Surgical Choices for Young Women

Genomic Research Holds the Key

Immunotherapy Brings One-Two Punch
TURNING POINT 2016

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About the cover
Ovarian cancer patient benefits from latest research. See page 23.
When J. Dirk Iglehart, MD, came to Dana-Farber in 1999 to direct its new women’s cancers program, the concept of a multidisciplinary center for the treatment and study of breast and gynecological cancers was still in its early stages.

Now, as he steps down from his role as director, the Susan F. Smith Center for Women’s Cancers at Dana-Farber is creating powerful possibilities as a worldwide destination for a growing number of patients. It has become a hub of innovative research and a training ground for future leaders.

Dr. Iglehart will retain his surgical and research roles until December. With his transition, Ursula Matulonis, MD, now serves as interim director of the Susan F. Smith Center, while remaining medical director of Gynecologic Oncology. Having worked with Dr. Iglehart for many years and understanding...
the value of caring for patients with breast or gynecologic cancers in the same center, she shares his commitment to an integrated approach.

Under Dr. Iglehart, the Susan F. Smith Center secured its first Specialized Program of Research Excellence (SPORE) in breast cancer, which brought five years of funding from the National Cancer Institute and was later renewed for an additional five years. Research in the SPORE laid the groundwork for additional grants, including a large award from the Department of Defense, a Stand Up 2 Cancer grant, and the current SPORE, which was awarded in 2013. Dr. Iglehart also led work that helped investigators gain new insight into the genetic similarities between triple-negative breast cancer and high-grade serous ovarian cancer – findings he hopes may unlock critical secrets behind both diseases.

“I am proud of what we’ve done here,” says Dr. Iglehart. “I’m very encouraged that the work we began will go on.”

While he was director of the Breast Cancer Program within Dana-Farber/Harvard Cancer Center, Dr. Iglehart and colleagues launched the first women’s cancers symposium in 2004, an annual meeting that gathers top clinicians and researchers from seven Harvard-affiliated institutions – and beyond – to share ideas and research and build collaborations. He played a pivotal role in initiating the Translational Breast Cancer Research Consortium to foster national collaborations specifically for innovative, high-impact clinical trials for breast cancer.

In recognition of his mentoring and collaborative skills, a lectureship and fellowship were each established with donor generosity. Through the J. Dirk Iglehart, MD, Visiting Scholar Lectureship, the first scholar will address the 2017 Symposium. In addition, a two-year fellowship in Dr. Iglehart’s name will be given to a physician-scientist who demonstrates its namesake’s values of mentorship, education, and sharing of knowledge.

“Dirk is a kind, generous person with a natural ability to see the benefit of collaborations for the greater good,” says Dana-Farber Trustee Susan F. Smith. “He is a highly skilled surgeon and a compassionate physician whose good nature, infinite patience, and unwavering commitment to his trainees made him the ideal mentor and role model – admired by many.”

For Director of Breast Oncology Eric Winer, MD, Iglehart’s longtime colleague at Dana-Farber and, previously, at Duke University Medical Center, the lectureship and fellowship are fitting legacies.

“Dirk is a great surgeon, an insightful and accomplished scientist, and a truly selfless leader, always wanting to credit others rather than himself,” says Dr. Winer. “He leaves a deep legacy as a true practitioner of team science, a tireless bridge-builder, and an inspired mentor.”

**Dr. Winer Appointed to Strategy Role**

Eric Winer, MD, chief of the Division of Women’s Cancers and director of Breast Oncology for the Susan F. Smith Center for Women’s Cancers at Dana-Farber, was recently appointed Chief Clinical Strategy Officer (CCSO) for Dana-Farber as a whole. “Dr. Winer is formalizing and building on the ongoing planning for clinical growth work that has already been done,” said Edward J. Benz Jr., MD, president and CEO, Dana-Farber.

Dr. Winer’s role as CCSO focuses on convening the right stakeholders to develop clinical strategies, including enhancing and leveraging successful partnerships with Brigham and Women’s Hospital and Boston Children’s Hospital. He is also serving as the senior physician leader for key business development-related activities contributing to the growth and innovation of Dana-Farber across all clinical services regionally, nationally, and internationally.
Dr. King Brings Surgical, Research Expertise to Leadership Position

As chief of breast surgery for the Susan F. Smith Center for Women’s Cancers at Dana-Farber/Brigham and Women’s Cancer Center, Tari King, MD, plays a key leadership role in the center’s efforts to provide the best multidisciplinary care to patients – as a surgeon, educator, and researcher investigating the causes and treatments of breast cancer.

Dr. King joined the Susan F. Smith Center in August 2015 after serving as deputy chief and director of research in the breast service at Memorial Sloan Kettering Cancer Center, as well as associate professor of surgery at the Weill Cornell Medical College (both in New York City). She also led an active laboratory-based research program focused on the molecular genetics of breast cancer and tumor progression before coming to Dana-Farber, and is currently heading up a multi-institutional prospective trial investigating the role of surgery in stage IV breast cancer, sponsored by the Translational Breast Cancer Research Consortium.

“Dr. King has extraordinary expertise in breast surgery and a track record of leadership in an academic medical center,” says Eric Winer, MD, director of breast oncology at the Susan F. Smith Center. “Her research interests are expanding our current efforts, and we are delighted to have her leading such an important component of our breast cancer program.”

Dr. Harris Continues Spreading the Word – and Expertise

Since starting his radiation oncology career at Dana-Farber in the 1970s, Jay Harris, MD, has been dedicated to making this therapy less invasive and more effective for breast cancer patients. At the same time, through his involvement with the Susan F. Smith Center for Women’s Cancers at Dana-Farber/Brigham and Women’s Cancer Center, he has helped develop a more multidisciplinary approach to breast and gynecologic cancer care – one in which breast surgery, radiation, systemic therapy, psychosocial support, and other components of patient care can take place in one centralized location.

Dr. Harris, who was succeeded by Daphne Haas-Kogan, MD, as chair of Radiation Oncology at Dana-Farber and Brigham and Women’s Hospital in September 2015 after 18 years, remains on staff at both institutions. He says that during his early years in the field, breast-conserving therapy (lumpectomy followed by radiation) was seen as controversial, and eschewed by many surgeons. Dr. Harris and colleagues proved the benefits of the process through research and clinical trials, and it soon became more commonplace – and, in his opinion, safer – than mastectomies.

Similarly, he recalls that while multidisciplinary care as delivered at the Susan F. Smith Center was seen as “revolutionary” when introduced, patients and clinicians quickly embraced the concept.

“Patients liked hearing their options and seeing all the experts together, and it gave us providers an opportunity to appreciate our colleagues in other specialties,” Dr. Harris recalls.

Today, Dr. Harris is helping new chair Dr. Haas-Kogan as needed while spending the majority of his time on research, teaching, and patient care.
What is the difference between invasive ductal breast cancer and invasive lobular breast cancer?

All breast cancers initially form inside the milk duct, near the area where the duct meets the milk gland, or lobule—a structure called the terminal duct lobular unit. As long as the abnormal cells remain inside the duct they are known as carcinoma in situ. When they break out of the duct and get into the fatty tissue of the breast, they become invasive breast cancers.

Invasive lobular breast cancers (ILCs) and invasive ductal cancers (IDCs) have very different growth patterns. Invasive lobular cancers tend to grow in single-file lines through the fatty tissue of the breast. Invasive ductal cancers, by contrast, tend to form masses that resemble the glandular structures of the breast.

ILC usually doesn’t form a lump. If the cancer is found by lightly pressing the breast, it is more likely to produce a feeling of fullness or thickening in one area that is different from surrounding parts. On a mammogram, ILC often appears as an area of distortion. The diagnosis is confirmed by extracting a small piece of the abnormal tissue with a needle and examining it under a microscope. The majority of ILCs are estrogen receptor-positive (ER-positive), meaning they need the hormone estrogen to grow.

Surgical treatment for invasive breast cancer follows the same approach whether the patient has an invasive lobular or invasive ductal cancer, says Tari King, MD, chief of breast surgery at the Susan F. Smith Center for Women’s Cancers at Dana-Farber/Brigham and Women’s Cancer Center. Depending on the size of the tumor, surgical options may include a lumpectomy (removing just the tumor and a margin of surrounding tissue) or a mastectomy (removing the whole breast). It is also important to determine whether cancer cells have spread from the breast to the lymph nodes under the arm.

Following surgery, treatment may involve radiation therapy to eliminate any remaining microscopic cancer cells at the site of the tumor, and/or chemotherapy to kill cancer cells that may have escaped into the bloodstream of lymph system. For patients with ER-positive tumors, endocrine therapy to reduce the amount of estrogen in the body is also an effective form of treatment, Dr. King says.
What is the latest research in endometrial cancer?

For endometrial cancer, as for virtually every form of cancer, advances in genomics are transforming the understanding and treatment of this disease, which arises in the lining of the uterus or womb.

As part of the Profile research project at Dana-Farber, Brigham and Women’s Hospital, and Boston Children’s Hospital, investigators have scanned hundreds of endometrial tumor samples for genetic abnormalities associated with cancer. As more and more samples are analyzed, scientists are exploring whether endometrial cancer is a fairly uniform disease, or, more likely, whether it comprises several molecular subtypes, each with its own set of genetic flaws.

These efforts have already yielded some valuable insights. Researchers recently found, for example, that the genes ARID1A and POLE are often mutated in endometrial cancers, says Panos Konstantinopoulos, MD, PhD, of the Gynecologic Oncology Program at the Susan F. Smith Center for Women’s Cancers at Dana-Farber.

Studies also have uncovered abnormalities in certain genetic “pathways” – signaling circuits consisting of multiple genes – in some endometrial tumors. These include the PI3K pathway, which is altered in a variety of cancers and is the subject of intense efforts to attack with new drugs, and the mismatch repair (MMR) pathway, which is involved in mending damaged cell DNA. Each abnormality represents a possible weak spot in endometrial cancer’s cellular machinery and a potential target for therapies.

“As this type of research progresses, we hope to move from traditional hormonal treatments to a more personal approach based on the molecular make-up of each patient’s tumor,” Dr. Konstantinopoulos says.

He notes that because endometrial cancer is often detected in its early stages, treatment with surgery, radiation and/or chemotherapy, as well as hormonal therapy, usually cures the disease. When the disease has spread beyond its initial site, the main treatments – chemotherapy and hormonal therapy – often aren’t as successful. For these cases, targeted therapies and, possibly, future immune system-based therapies hold the greatest promise. Research at Dana-Farber has shown, in fact, that endometrial cancers with a defective MMR pathway or POLE mutation appear to be more sensitive to immune system-based therapy.

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.” Help make it possible for basic scientists at the Susan F. Smith Center for Women’s Cancers to find the most effective, targeted treatments that will one day translate to patient care. To learn more or make a donation, contact Suzanne Kouri at 617-632-4055 or suzanne_kouri@dfci.harvard.edu.
A new technique is allowing breast surgeons to perform lumpectomies on non-palpable tumors with less inconvenience to patients.

When a breast tumor cannot be felt (palpated), a surgeon needs a guide to find it in the breast. Traditionally, an imaging specialist places a wire in the breast to the point of the tumor. While the wire provides accurate direction, it can also be problematic, says Tari King, MD, chief of breast surgery at the Susan F. Smith Center for Women's Cancers at Dana-Farber/Brigham and Women’s Cancer Center.

The wire has to be inserted on the morning of surgery, and hours may elapse before the surgery actually begins. Because the wire sticks out from the breast, it must be carefully secured with a bandage to prevent it from becoming dislodged during this waiting period.

In the new technique, the imaging specialist places a small radioactive pellet – or “seed” – in the breast next to the tumor. The seed can be placed up to five days before surgery. Patients do not need to take any special precautions, as the amount of radioactivity in the seed is very low, and patients can arrive at the hospital closer to their scheduled surgery time. Because the seed is nestled entirely within the breast, it doesn’t shift around the way a wire can.

During the operation, the surgeon uses a small Geiger counter to zero in on the seed and remove the tumor and surrounding tissue (including the seed).

“Seed localization offers a number of advantages for removing non-palpable tumors,” says Dr. King. “It allows

Several Dana-Farber researchers have been named to a three-year Dream Team devoted to ovarian cancer. The Dream Team will study therapies involved in DNA repair and was formed by several groups, including Stand Up 2 Cancer (SU2C), Ovarian Cancer Research Fund Alliance, National Ovarian Cancer Coalition, and the American Association for Cancer Research, a scientific partner to SU2C.

Alan D’Andrea, MD, director of Dana-Farber’s Center for DNA Damage and Repair, is co-leading the Dream Team with Elizabeth M. Swisher, MD, professor in the department of Obstetrics and Gynecology at the University of Washington.

By targeting DNA repair pathways, the Dream Team hopes to build and expand on the recent clinical advances seen with the drug olaparib and other PARP inhibitors in current clinical trials. The U.S. Food and Drug Administration last year approved olaparib to treat women with advanced ovarian cancer associated with defective BRCA genes, which are among a number of DNA repair genes identified as mutated in ovarian cancer. The existence of defects in DNA repair has emerged as a common weakness in ovarian cancer.
Improving Sexual Health for Ovarian Cancer Patients

Treatment for ovarian cancer often comes with sexual side effects. Although curing the cancer is the main goal for many patients and their doctors, Sharon Bober, PhD, director of Dana-Farber’s Sexual Health Program, is focused on preserving a patient’s quality of life – including her sexual satisfaction.

Dr. Bober, with co-investigators Alexi Wright, MD, MPH, a medical oncologist in the Gynecologic Oncology Program at the Susan F. Smith Center for Women’s Cancers, and Christopher Recklitis, PhD, MPH, director of research at Dana-Farber’s Perini Family Survivors’ Center, is leading an intervention to address sexual side effects such as pain, discomfort, and loss of libido in women who have been treated for ovarian cancer. Patients – at any point during their treatment – participate in a small-group, half-day workshop to educate them about these issues, while also exploring the psychological impact of changes in sexuality and intimacy.

The program offers relaxation exercises and information to relieve tension and address the mind-body components of intimacy, and includes practical education on how to improve sexual health and manage discomfort. Dr. Bober also discusses the negative way women might talk to themselves about changes in sexuality, and provides strategies for combating these thoughts. Patients leave the first-of-its-kind workshop with an action plan and realistic steps for improving their sexual satisfaction, and afterwards receive phone counseling and questionnaires to assess the intervention’s efficacy.

“This intervention is a powerful collaboration between psychosocial and medical oncology,” says Dr. Bober, principal investigator, who notes preliminary results have been overwhelmingly positive. “It allows us to address quality of life in a holistic, comprehensive way.”

Dr. Bober and her team are also conducting a focus group to assess the feasibility of moving the intervention online and, eventually, expanding to other types of gynecologic cancer.

Learn More
Find out how the Susan F. Smith Center creates powerful possibilities for patients. Visit www.susanfsmith.org to learn about patient care, research, expertise, and the latest advances in women’s cancer care.
Can Aspirin Help Prevent Breast Cancer Recurrence?

Researchers from Dana-Farber and Brigham and Women's Hospital received a $10 million Breakthrough Award from the Department of Defense's Office of the Congressionally Directed Medical Research Program to test whether aspirin helps women with breast cancer avoid recurrence and live longer.

The Aspirin for Breast Cancer (ABC) trial will recruit 3,000 women with stage II and stage III breast cancer through The Alliance for Clinical Trials in Oncology, a network sponsored by the National Cancer Institute. Half of the women in the trial will be randomly assigned to receive aspirin, and half to receive a placebo pill. The trial will start enrolling patients in the summer or fall of 2016.

In previous observational studies, investigators found that breast cancer survivors who were regular aspirin users had a 50 percent lower risk of breast cancer recurrence and death compared to those who did not use aspirin.

“Although chemotherapy and hormonal therapies have helped women with breast cancer live longer, they are expensive and have many side effects,” says Wendy Chen, MD, MPH, a senior physician at the Susan F. Smith Center for Women's Cancers and co-investigator for the study. “Women whose tumors are not sensitive to hormones have limited treatment options. The results of this trial, if positive, could have a huge impact on the disease.”

If proven effective, adding aspirin to current therapies may enhance survival. Outside the U.S., aspirin’s low cost ($6/year) would make it a major aid in developing nations unable to access expensive therapies.

The investigators plan to combine results with a large-scale international trial that is also exploring the role of aspirin in cancer and will allow researchers to analyze whether aspirin’s benefit is specific to certain subtypes of breast cancer.

Eric Winer, MD, director of the Susan F. Smith Center’s Breast Oncology Program, is a partnering principal investigator, along with Michelle Holmes, MD, DrPH, associate professor of medicine and epidemiology in the Channing Division of Network Medicine at Brigham and Women’s Hospital.

Support Clinical Research

Your donation helps make it possible for doctors to test new drugs and drug combinations in patients through clinical trials. To learn more or make a donation, contact Suzanne Kouri at 617-632-4055 or suzanne_kouri@dfci.harvard.edu.
Boston Jewish Population Offered Genetic Testing

Dana-Farber is one of five centers launching a pilot project that will screen individuals for genetic mutations associated with an increased risk of breast, ovarian, and prostate cancer. Aimed at the Ashkenazi Jewish population, whose members have a significantly higher frequency of \textit{BRCA1} and \textit{BRCA2} mutations than the general U.S. population, this vanguard program is intended to reduce cancer risk by providing them with genetic information that can help guide medical decisions. The other centers include Abramson Cancer Center, Beth Israel Deaconess Medical Center, Cedars-Sinai Medical Center, and Memorial Sloan Kettering Cancer Center.

Leading the project in Boston are Judy Garber, MD, MPH, director of Dana-Farber’s Center for Cancer Genetics and Prevention at the Susan F. Smith Center for Women’s Cancers, and Nadine M. Tung, MD, director of the Cancer Risk and Prevention Program at Beth Israel Deaconess Medical Center.

“The Ashkenazi Jewish population in Boston, which includes about 4,000 people, will be among the first to participate,” Dr. Garber explains. “Ultimately, our plan is to expand this screening initiative to a national level, involving millions of people.”

The genetic testing, conducted through blood or saliva samples, will screen women and men for three common \textit{BRCA1} and \textit{BRCA2} mutations, which are present in about 2.5 percent of the Ashkenazi Jewish population, whose roots are in central and eastern Europe. (Like women, men can pass \textit{BRCA} mutations to their daughters.)

Prior to submitting samples, participants will be asked about their family histories and be educated — through videos, printed materials, and website information — about the three possible outcomes of their test:

- If there is no family history of cancer and no mutations are found, participants will know they are not at elevated risk.
- If there is a family history of cancer but no mutations are found, participants will be encouraged to consider more complete genetic testing at a clinical facility.
- If any mutations are found, regardless of family history, participants will be given more detailed information, including recommendations to meet with genetic experts to develop risk-reducing strategies.

Testing is free and all participant information will be kept confidential. Samples can be submitted at Dana-Farber, Beth Israel, and other local sites, including offices of primary care physicians and Quest Diagnostics labs. Tests can also be mailed, using a kit.

“People often do not realize there is a genetic mutation in the family until someone is diagnosed with cancer,” says Dr. Garber. “Our goal is to change that. We want to make people aware of their status so they can avoid cancer rather than cope with it.”
Traditionally, the war on cancer has been waged from the outside in, with therapies such as surgery, radiation, and drugs entering the body from external sources. For more than 100 years, however, a notion has persisted that the most formidable tool against cancer may come from within: the immune system.

The immune system is the body’s defense against disease, but for decades, science’s attempts to use it against cancer have largely fallen short. Today, however, as researchers begin to understand the intricate thrust-and-parry of the immune system’s relationship with cancer, it has become possible to intervene in a way that gives the immune system the upper hand.

The success of a new generation of immune-based therapies has turned skeptics into believers. Melanoma has been driven into long remissions in many patients with an immunotherapy drug first tested by investigators at Dana-Farber. Many cancers, including lung and kidney cancer, have shown themselves vulnerable to immunotherapy agents in Dana-Farber-led clinical trials, as has Hodgkin lymphoma.

Today at the Susan F. Smith Center for Women’s Cancers at Dana-Farber, investigators are testing the mettle of immunotherapy against breast and gynecologic tumors.

Prime Candidates in Gynecologic Cancers

Many new immunotherapy drugs are based on a key insight made by researchers at Dana-Farber and other institutions: Although immune-system cells often recognize cancer cells as dangerous and target them for destruction, many cancer cells carry proteins...
that ward off the immune cells’ attack. Drugs known
as immune checkpoint inhibitors that blunt these
proteins are the new stars of immunotherapy.
There are sound biological reasons for believing
that ovarian and other gynecologic cancers will
prove susceptible to checkpoint inhibitors. Many
such tumors have a high “neoantigen load,” meaning
they carry proteins that advertise their cancerous
nature to the immune system, which can prepare an
attack against them. The right immunotherapy could
provide an opening for an attack to succeed.

Joyce Liu, MD, MPH, combines immunotherapies with other drugs.

Like most cancers, ovarian cancer comes in several
subtypes. The effectiveness of an immunotherapy
agent may depend on which subtype it is used for.
“We’re currently learning how and where immuno-
therapies work best,” says Ursula Matulonis, MD,
interim director of the Susan F. Smith Center and
medical director of Gynecologic Oncology. “Many of
the clinical trials now underway will help us match
immunotherapies to the patients who can most
benefit from them.”

Dr. Matulonis is leading the North American arm
of an international trial of the immunotherapy drug
pembrolizumab in women with recurrent ovarian
cancer. The trial will help determine whether the drug
works best if patients have had few previous treat-
ments or many, and whether it’s more effective against
platinum-sensitive or platinum-resistant tumors.
So far, immunotherapies have scored only modest
success in small, early-stage trials where they’ve
been used as solo treatments for ovarian cancer. As
a result, many of the newer trials combine immuno-
therapies with other types of drugs.

In one study involving patients with ovarian
cancer resistant to platinum chemotherapy, inves-
tigators are teaming the checkpoint-inhibitor drug
duvlumab with bevacizumab, a medication that
chokes off tumor blood supply.
“Research suggests that some of the same signaling
molecules that attract blood vessels to tumors can also
hold back an immune system attack,” says study leader
Joyce Liu, MD, MPH, of the Susan F. Smith Center.
“Blocking these signals with bevacizumab, while also
using a checkpoint inhibitor like nivolumab, may
further enhance the immune system’s ability to attack
the cancer.”

Panos Konstantinopoulos, MD, PhD, has opened a
phase 1 study of the immune checkpoint inhibitor
pembrolizumab and niraparib, a PARP inhibitor that
prevents cancer cells from repairing damaged DNA.
The combination may spur the formation of more
neoantigens, further stimulating an immune response.

Dr. Konstantinopoulos is also leading a trial of
immunotherapy agents for endometrial cancer. The
study will be open to patients whose tumor cells have
“microsatellite instability” and carry a mutation in the
gene POLE. (Microsatellites are short, repeated stretches
of DNA. The number of such stretches can be off-kilter,
or “unstable,” because of DNA repair problems.) “Both
of these conditions can lead to a high neoantigen load,
which can render the cancer cells highly visible to the
immune system,” Dr. Konstantinopoulos says. “Our
study will examine whether immune checkpoint
inhibitors can be effective in this group of patients.”

Exploring Immunotherapies for Breast Cancer

Immunotherapy is already proving to be a prom-
ising approach in breast cancer. “Over the past several
years, our view of immunotherapy for breast cancer
has evolved,” says Eric Winer, MD, director of Breast
Oncology for the Susan F. Smith Center. “Today this
appears to be one of the most promising treatment
approaches, particularly for patients who have the
most aggressive tumors.” Triple-negative breast cancer
(which lacks three key growth receptors) is a prime
target for immunotherapy because it tends to have a relatively high degree of DNA instability and frequently expresses immune-suppressing proteins. Investigators at the Susan F. Smith Center have helped lead a study of immune checkpoint inhibitors in patients with triple-negative breast cancer.

Ian Krop, MD, PhD, director of Breast Clinical Research at the Susan F. Smith Center, was senior investigator for a study showing that the checkpoint inhibitor atezolizumab could prevent the growth of triple-negative cancers for well over a year in some patients. Dr. Winer has led several studies of pembrolizumab, including an ongoing international study that could lead to FDA approval of this drug for triple-negative breast cancer.

While the results from the use of checkpoint inhibitors in triple-negative breast cancer look encouraging, other investigators are exploring the effectiveness of these agents against hormone-driven breast cancers. This is the most common type of breast cancer, but also the least likely to provoke an attack from the immune system.

“The challenge is to intervene in a way that converts a weak immune response in these tumors into a stronger one,” says Sara Tolaney, MD, MPH, who is leading three soon-to-open clinical trials of this approach for women with hormone-sensitive breast cancer. “That will involve combining immunotherapies with other treatments.”

In one phase 2 trial, women will receive chemotherapy and the immune-checkpoint inhibitor pembrolizumab when first diagnosed. “There’s evidence that chemotherapy can make tumors more susceptible to checkpoint inhibitors by activating the immune system,” says Ian Krop, MD, PhD, who is helping run the trial. “This trial will help determine whether the combination of these two drugs is effective in patients.”

A second trial will compare the effect of chemotherapy and pembrolizumab to that of chemotherapy alone in patients with metastatic, hormone-sensitive breast cancer. A third will examine the value of radiation therapy in combination with pembrolizumab in patients with hormone-sensitive breast cancer. The hypothesis here is that radiation leads to cell death, which may stimulate an immune response to the tumor. Still another trial will focus on a tandem of pembrolizumab and T-DM1 (a conjugate drug that fuses chemotherapy with a tumor-targeting antibody) in patients whose breast cancer carries the HER2 protein receptor.

Additional immunotherapy projects will be aided by a recent $1 million gift from the Carney Foundation.

**Tapping the Full Potential**

For all the promise of checkpoint inhibitors, they represent just one of many ways the immune system may be mobilized to fight cancer. As Kai Wucherpfennig, MD, PhD, chair of Dana-Farber’s department of Cancer Immunology and Virology, notes, the immune system consists of an array of specialized cells and proteins, many of which have anti-cancer potential.

“There are many ways to enhance the immune system’s work,” he says. “These include vaccines that increase the number or intensity of disease-fighting T cells; engineering T cells to hunt down specific tumor cells; using viruses to attack tumors; and harnessing natural killer cells. Mobilizing the immune system will be a very important part of how we treat cancer.”
Amanda Skypeck (left) chose a mastectomy, Judy Rosenbaum a lumpectomy.
A growing number of breast cancer patients, particularly young women, are choosing bilateral mastectomy (removal of both breasts) to treat or prevent cancer, even when it is not medically advised. Rates have jumped six-fold between 1998 and 2011, and eleven-fold among women under age 40, according to a recent study in the *Journal of the American Medical Association*.

Why are young women choosing more surgery when less is a viable option? Reasons are beginning to emerge through research led by Ann Partridge, MD, MPH, director of the Program for Young Women with Breast Cancer at the Susan F. Smith Center for Women’s Cancers at Dana-Farber. In surveys, patients report knowing that, statistically, bilateral mastectomy will not improve survival, yet they say they choose it for peace of mind. “They don’t connect the statistics to their own experience,” Dr. Partridge says.

Further research suggests that the disconnect may be related to the anxiety women feel when they receive a breast cancer diagnosis. Study data can be hard to hear when women are laser-focused on doing everything possible to eliminate their cancer and prevent it from coming back.

“Our job is to help women take a step back,” says Tari King, MD, chief of breast surgery at the Susan F. Smith Center. “Sit down, take a deep breath and talk about it. Bilateral mastectomy is not a decision to be made lightly.”

Bilateral mastectomy is major surgery with long-term consequences. The procedure causes a woman to lose sensation in the skin over her chest area. Women may also experience changes in posture or range of arm motion. And, while mastectomy is a safe operation, every surgery comes with a risk of complications. Even more worrisome, complications can delay important follow-up treatment, such as chemotherapy or radiation.

“Women sometimes feel like their breasts are the enemy,” says Dr. King. “They think they need to get rid of them to solve the problem. As physicians, we need to make sure they understand the risks and benefits of the procedure.”

So when is mastectomy advisable for a breast cancer patient, and when is it not? It depends. For women with metastatic tumors, mastectomy is not recommended, explains Dr. King, but it might be a good choice for early stage tumors that are large or directly behind the nipple.

“For women who are good candidates for breast-conserving lumpectomy, there is no difference in survival between keeping the breast or removing it,” Dr. King says.

**A Good Candidate for Mastectomy**

At age 33, Amanda Skypeck learned that several relatives on her father’s side not only had been treated for...
breast cancer, but also tested positive for a BRCA gene mutation. This mutation increases a woman’s lifetime risk of getting breast cancer seven-fold, according to the Centers for Disease Control and Prevention.

In January 2015, Skypeck learned that she, too, carried the mutation. A genetic counselor explained to her that many BRCA-positive women opt for a bilateral mastectomy as a preventive measure. “I knew immediately that I wanted to do that,” says Skypeck.

Skypeck is part of a high-risk population of women that includes BRCA mutation carriers and women who had mantle radiation during adolescence for a different kind of cancer. “Mastectomy substantially reduces the risk of breast cancer for these women,” says Dr. King. “The risks and benefits start to tip the scale in favor of surgery.”

Skypeck, a school guidance counselor, was considering scheduling her surgery over the summer when her doctor found a lump. It was breast cancer. She had a bilateral mastectomy right away, followed by chemotherapy and breast reconstruction. She now goes back every six months for screening and a physical exam, because mammography is not indicated after reconstruction.

Everything went smoothly for Skypeck, but it is not always so. Doctors are beginning to notice a pattern. Women who undergo this major surgery sometimes struggle with post-surgical treatment.

“Sometimes, they have a harder time with chemotherapy, or they experience delays because of surgical complications,” says Dr. Partridge. “Sometimes, they stop hormone therapy to undergo reconstruction. More research needs to be done to look at the downstream effects of taking on more surgery.”

When Breast Conserving Surgery Is Right

In 2010, when she was age 37, Judy Rosenbaum had a mammogram to ease her mind about breast cancer. Abnormalities in the results brought her back for more testing, repeated every six months. After two years and no changes, Rosenbaum thought she was in the clear. Then, she found a lump. After more tests and a biopsy, she learned she had breast cancer.

Rosenbaum, a church administrator, had no family history of breast cancer and, after genetic testing, found she had no increased risk for the disease. She considered her surgical options: mastectomy or lumpectomy. Dr. Partridge explained that for women with similar cases, studies show lumpectomy plus radiation yields the same long-term survival rates as mastectomy.

Rosenbaum chose lumpectomy. “I didn’t want a mastectomy,” she says. “I was worried that it’s a really big surgery and I’d still need reconstructive surgery later.”

While Rosenbaum’s decision is the most common, women like her are increasingly choosing to remove both breasts, even though lumpectomy plus radiation and/or chemotherapy has the same long-term benefits and substantially lower short-term risks. Women making this choice seem to be
motivated by worries about getting breast cancer in the remaining healthy breast, says Dr. Partridge. However, the greatest risk is that the original cancer will return in another part of the body, such as the lungs or liver. Bilateral mastectomy does not reduce that chance.

“Many young women with breast cancer don’t believe in statistics anymore,” says Dr. Partridge. “I tell them the odds are that they won’t get it again. They look at me and say, ‘I wasn’t supposed to get it in the first place.’ They feel like they have a bullseye on their backs.”

Driving Informed Decisions

In a recent study of young women with breast cancer, Dr. Partridge and Dana-Farber epidemiologist Shoshana Rosenberg, ScD, MPH, found that higher levels of anxiety were associated with the choice of bilateral mastectomy over lumpectomy or single mastectomy.

Dr. Rosenberg is now leading a study to dig deeper into the factors that influence women’s decisions about surgery. She plans to use her findings to develop better tools to guide women through the decision-making process. Such tools could include visual aids to help doctors clearly communicate risks and benefits, but they might also include anxiety management resources to help women manage their emotions while making this important choice.

“Our goal is to present information in a way that will help women process and understand it,” says Dr. Rosenberg. “We want to make sure they’re making decisions for the right reasons.”

Three years after her lumpectomy, Rosenbaum has regular checkups and mammograms. She still wonders if she made the right choice. “I guess there’s no way you can know,” she says. “But I’m really happy with the decisions I made.”

Skypeck is also happy with her decision, yet not completely at peace. “The psychology behind it is very interesting,” she says. “I’ve had such thorough treatment, but it’s still frightening to think about my cancer coming back.”

Supporting Young Women

The Susan F. Smith Center for Women’s Cancers has a dedicated program for young women with breast cancer that offers resources, education, and opportunities to participate in research studies. Visit www.dana-farber.org/YoungWomenBreastCancer, or follow @youngstrongDFCI on Twitter.
GENOMIC STUDIES REVEAL A TUMOR’S SECRETS

by Robert Levy

One day, the genome of a tumor will be as revealing as a tell-all memoir. Doctors will obtain a full report on each tumor’s genomic quirks — its vulnerabilities, defenses, survival strategies, even its history of advance and retreat. The revelations will help physicians decide which therapies, in which order and at what doses, are most likely to work.

At Dana-Farber and other centers around the world, the effort to understand tumors at such an intimate level is well under way. Advances in DNA sequencing are enabling scientists to catalog the full extent of genomic abnormalities in many types of cancer. (The field of cancer genomics studies changes in tumor DNA.) The Profile research project at Dana-Farber, Brigham and Women’s Hospital, and Boston Children’s Hospital has analyzed thousands of tumor tissue samples to identify the cancer-related mutations within them.

“Genomic research is key to our progress in women’s cancers,” says Eric Winer, MD, director of the Breast Oncology Program for the Susan F. Smith Center for Women’s Cancers at Dana-Farber.
Biology Influences Therapy

Breast cancer was the first solid tumor for which an understanding of the biologic features of the cancer had a major impact on therapy. Finding that many breast cancer cells carry the estrogen receptor – an antenna for growth messages from estrogen – led to the discovery that tamoxifen and similar drugs could halt the growth of these cells by standing in estrogen’s way. For almost 40 years, tamoxifen has been a standard treatment for women whose breast cancer is fueled by estrogen.

Similarly, learning that some breast cancers have a surplus of the growth-promoting protein HER2 led to the development of agents that block HER2, most notably the drug trastuzumab (Herceptin).

“Today, diagnosing breast cancer by its molecular subtype, and selecting the appropriate targeted treatments, has become routine,” says Dr. Winer. “As we gain more insights into the molecular make-up of breast cancer, we are refining treatment even further.”

At the Susan F. Smith Center, for example, when hormone-sensitive breast tumors are removed during surgery, they’re often sent for genomic analysis by a test called OncotypeDX. “Each tumor is assigned a score that helps us gauge how aggressive the cancer is and how likely it is to respond to chemotherapy,” says Erica Mayer, MD, MPH, a senior physician and breast oncologist in the Susan F. Smith Center. “The test helps provide assurance that chemotherapy is prescribed only for patients who are likely to benefit from it.”

Genomic information is also opening treatment opportunities in other areas. “When breast cancer arises in women who carry mutations in the genes BRCA1 or BRCA2, the tumor cells’ capacity to repair their DNA is reduced,” says Judy Garber, MD, MPH, director of the Center for Cancer Genetics and Prevention at the Susan F. Smith Center. (Normally, BRCA1 and BRCA2 are involved in repairing damaged DNA; when they’re idled because of a mutation, DNA repair is hampered.) “If you know a tumor can’t repair DNA errors as easily, then part of your treatment strategy could be to exploit that weakness. Drugs capable of doing so include platinum-based chemotherapy agents and PARP inhibitors.”

Dana-Farber investigators were among the first to study the potential of platinum agents in breast tumors with BRCA mutations. With colleagues at Beth Israel Deaconess Medical Center, they’re leading a clinical trial of standard chemotherapy versus platinum chemotherapy in breast cancer patients who carry a BRCA mutation.

How a Tumor’s Genome Changes

Tumors evolve over time, acquiring new mutations as they grow and spread and encounter drug treatment. A newly diagnosed tumor may look markedly different, genomically speaking, from a tumor that has been wounded by multiple drug attacks.

Nikhil Wagle, MD, of the Breast Oncology Program at the Susan F. Smith Center, is exploring how, or if, a breast tumor’s genome changes when it becomes metastatic. In a project run by the Center for Cancer Precision Medicine (a joint effort of Dana-Farber, Brigham and Women’s Hospital, and the Broad Institute of Harvard and MIT), patients can agree to have a tumor sample analyzed when their cancer becomes metastatic or begins resisting the original drug. By comparing the genomes of these tumors with samples obtained before resistance developed, researchers hope to find explanations for drug resistance and metastasis – and provide a blueprint for new therapies.

In another project, Dr. Wagle is using social media to enlist metastatic breast cancer patients around the country to share their medical records, saliva, and tumor samples with his team (see box). The project has a variety of research goals, including the identification of “exceptional responders” – patients who derive the greatest benefit from treatments that may not be effective for others. It has enrolled 1,500 patients in its first four months, a sizable number of whom qualify as exceptional responders. Researchers hope to learn what drives these tumors and why certain drugs are effective against them.
“We view this project as patient empowerment – a way for patients to participate in cutting-edge cancer research, no matter where they may live,” Dr. Wagle says.

Making Connections in Gynecologic Cancers

Scientists have made an impressive start in tracking the genomic irregularities in ovarian and other gynecologic cancers. They have discovered, for example, four common mutations in high-grade serous endometrial cancer.

From a molecular standpoint, gynecologic cancers are quite complex. “Every gynecologic cancer has a unique genomic composition,” Dr. Matulonis says. “High-grade serous ovarian cancers [HGSCs], for example, have few genetic mutations, but they have many copy number alterations – instances in which certain genes are deleted or amplified.”

Patterns are emerging amid the diversity. The Cancer Genome Atlas – a national effort to map the key genomic changes in several major forms of cancer – found that approximately 50 percent of HGSCs have alterations that hinder their ability to repair damaged DNA. As in breast cancer, researchers found that patients with HGSC whose tumors have mutations in the BRCA1 or BRCA2 DNA-repair genes often benefit from PARP inhibitors. Intriguingly, studies have shown that non-serous ovarian cancers, too, often have mutations in DNA-repair genes.

“The discovery of BRCA1 and BRCA2 mutations as indicators of a good response to PARP Inhibitors represents one of the most important steps in personalized treatment for ovarian cancer,” Dr. Matulonis says. “As we learn more about HGSC, high-grade serous cancer of the endometrium, and triple-negative breast cancer, we’re finding they have a great deal in common at the molecular level.”

Researchers have also learned that ovarian tumors with an oversupply of the cyclin-E1 protein tend to have a poor prognosis. One reason is that, unlike other ovarian cancers, tumors with extra cycline-E1 can promptly repair the damage caused by chemotherapy agents. They also don’t respond well to PARP inhibitors or existing targeted therapies.

Panos Konstantinopoulos, MD, PhD, of the Gynecologic Oncology Program at the Susan F. Smith Center, has received a large grant from the U.S. Department of Defense to explore three new strategies for disrupting the growth of this type of ovarian tumor. One involves drugs targeting a protein that helps cells respond to stress; another seeks to block the interaction of two key proteins in tumor cells; and the third involves molecules called microRNAs that may have a powerful anti-cancer effect when combined with other drugs.
When Cathy McCue, 44, tried to find words to tell her 8-year-old twin boys about her cancer, she turned to books like *Mom Has Cancer* and *Nowhere Hair*.

Her own story began in June 2015, when she felt a pain in her right breast while at the gym. After finding a lump later that night, McCue, a homemaker in Hanover, Mass., went to see her primary care physician, and was guided quickly through detection to diagnosis.

A biopsy revealed that she had triple-negative breast cancer, in which the cancer cells do not have estrogen, progesterone, or HER2 receptors, and therefore do not respond to some commonly used breast cancer drugs.

McCue began treatment 20 minutes from home at Dana-Farber/Brigham and Women’s Cancer Center in clinical affiliation with South Shore Hospital. Under the care of Meredith Faggen, MD, the center’s medical director of medical oncology, McCue started a clinical trial that involved taking the chemotherapy drug Taxol for 12 weeks before surgery to shrink the tumor. Dr. Faggen stopped the trial at 10 weeks because McCue’s tumor was growing.

McCue had a mastectomy, followed by a combination of two chemotherapy drugs. Then, she began a clinical trial of cisplatin and concurrent radiation therapy for patients with “residual disease following surgery,” Dr. Faggen explains. “It’s intended to decrease the risk of local recurrence and make radiation more potent.”

McCue’s case is unusual, because she was able to participate in two clinical trials in the course of her care. “Cathy is enthusiastic about participating in clinical trials, which will improve the care of future generations of patients,” Dr. Faggen says. “Because she’s relatively young, she can tolerate very well the treatment we’re giving her. She has remained strong.”

For McCue, who will have reconstructive surgery later this year, there is comfort in receiving care close to home. “I can’t imagine driving into Boston through all of this,” she says, praising everyone from front desk staff to physicians and nurses and staff in the boutique, who helped with scarves, prosthetics, and wigs.

Young women like McCue also have access to *Young and Strong: A Program for Young Women with Breast Cancer* at the Susan F. Smith Center for Women’s Cancers at Dana-Farber. The program was founded in 2005 on the Longwood campus and in 2014 began expanding to Dana-Farber satellites and affiliates with a grant from the Centers for Disease Control. The program helps young women with breast cancer deal with challenges unique to their time of life.

Like the little girl in *Nowhere Hair*, who searches the house for her mom’s missing hair, McCue’s sons have learned some very adult lessons: Although their mom is going through cancer treatment, she is still their mother – patient, loving, sometimes tired, and always honest. They know that love is sturdier than cancer and, for McCue, easing their hearts is a gift.
An Aggressive Treatment for a Strong Patient

Interview by Theresa Sullivan Barger

After triathlete Betsy Feldmann felt pressure in her abdomen while running, which seemed “as if her insides were slipping,” she saw four doctors before being diagnosed with stage II-C ovarian cancer.

Feldmann chose an aggressive approach recommended by Ursula Matulonis, MD, medical director of Gynecologic Oncology at the Susan F. Smith Center for Women’s Cancers at Dana-Farber. The recommendation included a chemotherapy treatment three times stronger than standard chemotherapy – one that has been shown, in stage III patients, to extend life by an average of 16 months.

“I had three or four triathlons scheduled for that summer,” Feldmann says. Her medical team didn’t place restrictions on her exercise routine, so she continued swimming, biking, walking, and a little running, as long as she felt up to it. “My goal was to do as much as I could,” reflects Feldmann, a married mother of three who was 58 when diagnosed.

Feldmann’s intensive treatment involved receiving the drugs cisplatin and Taxol through a method called IP/IV combined chemotherapy. One drug is delivered directly into the abdomen (intrapерitoneal) where it attacks the cancer, and the other is given intravenously (in Feldmann’s case, through a port in her chest).

When Feldmann broke out in hives and discovered she was allergic to Taxol, her medical team didn’t miss a beat. Feldmann was taken to a desensitization unit at Dana-Farber, where, under close watch, she received Taxol in a highly diluted, slower drip, just as people with food allergies are given tiny amounts to help them build up a tolerance.

“My nurses were really, really careful,” she recalls. Diet also helped Feldmann maintain her quality of life. As soon as she reported a queasy stomach, her nurse Catherine Earley, NP, connected her with a dietitian at Dana-Farber. “My dietitian suggested remedies for any issues I had,” Feldmann says, such as putting her on smart water and sugar-free Gatorade when her magnesium and potassium levels dipped.

“Betsy continued training throughout her treatment,” Earley explains. “Her experience shows that exercise can help keep your muscles in shape and counteract some of the fatigue.”

When treatment ended, Feldmann won first place in her age group in a sprint triathlon. She also participated in the Pan-Mass Challenge, a bike-a-thon that raises money for Dana-Farber, by riding the 188-mile route from Sturbridge to Provincetown. And, last summer, to help prove to skeptical Bostonians that the water is clean and safe for swimming, she competed in a mile-long swim in the Charles River.
How could a nanoparticle be used to treat cancer?

It’s like a tiny Trojan horse that contains either drugs or imaging agents and can carry them directly to tumor sites to help diagnose the cancer or treat it more effectively while minimizing toxicity to the rest of the body.

How would nanoparticles be useful in ovarian cancer?

Ovarian cancer is largely confined to the abdominal cavity. In my lab, preliminary findings show that if we inject nanoparticles into the abdominal cavity of animals with ovarian tumors, the vast majority of the nanoparticles end up in tumor sites. This is very different from putting the nanoparticles in the bloodstream, which distributes them throughout the body and into organs like the liver and spleen.

Once the nanoparticles are in the ovarian tumors, what comes next?

One of the reasons ovarian cancer comes back is that invisibly small tumor deposits can be left behind during surgery. So we want to create an imaging tool that will allow surgeons to see these tumor deposits. We are developing biodegradable nanoparticles that emit light signals, and we hope to administer them into the abdominal cavity during surgery. We’re collaborating with engineers at MIT to develop equipment that can pick up the signals from these nanoparticles and help surgeons remove invisible residual tumor deposits.

Are there other applications for nanoparticles in ovarian cancer?

We are working to create and use novel, very potent agents that help destroy tumors that are resistant to cisplatin or carboplatin, chemotherapy drugs often used in ovarian cancer therapy. By themselves, these new agents would be too toxic for human consumption, but they can be incorporated within nanoparticles to concentrate them in tumors.

We are also working on a way to diagnose ovarian cancer with a blood test that uses nanoparticle sensors that recognize biomarkers of ovarian tumors. If we could diagnose ovarian cancer earlier, we could save many women outright, since early-stage surgery can often be a cure.
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 $11 million for the Susan F. Smith Center. To learn more about the Executive Council, contact Brenda Goodell at 617-632-5089 or brenda_goodell@dfci.harvard.edu.

A Legacy of Support

Thanks to the ongoing generosity of our donors, the Susan F. Smith Center for Women’s Cancers at Dana-Farber has raised more than $135 million over the past 17 years, and more than $21 million in fiscal year 2015 alone. To learn more about how you can strengthen our ongoing work against women’s cancers, contact Suzanne Kouri at 617-632-4055 or suzanne_kouri@dfci.harvard.edu.

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