editorial

Implementation of Precision Cancer Medicine: Progress and the Path to Realizing the Promise of Tumor Sequencing

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Precision medicine, as described by Jameson and Longo[1] is a classic example of a disruptive innovation, one that challenges existing standards of practice and redefines how we classify cancer and select treatments. They noted that, given the complexity and volume of data that support this new paradigm of precision medicine, physicians will no longer be able to rely on memory or other traditional information sources to apply precision medicine in the clinic. Rather, precision medicine will need to rely on the development of robust informatics and decision supports to be effectively implemented in clinical practice.

In the article that accompanies this editorial, Levit et al[2] describe how three large, multisite community practices or networks have successfully incorporated precision cancer medicine (PCM) into their community oncology practices. Each of these practices has leveraged informatics and decision support as key components of successful implementation. They describe using standardized algorithms for testing, in-house sequencing, and molecular tumor boards, which provide guidance to physicians on how to interpret sequencing results. In addition, commercial or in-house clinical pathway programs and nurse navigators were used to match patients to clinical trials, and additional financial supports (eg, a drug navigation team) were used to interact with insurers to obtain approval for drugs. These are impressive implementation efforts that address many of the critical pain points for oncology providers who face a wide range of barriers as they implement PCM in their clinical practice.

ADDRESSING EXPECTATIONS AND PROVIDING EDUCATION ABOUT TESTING

As we continue down the path of implementing PCM in real-world practice, there are additional challenges that will be critical to address and that might benefit from similar technology and decision support systems. First, as the authors acknowledge, many patients have high expectations about the benefits of tumor sequencing, and providers need to clearly communicate its potential benefits as well as its risks and limitations.[3-5] Although patients have high expectations for and interest in tumor sequencing,[4] studies report that some patients are concerned about the complexity of the information, the potential for distress, and disappointment and loss of hope after testing, particularly when no actionable mutations are identified or clinical trials are not accessible.[5,6] Studies have shown that only a subset of patients who have undergone tumor sequencing enroll in clinical trials.[7-9] Addressing these expectations and possibilities at the time of testing could help mitigate negative patient outcomes. We do not know how best to approach pretest education and counseling for tumor sequencing, and it is likely not feasible or necessary for all patients to meet with a genetic counselor.[10] Thus, the responsibility for pretest education and counseling presents an additional burden for oncology providers as they implement PCM in their practice.

ADDRESSING THE POTENTIAL FOR SECONDARY GERMLINE FINDINGS

Second, an important component of provider communication about tumor sequencing is sharing the potential for secondary germline findings, which will vary depending on which sequencing platform is used. In the setting of tumor-normal sequencing, the American College of Medical Genetics and Genomics (ACMG) has recommended that 59 genes (including those in both cancer and cardiovascular conditions) be actively evaluated for pathogenic mutations and reported back to patients, unless they specifically decline to receive secondary findings.[11,12] ASCO and others have endorsed pretest communication to inform patients of the possibility of secondary germline findings and to determine their preference for receiving germline information.[10,13,14] Studies suggest that 3% to 18% of patients undergoing tumor-normal sequencing have a pathogenic germline variant.[15-19] Although most patients are likely to be interested in secondary germline findings, current studies suggest that a subset of patients may prefer not to receive information about secondary germline findings.[20-22] Qualitative studies have reported patient concerns about receiving secondary germline information, such as the complexity of the information, potential negative emotional impact, additional burden in the setting of

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Accepted on March 28, 2019 and published at jop.ascopubs.org on May 21, 2019: DOI https://doi.org/10.1200/JOP.19.00176

advanced cancer, concerns about sharing these results with relatives, and additional costs.[5,6,14,20,23,24]

The obligation to address secondary germline findings in tumor-normal sequencing introduces considerable challenges in implementing PCM, and many commercial and institutional laboratories have elected to offer tumor-only sequencing, in which the ACMG guidelines for returning secondary germline information do not apply. But tumor-only sequencing can still identify the potential for a germline mutation. Oncology providers will need to be aware of the potential for a germline finding, identify patients who may have a potential germline finding, discuss this possibility with their patients, and then refer them for germline testing or order germline testing themselves. How best to communicate the potential for a germline finding to patients remains unclear. Should all patients be made aware of this possibility before tumor-only testing? Or is it acceptable to discuss this with a select number of patients for whom a potential germline finding has been reported? For example, could this be discussed when the provider shares the tumor-only sequencing result? Although it has been recommended that laboratories highlight results from tumor-only sequencing that are suggestive of germline variants,[12] laboratories vary considerably in their reporting of potential germline findings, and some laboratories do not report them at all. Furthermore, there are currently not enough data to determine which patients should be referred for germline confirmation. Of note, several published studies suggest that at least half of patients with a secondary germline finding did not have other personal or family history to suggest that a germline finding was present.[13,15,18] While standards and criteria for confirmation testing are being developed, providers might wonder if they face liability if they neglect to inform their patients of a potential germline finding identified in tumor-only sequencing.

Equally important, many oncology providers said that they do not feel qualified to or have the time to have discussions with their patients about secondary germline findings.[25,26] Many oncology providers have suggested that genetic counselors should be involved in these discussions or in returning potential germline findings to the patient or confirming the findings, but many physicians in community settings do not have access to genetic counselors. Should physicians request confirmation germline testing themselves? Again, if they feel this is beyond their scope of practice and training, are they facing possible liability if they do not order the confirmation testing for a potential germline variant identified on tumor-only sequencing? Many patients may not have personal and family history suggestive of a germline finding, so germline confirmation testing may not be covered by their insurance. Thus, oncology providers must explain the out-of-pocket costs of confirmation testing and must also select the most cost-effective laboratory for the patient, which creates additional burdens for the practicing oncologist and potential barriers to successful implementation of PCM.

USING TECHNOLOGY, DECISION SUPPORT, AND COLLABORATIVE CARE MODELS TO IMPLEMENT PCM

The additional challenges of pretest education and communication of the risks, benefits, and limitations of tumor sequencing must be addressed as we continue to use PCM in clinical practice. Some of the strategies described in Levit et al[2] could be leveraged to address these additional implementation challenges. Print or electronic educational materials could be used to support pretest communication of the risks, benefits, and limitations of tumor sequencing, and could be tailored to the type of testing (eg, tumor-normal *v* tumor-only sequencing).[4,27] Clinical trials such as Pre-Test Genetic Education and Remote Genetic Counseling in Communicating Tumor Profiling Results to Patients With Advanced Cancer (NCT02823652) is evaluating the outcome of an eHealth intervention for pre-test education, which could help inform standards for pre-test education. With tumor-only sequencing, molecular tumor boards, clinical pathways, or nurse navigators could incorporate review of sequencing reports to help identify patients who are candidates for cancer genetic referral given a potential germline finding. These supports could also identify local cancer genetic service providers. Many practices may not have access to local cancer genetic services, but commercial and academic institutions are increasingly offering remote cancer genetic consultations, which could be of considerable assistance to community practices and providers that do not have genetic counselors on staff.[28,29]

Great progress is clearly being made as PCM is being implemented successfully in real-world practice. Technology, decision support, and collaborative practice models are critical to this success and will need to be leveraged to address optimal communication and patient outcomes as we redefine practice models to realize the promise of PCM.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the author and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JOP.19.00176.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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No potential conflicts of interest were reported.