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Editorial

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Evaluating clinical utility of comprehensive genomic profiling—challenges and opportunities

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Practice of cancer precision medicine relies on availability of advanced molecular diagnostic tools to guide use of targeted therapies, which now comprise a major component of the armamentarium to treat cancer. Although the conventional regulatory pathway for targeted therapies has required development of matched companion diagnostics, the paradigm of 1 drug-1 companion diagnostic has become increasingly challenging from the perspective of feasibility, especially in an environment with continually emerging targeted therapies, misalignment of drug and diagnostic development processes, and a proliferation of laboratory-developed tests.

Comprehensive genomic profiling entered into the precision medicine scene as one approach to address the need for information on a wide range of tumor molecular alterations to more fully reveal potential therapeutic options for each patient. Numerous laboratories now provide comprehensive tumor molecular testing; some restricted to genomic sequencing, while others additionally include assays such as immunohistochemical or in situ hybridization assays for select biomarkers. For this discussion, molecular alterations can be interpreted as encompassing this broader class of biomarkers, as the fundamental issues raised here generalize.

Evaluation of comprehensive genomic profiling for regulatory or reimbursement purposes has presented substantial challenges beyond those for single-biomarker tests, because of their large number of outputs and the increasing number of comprehensive genomic profiling tests available. Criteria used to make regulatory and reimbursement decisions for comprehensive genomic profiling are evolving and must often be applied to evidence that could be described as incomplete and of heterogeneous quality, at best. Currently, many comprehensive genomic profiling tests in clinical use are offered under the laboratory-developed test umbrella without review by the US Food and Drug Administration (FDA). However, on April 29, 2024, the FDA announced its intent to amend regulations to clarify that in vitro diagnostic products are devices and to phase out general enforcement discretion for laboratory-developed tests (https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests) to provide greater oversight of in vitro diagnostic products; although, targeted enforcement discretion policies may apply for certain categories of these in vitro diagnostic products. Meanwhile, payers have their own evaluation processes for coverage decisions that have not always aligned with regulatory processes. Given the importance of molecular alterations used for treatment decisions, further discussion of type and quality of evidence used in regulatory and coverage decision for comprehensive genomic profiling is timely and should be encouraged.

With this background, the article in this issue of the Journal from Stackland et al. (1) provides important insights into the challenges of culling and evaluating evidence to establish clinical utility of comprehensive genomic profiling. As a case study, the authors evaluated the rigor of the peer-reviewed literature cited in the Centers for Medicare & Medicaid Services (CMS) National Coverage Determination Memorandum for the FoundationOne CDx (F1CDx), a next-generation sequencing companion diagnostic. F1CDx interrogates 324 genes in addition to a few genomic signatures and tumor mutational burden; it was one of the in vitro diagnostic products to undergo parallel review by FDA and CMS in a novel program intended to reduce time to completion of premarket clearance and CMS coverage decisions.

Stackland et al. (1) focused on a sample 113 studies, which covered a variety of comprehensive genomic profiling platforms; only 4 studies focused solely on F1CDx. Therefore, their review has relevance to comprehensive genomic profiling beyond F1CDx. Likewise, the points discussed here are not unique to F1CDx. The authors sought to categorize the studies into a hierarchy of levels of evidence for efficacy, where efficacy refers here to diagnostics rather than the more familiar notion of therapeutic efficacy, according to a framework the authors adapted from Fryback and Thornbury (2) [table 2 of (2)]. Levels of comprehensive genomic profiling efficacy considered were diagnostic accuracy (accurately identify genetic variants of interest), diagnostic thinking (help make a diagnosis or better understand clinically relevant disease characteristics), therapeutic efficacy (test results in change in treatment), and clinical utility (test use associated with improved clinical outcomes). The heterogeneity in study types and quality was striking, and the studies varied regarding the levels of efficacy they addressed. Notably, only one-third (38 of 113) of the studies assessed clinical outcomes after comprehensive genomic profiling testing. Of those 38, only 25 involved testing of more than 5 genomic alterations. Among those 25, only 1 included a comparator group that did not receive comprehensive genomic profiling testing and that study used historical control patients. Eight of the

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studies included only patients who tested positive for mutations that had therapy matches. In 3 of those studies, all patients received matched therapy, whereas for the other 5 studies, patients were assigned to either matched therapy or standard of care. Only 1 of these studies randomly assigned patients to matched therapy vs standard of care, with the other 4 making observational comparisons. The 1 randomized study was the SHIVA trial (NCT01771458), which found no improvement in progression-free survival with matched therapy, but importantly, it was evaluating off-label use of matched therapies. Deciphering this confusing compilation of evidence to reach a CMS coverage decision was surely extremely challenging.

There are several insights to be gleaned from the review conducted by Stackland et al. (1) that might suggest better ways to generate and evaluate evidence to assess clinical utility of comprehensive genomic profiling. Several key points are elaborated on here.

Establishing clinical utility of comprehensive genomic profiling requires demonstration of a favorable benefit-to-risk balance achieved by use of the comprehensive genomic profiling, where benefits could include aspects such as improved outcomes, (eg, longer progression-free survival or overall survival, reduced toxicity) and greater convenience. However, improvement in clinical outcome is intimately tied to availability of effective treatments for the subgroups the comprehensive genomic profiling identifies. This intertwining emphasizes the importance of considering context of drug approval status when evaluating evidence for clinical utility of comprehensive genomic profiling. Evidence from studies that are simultaneously evaluating investigational therapies or those used off-label [eg, SHIVA (3) and Targeted Agent and Profiling Utilization Registry (4)] (https://society.asco.org/research-data/tapur-study; NCT02693535) may lead to different conclusions about utility of comprehensive genomic profiling testing than studies involving only approved drugs used according to label. A minimum requirement for a comprehensive genomic profiling should be that if the test will be used as a replacement for an approved companion diagnostic, then it should demonstrate high concordance with the companion diagnostic for the target molecular alteration; if it doesn't, then clinical evidence should be provided demonstrating that it performs at least as well at identifying the patients who benefit from the matched therapy.

Related to availability of matched treatment is the need for caution in use and interpretation of studies designed or analyzed as biomarker strategy designs, meaning that clinical outcome on comprehensive genomic profiling–directed therapy is compared with that for therapy selected without use of comprehensive genomic profiling (eg, standard of care or physician choice). Although this might seem like an intuitive comparison and is popular in the diagnostics literature, it is a fraught approach in the context of predictive biomarkers (5). When prevalence of molecular alterations associated with highly effective matched therapies is small (eg, neurotrophic tyrosine receptor kinase inhibitors targeting neurotrophic tyrosine receptor kinase fusions), comparing outcomes across all patients will dilute the therapeutic benefit by mixing in a large proportion of patients who have molecular alterations with no matched therapies who would receive the same therapy in both the testing and nontesting arms. Another limitation is that overall trial conclusions may be driven by 1 or a few subgroups in which matched therapies were either strongly beneficial or not beneficial. This situation reflects a tension between individual and societal perspectives—the rare individual benefitting greatly from a particular matched therapy vs large health-care expenditure for the comprehensive testing of a large number of patients, many of whom will not benefit. More judicious use of comprehensive genomic profiling with emphasis on scenarios where fewer effective therapy options are available and a comprehesive genomic profiling test could potentially reveal more therapeutic targets might help achieve a more equitable balance. Prioritization would likely depend on tumor type (some tumor types are expected a priori to have more therapeutically actionable mutations that could be easily and less expensively identified with a few single-biomarker tests) and other factors such as type and number of lines of prior therapy. Development of prioritization criteria with such specificity would be better handled by clinical guidelines bodies, which can review evolving data on a regular basis, than by bodies making broad coverage decisions.

As precision medicine is honed toward the point of personalization, there will be more therapies or combinations of therapies required to address the increasing number of specialized patient subgroups defined by less common molecular alterations or combinations of molecular alterations. This trend will strengthen the case for comprehensive genomic profiling if the matched therapies are shown to be effective, but this will require overcoming known challenges of conducting clinical trials in small patient populations (6). Wider availability of comprehensive genomic profiling presents an opportunity for innovation in clinical trials of precision medicine approaches to address these challenges. During the National Cancer Institute (NCI)–MATCH (Molecular Analysis for Therapy Choice) (NCT02465060) precision medicine platform trial (7), NCI initiated a collaboration with comprehensive genomic profiling providers to form a Designated Laboratory Network (DLN), comprising laboratories whose assays had been approved, through a vetting process, to refer patients to the trial. A DLN remains in operation for the follow-on NCI ComboMATCH trial [NCT05564377 (8)]. Laboratories in the DLN alert patients and their doctors, who have ordered genomic testing as part of routine cancer care, when a tumor molecular alteration that matches molecular eligibility requirements for the trial is identified. The commercial and academic laboratories participating in the DLN receive no funding for their collaborative efforts; they currently provide information about ComboMATCH, and often a variety of other treatment or trial opportunities, as a service to patients and their clinicians who have ordered comprehensive genomic profiling testing. Similar partnerships with payers, health systems, or professional societies could be developed as the basis for innovative clinical trials using real-world data to broaden the scope of treatment options for patients for whom standard options have been exhausted while simultaneously gathering outcome data in a more systematic and rigorous fashion to build the body of evidence for comprehensive genomic profiling and new therapies.

Data availability

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References

1. Stackland S, Schnabel D, Dinan MA et al. Strength of evidence underlying the CMS-FDA parallel review of comprehensive genomic profiling tests in the cancer setting. *J Natl Cancer Inst*. 2025;117(1):144-151.
2. Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. *Med Decis Making*. 1991;11(2):88-94. doi:10.1177/0272989X9101100.
3. Le Tourneau C, Delord J-P, Gonçalves A, et al.; SHIVA Investigators. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol*. 2015;16(13):1324-1334. doi:10.1016/S1470-2045(15)00188-6.
4. Mangat PK, Halabi S, Bruinooge SS, et al. Rationale and design of the targeted agent and profiling utilization registry study. *J Clin Oncol Precis Oncol*. 2018;2(2):1-14. doi:10.1200/PO.18.00122.
5. Freidlin B, McShane LM, Korn EL. Randomized clinical trials with biomarkers: design issues. *J Natl Cancer Inst*. 2010;102(3):152-160. doi:10.1093/jnci/djp477.
6. Korn EL, McShane LM, Freidlin B. Statistical challenges in the evaluation of treatments for small patient populations. *Sci Transl Med*. 2013;5(178):178sr3. doi:10.1126/scitranslmed.3004018.
7. O'Dwyer PJ, Gray RJ, Flaherty KT, Chen AP, et al. The Molecular Analysis for Therapy Choice (NCI-MATCH) trial: positive findings and perspectives. *Nat Med*. 2023;29:349-1357. doi:10.1038/s41591-023-02379-4.
8. Meric-Bernstam F, Ford JM, O'Dwyer PJ, et al. National Cancer Institute Combination Therapy Platform trial with molecular analysis for therapy choice (ComboMATCH). *Clin Cancer Res*. 2023;29(8):1412-1422. doi:10.1158/1078-0432.CCR-22-3334.

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