Implementation of a Novel Web-Based Lesion Selection Tool to Improve Acquisition of Tumor Biopsy Specimens

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Source of Support: National Cancer Institute at the National Institutes of Health (award number P30CA016672; used the Clinical Trials Support Resource, Biostatistics Resource Group, and Research Histology Core Laboratory).

Conflict of Interest: None.

Received: Feb 11, 2021; Revision Received: Mar 14, 2021; Accepted: Mar 17, 2021

Xu M, Tapia C, Hajjar J, et al. Implementation of a novel web-based lesion selection tool to improve acquisition of tumor biopsy specimens. J Immunother Precis Oncol. 2021; 4:45–52. DOI: 10.36401/JIPO-21-5.

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ABSTRACT

Introduction: For maximum utility of molecular characterization by next-generation sequencing (NGS) and better understanding of tumor microenvironment with immune correlates analysis, biopsy specimens must yield adequate tumor tissue, and sequential biopsy specimens should sample a consistent site. We developed a web-based lesion selection tool (LST) that enables management and tracking of the biopsy specimen collections. Methods: Of 145 patients, the LST was used for 88 patients; the other 57 served as controls. We evaluated consistency of the lesion biopsied in longitudinal collections, number of cores obtained, and cores with adequate tumor cellularity for NGS. The Fisher exact test and Wilcoxon rank sum test were used to identify differences between the groups. Results: The analysis included 30 of 88 (34%) patients in the LST group and 52 of 57 (91%) in the control group. The LST workflow ensured 100% consistency in the lesions biopsied compared with 75% in the control group in longitudinal collections and increased the proportion of patients in whom at least five cores were collected per biopsy. Conclusions: The novel LST platform facilitates coordination, performance, and management of longitudinal biopsy specimens. Use of the LST enables sampling of the designated lesion consistently, which is likely to accurately inform us the effect of the treatment on tumor microenvironment and evolution of resistant pathways. Such studies are important translational component of any clinical trials and research as they guide the development of next line of therapy, which has significant effect on clinical utility. However, validation of this approach in a larger study is warranted.

Keywords: lesion selection, biopsy specimen, biopsy acquisition, clinical study, biomarker
INTRODUCTION

Accumulating evidence suggests that tailoring anti-cancer treatment to immunological and molecular landscape of tumor enhances treatment outcomes. Since the launch of the US Precision Medicine Initiative and increasing focus on extensive characterization of biologic specimens, the role of performing image-guided biopsies is expanding.

However, insufficient biopsy samples can hamper their application as high-quality, tumor-rich tissue samples are required to perform immune correlates analysis and next-generation sequencing (NGS). At The University of Texas MD Anderson Cancer Center, 17% of percutaneous transthoracic core-needle biopsy specimens yielded insufficient tumor tissue for biomarker analysis in a prospective study and 30% of percutaneous core biopsy specimens yielded samples inadequate for NGS in a retrospective study. The investigators had concluded that better lesion selection capabilities could have improved the tissue yield. Thus, at our institution, as at others such as the National Cancer Institute, obtaining biopsy samples that meet genetic sequencing requirements remains a challenge.

In this era of personalized medicine, there is an increasing need to better understand the dynamic interaction among tumor cells, immune cells and the tumor microenvironment, modulation of pharmacodynamic biomarkers, evolution of cancer genomes, and progression of tumors. This assessment not only provides insight into response and resistance mechanisms but also guides the development of strategies to overcome drug resistance. However, tumor heterogeneity that occurs across lesions represent an important challenge. Although consistency in the lesion biopsied in longitudinal studies could minimize variability, in standard practice, the optimal biopsy site at the time of each procedure is chosen independent of previous biopsy site.

Barriers to adequate and consistent sampling include the involvement of multiple disciplines who approach the biopsy site from different perspectives. For example, radiation to the site selected for longitudinal tumor biopsy may induce architectural changes altering the immunological and molecular landscape of the tumor. Performing a biopsy of a lesion chosen for quantification of tumor response may result in erroneous tumor size measurements. Thus, for optimal biopsy specimen and evaluation of treatment response, clear communication between the oncologist treating the patient, the diagnostic radiologist identifying lesions on imaging, the interventional radiologist performing the biopsy, the pathologist evaluating the specimen, and the radiation oncologist planning radiotherapy is needed.

To address these challenges, especially given the risk and financial cost of performing a biopsy, we developed a web-based workflow, the lesion selection tool (LST), to coordinate and track the biopsy acquisition process between multiple disciplines. The purpose of the current study was to evaluate the consistency of sequential biopsy site and the adequacy of biopsy sampling for NGS attained with and without the LST.

METHODS

This study was conducted after obtaining institutional review board (IRB) approval. Informed consent to use and disclose protected health information was waived by the institutional review board because of the retrospective nature of this study.

Study Population

Patients enrolled in MD Anderson institutional review board–approved clinical trials that had standard-of-care tumor restaging assessments and biopsy collections as part of correlative studies were eligible for inclusion in the study. A total of 145 patients who were enrolled in four investigator-initiated clinical trials (NCT03217747, NCT01591356, NCT01529593, and NCT02721732) from August 15, 2016 through December 1, 2018, were included (Fig. 1). Radiation in this project is part of one of clinical trials (NCT03217747) to evaluate abscopal effect and immunogenicity of radiation. Eighty-eight patients were subjected to the LST workflow. The first 57 consecutive patients enrolled in NCT02721732 before the development of LST served as controls. For the final analysis, only patients who received treatment, had measurable lesions, underwent lesion selection (LST group), and had at least baseline percutaneous core biopsies performed were included.

Lesion Selection Tool Workflow

The LST is a web-based tool incorporated into Molecular and Clinical Data Integrated Application, the departmental database. The LST workflow comprises the following six steps (Fig. 2): (1) when a potential patient is identified, an oncology team member uses the LST to submit a request to Diagnostic Radiology to select measurable lesions from the most recent imaging of the patient. (2) A diagnostic radiologist selects measurable lesions, following which an automated email notification is sent to Interventional Radiology and Radiation Oncology (if applicable). (3) An interventional radiologist selects lesions amenable to the biopsy specimen, and a radiation oncologist selects lesions suitable for radiotherapy. After the lesion selection is completed by the individual teams, an automated email notification is sent to the oncology team. (4) The oncologist reviews their selections and determines the final lesion assignment, which is communicated by an automated email to the individual collaborators. This lesion selection will be maintained throughout the duration of treatment. (5) Based on the oncologist’s determination, an oncology team member submits request to Interventional Radiology specifying the lesion to be biopsied, to Diagnostic Radiology specifying the
lesions for tumor measurement, and to Radiation Oncology specifying the lesion to be irradiated (if applicable). (6) Based on the lesion assignment, a biopsy is performed by the interventional radiologist, tumor measurement by the diagnostic radiologist, and radiation by the radiation oncologist (if applicable). All data regarding lesion selection and final assignment are recorded in the LST and are easily accessible to all authorized collaborators.

Biopsy Specimens
The lesion selected for the biopsy specimen is specified in the LST by the date and type of imaging study, series number, image number, and anatomic location of the lesion. On the day the biopsy is performed, the interventional radiologist performing the biopsy correlates the preprocedure imaging of the assigned lesion with the procedure-day imaging and targets the selected lesion to perform the biopsy. The site of the biopsy specimen, imaging guidance, number of core specimens obtained, and gauge of core biopsy needle used are recorded in the LST by the interventional radiologist.

Data Collection
The demographic, clinical, imaging, and biopsy specimen data were obtained from patients’ electronic medical records. Metrics on the workflow of lesion selection were collected from the secure LST platform. Patient privacy was protected according to institutional and Health Insurance Portability and Accountability Act guidelines.

Consistency of the Lesion Biopsied at Multiple Time Points
In patients who underwent longitudinal tissue sampling, we assessed whether the same lesion was consistently biopsied at each time point in the LST and control groups by comparing the imaging from each procedure day.

Figure 1.—Flowchart summarizing patient selection.

Figure 2.—The lesion selection tool (LST) workflow. (A) The six-step LST workflow. (B) Schematic illustration of the LST workflow.
Adequacy of Tumor Cellularity of Acquired Biopsy Tissues

The number of tissue cores collected at each biopsy site were compared between the groups. All available biopsy cores were retrieved for both groups. Hematoxylin and eosin (H&E)-stained slides were evaluated by three pathologists, and at least two pathologists for each of LST and control group independently for tumor cellularity and viable tumor cells. In case of discrepancy, the pathologists reviewed the biopsy specimens together or a fourth pathologist reviewed the biopsy specimens to reach a consensus. Tumor cellularity was defined as the percentage of invasive tumor cells and was estimated as follows: (number of tumor cell nuclei/total number of nucleated cells) \times 100\%. Based on literature evidence, a cutoff of 20% or more tumor cellularity with 300 or more viable tumor cells was used to define cores with adequate tumor cellularity for NGS. [17–20]



Table 1.—Patient characteristics

| Measure                                      | All (N = 82) | LST (n = 30) | Control (n = 52) | p-Value |
|----------------------------------------------|--------------|--------------|-----------------|---------|
| Sex, n (%)                                   |              |              |                 |         |
| Male                                         | 41 (50)      | 14 (47)      | 27 (52)         | 0.82    |
| Female                                       | 41 (50)      | 16 (53)      | 25 (48)         |         |
| Age at enrollment, y                         |              |              |                 | 0.12    |
| Mean (SD)                                     | 54.7 (15.3)  | 58.6 (12.8)  | 52.5 (16.3)     |         |
| Median                                        | 59.0         | 61.5         | 56.5            |         |
| Range (24.0–78.0)                             | (25.0–77.0)  | (24.0–78.0)  |                 |         |
| Tumor type, n (%)                            |              |              |                 | < 0.001 |
| Gynecologic                                  | 23 (28)      | 12 (40)      | 11 (21)         |         |
| Genitourinary                                 | 12 (15)      | 2 (7)        | 10 (19)         |         |
| Carcinoma of unknown primary                 | 9 (11)       | 0            | 9 (17)          |         |
| Pancreatic                                   | 6 (7)        | 6 (20)       | 0               |         |
| Adrenocortical                               | 5 (6)        | 0            | 5 (10)          |         |
| Colorectal                                   | 5 (6)        | 5 (17)       | 0               |         |
| Paraganglioma-pheochromocytoma               | 5 (6)        | 0            | 5 (10)          |         |
| Others\(^a\)                                 | 5 (6)        | 0            | 5 (10)          |         |
| Skin                                         | 4 (5)        | 0            | 4 (8)           |         |
| Head and neck tumor                          | 3 (4)        | 3 (10)       | 0               |         |
| Vascular                                     | 2 (2)        | 0            | 2 (4)           |         |
| Gastric                                      | 1 (1)        | 1 (3)        | 0               |         |
| Lung                                         | 1 (1)        | 1 (3)        | 0               |         |
| Pituitary                                    | 1 (1)        | 0            | 1 (2)           |         |
| Treatment, n (%)                             |              |              |                 | < 0.001 |
| Avelumab-based combination therapy (NCT03217747\(^{[13]}\)) | 22 (27)      | 22 (73)      | 0               |         |
| EphA2 siRNA (NCT01591356\(^{[14]}\))         | 5 (6)        | 5 (17)       | 0               |         |
| Temsirolimus and metformin (NCT01529593\(^{[15]}\)) | 2 (2)        | 2 (7)        | 0               |         |
| Pembrolizumb (NCT02721732\(^{[16]}\))        | 53 (65)      | 1 (3)        | 52 (100)        |         |

LST: lesion selection tool.
\(^a\)Other tumor types were mesothelioma of the left testis, rhabdomyosarcoma of left parotid, alveolar soft part sarcoma, rhabdomyosarcoma of the right upper extremity, and desmoplastic round cell tumor (n = 1 each).

RESULTS

Patients

A total of 145 patients were included in this study (Fig. 1). Of 88 patients in the LST group, 30 (34%) patients completed the LST process, received treatment, and underwent a baseline biopsy. Of 57 patients in the control group, 52 (91%) patients received treatment and underwent baseline biopsy. Collectively, 82 (57%) patients were included in the final analysis. Patients’ baseline characteristics are shown in Table 1. There was no significant difference in sex or age between the two groups. The most common tumor types were gynecologic (28%), genitourinary (15%), and carcinoma of unknown primary (11%).

Biopsy Acquisition

At baseline, the most common sites in which biopsies were performed were the liver (18%), retroperitoneum (17%), abdomen/abdominal wall (13%), and lung (12%) (Table 2). There were no significant differences in

Statistical Analysis

Categorical variables were summarized by frequencies and percentages and assessed using either the Fisher exact test or its generalization. Continuous measures were summarized by medians and ranges and assessed using the Wilcoxon rank sum test. We defined success rate as the proportion of patients with at least one core obtained that met the criteria for adequacy. All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute Inc.). All statistical tests used a significance level of 5%. No adjustments for multiple testing were made.
biopsied sites, biopsy guidance method, or biopsy needle gauge size between the groups. Longitudinal tissue sampling was done at multiple time points (Supplemental Table S1). In the LST group, 24 of 30 patients had longitudinal collections. Six patients did not, either because they were off the study before the on-treatment biopsy time point (\(n = 5\)) or for safety reasons (\(n = 1\)) (Table 2). All 24 patients had biopsies performed at the on-treatment-1 time point, while 9 patients had an additional biopsy performed at the on-treatment-2 time point. In the control group, all 52 patients had an on-treatment-1 biopsy specimen, while 2 patients had an additional on-treatment-2 biopsy specimen. There was no significant difference in biopsy site or needle gauge size between the LST and control groups for on-treatment biopsies (Supplemental Table S2).

### Consistency of the Lesion Biopsied at Multiple Time Points

In the LST group, in all 24 patients, the same designated lesion was biopsied at baseline and at subsequent time points. In contrast, the same lesion was biopsied in only 39 of 52 (75%) patients in the control group (\(p = 0.007\)).

### Number of Cores Obtained

At baseline, 25 of 30 (83%) patients in the LST group had five or more cores collected, whereas only 14 of 52

### Table 2.—Biopsy characteristics

| Measure                                      | All (N = 82) | LST (n = 30) | Control (n = 52) | p-Value |
|----------------------------------------------|-------------|-------------|-----------------|---------|
| Biopsy site: baseline, n (%)                 |             |             |                 |         |
| Liver                                        | 15 (18)     | 8 (27)      | 7 (13)          | 0.65    |
| Retroperitoneum                              | 14 (17)     | 6 (20)      | 8 (15)          |         |
| Abdomen/abdominal wall                       | 11 (13)     | 3 (10)      | 8 (15)          |         |
| Lung                                         | 10 (12)     | 5 (17)      | 5 (10)          |         |
| Neck                                         | 6 (7)       | 1 (3)       | 5 (10)          |         |
| Pelvis                                       | 6 (7)       | 2 (7)       | 4 (8)           |         |
| Inguinal lymph node                          | 5 (6)       | 3 (10)      | 2 (4)           |         |
| Gluteal                                      | 3 (4)       | 0           | 3 (6)           |         |
| Adrenal/adrenal gland                        | 2 (2)       | 1 (3)       | 1 (2)           |         |
| Face                                         | 2 (2)       | 0           | 2 (4)           |         |
| Pectoral                                     | 2 (2)       | 0           | 2 (4)           |         |
| Thoracic spine vertebra                      | 2 (2)       | 0           | 2 (4)           |         |
| Chest wall                                   | 1 (1)       | 1 (3)       | 0               |         |
| Iliac bone                                   | 1 (1)       | 0           | 1 (2)           |         |
| Iliac bone                                   | 1 (1)       | 0           | 1 (2)           |         |
| Paraspinal                                   | 1 (1)       | 0           | 1 (2)           |         |
| Ribs                                         | 1 (1)       | 0           | 1 (2)           |         |
| Guidance method, n (%)                       |             |             |                 | 0.49    |
| CT                                           | 45 (56)     | 20 (66)     | 25 (49)         |         |
| US                                           | 26 (32)     | 9 (30)      | 17 (33)         |         |
| CT and US                                    | 6 (7)       | 1 (33)      | 5 (10)          |         |
| PET/CT and CT                                | 2 (2)       | 0           | 2 (4)           |         |
| PET/CT and US                                | 2 (2)       | 0           | 2 (4)           |         |
| Needle gauge size: baseline, n (%)           |             |             |                 | 0.42    |
| 14                                           | 1 (1)       | 0           | 1 (2)           |         |
| 16                                           | 1 (1)       | 1 (3)       | 0               |         |
| 18                                           | 70 (85)     | 24 (80)     | 46 (88)         |         |
| 20                                           | 10 (12)     | 5 (17)      | 5 (10)          |         |
| Biopsy timepoints, n (%)                     |             |             |                 | < 0.001 |
| Baseline only                                | 6 (7)       | 6 (20)      | 0               |         |
| Baseline and one on-treatment timepoint       | 65 (79)     | 15 (50)     | 50 (96)         |         |
| Baseline and two on-treatment timepoints      | 11 (13)     | 9 (30)      | 2 (4)           |         |
| Consistent lesion biopsied, n (%) *          | (n = 76)    | (n = 24)    | (n = 52)        | 0.007   |
| Yes                                          | 63 (83)     | 24 (100)    | 39 (75)         |         |
| No                                           | 13 (17)     | 0           | 13 (25)         |         |
| Total number of cores biopsied: baseline, n (%) |             |             |                 | < 0.001 |
| \(< 5\)                                      | 43 (52)     | 5 (17)      | 38 (73)         |         |
| \(\geq 5\)                                   | 39 (48)     | 25 (83)     | 14 (27)         |         |
| Total number of cores biopsied: on-treatment-1 timepoint, n (%) |             |             |                 | < 0.001 |
| \(< 5\)                                      | 38 (50)     | 3 (12.5)    | 35 (67)         |         |
| \(\geq 5\)                                   | 38 (50)     | 21 (87.5)   | 17 (33)         |         |
| Total number of cores biopsied: on-treatment-2 timepoint, n (%) |             |             |                 | 0.055   |
| \(< 5\)                                      | 3 (27)      | 1 (11)      | 2 (100)         |         |
| \(\geq 5\)                                   | 8 (73)      | 8 (89)      | 0 (0)           |         |

CT: computed tomography; LST: lesion selection tool; PET: positron-emission tomography; US: ultrasound.

*Only patients with longitudinal biopsy collections were included in this analysis.
(27%) patients in the control group did \( (p < 0.001) \) (Table 2). At the on-treatment-1 time point, five or more cores were collected in 21 of 24 (88%) patients in the LST group, versus only 17 of 52 (33%) patients in the control group \( (p < 0.001) \). At the on-treatment-2 time point, five or more cores were obtained in eight of nine (89%) patients in the LST group, versus zero of two patients in the control group \( (p = 0.055) \).

**Cores With Adequate Tumor Cellularity**

Biopsy cores from 25 patients in the LST group and 52 patients in the control group were retrieved and subjected to pathology evaluation. Biopsy cores from 5 patients in the LST group were not retrievable.

In the LST group, a total of 211 biopsy cores (110 baseline cores from 25 patients, 77 on-treatment-1 cores from 17 patients, and 24 on-treatment-2 cores from five patients) were retrieved and assessed. In the control group, a total of 349 biopsy cores (168 baseline cores from 52 patients, 176 on-treatment-1 cores from 52 patients, and 5 on-treatment-2 cores from two patients) were retrieved and assessed.

There was no significant difference between the two groups in the number of patients who had at least one core with adequate tumor cellularity for NGS (Fig. 3). At baseline, 15 of 25 (60%) patients had at least one core with adequate tumor cellularity in the LST group, versus 29 of 52 (56%) patients in the control group \( (p = 0.81) \). At the on-treatment-1 time point, seven of 17 (41%) patients in the LST group, compared with 25 of 52 (48%) patients in the control group, had at least one adequate core \( (p = 0.78) \). At the on-treatment-2 time point, three of five (60%) patients in the LST group, compared with zero of two patients in the control group, had at least one adequate core \( (p = 0.43) \).

**DISCUSSION**

A multidisciplinary research consensus panel assembled by the Society of Interventional Radiology Foundation suggested that the treating oncologist, the diagnostic radiologist, the interventional radiologist, the pathologist, and the radiation oncologist be collectively involved in the tissue acquisition process.\(^{[21]}\) A similar recommendation was also provided by the National Cancer Institute to improve the quality of biopsy specimens.\(^{[5]}\) To this end, this is the first report of a web-based LST being used to monitor and guide biopsy collections. The LST allows communication and coordination between the oncologist, diagnostic radiologist, interventional radiologist, and radiation oncologists in a timely manner to overcome the logistical challenges of multiple stakeholders targeting the same lesion with different priorities.

Consistency in the lesion biopsied is important as analysis of immunologically and biologically relevant samples provide a better understanding of the evolution of resistant pathways over time, which will likely inform and guide development of next-line therapy.\(^{[21]}\) In our study, we found that LST workflow ensured 100% consistency in the lesion biopsied (Table 2). In comparison, in the control group, when a biopsy specimen request was sent, the interventional radiologist usually selected the easiest or the safest lesion, which might not have been the original lesion biopsied. As there was no specific request to biopsy specimen the same lesion, only 75% of patients had the same lesion biopsied consistently in the control group \( (p = 0.007) \). Thus, the LST helped to optimize the longitudinal biopsy collections.

As tissue samples are a valuable resource to inform treatment plans based on immunologic and molecular data, collecting multiple cores without compromising patient safety is of significant value. In our study, the proportion of patients with five or more cores collected per biopsy specimen was significantly higher in the LST group compared with the control group (Table 2). In the absence of established guidelines for the number of core specimens to be collected, the interventional radiologists were guided by the protocol requirements (Supplemental Table S1), which could partially explain the lower number of cores obtained per biopsy specimen in the control group. In contrast, in the LST group, due to the concerted effort by the oncology team and diagnostic radiologists and due diligence by the interventional radiologists a greater number of cores were obtained per biopsy specimen. National Institutes of Health investigators have reported that collecting multiple cores during each biopsy procedure increases the likelihood of obtaining sufficient tissue samples for biomarker analysis;\(^{[8]}\) therefore, the use of the LST increases the probability of fulfilling the intended purpose of tissue sampling.

Image-guided biopsies are performed with expectation of obtaining high-quality, tumor-rich tissue samples for immune correlates analysis and NGS. In our study, there was no significant difference in the proportion of patients who had at least one core with adequate tumor cellularity for NGS between the two groups (Fig. 3). This can be attributed to the process used by the interven-
tional radiologist at MD Anderson to identify lesions that would provide adequate yield for NGS, regardless of the group the patients were in. Earlier, Sabir et al. [4] in the Department of Interventional Radiology, had shown that an imaging-based likelihood-of-adequacy score assigned by the interventional radiologist using specific criteria was significantly associated with improved yield for NGS. In our study, although the likelihood-of-adequacy score was not assigned to the lesion, the factors that comprise the score were used to identify the lesion to be biopsied for all patients in both, the LST and control group. Therefore, similar success rates were reported in both the groups. In our study, the success rate was lower than the 70 to 80% of analyzability of individual biopsy specimens that has been reported. [3,12] This could partly be explained by the variations in thresholds for determinants of adequacy, number of viable cells and tumor nuclei across institutions. [16] Most of the institutions included in the GENIE database only have a 10% tumor cellularity requirement to define success, [20] while in our study, at least 300 viable tumor cells with 20% or more tumor cellularity was used to define adequacy for NGS.

The limitations of our study include our limited sample size. Further, the LST workflow was not completed in 32% (28 of 88) of patients. This is primarily because, despite initial coordination among the collaborators, the workflow was not mandatory. Second, as with any new approach, the initial setup and adaptation to a novel workflow required additional time and subsequent effort from collaborators. Third, as LST was not integrated into the electronic medical records, there was a need to open a separate browser to access. Regardless, considering its demonstrated potential to improving accuracy and the potential payback to all stakeholders in advancing science and improving patient care, the LST could be valuable, and worthwhile validating. Hence, we recommend that, once the LST is validated, (1) its use be made a standard procedure for lesion selection and incorporated into clinical practice, and (2) the time, effort, and technical expertise contributing to this effort be adequately compensated.

**Conclusion**

The LST is a centralized, web-based platform that offers a unique opportunity to improve communication across disciplines to improve the quality of performing image-guided biopsies. This tool could easily be implemented in larger cancer centers and smaller community sites alike. Acquiring tissue samples from a lesion consistently before and on-treatment will accurately inform us the effect of the drug on tumor microenvironment. Thus, translational objectives of any clinical trials and research to characterize the resistance mechanism will have significant effect on clinical application and therapeutic impact as they inform the development of next line of therapy. To ensure reliability and generalizability of the tool, our next steps would be to validate our findings in a larger study and evaluate the utility of this approach by comparing NGS results from the LST group and the control group.

**Data Availability**

The dataset used during the current study is available from the corresponding author on reasonable request.

**Supplemental Material**

Supplemental data are available online with the article.

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