Lack of BRCA testing approval creates snag for cancer trials

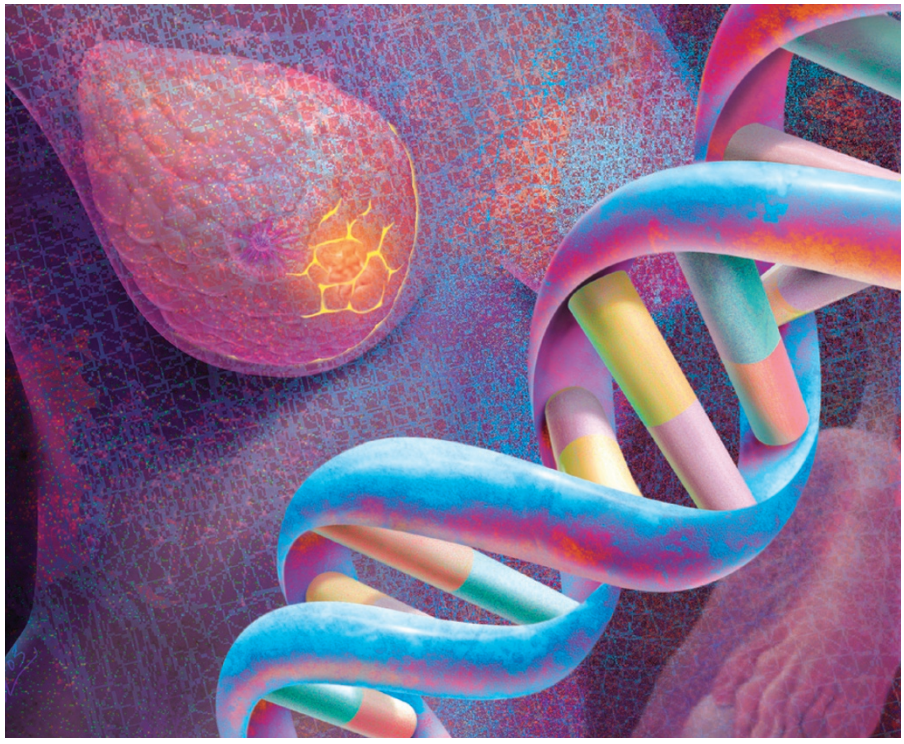
On 16 August, a US federal appeals court upheld the patent claims of Myriad Genetics, which holds the intellectual property surrounding certain sequences in the cancer-associated *BRCA* genes. These patents are commonly invoked when women try to assess their risk of developing heritable forms of breast and ovarian cancer. But as recent efforts to develop therapies that inhibit BRCA-mutated tumors indicate, these patents could have far-reaching repercussions for clinical trials and drug development, too.

Phase 2 trials have hinted at a possible clinical benefit of drugs that block an enzyme called poly(ADP-ribose) polymerase (PARP) for women with BRCA mutations. For example, a study of 97 women with a recurrence of ovarian cancer found that 31% of those assigned to receive a high dose of a PARP inhibitor called olaparib, developed by the UK pharmaceutical giant AstraZeneca, showed a certain degree of tumor shrinkage, compared with 18% of those that took a form of the chemotherapy drug doxorubicin (*J. Clin. Oncol.* **30**, 372–379, 2012).

Olaparib and veliparib, a similar drug from Illinois's Abbott Laboratories, represent the PARP inhibitors furthest along in the clinical pipeline. And at least five other PARP inhibitors, including rucaparib from Colorado's Clovis Oncology, are in phase 1 trials. But despite promising data and seven years of development, the progress of PARP inhibitors has slowed to a crawl. "There is frustration that these drugs appear to be effective and nontoxic," says Mark Robson, director of the clinical genetics service at the Memorial Sloan–Kettering Cancer Center in New York. "Yet for a set of reasons, we can't get them into the clinic."

Notably, late last year AstraZeneca announced it would not explore a phase 3 trial of olaparib for ovarian cancers. The decision is significant as some scientists had posited that PARP inhibitors could be particularly useful for tumors resulting from mutations in the *BRCA* genes. That is because mutations in these genes can disrupt BRCA's DNA repair function and ultimately lead to uncontrolled cell growth. The idea was that blocking PARP—which is involved in a separate DNA repair pathway—would result in a final, deadly blow to cancerous cells while leaving nontumor cells unaffected.

AstraZeneca's decision was largely based on the lackluster clinical results to date. But even if the data looked more promising, advancing such a PARP inhibitor further for BRCA-mutated cancers could by stymied by Myriad's patent profile: whereas phase 2 trials can use results from the Utah-based company's BRACAnalysis test, which women mostly undergo through their own insurance plans, when it comes to pivotal, phase 3 trials, the US Food and Drug Administration (FDA) requires that any companion diagnostic that is part of a study either be approved by the agency or submitted for approval.



Scott Bodell/Newscom

Double-stranded trials: Studies seek to combine gene tests for breast cancer with drugs.

Companion constraints

Herein lies the rub: Myriad's test is approved under the Clinical Laboratory Improvement Amendments (CLIA) regulations, which ensure the quality of laboratory testing of human samples, but not currently by the FDA. And developers of PARP inhibitors cannot get around this snag because Myriad holds US patents giving the company sole rights to BRCA testing.

Beside the regulatory hurdles, some researchers say that the high cost of Myriad's $3,500 test adds another barrier to clinical development. "Myriad is not giving the drug companies any discount, nor making any sacrifices to push the drugs forward," says Elizabeth Swisher, a medical oncologist at the University of Washington in Seattle and an expert witness in the patent lawsuit. "It comes down to paying for the test, which is a limitation for patients and adds a lot of cost to trials."

"When only one company commercially offers the test, there is no competitive market pressure to control the price of the test," adds Sara Hurvitz, a breast cancer oncologist at the University of California–Los Angeles David Geffen School of Medicine. "This is potentially problematic in a clinical trial setting where eligibility depends on proving a study participant is a carrier of a BRCA mutation."

Myriad has not divulged plans to get the BRACAnalysis test approved by the FDA, although a spokesperson told *Nature Medicine* that companion diagnostics are a top priority for the company and that discussions with the FDA and Myriad's pharmaceutical partners are ongoing.

In the meantime, however, the phase 3 holdup continues to frustrate researchers in the field. "I feel like I have misled my patients by saying that a PARP inhibitor will be available soon," Swisher says.

Anna Azvolinsky

Correction

In the July 2012 issue, the article entitled 'Cancer immunotherapy shows promise in multiple tumor types' (*Nat. Med.* **18**, 993, 2012) incorrectly stated that the PD-1 ligand (PD-L1) is found only on tumor cells, when in fact it is expressed more widely. The error has been corrected in the HTML and PDF versions of the article.