"Somatic" Tumor Genomic Profiling and Potential Germline Implications: Ethical Considerations for Children with Cancer

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Esther Knapp

About This Column

Mark A. Rothstein serves as the section editor for *Currents in Contemporary Ethics*. Professor Rothstein is the Herbert F. Boehl Chair of Law and Medicine and the Director of the Institute for Bioethics, Health Policy and Law at the University of Louisville School of Medicine in Kentucky. (mark.rothstein@louisville.edu)

Background

Given the potential diagnostic and therapeutic benefits of genomic sequencing and precision medicine, it is no surprise that such technologies have been heartily embraced in the field of oncology. It is becoming increasingly common for cancer patients to undergo genomic sequencing of their tumors, in hopes of finding potentially targetable mutations and other useful information. Previously, tumor genomic profiling was limited to research studies and conducted primarily at large academic institutions with the resources to perform sequencing on large cohorts of participants. Now, with several private companies offering this testing commercially, it has become easier for oncologists and other clinicians to order somatic tumor testing for their patients outside research protocols. As a result, the number of patients potentially able to benefit from precision cancer treatment has increased.

Unlike the genome sequencing (GS) or exome sequencing (ES) often used in research contexts, commercial panels are comprised of a limited list of genes known to be associated with cancer. The genes included in commercial panels typically differ depending on the type of cancer; however, gene panels often do not differ for pediatric and adult settings. The reports returned to providers typically include an interpretation, signed by a physician/scientist, including pathogenic variants for which a targeted therapy may exist. Some companies offer additional resources for the interpretation and clinical application of results, including consultation with an expert.

The process for ordering commercial tumor profiling is straightforward, in contrast to the time-consuming informed consent discussion generally required by research studies offering tumor sequencing. In current practice, neither health systems nor laboratory companies request or require that a consent form be signed by the patient or family.

Potential Benefits of Somatic Tumor Profiling

The primary goal of somatic tumor profiling is to find "targetable" variants that are thought to make cancer cells susceptible to specific therapies. Since most oncology patients (especially adult patients) are not treated at large academic medical centers, the commercial availability of somatic tumor profiling has dramatically increased the number of patients who are potentially able to receive these targeted therapies. This expansion of tumor profiling also offers the potential to advance research, since private corporations like Foundation Medicine are able to collect data from tumor samples at a scale that far exceeds even large academic research consortia.

At first glance, it may seem that the narrow focus of commercial tumor profiles for treatment purposes helps avoid some of the ethical quandaries that can surround the use of GS or ES, and in particular the challenges raised by germline genetic testing. After all, isn't getting more information about a patient's cancer cells a good thing? Testing the DNA of cancer cells long predates precision medicine, is generally not considered to be "genetic testing" in the same way that germline sequencing would be, and thus is typically treated quite differently in clinical contexts. There are several well described variants associated with various cancers that can provide helpful prognostic and therapeutic information; screening for these aberrations is considered a

Esther Knapp, M.D., M.B.E., *is with the Division of Pediatric Hematology/Oncology, Department of Pediatrics at University of Louisville/Norton Children's Hospital.*

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standard component of the appropriate diagnostic workup of a new cancer diagnosis. So what is different about somatic tumor profiling consisting of more comprehensive cancer-related gene panels?

Potential Germline Implications: Cancer Predisposition Syndromes

Despite the potential advantages of more comprehensive tumor profiling, it does raise a number of nuances that are worthy of careful consideration. Perhaps the most important of these is that some genetic variants identified in tumors might, in fact, have originated as an underlying germline variant. A number of reports in the literature document the discovery of heritable germline cancer syndromes via somatic tumor sequencing paired with germline sequencing. In fact, about 4–16% of patients undergoing tumor genomic profiling will be found to have a germline pathogenic variant.[1] Of note, these studies all included the option up front to participate in germline sequencing, along with tumor profiling. There are fewer reports looking at the incidence of germline pathogenic variants discovered via tumor-only sequencing (likely because most of the seminal prospective studies have routinely included paired tumor/germline sequencing), but this risk of identifying germline variants in tumor-only profiling is still well established.[2]

Of course, the percentage of germline variants found will vary greatly depending on the specific cancer diagnosis of patients undergoing somatic tumor profiling, and testing practices may vary greatly among institutions and individual clinicians. A research study that offers tumor sequencing to every new oncology diagnosis, for example, may be more or less likely to generate these findings than clinical contexts where tumor profiling is limited to only the most unusual or refractory tumors. The likelihood of discovering underlying germline variants may also be very different in pediatric patients, since children tend to develop different tumor types than adults, and their cancers often exhibit fewer acquired mutations than adult cancers.[3] Importantly, many people with cancer who are found to have germline pathogenic variants in cancer predisposition genes will have no significant family history of cancer, demonstrating that relying on family history alone (as has been the standard of care historically) will not reliably detect all patients at risk for such a condition.[4]

It can be helpful for patients to learn about their risks of having an underlying cancer predisposition syndrome. Such information can lead to better identification of cancer risk in the patient, thus guiding appropriate screening measures (such as yearly colonosocopies), which are aimed at detecting cancers early. Additionally, a diagnosis of a cancer predisposition syndrome can potentially help patients take measures to mitigate or prevent the development of cancer. Prophylactic mastectomies are one extreme example, but lifestyle changes (such as quitting smoking or avoiding alcohol) could also be important modifiable risk factors for someone who is predisposed to developing cancer. The discovery of a cancer predisposition syndrome could also trigger further evaluation of relatives who may also be at risk, and who themselves stand to benefit from cancer screening and prevention measures. Such information can also help parents make informed reproductive decisions when it comes to future children. In addition, some germline variants can predict response to therapy, thereby guiding important treatment choices for such patients.

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When Should Tumor Profiling Trigger Germline Testing?

Somatic tumor sequencing may provide information with possible implications for germline or inherited conditions. However, will such information always be welcome, or even useful? The potential benefits of identifying germline conditions are not always clear, nor are they applicable in all patient or family contexts. Also, since tumor profiling is relatively new, guidelines are not yet available on which variants should trigger germline evaluation.

First of all, the interpretation of even focused genetic panels is not always straightforward; the reports generated from tumor sequencing can be technically complex. Interpreting the results, and deciding which variants are clinically significant and which are pathologic, is quite complex and still retains a significant element of the "art" of medicine. There is evidence that even subspecialist oncologists (including both pediatric and adult oncologists) often express hesitation and uncertainty about their abilities to independently interpret tumor sequencing reports.[5]

Recommendations on when to consider germline testing, based on the results of tumor profiling have recently been developed, but even those recommendations recognize some limitations. The American College of Medical Genetics and Genomics (ACMG) has outlined 59 genes where pathogenic variants should generally be reported, even if these are incidental findings.[6] These

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include several genes well known to be associated with cancer predisposition, including BRCA1 and BRCA2 (associated with hereditary breast and ovarian cancer syndromes) and others.[7] For many well recognized cancer predisposition syndromes, recommendations are available on monitoring and screening efforts that can help identify and treat cancers earlier. However, some genes (such as TP53) are frequently mutated in cancer, but they can occasionally be associated with an underlying cancer predisposition syndrome. Thus tumor-only sequencing can raise questions without clear answers (whether a particular finding warrants further investigation).

Even if there is clear indication that further testing for a particular germline condition is clinically advisable, there are additional issues to consider: Many of the practices and guidelines surrounding germline genetic testing are not routinely implemented for somatic tumor profiling. Performing germline testing for cancer predisposition conditions often involves informing the patient when germline testing is recommended, having a discussion with the patient/family before proceeding, and appropriately counseling patients before and after such testing is performed. This process can easily be circumvented, or at least undermined, with somatic tumor sequencing. Thus, commercially available tumor genomic profiling can end up being a "back door" to germline testing. While the somatic results may not prove definitively that a germline variant exists, certain results can be suspicious enough that further investigation is warranted. Engaging patients in discussion about the significance of germline findings only after abnormalities have been detected on tumor sequencing is a backwards approach.

Current Recommendations Regarding Potential Germline Findings

Given the established risk of discovering germline abnormalities on tumor-"only" sequencing, several organizations have developed recommendations for clinicians who seek to perform such testing on patients.

The American Society of Clinical Oncology (ASCO), for example, counsels, "Patients undergoing tumor-only sequencing (and their physicians) should be aware, before testing, of the possibility that tumor profiling may suggest germline susceptibility, [and if] tumor-only profiling identifies a pathogenic or likely pathogenic variant in a gene linked to inherited susceptibility to cancer or other diseases, the clinician should be prepared to refer the patient and his or her family for further evaluation, including confirmatory germline testing."[10]

The ACMG suggests that informed consent may be obtained using traditional models (e.g., in person, or by phone with the ordering provider) or by using innovative methods (e.g., online videos, validated artificial intelligence–based methods such as chatbots).[11]

Finally, the Clinical Sequencing Exploratory Research (CSER) consortium goes a step further, recognizing that laboratories themselves should bear some responsibility for the results that they give to clinicians and families. At the very least, "Laboratories should consider highlighting results that are suggestive of germline variants and including enough information to allow for germline testing by a second laboratory, if not done by the initial testing lab."[12]

Germline Testing in Children: Unique Considerations

Genetic testing in children brings up even more complexities. There is well-established literature regarding the complex nature of performing germline testing on children, and when it may be clinically indicated and appropriate to do so. Current recommendations focus on assessing the potential benefits of genetic testing on children. If genetic testing may lead to screening or treatment that could improve the child's health, it is reasonable to consider such testing. However, if there is no likely anticipated benefit in childhood (that is, adult-onset conditions), then many believe that there is little rationale for performing such testing on children. The child can later choose to undergo genetic testing, as an adult, making an informed decision at that time. These guidelines include testing children for cancer predisposition syndrome where the risk of developing particular cancers does not generally become clinically relevant until adulthood. It is generally discouraged to subject children to genetic testing that is unlikely to benefit them during childhood, even if the parents desire testing, and even if there is a clear family history of a genetic condition, including a cancer predisposition syndrome. However, organizations such as the American Academy of Pediatrics and the ACMG recognize that there may be exceptional cases.[15]

Because germline pathogenic variants can be identified on tumor-"only" sequencing, this creates a particularly delicate situation when children undergo such testing. When should certain results trigger further germline testing, and how should this be handled for pediatric patients, who do not legally consent to their own medical care? While several investigators have chosen to discuss possible germline findings as part of the informed consent process for pediatric subjects undergoing tumor profiling in the context of a clinical research study, there are no general recommendations regarding how to approach potential germline conditions in pediatric tumor testing. The literature surrounding potential germline results in children whose tumors are sent for commercial somatic profiling is even less developed.

It should give us pause, then, to consider that children with cancer, whose parents are often uniquely motivated to pursue any diagnostic or therapeutic intervention that holds even a small chance of benefitting the child, are particularly at risk of being caught in a difficult scenario if somatic tumor profiling is pursued. For example, if the results reveal a variant that raises concern for a germline cancer predisposition syndrome, firstly, this may necessitate conversations that clinicians and patients/families were not prepared

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to have. If the germline variant can reasonably be associated with the child's cancer, then most likely the physician will then embark on a discussion about further confirmatory testing. This may not be straightforward: for example, what if one parent would like to pursue germline testing, but the other would not? What if the child has a different viewpoint from the parents?

Consider a different scenario, where the variant found is not thought to be related to the child's tumor, i.e. a secondary finding (for example, a variant in a gene associated with only adult-onset cancers). The physician will then have to explain to the patient's family that while the purpose of the testing was indeed to find genetic variants in the tumor, a different kind of variant was found: namely, one that is probably not related to the child's diagnosis (at least, as far as current research can account for). Furthermore, the physician may believe that it is unethical to pursue additional follow-up testing to see if this is truly a germline variant in a cancer-associated gene, because it is associated with an adult-onset condition.

Will families be satisfied with this explanation? That is, "We purposely sent a panel of tests on your child's tumor to see if we could find out more information about the cancer. We did find some abnormalities, but based on the literature, this variant (in a known cancer-associated gene) is unlikely to cause the phenotype of your child's cancer. And we do not recommend further germline testing to confirm whether this is indeed a germline variant. If confirmed, however, this variant could have implications not only for your child, but also for you and your other children." How many parents of children with cancer would accept this? And in an era of medicine where the data is constantly changing and we are discovering new information about genetic variants all the time, how confident can the physician even be in stating that the variant is unlikely to be related to the child's diagnosis? What if there just isn't enough established data yet regarding this particular variant?

Furthermore, if the child is indeed found to have a cancer predisposition syndrome, this has potential implications for other family members, which could include parents, minor siblings, or even future siblings. Thus, purportedly simple tumor sequencing of the child may in fact set off a cascade of resulting events, which could have far-reaching consequences for other family members. As Wilfond and colleagues point out, the discovery of a variant associated with adult-onset disease in a child could lead to the identification of other affected family members, which could be one potential benefit of germline confirmation of results found on somatic tumor profiling.[16] Given that it has been increasingly common for cancer predisposition syndromes to be diagnosed in patients lacking a suspicious family history, family members may argue that the discovery of a germline variant in a child, even if not linked with a cancer predisposition syndrome that typically affects children, may be the only way for other affected relatives to be identified.

For a family that never gave explicit informed consent for tumor profiling, or who was simply told that the purpose of such testing was to help obtain more information about the child's cancer, the discovery of possible germline variants could lead to difficult situations, and even mistrust that harms the patient/physician relationship. Testing may also leave ordering clinicians in a difficult position of having to choose whether to follow current recommendations (to discourage germline testing for adult-onset conditions), or to decide that a particular pediatric patient falls into the nebulous "possible exception" category. Patient and family autonomy may be harmed by the disclosure of information, if families are not given the latitude to make further decisions regarding the test results. Thus, we need to be cognizant of the issues facing pediatric oncologists when they are considering performing tumor profiling on children and try to anticipate potential issues before they develop. We especially need clearer recommendations for pediatric oncologists who frequently employ such tumor profiling, helping them to have informative discussions with patients and parents prior to and after testing.

Further Guidance

In order to foster patient autonomy regarding medical decisions, it will be necessary to provide the tools for them to make fully informed and collaborative decisions regarding tumor sequencing. What specific measures can improve patients' understanding of tumor profiling, and prepare them for possible germline variants? I propose that laboratories that offer tumor profiling take the initiative to improve the feasibility of complying with existing recommendations regarding discussion of tumor profiling. Specifically, during the process of ordering tumor sequencing, there could be a prompt/link to various resources, including informative videos, a list of commonly asked questions (with answers), and a suggested outline/discussion guide for discussion with the patient. Before submitting the sample, a clinician would be asked to check a box indicating that he/she had had a discussion with the patient about the purpose of the testing, and possible outcomes of the testing. (It need not be mandatory to answer "yes," but at least the ordering physician will have to acknowledge that such a discussion is strongly recommended.)

If we incorporate counseling with patients/families into part of the process for ordering tumor sequencing, and provide more guidance on what to discuss, it is more likely that clinicians will routinely follow existing recommendations, from professional organizations and others. These simple changes in process could make it more practical for ordering physicians, who may not be familiar with all the various recommendations regarding somatic tumor sequencing, to engage more regularly in brief but productive discussions with patients prior to testing. By encouraging the entities who market tumor profiling to take an active role in this process, we will increase the likelihood of more widescale compliance with these important recommendations. More

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importantly, this may help engender trust on the part of patients and families, and help build a therapeutic alliance. Taking steps to address and alleviate concerns on the front end will help ensure that genomic tumor profiling will see wider and wider adoption, in the appropriate clinical context.

Some key discussion points may include: What is the specific reason why the testing is being performed? For example, does the patient have a rare tumor, or has there been inadequate response to therapy, or does the clinical phenotype not correlate with the histologic diagnosis? What types of information may be gained with such testing, and how will that help the patient? Do we hope to gain diagnostic as well as therapeutic information? The clinician should make it clear if there is a possibility that a targeted agent may be recommended based on the results of testing. There should also be some dedicated attention to the possibility that testing results may find aberrations in genes that are associated with germline, inherited conditions (including genes that have been linked with cancer predisposition syndromes). For pediatric patients, it is especially important for parents/guardians to understand that germline testing of children is a different entity, subject to guidelines that attempt to protect a child's ability to make his/her own medical decisions as an adult.

While it would be unreasonable and overly burdensome for clinicians to discuss all the possible findings and ramifications of somatic sequencing, it would be a significant achievement to increase the frequency of such conversations, by giving physicians the tools they need to facilitate efficient yet productive discussions, addressing certain key questions and ensuring that decision makers are properly informed.

Though the rapid development of new technologies in genomic oncology may initially seem intimidating to medical practitioners and patients alike, facilitated conversations will help both parties become more comfortable with these new assays. Thus, ultimately we will improve the comprehensive care of medically complex children and adults with cancer, empower patients and families to make more fully informed decisions about complex medical testing, and also improve the public perception and more widespread adoption of new and potentially important diagnostic techniques.

Specific Suggestions for Pediatric Patients

Additionally, it is even more important in pediatric oncology to have informed discussions with families prior to performing tests that may reveal information pointing to possible inherited genetic conditions. Children with cancer are a unique and potentially vulnerable population, and as somatic profiling of pediatric tumors becomes more routine, we need to address the possible ethical issues that may arise. We need explicit recommendations that reflect the particular/unique situations faced by children with cancer and their parents, when undergoing somatic tumor sequencing.

Patients and families should have some understanding of what types of results may be found with tumor profiling. Adolescent patients, though they may lack the legal ability to make their own medical decisions, should be considered and respected as stakeholders in important conversations that directly impact their health. Clinicians should be encouraged to include patients in important discussions (as appropriate, depending on the patient's ability to understand his/her diagnosis, evaluation and treatment). Discussions should include several key points: Sometimes, tumor sequencing may reveal information that is potentially relevant to the child's cancer, and may lead to a change in recommended therapy. Results may even help families understand why their child developed cancer (this is often a central question for parents of children with cancer, as they struggle to understand why this has happened). Sometimes, somatic testing may even point towards a cancer predisposition syndrome, which would have various implications for the patient as well as family members, including siblings and other minor children. However, some results may be thought to be unrelated to the child's cancer, especially those associated with adult onset diseases, and could represent incidental discoveries. To pursue germline testing in such cases could represent a deviation from standard practice regarding genetic testing of children. Addressing these topics, and eliciting a family's thoughts and concerns prior to testing, will provide basis for the appropriate exercise of autonomy in medical decision making for children with cancer.

Thus, there are many additional ethical issues that may arise when somatic tumor profiling is performed on children, and there is a dearth of literature addressing how these problems should be addressed, particularly in the realm of commercial tumor sequencing. These particular concerns should be explicitly discussed with pediatric oncology patients and families prior to pursuing such testing, and it would be helpful to incorporate these sugges-

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tions into the process for ordering tumor sequencing.

Summary

Genomic sequencing of tumor samples will no doubt become an increasingly important tool for oncologists, especially as more targeted therapies are developed, and as new applications are found for current drugs. Since pediatric cancers often exhibit different genomic profiles from cancers in adults, it will be especially important to gather more information about potentially clinically actionable variants in children, as well as adult patients with cancer. However, given the possibility that even limited cancer-specific gene panels can point towards underlying germline conditions, it is important to address the potential ramifications of such results. These implications can become even more complex in patients who are children.

We should encourage the commercial laboratories to provide resources to help clinicians follow existing recommendations regarding discussions with patients and incorporate these resources into the ordering process. The goal is not to create barriers to genomic sequencing, or to contribute to pointless paperwork and administrative tasks that already overburden practicing oncologists and other physicians. Rather, by developing practical steps and resources that are easy to follow, and by calling on commercial laboratories to become actively engaged and invested in this process, we can help increase familiarity and compliance with existing recommendations. There should also be further consideration of the unique issues posed by performing tumor sequencing on children.

Though the rapid development of new technologies in genomic oncology may initially seem intimidating to medical practitioners and patients alike, facilitated conversations will help both parties become more comfortable with these new assays. Thus, ultimately we will improve the comprehensive care of medically complex children and adults with cancer, empower patients and families to make more fully informed decisions about complex medical testing, and also improve the public perception and more widespread adoption of new and potentially important diagnostic techniques.

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