

## A Vision for Success

Bridging research and clinical care  
in women's cancers



# SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

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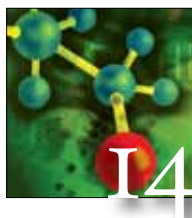
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# Turning Point 2011



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J. Dirk Iglehart, MD

## Susan F. Smith Center for Women's Cancers

By exploring the molecular workings of breast cancer and gynecologic cancers, researchers and clinicians at Dana-Farber Cancer Institute's Susan F. Smith Center for Women's Cancers (SSC) are gaining new insights into the many subtypes of these diseases. Under the leadership of J. Dirk Iglehart, MD, they are also studying how genetic similarities among different cancers can be exploited to develop more effective therapies.

The center's many clinical trials – about 65 are currently

open and a comprehensive list is available at [www.dana-farber.org/clinicaltrials](http://www.dana-farber.org/clinicaltrials) – provide patients with the latest treatments and therapeutic developments. Many trials evaluate treatments prior to surgery and study the vulnerability of a specific cellular process, allowing oncologists to quickly determine the effectiveness of a drug or drug combination and make necessary adjustments.

Critical to the success of this work is tissue from patients. A recent \$5 million pledge from the center's Executive Council has made it possible to significantly expand the center's tissue-banking capabilities. Researchers have established the Tissue Resource for Research (TRR), which includes detailed protocols for the collection and preparation of tissue samples for storage, as well as state-of-the-art storage facilities. The material will be used to uncover cancer-

related gene mutations and identify blood proteins that signal the presence of early cancer.

Physicians and researchers in the SSC expand knowledge of women's cancers through their own research and close collaborations with colleagues at Harvard Medical School and other leading institutions around the world.

Dana-Farber is a founding member of the Translational Breast Cancer Research Consortium, comprised of scientists from 16 academic medical centers nationwide. The consortium started as a center-funded meeting of clinical researchers from across the country.

"The center hosts several clinical and research meetings each year," says Dr. Iglehart. "Our faculty also present at and participate in leading national and international conferences to further the exchange of discoveries."



Andrea Richardson, MD, PhD

Andrea Richardson, MD, PhD, is a physician-researcher in the laboratory of J. Dirk Iglehart, MD. She studies the biology of breast cancer and directs the Women's

Cancers Program Tissue Bank at Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC).

Last year, Dr. Richardson, working with Zhigang (Charles) Wang, MD, PhD, identified genes that cause drug resistance in some cancer cells, a finding that could lead to the development of more individually tailored therapies.

Dr. Richardson is also on a Stand Up To Cancer research team whose current focus is on developing PI3K inhibitors.

“ Dana-Farber is a founding member of

the Translational Breast Cancer Research

Consortium, comprised of scientists from

16 academic medical centers nationwide.”



Eric Winer, MD

## Susan F. Smith Center for Women's Cancers Breast Cancer Program

Research into improving the effectiveness of therapies for breast cancer continues at a rapid pace in the Breast Cancer Program. More than 40 clinical trials for breast cancer are taking place at Dana-Farber or our affiliated institutions. Researchers are working to develop new agents for drug-resistant cancers, identify additional subtypes of tumors that respond to targeted treatments, uncover the biochemical signs of a tumor's aggressiveness and vulnerability to therapy, and devise new approaches to cancer prevention and supportive care.

Susan F. Smith Center for Women's Cancers (SSC) investigators are tackling cancer on multiple fronts, including triple-negative breast cancers (so called because they lack estrogen, progesterone, and human epidermal growth factor receptors that are known to fuel most breast cancers), HER2-positive breast tumors that have become resistant to trastuzumab (Herceptin), and metastatic breast cancers.

Promising laboratory research by Dana-Farber scientists has implicated a microRNA molecule called miR-182 as a source of decreased expression of a protein made from the *BRCA1* gene in women who develop breast cancer without inheriting a susceptibility to the disease. (MicroRNAs are tiny jots of RNA whose role in gene expression has recently begun to be unraveled by scientists.)

This finding builds on earlier research into the link between reduced *BRCA1* expression and breast cancer. Several Dana-Farber researchers are conducting clinical trials of new drugs called PARP inhibitors in women whose breast cancer arose from an inherited mutation in *BRCA1* (as well as in patients with triple-negative breast cancers). The theory is that cells with poorly or non-functioning *BRCA1* repair proteins will become dependent on another DNA repair pathway involving an enzyme called poly (ADP-ribose) polymerase – or PARP. The combined loss of *BRCA1* and PARP (via inhibitors) leaves cancer cells too damaged to survive.

In clinical trials, PARP inhibitors have shown promise in breast cancer patients with inherited *BRCA1* mutations, leading researchers to open new trials of the drugs to patients without an inherited susceptibility to the disease. (For more on the promise of PARP inhibitors, see the story on page 17.)

SSC investigators are also continuing research into the safety and effectiveness of shutting down or blocking a protein called PI3 kinase which early research has shown can lead to cancer cell death.

Investigators have widened their focus from a concern with cancer cells themselves to a consideration of the interactions of tumor cells with surrounding, healthy tissue. SSC researchers have shown that the ability of tumor cells to disrupt the normal development of milk duct cells enables the tumor cells to escape the ducts and travel to other parts of the body; that is, to metastasize. Specifically, there are several studies of drugs that may act against breast tumor cells that have spread to the brain, a particularly challenging site.



Kathryn Ruddy, MD

Breast cancer clinician and researcher Kathryn Ruddy, MD, focuses on the development and treatment of breast cancer in young women, the genetic variation among these cancers, and survivorship care. She joined the Susan F. Smith Center for Women's Cancers in 2010.

Her current research deals with endocrine and hormonal therapies, a long-term breast cancer study, and cancer survivorship, among other subjects. Dr. Ruddy also studies and treats male breast cancer. She sees patients in Dana-Farber's Yawkey Center for Cancer Care and at Dana-Farber/Brigham and Women's Cancer Center at Faulkner Hospital.



Ursula Matulonis, MD

## Susan F. Smith Center for Women’s Cancers Gynecologic Cancers Program

Sometimes it is not what you see on the surface that matters, but what lies underneath. In the case of gynecological cancers – including those of the ovary, cervix, uterus, and vulva – physician-scientists in the Susan F. Smith Center for Women’s Cancers (SSC) at Dana-Farber are delving deeper into the genetic underpinnings of these challenging diseases to find the mutations responsible for them. With this knowledge will come more targeted therapies and better patient outcomes, they believe.

Ovarian cancer, for instance, had traditionally been split into four different histological subtypes for study: serous, clear cell, endometrioid, and mucinous tumors. Now, however, Dana-Farber researchers are breaking them down still further – into high- and low-grade serous tumors, for example – to better understand the specific mutations that cause cancer cells to survive and thrive.

“The more that we can molecularly interrogate ovarian cancers and other gynecological cancers – endometrial and cervix cancer – the better we’re going to be able to not just elect for therapies, but also choose therapies for specific patients and specific tumors,” says Ursula Matulonis,



Larissa Lee, MD

Larissa Lee, MD, a radiation oncologist at Dana-Farber, joined the gynecological oncology program at the Susan F. Smith Center for Women’s Cancers in 2010. She specializes in image-guided brachytherapy, in which she uses three-dimensional visualization to precisely locate, and place radioactive “seeds” within, tumors in the body.

MD, medical director of gynecologic oncology for the SSC.

It has been known for some time that women with mutations in their *BRCA1* and *BRCA2* genes have an increased likelihood of developing ovarian and breast cancer. Phase I and Phase II clinical trials are underway at Dana-Farber using new drugs called PARP inhibitors on ovarian cancer patients, and Dr. Matulonis says that for some women with high-grade serous tumors and *BRCA* mutations, the response rates have been higher than would be expected from traditional chemotherapy. She says this is “very encouraging,” and the PARP inhibitors are now being tested on patients with high-grade serous tumors who do *not* have *BRCA* mutations in hopes of similar results. (See the

related story on page 17.)

In addition, there are several clinical trials underway looking at more targeted therapies for patients with recurrent endometrial cancer. A cellular signaling network known as PI3 kinase has been found to be abnormally active in this and other women’s cancers; using PI3-kinase inhibitors, SSC physician-scientists are seeking to block the overactive PI3-kinase network.

“Women’s cancers don’t have one specific mutation you can hang your hat on like lung cancer,” says Dr. Matulonis. “They have a lot of mutations, and just because we find one it doesn’t mean a drug that targets that mutation is going to work. We need to learn more and figure the true predictors for drug response.”



Judy Garber, MD

## Susan F. Smith Center for Women's Cancers Center for Cancer Genetics and Prevention

The Center for Cancer Genetics and Prevention (CGP) is on the leading edge of cancer prevention, using the newest and most sophisticated genetic tests to help people assess and manage their risk for developing the disease. But staff members go beyond simply providing test results. They offer patients and their families personal genetic counseling, screening evaluations, and strategies to reduce cancer risk.

"It's one thing to talk with people about their risk of developing cancer, and it's another to try to help them deal with it," says Judy Garber, MD, MPH, director of the center. "We don't just conduct an assessment. We follow these patients. We help them manage their lifestyle. We care for them, and for their families."

In 2010, the center and its Friends of Dana-Farber Cancer Genetics and Prevention Clinic helped around 1,200 patients and family members. The clinic offers its services not just on Dana-Farber's main campus in the Longwood Medical Area, but also at Dana-Farber satellite centers throughout the region, including Milford, Mass., South Weymouth, Mass., Londonderry, N.H., and Boston's Jamaica Plain neighborhood.

The clinic works to help women better understand their risk of developing ovarian and breast cancer, as well as associated prevention and treatment strategies. While all women have some risk, women with a family history of breast cancer in close relatives younger than age 50 have a greater probability of developing one or both diseases over their lifetimes.

About 10 percent of breast cancers are hereditary, and women who carry mutations in either of two genes, *BRCA1* or *BRCA2*, have a lifetime risk between 55 percent to 85 percent of developing breast cancers, and a similar risk of developing ovarian cancer. Staff members tailor strategies to help these women adopt a healthier lifestyle and potentially ward off cancers before they materialize.

Research is also a key component of the center, where multiple studies are under way to examine methods to reduce breast cancer in higher-risk women and explore the complex psychosocial issues related to genetic testing and harboring a susceptibility gene. Findings from one large study suggest that PARP inhibitors could form the basis of effective prevention strategies for women with inherited breast cancer risk. Additional research is focused on the potential use of PARP inhibitors against advanced ovarian cancer. Dr. Garber and others at the center are also working with Dana-Farber colleague Jennifer Ligibel, MD, to examine the effects of exercise on reducing cancer risk.

Dr. Garber says she can envision a day when a breast cancer gene test will screen for a larger percentage of diseases, help identify at-risk women, and guide cancer prevention strategies. Dr. Garber says, "This is true of heart disease already, and, in many ways, it's what we hope for in cancer."



Susan Moody, MD, PhD

2008 Friends of Dana-Farber Cancer Institute Fellow Susan Moody, MD, PhD, joins the Susan F. Smith Center for Women's Cancers in the summer of 2011.

Dr. Moody is studying gene expression and suppression with the goal of developing targeted and less toxic therapies. She is working to identify weak points in cancer cells, which may serve as useful opportunities for future therapies.



J. Dirk Iglehart, MD

## Susan F. Smith Center for Women’s Cancers Basic Science

Vulnerability, or the belief that all cancer cells have at least one weakness, is a concept embraced by many in the cancer research community. This theory holds that you can beat cancer by finding the molecular Achilles’ heel of particular cancer cells and designing drugs that interfere with this particularly vulnerable spot. Increasingly, Dana-Farber scientists are focusing on the complex interactions of genes and proteins that enable specific types of tumor cells to proliferate and sometimes spread to other areas of the body.

While researchers have identified several molecular weak spots in breast cancer that can be targeted with therapy – the best known are the estrogen receptor and a protein known as HER-2/neu – the search has more recently gotten under way in cervical cancer. Alexi Wright, MD, of the Susan F. Smith Center for Women’s Cancers, for example, has undertaken an intensive hunt for mutated genes in stored samples of cervical cancer tissue. (See the story on page 8).

The article on page 14 traces scientific advances in women’s cancers over the past decade, looking at the impact that basic research discoveries are already having on the treatment of those cancers. This is just the beginning of what we expect will be an era in which treatments will be tailored to the specific malfunctioning genes and proteins in each patient’s tumor, promising more effective control of cancer with fewer complications.

From discoveries of the mechanisms of DNA repair and drug resistance, to the search for biomarkers that aid in early detection of malignancies, to an increased understanding of gene mutations that raise the risk of developing cancer, research from the center continues to advance our understanding of the fundamental processes within cancer cells, leading us toward more effective and less toxic treatments for breast and gynecologic cancer patients.



Nikhil Wagle, MD

Medical oncologist Nikhil Wagle, MD, joins the Susan F. Smith Center for Women’s Cancers in the summer of 2011.

Dr. Wagle is studying the susceptibility of cancer cells to chemotherapy. He and other researchers are also working on ways to improve the diagnosis and management of colorectal cancer, using “biomarkers” of the disease’s progress and response to treatment.

Dr. Wagle also is a volunteer and member of the board for Doctors of America, a non-profit organization that advocates for health care reform to ensure medical services are available to all.

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Vulnerability, or the belief that all cancer cells have at least one weakness,

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is a concept embraced by many in the cancer research community.

# Ask the Care Team



## I have a family history of ovarian cancer and I'm worried about developing it myself. Should I have a prophylactic (preventive) oophorectomy?

A prophylactic oophorectomy, the surgical removal of one or both ovaries, is usually reserved for women who are at high risk of developing ovarian cancer. To be considered high-risk, you must have a *BRCA1* or *BRCA2* gene mutation (both genes have a known link to breast and ovarian cancer) or a strong family history of ovarian cancer. For these high-risk

women, having an oophorectomy can significantly reduce the possibility of developing breast and/or ovarian cancer.

That said, the decision to undergo an oophorectomy should not be made lightly. Ovary removal reduces amounts of estrogen and progesterone, hormones in the body that women's cancers need to grow, which also results in early meno-

pause. Early menopause carries additional risks including osteoporosis and increased chance of heart disease. And, once the ovaries are removed, a woman will not produce any more eggs and therefore can no longer have children naturally.

To make sure you make the right decision for you, consult with your gynecologic oncologist and a genetic counselor.

## What percentage of women's cancers have a genetic component? Am I more at risk if there is a history of breast cancer on my mother's side or my father's side?

Based on what we know today, about 5 percent of all cancers, including women's cancers, result from an inherited predisposition to cancer. That means the majority occur independent of a family history and instead are likely a result of environmental or behavioral risk factors.

With new research constantly under way, leaders in Dana-Farber's Center for Cancer Genetics and Prevention believe there are many more cancer genes still to be identified. These discoveries could help researchers understand why some families are more prone to certain cancers, which would lead to better screening or other prevention methods.

If you are concerned that cancer runs in your family, the signs that suggest a hereditary link include:

- Multiple cancers within a family
- Cancers occurring at an early age (before the age of 50)
- Multiple cancers in the same person
- Male breast cancer

There is no evidence to show that a history of breast cancer on a mother's side versus a father's side is more significant when it comes to determining cancer risk. When a parent



has genetic predisposition to breast or ovarian cancer, each child has a 50-50 chance that the cancer predisposition will be passed along to him or her, according to the National Cancer Institute. It is significant to note, not everyone with a predisposition will develop cancer.

It is important to visit your doctor to get regular Pap smears and mammograms, and to know your family history so you and your doctor can determine a proper screening plan and access your true risk.

# A ‘STEPP’ Toward Personalized Medicine

Using a powerful new statistical tool, biostatistician Richard Gelber, PhD, and his colleagues say they can find statistical patterns within clinical trial outcomes that predict how different groups of patients will respond to drugs.

Gelber, a member of Dana-Farber’s Department of Biostatistics and Computational Biology, explained that the analytical tool helped researchers determine which patients with early breast cancer would do better with various combinations of estrogen-blocking compounds.

“It is a methodology that allows you to extrapolate from one-size-fits-all to a more reasoned, personalized approach in deciding what treatments to choose,” says Gelber.

The approach, called STEPP (Subpopulation Treatment Effect Pattern Plot) is an alternative to the widely-used technique of subgroup analysis, which evaluates drug responses for specific subsets of patients within the overall

study group. Such analysis might suggest, for example, that subgroups of patients whose tumors expressed particular levels of a protein “biomarker” in their blood or urine benefited more than other patients.

However, the range of biomarker values in each of the subsets is arbitrary. For instance, all patients with biomarker levels from 1 to 10 might be in one subgroup; 11 to 20 in another, 21 to 30 in another, and so on. A STEPP analysis, by contrast, has the power to examine the pattern of responses to treatment in terms of a continually varying factor, such as increasing amounts of the biomarker, rather than merely in arbitrarily defined “buckets.”

Gelber says the STEPP method is more informative and yields better predictions of response based on biomarkers. “You’re less likely to be misled by wrongly interpreting the outcome data,” he says.

Gelber described a new study in

which STEPP analysis proved valuable in determining which postmenopausal women with early breast cancer would benefit the most from tamoxifen, an aromatase inhibitor (letrozole, or brand name Femara), or a combination of the two given in different sequences. The STEPP was applied to the previously reported findings of a large international clinical study involving more than 8,000 patients.

The main finding of that study was that women who took letrozole did better than those who took only tamoxifen. The STEPP analysis allowed the researchers to weigh the benefits and side-effect profiles of the different treatment options as a function of the patients’ initial risk of cancer recurrence.

“This STEPP analysis clarified which patients might benefit the most from letrozole, and which obtain sufficient benefit from tamoxifen,” Gelber says.

## Solving a Puzzle in *BRCA1*-caused Breast Cancers

Women who carry a mutant *BRCA1* gene are at high risk of developing aggressive breast cancers. Most of the tumors are “ER-negative,” meaning they aren’t driven by the estrogen hormone and thus don’t respond to estrogen-blocking agents.

But about 20 percent of breast cancers in *BRCA1* carriers are ER-positive. Research by Susan F. Smith Center for Women’s Cancers scientist Daniel Silver, MD, PhD, is exploring this puzzling minority.

“We were wondering about these ER-positive tumors,” says Dr. Silver, “Where do they come from? Are they caused by the mutant *BRCA1* gene, or are they sporadic, meaning they just happen to develop in a *BRCA1* carrier but aren’t related to the mutation?”

The latter explanation seemed unlikely after a recent study found that the ER-positive tumors in *BRCA1* carriers differed from those that developed in women without the *BRCA1*

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*BRCA1* is a human gene that belongs to a class of genes known as tumor suppressor genes.

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mutation. Among other things, the tumors associated with *BRCA1* mutations were more aggressive.

In the current study, Silver’s team found that ER-positive and ER-negative tumors in mutation carriers shared similarities. Both tumor types arose from *BRCA1*-deficient cells. This is important clinically, says Silver, because “it is likely that the ER-positive cancers will benefit from some of the new therapies used to treat ER-negative tumors in these patients.” These include platinum-based chemotherapeutic agents and new targeted drugs known as PARP inhibitors. (See “PARP Inhibitors on Trial,” on page 17.)

# Seeking Genetic Culprits in Cervical Cancer

Cervical cancer is down but not out. The cancer, which is caused by the sexually transmitted Human Papilloma Virus (HPV), is still diagnosed in some 12,000 women annually in the United States. But deaths from the disease – once the leading cancer killer of American women – plummeted by 70 percent between 1955 and 1992, the result of earlier diagnosis thanks largely to Pap smears, and the development in recent years of a preventive vaccine for certain types of HPV.

Still, in advanced cervical cancer that has recurred, treatment options remain limited. Using the powerful tools of genomic research, Alexi Wright, MD, a gynecologic oncologist in Dana-Farber's Susan F. Smith Center for Women's Cancers, has begun probing the relatively unknown cellular territory of cervical cancer, hunting for new opportunities to block the mutated gene pathways driving the cancer.

"We want to get a better understanding of the mutations, and find those that can be drugged. In the long term, we hope to help these women," says Dr. Wright, adding that many cervical cancer patients are only in their 30s and 40s.

Dr. Wright, with funding from the Friends of Dana-Farber Cancer Institute and a private donor, has launched a systematic search for cervical cancer mutations in stored patient tissue samples.

The study will make use of cervical cancer specimens from 100 consenting patients treated at Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) over the past decade. To sift the DNA of cancer cells for mutated oncogenes or tumor-suppressor genes, the scientists will use a system called OncoMap, developed by scientists in Dana-Farber's Center for Cancer Genome Discovery.

The OncoMap search will look for molecular opportunities such as cell-cycle and cell-growth regulators that behave differently in the cancer cells. The scientists will then determine which are potentially responsive to drugs, leading to clinical trials of specifically targeted agents. Ursula Matulonis, MD, medical director of gynecologic oncology at the Susan F. Smith Center for Women's Cancers, and Michelle Hirsch, MD, PhD, genitourinary pathologist at Brigham and Women's Hospital, will provide additional expertise and mentorship.

# Blocking the Path to Cancer Growth



Dana-Farber's Yawkey Center for Cancer Care features the Gene Display Connector (above), a visual representation of the genetic underpinnings of cancer.

The story of HER2 is well known. This growth factor receptor molecule is overactive in many breast cancers and is the target of Herceptin (trastuzumab), a drug that has contributed to major improvements in the treatment of those advanced cancers. A genetic test identifies tumors in women that are HER2-positive and good candidates for therapy with trastuzumab.

HER2 is also overexpressed in a very small number of ovarian cancers but its genetic cousin, HER3, has been estimated to be abnormal in 25 to 30 percent of ovarian tumors, says Joyce Liu, MD.

Building on promising results in animal studies, Dr. Liu is now working to test the effectiveness of a new HER3-

inhibitor, MM-121, in a clinical trial. In 2010, Dr. Liu and colleagues showed that the drug, which turns down activity in the HER3 signaling pathway, slowed the growth of ovarian tumors in mice. In the current trial, women with breast and ovarian cancer whose tumors have become treatment-resistant are receiving the MM-121 antibody in combination with taxol chemotherapy.

Dr. Liu and her colleagues are also hunting for biomarkers that could be made into a test, helping identify which patients might benefit most from the treatment. In addition, she says, "our lab is investigating which molecular partners are involved with HER3 function and might contribute to the development of ovarian cancer."



Judy Garber, MD, MPH, leads Dana-Farber's Center for Cancer Genetics and Prevention.

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Since establishing its grant program in 1993, AACR has awarded nearly \$111 million to support 290 deserving research projects.

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## Dr. Garber Takes AACR Lead

Dana-Farber's Judy Garber, MD, MPH, recently began her year-long leadership role as president of the American Association for Cancer Research (AACR), the world's largest and oldest scientific organization dedicated to cancer.

Founded in 1907, the AACR's membership includes 30,000 researchers, health care professionals, cancer survivors, and advocates from around the world.

"I am excited to have the opportunity to work with the talented and committed AACR membership to sustain the momentum going forward, and to help attract the most talented young minds to cancer research," says Dr. Garber, who directs the Center for Cancer Genetics and Prevention. "We are in a period of extraordinary scientific progress in cancer research and exciting translation of that knowledge

to benefit patients."

Dr. Garber has held numerous other leadership positions with the AACR and is the recipient of numerous awards, including the Claire W. and Richard P. Morse Research Award and the Tisch Family Outstanding Achievement Award, both from Dana-Farber, and the Statesman Award from the American Society of Clinical Oncology.

She is an elected member of the American Society for Clinical Investigation, a member of the scientific advisory board of the Breast Cancer Research Foundation, and a member of the scientific advisory council of Susan G. Komen for the Cure.

A member of Dana-Farber's faculty since 1988, Dr. Garber is also a professor of medicine at Harvard Medical School. Her research focuses primarily on breast cancer risk assessment and risk reduction.

## Executive Council Spurs Tissue-banking Effort

In 2010, the Susan F. Smith Center for Women's Cancers Executive Council announced a \$5 million initiative that will significantly expand the center's tissue-banking capabilities. The commitment will fund the creation of the Tissue Resource for Research (TRR), a state-of-the-art bank to collect and store tissues that will be used for vital research into breast and gynecologic cancers.

"The TRR will help us stay true to a key part of Dana-Farber's mission, which is to ensure that discoveries made in the laboratory are quickly translated into clinical applications that can help patients," says J. Dirk Iglehart, MD, director of the Susan F. Smith Center for Women's Cancers. "Through this effort, we'll be able to collect a diverse range of tissue samples that will be readily available to cancer investigators. It will help accelerate discovery in women's cancers."

Staff members working in the TRR will work to collect malignant and non-malignant samples from consenting patients with breast or gynecologic cancers, and use those



The Tissue Resource for Research (TRR) in the Susan F. Smith Center for Women's Cancers will be a state-of-the-art tissue bank for breast and gynecologic cancers.

samples to identify gene mutations and proteins, and examine genetic profiles.

The TRR will be closely integrated with Dana-Farber's Clinical Research Information System, a powerful software application that can collect, store, and access clinical, treatment, and outcomes data. Through this system, the tissue resources collected and maintained in the TRR will be fully linked to all patient data, providing a powerful tool for researchers.



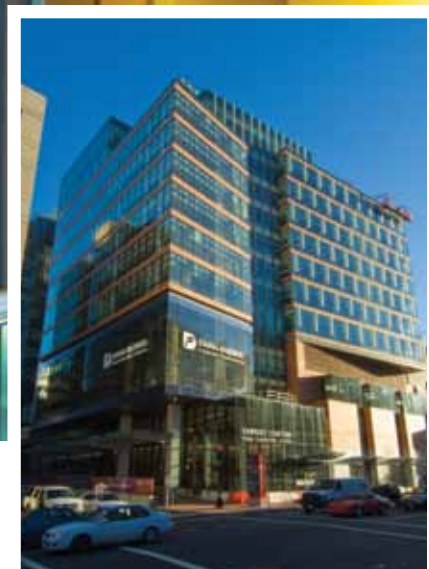
# A New Center, An Ongoing Mission

by Robert Levy

The Susan F. Smith Center for Women's Cancers began with an insight into the nature of cancer – and of human psychology. Researchers were discovering that cancers of the breast and female reproductive tract were more closely related at a basic biological level than had been thought. It was also clear that women's cancers – wherever they originate – unite patients in a kind of sisterhood of shared concern and experience.

**B**ringing research and clinical programs in all women's cancers under a single umbrella would, it was thought, create a natural alliance for better care and smarter science. That goal proved well-founded. Since its creation in 1993 as a research collaborative,

the center has expanded its scientific portfolio multiple times, producing scientific advances that continue to shape the course of patient care. Since 1996, when the center's clinical service opened, its physicians have cared for tens of thousands of patients – more than 10,000 in 2010 alone.



The original impetus for the center came in a meeting between David Livingston, MD, and Dana-Farber Trustee Susan F. Smith in 1993, in which Dr. Livingston suggested combining the Institute's then-separate breast and gynecologic cancer programs. This somewhat unorthodox notion – of a center dedicated to studying and treating all women's cancers – captured Mrs. Smith's imagination. Her determination, and that of many others, to make it a reality has been a constant force behind the center's growth.

"Dr. Livingston explained there was a great deal of research being done in breast and other women's cancers that would benefit from more coordination and collaboration among scientists," Mrs. Smith recounts. "The best way to create a strategic direction for women's cancers at Dana-Farber was to bring together all this research and the clinical care it supports."

In 1993, Mrs. Smith formed a National Advisory Council of leaders in health, education, philanthropy, and the news media to make recommendations on the program's structure and composition. In 2001, Dana-Farber's Board of Trustees established a Visiting Committee which serves as a liaison between women's cancer specialists and the community at large. The committee informs scientists and physicians about the public's major interests and questions concerning cancer care for women, and spreads the word about recent advances at Dana-Farber, while helping raise funds for research. Its leader since its founding has been Mrs. Smith, joined by trustee Jane Jamieson as co-chair in 2008.

From left: Ian Krop, MD, PhD, Kornelia Polyak, MD, PhD, and Eric Winer, MD, meet in one of the bridges that connect Dana-Farber's new Yawkey Center for Cancer Care (inset) with the adjoining Richard A. and Susan F. Smith Laboratories building.

The committee has sparked a range of innovations. One of the most far-reaching was the development of an Executive Council, which has mobilized thousands of women in Greater Boston to learn about and support research into women's health and women's cancers at Dana-Farber.

### All Together Now

The all-in-one philosophy is visible in the physical structure and layout of the new Susan F. Smith Center (SSC), in its scientists' ability to garner major research grants, and in the direction of research itself.

The center's clinical areas occupy adjacent floors of the newly opened Yawkey Center for Cancer Care on Dana-Farber's Longwood Medical Area campus. Patients with breast cancer are treated on the 9th floor, and women with gynecological cancers on the 10th.

Designed with broad input from patients, the clinical floors

“

*We're creating a tissue bank – called the Tissue Resource for Research gynecologic tumor samples. It will streamline our process and spur, we communication and creative interchange among our scientists.*”

of the SSC resemble the other treatment areas in the Yawkey Center, an indication of how fully a center for all women's cancer patients – something non-existent or novel at other cancer centers – has been integrated into Dana-Farber's concept of care.

The attention to detail is visible as soon as one steps off the elevator. Shoulder-high, wood-and-etched-glass partitions divide the waiting area into a variety of spaces – some large and open, some more secluded. Nooks with easy chairs and floor lamps create an almost living-room feel. Paneled walls hung with artwork – still-lives and landscapes, primarily, in a variety of media – meet a bank of picture windows with views of the surrounding area. A pantry holds drinks and snacks.

The new Susan Smith Center, as with the entire Yawkey Center, was designed to increase the opportunities for scientific collaboration. SSC physicians and scientists don't have to travel far to meet: an enclosed bridge furnished with chairs, tables and a small café station connects clinical units with corresponding research facilities in the Richard A. and Susan F. Smith Research Laboratories next door. The proximity promotes translational research that converts scientific advances into new treatments.

### Meetings of the Minds

The SSC's research initiatives have expanded in unison with its clinical growth. In 2000 and 2005, center scientists led by J. Dirk Iglehart, MD, secured Specialized Program of Research Excellence (SPORE) grants in breast and ovarian cancer research, which support precisely the kind of inter-disciplinary, collaborative work that the SSC was created to enable. SSC scientists are also recipients of a much-sought-after Stand Up to Cancer grant to study gene pathways linked to several types of women's cancers. Several are participating in a large program project grant to study the biology of mammary epithelial cells, the cells where most breast cancers originate.

The grouping of scientists who specialize in breast cancer with those who focus on gynecologic cancers foreshadowed a host of later discoveries about the basic biology of tumors. Scientists have found that cancers once thought to be radically different because they arose in different tissues and organs harbor surprising similarities at the molecular level.

“It's become increasingly apparent that many of these diseases share a great many molecular features,” says J. Dirk Iglehart, MD, director of the Susan

Smith Center. “One example is PI3 kinase, a protein involved in a pathway that is frequently altered in both breast and gynecologic cancers.” As cancers come to be identified by their genetic signatures as well as by their tissue of origin, more precisely honed therapies will be possible.

### Beyond the Walls

A key element of the center's growth has been its outreach to medically underserved groups in Greater Boston. Center clinicians have visited the Suffolk County Jail, elderly housing facilities, community centers, police stations, and other sites to teach women about health issues and the importance of early cancer detection and treatment.

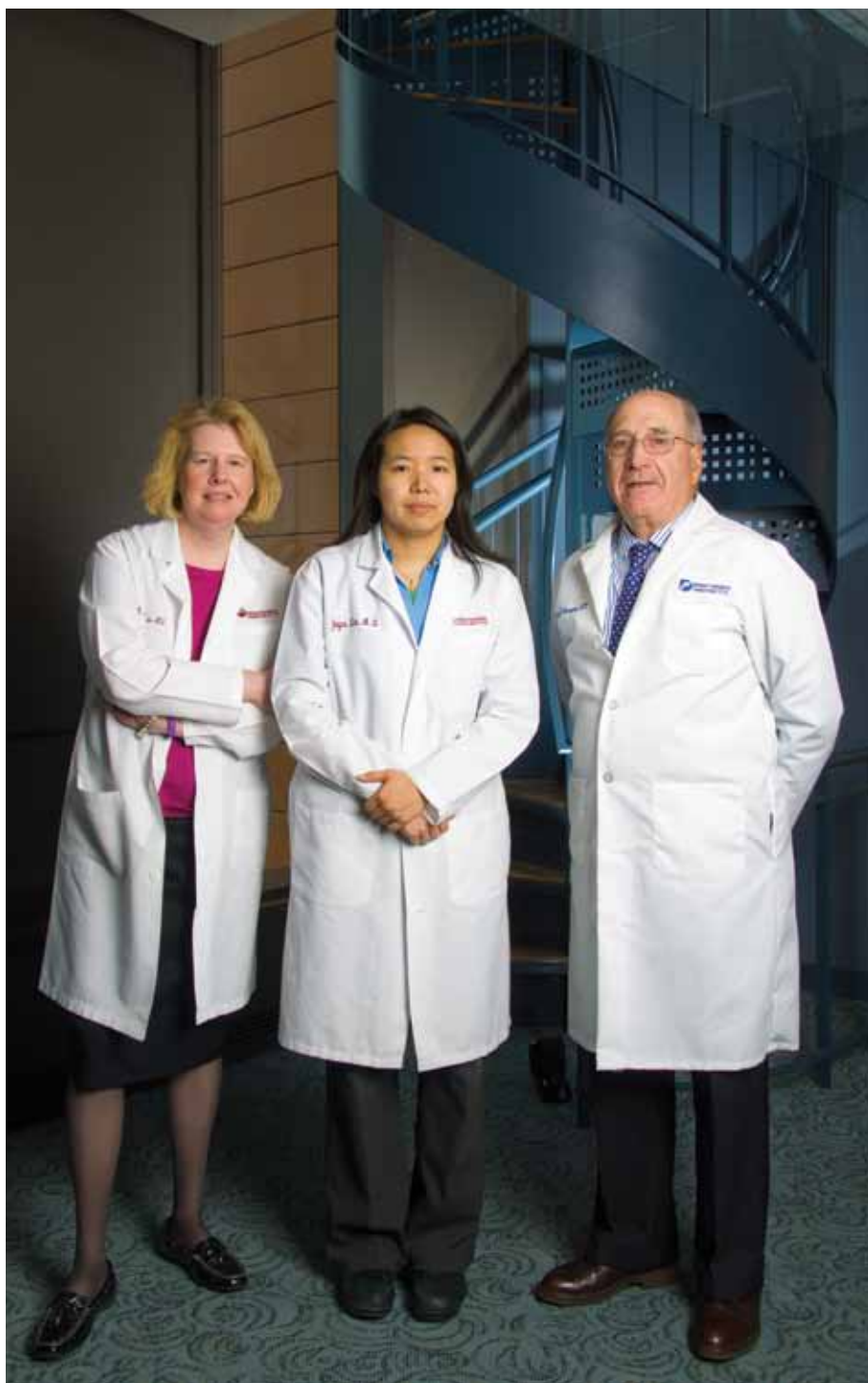
The increase in patient visits to the center is mirrored in the expansion of the clinical staff. When Eric Winer, MD, director of the Breast Oncology Center, arrived at Dana-Farber in 1997, there were five medical oncologists specializing in breast cancer. Now there are more than 20. Six years ago, when Ursula Matulonis, MD, became director of gynecologic oncology, she was one of just three physicians focusing solely on ovarian cancer. She recently hired two physician/scientists whose specialty is ovarian cancer

*– for both breast and  
think, a great deal of*

treatment and research. Over the past decade, the number of breast cancer surgeons has risen from three to 10, the number of breast cancer pathologists, from two to five, and the number of gynecologic pathologists from one to four.

As the size of the clinical and scientific team has increased, so have the opportunities for people in different specialties to work together. “The extent of cross-disciplinary research we’re able to do has risen dramatically,” Dr. Iglehart remarks. “We’re creating a tissue bank – called the Tissue Resource for Research – for both breast and gynecologic tumor samples. It will streamline our process and spur, we think, a great deal of communication and creative interchange among our scientists.”

That determination to create ways for people to work together has always been the center’s hallmark, Mrs. Smith says. “I look back with pride at what we’ve accomplished, not only in the research area, but also in the compassion with which we’ve treated patients. I look forward to and hope for more and deeper collaboration between the research and clinical faculty to translate scientific findings into better and more effective treatments for patients.” **TP**



From left: Ursula Matulonis, MD, Joyce Liu, MD, and David Livingston, MD, from the Susan F. Smith Center for Women’s Cancers, on one of the bridges that link Dana-Farber’s Yawkey Center for Cancer Care with research areas in the Richard A. and Susan F. Smith Laboratories building.



# Progress Made, Challenges Ahead

by Robert Levy

**m**ore evolution than revolution, the advance of science and medicine doesn't fall into neat chapters and stages. But in the annals of women's cancers research, the year 2000 marks a rough dividing line between an old era and a new.

With technology that was barely on the drawing board 20 years ago, scientists over the past decade have uncovered errors in DNA that can send cells on a spree of unfettered growth and division. They've come to understand tumors not only by their similarities, but also by their most fundamental differences – the particular set of abnormal genes and proteins within them. And they've begun developing therapies against the genes that make tumors tick.

“As recently as the mid-1990s, breast cancer was viewed as, essentially, one disease, with a standard course of treatment. Then came a series of research advances between 2000 and 2002 that revealed several subtypes of breast cancer, each with its own genetic signature, or collection of cancer-related genes,” says J. Dirk Iglehart, MD, director of the Susan F. Smith Center for Women's Cancers (SSC). “At every phase of this research, from genetically analyzing tumor tissue to exploring practical applications of the findings, Dana-Farber scientists were active participants.”

In ovarian and other gynecologic cancers, the trend toward identifying additional subtypes has been equally prominent, if a bit slower to develop. Researchers' curiosity has been piqued by discoveries of abnormal genes within some of these tumors; the challenge now is to determine if these genes affect the course of the disease, and if they make tumors vulnerable to specific drugs.

### Diving Into the Genome

It's fair to say that genomic research – which surveys genes in the entire expanse of human chromosomes – has

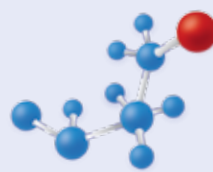
had a greater impact on breast cancer treatment than on any other solid tumor.

“By 2002, it was clear that, with non-inherited breast cancer, we're dealing with at least four separate diseases, known as ER-positive, ER-negative, HER2-positive, and triple-negative,” Dr. Iglehart remarks. (ER-positive tumor cells produce receptors for growth-promoting estrogen and progesterone molecules; ER-negative cells do not; HER2-positive cells carry an overabundance of receptors known as Her2/neu; and triple-negative cancer cells lack estrogen, progesterone, and Her2/neu receptors.)

Although the estrogen receptor was identified in the 1970s and the Her2/neu receptor in the 1980s, the strategy of treating the four types of breast cancer with specially-matched thera-

This break with the past is almost palpable for Dr. Iglehart. “I remember when it was considered improper to treat HER2-positive breast cancers differently than other types,” he remarks. “There was a concern that if they were treated differently, patients might do worse than with standard treatment. Research has brought us to the point where we can improve the outlook for many women based on their specific variety of tumor.”

As recently as the year 2000, breast cancer treatment almost always involved chemotherapy (as well as surgery and/or radiation therapy). Today, for ER- and HER2-negative tumors – which account for about 70 percent of all breast cancers – the use of chemotherapy has increasingly been called into question and for many it is “more of an option than a



*“Serous, endometrioid, clear-cell, and mucinous: they're all ovarian cancers, yet each one behaves differently and entails different treatments.”*

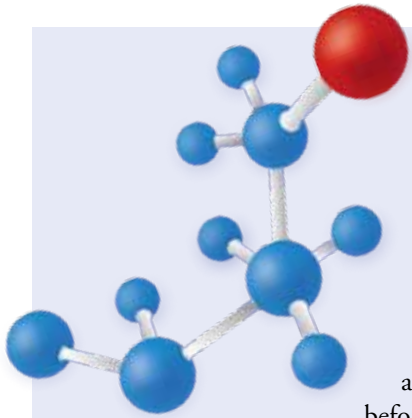
pies truly took hold in the mid-2000s. Some milestones along the way were the development of the ER-inhibiting drug tamoxifen in the 1980s, and the introduction of Herceptin, which blocks the gene responsible for HER2-positive breast cancers, in the 1990s. If the era of targeted therapy in cancer can be said to have an official starting point, federal approval of tamoxifen for use in patients would be it.

“The identification of various subtypes has made it possible to test new treatments within these groups, rather than across them, and to study therapies in patients for whom they were specifically designed,” Dr. Iglehart states. “The breast cancer care we offer today is personalized to the molecular features of a tumor, as well as the stage of disease, the patient's overall health, and other factors.”

requirement,” says Eric Winer, MD, director of the Breast Oncology Center at Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC).

“The ability to distinguish between different genetic varieties of breast cancer has led to more refined treatments, reducing the use of therapies that are less likely to be effective – an important consideration for patients' quality of life,” Dr. Winer remarks. The improvements in drug therapy have been mirrored in radiation therapy and surgery, where doctors can better determine which patients are likely to benefit from which form of treatment, and can deliver treatment more precisely.

The result of these advances is most clearly seen in the setting of HER2-positive breast cancer. “Eighty-five percent



of women with HER-positive stage II/III breast cancers are alive and free of cancer four to five years later,” Dr. Winer says, “and those with metastatic cancer are living longer and better than before. Ten years ago, HER2-positive

breast cancer was one of the least treatable forms of the disease, now it’s one of the most.”

## Screening Questions

The past decade has also seen important advances in breast cancer prevention and early detection, remarks David Livingston, MD, director of Dana-Farber’s program in Human Genetics and deputy director of the Dana-Farber/Harvard Cancer Center. Research published in 2002 showed that standard doses of estrogen supplements – once taken by millions of women to ease the symptoms of menopause – were linked to higher rates of breast cancer, as well as heart disease and stroke.

The finding changed the treatment of menopausal symptoms almost overnight, with many women opting for alternate approaches. In the next few years, long-term studies now underway at SSC and elsewhere will show whether the decreased use of estrogen replacement therapy is generating lower death rates from breast cancer, Dr. Livingston says.

Guidelines for mammography screening also underwent a significant, and highly contentious, adjustment in the 2000s. There was tremendous controversy regarding at what age women should start having mammograms for breast cancer detection. What was not controversial was the fact that mammograms reduce breast cancer deaths.

Research breakthroughs at the molecular level promise even greater gains. One of the most far-reaching of these was a discovery involving the chromosome repair function of the *BRCA1* and *BRCA2*, genes best known for raising breast and ovarian cancer risk when either is inherited in a flawed form.

“*BRCA1* and *2* become activated when both strands of the DNA helix are broken,” says Dr. Livingston, whose research was pivotal in revealing the genes’ role in DNA repair. “An enzyme known as PARP helps to protect the cells against breakage in just one strand. If PARP were blocked by a drug, a single-strand break is more likely to become a double-strand break. If a double-strand break occurs in a cancer cell with nonfunctioning *BRCA1* or *2*, the chromosome break cannot be normally repaired. A cell’s likelihood of surviving this kind of disruption is not good.” Research on PARP-inhibiting drugs for women with breast or ovarian cancer linked to inherited *BRCA1* or *2* mutations is progressing.

In gynecologic cancers, as in breast cancer, advances in classifying tumors are yielding better ways to treat them. “In

ovarian cancer, for example, we’ve improved our understanding of different subtypes based on their histology – the structure of their cells,” says Ursula Matulonis, MD, director of Gynecologic Oncology at DF/BWCC. “Serous, endometrioid, clear-cell, and mucinous: they’re all ovarian cancers, yet each one behaves differently and entails different treatments.”

Increasingly, these histological groupings are being complemented by molecular research. “We generally categorize serous ovarian cancers as either high-grade [aggressive, fast-growing] or low-grade,” Matulonis remarks. “Many high-grade tumors carry *BRCA1* mutations, and low-grade tumors often have mutations in the gene *BRAF*. Mucinous ovarian tumors have a high rate of mutations in *KRAS*, and some clear-cell tumors have PI3 kinase mutations. We now test tumors for mutations in all these genes, and, if they test positive, patients can enroll in clinical trials of targeted drugs.”


Abnormalities in proteins that interact with PI3 kinase can also contribute to endometrial cancer, which originates in the lining of the uterus. Patients are currently participating in clinical trials of drugs directed at this pathway. Cases of endometrial tumors are rising more quickly than any other women’s cancer, partly because some forms of the disease are associated with obesity, which is increasing in the U.S. at alarming rates. A significant advance in treating such tumors has been the introduction of robot-assisted surgery, which enables doctors to remove growths that otherwise would have been inaccessible in highly obese patients.

## Only the Start

For all the progress made against women’s cancers, its greatest value may be the foundation it creates for future advances, experts say. The next 10 years will see the development of more precisely targeted drugs. To support that work, SSC investigators are creating a bank of breast and gynecologic tumor tissue and building new databases to analyze genomic research results.

One of the chief reasons for optimism is the influx of scientific talent, experts say. “Scientists who might never have considered working on breast and gynecologic cancers are now doing so, with an eye toward linking basic discovery to future avenues of prevention and treatment,” Dr. Livingston says.

The newcomers are motivated not only by a desire to emulate the gains made so far, but also by the magnitude of the scientific problem that women’s cancers represents and by the number of people they affect. “We need to understand why breast and gynecologic cancers are so prevalent,” Dr. Livingston says. “The more we understand the environmental, behavioral, genomic, and other molecular roots of these diseases, the better we can intervene to prevent and treat them.” **TP**



# PARP Inhibitors on Trial

*What are the real promises and limitations of a new class of cancer drugs?*

In the tiny and turbulent world of the cell, the double-stranded DNA that runs the cell's control program is constantly breaking. Cells have about half a dozen ways to combat their DNA damage — and if these self-repair jobs fail badly enough, cells die.

For decades, chemotherapies have bludgeoned away at this potential weakness in tumor cells, trying to destroy the cancer as it attempts to grow unchecked. But a new class of agents called PARP inhibitors offers a much more targeted attack on tumors whose self-repair is already under fire.

To date, the leading indications for these new drugs are tumors that develop in patients with mutations in the *BRCA1* or *BRCA2* genes, which dramatically heighten a woman's risk of breast or ovarian cancer.

"DNA repair pathways are very promising targets for therapy, particularly so for *BRCA*-related and triple-negative breast cancer and *BRCA*-related ovarian cancer," says J. Dirk Iglehart, MD, director of the Susan F. Smith Center for Women's Cancers. "We are hopeful that PARP inhibitors will become an important addition to the treatment of those cancers."

## Wrecking Tumor Self-repair

PARP, which stands for "poly (ADP-ribose) polymerase," is a family of enzymes found throughout the body. PARP is needed for a form of DNA repair known as break excision repair, which fixes glitches in one strand of DNA.

In 2003, work at Sheffield University in England showed that cells lacking PARP activity switch over to another repair mechanism that can fix breaks in both strands of DNA and is known as homologous recombination.

It so happens that the *BRCA1* and *BRCA2* genes are linchpins for this repair activity. If both copies of one *BRCA* gene are mutated in a tumor cell, the cell loses the ability to fix itself by homologous recombination. *BRCA*-related tumors thus must fall back on other ways to repair their DNA. But, in theory, if both *BRCA* and PARP mechanisms are broken, the cell dies.

Dr. Iglehart likens the situation to a pair of suspenders. “If your pants are held up by two suspenders, but one suspender is missing as it is in the tumor cell, all I have to do is cut one suspender and the pants fall down,” he says. “But all the other cells still have another suspender.”

“This could be a very elegant way to utilize a defect in DNA repair without inflicting the same amount of damage to normal cells, because normal cells aren’t defective in this compensating repair pathway,” adds Daniel Silver, MD, PhD, a physician-scientist in Dana-Farber’s Breast Oncology Center.

Dr. Silver points out that this approach taps a concept in molecular biology called synthetic lethality, “a relationship between two genes, in which cells are perfectly happy if they’re missing either one of the genes, but the cell dies if you have mutations in both genes,” he says. “One of the reasons that PARP inhibitors have garnered a lot of attention is that they are really the first fruits of this idea of synthetic lethality to enter the clinic.”

### Fighting Inherited *BRCA*-related Cancers

Pharmaceutical companies already had agents that inhibit PARP, developed with other applications in mind, on their shelves. In tests in human cells and in mice by Dana-Farber and other institutions, the drugs proved effective in killing *BRCA*-related tumors. Next came clinical studies.

Judy Garber, MD, MPH, director of the Center for Cancer Genetics and Prevention at Dana-Farber, led the Institute’s effort in an early trial of AstraZeneca’s PARP inhibitor olaparib for women with *BRCA*-related metastatic breast cancer. Rather than examining a tumor biopsy, “we had to do a blood test and find out if they had a mutation,” she notes.

The trial results were quite positive. “In the trial, more than 40 percent of women had a measurable response to the PARP inhibitor alone, even though most of the women had needed a number of previous treatments, which can make their tumors resistant to new treatments,” says Dr. Garber. “We did learn that the drug is not as selective as we had hoped. There are some side effects on normal cells, though most were manageable.”

Results from this investigation, and other early studies of *BRCA*-related breast and ovarian cancers at Dana-Farber and elsewhere, then raised a clear question: If PARP inhibitors worked well by themselves, would

they work better in combination with other cancer drugs?

Cisplatin, a conventional “platinum-based” chemotherapy agent that causes double-stranded breaks in DNA, was a likely candidate to make PARP inhibitors more effective. One study looked at the effect of combining cisplatin with olaparib in treating women with inherited *BRCA*-related breast cancer. It has been challenging to find the right combination of doses to maximize efficacy and simultaneously minimize side effects.

Another study will examine a preventive role for PARP inhibitors. The study, called the PIONEER Trial, will enroll healthy women with a *BRCA* mutation who are planning to have prophylactic mastectomies. Patients will receive veliparib, a PARP inhibitor from Abbott Laboratories, for a month before surgery. Researchers will then examine the breast tissue that was removed, to look for early changes that are consistent with a preventive effect.

“I don’t envision women taking a PARP inhibitor every day all their lives to prevent breast (and ovarian) cancers, because it doesn’t seem wise to turn off DNA repair altogether,” Dr. Garber adds. “But it might be safe and effective to take a PARP inhibitor for short times – say, a month each year – to eliminate early cancer cells before a tumor can get started.”

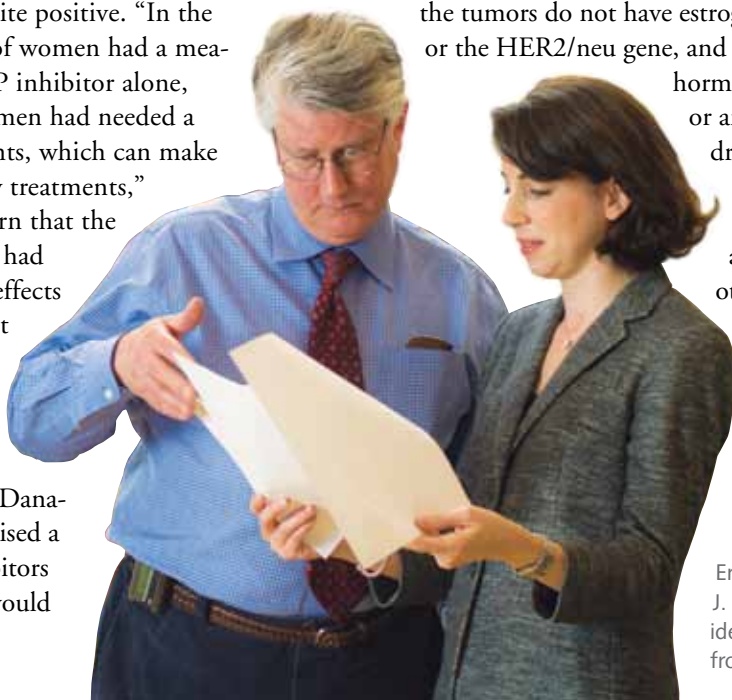
She points out, however, that one limitation for PARP inhibitors is the relatively small population of women with *BRCA* mutations, making pharmaceutical firms reluctant to invest heavily in drug development.

### Attacking Triple-Negative Breast Cancer

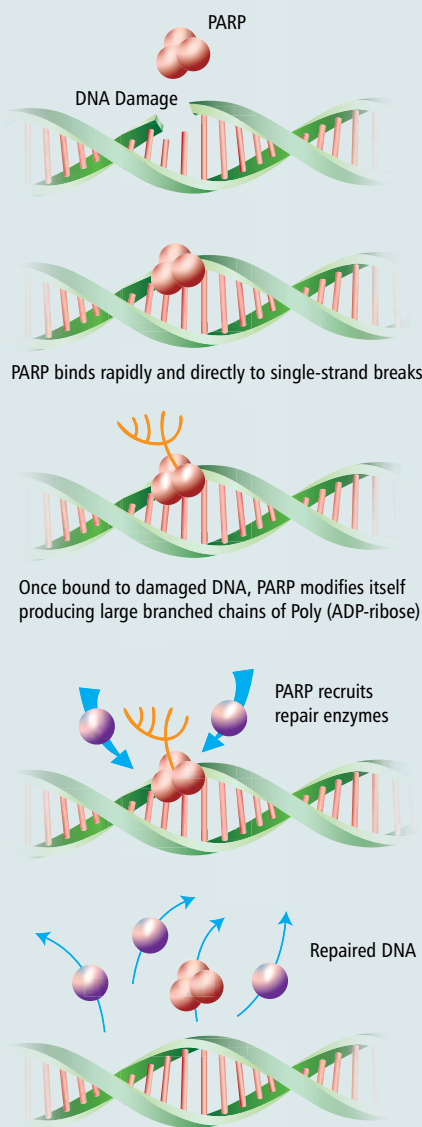
Most *BRCA*-related breast cancers are triple-negative. This difficult-to-treat group makes up about 10-15 percent of all breast cancers. (The disease is called triple-negative because the tumors do not have estrogen or progesterone receptors or the HER2/neu gene, and therefore are not sensitive to hormonal treatments like tamoxifen or aromatase inhibitors, or to the drug herceptin.)

Triple-negative cancers show very high levels of DNA damage, Dr. Iglehart’s lab and many others have found. Those triple-negative tumors that lack an inherited *BRCA* mutation also look much like those that do show such a mutation. “These tumors tend to be high-grade, have similar growth patterns

Erica Mayer, MD, MPH, (right) and J. Dirk Iglehart, MD, are working to identify which patients might benefit from treatment with PARP inhibitors.



## PARP Acts to Repair Broken DNA



When a strand of DNA is damaged within a cell, an enzyme known as PARP orders repairs to begin. Drugs that block PARP have been shown to kill tumor cells in which a backup repair system also is broken. Breakdowns in that second pathway are found in breast and ovarian cancers caused by inherited mutations in the genes *BRCA1* or *BRCA2*, as well as in some tumors with nonhereditary *BRCA* mutations.

under the microscope, and have similar patterns of gene activation,” notes Dr. Silver. “So a number of us were wondering whether they had similar defects in DNA repair.”

Even before PARP inhibitors appeared, researchers led trials that treated women with triple-negative cancer with cisplatin or other conventional DNA-repair-damaging drugs. Many researchers hoped that PARP inhibitors would heighten the effect on the cancer.

In some early trials, the hopes appeared to be realistic. One small study that drew much attention in 2009 examined the effects of a PARP inhibitor called iniparib, made by Sanofi-aventis subsidiary BiPar Sciences. When added to a treatment with carboplatin and gemcitabine (another conventional chemotherapy agent) for women with metastatic triple-negative breast cancer, iniparib significantly improved survival compared to treatment with carboplatin and gemcitabine alone.

But in January 2011, Sanofi-aventis released preliminary information from a Phase 3 trial of the same combination. While full data won't be available until June, “the results from the Sanofi trial are disappointing,” says Eric Winer, MD, director of the Breast Oncology Center, in Dana-Farber's Susan F. Smith Center for Women's Cancers. “The treatment improved clinical outcomes to a limited extent, but not enough to lead to a drug approval. In the end, it probably makes chemotherapy work better in a small group of patients, but we don't yet know how to identify them.”

“We'll have to work harder to find out who are the right patients for these agents,” comments Erica Mayer, MD, MPH, a medical oncologist in the Breast Oncology Center who leads clinical studies in triple negative breast cancer. “This will involve even closer

collaboration with our laboratory-based colleagues.

“Figuring out how to treat triple negative breast cancer is just not that simple,” she adds. “Even something that looks like a home run may turn out to be a ground-rule double.”

How the trial results apply to other PARP inhibitors also is not yet clear, especially since iniparib is very different from all the other PARP inhibitors that are currently in testing.

More generally, “DNA repair is kind of an Achilles heel to attack *BRCA1*- and *BRCA2*-related tumors,” Dr. Silver adds. “But the bad news is that the Achilles heel has its own Achilles heel.” Studies in *BRCA*-mutated breast cancer cells and in platinum-based drugs in *BRCA*-related tumors suggest that additional mutations may restore DNA repair, he explains.

### Putting PARP in Perspective

“It is clear that women who have advanced disease and take these drugs are not cured by them,” says Dr. Garber. “But there are reasons to be very hopeful that we will make them an important part of therapy, at least for certain groups.”

In addition to their potential roles in breast cancer, “these agents are quite promising for treating *BRCA*-associated inherited ovarian cancer,” notes Dr. Winer. “They also appear to work in sporadic ovarian cancer, which may share many of the features of inherited ovarian cancer.

“While some of the clinical studies have been disappointing, and the preliminary results are not what we had hoped for, PARP inhibitors are a promising class of drugs for some of the most difficult-to-treat cancers,” he sums up. “They certainly merit intensive research.” **TP**

# Exploring New Terrain

When she describes living with breast cancer for the last five years, Kathy Bennett repeats a story a friend told her.

Dreaming of gondolas, coliseums, and Michelangelo, the story's character had long planned a journey to Italy. When at last she departed, the plane landed and the pilot announced: "Our flight was re-routed. Welcome to Holland." The character had to reset her expectations and navigate different terrain than she had planned. Eventually she adjusted, began to notice fields of brilliant tulips, and realized that Holland had its own appeal.

"This is what having cancer can be like," explains Bennett.

After being diagnosed in 2006, Bennett sought a second opinion from Eric Winer, MD, in the Susan F. Smith Center for Women's Cancers. Bennett chose him as her doctor, and since then, she and her partner, Sharon Hanson, have been living a life they did not plan for.

Breast cancer can be complicated. She underwent surgery, chemotherapy, hormone therapy, and radiation treatments for a cancer that was stage 3 (spread beyond the breast). In

addition, her cancer was HER2-positive, which means extra copies of the *HER2* gene caused certain breast cells to grow and divide too quickly.

"I had every treatment there was to offer," Bennett recalls. "I began to regain my confidence, energy, and stride." Then, in 2008, she learned that the cancer had spread to her liver and, in 2010, a small lesion was found in her brain – which was treated with a targeted type of radiation. Bennett reluctantly left her job as a physician at Upham's Corner Health Center in Dorchester, Mass., where she'd worked for 22 years.

Since January 2010, Bennett has been on a targeted, experimental therapy known as T-DM1, in which an antibody combines with chemotherapy to reach the receptors on the cells of the HER2-positive breast cancer, explains Jennifer McKenna, NP, her nurse practitioner.

Five years after her diagnosis, Bennett is balancing her sense of gratitude with the fatigue that accompanies living with cancer for so long. She says it is not easy to hold the notion of living, and dying, in the same pair of hands. "You can build your life around one or the other. I choose to focus on living," she says, adding that she sought support from a DF/BWCC social worker while Hanson found camaraderie and courage in a support group for caregivers.

"Kathy has an amazing spirit and strong support from Sharon," says McKenna. "Whatever life throws at them, they face together. Our mutual goals are for Kathy to live as long as she can, with the best possible quality of life."

The couple continues to do the things they can do, such as gathering with neighbors in Boston's South End, starting the day with a song, or recognizing the importance of humor. "When Kathy and Sharon and I meet, we laugh the whole time," says McKenna. One night, Hanson recalls, Bennett couldn't sleep because of a side effect of one of her medications, so they cleaned the house together at 4 a.m., laughing all the way.

"We don't have all the answers," says Hanson. "We have to figure this out as we go, and find our own truth." Yet, like the traveler in Holland, this couple has discovered that an unfamiliar landscape can be dotted with exquisite beauty.



Kathy Bennett (at right) consults with Jennifer McKenna, NP.

# Finding Courage to Speak Out

**D**ebbie First says that when she had ovarian cancer in 1977, the word “cancer” was rarely said out loud.

“I did not want to believe I had cancer, and most people didn’t want to hear about it,” she recalls. “It was too frightening. Talking about the type of cancer I had would be like saying I might die.”

Instead, she said she had a tumor on her ovary or that she had a teratoma, the name for the rare cancer she had.

First, a public relations and marketing professional, says that when she was diagnosed in 1977, her own personal style, combined with the climate of the times, kept her from speaking openly. Even though her husband and small group of friends formed an informal group to listen to her whenever she needed it, First recalls, “My ability to deny took over. Maybe if I didn’t say cancer, I didn’t have it.”

Last fall, she spoke publicly about her cancer for the first time at an event sponsored by Dana-Farber Cancer Institute’s Susan F. Smith Center for Women’s Cancers.

First described being a mother of three and a successful public relations and marketing executive living in Weston, Mass., when, in her 30s, she was found to have a malignant mass on one ovary. At the time, there was no precedent for treating her cancer, and she called it a miracle that she found Dana-Farber physician David Livingston, MD, who recommended a treatment protocol based on one that had been effective in treating testicular cancer in men under age 25. She had a full hysterectomy and 13 months of chemotherapy at Dana-Farber and was sick from the treatments. When she went to work, people assumed she had breast cancer because that was the only women’s cancer anyone knew about.

“The only name I associated with ovarian cancer was comedienne Gilda Radner, and she died,” she told the audience.

First also explained how she built her strength

back by walking and hitting tennis balls with her husband, Bob. She also began cycling and eventually in 1995 rode the 192-mile Pan Massachusetts Challenge with him, wearing an “I am Living Proof” pin. She crossed the finish line holding his hand high, tears streaming down her face.

Her involvement in Dana-Farber’s Susan F. Smith Center for Women’s Cancers helped her open up to herself and to others. Her decision to speak publicly grew out of her realization that a generation of younger people don’t know about the strides made in treating cancer and a new climate that welcomes patients talking openly about it.

“Telling my story of surviving ovarian cancer offers hope,” she says. “Today, there is no reason not to talk about it. There are many good stories, and more coming.”



Photo: Aaron Washington

Debbie First (second from right), with her husband, Bob, and their two daughters, Liz (left) and Pam.

Dana-Farber Cancer Institute  
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A teaching affiliate of  
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 **NCI** DANA-FARBER/HARVARD CANCER CENTER  
**CCC** A Comprehensive Cancer Center  
Designated by the National Cancer Institute

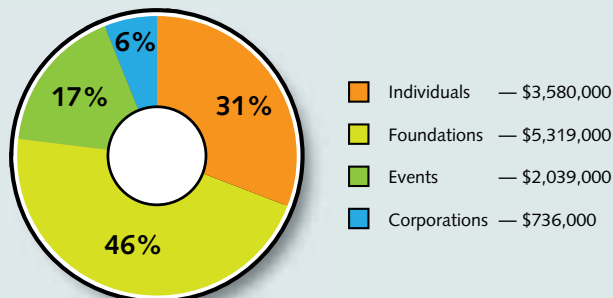
# Making a Difference



## Donating Funds

Through the generous support of donors, Dana-Farber's Susan F. Smith Center for Women's Cancers has raised more than \$83 million over the past 12 years, and \$11.7 million in fiscal year 2010 alone.

To learn more about how you can support our ongoing work against women's cancers, call Danielle Reddy at 617-582-8832 or email [danielle\\_reddy@dfci.harvard.edu](mailto:danielle_reddy@dfci.harvard.edu).



The American Cancer Society estimates that in 2009 more than a quarter million women were diagnosed with breast or gynecological cancers; more than 68,000 lost their lives to these diseases. Thanks to the vision and generosity of our donors, Dana-Farber continues to offer women diagnosed with cancer the best in care while pursuing research that will lead to more effective and less toxic treatments. Our scientists continue to make progress on many fronts in their ongoing battle against these complex diseases. There are many ways in which patients, families, and friends can contribute as well.

## Gifts that Save Lives

Donating blood or platelets can help a diverse range of patients at Dana-Farber/Brigham and Women's Cancer Center. For information on how to donate, visit [www.dana-farber.org/blooddonation](http://www.dana-farber.org/blooddonation). For information on donating platelets, call Dana-Farber's Kraft Family Blood Donor Center at 617-632-3206. To donate blood, call the Blood Donor Center at Brigham and Women's Hospital at 617-732-6620.

To learn more about becoming a potential stem cell donor, visit [www.dana-farber.org/nmdp](http://www.dana-farber.org/nmdp) or call Dana-Farber's National Marrow Donor Program Donor Recruitment office at 617-632-2561 or 866-875-3324.



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