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Clinical Cancer Research

The Molecular Profiling Lottery: More Accuracy, Less Precision, and No Cost

Mark J. Ratain

The concept of complete molecular profiling to select investigational treatment options is appealing, theoretically allowing the matching of patients to investigational drugs specifically targeted to molecular features of each patient's cancer. Although some patients do benefit from such a strategy, the vast majority do not.

See related article by Tuxen et al., p. 1239

In this issue of *Clinical Cancer Research*, Tuxen and colleagues report the results of the Copenhagen Prospective Personalized Oncology (CoPPO) study, which enrolled 591 patients, 500 of whom underwent biopsy for the purpose of individualizing investigational therapy (1, 2). The samples were extensively analyzed, including both whole-exome sequencing (WES) and quantitation of RNA expression of prespecified therapeutic targets. Although the study confirms the feasibility of molecular profiling, it does not provide evidence that this approach should be broadly utilized to prioritize investigational treatment options for patients with refractory advanced solid tumors.

The originally stated objective of the CoPPO study was to measure the percentage of patients who benefited from molecular profiling, using the same approach used by Von Hoff and colleagues (3), where benefit was defined as progression-free survival for the selected therapy that was at least 30% longer than that for the last prior regimen. Tuxen and colleagues appropriately conclude that the PFS ratio endpoint is highly flawed and cannot be used to assess the validity of a diagnostic approach, a refreshing conclusion.

So if the primary endpoint is invalid, how should one assess the results of the CoPPO study? Should one use an "intention to treat" analysis, where there were 500 patients who underwent biopsy, 15 (3%) of whom responded to the matched treatment? (while only 101 patients received "matched" therapy, one can reasonably assume that the remaining patients did not benefit from the molecular profiling.)

And if the response rate was 3%, is that good or bad, given that there were 15 patients (3%) who suffered serious biopsy complications? But were there really 15 patients who benefited from the molecular profiling itself? A closer look at the data suggest otherwise.

The 15 patients who had partial responses included seven with *BRAF* V600E mutations, all treated on studies of BRAF inhibitors in combination with one or more other drugs. Thus, there is no question these patients benefited, but because all patients had colorectal or non–small cell lung cancer, such information may have been available prior to entry in the study, as part of the standard molecular diagnostic workup of these diseases, and if so, the molecular profiling in the study—requiring rebiopsy—was unnecessary. Regardless, it is now common clinical practice to test for BRAF V600E mutations in these diseases, given the progress in treating this molecular subset of melanoma and other solid tumors (4).

In the remaining eight responders, the benefit of the rebiopsy for molecular profiling is even less clear. For example, 1 patient with gastric cancer that had previously been treated with capecitabine, oxaliplatin, and trastuzumab was enrolled on a study of epirubicin and trastuzumab because of the presence of *ERBB2* R678Q. However, this has been suggested to be a marker of resistance to trastuzumab, not surprising as the patient had just received the drug. Given that epirubicin is an active agent in gastric cancer, trastuzumab probably only added toxicity, not to mention the risk of the biopsy.

Close review of the other responders also diminishes one's enthusiasm for the benefit of broad molecular profiling. A patient with breast cancer responded to palbociclib and fulvestrant, although the identified molecular feature (*CCND1* amplification) is likely irrelevant. A patient with EML4-ALK lung cancer responded to an ALK inhibitor, yet testing for *EML4-ALK* is now standard practice. Similarly, 2 patients with *BRCA1* (breast) or *BRCA2* (prostate) mutations responded to olaparib, yet one would not need rebiopsy today to test for BRCA mutations.

In addition, the actual tumor response is uncertain for at least 1 patient, the patient with adenoid cystic carcinoma (ACC) who was treated with a Notch inhibitor, presumably LY3039478. However, in the primary report of the phase I study of LY3039478 (5), there were no partial responses in ACC, as the only responder had breast cancer and the 1 patient with a 100% decrease in the target lesion actually had progressive disease due to the development of new lesions.

Thus, putting these results in context with what we know now, one cannot recommend obtaining a new tumor specimen for molecular profiling as a generalized strategy for prioritization of investigational agents. One can envision that this would be appropriate in select circumstances (Fig. 1), especially when there is a protocol that requires the presence of a particular mutation that is known to arise due to resistance to a previous agent, such as utilized in the development

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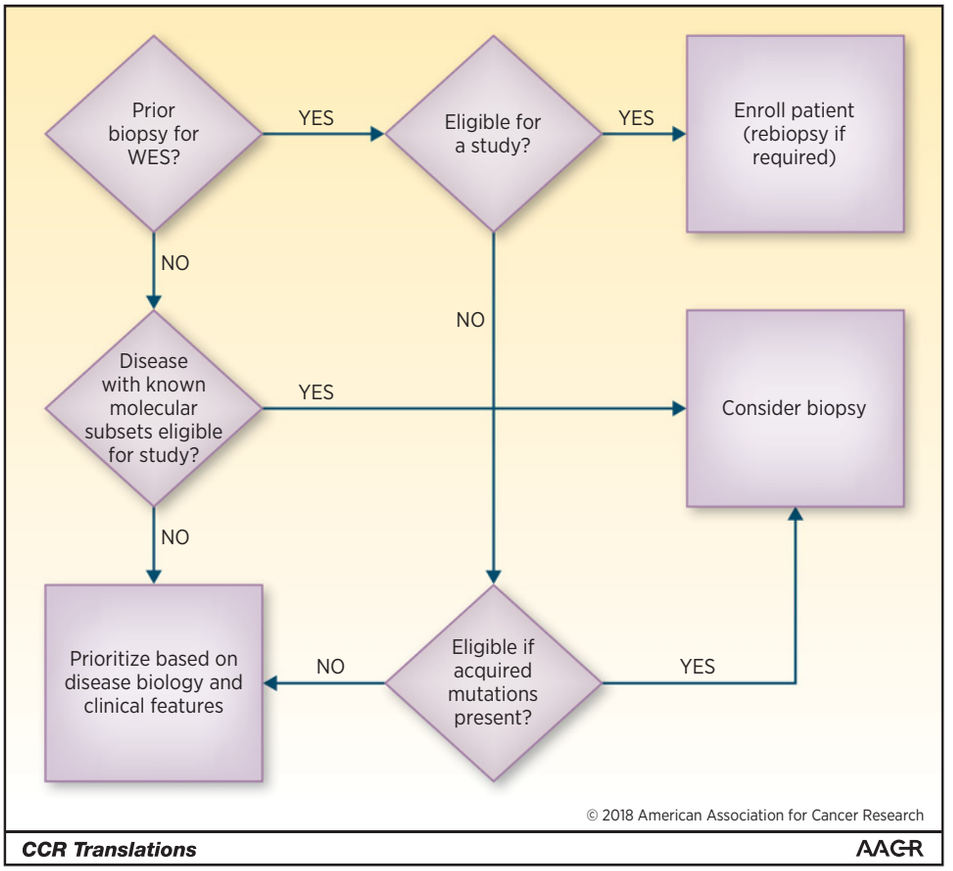

Figure 1.
Proposed algorithm for consideration of biopsy for WES in patients with refractory cancer. For patients who have had prior WES, a repeat biopsy can be considered if there is a reasonable likelihood of finding new mutations that would confer eligibility for an ongoing protocol. For patients without prior WES, a biopsy can be considered for the purpose of determining eligibility but should not be utilized to guide investigational treatment options in general.

of EGFR T790M inhibitors. Furthermore, with advances in "liquid biopsies," the risks of deep tissue biopsies can be avoided.

One challenge is overcoming the political cache of "precision medicine," particularly as oncologists are enthralled with the notion of precision. After all, most of us were trained to calculate body surface area (BSA) to the nearest hundredth of a square meter, despite the lack of evidence that BSA-based dosing is superior to alternative dosing strategies.

However, what we really need is accuracy; administering treatments that are effective, even if not tailored to the individual patient, because the drug is so effective. Furthermore, we do not need precise dosages, but simply dosages that are effective without undue toxicity. Of great importance, the effective dosage may be a fraction of the labeled (and often precise) dose recommended by the manufacturer.

We should also reconsider the cost-effectiveness of WES, in the absence of drugs indicated for specific molecular subsets known to be prevalent in a particular disease. Although there is no question that WES facilitates enrollment of patients on some clinical trials, the cost of such testing should perhaps be borne by the pharmaceutical industry, rather than by payors and patients. In particular, who should pay the cost of testing for very rare variants, such as *NTRK* fusions amenable to treatment with larotrectinib? How many patients will we need to test to identify 1 patient who will benefit from that drug?

One potential solution would be for the pharmaceutical industry to create and fund a nonprofit precompetitive entity that performs WES for all patients with cancer. Because this would identify patients who would be eligible to receive expensive drugs and/or participate in expensive trials of investigational drugs, this would be in the interest of the industry, patients, and physicians. It would also be in the interest of global regulatory agencies, which could review and approve a single test that would become the global standard-of-care, given that it would be provided for free to all patients with cancer. In an era where pharmaceutical companies are demonized daily, this would truly allow that industry to give something back to patients and payors. If not, perhaps payors should offer our patients the choice of WGS or repurposing the funds to purchase real lottery tickets, given current concerns regarding the increasing financial toxicity of modern oncology care.

Disclosure of Potential Conflicts of Interest

M.J. Ratain is director and treasurer of Value in Cancer Care Consortium, reports receiving commercial research grants from AbbVie and Genentech, is a consultant/advisory board member for Aptevo, Cyclacel, AbbVie, Amgen, Ascentage, BioMarin, Elion Oncology, Genentech, Portola Pharmaceuticals, and Shionogi, and has provided expert testimony and patent litigation consulting for multiple generic pharmaceutical companies.

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