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## Cancer Care Revolution

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Nine years ago, Jane Lee was diagnosed with late-stage breast cancer.

At the time, it seemed a death sentence. The Piedmont resident, then 62, was among the 20 to 25 percent of breast cancer patients with the HER2 gene, which causes abnormal cells to divide quicker. Women with HER2 usually relapse more often and die quicker.

But Lee received a just-approved cancer drug Herceptin from Genentech Inc. of South San Francisco that targets the HER2 gene. Within six months, her cancer had gone into remission. This summer, she plans to travel to Scotland and golf at legendary St. Andrews Links.

"When they say the word 'cancer' you just can't believe what word was just said. ... Your life flashes in front of your eyes," Lee said. "But thanks to Herceptin, my life was saved. There's no question I would not be here today if it were not for the therapy."

Lee is on the front lines of a cancer care revolution. Thanks to targeted therapies and better diagnostic tools- many of them developed by Bay Area companies and research institutes- cancer patients are living longer and have more hope of surviving the disease.

"It's an incredible time, because every day there's a breakthrough in cancer, and it seems like a new drug is coming out all the time," Lee said. "And most of it is happening right here in the Bay Area."

The progress is clear, as cancer specialists gear up for this week's annual meeting of the American Society of Clinical Oncology in Chicago. According to numbers released this year by the American Cancer Society, for the second consecutive year, between 2003 and 2004, the number of cancer deaths dropped despite a rise in total population.

"Those are numbers that are most important, because they are the ones that tell us we're making progress," said Peter Jones, director of the Cancer Center at the University of Southern California.

Dr. David Nathan, author of "The Cancer Treatment Revolution," said many patients who years ago would have been given a fatal diagnosis can now enter complete remission and live in good health because of the innovations.

"In the 1950s, women with breast cancer were being treated terribly, and if they had a Stage 3 cancer where it had spread beyond the breast, only 20 or 30 percent survived very long," said Nathan, a professor of medicine at Harvard Medical School. "Today, with the combination of chemotherapy, drugs that block estrogen and radiation therapy, 80 to 85 percent of patients with that diagnosis can survive to live a good life."

"That is what we call a true revolution," he said.

South San Francisco's Genentech is the top U.S. cancer company based on sales. In the Bay Area alone, at least 30 companies have some kind of cancer therapy or diagnostic tools on the market, seeking approval or in clinical trials. More than 160 cancer drugs and devices are in mid-or-late stage trials in

Northern California, according to trade association BayBio. And in California, more than 460 clinical trials are focused on various forms of cancer, according to Cancer411.org.

"The critical mass of companies we have here in the Bay Area involved in cancer drug research is incredible," said Alex Tkachenko, vice president of corporate affairs for Hana Biosciences Inc. in South San Francisco.

Hana is devising therapies to target side effects of cancer therapies, such as a severe rash prominent in patients who take Genentech's Tarceva.

"We are, without a doubt, in the midst of a dramatic improvement that is unparalleled to anything we have ever seen before," Tkachenko said.

'Smart drugs'

Today, Lee goes to San Francisco several times a month to make sure her cancer stays in control.

It's Herceptin's ability to help a patient like Lee lower her chance for recurrence that makes this drug so revolutionary, said David Schenkein, head of Genentech's oncology clinical trials.

"If you have a drug where you can drop the recurrence by 50 percent where if they don't recur, they won't die, then you've basically changed the game for HER2-positive breast cancer," he said. "Finally, we are seeing breakthroughs that are turning an incurable illness that has a short survival rate to one that's a chronic illness where a longer more normal life is possible."

Genentech is at the forefront of the battle against cancer, having developed three of the most promising drugs- Herceptin, Rituxan for non-Hodgkin's lymphoma and Avastin for non-small cell lung cancer and colorectal cancer. Another key cancer drug is Novartis' Gleevec for chronic myeloid leukemia.

Between 1997 and 2001, Rituxan, Herceptin and Gleevec were the first targeted therapies to be approved by the U.S. Food and Drug Administration. Gleevec, the drug state Sen. Carole Migden said she is taking to treat her chronic myeloid leukemia, was the first small molecule cancer therapy, which means it is taken as a prescription pill rather than intravenously.

Genentech's Avastin, already a blockbuster drug, has even broader potential, as it is in more than 100 clinical trials including breast, kidney, prostate and pancreatic cancer.

Other Bay Area **biotechnology** companies, some Genentech spinoffs, also are focused on fighting cancer. For Exelixis Inc. in South San Francisco, the more compounds it can develop and throw at the cancer tumors to see how they react, the better. Exelixis has 14 compounds in development that are made to address certain liabilities some cancers have, including XL 647, which will hit three molecular targets that are already the subject of Genentech's Tarceva, Herceptin and Avastin at the same time.

Targeted therapies such as XL 647 are often referred to as "smart drugs" because they aren't a one-size-fits-all approach to cancer treatment, but use drugs focused on specific characteristics of the gene. Smart drugs work because they bind to one specific gene or protein in a cell.

"We still have a long way to go in this battle," said George Scangos, chief executive of Exelixis, "but as we understand more and more about cancers, I'm confident we will come up with the right combinations for treating specific cancer diseases."

A nasty disease

The first description of cancer is believed to have come in 1600 B.C., when eight tumors or ulcers of the breast were identified.

In its simplest definition, cancer is a disease in which abnormal cells divide without control. Because there are so many variations of cancer from person to person and organ to organ, it is considered one of the nastiest diseases to treat.

The most common way of treating cancer is combination therapy. In this method, first devised in 1960 at Stanford University, a patient is given three to five drugs that indiscriminately kill rapidly dividing cells, thus trying to contain the disease.

This chemotherapy was a breakthrough in some instances, such as pediatric leukemia, but not others. Moreover, its toxic nature, "often likened to Napalm," would kill cancer cells but also damage normal cells, Schenkein said.

When targeted agents were added to chemotherapy, incredible strides started to be made against cancer.

"In the 1950s, 1960s and 1970s, the way we fought cancer was to scour the Amazon for leaves, grind them up and look for a chemical that shrinks a tumor," Schenkein said. "The biggest thing that has changed is we are finally able to better understand the basic biology that causes a tumor to develop and grow and spread."

In 1971, President Nixon declared war on cancer by signing the National Cancer Act, which established a national cancer research program. The fruit of some research begun several decades ago is just now showing its significance.

Still, the battle never has been easy. And total victory is far off.

In 2007, the American Cancer Society estimates that about 1.4 million new cancer cases will be diagnosed in the United States- more than half from prostate, lung, breast and colon cancers- and there will be nearly 560,000 deaths. In 2007, it's estimated that 133,225 Californians will be diagnosed as having cancer and 54,300 people will die of the disease.

"It has always been extremely challenging and frustrating, because for so long we were only able to just chip away at the battle against cancer," Schenkein said. "But just in the last few years, suddenly we are taking huge leaps against some of these cancer diseases that we never imagined possible before."

### Managing the disease

In 2001, Miles Afflek of Vacaville was diagnosed with Stage 4 colorectal cancer and his future looked bleak. He entered a clinical trial at Stanford with 56 other patients with different backgrounds but the identical diagnosis. Afflek is one of only two who are still alive.

"Maybe I just had a better attitude, but honestly I really don't know. I was just fortunate," said Afflek, 55.

And that's one of the big challenges, determining why someone like Afflek responded to the therapies so much better than anyone else.

"Because the human body and cancer itself is so complex, comparing one person's cancer to another may appear the same on an X-ray, but they may be driven by completely different proteins and different pathways in reality," Schenkein said.

Doctors have more treatment options now. In 1991, there was only one drug available to treat colon cancer. In 2001, at the time of Afflek's initial treatment, 13 drugs were available. Today, there are more than 35, with a handful more seeking regulatory approval.

"There's absolutely no question that more would still be alive today, if that same trial was started in 2007," Afflek said. "I know when I say this, it sounds crazy, but if you're ever going to get cancer, this is a

pretty good time to get it. While it's still not curable, there is such a better opportunity to try and control and manage the disease now than when I was first diagnosed. I try to tell people that we are getting to the point where cancer like I have no longer has to be a death sentence."

In fact, Afflek credits Genentech's Avastin with helping save his life. He started the drug two years after his initial diagnosis.

This drug has garnered special industry attention because it targets a process called angiogenesis that is present in nearly all types of cancer and works to suppress tumor growth.

"Basically, the idea is if the tumor doesn't have a blood supply, it can't grow," Schenkein said.

Because every cancer depends on new blood vessels for its growth, Avastin has broad potential. Companies often test the same drug several times to fight the same disease at different stages of the cancer process.

"It's these early stages of cancer where we believe that the highest potential of possibly finding a cure for cancer might be found," said Krysta Pellegrino, a spokeswoman for Genentech.

'Like an armadillo on a highway'

For some cancers, though, progress has been slow.

Lung cancer, for example, accounts for the most cancer-related deaths in both men and women, followed by colon, breast, pancreatic and prostate cancers.

Once a person is diagnosed with lung cancer, the prognosis is grim. The five-year survival rate for all stages combined is only 16 percent. If the cancer is detected when the disease is still localized, survival is 49 percent, but only 1 in 6 lung cancers are diagnosed at this early stage, according to the American Cancer Society.

Because much of lung cancer is caused by cigarette smoking, most of the headway made here is in prevention. Still, scientific breakthroughs have given hope to patients in even the most dire of situations.

For Sarah Schneider, 64, of Concord, her bout with lung cancer started with a lingering cough and tiny traces of blood in the mucous in March 2006. Her doctor said she shouldn't worry but did order X-rays. She said she knew right away it was her lungs.

Her mother, two uncles and an aunt died of lung cancer.

"I remember asking my mother once, 'How did you know you had lung cancer, and she said she had a pain in her back,'" Schneider said. Schneider, too, had pain in her back.

Shortly after, doctors found cancer cells that were very deep. Her surgeon had to do an invasive procedure to see how bad it was.

"I'll never forget my surgeon who said she reached inside me and when she found the tumor, it felt something like an armadillo on a highway," Schneider said.

Having seen the misery her mother went through, Schneider realized her prognosis was bad.

"When I left the hospital in March (2006), I didn't really think I would make it to Christmas," she said.

That's when her oncologist told her about Genentech's Tarceva. She was told that it only had a 15 percent chance of working, but if it works, "she'd hit a home run."

Like Herceptin, Tarceva is a targeted therapy that goes after a specific receptor that is most notably in lung and pancreatic cancer, but could play a role in head and neck cancer and colon cancer.

Schneider's tumor responded almost immediately to Tarceva.

Schneider did survive to see Christmas and resumed her part-time tutoring of grade school children.

But in December, she decided to stop taking the Tarceva because there was swelling in her leg, which is not a common side effect. This spring, the cancer returned, and she just began chemotherapy.

With only 2 percent of patients with Stage 4 cancer surviving more than five years, she knows her situation is still grim but remains hopeful. "Compared to what I saw my mother go through, it's completely different," Schneider said. "I look fantastic and I can still carry on a normal life no matter what the future has in store."

Filled with challenges

The future looks bright in the battle against cancer, but it is filled with challenges. The average cost for a company to develop a new drug is \$800 million, and the time for FDA approval is 14 years. And only a single-digit percentage of drugs that enter clinical trial ever make it to market.

"Right now we are riding a wave of enthusiasm, but it is going to come to a screeching halt if we can't pay for what we feel we are capable of doing," Nathan said.

These targeted drugs are expensive. A treatment of Genentech's Avastin for lung cancer runs about \$100,000 a year and for colorectal cancer about \$30,000 to \$50,000 a year. Tarceva treatment costs about \$30,000 to \$36,000 a year. The Avastin Patient Assistance program, which went into effect this year, places an annual cap on the cost of the drug in approved indications, regardless of the patients' insurance, so the yearly wholesale average cost would be \$56,320 for lung cancer and \$46,640 for colorectal cancer.

"When the public realizes more and more what is possible, I believe they will rebel against and stand up to health care to make sure a drug like Herceptin is available to them," Nathan said.

An ally is FDA Commissioner Dr. Andrew von Eschenbach, who has helped lead the fight against cancer for the last 30 years. As a respected oncologist, a cancer survivor and former director of the National Cancer Institute, von Eschenbach understands the important changes in medicine and the challenges ahead.

"The medicine we have available today will look no more like the past than a butterfly looks like a caterpillar," von Eschenbach said at a biotech conference in the Bay Area in April. "This personalized medicine offers enormous opportunities, but also tremendous challenges."

"Our role," he added, "is going to be a bridge from discovery to delivery and not a barrier."

One way experts say to drive down costs is to determine which patients are most likely going to benefit from new therapies. That's where the importance of diagnostic companies and predictive medicine comes in. Not only are they able to determine what kind of disease a person has, but also the best combination of drugs to treat the patient.

"I think in five years you will see a number of products on the market that will help guide doctors in making this decision," said Bill Young, chief executive of Monogram Biosciences Inc. in South San Francisco, whose technology helps speed development of targeted cancer treatments.

Some experts liken the cancer care revolution to the HIV/AIDS epidemic. In the 1980s, an AIDS diagnosis was akin to a death sentence, whereas today the virus is treated more like a chronic illness, such as

diabetes and high blood pressure.

“In the near future, we'll be talking about some of the drugs that are being invented today combined with new ones that will be out in 2011, and we will see survival lengths that 10 years ago were never even in the mind of thought,” Schenkein said. “In the past, where the only hope we could provide for patients might have been a compassionate arm, now we can do something to give them a much better chance at survival.”