Pink isn’t just for ribbons any more. There are breast cancer-awareness batteries, rugby balls, even buckets of chicken. In the past 25 years, the efforts of the Susan G. Komen for the Cure Foundation and many others have succeeded in far more than destigmatizing the disease—they’ve made the fight against breast cancer a headliner. Today, our understanding of breast cancer surpasses that of all other common cancers. Screening and treatment continue to improve, and the research dollars keep coming. The vast majority of women diagnosed with breast cancer in 2011 will survive it.
It can seem inequitable at times—you don’t see, for example, M&Ms repackaged in teal, the official color of breast cancer’s rarer yet far more lethal sister, ovarian cancer. But those suffering from such so-called “orphan diseases” stand to gain from the rosy renaissance, too. Breast cancer is a trailblazing sort of disease. The more we discover about it, the more clues we gather about how molecules can mutiny to form tumors throughout the body—and how to stop them.

Of course, anyone who’s been affected even tangentially by breast cancer will tell you we have a long way to go. Each year, it kills more than 40,000 women, 18 percent of whom were diagnosed during their 40s. Additionally, confusion abounds about how best to screen for breast cancer (more on that later). Nonetheless, it’s far and away the cancer that’s closest to becoming a chronic disease.

“I have to give the surgeons credit for this,” says Adam Brufsky, professor of medicine and codirector of the Comprehensive Breast Cancer Center at Magee-Womens Hospital and the University of Pittsburgh Cancer Institute (UPCI). “Many years ago, surgeons here in the Pittsburgh area realized that this is a multidisciplinary disease that they couldn’t take care of alone.”

Namely, Brufsky credits Bernard Fisher affected nodes might be enough. And Gretchen Ahrendt, associate professor of surgery at Pitt and director of Surgical Breast Services at Magee, is leading the University’s part of a multicenter trial to determine whether more limited lymph-node surgery can be performed in women who received chemotherapy prior to surgery. She’s hoping they will be able to offer women a less-invasive procedure with fewer long-term side effects.

Perhaps even more important than Fisher’s contribution to breast surgery was his ushering in an era of cross-disciplinary, cross-institutional cancer research. As he launched his landmark trial, he founded the National Surgical Adjuvant Breast and Bowel Project (NSABP), a co-op supported by the National Cancer Institute (NCI). The project is still based in Pittsburgh and includes nearly 1,000 sites worldwide. More recently, Pitt joined the Translational Breast Cancer Research Consortium, a 14-center collaboration chaired by Nancy Davidson, director of UPCI and UPMC Cancer Centers. She is also Pitt’s associate vice chancellor for cancer research and professor of medicine.

Brufsky explains that UPMC’s medical oncology program in breast cancer started small and has grown steadily since he arrived in the 1990s. In that time, he’s studied, among other things, the baffling way that bone-loss-prevention drugs also seem to prevent breast cancer recurrence in postmenopausal women—one of the disease’s many enigmas. “We’ve pushed our clinical trials pretty far. But we realized we really needed to beef up the basic science part of our group.”

As an MD/PhD, Brufsky would have loved to have done it himself, but that wasn’t possible with his patient load. He and his colleagues realized that what they needed were people who “lived and breathed” the study of cancer at the cellular level and thought endlessly about how to apply those insights to treating patients. To this end, Pitt and UPMC have recently brought on a number of new recruits, beginning with Davidson, who joined UPMC two years ago. “They’re the missing piece of our program that’s really going to take us to the next level,” says Brufsky.

In recent decades, we’ve learned that breast cancer is not one disease, but several—one for each specific biological misstep that can turn breast tissue into a hospitable home for tumors. Heterogeneity is proving to be the case in other cancers as well and is perhaps the most powerful example of breast cancer teaching us about cancer biology in general. Some breast cancer cells have nuclear molecules that bond to and react with estrogen—they’re estrogen-receptor (ER) positive, that is, dependent on estrogen to grow. Starting in the late ’70s, Fisher conducted groundbreaking studies on tamoxifen, the first cancer treatment to exploit a biological vulnerability. It is still widely used.

Sixty percent of breast tumors are ER positive and can be treated with this life-saving drug. But puzzlingly, two-thirds of those become resistant to tamoxifen.

“When I look into the future, tomosynthesis is [the new] mammography.”

(MD ’43), Pitt Distinguished Professor of Surgery, who led the first clinical trials for breast cancer. (See our July 2002 story “Bernard Fisher in Conversation” online.) Bothered by the lack of scientific evidence justifying the radical-mastectomy paradigm that ruled the day, Fisher put it to the test and disproved it for good in 1974. Lumpectomy plus radiation, he found, was just as effective as the disfiguring, even disabling surgery that took women’s entire breasts and chest-wall muscles.

This February, the American College of Surgeons carried on his legacy in a new study, finding that many women with breast cancer can be spared aggressive lymph-node surgery, as well. Current guidelines state that if any nodes are affected at all, the whole adjacent lot should go—a procedure that often causes devastating, permanent damage to the lymphatic system. But as it turns out, removing just the
We don’t know why,” says Steffi Oesterreich, a PhD visiting professor of pharmacology and chemical biology. “That’s one of the questions we want to answer.”

Oesterreich’s lab is using cellular techniques, mouse models, and specimens from UPMC’s sizeable tumor bank to better understand this particular breed of hormone-hungry tumor.

Adrian Lee, Oesterreich’s husband and visiting professor of pharmacology and chemical biology at Pitt, helped to classify another breed. It’s fueled by insulin-like growth factors (IGFs), chains of amino acids that regulate glucose levels. Lee has had promising early clinical trials of a drug that targets this mechanism, and he’s now working to refine a second-generation version.

Oesterreich and Lee met in the lab of William McGuire, who headed the top U.S. breast cancer translational-science group in the 1980s; it was based at the University of Texas Health Science Center, San Antonio. The group then moved to Baylor College of Medicine in Houston, where Lee and Oesterreich spent 10 years at Baylor’s renowned Breast Center. They also helped establish a translational biology and molecular medicine program there. Oesterreich hopes to establish a similar program here at Pitt.

Last year, the couple was recruited for the launch of the Women’s Cancer Research Center, a joint venture of UPCI and Magee-Womens Research Institute. Lee codirects the center with Robert Edwards (MD ’84), professor and vice chair of the Department of Obstetrics, Gynecology, and Reproductive Sciences at Pitt; Oesterreich is the center’s director of education.

Another especially aggressive subgroup of breast cancer feeds on a protein called human epidermal growth factor receptor 2 (HER2), which plays a role in cell growth and differentiation. Some 15 to 20 percent of breast tumors are HER2 positive. Most of these patients respond to the popular drug trastuzumab (the brand name is Herceptin), which targets HER2.

Before coming to Pittsburgh from Johns Hopkins, Davidson began pursuing the first drug that targets what are called the epigenetics of breast cancer, which she’s shown to be implicated in trastuzumab resistance. Epigenetics are the nongenetic factors that interfere with gene expression. Davidson now continues this work with Pitt’s Yi Huang, an MD/PhD research assistant professor, in collaboration with colleagues back at Hopkins. They’ve won several grants, including one from Stand Up to Cancer. It’s a “very high-profile, Hollywood sort of grant,” she says—it’s funded by the Entertainment Industry Foundation.

About 20 years ago, scientists learned that mutations in BRCA1 and BRCA2, two genes involved in DNA repair throughout the body, increase the risk of cancer of the breast and ovary, as well as certain types of skin and pancreatic cancer. But only in these organs and nowhere else. No one knows why.

BRCA mutations foul up the DNA-repair mechanism known as homologous recombination; so the cells resort to their plan B, which, in this particular case, is what’s called base excision repair. This repair mechanism makes use of a protein called PARP (ADP-ribose polymerase), which helps to ensure a cell’s normal cycle of life and death. Unfortunately, the products of plan B are not always so good at the dying part.

Shannon Puhalla, assistant professor of medicine at Pitt and breast oncologist with Magee-Womens Cancer Program, is conducting a series of clinical trials of ABT-888, a drug designed to treat cancer in people with BRCA mutations. By blocking PARP, it shuts down plan B. Instead of replicating their
DNA again and again unchecked, the cells die like they’re supposed to.

Puhalla’s team started with a study that treated patients with BRCA mutations with ABT-888 alone. About 40 to 50 percent had responded to a similar drug; it’s too early to say how effective ABT-888 is. They’re also working on five phase I trials for ABT-888 plus chemo (looking for the best regimen and dosage), which includes trials for patients with pancreatic, lung, ovarian, and bladder cancers. In addition, they are conducting the first-ever trial of the effect of ABT-888 plus chemotherapy on women who have what are called triple-negative breast tumors, which are molecularly similar to tumors with BRCA mutations.

Triple-negative breast cancer is the disease’s great unknown. It does not have receptors for HER2, ER, or progesterone receptors (PR). For these patients, who account for 15 to 20 percent of all breast cancer cases, there are no biologically based therapies, no options other than chemotherapy. Cruelly, in addition to being difficult to treat, triple-negative breast cancer is the most aggressive form of the disease.

So far, it appears that about 28 to 38 percent of the team’s triple-negative study participants are responding to the drug.

Puhalla came to Pitt because of “all the good people who were already here,” she says. “And the fact that Dr. Davidson, a world-class breast cancer researcher, and now Adrian and Steffi have come here since then, that’s reinforced the fact that this is a great place to study breast cancer. And I’d heard wonderful things about Dr. Egorin, too, but I didn’t realize what a wonderful impact he’d have on my career until I got here.”

Merrill Egorin, former codirector of the Clinical Pharmacology Analytical Facility at UPCI, led the phase I program before his death last August. Because of Egorin’s expertise in pharmacology, in spring 2008 the National Cancer Institute (NCI) had sought his help in developing new drugs through the Cancer Therapy Evaluation Program.

Puhalla recalls, “He used to have a saying: ‘Our job is to be rich and famous’—rich enough in terms of grant funding to do the research you want, and famous from publishing your work and helping patients.” Puhalla had been at Pitt for about six months when Egorin called her, told her about the good news from NCI, and asked whether she’d come onboard. “He said, ‘Do you want to be rich and famous?’ and I said, ‘Of course.’

“What’s great about phase I research is that these drugs and concepts either work or they don’t, but either way you learn something about cancer.”

**READY FOR A CLOSEUP**

If you have a mammogram, there’s about a 10 percent chance your doctor will need to clarify the results with more imaging tests, such as an ultrasound or MRI (magnetic resonance imaging). In that event, there’s a 15 percent chance you’ll be called back in for a biopsy. And if you have a biopsy, there’s a one in five chance it will confirm that you have cancer.

In November 2009, the U.S. Preventive Services Task Force (USPSTF)—a panel of independent experts in breast cancer prevention appointed by the U.S. Department of Health and Human Services—released new recommendations for breast cancer screening. The panel recommended against screening mammography for healthy, symptom-free women in their 40s.

For breast-imaging specialists, the idea was appalling: USPSTF itself acknowledged that breast cancer is a leading killer of 40-something women, and regular mammograms significantly reduce risk. After a weeks-long firefight, the task force tweaked its language, advising women to speak with their physicians, consider their family histories and general health, and decide for themselves. Still, confusion persists in both the medical and lay communities.

USPSTF had used statistical models to compare potential harms of annual screening against potential benefits. They concluded that regular mammograms should not be routine until age 50; the incidence of breast cancer rises with age. But even then, USPSTF found, these women need only screen every other year—tumors grow more slowly as women age. With biennial screening, women 50–74 could still get most of the benefits of this test, while their false-alarm biopsies would be cut in half. (For women 75 and older, the task force found the data insufficient to draw any conclusions.)

“I understand the point they were making,” says Margarita Zuley (MD ’91, Res ’96, Fel ’97), visiting associate professor of radiology at Pitt and director of Breast Imaging at Magee-Womens Hospital of UPMC. Yet, “I don’t know that we should reissue guidelines based on a statistical model when we have population-based studies showing real survival rates that are higher with annual screening.”

Some cancers are biologically bound to follow a swifter and deadlier course. For the small subset of women with aggressive, fast-growing tumors, USPSTF stated, even annual screening is not likely to confer a survival advantage.

The problem with that reasoning, says Zuley, is that there is still no way to be sure who will fall into that category. Until there is, she says, “we are still recommending annual screening mammography for everyone 40 and over”—a recommendation that’s been steadfastly supported by the American Society of Clinical Oncology and others throughout the debate.

So, what if screenings were more accurate? In mammography, low-dose X-rays are used to create two, two-dimensional, black-and-white images of the breast, with all of the tissues overlapping. Fatty tissue appears darker. Tumors and their byproducts—little specks of calcification—appear much lighter, but unfortunately, in about half of women, so will much of their breast tissue, because the cells of their breasts are much closer together. To make matters worse, dense breast tissue is significantly more cancer prone.

There are other challenges: Lighter areas also mark benign lumps, cysts, and fine ducts where the seeds of cancer can hide. Looking for tumors in a mammogram has been likened to hunting for a polar bear in a snowstorm.

On the first morning of spring, Zuley and Breast Imaging Research Coordinator Linda Lovy demonstrate digital breast tomosynthesis (DBT)—a technology recently approved by the FDA that Pitt has been testing for the past
few years—using a gelatinous model breast, “Betty” to her friends. DBT is similar to computed tomography (CT), but involves only a partial rotation around the patient rather than a full 360. Once Betty is compressed and ready for her closeup, we stand behind a leaded piece of glass in the corner of the room where a touchscreen is set up. Love initiates the X-ray tube, and it starts to beep, snapping 15 images as it glides along an arc over Betty. Next, the software compiles the images to produce dozens upon dozens of two-toned images representing one-millimeter slices of our patient.

Before Betty is unsqueezed, the scanner quickly switches filters and snaps two mammogram images, too—it’s designed to allow researchers to compare these technologies. But there’s hardly a comparison, Zuley explains later as she opens a real patient’s files in an office across the hall. Sliding her mouse, she takes a virtual tour through the woman’s breast, pointing out knobby, irregular shapes and other hallmarks of tumors.

All of this detail, but with only about the same, low radiation dose as a mammogram.

Zuley and colleagues Jules Sumkin (Fel ’86)—a DO, chief of radiology at Magee, and professor of radiology at Pitt—and David Gur—an ScD and professor of radiology at Pitt—have shown that DBT reduces recall rate. Right now, it’s used only as a second-line technique, but Sumkin is optimistic that will change. “When I look into the future, tomosynthesis is [the new] mammography.”

DBT was just approved by the FDA for clinical use this February, and Pitt is well positioned to bring it to the region. Zuley says, “We probably have more experience with [DBT] than anyone else in the country.”

CT scans aren’t generally used for breast imaging—the radiation level is too high. But recently, the team acquired a prototype unit that’s designed for the breast—it’s called cone-beam CT, or CBCT, and it uses the same low radiation dose as a mammogram. This technology shows not only the anatomy of the organ, but also its functional activity—invalidable data normally available for breast imaging only through an MRI. But CBCT does the same job with what will likely be a smaller price tag and footprint, to boot.

With grants from the Shapiro and Komen foundations, the team is working on a blind study of biopsied cases, measuring their detection accuracy using CBCT, MRI, tomosynthesis, mammography, and ultrasound.

Yet another budding technology coming to Pittsburgh is a new-and-improved version of ultrasound, thanks to Wendie Berg, professor of radiology, who joined the School of Medicine in March.

Right now, ultrasound is the most-common additional test to follow a mammogram. It uses sound waves to image tissues subtly differentiated in shades of gray. A lot of the shadowy shapes that imagers worry about in these scans are later proven harmless in a biopsy. But this unit will include an extra measure to make things easier: elasticity. Most cancers are much stiffer than benign masses. If any abnormally stiff areas are in the ultrasound wand’s sight, it will appear on the screen in an overlay of color.

Berg expects to begin implementing ShearWave Elastography and supplemental screening with ultrasound in women with dense breast tissue in the near future. Before Berg moved to Pittsburgh, she reviewed cases and results of a multicenter, multinational trial for the technology’s developer and was very encouraged by its potential.

“There are lots of reasons to be optimistic,” says Berg. “The task force [USPSTF] downplayed [screening], but that’s like telling an ostrich to put its head in the sand. There’s no reason to stop looking. I think what we should be doing is demanding better of what we do right now.

“We can do a lot better—and should.”

For a peek at cone-beam CT, see this Web Extra: http://pittmed.health.pitt.edu/Summer_2011/web-extra.htm.

SISTER ACT

On March 16, 2007, DeDee Rawlins, an RN from Bridgewater, Mass., learned that the enlarged ovary she’d been worrying about for months was no fibroid. This was before Rawlins, who was adopted, tracked down her biological father’s family and learned they had all the hallmarks of BRCA mutation. She was diagnosed with stage 4, grade 3 ovarian cancer.

It’s an orphan disease, but, fortunately, it has a very powerful sister in breast cancer.

After her surgery, Rawlins spent years on various medically based therapies and chemotherapies, and though she was able to quell the tumours’ growth, the side effects were too much: nausea, high blood sugar, numbness, joint pain, and hypertension at potentially fatal levels.

She desperately wanted to get on a PARP-inhibitor trial—she’d done her homework and was impressed by its success in breast cancer patients—but she didn’t quite fit into the criteria of any of the studies in her area.

And then she found Shannon Puhalla.

Last October, after completing her qualifying physical for the study, Rawlins began a series of trips to Western Pennsylvania for her new regimen. By the holidays, a scan confirmed that both of her masses were shrinking and absorbing less dye. “Which means those cells are dying,” she says. “It was a fabulous Christmas present.”

The kindness of her new friends in Pittsburgh, which she calls her second home, has been overwhelming—the manager of her hotel cried for her good news. “Everyone is so nice,” she says. “I don’t know what you guys eat for breakfast.”

On this treatment, Rawlins’ cancer continues to shrink, and her side effects are minimal: occasional pain, nausea, fatigue, and odd cravings for pickles. But for the most part, she’s living a normal life, even helping out in her son’s law office. It’s almost as though she’s merely maintaining a chronic disease.

“I forget I have cancer,” she says.