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When “Actionable” Genomic Sequencing Results Cannot Be Acted Upon

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On the day that I called her, a few weeks after the genomic sequencing of her cancerous tumor had been completed, I thought we would be discussing how participating in our tumor sequencing study had compared to her expectations. Sequencing tumors from patients like this woman, those for whom either the standard of care is ineffective or no standard of care exists, can inform choices regarding clinical trials or targeted therapy based on the molecular characteristics of the cancer. So, my planned questions focused on whether the patient’s results had changed her treatment or been helpful in any other way.

What I did not expect was to hear the story of a patient in deep anguish. Not as a result of what one might anticipate—distressing test results, a misunderstanding of information, or uncertainty about the meaning of the genetic findings—but because of expectations. By a combination of misfortune and circumstances, this woman had come to believe that participation in a clinical trial uniquely appropriate for treating her type of cancer was achievable, and then it couldn’t be achieved.

In genetic studies in which individual results are returned to patients, the informed consent process often discusses the possibility that patients might find out information that could be distressing to them, with genetic counseling an integrated part of the process.

Furthermore, in this trial protocol, we have recognized that patients’ interest in tumor sequencing doesn’t necessarily imply they want to learn about their germline findings (i.e., alterations in the patient’s non-cancerous tissue with potential implications for family members’ disease risk). Our research protocol only analyzes the sequence of cancer related genes and explicitly asks participants about return of germline findings; patients who decline such disclosures only receive results that (to quote the consent document) have “direct impact on care of [the patient’s] current cancer.”

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This patient had fully understood that the sequencing process might uncover undesired information and that there was no promise that her participation would lead to a clinical drug trial or novel treatment option. Unlike most of our study participants, she had declined the optional disclosures of significant germline findings. In her mind she had stated clearly that she didn't want to know any information that did not lead to personal benefit.

And yet, there she was, extremely distressed because of her test results.

The harm that befell this patient wasn't that she received bad news from these results. Instead, she was harmed through the unfulfilled hopes and emotions evoked in her by receiving news of having an "actionable mutation" that was not, in fact, able to be acted on in any way that actually mattered to her.

The patient's sequencing profile revealed several genetic aberrations, including mutations with known drug targets. Because of these associations, the result was classified as "medically actionable" and hence was passed down to her treating oncologist and ultimately to her. A current clinical trial of an investigational combination therapy designed for patients with mutations matching those identified in this patient was open. In terms of the research project's goal, we had succeeded in identifying clinically important information that could potentially help her doctor manage her cancer.

But, to the patient, actionable information implies being actually able to act. And that's where things went wrong. When the patient tried to enroll in the trial, she was screened out due to a benign condition. Even after her oncologist attempted to address the relevant symptoms, she was still excluded. Action, from her perspective, was denied her.

What was so heart wrenching about this patient's story is that she had not had unrealistic expectations about the likelihood of benefit from genomic sequencing. She was very clear that she hadn't expected to get good news and had not believed that the genomic sequencing would save her. At least until it was communicated to her that an "actionable mutation" had been found and that related clinical trials existed. Then, of course, her hopes rose. She became excited about the possibility of a therapy that might actually work on her otherwise treatment-resistant cancer. She began to dream. Yet, ultimately, those hopes and dreams were dashed.

When I interviewed her, this patient repeatedly talked about the "burden" of knowing things she couldn't do anything about. She commented that it was bad enough to have a fatal illness, but worse to know that potentially useful treatments existed beyond her reach.

In her own words, she was "bitter." And even though she acknowledged that her situation was unintentional, she "experienced [the gene sequencing study] as a kind of exploitation," one in which the science benefitted but she was left fundamentally worse off. Her parting words were advice to researchers to think more about their obligations to emotionally "fragile" patients. "No participant can know when they get involved with something like this, what emotionally will be the outcome of participating," she said.

This case reminds us that more information is *not* always a good thing, and test results that are “actionable” from the standpoint of increasing medical knowledge can be profoundly negative for the individual patient. Barriers exist at the levels of individual, institution, and society, especially with this clinical technology in its nascent phase. When test results identify possible therapeutic approaches that are not, in fact, available to the patient, this false hope can be far worse than simply remaining ignorant.

From a research ethics standpoint, harms to research participants are usually conceived of as being attributable (or not) to a given individual study. Here, however, the harm resulted from an interactive effect—a certain type of sequencing result coupled with an inaccessible subsequent trial. Even though the policies and actions of the clinical trial arguably fell outside the purview of our research study, the truth is that this patient would not have even known the trial existed, let alone pursued it, without her suggestive sequencing results.

The lesson to be drawn from this case is that precision medicine initiatives need to address potential harms resulting from “chain reactions” involving other clinical research studies. While unanticipated economic or medical barriers to treatment or clinical trials are hardly new, there is something uniquely painful about the psychological experience of being told that a precision therapy, designed for your tumor’s particular genetic signature, is nonetheless unavailable to you. Warning patients undergoing genetic sequencing that they might learn upsetting information is not enough. Precision medicine initiatives have a responsibility to anticipate potential barriers to implementation of sequencing findings and at least ask the question whether disclosure of results is ethically justifiable if those results are not actionable in practical terms.

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