cancers in the United States arise in women age 45 or younger. Recognizing the distinct needs of such patients, Dana-Farber/Brigham and Women’s Cancer Center founded the Young and Strong Program for young women with breast cancer in 2005.

The first program of its kind in New England and one of the only such programs in the U.S., Young and Strong has provided care and support to thousands of patients over the past decade, helping them navigate their journey through cancer and beyond. The program recently received a major grant to expand its services.

Directed by Ann Partridge, MD, MPH, of the Susan F. Smith Center for Women’s Cancers at Dana-Farber, the program focuses on treatment as well as research. “We created the program to focus not only on the treatment of the disease — and on research to improve that treatment — but also on providing support, education, and information for our young patients and the professionals who care for them,” Dr. Partridge says.

The program’s clinical services include:

- **Fertility and reproductive counseling:** Physicians ensure that fertility options are addressed right away, so patients will have time to consider which is best for them.

- **Genetic testing:** Patients have the option of being tested for inherited mutations to the genes *BRCA1* and *BRCA2* — information that can impact their treatment options.

- **Psychological support:** A social worker is identified on a young woman’s first visit to provide individual counseling throughout the course of treatment. The women also have access to a telephone support group, an online support group of young breast cancer patients, and mental health services.

- **Survivorship:** Patients can utilize services for fertility, sexual health, weight management and other issues once they complete treatment. These young women also have the opportunity to participate in a variety of research projects designed to improve the care of young women with breast cancer in the future.
When Donna Gregory’s ovarian cancer came back for the third time, she began looking for alternatives to chemotherapy. She’d been diagnosed, during an unrelated surgical procedure, with stage III ovarian cancer in 2003, at age 58. After having surgery to remove the tumors, she tried platinum-based chemotherapy, but her cancer did not respond. Another chemotherapy drug worked, though. And then another. “Everything was fine,” she says. “Until last summer.”

Gregory had already defied the odds. The five-year survival rate for women with similar disease is about 39 percent, according to the American Cancer Society. “You’re absolutely thrilled to be alive after five years of ovarian cancer,” she says.

Having run out of traditional therapeutic options, Gregory searched online for experimental alternatives and found news of a clinical trial under way at Dana-Farber/Brigham and Women’s Cancer Center (DF/BWCC). The trial was open to women with recurrent ovarian cancer, and wasn’t restricted to BRCA mutation carriers or platinum-sensitive cancers. “I thought, oh, this is perfect for me!” she says.

The trial offered Gregory a new approach to ovarian cancer therapy that takes two targeted drugs (agents that interfere with the biological machinery that drives tumor cell growth), and teams them up as a unified, potentially synergistic force. Gregory immediately flew to Boston from her home in Miami, Fla., and enrolled.

A New Strategy

When Joyce Liu, MD, MPH, a gynecologic oncologist at the Susan F. Smith Center for Women’s Cancers at Dana-Farber, first proposed combining two targeted drugs, the reaction from colleagues was lukewarm. Previous efforts to combine chemotherapy drugs for ovarian cancer patients had not produced profoundly better results, and targeted drugs were showing only modest benefits as single agents.

But Dr. Liu persevered. She had science on her side, with evidence from the National Cancer Institute that the combination she was proposing had promise. She also had a clear purpose. Each year in the United States, approximately 22,000 women are diagnosed with ovarian cancer. While many women respond to initial chemotherapy, the cancer often comes back. “There’s a definite unmet need for new therapies and new approaches to attacking this disease,” says Dr. Liu.

While Dr. Liu’s trial was the first of its kind for ovarian cancer, it was certainly not the last. Since then, Dana-Farber clinical researchers have begun several other trials of novel combinations in women with recurrent ovarian cancer. “We’re here to expand the options for our patients and provide options that are based on the genomic abnormalities of their particular cancers,” says Ursula Matulonis, MD, medical director for Gynecologic Oncology at the Susan F. Smith Center. “We really need to think about a multi-pronged, multi-drug approach.”
Molecular Mixology

Dr. Liu’s trial combines two drugs that target specific aspects of ovarian tumor biology. One is olaparib, a PARP inhibitor that compromises the way cells repair broken strands of DNA, thereby making them more vulnerable to death. The other is cediranib, an antiangiogenic drug that interferes with the machinery that builds new blood vessels.

In early results reported in 2014, the combination showed exciting results in women with recurrent ovarian cancer. One patient’s cancer vanished. In almost half of the patients enrolled in the trial, tumors shrunk by more than a third, and several patients have remained stable. Dr. Liu is now leading additional trials that will enroll more women and compare the drug combination in a head-to-head test with the current standard of care.

It isn’t clear yet how the drugs synergize to support or amplify one another’s effects, but Dr. Liu has a hypothesis. PARP inhibitors typically work best in women with BRCA mutations because they help deliver a DNA repair double-whammy. The BRCA gene mutation knocks out one form of DNA repair, leaving only the PARP mechanism to do the work. This mechanism helps BRCA mutation carriers stave off cancer for a time, but once cancer has begun to grow, it also helps tumor cells stay alive. Disabling it with a PARP inhibitor pushes tumor cells a step closer to death.

In Dr. Liu’s trial, women without BRCA mutations, like Gregory, are responding to PARP inhibitors plus antiangiogenics. Dr. Liu speculates that the antiangiogenic drugs are mimicking the effects of BRCA mutations by starving the tumor of blood and oxygen. In this state, DNA repair falters, making the cells more vulnerable to the PARP inhibitor. In upcoming clinical trials, Dr. Liu is planning to collect tissue samples from patients so she can test this theory more thoroughly.

Selection Science

Finding new combinations that are as complementary as the two Dr. Liu is testing is a challenge. There are many molecular agents, immunological agents, and other biologically-based targeted drugs available, so the number of potential combinations is enormous and growing.

One way to narrow down the options is to test large numbers of different combinations on models of ovarian cancer to see which ones show promise. Drs. Liu and Matulonis are collaborating with colleagues at Dana-Farber on a project to screen a host of drug combinations in cultured ovarian cancer cells.

From there, the most promising combinations will be tested — in a much more labor-intensive and expensive process — in mouse models of ovarian cancer. The mouse models Drs. Liu and Matulonis are using are sometimes called mouse “avatars” because they are derived from tumor samples of real patients and implanted in mice. These cancers more closely resemble those of real patients than cultured cells. (See Avatars, page 9.)

The avatars also allow more detailed scrutiny of the response to new therapies. “We can learn which cancer types respond well and why; and if the cancer does not respond, we can also begin to understand the mechanisms of resistance,” says Dr. Matulonis.

For example, a drug combination now being tested in patients — an experimental PI3K inhibitor plus olaparib, a PARP inhibitor...
By combining two targeted drugs, Joyce Liu, MD, MPH (opposite page), helped ovarian cancer patients achieve a shrinkage in their tumors. Donna Gregory (above left), shown with Ursula Matulonis, MD, has benefited from the new combination.

— was first studied in mouse avatars representing triple-negative breast cancer at Beth Israel Deaconess Hospital. The researchers learned that the PI3K inhibitor impairs DNA repair and, in turn, amplifies the effects of the PARP inhibitor.

Because high-grade serous ovarian cancers genetically resemble triple-negative breast cancers, Dr. Matulonis launched a trial of this combination in women with these types of breast and ovarian cancers. Based on promising early results, she recently expanded the trial to offer two options: olaparib plus one of two different experimental PI3K inhibitors. Results are expected in 2016. Trials of drug combinations are also under way for other gynecologic cancers including cervical.

Combination Caveats

While these novel drug combinations show promise, they also present challenges. Just as two drugs may benefit patients more than either one alone, they may also result in additional side effects.

“We are learning that there can be synergistic toxicities,” says Sara Tolaney, MD, MPH, a breast oncologist at the Susan F. Smith Center who is also involved in the Early Drug Development Center at DF/BWCC. “We need to figure out which patients will benefit, and prevent patients who are not going to respond to the treatment from getting toxicities with no gain.”

Gregory, for instance, has found a good match. After just eight weeks on the drugs, a twice-daily set of pills, her tumor shrank by 57 percent and the side effects have been tolerable. Dr. Liu lowered Gregory’s dose of cediranib to manage her blood pressure, which had been high and had increased on the drug. The biggest hardship has been the weekly flights to Boston. “You never know how your body is going to respond,” she says. “You plan for all the variables and get an aisle seat in back near the bathroom.”

Gregory has been on the treatment regimen long enough that her check-ups at Dana-Farber are now monthly, rather than weekly, giving her time for one of her favorite activities: attending art fairs.
When Estrogen Goes from Friend to Joe
An essential part of women's reproductive health, the hormone estrogen also fuels the majority of breast cancers. Susan F. Smith Center investigators are exploring new ways of halting such tumors, particularly those that have become metastatic.

For many cancer survivors, the five-year anniversary of finishing treatment is a biological as well as psychological milestone. By that point, the cancer may be so unlikely to return that it can realistically be considered cured. Some survivors treat themselves to a “cancerversary” party to mark the occasion.

For women with the most common form of breast cancer, however, the benchmarks can be somewhat different. Although the vast majority are treated successfully, breast cancers apparently banished from the body can recur – often more than five years after treatment, and often at a location, such as the bones, far from the site of the original tumor.

Preventing this stealth metastasis, and treating it more effectively when it does occur, has become the next frontier in the treatment of this form of breast cancer, known as estrogen receptor-positive (or ER-positive). At the Susan F. Smith Center for Women’s Cancers at Dana-Farber, investigators are leading the attack on the problem – both in developing new agents and testing them in patients.

“Most women with ER-positive breast cancer have an excellent prognosis, especially in the United States and Europe, where there is widespread screening for the disease,” says Harold Burstein, MD, PhD, a breast cancer specialist at the Susan F. Smith Center. “Still, there is a substantial subset of patients who could benefit from innovative therapies. These patients are the center of a renewed research effort.”

A Clear Majority

ER-positive breast cancer is diagnosed in an estimated 175,000 women in the U.S. every year, accounting for about 70 percent of all breast cancer cases. As its name implies, ER-positive breast cancer grows in response to the hormone estrogen. The tumor cells carry receptors for the estrogen molecule: When estrogen docks there, the cells get a signal to grow and divide.

Despite being needed by ER-positive tumor cells, estrogen usually is a most beneficial hormone. It plays a key role in the development of the breasts, regulates the menstrual cycle and reproductive system, helps maintain bones, protects against coronary artery disease, protects nerves from damage, and more.
Treatment for ER-positive breast cancer can include surgery and/or radiation therapy to remove or destroy the tumor, chemotherapy to eliminate remaining tumor cells, and hormonal therapy. Hormonal therapy seeks to deprive tumor cells of estrogen – either by lowering the amount of estrogen in the body or barring estrogen from acting on the cancer cells.

These treatments are compellingly effective, particularly for women with small, newly-formed tumors: Five years later, virtually 100 percent of patients who had small, stage I tumors are alive, according to the American Cancer Society. The five-year survival rate for patients who had stage II tumors (which are still small and confined to the breast) is 93 percent, and, for those with invasive, stage III tumors, 72 percent. For women with metastatic, stage IV disease, the five-year survival rate drops significantly.

**From Five to 10**

The divergence in survival rates for patients with early- and late-stage ER-positive breast cancer has spurred efforts to prevent the cancer from coming back after years of dormancy. One strategy is to extend the period in which patients take anti-estrogen therapies. Clinical studies have shown that extending the duration of treatment beyond five years – and closer to 10 years – can lower the risk of recurrence. Another approach, using drugs that curb estrogen production in the ovaries, can also reduce the recurrence risk in young women with breast cancer.

In a clinical trial co-led by Dana-Farber biostatisticians, investigators found that a combination of tamoxifen and an ovary-suppressing, injectable medication was better than tamoxifen alone in preventing a recurrence of the cancer in women age 35 and younger and in women who had been treated with chemotherapy but remained premenopausal. In both sets of patients, adding an aromatase inhibitor, a drug that blocks the formation of estrogen, decreased recurrence rates even further. (A downside of these ovary-suppressing treatments is that they can cause more menopausal-type symptoms such as hot flashes and night sweats, contribute to sexual dysfunction, and lead to osteoporosis. It remains unclear, however, which premenopausal patients should receive this new treatment approach; the potential benefits need to be weighed against the risks.)

For the thousands of ER-positive breast cancer patients whose cancer recurs at a distant part of the body – and for women first diagnosed with an advanced, metastatic form of the disease – researchers are finding novel ways of bringing the disease to heel.

One area of focus is the estrogen receptor itself. “We’ve worked for a long time to understand why some women with this form of breast cancer respond well to hormone-blocking therapies while others have a relapse of disease,” says Dana-Farber’s Myles Brown, MD, who is leading research in this area. He and Rinaht Jeselsohn, MD, of his lab, recently found that some women who experience a relapse have mutations – structural abnormalities – in the estrogen receptor that allow it to function even when estrogen is absent. “We’ve started looking at drug agents that may be able to overcome this mechanism of resistance to standard therapy,” says Dr. Brown.

Dr. Jeselsohn is looking for other signs of whether – and why – some ER-positive breast cancers are likely to barge past conventional agents. She’s found that tumor cells that underproduce two microRNAs (molecules that prevent certain genes from acting) resist anti-estrogen therapies. She and Dr. Brown recently reported that tumors with certain genetic abnormalities often shrink in response to a long-approved but little-used ER-blocking drug called fulvestrant.

A particularly promising class of drugs for advanced, metastatic ER-positive breast tumors is known as selective estrogen receptor degraders (or SERDs). These work by clamping onto the estrogen receptor and causing it to crumble, blinding tumor cells to estrogen’s cues.
cells to the presence of estrogen. Dr. Brown has studied the drugs’ activity in laboratory cultures of tumor cells, and Dr. Jeselsohn is working with a pharmaceutical company to bring the drugs to patients in clinical trials.

An Added Punch

Even as new drugs are being developed, investigators are exploring whether “piggybacking” existing agents with tamoxifen or aromatase inhibitors can improve results in both early- and late-stage ER-positive cancers. Researchers hope that by attacking multiple vulnerabilities within tumor cells — a dependence on estrogen and on certain growth-related proteins — the cells will succumb more easily than they would with a single agent.

One approach takes advantage of the fact that ER-positive breast cancer cells tend to have an oversupply of cyclin D, a protein that propels the cycle of growth and division. Drugs known as CDK4/6 inhibitors block cyclin D, essentially putting the tumor cells to sleep. Early testing suggests that these drugs, in combination with standard hormone-blocking therapy, can control ER-positive breast cancers twice as long as standard therapy alone.

Susan F. Smith Center researchers are leading clinical trials of CDK4/6 inhibitors in women with early-stage ER-positive breast cancer, as well as those whose cancer has metastasized. Erica Mayer, MD, MPH, directs a clinical trial of palbociclib — a CDK4/6 inhibitor that has already showed promise in controlling metastatic breast cancer — and standard hormonal therapy in women with early-stage disease. In a recently completed phase 1 trial Sara Tolaney, MD, MPH, and colleagues found that the CDK4/6 inhibitor abemaciclib caused tumors to shrink or stop growing in one-third of participants with hormone-receptor-positive metastatic breast cancer.

Another candidate for combination therapy is a class of drugs known as PI3-kinase (or PI3K) inhibitors, which foil a gene pathway that is often overactive in metastatic ER-positive breast cancers. A phase 2 trial led by Ian Krop, MD, PhD, director of clinical research for the Susan F. Smith Center’s Breast Oncology Program, found that adding a PI3K inhibitor to a hormone blocker may restore the blocker’s effectiveness and delay the advance of the disease.

Bringing much of this work full-circle, Dr. Tolaney is running a trial that teams a PI3K inhibitor (either BYL719 or BKM120) with a CDK4/6 inhibitor called LEE011, and an anti-hormone agent for women with metastatic disease. “Discoveries about the basic biology of ER-positive breast tumors have reinvigorated the search for new treatments,” she says. “Some of the agents currently being tested are showing great promise.”
Elizabeth Stover, MD, PhD, and Daniel Stover, MD, have more than a last name in common. Fellows at the Susan F. Smith Center for Women’s Cancers at Dana-Farber, they are physician-scientists who share an interest in women’s cancers. Both were drawn to medical science when they were growing up near Columbus, Ohio — in the same house, with the same parents.

The Stovers have earned many distinctions in their lives, including being the first brother-sister fellows studying at Dana-Farber/Brigham and Women’s Cancer Center [DF/BWCC] at the same time. Elizabeth, who focuses on ovarian cancer, is in her fourth year of the medical oncology training program, while Daniel, who is concentrating on breast cancer, is in his third.
What brought you to Dana-Farber?

Elizabeth: The opportunity to learn from great mentors. Oncologists who trained at DF/BWCC became leaders in patient care and research as well as in administration and policy. And Dana-Farber is at the forefront of research technology.

Daniel: As a pre-eminent cancer center, DF/BWCC is an incredible place to train. Giants in the field make time for me on a weekly basis. And I consider it a bonus to be in the same city and program as my sister.

What is your research focus?

Elizabeth: I’m interested in ovarian cancer, specifically tumor resistance to platinum-based chemotherapy. Many ovarian cancer patients who initially respond well to these therapies eventually develop resistance, which means their cancer continues to grow. I’m looking at this problem from a number of different angles, including laboratory experiments and patient sample analysis.

Daniel: The theme of my research is resistance to therapy in triple-negative breast cancer, which can be the most difficult of all breast cancer subtypes to treat. My goal is to understand why this type of cancer either responds to or resists therapies, so we can develop new, more effective drugs.

Do you collaborate on your research?

Elizabeth: We collaborate informally. Since Dan and I have common interests—doing research that is very clinically focused, and taking advantage of exciting new technologies such as next-generation gene sequencing to apply to clinical problems—we always find that our conversations generate new methods or connections to other researchers. Having those kinds of discussions, particularly with Dan, really enriches and broadens my ideas and experiments.

Daniel: We try to meet regularly to talk about what is happening in our scientific lives, comparing notes and celebrating successes. Even though we do not collaborate directly now, it would be fun in the future.

What challenges lie ahead for physician-scientists launching their careers?

Elizabeth: We now have an amazing array of methods to study patient samples and integrate research with clinical trials and patient care. But funding is an ongoing challenge. Many scientists who are very talented, with very good ideas, are struggling to come up with funds to support their research.

In the absence of funding, a career in the lab isn’t sustainable. That’s why financial support from donors and nonprofit organizations is so important. It enables us to get projects underway that may generate data and further grant funding for years to come.

Clearly you share many key interests. In what ways are you different?

Elizabeth: Dan will have presentations prepared weeks in advance, while I fine-tune text and slides right up until the last minute, even though I’ve been working on it for a while. We also share the challenges of work/life balance. Dan recently got married, and I have two daughters.

Daniel: It’s funny. On paper we look remarkably similar, but to people who know us, we’re pretty different people. Elizabeth carefully considers every element, while I’m a little more big-picture. When you first meet us, she’s more reserved and I’m more outspoken.

What are your interests outside of work?

Elizabeth: I have very little time other than work and parenting. I love spending time with my husband and our two little girls, who are ages 6 and 2. They’re a lot of fun at this age. Dan and I grew up with parents who considered family life very important. I think that was a major factor in shaping who we are today. I want to be able to give that same gift to my own children, and help them to be the best people they can.

Daniel: I love to spend time with my wife, who is doing a fellowship in high-risk obstetrics/gynecology. We like to cook and travel together. I enjoy listening to music, too, and I’m a runner—when there’s no snow on the ground.
Every day, Pat Hastings is in the barn by 5 a.m. As steward of the Hamilton Rare Breeds Foundation in Hartland, Vt., Hastings oversees herds of Poitou donkeys, Choctaw mustangs, Dales ponies, and American Cream draft horses.

She has worked on farms for 35 years, and it’s here, with her horses, that she recovers from treatments for metastatic breast cancer. “Animals and farming are in my blood,” she says.

First diagnosed with inflammatory breast cancer in April 1998, Hastings had a radical mastectomy at a hospital near her home in Vermont. Eleven years later, she felt a lump in the other breast and was diagnosed with HER2-positive breast cancer.

“Breast cancers are classified as HER2-positive if their cells have too many copies of the human epidermal growth factor receptor gene which allows them to grow and divide,” says Nancy Lin, MD, clinical director of Breast Oncology in the Susan F. Smith Center for Women’s Cancers at Dana-Farber, and Hastings’ doctor. The standard treatment is surgery followed by chemotherapy and the targeted breast cancer drug trastuzumab (Herceptin), and also often includes radiation treatment.

After a second mastectomy, Hastings flew south to be with her horses, which she shows up and down the east coast.

She returned to Dana-Farber/Brigham and Women’s Cancer Center (DF/BWCC) eight weeks later to begin treatment. But before she could start, tests revealed that the cancer had spread to her liver. While metastatic breast cancer is generally not curable, treatments can keep the cancer at bay, at least for periods of time. For the next eight months, she received chemotherapy and Herceptin, traveling to and from DF/BWCC in Boston every Monday – a two-hour drive from her home in Vermont.

About a year later, when Hastings began stumbling, an MRI showed that the cancer had spread to her brain stem. She began six weeks of radiation at a facility in Vermont, which shrank the tumors until they were tiny.

“Throughout my treatment, I could still run the farm and show my horses, and that was so important to me,” says Hastings.

The tumors in her liver are gone, and she comes to Boston every three weeks for Herceptin alone. “The antibody, which interferes with the HER2 receptor, gives a better quality of life without the side effects of chemo,” Dr. Lin explains. She adds that since Hastings’ diagnosis, new treatments have come on board for patients with HER2-positive breast cancer, and these will be options for her in the future should she need them.

Hastings’ disease has not become active again – a remarkable response that researchers at Dana-Farber and the Broad Institute of Harvard and MIT are studying, says Dr. Lin.

Back in Vermont, Hastings works on her farm seven days a week. “I don’t even think about it,” she says of her illness. “People who know me say, ‘don’t you have cancer?’ I am so busy caring for the horses that I don’t have time to worry. Dana-Farber gives me the best chance to live a long life.”

On the farm in the early morning, as the sun crests the horizon, Hastings finds comfort in the absolute stillness and solitude. A new day has begun.
Making a Difference

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

The Executive Council is guided by a commitment to eliminating breast and gynecologic cancers through education, advocacy, and fundraising. The council dedicates all funds raised for immediate use to the Susan F. Smith Center in pursuit of ongoing breakthroughs in women’s cancers research. Founded in 2003, the council has to date raised $10.4 million for the Susan F. Smith Center.

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 $135 million over the past 16 years, and almost $14 million in fiscal year 2014 alone. To learn more about how you can strengthen our ongoing work against women’s cancers, contact Emily Horsford at 617-632-8832 or emilyc_horsford@dfci.harvard.edu.

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