found that risk of heart failure was highly increased over 5 years in those taking trastuzumab alone or with an anthracycline as adjuvant therapy, compared with those given chemotherapy or anthracyclines alone, with risk rising with age (JNCI, Sept. 5, 2012). Risk of anthracycline-associated cardiac problems among women younger than 65 years was similar to that seen in randomized clinical trials, but trastuzumab-associated risk was greater than reported previously. Most studies are done in the context of clinical trials, with patients selected for few comorbidities, and show fairly low rates of cardiotoxicity, about a 2% increase with anthracyclines, and 4% over 3–5 years adding trastuzumab, Bowles said.

Her study indicates that damage increases in the last year, with no evidence of plateau, Ann Geiger, Ph.D., M.P.H., of Wake Forest School of Medicine in Winston-Salem, N.C., commented in an editorial. The risk of heart failure in women with nonmetastatic disease taking trastuzumab is equivalent to or greater than that reported by clinical trials, Geiger concurred.

But a third study, a phase III 7-year follow-up trial part of the National Surgical Adjuvant Breast and Bowel Project (B-31), analyzed a younger, healthier population. E.H. Romond, M.D., professor of medicine at the University of Kentucky Medical Center in Lexington, found that risk of cardiotoxicity increased only for those on trastuzumab or anthracyclines plus trastuzumab, and late heart failure was uncommon (online Sept. 17, 2012, Journal of Clinical Oncology). Perez, an author, noted that the first two studies were retrospective, with limitations. “We don’t see those high rates in our clinic, and we believe that the combination provides an edge for patients in survival and recurrence,” she said, adding that much more data are needed before one can change regimens from anthracycline to taxanes and that evaluation of ejection fraction should be done before starting therapy.

Anticipating and Modifying Risk
Anthracyclines and trastuzumab act synergistically to damage the heart, but in different ways, and risk and damage from both may be modifiable. Type I damage from anthracyclines generally produces irreversible, dose-dependent death to heart muscle cells, which increases over time, taking months to years to manifest, but may be reversible when caught early. Risk factors for anthracycline damage include prior use of these drugs, hypertension, and age.

Monitoring cardiac function before, during, and after anthracycline and/or trastuzumab helps physicians detect early damage, enabling regimen modifications—but this too is controversial, and practice varies widely, less so in patients with preexisting risk factors. Monitoring no- or low-risk patients after four to five cycles of doxorubicin treatment could help identify patients with asymptomatic decrease in systolic function, Ewer said. The iron chelator dexrazoxane may be given to protect against anthracycline cardiotoxicity, as can other cardioprotective drugs, including ACE (angiotensin-converting enzyme) inhibitors and statins.

Researchers believe that trastuzumab affects cell repair mechanisms of the heart, which expresses HER2. Type II heart damage from trastuzumab is not tied to cumulative dose but to number of treatment sessions, manifesting as an asymptomatic decrease of left ventricular function, and is more reversible than anthracycline damage. Used sequentially, especially 3 months after an anthracycline, it causes less damage than when given with or near the same time as anthracyclines. Researchers are investigating echocardiography as a means to both detect presymptomatic damage and evaluate cardioprotective treatments. Biomarkers such as cardiac troponins may someday be used to predict and detect early chemotherapy-induced damage.

“Ultimately, these drugs have been shown to extend survival,” said Bowles. “We just need to be careful whom we give these drugs to, because there are risks, which shouldn’t be ignored,” she said.

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How Next-Generation Sequencing Could Change Cancer Care

By Leslie Harris O’Hanlon

Next-generation sequencing (NGS) has improved how clinicians better gauge risk of developing cancer and increasingly has helped doctors tailor therapies to treat cancers with specific genetic mutations.

As more clinics use NGS—techniques that probe millions of DNA fragments for mutations at a time—more changes are coming for both cancer prevention and care.

NGS To Improve Cancer Treatment
Genes consist of linear sequences of four DNA nucleotides, or bases. In humans, every cell with a nucleus contains a copy of the entire genome—more than 3 billion DNA base pairs. Sequencing, then, is figuring out the order of DNA bases in a genome and seeing whether any letters are out of order, called a mutation, or variant. Most variants are harmless, but some can put people at higher risk of developing cancer and other diseases. Older gene
sequencing techniques can check only small fragments of DNA at a time. NGS, however, can scan many millions of base pairs—or the entire genome—for mutations at once. These sequence fragments are then checked against a reference genome to look for variants.

Through NGS, doctors can target scores of genes or unravel the genome of one's cancer, searching for mutations that cancer-fighting drugs could then target.

“In tumor genetics, there is no question that the introduction of NGS technologies has already added substantially to the care of individual patients with cancer, as therapies aimed at genomic targets offer the promise of improved efficacy and decreased toxicity,” said Kenneth Offit, M.D., chief of the clinical genetics service at Memorial Sloan-Kettering Cancer Center in New York.

For example, researchers used whole-genome sequencing to delve into tumor tissues of women with notoriously hard to treat triple-negative breast cancer. They found alterations in several genes, which led to placing these women in clinical trials of drugs that target some of those pathways. The study was published online last November in *Molecular Cancer Therapeutics.* Jeff Boyd, Ph.D., senior vice president of Fox Chase Cancer Center in Philadelphia, spoke of a man with pancreatic neuroendocrine cancer who had a panel of genes sequenced in his tumor. Doctors discovered that the man carried a mutation in the KIT gene, a mutation implicated in many gastrointestinal stromal tumors and other cancers, and can be treated with imatinib (Gleevec). So, doctors then gave the man imatinib as well.

“This patient received imatinib and is alive and well 2 years later, when he would have been dead otherwise,” Boyd said.

Fox Chase is one of a few cancer centers that are, or soon will be, using next-generation techniques to sequence genes in tumors of cancer patients. The center uses a test that targets 45 genes related to cancer.

“We are finding more genes that are relevant, druggable, and of prognostic significance,” he said. “And that can make all the difference in prolonging someone's life.”

Massachusetts General Hospital in Boston will move to NGS this summer, said Leif W. Ellisen M.D., Ph.D., co-executive director of the hospital’s translational research laboratory. The new test will conduct exome sequencing for about 1,000 genes known to play a role in cancer.

“Rather than being enrolled in clinical trials based solely on cancer site of origin, patients can have access to trials designed for specific cancer mutational subsets,” Ellisen said.

The Institute for Translational Oncology Research at Greenville Hospital System University Medical Center in Greenville, S.C., is just starting to use NGS technology to sequence some patients’ tumors. One goal is to better match patients to clinical trials offered at the center, explains Joe Stephenson, M.D., medical director of the institute.

“The traditional way of taking patients—exposing them to a drug, looking to see whether there was some modicum of activity, and trying to advance that into a phase II or III trial—was cost prohibitive and in need of significant change,” he said.

Stephenson hopes that DNA sequencing will become as routine as blood work. He envisions that patients’ tumor genetic profiles will be part of their chart, along with information about their health, whether they smoke, and other lifestyle factors. The ultimate goal is for all patients who have cancer surgery to have their tissue harvested and preserved, as well as to put molecular information about that tumor in a registry. And if a drug comes along that targets that person’s particular tumor profile, he or she would get it.

But finding the right drug to match specific mutations isn’t easy. Mutations in a cancer can be numerous and different, said Eric Collisson, M.D., assistant adjunct professor in the division of hematology–oncology at the University of California, San Francisco. Some play a bigger role in spurring the cancer than others.

“Not all mutations are equal. There could be different mutations in different subpopulations of cancer cells,” Collisson said. “We are now beginning to understand that every cancer is a little ecosystem interacting with its microenvironment.”

So sequencing the genes in patients’ tumors may not yet translate into better care for all of those patients—but it could someday. Researchers need to gather as much information as they can about different genes and mutations and show that focusing on those pathways can slow or stop the spread of cancer.

**NGS and Hereditary Cancers**

Most cancers occur because of random genetic mutations. However, about 5%–10% of all cancers are hereditary. NGS has allowed genetic counselors and doctors to study 20 or 30 genes (maybe add “at a time” here) of all cancers are hereditary. NGS has allowed genetic counselors and doctors to study 20 or 30 genes (maybe add “at a time” here). I don’t want people to think that there are only 20 to 30 genes known to predispose people to cancer. There are about 70 such genes. NGS allows clinicians to look at 20 to 30 of them in one go instead of looking at single genes. That could predispose someone to cancer, including breast, ovarian, colon, renal cell carcinoma, and endocrine tumors, instead of looking at genes individually. But some of the genes included in these panels may confer a slightly elevated risk of developing cancer, explained Kristen Mahoney, MS, CGC (certified genetic counselor), program manager and senior genetic counselor at Mass General. For instance, a mutation in...
the CHEK2 gene gives a twofold increased risk of developing breast cancer over the general population.

“It’s not a huge risk, but a little bit higher,” Mahoney said. “Also, there are other genes on these panels that scientists think might play a role in hereditary cancer, but the data are really not there yet.”

Also, as sequencing technology improves, many suspect that it will be more cost efficient to sequence genomes rather than a slew of specific genes. If this happens, health care providers could find mutations that have nothing to do with cancer.

“In 5 years or less we are going to be doing more whole-genome sequencing. But it has to be done with more thoughtfulness,” said Mahoney. “When I see a cancer patient and order one of these genetic tests, I will be getting not only information about cancer risk but also information about Alzheimer, Huntington disease, diabetes, and other things. So it’s very important to have a genetics professional there at the very beginning who can say, ‘Yes, you may want to know about your cancer risk, but do you really want to know about your Alzheimer risk?’”

NGS Offered as Routine Screening

As sequencing technology improves and gets cheaper, some suggest that clinicians may need to think about offering NGS as part of routine preventive care. Sequencing 30 or so genes to detect mutations known to cause serious but preventable diseases—such as some cancers and forms of cardiovascular disease—may be feasible, said James Evans, M.D., Ph.D., a professor of genetics and medicine at the University of North Carolina at Chapel Hill. Evans cowrote an editorial on the matter in the March issue of *Genetics in Medicine*.

“Because we can now find these mutations in people for several diseases and we have good preventive techniques for these diseases, the time is right for us to begin thinking of ways to prevent these diseases in the first place,” Evans said. “There’s no reason that we couldn’t look at a handful genes for mutations and turn those results around in a week. In the past, that would have been so expensive and cumbersome to do.”

Evans said about 1% of the general population is unaware that they carry mutations that put them at higher risk for preventable diseases. For instance, about 1 in 400 people in the United States are at risk for Lynch syndrome, an inherited genetic predisposition that causes people to develop colon and other gastrointestinal cancers at an early age. Usually, people with this predisposition wouldn’t know it until several close family members developed colon cancer, prompting a doctor to suggest screening for the mutation. So, instead of waiting until a family member is diagnosed with cancer, people could be routinely screened, at a cost of a few hundred dollars, to see whether they carry the mutation. If so, they could be given colonoscopies earlier and monitored for colon polyps, which can be removed before they progress to cancer.

Discussions of which genes to include in such a panel will take time, as will researching the expense of offering these tests to the public, as well as exploring ethical and legal implications, the researchers wrote. Robert Nussbaum, MD, chief of the division of genomic medicine at UCSF added that widespread NGS would have to be done with care and good genetic counseling in place.

“If this technology is not used properly, there will be large numbers of people who think they are at much greater risk of cancer than they are,” he said. “And they will turn into very anxious, worried people who constantly go to the doctor, use medical care, and undergo lots of unnecessary testing.”

Whatever happens, NGS will continue to be an important part of cancer risk detection and cancer care.