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Brief Communication

BRIEF COMMUNICATION

Prospective Clinical Study of Precision Oncology in Solid Tumors

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Abstract

Systematic studies evaluating clinical benefit of tumor genomic profiling are lacking. We conducted a prospective study in 250 patients with select solid tumors at the Cleveland Clinic. Eligibility required histopathologic diagnosis, age of 18 years or older, Eastern Cooperative Oncology Group performance status 0–2, and written informed consent. Tumors were sequenced using FoundationOne (Cambridge, MA). Results were reviewed at the Cleveland Clinic Genomics Tumor Board. Outcomes included feasibility and clinical impact. Colorectal (25%), breast (18%), lung (13%), and pancreatobiliary (13%) cancers were the most common diagnoses. Median time from consent to result was 25 days (range = 3–140). Of 223 evaluable samples, 49% (n = 109) of patients were recommended a specific therapy, but only 11% (n = 24) received such therapy: 12 on clinical trials, nine off-label, three on-label. Lack of clinical trial access (n = 49) and clinical deterioration (n = 29) were the most common reasons for nonrecommendation/nonreceipt of genomics-driven therapy.

The strategy of identifying genomic alterations for the possibility of matching targeted therapies to individual patients—referred to as "precision medicine"—is considered particularly promising in oncology (1–4). However, rigorous prospective evaluations are few (5–9). We conducted a prospective clinical study to evaluate the feasibility of routine next-generation sequencing of solid tumors at a large academic medical center and its impact on enrollment in clinical trials and therapeutic decision-making.

We enrolled outpatients at the Cleveland Clinic from August 2013 to October 2014. Key eligibility criteria were: confirmed histopathologic diagnosis of select solid tumor malignancies, metastatic disease without a curative therapeutic option, age 18 years or older, Eastern Cooperative Oncology Group performance status of 0–2, measurable disease (10), and written informed consent. The study was approved by the Institutional Review Board of the Cleveland Clinic. Available tumor specimens were shipped to Foundation Medicine, Inc. (Cambridge, MA), for sequencing using the FoundationOne platform (11); the test involves sequencing the entire coding region of up to 315 cancer-related genes and rearrangements in introns from 28 genes. Results were reviewed at a weekly genomics tumor board comprising oncologists and translational cancer scientists to identify actionable alterations—defined as being linked to an approved therapy in the solid tumor under study (on-label use) or another solid tumor (off-label use), associated with a known or suspected contraindication to a given therapy, or linked to an agent in an accessible (within approximately 200 miles from the patient's primary residence) clinical trial. Therapeutic recommendations were communicated to the treating oncologist.

The primary endpoint was feasibility of genomic sequencing, defined as the proportion of samples shipped within 14 days of consent, estimated using a 95% confidence interval. The focus

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was to evaluate real-world applicability of this approach. The accrual goal was set at 250 patients to ensure a fairly precise estimate of feasibility (the maximum half-width of the resulting confidence interval would be 6%-7%). An interim analysis was planned at 125 patients; if 105 (84%) patients or more met the 14-day cutoff, the study would continue. Secondary objectives focused on clinical impact, including proportion of patients with actionable alterations, recommendations made by the genomics tumor board, whether and what type of therapy was ultimately received by the patient, and patient outcomes.

Baseline characteristics of the study population (n = 250) are shown in Table 1. Colorectal (25%), breast (18%), lung (13%), and pancreatobiliary (13%) cancers were the most common diagnoses.

Table 1. Baseline characteristics of study participants*

Characteristic	N = 250
Age, median (range), y	60 (24–94)
Women, No. (%)	128 (51%)
Whites, No. (%)	220 (88%)
Time since index cancer diagnosis, median (range)	1.5 y (0.1 mo – 22.7 y)
Prior lines of therapy for index cancer, median (range)	5 (0–22)
Prior chemotherapy, No. (%)	183 (73%)
Prior targeted therapy, No. (%)	90 (36%)
Prior surgery, No. (%)	147 (59%)
Prior radiation, No. (%)	106 (42%)
Index cancer diagnosis, No. (%)	
Colorectal cancer	63 (25%)
Breast cancer	44 (18%)
Non–small cell lung cancer	33 (13%)
Pancreatobiliary cancer	31 (13%)
Head and neck cancer	25 (10%)
Carcinoma of unknown primary	16 (6%)
Glioblastoma	11 (4%)
Mesothelioma	10 (4%)
Bladder cancer	4 (2%)
Glioma	3 (1%)
Prostate cancer	3 (1%)
Meningioma	3 (1%)
Adrenocortical cancer	2 (1%)
Non–clear cell renal cell cancer	2 (1%)

* Median (range) values are presented for continuous variables; absolute (percentage) values are presented for discrete variables.

A tissue sample was retrieved and shipped for 242 patients (2 patients withdrew consent, 1 died before sample could be sent, and 5 specimens had no/inadequate tissue for retrieval), within a median of seven (range = 0–82) days from informed consent. As defined above, the process was feasible in 82.2% (95% confidence interval [CI] = 77% to 87%) of case patients. A result was obtained within a median of 18 (3–132) days of sample shipment and 25 (3–140) days of patient consent. Of the 242 samples, 19 (8%) had insufficient tissue for analysis. For 223 analyzed samples, 214 (96%) had at least one alteration, with a median of four (0–20) alterations per specimen. There were 146 genes with alterations (Figure 1).

The genomics tumor board reviewed all 223 reports, within a median of six (3–45) days of result. Although a therapeutic recommendation was noted in 200 (90%) reports, an actionable alteration per the study definition was seen in 109 (49%) case patients. The discrepancy was because of nonactionable targets (eg, *TP53*, n = 59) and nonavailability of trials targeting potentially actionable alterations (eg, *NRAS*, n = 32). There were 134 treatment recommendations (1–2 per patient), comprising 102 (77%) for clinical trials, 22 (17%) for off-label use, eight (6%) for on-label use, and two against the use of epidermal growth factor receptor (EGFR) antibodies in colorectal cancer with previously unknown *RAS* alterations. The most common actionable targets were *KRAS* (n = 22), *CDKN2A/B* (n = 16), *PIK3CA/PIK3R* (n = 15), *FGFR* (n = 13), *PTEN/AKT* (n = 12), and *HER2* (n = 8). Of the 109 patients with a treatment recommendation, 24 (22% of those with actionable alterations, 11% of all resulted case patients) received genomics-driven therapy: 12 on clinical trials, nine off-label, three on-label (Supplementary Table 1, available online).

Of the 83 patients who did not have their treatment influenced by tumor genomic profiling, causes included clinical deterioration or death (n = 29), use of other therapies (n = 22), ineligibility on screening for recommended trial (n = 10), enrollment in a non–genomics-driven clinical trial (n = 7), patient refusal or transfer of care (n = 9), insurance refusal of reimbursement for off-label therapy (n = 1), and loss to follow-up (n = 5). Of the 22 patients receiving other therapies, the most common reason (n = 17) was nonavailability of recommended clinical trial; overall, for 49 patients, lack of clinical trial access was the reason for nonrecommendation/nonreceipt of genomics-driven therapy.

We show that in a multidisease setting, 26 (10%) of 250 patients had their treatment decisions influenced by the result. Other studies show that 0% to 21% of enrolled patients receive genomics-driven therapy, even with the inclusion of

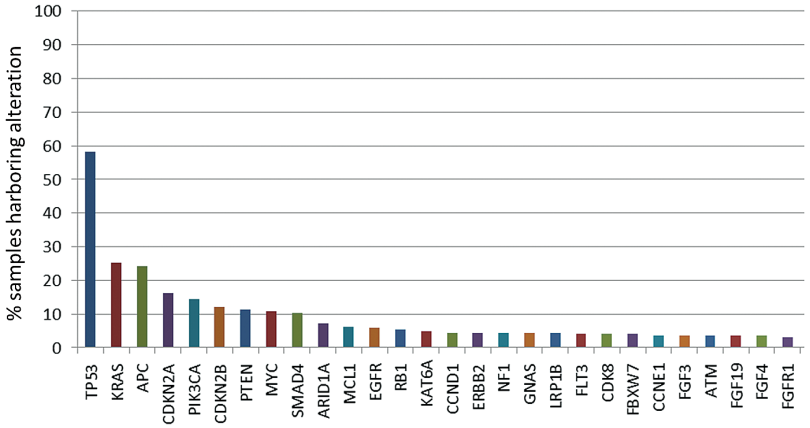

Figure 1. Common genomic alterations detected (percent cases, n = 223).

predetermined off-label therapies in some studies (5,6,8,9,12). The interpretation of molecular profiling results is another major challenge in this process. The definition of "actionable" is somewhat subjective and varies across studies, with a target identifiable in 24% to 64% of cases (5,8,9,12,13). The spectrum of "actionability" can range from on-label use to very preliminary data on *TP53* targeting (9,14). We had strict criteria to deem an alteration actionable; for example, results acted upon previously during routine care, "equivocal" and "subclonal" results, overly permissive target-drug combinations such as *BRAF*-sorafenib (15), and impractical trial options, were not considered actionable.

Other studies show similar feasibility results, with sequencing possible in 48% to 77% of cases and median turnaround times of 22 to 31 days (5,8,9,12,13). Our study was limited by archived specimens, use of only one of several platforms available, and internal funding precluding reimbursement issues for tumor genomic profiling.

In conclusion, this real-world test of precision oncology demonstrates that it is feasible. Almost two-thirds of samples tested have biologically actionable alterations. However, the clinical success of precision oncology largely hinges on increasing availability of genomics-driven clinical trials and drugs targeting specific alterations for most patients with cancer.

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