trition," so that should be the focus in the future, along with smoking status, McCarthy said. "Now, thanks to the microbiome, we can get a more nuanced view—opening up a whole string of new opportunities."

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Mammaprint Reveals Who Can Skip Chemotherapy for Breast Cancer

By Charles Schmidt

Commercial biomarkers that guide clinical decisions in breast cancer appeared on the market just over a decade ago. In April, researchers unveiled long-awaited, prospective phase III results for the European market leader: a 70-gene assay called Mammaprint. The new data show that many patients whom the assay identified as having low risk of recurrence can safely avoid chemotherapy. Researchers presented the results at the American Association for Cancer Research's annual meeting in New Orleans.

The U.S. Food and Drug Administration approved Mammaprint in 2007, citing evidence that it could predict whether a woman's breast cancer is likely to return within 5–10 years. Published a year earlier in *JNCI*, the evidence came from a study of 302 women diagnosed with node-negative, stage T1–T2 breast cancer between 1980 and 1998 who hadn't received adjuvant systemic therapy. The authors concluded that Mammaprint adds independent prognostic information and identifies women with a low risk of metastases and death more reliably than clinical factors such as age, tumor size, and tumor grade. But that retrospective early study relied on frozen tumor samples for genetic analysis. Despite FDA approval, many U.S. experts were therefore unconvinced that Mammaprint should play a role in chemotherapy treatment decisions. Indeed, in updated clinical practice guidelines published last February, the American Society of Clinical Oncology (ASCO) recommended against using Mammaprint for that purpose. ASCO panelists claimed they couldn't determine whether the assay identifies women for whom chemotherapy is likely to be ineffective. But they also wrote that they were awaiting results from MINDACT, the prospective phase III trial sponsored by the Brussels-based European Organisation for Research and Treatment of Cancer (EORTC).

According to Lyndsay N. Harris, M.D., chair of the ASCO Breast Cancer Guidelines Advisory Group and director of the Breast Cancer Program at Case Western Reserve University School of Medicine in Cleveland, the data appear to offer "level 1 evidence that the 70-gene assay is associated with improved patient outcomes." However, ASCO panelists still need to review the published MINDACT data before possibly revising their decision against it, she said. Those data are expected later this year.

The ASCO guidelines approved five molecular assays in various stages of development. The guidelines limited recommended uses to women with hormone receptor (HR)–positive, HER2-negative, node-negative breast cancer. Many such women have low risks of incurable recurrence after treatment with surgery, radiation, or hormonal therapy. Chemotherapy can reduce that risk by an additional 30%, but it also produces potentially life-threatening toxic effects in 2%–3% of otherwise healthy women. Whether chemotherapy's added benefits justify the potential harm to low-risk patients often isn't clear. Therefore, clinicians are turning to molecular assays for new insights.

[Some 94% of patients in which Mammaprint predicated a low recurrence risk had metastasis-free survival at 5 years regardless of whether they underwent chemotherapy.] "That's the fundamental message. This is the group for which Mammaprint could be most helpful."

The test with the longest history, the 21-gene Oncotype DX assay (among those ASCO recommended), classifies risk of recurrence as low, medium, high. A massive National Cancer Institute–sponsored study, the TAILORx trial, is evaluating Oncotype DX. That study recently published data showing that 98% of women in the low-risk group remained free of distant metastases 5 years after hormonal therapy. Researchers generally agree that high-risk women need chemotherapy. But whether chemotherapy benefits the roughly 60% of patients in the medium-risk category remains an open question. Therefore, TAILORx randomized medium-risk patients to treatment with either hormonal therapy alone or hormonal therapy plus chemotherapy. Those results are not yet available. But according to Nancy Davidson, M.D., professor of oncology at the University of Pittsburgh Cancer Institute, the results should eventually offer information to help predict how treatment decisions informed by molecular screening influence survival.

Oncotype DX and Mammaprint both address similar needs, but their gene signatures are dissimilar. The former measures genes associated with the estrogen receptor and HER2 pathways, whereas the latter measures genes involved in tumor proliferation, metastasis, angiogenesis, and other disease processes. Moreover, whereas Oncotype DX groups risk into three categories, Mammaprint describes risks as only high or low.

The MINDACT trial evaluated nearly 7,000 patients in two ways. Researchers both used Mammaprint to genetically screen patients' tumors and assessed patients with Adjuvant! Online, a tool that uses clinical criteria such as age and tumor size to predict breast cancer recurrence. Often, patients deemed high risk by Mammaprint were likewise deemed high risk by Adjuvant Online! and vice versa. However, in about 1,500 patients, Mammaprint predicted low recurrence risk, whereas Adjuvant! Online predicted the opposite. According to Martine Piccart, M.D., Ph.D., professor of oncology at


Martine Piccart, M.D.

the University of Brussels in Belgium and MINDACT's principal investigator, 94% of patients in that discordant group still had metastasis-free survival at 5 years regardless of whether they underwent chemotherapy."That's the fundamental message. Piccart said. This is the group for which Mammaprint could be most helpful."

Unlike TAILORx, which enrolled only women with HR-positive, HER-negative, node-negative disease, MINDACT combined those groups. About 10% of enrolled patients were HER2 positive, 12% were HR negative, and 20% had one to three positive nodes. Jan Bogaerts, Ph.D., a statistician and methodology director at EORTC , said investigators adopted that approach because they wanted the trial to more broadly represent women with breast cancer (though approximately 80% of women so diagnosed are HR positive). According to Harold Burstein, M.D., Ph.D., associate professor of medicine at Harvard Medical School in Boston, the hope was "that you could take a more unselected group of patients and use genetic tumor screening to find out who needs chemotherapy and who doesn't." But because MINDACT included so few of these other groups, Burstein said, the study's relevance to them was limited at best. "MINDACT covers the same terrain as the other tests," Burstein said.

Piccart said that Oncotype DX is so broadly used in the United States that clinicians here might not change habits. "However, we now have a very robust demonstration that the 70-gene signal is powerful, and I'm confident that ASCO leaders will agree and revise their recommendation," she said.

According to Harris, the final outcome will hinge on the published data. "We have to look at that and be convinced that it shows clinical utility," she said.

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PDQ (Physician Data Query) is the National Cancer Institute's source of comprehensive cancer information. It contains peer-reviewed, evidence-based cancer information summaries on treatment, supportive care, screening, prevention, genetics, and complementary and alternative medicine. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:

Torres-Mejía G, Royer R, Llacuachaqui M, et al.: Recurrent BRCA1 and BRCA2 mutations in Mexican women with breast cancer. Cancer Epidemiol Biomarkers Prev 24 (3): 498-505, 2015. PMID: 25371446

The **PDQ Genetics of Breast and Gynecologic Cancers summary** was recently updated to include the results of a study of 810 women of Mexican ancestry with breast cancer who were tested for *BRCA1* and *BRCA2* mutations. Eight of the 35 *BRCA* mutations identified in the cohort were the *BRCA1* exon 9–12 deletion, suggesting that this may be a Mexican founder mutation. To review the summary, please use the following link: http://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq#link/_2612

Klein RD, Salih S, Bessoni J, et al.: Clinical testing for multiple endocrine neoplasia type 1 in a DNA diagnostic laboratory. Genet Med 7 (2): 131-8, 2005. PMID: 15714081

The **PDQ Genetics of Endocrine and Neuroendocrine Neoplasias summary** was recently updated to include the results of a study that assessed the rate of germline *MEN1* mutations in apparently sporadic cases of parathyroid, pancreatic islet, and pituitary tumors and found a germline mutation yield of 16% to 38% across these tumor types. These findings suggest the need for consideration of genetic testing in individuals with these tumors because a diagnosis of multiple endocrine neoplasia type 1 (MEN1) would prompt screening for other MEN1-related tumors. To review the summary, please use the following link: http://www.cancer.gov/types/thyroid/hp/medullary-thyroid-genetics-pdq#link/_799

Fuchs CS, Tomasek J, Yong CJ, et al.: Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 383 (9911): 31-9, 2014. PMID: 24094768

Wilke H, Muro K, Van Cutsem E, et al.: Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 15 (11): 1224-35, 2014. PMID: 25240821

The **PDQ Gastric Cancer Treatment** summary was recently updated to include information about ramucirumab, a fully humanized monoclonal antibody directed against the vascular endothelial growth factor receptor-2.

In the international, phase III, placebo-controlled, REGARD trial (NCT00917384), 355 patients with stage IV gastric or gastroesophageal junction cancer that had progressed on a first-line fluorouracil- or platinum-containing regimen were randomly assigned in a 2:1 fashion to ramucirumab or placebo (Fuchs et al., 2014) Patients who were assigned to ramucirumab had a significantly improved median overall survival (OS) of 5.2 months compared with patients assigned to the placebo, who had a median OS of 3.8 months. Rates of hypertension were higher in the ramucirumab group than in the placebo group. Ramucirumab is an acceptable treatment in cisplatin- or 5-fluorouracil-refractory, stage IV, gastric cancer.

In the international, double-blinded, phase III RAINBOW trial (NCT01170663), 665 patients were randomly assigned to receive paclitaxel (80 mg/m^2) on days 1, 8, and 15 every 28 days, with ramucirumab (8 mg/kg) added on days 1 and 15 or a placebo added on days 1 and 15 (Wilke et al., 2014). Patients assigned to ramucirumab had a significant improvement in median OS of 9.6 months compared with patients assigned to a placebo, who had a median OS of 7.4 months (HR, 0.807; $P = .017$). Grade 3 or higher neutropenia, fatigue, hypertension, and