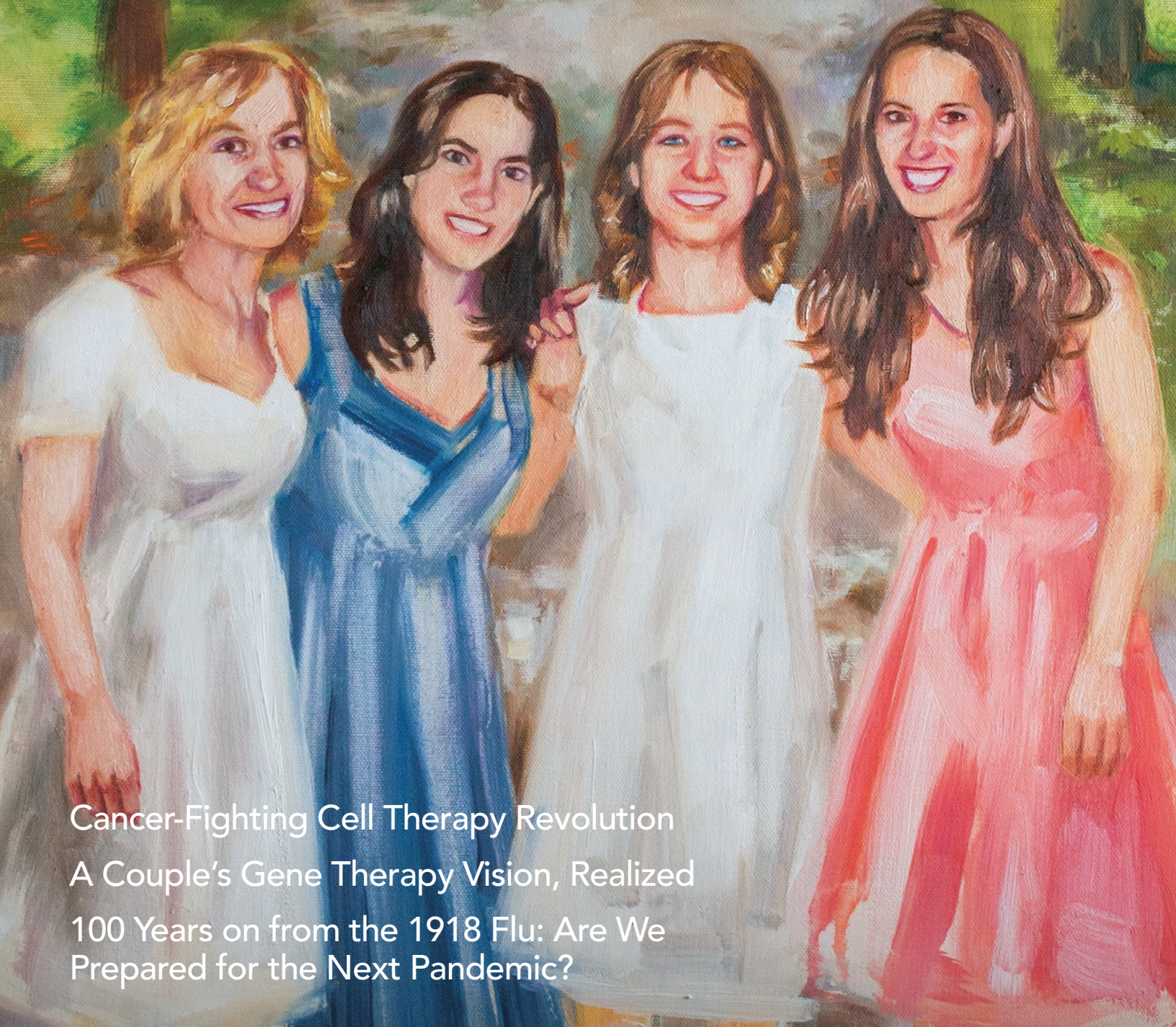


PENN Medicine



A FAMILY'S FATE

NEW HORIZONS FOR HEREDITARY CANCER



Cancer-Fighting Cell Therapy Revolution
A Couple's Gene Therapy Vision, Realized
100 Years on from the 1918 Flu: Are We
Prepared for the Next Pandemic?

By Jill Neimark and Rachel Ewing

Painting by Lizz Card

FAITH, FATE, AND



The Basser women: Pearl Basser with her daughters Shari, Faith, and Mindy.

Faith Basser died in 2002, at age 44, of ovarian cancer. She left behind a young son and a devoted husband, her parents, and three siblings, including two younger sisters. Shari, seven years younger, and especially Mindy, 12 years younger, had grown up seeing Faith as much as a mother figure as a sister, best friend, and partner in adventure.

The family's loss came with one extra kick.

"We knew nothing of BRCA gene mutations when we lost Faith," says Mindy. "We only learned then that this mutation is hereditary and can lurk beneath the surface, silently passed down from generation to generation."

Through a series of fateful events, Faith's death ultimately led to the establishment, in 2012, of the Basser Center for

BRCA at the University of Pennsylvania's Abramson Cancer Center as the world's first center devoted to the study of BRCA-related cancers. In its first five years, led by Executive Director Susan M. Domchek, MD, the Basser Center has built on Penn's long prominence in BRCA research to spearhead standards for prevention, screening, and treatment for men and women with these gene mutations. Its unique bench-to-clinic model of cancer care supports entire families—mothers, daughters, and sisters in particular—through the challenges that an inherited high risk of cancer presents. Today, it is clear that the center's work has implications not just for cancers caused by BRCA mutations, but for the cancer world writ large.

FAMILIES

At the Basser Center for BRCA at Penn, a unique philanthropic investment is making rapid progress toward new horizons in preventing and treating heritable cancer.

Risk that Ripples through Families

“It’s harder to find out your sister has cancer and a BRCA mutation than to find out for yourself,” says Laura Temple, a Basser Center patient who is in a position to know. Temple discovered that a mutation in the *BRCA2* gene ran in her family during her own course of treatment for breast cancer. She found a lump in her breast just six months after losing her mom to ovarian cancer in 2009. The youngest of her three sisters, Jen Schmidt, tested positive for the mutation soon after Temple did. Schmidt discovered she had breast cancer, too, upon her first mammogram after her genetic test.

BRCA stands for BReast CAncer susceptibility gene. Both of the two BRCA genes, *BRCA1* and *BRCA2*, are tumor-suppressor genes. In their normal form they help prevent cancer from developing. But certain inherited mutations on the genes can disable an important DNA repair process and dramatically increase the risk of breast and ovarian cancer, as well as some other cancers. Women with a *BRCA1* mutation have a 60 to 80 percent lifetime risk of breast cancer and a 20 to 45 percent lifetime risk of ovarian cancer. Women with a *BRCA2* mutation like Temple and Schmidt have a 50 to 70 percent lifetime risk of breast cancer and a 10 to 20 percent lifetime risk of ovarian cancer. BRCA mutations can be passed down by either parent to sons and daughters. For males, the risk of BRCA-related breast cancer is higher than normal, but still low; however, aggressive prostate cancer risk is significantly elevated. Both men and women with BRCA mutations have a higher risk of pancreatic cancer and melanoma than the general population.

What we know about the BRCA gene mutations began with familial studies of breast and ovarian cancer and a flurry of competitive research to identify the underlying genes in the early 1990s. Penn has been at the forefront of such re-

search since the beginning; among the researchers who identified *BRCA2* as a breast cancer susceptibility gene was Barbara L. Weber, MD, a longtime Penn researcher who left for industry in 2005 and who was a mentor to both Domchek and Katherine L. Nathanson, MD’93, director of genetics at the Basser Center and deputy director of the Abramson Cancer Center.

Though BRCA genetic testing has been available for more than two decades since then, most people at risk for carrying a mutation have not been tested. A family history of breast or ovarian cancer is a ‘red flag’ that a BRCA mutation might be present. But not every family has an extensive, known health history. The Basser siblings—sisters Faith, Shari, and Mindy, and their older brother, Stephen—were the children of first-generation immigrant parents who, like many families, didn’t keep a written family history or know about early cancer deaths in past generations. The only known risk factor was that their ancestry was Ashkenazi Jewish, originally from Eastern Europe, one of a handful of groups known to have a higher frequency of BRCA mutations than the general population. Nobody knew that Faith had inherited one of these vulnerable genes until after she passed away. Likewise, even after Temple and Schmidt’s mother died of ovarian cancer, nobody in the family underwent genetic testing until Temple herself was in treatment for cancer.

Once a person discovers she carries a BRCA mutation, the discovery has rippling effects through families. Genetic counselors work with patients to guide conversations about testing for at-risk family members. These family members in turn may begin their own journeys through the choices

The center’s unique bench-to-clinic model of cancer care supports entire families—mothers, daughters, and sisters in particular—through the challenges that an inherited high risk of cancer presents.

of testing, screening, and, in some cases, cancer treatment or preventive surgical procedures. These conversations are infused with and informed by knowledge about risk and prevention in areas where Penn has led for decades, such as with models to predict the risk of carrying *BRCA1/2* mutations, and with research to understand the elevated cancer risks associated with *BRCA1/2* mutations, as well as in work pioneering the use of risk-reducing prophylactic surgeries based on empirical data. For families having these discussions about their evolving clinical options to deal with a BRCA mutation, the ripple effect can be daunting—the shadow of a deadly disease stalking them with the possibility of future losses. But it can also be a source of strength and connection.



Photo by Peggy Peterson

Susan Domchek, MD, executive director of the Basser Center for BRCA

Mindy and Jon

One great ripple from Faith Basser's death, as her family mourned her, was that it spurred her sisters, Mindy and Shari, into action that is evident in the existence and activities of the Basser Center. But the first stones that shaped that ripple dropped much earlier.

Pearl and Philip Basser raised their family in Center City Philadelphia, working hard and sacrificing so their children could have opportunities and education. Mindy, the youngest, adored and admired Faith. When Mindy was a child, she and Faith shared late-night binges on macaroni and cheese, watched soap operas, and often took long walks together. One season they walked so much, eyes to the ground, collecting candy wrappers around the city, that they reached their goal of 500 to win a prize.

In 1992, on another long walk, fate and Faith mingled in a vital moment in Mindy's relationship with a new beau. A senior English major at Penn, Mindy had been dating a classmate, Jon Gray, only three weeks when the young couple flew to Florida on \$99 travel vouchers to visit Faith. It was Mindy's idea to walk along the highway back to Faith's house after seeing a Steve Martin movie, *Father of the Bride*. "She's a big walker, and I was just learning that," says Jon, "and I

"We're in it for the long term with families. We're with these women through dating, marriage, and children. It's a true privilege that happens so rarely in medicine." – Susan Domchek, MD

turned to Mindy and said, 'I know we've only just met but I'm planning on spending the rest of my life with you.'"

The couple's relationship continued to deepen, strengthened by their similar values, including a central focus on family and on education. The couple moved to New York after graduating and married in 1995. By the time Faith died, the Grays were raising their first three daughters, Mindy worked in editing and marketing, and Jon was making a name in real estate for himself and his employer, the Blackstone Group.

After Faith died, the couple was spurred to action. They not only gave their fourth daughter the middle name Faith in her honor, but became supporters of research into her illness and the gene that put her at risk. Mindy began volunteering for the Ovarian Cancer Research Fund Alliance, eventually becoming a member of the executive board of directors. But in these efforts, over a span of years, she and Jon noticed that information about new research and resources for counseling families with BRCA mutations like Faith's were largely separate. There was no central hub for BRCA.

Then came another fateful day. One summer morning, Mindy was having tea and breakfast when Jon came in from a run. "He was so excited," Mindy says. "He said to me, 'I've had an epiphany. We are going to found the Basser Research Center—the BRC for BRCA.'"

They would fund a major center for counseling, research, cancer prevention and treatment for those with BRCA mutations, and name it after Faith.

"I welled up with tears," recalls Mindy.

Mindy and Jon's contributions to establish the Basser Center and commitments in support of its ongoing work since then now total \$55 million.

A New Kind of Family Medical Care

For Laura Temple, the discovery of her BRCA mutation during cancer treatment meant, first, pursuing a more aggressive course to prevent future cancers—a double mastectomy, when initially she'd hoped for a "band-aid" lumpectomy. The next ripple was seeing her youngest sister, Jen Schmidt, begin breast cancer treatment while she was still undergoing her own. As time went on, the shared BRCA experience also brought the sisters together.

Now seven-year survivors of their breast cancer treatments, Temple and Schmidt share the experience of seeing Susan Domchek at the Basser Center for their follow-up care. So does another sister, Sarah Matos, who was treated



Seeing Your #InvisibleGenes

On Nov. 14, 2017, Mindy and Jon Gray addressed a sold-out crowd of over 1,100 people at the second biennial Basser Jean Bash, a fundraiser for the Basser Center for BRCA. In addition to celebrating five years of remarkable progress in the understanding, prevention, and treatment of BRCA-related cancers since the couple established the center in 2012, the Bash featured the launch of an awareness campaign about hereditary cancer, called #invisiblegenes. The campaign encourages genetic testing and counseling.

“Not everybody is getting tested who should be,” says Domchek.

The #invisiblegenes video and social media campaign launched with the help of celebrities like Ryan Seacrest and actress Cobie Smulders, star of television comedy series “How I Met Your Mother” and in the Marvel Cinematic Universe, aims to highlight illnesses that can be prevented or treated with early detection. The campaign features families, especially parents and children, talking about the qualities they inherited or passed along, from personality quirks to body oddities to health risks like BRCA.

It is just the latest of the Basser Center’s efforts to raise awareness about genetic cancer risk. The center has also partnered with more than 1,500 Jewish congregations across the country to distribute posters and fact sheets with details on BRCA gene mutations, which disproportionately impact the Jewish community (due to a phenomenon called the “founder effect,” in which a few specific heritable mutations became concentrated in an Ashkenazi Jewish population that was initially confined to Eastern Europe). The center also works to reach individuals and families around the world, providing education and information via webinars, live seminars, and shareable messages on social media channels to help every person with or at risk for a BRCA mutation make informed choices.

“Tonight, we’re asking you to take the courage to look at your genes,” Mindy told the crowd at the Jean Bash. “Check your history; uncover your risk and ask others to do the same.”

Clinical Context

When getting tested for BRCA mutations, it is vital to undergo that testing in a context where counseling and follow-up care are available and accessible. To that end, the Basser Center also offers remote cancer genetic services for at-risk patients. Using real-time videoconferencing in community practices, Penn’s genetic counselors are able to remotely screen and counsel patients who would otherwise not be able to utilize these services at their current location. But the effort to improve patients’ access to appropriate testing in the context of care does not stop there. A multi-institution collaborative team including Penn’s Basser Center, Memorial Sloan-Kettering Cancer Center, and Dana Farber Cancer Center, recently launched the BRCA Founder Outreach (BFOR) study to find new ways to integrate genetic testing into comprehensive medical care.

The BFOR study launched in January 2018, offering genetic testing at no cost to a total of 4,000 participants of high-risk Ashkenazi Jewish descent, age 25 or older in four US cities—New York, Philadelphia, Los Angeles and Boston. The test will be taken in consultation with a patient’s primary care physician or gynecologist, and thus will combine direct-to-consumer genetic testing with the guidance of a physician to discuss the results.



In general, Basser Center experts recommend BRCA testing for both men and women whose family history includes cancer clusters or people of Ashkenazi Jewish descent with a family history of breast, ovarian, pancreatic cancer or high grade prostate cancer.

“The ultimate goal is determining how this testing and care would actually get done in the long run,” Domchek says. “When we talk about improving population screening, it only works if physicians are engaged. Patients want to know whether their doctors think they should do it.”

at Penn for BRCA-related breast cancer over the last year, and a cousin. A fourth sister tested negative for the BRCA mutation. The three BRCA-positive sisters all feel a connection with Domchek, who takes time to answer every question they have about their follow-up care and about ongoing research on BRCA that could benefit their children. She also connects with them on a personal level; Domchek, Temple, and Schmidt are all moms of boys, sharing tips about raising young men and seeing them through the college application process.

The sisters also find their shared experience keeps them close and keeps them healthy. They occasionally go to appointments together, but more often call and text each other afterward, providing each other with a built-in support system. It's sometimes fun and friendly ("Have you seen her [Domchek's] boots? How does someone with so

Counseling women through personal decisions about preventive surgery is part of the mission of the Bassler Center—and so is the quest for better alternatives for effective cancer prevention.

much on her plate find time to have great shoes?") and sometimes plainly health-focused ("Are you taking your calcium?" "Oh no, I need to get on that!"). Far from considering their situation tragic or trying, sisters Temple, Schmidt, and Matos all maintain a positive outlook, bolstered by one another and by their religious faith. "We are all happy people, doing well," Temple says. "We stick together and we're always after each other to take good care of our health."

For Domchek, treating patient-families like theirs is part of a unique style of care at the Bassler Center. It feels, she says, as if her practice harkens back to old-style family physicians who saw multiple generations of patients. "Sisters come to clinic together, or a mom and a daughter," she says. "We're in it for the long term with families. We're with these women through dating, marriage, and children. It's a true privilege that happens so rarely in medicine."

Yet that's just one part of Domchek's typical day, which veers from the clinic where she sees patients to overseeing the Bassler Center's broad mission and slate of activities, from the lab bench to the clinic to educational outreach in at-risk communities.

Domchek's own genetics research, for decades, has focused on BRCA mutations and their clinical implications. For most of her career, though, treating patients like Laura Temple and her sisters who had a BRCA-associated cancer, the course of cancer treatment itself wasn't much different than any other type. The BRCA mutation was a marker of sus-

ceptibility and of prognosis—but it had limited direct bearing on standard treatment options.

In the years since the establishment of the Bassler Center, thanks in part to the center's research on the biology of BRCA-associated disease, that picture is beginning to change.

Repair, Interrupted

In its most fundamental mechanisms, cancer arises from our own biology—our cells' ability to repair errors, to replace aging cells by creating new cells, to utilize astonishing feats like building new blood vessels and repairing wounds. Cancer cells hijack our innate and life-sustaining biology. In the case of the BRCA genes, the healthy, life-sustaining purpose when the genes work correctly is protection and restoration.

"For BRCA, the important thing to remember is that it is a protein involved in DNA repair," says Roger Greenberg, MD, PhD, the Bassler Center's director of basic science research and a professor of Cancer Biology. "When a cell acquires damage to the DNA, it elicits a very complex and multilayered response that comes in and repairs the DNA to maintain the fidelity of our genome." In the absence of two working copies of the BRCA genes, DNA left is vulnerable to additional mutations and changes that eventually can lead to cancer.

In recent years, a growing understanding of how the BRCA genes function and dysfunction in DNA repair has begun to yield new strategies for treatment. Nathanson's collaborative medical genetics research, for example, has identified different specific types of errors on mutated BRCA genes that confer greater risks of certain cancers, helping to inform risk assessment and prevention strategies. Greenberg's basic science lab, meanwhile, is working to understand how BRCA-associated complexes of proteins coordinate to accomplish DNA repair, how these mechanisms are involved in a tumor's responses or resistance to chemotherapy, and even how chemotherapy and the body's immune response work in tandem to kill off cancer cells with damaged DNA.

"I think that's a major question in the field," says Greenberg. "How does the cell handle this catastrophic loss of DNA repair function in the context of *BRCA1* and *BRCA2* deficiency?"

One answer to that question that researchers already know is that cells with mutated BRCA genes rely on other proteins and mechanisms for cellular repair. One of the most important of these repair proteins is called PARP (poly ADP-ribose polymerase). In cancer cells that have mutated BRCA genes, drugs that interfere with PARP-related repair of DNA can push the DNA error rate in the cell over a cliff. The cells may soon be so full of errors that they die. These PARP inhibitor drugs are a form of medicine that uses a tumor's own biological vulnerability to kill it.

The first such PARP inhibitor, olaparib, was approved in December 2014, following Penn-led Phase II clinical trials, and two other drugs in the class have been approved since. These novel medications have transformed ovarian cancer treatment, especially since this cancer is often discovered late



Sisters Jen Schmidt, Laura Temple, Sarah Matos, and Kathy Kilby learned that a *BRCA2* mutation ran in their family a few months after losing their mother to ovarian cancer. Today, three of the sisters have tested positive for the mutation and are breast cancer survivors.

and until recently has had few options. The Basser Center also had significant involvement in a seminal study in *BRCA1/2*-associated metastatic breast cancer patients showing improved outcomes with olaparib compared to chemotherapy, leading to the first FDA approval of a drug specifically for *BRCA*-related breast cancer, in January 2018.

Studies of PARP inhibitors in prostate cancer and pancreatic cancer are underway. Other ongoing avenues of research at the Basser Center that aim to improve the usefulness of PARP inhibitors that are already approved include efforts to understand why some *BRCA*-related tumors do not respond to the drugs, and why most tumors develop resistance. Nathanson is investigating the impact of tumor genomics on these issues. Specifically, she has shown that *BRCA*-related tumors look very different if they lose the second copy of *BRCA* than if one copy still works correctly. She has shown that this has significant implications for prognosis. “Understanding the mechanisms by which *BRCA* tumors develop will help us understand both primary and acquired resistance,” Nathanson says. Domchek and others are still learning about how to use these drugs and how best to combine them with other drugs.

It turns out that PARP inhibitors might have broad implications for cancer treatment. “We’ve already seen that knowl-

edge about PARP inhibitors has translated more broadly to ovarian cancer, and we hope to find groups within other tumor types,” Domchek says. The study of inherited *BRCA* gene mutations has opened the door; there are almost certainly other ways cancers can develop to the point where there are failures in the DNA repair process in which *BRCA* proteins are normally active. “The more you understand how cells respond to damage,” Domchek says, “the broader the implications might be.”

A Global Hub

The Basser Center’s focus on discoveries with PARP inhibitors is no coincidence; it has been the result of a concerted effort to make discoveries in a promising area—and that owes a lot to the influence of Mindy and Jon Gray and their active role in partnering with Basser Center leaders. Mindy applies her marketing savvy and sophistication as a philanthropic leader to forge connections that extend the center’s impact, while Jon complements her approach with his business-minded focus on getting results. Their influence includes philanthropic engagement, such as co-chairing the biennial designer-bluejean-attired “Basser Jean Bash” fundraisers that, between 2015 and 2017, have raised more than \$15 million for the center. But it is not limited to that. “In



Mindy and Jon Gray at the biennial Basser Jean Bash fundraising event.

work, your greatest success happens when you identify something you believe in passionately, hire the right people, and throw your resources behind it,” Jon explains. “Philanthropy, and our work with the Basser Center, is a bit like an investment portfolio in that way. We have a very active dialogue with Penn, engaging with the experts to focus more on really promising research as opposed to sprinkling things around. In this, and in Mindy’s work with the team on social media and awareness outreach, we have a true sense of partnership.”

That partnership comes with the knowledge that helping families with BRCA mutations, like any great challenge in science or medicine, is a global effort, with challenges that can only be solved through the cooperation of the best and the brightest around the world.

To that end, in 2013, Mindy’s sister Shari (who is also a Penn graduate), and her husband Len Potter, established and permanently endowed the Basser Global Prize initiative at the center. The annual \$100,000 prize honors a visionary scientist whose *BRCA1/2*-related research has led to improvements in clinical care. The grant is unrestricted. “Researchers spend too much time writing grant proposals and not enough time in their labs,” explains Len. “Sometimes private philanthropy can be a better means for financing new ideas. This prize acknowledges the great things a scientist has done, but gives them unrestricted money they can apply to the research closest to their heart.”

Prizes have been awarded to Alan Ashworth, a leader of UCSF’s cancer center who has been instrumental in the development of PARP inhibitors and in the discovery of the *BRCA2* gene; University of Washington’s Mary-Claire King; David Livingston, of Harvard’s Dana Farber Cancer Institute; and Steven Narod, director of the Familial Breast Cancer Research Unit at the University of Toronto and a world leader in breast and ovarian cancer genetics. This year’s winner is Ashok Venkitaraman, MBBS, PhD, of the University of Cambridge.

At an annual scientific symposium hosted at the Basser Center to bring BRCA researchers and clinicians together, the Basser Global Prize winner each year is invited to deliver the keynote address. Prize winners also participate on a panel discussion of BRCA that is webcast live for patients and families affected by BRCA mutations to learn about the newest developments. “Penn has become a global center for immunotherapy and cancer research,” explains Shari, “in part because it’s willing to share what it does and be part of larger, worldwide initiative.”

In the same vein, the Grays have asked that Basser Center funds flow to research both within Penn Medicine and to outside, collaborative institutions as well. They donated \$5 million in 2013 for the Basser External Research Grant Program, a program for research projects aimed at advancing the care of people living with *BRCA1/2* mutations. External grants are rare among academic institutions. “It is particularly unusual for a large institution to open its doors to its competitors,” says Mindy. “Susan is a leader who is ego-free and fully believes in the importance of collaboration.”

For the Penn team, global collaboration on BRCA research is a natural fit. Penn was a founding member of CIMBA (Consortium of Investigators of Modifiers of *BRCA1/2*) which has analyzed more than 45,000 mutation carriers around the world to investigate “modifier genes”—changes in genes other than *BRCA1/2* which may impact the likelihood that a particular individual will develop breast cancer. Penn is also part of ENIGMA (Evidence-based Network for the Interpretation of Germline Mutant Alleles). With its vast collection of genetic samples from BRCA-positive patients who opted to participate in research since the 1990s, Penn is the largest single-institution U.S. contributor of samples to these key international efforts.

Decisions that Cut Deep

Susan Domchek was the expert sounding board for Sarah Matos after she tested positive for the *BRCA2* mutation, in addition to her sisters Laura and Jen and the Basser Center’s genetic counselors. They talked about options.

Matos, recalling her mother’s suffering with ovarian cancer, which remains difficult to detect early and is often lethal when detected late, decided to remove her ovaries and fallopian tubes. “I was 49 at the time, and I knew I wasn’t going to have any more children, so it was not a hard choice for me,” Matos says. Plus, her sisters had already gone

through the procedure after their breast cancer treatments several years earlier. The surgery can reduce risk of BRCA-related ovarian cancer by about 90 percent and breast cancer by half.

But when it came to removing her breasts, Matos waited. Although Domchek advised her that prophylactic mastectomy can reduce risk of BRCA-related breast cancer by 95 percent, Matos reasoned that regular mammograms and MRI could catch breast cancer early. That's exactly what happened. Matos had a mastectomy then, as part of her treatment. Her two BRCA-positive, cancer-survivor sisters were her experienced support network during treatment and remain so now that she is in remission.

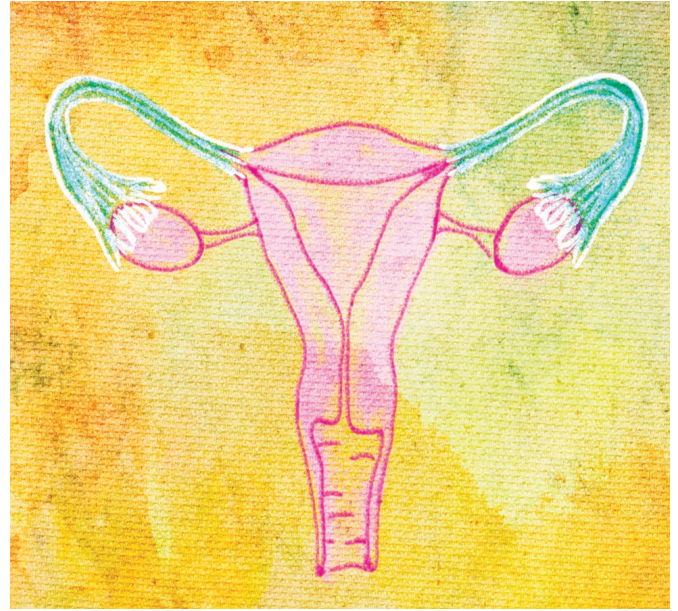
Because BRCA mutations are hereditary, all three sisters know that similar questions about preventive surgeries could lie ahead for some of their own children and future generations beyond. A naturally optimistic person, Matos doesn't spend a lot of time thinking about that. "But when I do think about it," she says, "it is a worry. I have four girls. It's kind of a heavy thing and something they're each going to have to make a decision about." She believes that her two oldest daughters, one 24 and newly married, one 22, will be proactive and get tested for the BRCA mutation at the earliest recommended age, 25. They have already discussed it with their doctors. It's not always easy, but it is part of the fabric of life for families like theirs. Matos's youngest sister, Jen Schmidt, keeps it light, but still top of mind, with her teenage sons, half-scolding them, "You might have that gene so you have to wear your sunscreen!"

Each patient's decision about preventive surgeries for BRCA-related mutations is inevitably a personal one. As effective as these surgeries are in reducing risk, they are serious procedures and they come with trade-offs, especially for younger women. Premenopausal women must weigh their

A growing body of research supports the idea that ovarian cancer in BRCA mutation carriers (and probably most women) originates in the fallopian tube and then migrates to the ovary.

plans for fertility and the timing of childbearing into these choices and also consider that removal of the ovaries will induce menopause virtually overnight—instead of a gradual, five-to-seven year process. Because this surgically induced menopause is so sudden, its uncomfortable symptoms can be severe. Long-term, this early menopause increases risk of heart disease and decreases bone density. Hormone replacement therapy is an option that can be discussed.

Counseling women through these personal decisions is part of the mission of the Bassett Center—and so is the quest for better alternatives for effective cancer prevention. "What we want is a better choice for women," Domchek says.



Rethinking an Afterthought

One of the promising alternatives that may lie ahead is the possibility of removing only the fallopian tubes, while preserving ovaries until after menopause.

Historically, pathologists only examined the ovaries removed during cancer surgery because the tumors there were an obvious problem, notes Ronny Drapkin, MD, PhD, a professor of Pathology and director of the Penn Ovarian Cancer Research Center and of gynecologic cancer research at the Bassett Center. "The fallopian tube was an afterthought," Drapkin says. Tubes were removed along with ovaries simply because that was convenient to surgeons.

Yet scientists never actually found reproducible evidence for precancerous lesions in the ovaries, despite years of intent examination, Drapkin notes. Around the early-mid 2000s, pathologists began to examine tissues from BRCA-positive patients who had undergone prophylactic surgery, and, at last, a few papers noted abnormal or precancerous cells. But the precancerous cells were not in the ovaries. They were in fallopian tubes.

Then a young faculty member at Dana Farber, Drapkin worked with his former clinical mentor at the Brigham and Women's Hospital, pathologist Christopher Crum, to thoroughly examine every bit of these tissues. "That's when it hit us," says Drapkin. "Oh, my. The fimbria, the end of the fallopian tube that fans out over the ovary, it has all the precursors, dysplastic cells that everybody has been looking for. It's all there."

A growing body of research since that time supports the idea that ovarian cancer in BRCA mutation carriers (and probably most women) originates in the fallopian tube and then migrates to the ovary. This is called a "seed and soil" hypothesis—the fallopian tube may be where the seed begins, but the ovary has the "soil" (growth factors and hormones) that allows the cancer to flourish.

Drapkin and his colleagues have created sophisticated animal models and conducted comprehensive genomic studies on human tissues showing that indeed, the fallopian tube's precursor cells and the ovarian tumors are the same. The latest such study, published in *Nature Communications* in

Research at the Bassett Center is focused on finding better solutions to prevent cancer, including some that do not involve going under the knife.

October 2017, provides genomic evidence that the most common form of ovarian cancer, high-grade serous carcinoma, can trace its origins directly to tumor cells that can be found in fallopian tubes an average of 6.5 years before ovarian cancer begins to grow.

Today, there are already a few clinical practice changes that reflect the general acceptance of this model for ovarian cancer. The American Board of Obstetrics and Gynecology now recommends that even women who don't have any elevated risk for ovarian cancer get their tubes removed if they are undergoing a hysterectomy for any reason, such as fibroids or prolapse. When it comes to young women with BRCA mutations, some doctors are already having conversations about preserving ovaries until after menopause and removing only tubes, though there is a risk that a few cancerous cells might already have left the tube to seed the ovary.

Removing both tubes and ovaries is still standard of care best supported by clinical evidence for women who opt for the surgery, but new long-term studies may one day change that standard. In 2017, Penn joined fifteen other institutions across the country on a twenty-five year prospective trial to study the impact on quality of life as well as cancer risk in women who have both the ovaries and fallopian tubes surgically removed at the same time, compared to women who initially have their tubes alone removed, followed by removal of the ovaries at a later date, usually after menopause.



For Domchek, finding discoveries in the spaces where top experts' skills overlap is the only way to make a vision as large as that of the Bassett Center a reality. "In the medical sciences, people talk a lot about service teams and collaboration," she says, "but truly it takes different people with tremendously different expertise, and getting all of these people to collaborate and talk to each other. We're really fortunate to be at Penn, where that happens." (Bassett Center leadership team, L-R: Domchek; Beth Stearman, administrative director; Ronny Drapkin, MD, PhD, director of gynecologic cancer research; Katherine Nathanson, MD, director of genetics; Roger Greenberg, MD, PhD, director of basic science research)



Towards A “Smallpox” Vaccine for Cancer

The preventive surgeries that are standard of care today already dramatically reduce the risk of cancer in women with BRCA mutations—but, although the surgery can save and dramatically extend women’s lives, it is still not an ideal solution. Research at the Basser Center is focused on getting closer to those ideal solutions, including some that may help women avoid cancer without going under the knife.

“We want to develop what is essentially a smallpox vaccine to prevent cancer,” says Robert Vonderheide, MD, DPhil, director of the Abramson Cancer Center. “But we won’t be targeting a virus. We’ll be targeting a genetic mutation.”

Vonderheide and a team of Basser Center colleagues are leading vaccine-based trials for the prevention of cancers associated with BRCA mutations. They are focusing on human telomerase (hTERT), an enzyme that is crucial for the survival of cancer cells—so much so that its production is overactive in about 90 percent of human cancers, including *BRCA1*- and *BRCA2*-related cancers. Laboratory studies at Penn have shown that vaccinating against telomerase induces an immune response that attacks and kills cancer. For clinical testing now underway, the vaccine has been tweaked with other molecules and a special method of enhancing its delivery, in order to maximize its effectiveness.

Patients in remission after treatment for any one of multiple forms of cancer, including, breast, ovarian, and pancreatic, are now enrolled in a first-in-human Phase I trial at Penn. So far, the clinical trial data indicate that the vaccine is safe, and results on the participants’ immune response to the vaccine are forthcoming. Testing the telomerase vaccine approach in patients who are considered to be at high risk of a cancer relapse is a first step toward its potential use to prevent novel cancers in healthy people at high risk, such as BRCA mutation carriers.

“I believe we are entering an era of using the immune system to prevent cancer,” Vonderheide says. “This is a watershed moment in cancer research.”

Partnering with the Right People

The torrent of progress in immunological approaches to cancer has unexpectedly brought together the previously disparate professional efforts of Vonderheide and Domchek, who are married to one another and have raised their sons into teenagers in the years since the pair was recruited to Penn more than a decade ago. “I was always interested in genetics, he was always in immunology, and all of a sudden they intersected,” Domchek says. “It wasn’t planned but it certainly has been an interesting development that the big circles in our Venn diagram are overlapping in this way that can really make a difference.”

It was a stroke of fortune, too, that Domchek came to work with Mindy and Jon Gray to bring the Basser Center to life. The day of Jon’s 2011 epiphany, coming in from a run to interrupt Mindy’s breakfast with the idea to start such a center, it was not a foregone conclusion that the center would be at Penn. But their Google searches on BRCA research kept turning up Domchek, so they cold-called her. When Domchek recalls the conversation today, it is with some embarrassment: She didn’t know who Jon and Mindy were, how important they would turn out to be in her life’s work. Without any fanfare, speaking to them as she would to any family affected by BRCA, she impressed them with her knowledge and enthusiasm. She talked about the decades of research at Penn on BRCA that had established so much of our basic knowledge about the gene mutations and how they confer risk; that had examined prophylactic surgery and helped demonstrate the benefits in cancer risk reduction and improved survival, along with describing the side effects, laying the groundwork for how clinicians worldwide work with BRCA-positive patients today; that had performed early studies of PARP inhibitors and continued through demonstrating the effectiveness of these drugs; that was a key player in global collaborative efforts; and that was poised to draw on its history to continue pushing further to help more families with hereditary cancer risk, in more places, for many years to come.

“She gave us over an hour of her time, without knowing anything about us,” says Jon. “She was measured and passionate. And she was at Penn, our alma mater. It seemed to be fate.”

“Fate and Faith,” says Mindy. “They are the guiding themes of our lives.” ▢

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