

Clinical Tumor Sequencing: An Incidental Casualty of the American College of Medical Genetics and Genomics Recommendations for Reporting of Incidental Findings

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In 2013, the American College of Medical Genetics and Genomics (ACMG) issued recommendations for reporting incidental findings, defined as results of potential medical utility that are not related to the indication for ordering the sequencing test, in a panel of 56 disease-associated genes when performing clinical exome and genome sequencing.¹ Given the increasing use of clinical sequencing for characterization of both germline and tumor genomes in diverse clinical settings, these recommendations reflect careful consideration of the complex issues related to these tests. Unsurprisingly, they have provoked vigorous discussion and debate regarding issues of patient autonomy and the ethics of returning results for pediatric patients.²⁻⁶ Although there has been comparatively little discussion of the impact of these recommendations on testing of tumor specimens,⁷ the scope of these recommendations does extend beyond germline genetic testing into the realm of tumor-focused testing with the statement that “incidental variants should be reported for the normal sample of a tumor-normal sequenced dyad.”

It is certainly the case that exome and genome sequencing may uncover incidental findings that may prove relevant to the health of patients with cancer and their families. Thus, at face value, the ACMG recommendations have potential repercussions for oncologists and patients with cancer. It therefore seems unfortunate that development of the recommendations appears, on the basis of the information provided by the expert panel, not to have included input from medical or surgical oncologists experienced in tumor genomic testing or from cancer professional societies.¹ This is in contrast to other ACMG guidelines, for which the organization has partnered with other professional societies such as the American Academy of Pediatrics and American College of Obstetricians and Gynecologists.⁸ Despite this paucity of oncology stakeholder input, the ACMG statement could, in its fullest implementation, have significant implications for the field of oncology, with an impact on cancer genetics laboratories, oncologists, surgeons, pathologists, and patients. The oncology community should therefore carefully consider whether these guidelines are appropriate in the context of cancer genomic testing for somatic mutations and the appropriate approach to adherence to the

guidelines for those patients who would not otherwise have a germline genetic evaluation.

Germline exome or genome sequencing of a blood or buccal sample in selected oncology patients has potential clinical utility when ordered by a clinician for the purpose of detecting germline variants that convey cancer susceptibility.⁹ Recommendations for the appropriate use of germline testing for cancer susceptibility have been well described by the American Society of Clinical Oncology and generally apply to a minority of patients with cancer.¹⁰ This testing has implications for genetic testing of family members, cancer surveillance and prevention strategies and, in rare cases, selection of cancer treatments for the patient. Of note, the infrastructure and expertise required for cancer susceptibility testing of patients with cancer are consistent with those used for germline sequencing tests for nononcologic indications such as developmental delay. The reporting of incidental noncancer findings detected after clinical germline exome or genome sequencing for detection of cancer susceptibility mutations should therefore be considered on the same basis as for these other diseases.

However, it is anticipated that the vast majority of clinical sequencing tests ordered for oncology patients in the foreseeable future will be tumor exome or genome sequencing for the purpose of identifying somatic (tumor-specific) mutations that might guide optimal cancer therapy, specifically in relation to the selection of molecularly targeted agents.¹¹ At present, the motivation for oncologists to order such a tumor sequencing test is strongest for their patients with cancer for whom treatment choices are unclear and/or for whom the prognosis is poor—primarily patients with incurable metastatic and recurrent cancers seeking trials with investigational agents. For these patients, germline questions (and resultant findings) are at best tangentially relevant to the oncologist's rationale for ordering the test. Instead, oncologists typically desire to learn more about their patient's tumor to aid in treatment decisions. Medical geneticists and genetic counselors are typically not consulted as part of this evaluation. In this clinical situation, germline variants that cause cancer susceptibility could actually be considered “incidental” findings from the perspective of the oncologist or patient, even though they are directly related

to the cancer diagnosis. The germline variants that cause the nononcologic diseases on the ACMG list, such as long QT syndrome or familial hypercholesterolemia, are therefore “doubly incidental” results. Consequently, the recommendation of the ACMG to routinely report the incidental finding of germline mutations in 56 different disease genes when performing tumor and matched normal gene sequencing, essentially considering these tumor tests to be equivalent to germline tests, raises several key challenges.

Implications for Clinical Laboratories

Acceptance of the ACMG recommendations could have substantive consequences for clinical laboratories that are already confronting numerous technical and interpretative challenges to the effective clinical implementation of tumor exome/genome sequencing (such as tumor heterogeneity and clonal evolution). The final product of the tumor sequencing test is an annotated and clinically interpreted rank-ordered list of somatic mutations generated by automated subtraction of variants found in the patient’s normal sample from the total compendium of variants in the tumor; the generation of this somatic mutation list and clinical report involves no specific analysis or annotation of germline variants, and laboratories need not have this capability to produce the tumor-focused clinical report ordered by the treating oncologist. Furthermore, tumor sequencing and germline sequencing require analogous but distinct setups, with each test entailing distinct bioinformatics analytic pipelines and specialized personnel expertise in variant interpretation, clinical reporting, and participation on multidisciplinary tumor boards.¹²⁻¹⁴ Decisions about the classification of germline variants as pathogenic can be extremely challenging for a number of genes on the ACMG list, including cancer susceptibility genes.¹⁵ The ACMG guidelines would require cancer-focused laboratories to also include expertise in noncancer conditions (eg, the cardiomyopathy-related genes) and require a distinct expertise from that needed for the sign-out of tumor sequencing results. For example, at the Baylor College of Medicine, we have two separate exome sign-out teams and two separate review conferences for the germline and tumor tests, respectively, with different expertise present at the meetings. Moreover, these incidental findings are not rare. A recent review of exome data from 1,000 patients identified incidental findings from genes on the ACMG list in 2.3% of them.¹⁶

To summarize, requiring clinical cancer genetics laboratories that perform tumor sequencing to conduct a separate and deliberate search for incidental germline findings in the normal specimen of a tumor-normal pair, as recommended by the ACMG, would require a parallel setup to identify, validate, and report the germline variants, which would substantially add to the cost of the tumor sequencing test. Data are not yet available to demonstrate that the benefits of these efforts would justify this additional cost and labor. Furthermore, the inclusion of incidental germline findings would potentially extend the turnaround time for reporting tumor sequencing results (or necessitate that two separate reports be issued for each test), which is a significant concern given the time-sensitive nature of the clinical decisions that must be made for patients with both newly diagnosed and recurrent cancers.

Implications for Oncologists

The inclusion of incidental germline findings as a required component of tumor exome or genome sequencing tests could also have a significant impact on oncologists and their clinical practice. The po-

tential for detection of incidental germline results would substantially alter the nature of the discussions between oncologists and their patients about the performance of tumor sequencing tests and would increase the clinic time (and expense) required for this aspect of patient care. Educating a patient about the potential risks and benefits of a tumor sequencing test is relatively straightforward and does not necessitate discussion of complex germline-related considerations such as privacy, insurability, or the potential implications of findings for other family members, all of which would need to be included in pretest counseling according to the ACMG guidelines on exome sequencing.¹⁷ Clear communication between the ordering oncologist and patient about the potential for inclusion of germline analyses as part of the tumor test would become a critical component of this clinical interaction, particularly given that the types of molecular tests performed on a tumor are not typically discussed in detail with patients before tumor biopsy or resection. The return of tumor sequencing results from the oncologist to the patient would be similarly complicated by the inclusion of incidental germline findings. Both the pre- and post-test discussions would theoretically require the expertise of a genetic counselor or geneticist—a limited resource in oncology clinics in particular and the United States in general, where the focus is typically on patients undergoing germline susceptibility testing. This again may result in increased patient care costs. The requirement to report incidental findings may also be taken into consideration by oncologists when determining whether to order whole exome sequencing or whole genome sequencing or alternative genomic tests that focus on a limited number of cancer genes in tumor specimens.

Implications for Patients

Most importantly, these recommendations could have negative consequences for patients with cancer. Picture a typical patient for whom an oncologist might order clinical tumor sequencing, such as a 65-year-old woman with no family history of cancer who has been diagnosed with metastatic lung cancer for which there is no proven curative therapy and a relatively short life expectancy. In order for this patient’s oncologist to obtain potentially clinically relevant information to guide the treatment of her acutely life-threatening condition, she would be required to spend time, thought, and energy at this already exhausting time on consideration of the possible incidental germline findings which the test could reveal, some of which could be unrelated to cancer and all of which would have implications for other family members. This decision would be even less straightforward for the parents of a pediatric oncology patient. The mandated inclusion of incidental germline findings involves a relatively larger degree of infringement on patient autonomy for tumor sequencing than for germline sequencing (which already necessitates consideration of the complex issues inherent in germline analysis). This could presumably prevent some patients who could benefit from a tumor sequencing test from having the test performed.^{2,3} It would certainly involve additional costs (financial and otherwise) for all patients who do decide to pursue the testing.

The questions raised by the consideration of these issues are critical ones for the practice of oncology and therefore are the subject of significant ongoing research efforts, including three projects funded by the National Human Genome Research Institute and the National Cancer Institute through the Clinical Sequencing Exploratory Research program that are investigating the utility and ethical aspects of clinical tumor and germline exome sequencing.¹⁸

Recommendations for the inclusion of incidental germline findings in clinical tumor exome and genome reports will be more informed, and therefore more useful, after relevant data have been obtained and guidelines have been developed by those in the oncology community and professional societies most directly involved in the care of patients with cancer, such as the American Society of Clinical Oncology and the Association of Molecular Pathologists. Although the ACMG process for review and adaptation of the recommendations is ongoing, we believe that the development of tumor-specific reporting guidelines by these cancer professional societies would be beneficial.

Specifically, data on the clinical benefits of return of incidental results for cancer patients and the preferences of patients and oncologists regarding reporting of tumor sequencing tests will be critical for guiding these decisions. For example, an alternative approach that preserves patient autonomy would be to offer oncology patients the opportunity to include germline results in their tumor sequencing report (an opt-in testing approach) if they elect to meet with a genetic counselor for pretest counseling, which would allow each individual to assess the potential personal and familial benefit of obtaining such information. This opt-in approach would require oncologists and clinical laboratories to be able to comply with ACMG guidelines for those patients who choose to include germline results and would avoid the possibility that a blanket requirement might reduce access to tumor sequencing tests for patients with cancer. Notably, the ACMG Board of Directors released an update to these guidelines in April 2014 that recommends an opt-out option be offered to patients considering clinical genome-scale testing.¹⁹ The use of opt-out procedures for patients does not reduce responsibility on the oncologists to fully counsel each patient on the implications of incidental findings or on the testing laboratory to provide them. Thus, laboratories and oncologists who perform and use cancer genomic testing will need to make difficult decisions about implementing the ACMG guidelines and about their approach to informing patients of these potential results.

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