Genomic Profiling
Building a Continuum From Knowledge to Care

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The greater availability and reduced cost of next-generation sequencing has allowed some major academic cancer centers to integrate genomic profiling into clinical practice. In principle, prospective genomic profiling has the potential to inform treatment decisions, identify patients for relevant clinical trials, and trigger additional exploratory studies.

In this issue of JAMA Oncology, Beltran and colleagues reported the experience of the prospective whole-exome sequencing (WES) for patients with advanced cancers in the setting of routine practice at an academic institute. Although prescreening may have been required, it is remarkable that, in a cohort of 97 patients predominantly composed of those with prostate (51%) and bladder cancers (21%), more than 90% had adequate biopsies of the metastases for WES. All somatic alterations were listed in reports to patients by relevance to treatment or cancer biology; 92% of patients had “clinically or biologically informative” alterations, although it is not clear how many patients actually had alterations considered to be “clinically actionable” with an investigational or commercially available agent. Notably, less than 5% of patients received therapies recommended on the basis of the genomic analysis, in part as a result of issues with drug availability. The application of WES was highlighted in 2 examples, including immediate utility to a patient with urethral cancer who received trastuzumab and paclitaxel on the basis of HER2 amplification and achieved a complete remission.

In the other example, WES was used retrospectively to investigate the molecular basis of an exceptional response to cisplatin and docetaxel combination therapy in a patient with advanced prostate cancer. Genomic interrogation revealed a somatic hemizygous deletion of the FANCA gene and a germ-line missense variant in the other allele. Because FANCA is a member of the Fanconi anemia core complex critical to DNA crosslink repair, the biallelic alterations provided a plausible explanation for sensitivity to platinum. Impressively, FANCA-modified cell lines and patient-derived xenografts (PDX) were generated for functional testing.

Fanconi anemia pathway gene alterations are well known in platinum-sensitive tumors such as ovarian cancer but are underrecognized in prostate cancer. The finding here highlighted the power of WES in revealing rare genomic events that are otherwise unsuspected. However, it should be noted that the specific FANCA genotype alone may not fully explain the dramatic response in this patient. Indeed, the functional loss of FANCA variant S1088F appeared to be partial, and the PDX response to cisplatin alone was modest (growth inhibition). To optimize the value of this anecdotal clinical finding, additional studies in PDX
and other models are needed to clarify the role of paclitaxel in this combination, as well as additional molecular changes that might have contributed to the response.

Analysis of exceptional responders can lead to important scientific insight and clinical application, as demonstrated for EGFR mutations and EGFR inhibitors, and more recently for multiple discoveries derived from high-throughput genomic profiling.\(^2\) The National Cancer Institute has recently launched national effort, the Exceptional Responders Initiative,\(^3\) to systematically collect and analyze samples from patients with exceptional responses to chemotherapy or targeted therapies that have low probability of response in given indications. It is noted that identifying the gene-to-response links is not straightforward. As exemplified by this and other reports,\(^1,2,4\) the underlying biology can be previously unknown, obscure, or indirect and complex. Expertise in biology and informatics, as well as cancer therapeutics, is needed for lead identification, hypothesis generation, and in-depth studies and validation.

Similar to the experience reported here, other major cancer centers have shown that routine tumor genomic profiling is feasible.\(^5,6\) A question often asked is whether preemptive profiling is cost-effective and what extent of gene coverage is optimal. Obviously, the answer would vary with specific clinical settings, and the balance may change over time. For prospective testing for immediate clinical decision making, targeted sequencing for known actionable mutations may be more economical with less DNA required. However, fixed panels based on available knowledge may become outdated with emerging discoveries, and their value for exploratory studies is limited. Whole-exome sequencing, on the other hand, may not only reveal immediately actionable information but may also “pre-identify” alterations potentially relevant to future agents or treatment strategies. With increasing use of immunotherapy in oncology, WES may have the added value of revealing somatic mutations, which passengers or drivers, for analysis of patient-specific neoantigens that may have potential therapeutic relevance.

Currently, however, the value of routine prospective genomic profiling may be limited, especially for tumor types with low prevalence of actionable alterations. The clinical utility can be further limited by lack of access to relevant drugs not commercially available or approved for the indication.\(^7\) Comprehensive profiling in exceptional responders, as demonstrated in this report, could be obtained retrospectively. Nevertheless, it is anticipated that the cost-effectiveness of prospective WES is likely to substantially increase over time, with new technologies allowing deeper coverage with less input DNA and rapidly accumulating knowledge about new targets and agents.

To maximize the value of genomic data for individual patients, access to a wide range of agents in clinical studies is desirable. As an example, basket trials including National Cancer Institute MATCH\(^2\) are designed to evaluate multiple investigational or approved agents in matched molecular cohorts. Because no single trial or profiling effort will be sufficient to cover all relevant agents or capture all study participants for rare molecular subtypes, development of a “matchmaking” database could be envisioned that would vastly facilitate patient assignment or referral to appropriate studies. Finally, to enhance the collective power of scientific discovery and cross-validation, standardized platforms and interconnected repositories are critical to enabling systematic input and curation of genomic and outcome data from clinical trials, response anecdotes, and preclinical studies. Various initiatives from government, academics, nonprofit organizations, and diagnostic companies to accomplish this are under way or being planned.\(^3,7-10\)

In summary, the clinical utility of routine preemptive genomic profiling may be limited by available knowledge at present. However, the potential for value to patient care and scientific discovery has been demonstrated, and both technical improvements and rapid scientific advancement are likely to enhance its cost-effectiveness over time. Yet, to capitalize fully on all the information available from WES and other nascent technologies, oncology stakeholders, including patients, researchers, and physicians, will need to be able to share and interrogate genomic information routinely if the potential of these new diagnostic tools is to be realized.

ARTICLE INFORMATION

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REFERENCES