



BREAST CANCER EXPERT NANCY DAVIDSON  
TO LEAD UPCI | BY ELAINE VITONE

# A CHOICE CHOICE

On a bitter cold, windswept day in November 2008, Nancy Davidson is packing all she can into a whirlwind trip to the city that will, in a few months, become her home. At 1:30, she has an interview with the *Pittsburgh Post-Gazette*; at 2:10, with the *Pittsburgh Tribune-Review*. At 2:30, she'll pose for a photo shoot. Her mission later this afternoon: Find an apartment.

Davidson wears no trace of fluster on her face, no falter in the strides of her Michelle Obama–tall frame, despite the excitement building around her. Just days ago, Davidson, an internationally renowned breast cancer researcher, was named the new director of the University of Pittsburgh Cancer Institute (UPCI).

“Are there any plans to move any of your research here?” one reporter asks.

“This decision is pretty fresh—I only made it last week,” Davidson says. “These discussions are ongoing with my colleagues at Johns Hopkins. But we’re hopeful that we’ll be able to set up a collaboration.”

Davidson’s reputation precedes her: As a physician scientist. As the director of the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center’s Breast Cancer Program, one of the National Cancer Institute’s Specialized Programs of Research Excellence, or SPOREs.

Nancy Davidson  
assumes the director-  
ship of the University  
of Pittsburgh Cancer  
Institute on March 1.



(Her husband, Tom Kensler, a basic scientist who studies liver cancer at Hopkins, heads one of the subprojects of this grant.) As a former president of the American Society of Clinical Oncology, the largest and most prominent society of cancer physicians in the world.

In the coming weeks, Davidson's colleagues back in Baltimore react to the news with grace and good humor, despite their disappointment. "It's a win-win for everyone—except us," says her mentee Ben Ho Park, assistant professor of oncology at Hopkins and one of several who gave up time they didn't have for these bittersweet discussions. In stolen moments—while boarding a plane, taking a lunch break, driving home from the hospital late in the evening—they gush about what an exceptional director UPCI is gaining.

Park likens academics to professional sports—turnover and trades are just part of the game. Still, he says, losing a strong leader and team player like Davidson isn't easy.

"It's a shame for us and a huge, huge gain for you all," Park says. "The only reason I'm doing this is I feel like you all should know how lucky you really are."

Breast cancer research has come a long way since Davidson began her career in the early 1980s. At that point, lumpectomy as an alternative to radical mastectomy was a relatively new development, as was tamoxifen, a drug that is still widely used today. Much of the research that convinced doctors of the usefulness of these paradigm-shifting treatment strategies was spearheaded by Pitt's own Bernard Fisher (MD '43), Distinguished Service Professor of Surgery.

"It is an honor to take the lead at the University of Pittsburgh, where Bernard Fisher has led so many practice-changing clinical trials," says Davidson.

About 70 percent of breast cancers produce a protein called estrogen receptor, or ER—meaning they're dependent on the presence of estrogen to grow. Drugs that were designed to capitalize on this need—either by decreasing estrogen levels, decreasing ER expression, or stymieing the interaction between the two (like tamoxifen does)—were among the first cancer treatments of any kind that homed in on a particular, critical biological signaling pathway of a cancer cell in a relatively safe, nontoxic way.

For much of her career, Davidson has focused on how hormonal therapies worked for premenopausal women with breast cancer. She also ran one of the major clinical trials on

the efficacy of hormone therapy when combined with chemotherapy in younger women.

Unfortunately, not all women respond to hormone therapy. Some have tumors that do not express ER. Others have ER-positive tumors that respond to hormone therapy for a while, but then, after a time, the treatment stops working.

"I was distressed by that in the clinic," says Davidson. "So I went back to look at this in the laboratory. I think that bidirectional flow is really important."

In work published in several journals since 1994, Davidson found that one of the reasons certain cancer cells stopped producing ER was because of epigenetics—the environment, events, and mechanisms that contribute to the gene's silencing. That is, though the structure of the DNA remains intact, other changes are introduced that prevent the gene from being expressed.

Other laboratories have begun to develop two new types of therapies, which Davidson's team has begun to test in her lab and clinic: DNA methyltransferase inhibitors (drugs that prevent epigenetic changes to the DNA itself)

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and histone deacetylase inhibitors (drugs that counteract the epigenetic changes to certain proteins that work closely with DNA and directly influence its functioning).

"The notion of restoring the ability to treat these breast cancer cells with tamoxifen is very exciting," says Bill Nelson, director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. "That's been a major discovery of the basic biology of the disease."

"This is the next level of understanding the complexity of cancer," says Pitt's Allegheny Foundation Professor John Lazo, who cochaired UPCI's search committee for a new director.

The story of hormone therapy illustrates something Davidson describes as one of the more "insidious" characteristics of the disease she's spent decades fighting—or we should say "diseases."

"Although we call it one disease," she says, "breast cancer is in fact a whole bunch of different diseases. A lot of things have to go awry in a cancer cell, and they may be very different depending on the cell of origin. Increasingly, [research] is going to be very focused on specific biological subsets of breast cancer."

Davidson has contributed to numerous clinical trials that illustrate this biologically based approach. One was for a study of trastuzumab (Herceptin), an antibody that interferes with the tumor growth receptor HER2. This trial led to FDA approval for the drug to treat early breast cancer.

She was instrumental in a large international trial of aromatase inhibitors, agents that decrease the body's production of estrogen. The study was initially intended to last five years, but its results were so promising so early on that organizers discontinued the placebo group after three.

Davidson also led several studies of an angiogenesis inhibitor—a drug that chokes off cancer's blood supply. Most recently, she published in *The New England Journal of Medicine* her findings on one in particular: bevacizumab (Avastin), a drug that the FDA approved last spring. She found that, though bevacizumab did stave off breast cancer recurrence, it offered no advantage in actually prolonging life. Given the side effects of this toxic agent—not to mention the high costs associated with it—the study brought controversial issues of oncology to the fore.

Clinical research is by nature a slow process.

And in the case of breast cancer, it takes a long time to compare one course of treatment to another. It's the best possible problem: Patients are living longer, healthier lives now than ever before.

"It takes a lot of patience," Davidson says as she recalls one large clinical trial she began working on more than 20 years ago. It studied what hormone therapy might add to chemotherapy for premenopausal women with certain kinds of breast cancer. "I remember I wrote [the clinical protocol for the trial] around Christmas 1987—because that was the year my son was born," she says. "And I had the chance to actually publish [the results] in the month that my son went to college."

The paper, which was published in the *Journal of Clinical Oncology* in 2005, got its start with the support of ECOG (Eastern Cooperative Oncology Group), a collaboration between multiple clinical cancer research organizations. Like its Pittsburgh-based counterpart, NSABP (National Surgical Adjuvant Breast and Bowel Project, of which Fisher was the founding chair), ECOG was established to allow researchers to pool their most precious and critical resources—patient volunteers.

Davidson is a big believer in the value of collaborative efforts—particularly when it comes to

the earliest stages of clinical trials, where blood and tissue sample results can help researchers triage potential therapies in the pipeline.

To this end, she helped organize the Translational Breast Cancer Research Consortium. As the consortium's chair, Davidson hopes that eventually the 15-member consortium will add Pitt.

"There are a lot of ideas and opportunities," she says, "and a finite amount of resources. Financial resources are even more constrained right now. We want to make sure we've used patients who volunteer in the wisest path possible."

"It is a pleasure to succeed Dr. Herberman, the founding director of the UPCI," Davidson says. "Ron is revered by all because of all that he has accomplished. He has put UPCI on the cancer landscape map, making it one of the top NCI-funded institutes in the country." (See story on p. 12.)

Davidson has her own admirers. Colleagues marvel at how she's able to wear so many hats with such apparent ease. "Physician-scientists are kind of a dying breed," says Park. "But Nancy has managed to do both—and do both extremely well. She doesn't do anything halfway."

Eric Winer, director of the Breast Oncology Center at Harvard University's Dana-Farber Cancer Institute, has known Davidson for 18 years and most recently worked with her through the Translational Breast Cancer Research Consortium.

"All of this is done in this very calm and quietly confident way," says Winer of Davidson's role with the consortium. "She leads very large efforts without making a fuss."

Davidson has honed a particular skill as a unifier. Lazo notes that after years of large-scale collaborative efforts, she's been able to bring together surgeons, internists, basic scientists, geneticists, biochemists, surgeons—you name it—and learned to speak everyone's language.

She doesn't panic or get overwhelmed, her friends and colleagues say. And Davidson knows when she needs help and isn't afraid to delegate. When she does, people don't mind.

"As long as I know what the plan is, I'll do anything for her. I'll do back flips," says Carol Riley, a nurse practitioner who's known Davidson for 20 years and worked with her for 10.

Davidson's mentor Marc Lippman—former head of the Medical Breast Cancer section of the National Cancer Institute and current chair of the Department of Medicine at the University of Miami—calls her knowledge of breast cancer "encyclopedic." In Davidson's leadership roles, scientific sleuthing, and one-on-one interactions with patients, she's known as a reassuring, neutral voice, a wise mediator who can systematically take apart even the most dauntingly complex problem and formulate a plan.

For instance, when patients come to Davidson's clinic, it's not uncommon for them to feel paralyzed by all the forks in the road: Radiation or not? Chemo or not? Standard of care or clinical trial? And how on Earth to manage working *and* taking care of the kids *and* undergoing treatment?

"She has a way of cutting through all the nonsense and getting right into the issue," says Riley. "She'll give them a time frame and say, 'Okay, for the next five days we'll think about this decision only,' or 'You need to decide that in three weeks you will have made this decision and put it behind you.' She's very methodical."

But as people point out all of this, they're quick to add that Davidson is no robot. She inspires loyalty in her colleagues and forms close bonds with her patients. "As we've been announcing to her patients that she's leaving," says Riley, "several have cried."

Davidson has a delightfully wry sense of humor, people say again and again with knowing laughs. Funny thing, though: They all have trouble coming up with examples.

"Nancy is not a stand-up-in-front-of-the-room-and-crack-10-jokes kind of person," says Nelson. "You'll share a more private exchange with her that will leave you chuckling."

Perhaps her indifference to the spotlight plays a part in why she's become so accomplished—and, ironically, so lauded.

"From the top down," says Park, "Nancy has always impressed upon all of us that our mission is not winning awards or money or accolades."

"It's really about making a difference across the street, where our patients reside."

Carolyn De Wilde Casswell was 34 when she was diagnosed with late-stage breast cancer. It had spread throughout her bones, from her head to her pelvis. And yet she felt no pain.

When it was time to choose an oncologist, De Wilde Casswell chose carefully—in all, she met with seven doctors. "And it was a team approach," she says, recalling that day in 2002 when she first met Davidson. De Wilde Casswell brought her entire family—her husband, parents, brother, and sister.

"We had to keep bringing in more chairs," she says with a laugh.

"On that first day Nancy met me, she had to tell me I don't have a normal life expectancy, that I can't have children, and that I needed to be thinking about breast cancer as a chronic illness. The only good news—I was an excellent candidate for hormonal therapy."

"She looked me straight in the eye, even with my whole family in the room, and said, 'This is what you're up against.'"

De Wilde Casswell felt like she was getting the absolute truth and best possible care from an expert. At the same time, Davidson was able to deliver the very worst imaginable news with kindness and a sense of hope.

That was it. Davidson was drafted to the team. De Wilde Casswell began a hormonal therapy and years later added a phase I vaccine clinical trial, all recommended by Davidson.

Every month, when De Wilde Casswell leaves Hopkins after her treatments, she makes a point to do something special. She started this tradition purely by accident. On the day of her first treatment, as she was leaving the hospital, she noticed that just down the street, her alma mater, Cornell University, was playing in the NCAA women's lacrosse championship semifinals. De Wilde Casswell had played lacrosse in college. She took a place at the sideline.

"It was incredible," she says. "Seeing those running, vibrant athletes and all the cheering and the exertion. It reminded me how hard I needed to work, given what I was up against."

And as she cheered, her own voice becoming part of a chorus, perhaps she was also reminded of who was on her side. ■

