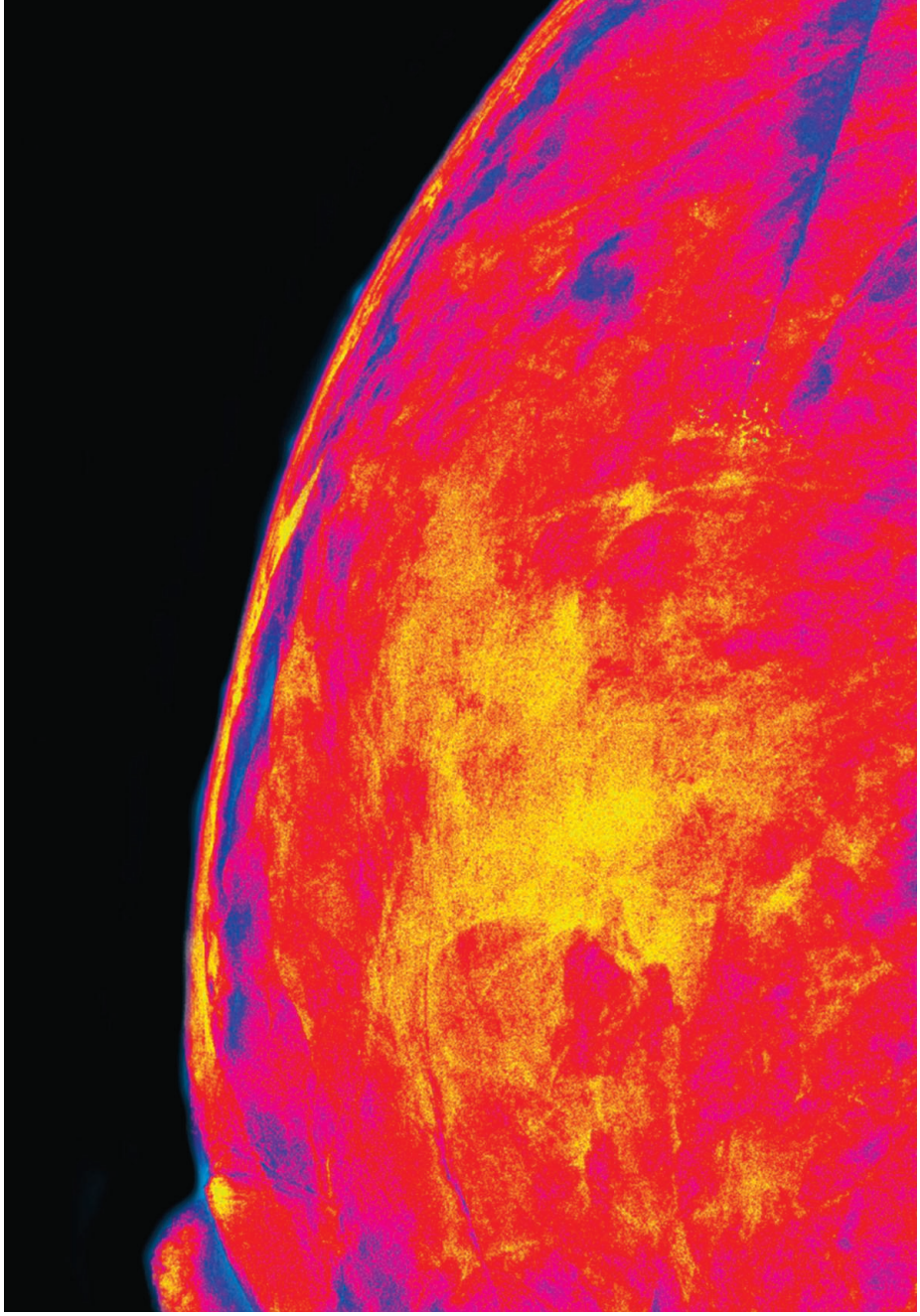

Stage zero. Each year, U.S. clinics detect more than 60,000 precancerous breast lesions known as DCIS; this scan shows a risky "high-grade" lesion (yellow).

CREDIT: CUSTOM MEDICAL STOCK PHOTO

Dare to Do Less

Scientists are looking for ways to spare women from aggressive treatment of ductal carcinoma in situ, a diagnosis that only sometimes leads to invasive breast cancer

Shelley Hwang, a surgeon who has treated women with breast cancer for 17 years, is troubled by the thought that many who have gone under her scalpel really didn't have cancer. What they had, she says, was irregular tissue that may increase the risk for cancer. Not knowing much about these abnormalities, however, oncologists decided decades ago that the right thing to do was to remove them. That's still being done.

A tidal wave of such ambiguous cases began to pour into clinics in the early 1980s. They were the product of a drive to catch cancer early, aided by new breast imaging methods that found lumps or tissue aberrations that would not have been noticed before. Hundreds of thousands of patients were told that they had "ductal carcinoma in situ," or DCIS—cancer confined to a milk duct. It has also been called "stage zero" cancer. In the past, these women typically received mastectomies, followed by radiation and drugs.

Hwang, now at the Duke University School of Medicine in Durham, North Carolina, says that, with no decisive evidence, oncologists felt they had to treat each DCIS case as if it were invasive cancer. "We were removing all these breasts" to take out DCIS lesions, "the majority of which might never become clinically significant," she says. Today, the diagnosis of DCIS usually leads to less radical surgery—removal of a few cubic centimeters of tissue (a "lumpectomy"), followed by radiation and hormone therapy. The cohort of U.S. women living with the diagnosis has risen steadily; one forecast estimates they will number 1 million by 2020.

But Hwang and other oncologists worry that women are still overtreated for DCIS that would never become life-threatening. They hope it will become possible to do more sophisticated analysis of each DCIS patient's risk for invasive cancer and adjust treatment accordingly, avoiding radiation treatment, for example, or even in some cases surgery. Some, like oncologist Laura Esserman of the University of California, San Francisco (UCSF), have argued for years that the diagnosis should have a gentler name, one that omits "carcinoma." She proposes calling these and similar slow-growing tissue irregularities "indolent lesions of epithelial origin," or IDLE. The goal, Esserman says, is to let doctors and patients "take a step back" and be less aggressive with therapy.

Five years ago, leading physicians and researchers met at the Bethesda, Maryland, campus of the National Institutes of Health to review what's known about DCIS. They concluded in a consensus document that it would be worth considering a less "anxiety-producing" name, as well as "less therapeutic intervention" if it could be done without increasing the risk of subsequent cancer. Testing new approaches to treatment is difficult, given that current practice is judged a success: Ninety-eight percent of U.S. women treated for DCIS die of something else. Yet even this small risk can be lowered with postsurgery radiation, which reduces the chances of subsequent invasive cancer by 50%, according to a 2011 study led by Irene Wapnir of Stanford University in California. Few people may try the experimental therapy when the norm looks so good. But Esserman and Hwang are running trials in which women diagnosed with DCIS opt out of some parts of standard therapy.

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To guide such treatment, Hwang says, "we need to have better predictors of which DCIS will likely become invasive and which won't." Progress has been slow, but a U.S. company—Genomic Health Inc. (GHI) of Redwood City, California—launched a test in December 2011 called DCIS Score, which monitors seven cancer genes in DCIS tumors to rate the risk that they will become invasive. Many physicians argue that its predictive value is small, and several university-based groups claim to have molecular markers that are better for detecting certain high-risk types of DCIS.

Still, both Hwang and Esserman describe the DCIS Score test as a useful first step. Such tools will help women decide which DCIS cases to wait and watch over, Esserman says. "We have to put just as much effort into making sure we don't overreact" to the fear of cancer, she says, as we put into treating it.

Fear is the driver

"We didn't have much DCIS in the United States until we got into mammography screening," says Joann Elmore, an oncologist at the University of Washington, Seattle. Now, Elmore says, "we are seeing little calcifications, little white dots [on breast scan images]. We don't want to miss anything," especially because failure to detect cancer is "the number one cause" of malpractice allegations. When doctors do spot an anomaly, they are likely to ask for a biopsy.

For more than 60,000 women per year in the United States, that leads to a diagnosis of DCIS. The diagnosis is not new, but Hwang and others believe that the lesions now diagnosed as DCIS may differ from those with the same label in the 1940s and 1950s. They are smaller and, unlike earlier ones, most are not palpable. Under a microscope, Hwang says, the cells in the DCIS lesion look very similar to cells in an invasive breast cancer and are scored on three grades of abnormal appearance like those used for invasive cancer. But they are contained within the milk duct and may remain there safely for a lifetime. It's not known what enables some to escape. But it is clear that some do—and become dangerous.

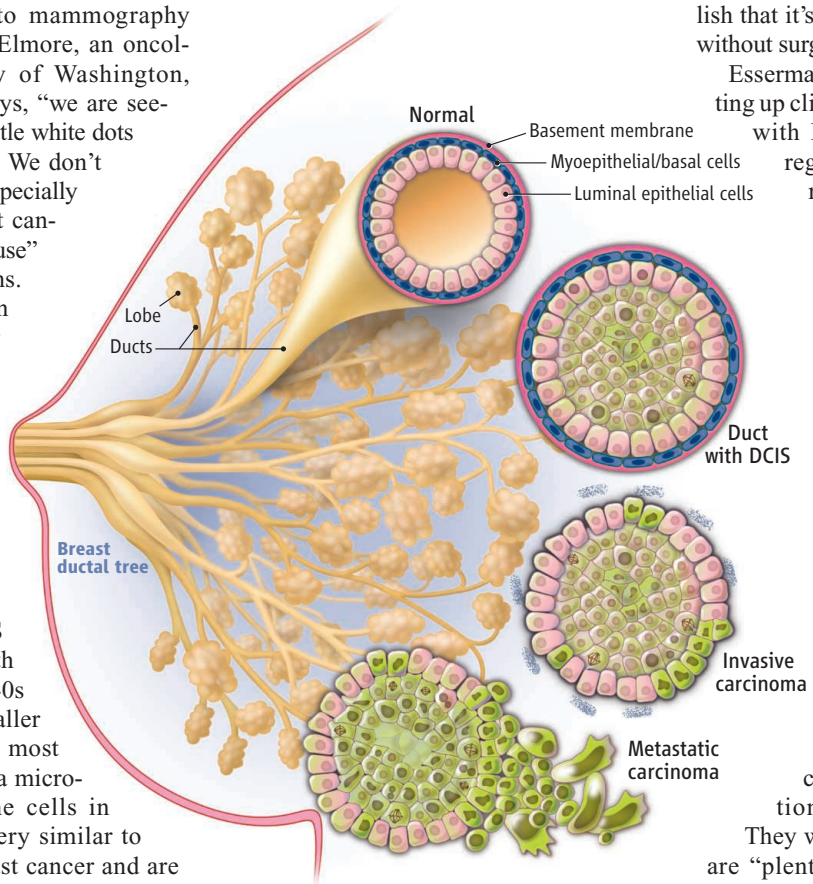
The reported U.S. incidence of DCIS has increased dramatically over the past 3 decades, especially among women over 50. Estimates of the fraction of women diagnosed with DCIS who might go on to develop invasive cancer without treatment range from 14% to 50%. But because almost all cases are treated to prevent invasive cancer, it is difficult to get firm data. Pathological and molecular analyses of biopsies have already shown that some types of DCIS are more likely to be invasive, others far less, Esserman says. Yet even as doctors in the United States found and treated far more DCIS, the incidence of invasive breast cancer has remained fairly steady. To some, this suggests that treating all DCIS does not do much to stop more dangerous cancers. This was the conclusion of a 2011 computer modeling study of cancer trends from 1978 to 2003 by Elissa Ozanne, then at Massachusetts General Hospital in Boston; Esserman; Hwang; and three others.

> "We were removing all these breasts" to take out DCIS lesions, "the majority of which might never become clinically significant."
>
> —Shelley Hwang, Duke University School of Medicine

Forgoing the knife

A few clinicians have begun to offer experimental ways of managing the disease. At Duke, for example, Hwang leads a cooperative trial at 23 U.S. sites that offers some women with DCIS an opportunity to try hormone therapy alone. Only postmenopausal women are enrolled, and only if their DCIS is rated low-risk based on traditional pathology measures and their lesions are estrogen-dependent. They are monitored closely to see if the DCIS starts to recede. Hwang hopes the trial, which ends in 2015, will establish that it's possible to treat low-risk DCIS without surgery.

Esserman and colleagues at UC are setting up clinical trials to offer some women with DCIS a chance to enroll in a regime of "watchful waiting" and reduced treatment, similar to that offered to men with prostate cancer judged to be low-risk. They rolled out a plan they call the Athena Breast Health Network in 2009, linking five UC medical centers. Esserman says the network is developing new classifications of breast lesions, using DCIS Score in combination with standard pathology to rate the chances that patients might develop invasive cancer. Patients judged to be high-risk will be treated as in the past, but others will be offered a choice of going without radiation, or even skipping surgery. They will be monitored closely. There are "plenty of people" who are willing to live with some uncertainty, Esserman says, and "we should not browbeat them into having treatments" that may not benefit them.



Crossing the border. Tissue abnormalities known as DCIS may stay confined within a milk duct for a lifetime; a minority break out to become invasive cancer.

CREDIT: K. SUTLIFF/*SCIENCE*

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Testing times

As cancer physicians and their patients wait for results, women are left with little to guide them if they wish to avoid surgery, radiation, and drug treatments. Beyond the standard biopsy and personalized risk analysis based on genetics, they do have GHI's test, the only U.S. Food and Drug Administration-approved option on the market. Priced at $4380, DCIS Score is a modified version of Oncotype DX, the test the company has sold for a decade as a way to classify the aggressiveness of invasive tumors.

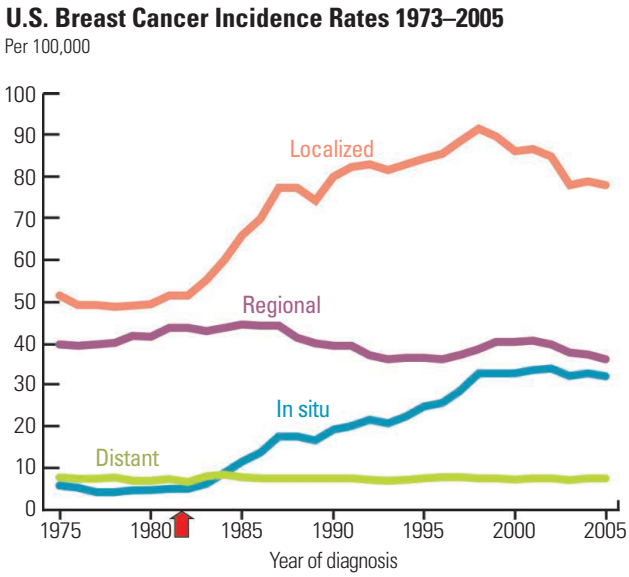
DCIS Score probes tissue samples taken during breast biopsies for the activity of seven genes linked to cancer and five other reference genes. (Those genes include *Ki-67*, *STK15*, *Survivin*, *CCNB1* [cyclin B1], *MYBL2*, *PR*, and *GSTM1*.) Based on gene expression levels, an algorithm calculates whether a woman who has already had surgery (but not radiation) for DCIS is likely to see the lesion come back or even develop into invasive cancer.

Lawrence Solin, an oncologist at the Albert Einstein Medical Center in Philadelphia, Pennsylvania, led the first and, so far, only published effort to validate DCIS Score. With support from GHI, the U.S. government, and the Breast Cancer Research Foundation, Solin's group retrospectively analyzed tissue from 327 DCIS patients who had undergone surgery but not radiation. The team reported in 2013 that the three levels of risk scores the test gave for tissue samples correlated well with patient outcomes.

Women judged to have a low DCIS Score, for example, turned out to have only a 3.7% risk of developing invasive cancer within 10 years. Those with middling scores had a risk of 12.3%. And the highest scoring group had a risk of 19.2%. According to the authors, in their 327-patient sample, the gene test forecast risk better than current pathological methods, which rely mainly on the analysis of cell structure and physiology in biopsied tissue.

Many researchers aren't wowed by the test, however. Karla Kerlikowske, an oncologist and epidemiologist at UCSF, calls DCIS Score "OK," saying that at least it doesn't exaggerate risk. But she thinks that it doesn't flag some of the most dangerous subtypes of DCIS, which are known to exist but are not fully defined. She and a group of researchers at UCSF have been analyzing additional potential markers of high-risk DCIS, which they would like to combine in a test. For example, they would include the activity of genes *p16* and *COX-2*, which are not in GHI's test.

Kerlikowske says the UCSF team has run comparative checks and found that DCIS Score "misses about half the invasive cancer" their method finds. The results are unpublished so far, however; Kerlikowske says she failed to win funding for a proposed full head-to-head comparison of the two assays. A company that was interested in the test 2 years ago has not yet moved ahead with it, she says.



Mammography's mixed impact. Breast screening surged in the 1980s (arrow), as did the detection of DCIS and localized cancers, but this didn't seem to reduce the worst, distant or metastasized, cancers.

Pathologist Agnieszka Witkiewicz and researcher Erik Knudsen of the University of Texas Southwestern Medical Center in Dallas have flagged a gene set that overlaps with UCSF's but also includes the well-known oncogenes *RB* and *PTEN*. "*RB* is probably our favorite," Knudsen says, because it gives more prognostic information in the group they've examined—DCIS patients from a Philadelphia clinic who had surgery but no radiation. He claims that this index "outperforms" DCIS Score in spotting the risk for certain types of invasive cancer. "If money were no object and I had a staff of thousands," Knudsen says, he would try to develop it.

Another DCIS risk assay still in the earliest stages of study focuses on protein levels in the duct's structure versus protein levels in the tumor. DCIS becomes invasive only when the duct gives way. In laboratory studies, Michael Allen and Louise Jones of the Barts Cancer Institute at Queen Mary University of London found that a protein known as integrin αvβ6, involved in cell signaling and attachment, was present at higher levels in the duct's myoepithelial cells when DCIS had become invasive. They report that this causes these ductal cells to change from tumor suppressors to tumor promoters. And they found a similar high level of αvβ6 in breast tissue from DCIS patients with invasive cancer. But Allen acknowledges that before these insights can be translated into a practical test, they must be tested in a clinical trial—and that would be difficult to carry off for many reasons.

Until these would-be rivals standardize their methods and carry out trials, says Steven Shak, executive vice president of R&D and co-founder of GHI, their claims must be taken as interesting but not proven. Shak, who is a co-author on the Solin paper, claims that DCIS Score is "widely used." He adds that it is being validated in a second, independent patient group, although he declines to "upstage" the researcher who's running the trial by releasing details.

Competition for all the test designers may be on the horizon. The U.S. Department of Defense's Breast Cancer Research Program has proposed to aid the hunt for better DCIS risk markers. So has the U.S. National Cancer Institute, which plans to spend about $5 million a year on such work, according to the director of its cancer prevention division, Barnett Kramer.

The help can't come fast enough, says Fran Visco, an attorney who heads the National Breast Cancer Coalition, an advocacy group in Washington, D.C. "We keep running down these roads putting a lot of time and money behind things but … we don't have the basic information that we need." She gets calls from women "all the time" asking what they should do about a DCIS diagnosis. Visco tells them to study the data and balance the risks and benefits for themselves, because, "we don't really know the answer." **–ELIOT MARSHALL**

GRAPH: ADAPTED FROM SEER DATA FROM OZANNE *ET AL.*, *BREAST CANCER RESEARCH AND TREATMENT* (9 MARCH 2011)