Next-Gen Sequencing: The Clinical Conundrum

— Future appears bright, but drawbacks can range from annoying to disheartening

by Craig Hildreth, MD
May 06, 2018

In the past 16 years, the cost of determining the sequence of the human genome has fallen from $100 million to south of $15,000, making this technology widely available to identify and target cancer producing genetic alterations. Several of these tests using high-throughput or next-generation sequencing (NGS) are commercially available to oncologists.

GPS Cancer interrogates all 3 billion base pairs and also compares the tumor genome to the patient's germline genome, reducing the incidence of false positive driver mutations. Foundation One bases its test on discovering pathogenic alterations in a panel of 315 genes associated with malignancies.

As exciting as it sounds, in my practice I have encountered drawbacks to the successful use of NGS that range from annoying to disheartening.

Insufficient tissue for analysis. I recently had to tell a patient that her

biopsy did not contain enough tissue to determine which one of her two previous cancers had returned, let alone whether the tumor harbored a mutation that I could target. The result is that she had to undergo another biopsy, and then wait to see if that specimen was adequate. Fortunately, her tumor was accessible with core needle biopsy. Patients with small, deep tumors next to large blood vessels are usually out of luck.

Denial of NGS by insurance. It is no longer a surprise when we are informed that the pre-certification for NGS has been denied. The usual excuse is that the health policy does not cover any genetic testing. Insurance companies seem to be wary of any test that may provide more scientific than practical information -- another grim reminder of the discordance between the business and the science of cancer medicine.

Mutation found -- no treatment available. Some tumors contain mutations that make them vulnerable to novel drugs -- think of PARP inhibitors for *BRCA*-mutated breast and ovarian cancer. Since NGS screens hundreds of candidate genes it is not uncommon to reveal a polymorphism for which there is no commercially available agent. An example is the *NOTCH1* mutation in chronic lymphocytic leukemia, which predicts an adverse outcome yet lacks any approved therapy.

Mutation found and drug commercially available drug -- insurance denial of coverage. I once had a patient with metastatic salivary gland carcinoma whose tumor was found by NGS testing to contain androgen receptors, which can be targeted with anti-androgen therapy similar to treating prostate cancer. He ended up paying for his treatment out of pocket. This dilemma can obviously be remedied by enrolling in a clinical trial.

Mutation found and drug approved by insurance -- no evidence of benefit reported. A patient of mine recently found out via NGS that her tumor has mutations in both *PIK3CA* and *KRAS*. Blocking the signaling pathway that includes the PIK3 protein with FDA approved drugs has been reported to produce a 38% response rate if *PIK3CA* alone is mutated but no response if *KRAS* is also mutated -- not exactly encouraging news for my patient. Read the fine print and you will

discover that the response rate in *PIK3CA*-only mutated patients is still zero unless you add another drug to the regimen, preferably chemotherapy. After the eye strain I got scrutinizing these data I certainly advise caution in starting an NGS-recommended treatment without confirming its value.

Despite these limitations, I think the future is bright for high-throughput DNA testing of malignancies. A recent report revealed that both children and adults with tumors harboring fusions in the tropomyosin receptor kinase (*TRK*) gene can be successfully treated with the TRK inhibitor larotrectinib, which has a 75% response rate, and appears to be durable. Outcomes like this are enough to keep spirits high that better days for our patients lie ahead.

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