Preanalytic Variables in Cytology

Lessons Learned From Next-Generation Sequencing—The MD Anderson Experience

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• Context.—As our understanding of genomic alterations underlying solid tumor malignancies continues to evolve, molecular testing of tumor samples is increasingly used to guide therapeutic management. Next-generation sequencing (NGS) provides a novel platform for the simultaneous screening of multiple genes using small amounts of DNA. Several recent studies have described NGS mutational analysis using cytologic specimens. The cytopathologist’s role in specimen assessment and triaging is critical to effectively implementing NGS in routine cytology practice.

Objectives.—To review the NGS experience and a variety of preanalytic factors that affect NGS success rates of cytologic specimens at our institution.

Data Sources.—To evaluate cytology specimen adequacy rates for NGS, we reviewed a 14-month period of image-guided fine-needle aspiration and core needle biopsies used for testing. In addition, we reviewed data from our previously published studies to evaluate preanalytic factors affecting NGS success in these specimens.

Conclusions.—Identifying factors that affect NGS success rates in cytology specimens is crucial for a better understanding of specimen adequacy requirements and for proper use of limited-volume tissue samples. In our practice, which uses direct smears as well as cell block sections, NGS success rates in core needle biopsy and fine-needle aspiration samples are comparable. The chance of successful testing is further increased by procuring concurrent fine-needle aspiration and core needle biopsy samples. The type of glass slides used for direct smears and the method of tissue extraction affect our DNA yield. Validating a DNA input for cytology samples that is lower than that recommended by the manufacturer has significantly increased our NGS success rate.

Several groups, including from our own institution, have shown the feasibility and utility of cytologic specimens for NGS analysis.4,19–30 Mutational analysis by NGS was implemented as a routine diagnostic assay in the Clinical Laboratory Improvement Amendments (CLIA)–certified molecular diagnostic laboratory at our institution in April 2012.31 The Ion Torrent Personal Genome Machine (PGM; Life Technologies, Carlsbad, California) platform was selected for solid tumor testing primarily because of the low 10-ng input DNA requirement, which can be easily achieved from a modest 1000– to 1500-cell sample. In contrast, the input DNA requirement for the Illumina MiSeq (Illuma Inc, San Diego, California) platform is 250 ng and requires between 5000 and 15 000 cells per sample for successful testing.3,2 Further, the Ion Torrent PGM has a short run time (under 5 hours), allowing for reduced turnaround time and faster results for patients and oncologists.7

The cytology samples used for the NGS validation study at our institution showed comparable sequence performance metrics (median filtered AQ20 reads, depth of coverage, and variant call frequency) compared with surgical biopsy/resection specimens from different patients analyzed concurrently on the same NGS run.3 All mutations detected by NGS showed 100% concordance with the mutations detected by orthogonal conventional sequencing platforms.3 Therefore, if the specimens met the minimum tumor fraction and yielded adequate DNA, the NGS analysis of cytology specimens demonstrated sensitivity and specificity comparable to those of surgical specimens.

In the current era of targeted therapy, the role of cytopathology has expanded beyond morphologic diagnosis to include providing suitable substrates for molecular diagnostics. The involvement of the cytopathologist in this rapidly evolving field is essential. By implementing standards of specimen collection, cell preservation, fixation, and staining, and by applying molecular adequacy criteria (primarily, specimen cellularity, and tumor fraction), the use of cytologic specimens for NGS can be optimized.32–34 Here, we review our experience of NGS analysis of cytologic specimens at The University of Texas MD Anderson Cancer Center (Houston, Texas), with an emphasis on preanalytic variables affecting NGS success.

**CYTOLOGIC SPECIMEN ACQUISITION AND PROCESSING**

Next-generation sequencing testing at MD Anderson is typically deferred to surgical pathology material. In cases when the histologic samples are deemed insufficient for molecular testing, the request is forwarded to cytopathology to review any concurrent or archival cases for adequacy (Figure 1).

Most small biopsies used for molecular testing are procured by interventional radiology (IR), using computed tomography, magnetic resonance imaging, or ultrasound (US) guidance. Typically, both a CNB and an FNA sample are obtained in the same procedure. However, sometimes only an FNA sample is procured, such as when the lesion is situated in an anatomically challenging area (eg, adjacent to a major blood vessel). At other times only a CNB sample is obtained, such as when the lesion is small and the interventional radiologist can sample just once before it becomes obscured by blood. At our institution, the non–IR procedures—which include endobronchial ultrasound (EBUS)-guided FNA, US-guided FNA, endoscopic US FNA, and body cavity fluid collection—typically do not have a concurrent CNB. For these cases, the cytology specimen is often the only sample available for diagnosis as well as molecular testing, especially when the patient presents with advanced-stage disease.

All image-guided FNA procedures have rapid on-site evaluation performed on the direct smears for adequacy assessment (Figure 1). The FNA needle rinse (collected in RPMI 1640 media) is centrifuged to a cell pellet, mixed with equal amounts 10% formalin and 95% ethanol, and centrifuged; the resulting cell button is then fixed in 10% formalin and processed as a cell block.35 Fluids/effusions are centrifuged directly onto slides to create a cell monolayer cytospin preparation, and the residual fluid is processed as a cell block. At our institution, we perform NGS using both cell block and direct smears/cytospin preparations, which significantly increases the number of cytology cases that are adequate for molecular testing (discussed further below). Image-guided procedures with concurrent CNB samples are fixed in 10% formalin, are paraffin embedded, and are sectioned at 4- to 5-micron-thick sections. For NGS requests on CNB samples, if the sample meets the 20% or greater tumor fraction criteria, 10 to 15 unstained sections are sent for tissue extraction and molecular testing (Figure 1).

**ASSESSMENT OF CYTOLOGIC SPECIMEN CELLULARITY**

For cytology samples with high cellularity and high tumor fraction, either cell block sections or smears can be used for testing (Figure 2). In these cases the cell blocks are usually chosen because they are easier to process. For samples with high cellularity but low tumor fraction (frequently encountered in EBUS FNA and effusions), tumor mapping is needed to enrich for tumor to minimize the risk of a false-negative result (Figures 3 and 4). In these cases, the direct smears are typically superior to the cell blocks because the smeared sample is more dispersed with a greater variation in the proportion of tumor/benign in different areas of the slide (Figure 4). Therefore, it is easier to find and delineate areas of tumor enrichment on smears, even in cases with overall low tumor fraction. The request for NGS is canceled when the tumor fraction cannot be enriched to greater than 20% and no other current or archival case is suitable for testing (Figure 1). Low-cellularity samples with high tumor fraction can often be tested by increasing the number of unstained sections from the cell block (>15 unstained sections) and/or by increasing the number of smear/cytospin slides submitted for testing (Figure 2). Samples with low cellularity and low tumor fraction result in cancellation of test request, if no other current or archival case is available for testing (Figures 1 and 2). At our institution, cellularity on smears is assessed as: high, at least 1 or 2 slides with more than 5000 cells; moderate, 1000 to 5000 cells; and low, fewer than 1000 cells. Cellularity for cell blocks is assessed on the corresponding hematoxylin–eosin–stained slide as: high, more than 2000 per section; moderate, 300 to 2000 per section; and low, fewer than 300 per section.

**CYTOLOGIC SPECIMEN ADEQUACY**

Several studies have described the utility of cytologic specimens in NGS analysis,19,20,23–28,36–37; however, adequacy rates vary among institutions. We reviewed a 14-month period (January 2013–February 2014) for all IR-guided CNB and/or FNAs that were evaluated for NGS analysis (Figure 5). During this time, molecular testing was requested in 601 IR-guided cases (71 CNB–only samples; 503 CNB + FNA).
samples; and 27 FNA-only samples). Following review by the pathologist, 83 samples were canceled because of insufficient tissue and were not sent for further testing. The NGS success rate of the IR-guided samples sent for testing was 63% (376 of 601), with comparable success rates between CNB and FNA samples (59% [336 of 574] and 54% [40 of 74], respectively; Figure 5). Failure of NGS was most commonly due to library preparation or sequencing failure. Of note, the FNA samples that are tested because of an inadequate CNB specimen may be somewhat disadvantaged by a selection bias. Inadequate CNB samples tend to be associated with paucicellular concurrent FNAs. The cytopathologist reviewing an NGS request on an FNA sample after the concurrent CNB was deemed inadequate will often attempt testing on the borderline FNA sample to avoid rebiopsy for molecular testing. This is evidenced by the fact that FNA-only samples demonstrate higher NGS success rates (59%) than FNA samples with inadequate concurrent CNB samples (51%; Table 1).

We also reviewed the EBUS FNAs that were analyzed by NGS for the same 14-month time period. A total of 62 cases were requested for NGS analysis, of which only 8 were canceled because of insufficient tumor fraction from high-background lymphocyte content. The overall NGS success rate was 60% (37 of 62), in keeping with the success rates of IR-guided samples of FNA-only samples (Table 1).

**PROCEDURE TYPE**

Cytology specimens commonly sent for molecular testing at our institution include: IR-guided procedures, US-guided FNAs, EBUS FNAs, endoscopic US FNAs, and body cavity fluids. In a 10-month retrospective study (October 2013–July 2014) of 207 cytology cases, NGS success rates were similar for the different procedure types without any significant

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**Table 1. Next-Generation Sequencing (NGS) of Cytologic Specimens**

<table>
<thead>
<tr>
<th>Procedure (January 2013–February 2014)</th>
<th>No. (%) of Cases</th>
</tr>
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<tbody>
<tr>
<td>NGS success of IR-guided FNA (samples with inadequate CCNB)</td>
<td>24/47 (51)</td>
</tr>
<tr>
<td>NGS success of IR-guided FNA (FNA only)</td>
<td>16/27 (59)</td>
</tr>
<tr>
<td>NGS success of EBUS-guided FNA</td>
<td>37/62 (60)</td>
</tr>
</tbody>
</table>

Abbreviations: CCNB, concurrent core needle biopsy; EBUS, endobronchial ultrasound; FNA, fine-needle aspiration; IR, interventional radiology.
In addition, as previously mentioned, NGS success rates (January 2013–February 2014) from IR-guided FNAs (59%) and EBUS FNAs (60%) were comparable (Table 1), indicating that the procedure type does not correlate with NGS success rate.

**TUMOR TYPE AND SITE OF LESION**

The molecular adequacy of cytology specimens likely correlates with the overall cellularity and tumor fraction of the sample. Tumors with dysesive cells typically have more cellular aspirates than fibrotic tumors. In our experience, however, the tumor type and site of lesion do not affect the success of NGS testing. In a retrospective review of 207 cytology samples, the NGS success rate of the most common tumor types tested (lung adenocarcinoma, melanoma, gastrointestinal adenocarcinoma, breast carcinoma, hepatocellular carcinoma, papillary thyroid carcinoma) and the most commonly sampled lesional sites (lung, lymph node, soft tissue, liver, and body cavity fluids) did not vary significantly. This suggests that if a sample meets minimum adequacy for overall cellularity and tumor fraction, the NGS success rate was independent of tumor type or site of lesion.

**TUMOR FRACTION**

The criteria for minimum tumor fraction in a sample required for mutational analysis depend on the analytic sensitivity of the assay platform and are determined by the molecular diagnostic laboratory during validation of the assay. As mentioned previously, we use 20% as our minimum tumor fraction threshold for all solid tumor samples analyzed on Ion Torrent PGM. In our experience, the estimated tumor fraction is similar in both the NGS success (median, 65%; range, 25%–100%) and failure (median, 70%; range, 30%–100%) groups. This indicates that NGS success is independent of tumor fraction, provided the minimum tumor cellularity of 20% is achieved.

**TYPE OF CYTOLOGIC SUBSTRATE**

One of the distinct advantages of cytologic specimens is the wide selection of substrates that are amenable to next-generation sequencing (NGS) based on cellularity and tumor fraction. Low-cellularity samples (left) have an increased risk of test failure (insufficient DNA/polymerase chain reaction failure), whereas low–tumor fraction samples (bottom) have an increased risk of false-negative results. Tumor mapping increases the tumor fraction above the analytic threshold (shown in red horizontal line). Tumor mapping always decreases the cellularity and DNA yield, which is not a problem provided the circled areas contain a sufficient amount of cells to meet the DNA input threshold (shown in blue vertical line).

Figure 2. Specimen triaging for next-generation sequencing (NGS) based on cellularity and tumor fraction. Low-cellularity samples (left) have an increased risk of test failure (insufficient DNA/polymerase chain reaction failure), whereas low–tumor fraction samples (bottom) have an increased risk of false-negative results. Tumor mapping increases the tumor fraction above the analytic threshold (shown in red horizontal line). Tumor mapping always decreases the cellularity and DNA yield, which is not a problem provided the circled areas contain a sufficient amount of cells to meet the DNA input threshold (shown in blue vertical line).
molecular testing. There has been extensive discussion regarding the optimal cytology substrate for molecular analysis.32,38,39 Multiple groups have demonstrated that a variety of cytology substrates are suitable for molecular testing, including direct smears, cytospin preparations, formalin-fixed, paraffin-embedded cell block preparations, and liquid-based preparations (monolayered preparations—eg, ThinPrep [Hologic Inc, Marlborough, Massachusetts] or SurePath [Becton Dickinson, Franklin Lakes, New Jersey]—created on proprietary instruments and originally developed for gynecologic cytology but commonly used for non-gynecologic cytology samples, including FNA needle rinses and effusions), as well as samples taken directly from cells in preservative suspension. Each substrate has specific advantages and disadvantages, as illustrated in Table 2. The CLIA-certified molecular diagnostic laboratory at our institution validated the NGS assay using both direct smears/cytospin preparations as well as cell block sections. The initial validation study set did not show any significant difference in NGS success rate between the cell blocks and the smears.19 In a follow-up study of 207 cytology samples, only 44% of the cases had adequate cellularity on cell blocks for NGS analysis.10 Including direct smears and cytospin preparations allowed testing of an additional 116 cases (56%), thus avoiding the need for a repeat biopsy/FNA procedure. In addition, the superior quality of nucleic acids retrieved from smears/cytospin preparations makes them ideal substrates for most PCR-based assays.39 The sacrifice of the slide(s) from the diagnostic archives may occasionally present some medicolegal challenges, but this potential problem can be mitigated by digital archiving (either whole-scan imaging or conventional photomicroscopy) prior to tissue extraction. The College of American Pathologists recently updated its guidelines to allow the sacrificing of smears for molecular testing when beneficial to the patient.

STAIN/FIXATIVE

Most studies using previously stained cytology smears have shown that molecular testing can be performed successfully using both air-dried Diff-Quik (methanol fixed during staining) as well as Papanicolaou (ethanol fixed) stained slides. There have been conflicting data in the literature, with some groups showing DNA extracted from archival Diff-Quik slides to be superior to that from Papanicolaou slides,40 and others showing better DNA yields from the latter.51 In our experience, the cytologic stain
or fixative does not show a significant difference in the NGS success rates; however, the sample size that was reviewed during the validation was relatively small (3 cases with Diff-Quik–stained slides versus 13 cases with Papanicolaou-stained slides). ¹⁹ In practice, we routinely employ both Diff-Quik–stained and Papanicolaou-stained slides, frequently in combination, without any noticeable difference in NGS outcome. Additional studies are needed to determine whether and to what degree cytologic stains/fixatives affect DNA yield and NGS success rates.

**NUMBER OF SLIDES**

The number of slides sent for NGS analysis varies depending on the overall cellularity of the case. The

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**Table 2. Advantages and Disadvantages of the Cytologic Substrates Commonly Used for Molecular Testing**

<table>
<thead>
<tr>
<th>Cytologic Substrate</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Direct smear ³</td>
<td>• Immediate assessment for adequacy</td>
<td>• Sacrificing slide from archival material (potential medicolegal issues)</td>
</tr>
<tr>
<td></td>
<td>• High-quality nucleic acid</td>
<td>• Additional validation</td>
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<tr>
<td></td>
<td>• Whole cells with whole nuclei</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Superior tumor mapping in samples with low tumor fraction</td>
<td></td>
</tr>
<tr>
<td>Liquid-based cytology ²</td>
<td>• Standardized processing with optimal preservation of cells</td>
<td>• Lack of immediate assessment</td>
</tr>
<tr>
<td></td>
<td>• Whole cells with whole nuclei</td>
<td>• Additional validation</td>
</tr>
<tr>
<td></td>
<td>• High-quality nucleic acid</td>
<td>• Nucleic acid retrieval may be variable based on preservative/fixative</td>
</tr>
<tr>
<td>Cell block ³</td>
<td>• Ease of acquisition</td>
<td>• Lack of immediate assessment</td>
</tr>
<tr>
<td></td>
<td>• Multiple serial sections</td>
<td>• Frequently suboptimal cellularity</td>
</tr>
<tr>
<td></td>
<td>• Standardized validation in most molecular laboratories</td>
<td>• Nucleic acid may be suboptimal because of formalin fixation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Partial nuclei on standard 4- to 5-micron sections</td>
</tr>
</tbody>
</table>

¹ Direct smear, smear preparations (air dried or alcohol fixed) usually prepared from aspirates.
² Liquid-based cytology, similar to processing of gynecologic samples, collecting needle rinse in an alcohol-based proprietary fixative and preparing a cell monolayer slide.
³ Cell block, prepared from the needle rinse of aspirates or residual fluid from body cavity fluid collections/effusions, usually by fixing in 10% formalin and embedding in paraffin, akin to surgical pathology tissue block.
molecular diagnostics laboratory at our institution usually recommends 10 to 15 unstained sections of the cell block per case, which can be less if the cell block is large or highly cellular (Figure 6). In our experience, the number of slides that are used for tissue extraction does not have any significant correlation with the NGS success rate (Table 3).

**TYPE OF SLIDES**

At MD Anderson, unstained sections from cell blocks are usually prepared on positively charged glass slides in anticipation of ancillary studies (immunoperoxidase staining and molecular testing). Cytology smears and cytospin preparations are prepared on fully frosted, nonfrosted (frosted-tip), and/or positively charged slides. In our experience, the fully frosted slides have far superior adhesion of cells compared with the other glass slides and are often the slide of choice for paucicellular aspirates. However, tissue extraction from fully frosted slides is technically more difficult. Cells dislodge (whether by scraping or cell-lifting techniques) less readily from fully frosted slides because of the slide’s rough surface, resulting in significantly lower DNA yields relative to nonfrosted or positively charged slides.42 Although we did not see a significant difference in NGS success rates between cases that used different types of glass slides, the lower DNA yield from fully frosted slides may affect downstream molecular analysis.10

**EXTRACTION METHOD**

Most laboratories use either direct scraping or cell-lifting methodology for tissue extraction from glass slides. For scraping, a scalpel or a razor blade or a dissecting needle is used to scrape cells directly from the entire slide (in cases where microdissection is not necessary) or from circled tumor-rich areas (in cases where tumor enrichment is required). Tumor mapping (i.e., circling tumor-rich areas for targeted dissection) greatly enhances the tumor fraction and is done by our cytopathologists in most cases. Direct smears are tumor mapped by circling tumor-enriched areas and etching the underside of the slide using a diamond-tip pen followed by removal of the coverslip. Depending on the size and complexity of the tumor map, the areas of interest are then scraped with (microdissection) or without (macrodissection) the aid of a microscope. Laser capture is rarely ever employed for NGS cases. For cell blocks, unstained sections are lined up with a corresponding hematoxylin–eosin–stained slide, and circled tumor-rich areas are scraped either by macrodissection or microdissection. A number of groups have described cell lifting using the Pinpoint Slide DNA Isolation System (Zymo Research, Orange, California) for tissue extraction. In our experience, scraping gives higher DNA yield than cell lifting from all glass slide types and remains our preferred method for tissue extraction.42

**DNA YIELD**

As expected, the DNA yield correlates significantly with the success of NGS analysis. In our initial validation study as well as a follow-up retrospective study, the median DNA yield (cell blocks and smears) was significantly higher in the cases with successful NGS than the cases where NGS failed10 (Table 3).

**INPUT DNA**

The choice of Ion Torrent PGM as the NGS platform for solid tumor samples is based on the low input DNA

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**Table 3. Preanalytic Parameters of Cytology Cell Blocks and Smears That Succeeded or Failed by Next-Generation Sequencing (NGS)**

<table>
<thead>
<tr>
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<th>Validation Study, Median (Range)</th>
<th>Follow-up Study, Median (Range)</th>
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<tbody>
<tr>
<td></td>
<td>NGS Success</td>
<td>NGS Failure</td>
</tr>
<tr>
<td>No. of slides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell block</td>
<td>4 (1–10)</td>
<td>3.5 (1–8)</td>
</tr>
<tr>
<td>Smear</td>
<td>1 (1–2)</td>
<td>1 (1–4)</td>
</tr>
<tr>
<td>DNA yield, μg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell block</td>
<td>0.07 (0.01–0.6)</td>
<td>$4 \times 10^{-3}$ (0.0–0.02)</td>
</tr>
<tr>
<td>Smear</td>
<td>0.12 (0.01–0.8)</td>
<td>0.01 ($4 \times 10^{-3}$ to 0.03)</td>
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</table>
requirement (10 ng as recommended by the manufacturer). However, we noticed a large fraction of cases that had DNA yields just below the minimum required threshold and thus failed to meet the adequacy criteria. We performed a validation study using DNA samples less than 10 ng and were able to successfully perform the NGS assay in 15 of 16 cases (94%), with DNA concentrations ranging from 0.1 to 0.84 ng/µL. Therefore, our molecular diagnostic laboratory implemented a new workflow that does not require the 10-ng threshold DNA input, and samples are tested irrespective of the DNA yield. The NGS success rate in cytology samples following implementation of this change increased significantly from 59% to 90%.10

PATHOLOGIST BIAS

Pathologists’ personal biases affect the assessments of adequacy and selection of material for NGS testing. Similar to surgical pathologists, there is a wide interobserver variation among cytopathologists in estimating tumor fraction. Even with predefined adequacy criteria at our institution, tumor fraction estimation and selection of cases vary widely. Some of our cytopathologists demonstrate high cancellation rates, resulting in low NGS failure rates, whereas others have low cancellation rates with corresponding high NGS failure rates.10 This variation among pathologists in tumor fraction estimation and selecting cases for NGS analysis is also seen in the selection of substrates (cell block versus smears) and the number and type of glass slides sent for testing.

CONCLUSIONS

In the current era of targeted therapeutics, cytopathologists need to recognize the opportunities, limitations, and pitfalls of NGS on limited-volume samples in order to fully use the resources available in cytologic specimens. A working knowledge of the preanalytic variables affecting downstream NGS analysis is needed to critically evaluate existing workflows and maximize DNA yield for optimal testing.

Most of the studies reported in the literature were performed in-house on cytologic specimens selected for NGS. Laboratories lacking in-house testing, however, outsource testing to large reference laboratories and must conform to the validation standards of these individual laboratories and their NGS platforms.43 Most molecular laboratories prefer using formalin-fixed, paraffin-embedded material, thereby avoiding additional validations for the various cytologic substrates. However, the exclusion of direct smears, cytospin preparations, fresh/frozen samples, and liquid-based preparations significantly decreases the fraction of cases that can be used for testing. Although the advantages of using non–formalin-fixed, paraffin-embedded material for molecular testing cannot be overemphasized (Table 2), there are disadvantages, including increased effort required for validation, sacrifice of archival smears/cytospin slides, and increased time required for careful tumor mapping of smears.

The selection of the NGS platform and an optimal mutational panel is critical, especially in the context of limited tumor volume. Of the currently available benchtop NGS sequencers, Ion Torrent PGM offers the advantage of low input DNA requirement and faster turnaround time compared with Illumina MiSeq; however, the former suffers from a higher error rate and lower throughput than MiSeq.24,45 Several groups have reported high success rates from both sequencers using cytologic samples. In our experience, a large fraction of cytology specimens would not yield sufficient DNA for MiSeq. However, the superior quality of non–formalin-fixed, paraffin-embedded cytologic substrates allows for some flexibility in reducing the input DNA below what is recommended by the manufacturer, when appropriately validated. The choice of a hotspot-based targeted NGS panel with an amplification-based approach allows for the use of extremely small amounts of DNA, characteristic of many cytologic samples.

Exploiting the full potential of cytologic samples requires a basic understanding of the molecular workflow and recognition of the opportunities and challenges of performing NGS testing on limited-volume samples. In the current era of targeted therapy, the role of cytopathology has expanded beyond morphologic diagnosis to include providing suitable substrates for molecular diagnostics, by which critical prognostic and predictive therapeutic targets can be identified. In this rapidly evolving field, although the involvement of the cytopathologist is essential for the judicious use of available materials for testing, it is equally important for the surgical and molecular pathologist to be aware of the utility of cytology specimens in molecular testing and to adopt institutional processes that can best use these specimens.

References