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Editorial

One Step Further Toward Defining the Exceptional Cancer Responder

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Precision oncology defines an approach to personalized medicine that uses technological advances in genomics and molecular profiling of tumors and individuals to develop mechanism-based therapeutics designed to improve clinical outcomes. Moving the characterization of cancers from their historical histology base toward a more molecular orientation has resulted in many new approaches to data acquisition and utilization aimed at developing new therapies. These approaches include the use of functional data and informatics to identify targetable driver mutations, efficient means of gathering clinical outcomes data from *N-of-1* studies and nontraditional trial designs, new statistical methods applied to bucket trials of genomically targeted drugs, and the use of large and complex datasets to develop consistent guidelines for patient care. These innovations may largely replace the highly individualized approach to genetic and genomic assessment of patients and their tumors that makes traditional statistical analyses of large randomized trials and clinical endpoints difficult (1).

One intuitively attractive approach to using the power of next-generation sequencing for cancer therapeutics discovery is coupling it to analyses of tissues from "exceptional responders." Though anecdotal cases of remarkable outcomes to chemotherapy are frequently shared among cancer clinicians, our ability to identify the molecular mechanisms underlying such rare outlier responses has been limited. A powerful example of this possibility was demonstrated by the well-documented exceptional response of a patient with bladder cancer to the mTOR inhibitor everolimus. The concept that *TSC1* and *NF1* gene mutations were factors potentially underlying the response was validated in a subsequent phase II clinical trial (2,3). This example clearly demonstrated that exceptional responders could help to identify novel or known molecular abnormalities that may be predictive of response to agents targeting a relevant biological pathway.

In response to that proof-of-principle case, the National Cancer Institute embarked on a highly ambitious Exceptional Responders Initiative to use next-generation sequencing to discover the molecular underpinnings of exceptional responses to chemotherapy treatment of cancer patients. The initial intent was to gather tumor tissue samples from patients who had unusually excellent responses on early-phase clinical trials of novel therapeutic agents as an attempt to "rescue" drugs that would otherwise fail such trials (where, eg, only 1 of 20 patients had a response). In practice, this national initiative put out a wide net for cases with clinical data and tissue, including patients treated with established chemotherapy but exhibiting responses judged beyond those of 90% of those treated similarly.

In this initial report by Conley et al. (4), the investigators show that such an initiative is indeed feasible, at least in terms of gathering appropriate clinical data and tissue samples from more than 100 eligible cases. As noted, whole-exome sequencing and other molecular studies have been performed on these samples, the results of which will be reported elsewhere. However, recent advances in genomic analyses of tumors suggest such an approach may prove successful. For example, combined tumor and germline multigene DNA sequencing has found an unexpectantly high number of mutations in *BRCA1*, *BRCA2*, and other homologous-recombination genes in prostate and pancreatic cancers, leading to demonstrated activity of agents targeting these DNA repair pathways, such as platinums and PARP-inhibitors (5–7). High levels of microsatellite instability, known to confer sensitivity to PD-1 inhibitors in Lynch syndrome-associated colon and endometrial cancers, also occur in a small subset of most other cancers and predict for immunotherapy responses (8). These examples and many case reports suggest that the reverse process, discovering rare genetic predictors to cancer therapies through analyses of exceptional responders, may be feasible.

A recent perspective on exceptional responders (9) contains a number of recommendations that may enhance future studies with similar objectives. Among them, and as noted in this article, is a comparison of the data from such responders with those from individuals with poor outcomes undergoing the same treatment. In addition, it will be advantageous to make optimal use of clinical trial data in which tumors are collected prospectively and tumor histologies and treatments are more homogeneous. Given the tremendous complexity of factors

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involved in tumor responses, among which are epigenetic, immunological, and host factors, it will take truly large-scale efforts to more broadly define additional characteristics contributing to exceptional responses. To that end, we greatly look forward to the genomic results from this trial. Just the ability to gather such a large number of rare and valuable tumor samples with clinical data is remarkable and, similar to the NCI-MATCH trial, demonstrates the unique strength of our national research program. Clearly, the analysis and validation of these results will prove critical to determining the success of this approach. Ultimately, prospective studies of tumors from exceptional responders, particularly to novel, genomically targeted agents, may provide a powerful approach to cancer treatment discoveries.

Notes

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