Precision Oncology Marches on Amid Manufacturing Woes, Regulatory Debates, Guideline Limitations

The field continues to grapple with the tension between increasing patient demand for the latest drugs and tests amid evolving evidence and regulatory uncertainty.

By Turna Ray

AS A STEADY stream of new precision oncology drugs and tests entered the market during the first months of 2023, healthcare providers continued to struggle with patient demand for these products amid evolving evidence, manufacturing backlogs, and limited guidelines.

Among the precision oncology drugs that came to market in the first five months of the year, **Menarini**'s Orserdu (elacestrant) stood out because it's the first new hormone therapy the **US Food and Drug Administration** has approved for breast cancer in more than two decades and the first treatment specifically for those with ESR1-mutated tumors. Alongside Orserdu, the agency approved a companion diagnostic to help doctors identify patients eligible for treatment, in this case, **Guardant Health**'s liquid biopsy test, Guardant360 CDx.

Other companion diagnostics the agency has recently approved for informing precision oncology include **Tempus**' xT CDx, which allows the Chicago-based firm to join the ranks of **Foundation Medicine**, Guardant, and other labs in having FDA approval for a lab-developed next-generation sequencing panel. The FDA-approved 648-gene panel test is indicated as a companion diagnostic for identifying best responders to two colorectal cancer drugs, **Eli Lilly**'s Erbitux (cetuximab) and **Amgen**'s Vectibix (panitumumab).

In the emerging radiopharmaceuticals space, the FDA approved **Telix Pharmaceuticals**' Illuccix (Ga-68 PSMA-11) for identifying advanced

prostate cancer patients who might benefit from **Novartis**' Pluvicto (Lu-177 vipivotide tetraxetan). The FDA had originally approved Pluvicto last year for previously treated prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer alongside Novartis' imaging agent Locametz (Ga-68 gozetotide) to identify treatment eligible patients. With Illuccix's approval, the agency aimed to expand the imaging tools available to doctors for identifying best responders.

However, the availability of new diagnostic tools can't facilitate access to a drug that's not widely available. In the months following Pluvicto's approval, Novartis struggled to keep up with demand for the drug, having secured FDA approval for only one manufacturing facility in Italy that could produce the radiopharmaceutical for the commercial US market. As late-stage prostate cancer patients waited for months – and some died waiting – to receive the much-hyped radioligand therapy that Novartis had projected as having $2 billion market opportunity, the company in March stopped distributing Pluvicto to new patients.

More recently, Novartis has said it will begin slowly ramping up Pluvicto supplies, as it recently secured FDA approval for a second commercial manufacturing site in New Jersey. Still, the experience with the radioligand treatment demonstrates how advanced precision oncology drugs are putting pressure on the entire healthcare ecosystem, from drugmakers' manufacturing processes to market distribution channels.

In other areas of precision oncology, access is slowed by the friction between rapidly evolving genomic technologies and slower uptake in medical practice. At the **American Association for Cancer Research**'s annual meeting in April, researchers shared data from the TAPESTRY study, in which they performed whole-exome sequencing on more than 44,300 patients at **Mayo Clinic** sites in Arizona, Florida, and Minnesota, and found that 550 people, or 1.24 percent, had genetic abnormalities indicative of hereditary breast or ovarian cancer syndrome or Lynch syndrome. Study participation was not restricted to individuals with a cancer diagnosis or family cancer history; individuals who had gotten treated at Mayo for any condition and had consented to genetic testing could partake.

That 39.2 percent of patients in this study with an inherited cancer predisposition syndrome wouldn't have qualified for genetic testing under the **National Comprehensive Cancer Network**'s guidelines yielded calls for change. "Our results really emphasize the need for increased access to genomic screening for the [**Centers for Disease Control and Prevention**'s] Tier 1 genetic conditions, and potentially the use of exome sequencing in large populations," Jewel Samadder, director of the high-risk cancer clinic at Mayo Clinic, said at AACR.

Among patients who did meet NCCN criteria for genetic cancer risk assessment, 34 percent didn't know they had hereditary breast and ovarian cancer syndrome or Lynch syndrome. "This suggests that the NCCN guidelines are underutilized in clinical practice, potentially due to the busy schedule of clinicians, or because of the complexity of using these criteria," Emily Gay, a graduate genetic counseling student at the **University of Arizona**, noted in presenting the TAPESTRY data at the meeting.

> At AACR, oncologists discussed the opposite problem: growing demand for multi-cancer early detection tests amid limited evidence supporting their widespread use.

In another AACR session, oncologists discussed the opposite problem: growing demand for multi-cancer early detection tests amid limited evidence supporting their widespread use. Doctors described patients coming into their offices and asking for tests like **Grail**'s Galleri because they had heard about how it can detect cancer early while it is still curable. But experts at the meeting said that these increasingly frequent interactions are becoming difficult because they remain unconvinced of the broad benefit of these tests, despite modeling data advanced by the test makers suggesting as much.

"There's been a lot of hand-waving to justify these [tests] that is not scientifically valid. So, just caveat emptor, buyer beware of what's being put out there," Philip Castle, director of the Division of Cancer Prevention at the **National Cancer Institute**, said of the modeling data advanced by test developers at the meeting.

Part of the problem, according to Angela Bradbury, a **University of Pennsylvania** physician and ethicist, is that unlike drugs, whose safety and efficacy the FDA vets before they enter the market, most laboratory-developed tests (LDTs) currently do not have to undergo evaluation by the agency, as long as they're commercialized through a lab certified under the Clinical Laboratory Improvement Amendments.

"I keep thinking: why do we keep doing this? … And part of the challenge is that we have two different pathways for approval [for LDTs]," Bradbury said at the meeting. "If my patient comes to me and says, 'Oh, there's a new drug for ESR1 mutations. When can I get that?' It's very easy because I say, 'You have to wait for FDA approval.'"

The debate over whether the FDA has the authority to regulate LDTs has been raging for three decades. Although the FDA has said it has the power to regulate lab tests, every time it has tried to lift its enforcement discretion, the lab industry and pathologists have thwarted the agency's efforts. More recently, even healthcare institutions and cancer centers that have implemented cancer genetic tests within in-house labs have begun to speak out against FDA regulation of LDTs.

Last year, the FDA and pro-agency regulation groups failed to pass the Verifying Accurate Leading-edge IVCT Development Act through **Congress**, which would have given the government regulator broad authority over all diagnostics. The experience seems to have motivated the FDA to advance regulations through the rulemaking process, despite the lab industry's continued insistence that the agency lacks statutory authority to do so.

The move to pursue rulemaking could land the FDA in court, according to legal experts. "There is … a live question as to whether FDA really does have the power to regulate what labs are doing under the FDA law," Jeff Gibbs, a director at the law firm **Hyman, Phelps, & McNamara** and a former associate general counsel for enforcement at the FDA, said recently. "There is no question FDA is going to run into a court challenge when they do this."

Any significant change to the regulatory framework for LDTs stands to have widespread impact on the entire healthcare ecosystem, not to mention in precision oncology where some of the more complex and pricey tests are used to guide therapy, assess risk, and gauge prognosis. At least for the moment, it seems the LDT regulatory debate will likely drag on and the status quo will remain for some time still, and it'll be up to doctors to manage patient demand for marketed cancer tests that they feel lack evidence. PMQ

Turna Ray

Turna Ray has been covering the personalized medicine and molecular diagnostics industries for *GenomeWeb* since 2006. She closely tracks the evolving regulatory, reimbursement, and business environment for precision medicine products. In 2019, she became managing editor of *Precision Oncology News* and now guides coverage for the newly launched *Precision Medicine Online*.