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Improving Patient Outcomes With Cancer Genomics: Unique Opportunities and Challenges in Pediatric Oncology

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Precision medicine, the individualization of health care based on unique patient-specific variables, is not new, especially within oncology. Historically, there has been a "depersonalization" of cancer care by defining histotype-specific standard-of-care treatments for the majority of malignancies, although in contrast oncologists have been adept at individualizing therapy, especially when confronted with disease relapse. Practicing oncologists seek evidence-based approaches to improve patient outcomes, but much of the current personalization of care remains largely empirical. Nevertheless, over the past decade there has been increasing enthusiasm for using genomic data to more precisely diagnose cancer, predict outcomes, and prescribe "targeted" therapies. Although substantial progress has been made, both anticipated and unanticipated barriers exist in integrating sequencing technologies into the care of patients with cancer. Clearly, for multiple reasons, many challenges remain to prove that personalized genomic medicine can substantively improve outcomes for patients with cancer. These challenges are further accentuated with childhood cancers.

Pediatric oncology has a long history of innovation and early adaptation of personalized approaches to care. The first examples of heritable germline mutations affecting cancer susceptibility and informing family counseling were realized in the embryonal cancers of childhood such as retinoblastoma, Wilms tumor, and rhabdomyosarcoma.[1-3] Considering the somatic genome, pediatric oncologists also set the stage for modern molecular diagnostics, demonstrating the clinical relevance of recurrent driver-gene-fusion events in childhood sarcomas[4,5] and for high-level genomic amplification of *MYCN* in neuroblastoma.[6] However, even though use of genomic medicine for diagnostic and risk stratification purposes is now the standard of care for many pediatric malignancies, the field has yet to realize the major goal of targeting mutated oncogenic drivers, with the exceptions of Philadelphia chromosome-positive leukemias[7] and rare *ALK* translocated malignancies,[8] and these were largely derived from prior experience in adult malignancies.

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Several unique challenges in the pediatric cancer population must be overcome to even begin to test the hypothesis that sequencing data from patient tumors can improve outcomes in a meaningful way. First, childhood cancers are on the low end of the spectrum in terms of mutation frequency, with some diseases having very few recurrent events.[9] However, the majority of studies to date have focused on newly diagnosed disease. Almost all children with cancer are treated initially with dose-intensive chemotherapy, radiation therapy, or both. Emerging evidence indicates that posttherapy relapse samples accumulate substantially more mutations and may select for mutations in targetable oncogenic pathways as a mechanism of chemotherapy resistance.[10-12] Second, the relapsed pediatric cancer genome remains poorly studied because modern radiographic techniques are so sensitive and specific that a biopsy to document disease progression is rarely clinically indicated. Third, when considering an invasive procedure in a child, the clinician must be certain that there is the potential for benefit to ensure clinical equipoise.

In this issue of *JAMA*,[13] Mody and colleagues report findings from a prospective integrative clinical sequencing observational case series that accrued 102 children and young adults (mean age, 10.6 years; median age, 11.5 years; range, 0-22 years) with cancer. The investigators performed exome sequencing of paired blood mononuclear cell (germline) and tumor DNAs, as well as sequencing of tumor RNA, in 91 of the 102 enrolled patients who had adequate tissue samples. A total of 63 patients (69%) had solid tumors, and the majority (but not all) of patients with solid tumors and leukemia were accrued to the study at the time of disease progression. The study was designed to identify “potentially actionable findings” that were in 1 of 3 categories: (1) germ-line mutations that could affect the patient, relatives, or both; (2) tumor-specific alterations that would alter the histopathologic diagnosis, change risk status, or both; and (3) medically targetable somatic mutations. The study also implemented a precision medicine tumor board that the investigators highlighted as a key component in determining what alterations were potentially actionable and how to act on each potentially actionable finding.

The major findings from this important investigation were that potentially actionable findings were documented in 42 of 91 cases (46%) with sequencing results and that an action was taken in 23 of these 42 patients (54%). These actions included a change in therapy for 14 patients (15% overall). In 2 cases, the original diagnosis was changed based on a pathognomonic chromosomal translocation. In 9 patients, an incidental germline mutation was detected and deemed to be clinically relevant. The investigators also reported that 9 of 14 patients with a therapeutic intervention derived clinical benefit, but were appropriately cautious regarding the percentage of pediatric patients who might benefit from combined DNA and RNA sequencing of tumor material.

The study by Mody and colleagues represents an important contribution to the care of children with cancer. It makes clear that approaches that are rapidly evolving in adults are applicable to the care of children with cancer. These data strongly suggest that precision medicine enhanced by genetic evaluation may improve the outcomes of children with cancer. However, like all innovative research, this report leads to several additional questions and issues that will need to be addressed in the future.

Human cancers continuously evolve. This is likely accelerated by the intense selective pressure of chemoradio-therapy. Thus, access to tissue at or near the time of therapeutic intervention is key to informing the best clinical decisions. For children with relapsed cancer, this often means obtaining high-quality tumor material from difficult to access anatomic locations (cortical bone metastases or paravertebral lesions). In the study by Mody and colleagues, 90% of eligible patients reportedly had interpretable sequencing data. Moving forward, oncologists, pathologists, and interventional radiologists will need to collaborate to drive this percentage as close to 100% as possible. In addition, because pediatric solid cancers are often markedly proliferative and widely metastatic at diagnosis or relapse, they seem to be perfect models to determine the clinical utility of circulating tumor cells, cell-free DNA, or both for mutation detection and monitoring.

The exponential improvement in next-generation sequencing and computational biology has enabled the clinical adaption of this transformative technology. While sequencing costs will continue to decline, the turnaround time from biopsy to an actionable therapeutic plan remains a major hurdle. Mody and colleagues reported a median turnaround time of 53 days, which will need to be significantly shortened if this information is going to meaningfully guide clinical care decisions. Importantly, the investigators used both whole-exome and RNA-sequencing technologies, with the delay in turnaround time not attributable to data generation but rather to its interpretation. RNA sequencing was a key feature of their study design. This technology discovered 20% of the potentially actionable findings that were silent in the DNA sequencing (mainly gene-fusion events). Although comprehensive sequencing is clearly optimal for discovery efforts, gene panel next-generation sequencing strategies that provide robust depth of coverage (necessary to detect potentially important subclonal events) and that can now be manufactured to cover the majority of known gene-fusion events have significant advantages as a companion diagnostic when the goal of the assay is to promptly assign therapy because results generally can be returned in less than 2 weeks. There is clearly no single best technology, and the field will likely adapt a hybrid approach to address practical, clinical, and financial pressures.

Mody et al also indicate that a key feature of their study was the implementation of multidisciplinary precision medicine tumor boards. However, tumor boards have a unique historical niche in cancer medicine, have always been multi-disciplinary, and have continuously evolved to address emerging technologies such as 3-dimensional imaging and modern pharmacodynamics. Indeed, the authors suggest that a major contributing factor for the longer-than-desired turnaround time was organizing the tumor boards. As highlighted by the many patients in this study whose tumor progressed before an actionable finding was acted upon, part of improving turnaround time is not just delivering a test result but developing algorithms that match genomic alterations to drug (or drug combinations) with evidence for antitumor activity. Future next-generation sequencing-based cancer clinical trials should be designed with strict protocol-defined mutation-drug matches to rigorously test the utility of precision medicine both in patients with refractory disease and with newly diagnosed cancer.

New drug development has entered an exciting era, with a recent rapid acceleration of novel anticancer agents receiving regulatory approvals for a variety of molecularly defined

entities.[14] However, as evidenced by this study and many others, cancer mutations are highly cell-type specific. Activity against one cancer histotype harboring a mutation does not necessarily translate to activity in a different cancer harboring the identical mutation. Genomic medicine is not as simple as matching a drug to a mutation based on computational inference but requires validation in appropriate model systems. One of the largest unmet needs in genomic medicine is rigorously preclinical testing of candidate therapies in genetically appropriate preclinical models. Even though this will require enormous effort, this approach must be addressed for sequencing results to guide curative therapies in the future.

The study by Mody et al also directly addressed major ethical challenges, ranging from terms of equipoise around biopsy procedures to issues of what information to return to patients and their families and how best to do so. Importantly, the authors integrated genetic counselors into every step of the procedure. Their data are consistent with a relatively large proportion of children with solid tumors harboring a heritable germline mutation, but essentially nothing is known about the penetrance of many of these described variants or the ultimate influence of these variants on tumorigenesis. Extensive additional investigation is required to understand the heritable genome in pediatric patients with cancer and the psychosocial effects of the return of genetic information for which no definitive data on screening or penetrance exists.

Perhaps the most troubling reality highlighted in the study by Mody and colleagues is the number of children with currently incurable refractory cancer and a potentially actionable finding in which the investigators simply could not find a drug that might have provided some measure of antitumor benefit. Reasons cited ranged from lack of pediatric dosing information to no available clinical trial. The pediatric oncology community will need to completely rethink models of drug development in the genomic era as rare diseases become even more rare based on genetically defined subsets. Academic, federal, and industry leaders must overcome the current risk-aversion mentality that interferes with translational innovation and develop new mechanisms to more deftly develop and deliver drugs to children with cancer.

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