Hospital of Philadelphia and the University of Pennsylvania. For example, in a recently published study, researchers sequenced tumors from 91 children and young adults and found potentially actionable mutations in 46%, some of which triggered changes in treatment (JAMA 2015;314:913–25).

However, the study's authors highlighted significant barriers to delivering appropriate therapies, notes Maris, including a dearth of pediatric clinical trials and often nonexistent pediatric dosing information. As a result, they may be prevented from accessing potentially effective treatments even if an appropriate targeted therapy exists.

"The pediatric oncology community is facing the very urgent issues of defining proper mutation drug matches, making sure they work in the preclinical setting, and figuring out how to get them to children," says Maris. "Routine genetic sequencing and prospective clinical trials in children are the first steps toward breaking down those barriers." –*Janet Colwell* ■

Liquid Biopsy Holds Its Own in Tumor Profiling

According to results from the largest liquid biopsy study to date, the genetic changes detected by analyzing circulating tumor DNA (ctDNA) in blood samples largely reflect those identified through conventional tissue biopsy. The data were presented by Philip Mack, PhD, director of molecular pharmacology at the University of California, Davis, Comprehensive Cancer Center in Sacramento, during the American Society of Clinical Oncology's annual meeting in Chicago, IL, June 3–7.

The investigators used Guardant360 (Guardant Health), a commercially available liquid biopsy that profiles 70 genes, to assay blood samples from 15,191 patients with 50 cancer types. They looked for four classes of genetic changes: point mutations, small insertions or deletions, amplifications, and chromosome fusions. Guardant360's digital sequencing platform "is highly sensitive," Mack said, "which was crucial for our study, because even at very low ctDNA fractions—often below 0.4% of the total DNA in circulation—we were able to detect genetic abnormalities."

Mack reported that the mutation patterns detected via liquid biopsy were "highly consistent" with published tissue biopsy data from The Cancer Genome Atlas (TCGA). In *EGFR*, for example, "the exact same activating mutations reported in tumor tissue by TCGA were observed in our study," he said. When the investigators compared ctDNA sequencing data with matched tissue biopsy results from 386 patients, they found that the former's overall accuracy was 87%, increasing to 98% in cases where blood and tumor samples were collected less than 6 months apart.

The key difference with ctDNA sequencing, Mack added, is that it detected the presence of resistance mutations such as T790M and C797S in *EGFR*. T790M typically emerges as non–small cell lung cancer begins to circumvent erlotinib (Tarceva; Genentech). Although antitumor activity can be restored with next-generation tyrosine kinase inhibitors like osimertinib (Tagrisso; AstraZeneca), secondary resistance mutations, namely C797S, often appear.

"These alterations aren't present in the tumor at the time of an initial tissue biopsy—you'd need follow-up biopsies of metastatic lesions to spot them," Mack explained. "That's still the gold standard, but if you could use plasma instead—and I think our study shows that this is feasible—it would be much less invasive for patients."

Liquid biopsies are "a useful alternative to tissue-based testing, especially for patients with tumors that are challenging to access," said Sumanta Kumar Pal, MD, a medical oncologist at City of Hope Comprehensive Cancer Center in Duarte, CA. "Given the availability of other platforms besides Guardant360, rigorously defining which one provides optimal results will be key." Pal also opined that to fully utilize blood tests in cancer, an oncologist should enroll the patient in a clinical trial like NCI-MATCH or MyPathway.

"A tissue biopsy will always be required upon initial diagnosis to assess the cancer's morphological features," Mack emphasized. "I see ctDNA analyses as having more of a complementary role, mainly for serial assessments of a tumor's evolving sensitivity to therapy as disease progression occurs." –*Alissa Poh* ■

Trial Validates Biosimilar for Trastuzumab

A trastuzumab (Herceptin; Genentech) biosimilar is as safe and effective as its brand-name counterpart for women with HER2-positive advanced breast cancer, according to data presented during the annual meeting of the American Society of Clinical Oncology in Chicago, IL, June 3–7. The findings pave the way for the first FDA approval of a biosimilar for cancer.

In the international Heritage trial, 500 patients with metastatic HER2-positive breast cancer were randomized to receive taxane chemotherapy (docetaxel or paclitaxel) with either the biosimilar MYL-14010 (Mylan) or trastuzumab every 3 weeks for 24 weeks, followed by trastuzumab alone until disease progression.

Women treated with MYL-14010 had a 69.6% objective response rate—the primary endpoint—compared with 64% among women in the trastuzumab arm. The rates of serious adverse events were comparable at 36% (trastuzumab) and 38% (MYL-14010), with neutropenia being the most common.

If approved, the biosimilar could offer a lower-cost alternative to trastuzumab, which has been the cornerstone of therapy for HER2-positive breast cancer, said the study's lead investigator, Hope Rugo, MD, professor of medicine at the University of California, San Francisco, who presented the findings. Investigators will evaluate progression-free survival after participants have completed therapy with trastuzumab alone, she added.

Mylan has already received approval to market MYL-14010 in India, where it is branded as Hertraz. The FDA will consider data both from its use in that country and from the Heritage trial when evaluating the drug's safety and efficacy, said Rugo.

Several other companies—including Pfizer and Amgen—are working on their own versions of trastuzumab, which loses U.S. patent protection in 2019. In addition, ongoing trials are exploring biosimilars of other commonly used cancer drugs, such as rituximab (Rituxan; Genentech) and bevacizumab (Avastin; Genentech).

Thus far, the FDA has approved only one biosimilar: Sandoz's Zarxio (filgrastim-sndz), a biosimilar for