Prostate Biopsy Processing

An Innovative Model for Reducing Cost, Decreasing Test Time, and Improving Diagnostic Material

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ABSTRACT

Objectives: *Current protocols for processing multiple prostate biopsy cores per case are uneconomical and cumbersome. Tissue fragmentation and loss compromise cancer diagnosis. We sought to study an alternate method to improve processing and diagnosis of prostate cancer.*

Methods: *Two sets of sextant biopsy specimens from near-identical locations were obtained ex vivo from 48 prostate specimens. One set was processed in the standard fashion while the other was processed using the BxChip, a proprietary biomimetic matrix that accommodates six cores on a single chip. Parameters including grossing, embedding, sectioning and reading time, length of tissue, and degree of fragmentation were compared.*

Results: *A significant reduction (more than threefold) in preanalytical and analytical time was observed using the multiplex method. Nonlinear fragmentation was absent, in contrast to standard processing.*

Conclusions: *The BxChip reduced tissue fragmentation and increased efficiency of prostate biopsy diagnosis. It also resulted in overall cost savings and significantly increased tissue length.*

Prostate cancer is the second highest incident cancer in American men, with a rising rate over the past 60 years and an incidence of 164,690 cases in 2018.[1] A systematic transrectal ultrasound (TRUS)–guided prostate needle biopsy diagnosis is the cornerstone of risk stratification for appropriate patient management. The diagnosis involves evaluation of each mapped site for the presence of carcinoma, with subsequent quantification and Gleason score/Grade Group assignment. This information is critical for determining disease management strategy (active surveillance vs definitive management). In addition, when definitive therapy is indicated, it guides the extent of surgery as well as the type and dose of radiation therapy.[2]

Historically, six-core "sextant" biopsy specimens that sampled the bilateral base, middle, and apical regions were used to survey the prostate. Due to concerns of insufficient tissue for analysis and inaccurate cancer detection rates (CDRs), the current standard of care is to use a 10- to 14-core sampling technique that allows for more extensive investigation of the peripheral zone.[2-6] The extended biopsy protocol not only has increased the CDR but also has resulted in better concordance with the prostatectomy Gleason score. Increasing the number of cores beyond 12 (up to 24 cores for saturation biopsy specimens) has in general yielded modest improvements in the CDR[6] but may be warranted in patients with negative biopsy specimens and persistent suspicion of prostate cancer.[5]

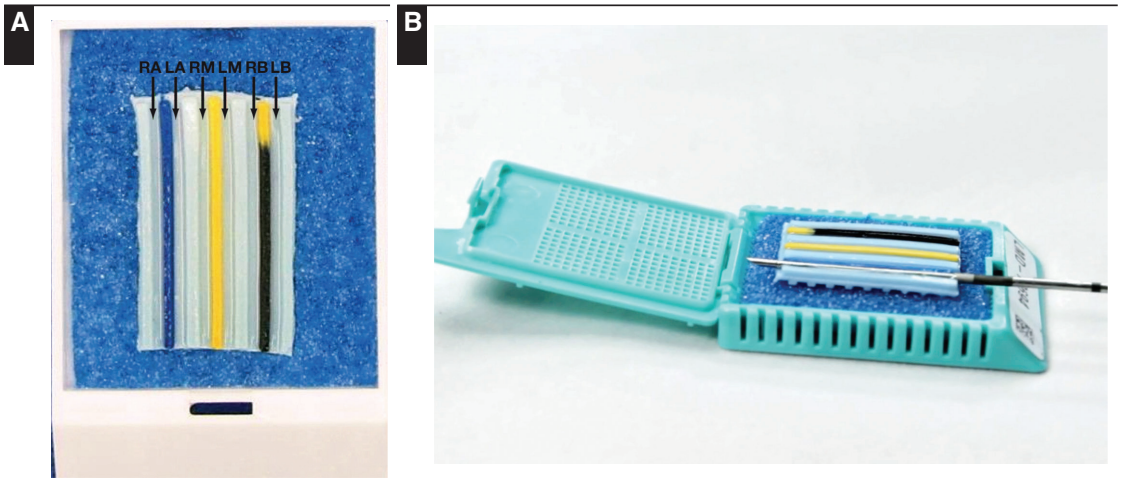

Figure 1 **A**, Multiplex chip (BxChip): a 22-mm × 14-mm sectionable biomimetic matrix with 0.8-mm-wide grooves separated by color-coded partition ridges that can be custom designated by biopsy location. The chip is placed in a standard tissue cassette, supported by sponges. LA, left apex; LB, left base; LM, left mid; RA, right apex; RB, right base; RM, right mid. **B**, Direct loading of the biopsy core from needle tip into the designated matrix groove by capillary action.

Despite extended sampling protocols, prostate needle biopsy specimens can have a false-negative rate higher than 30%.[3] While sampling error, especially in cases with low cancer volume, is a significant reason for generating false-negative results, tissue loss due to poor orientation and fragmentation also plays a role. Tissue fragmentation, which can be present in nearly 30% of cases,[7] may distort cancer quantification and Gleason scoring with considerable treatment implications.[8]

Given the significance of the diagnostic results and the unique biopsy protocol, the submission, handling, and processing of prostate biopsy specimens assume a pivotal role. However, processing multiple sets of biopsy specimens per case remains uneconomical, time-consuming, and burdensome with concerns for diagnostic error. Our study demonstrates a potential solution that improves this practice, using a biopsy chip-facilitated multiplex approach.

Materials and Methods

In this prospectively designed single-institution study, 48 consecutive prostate specimens were subject to the experimental protocol. Institutional review board approval was obtained as per institutional requirement. An 18-gauge prostate biopsy gun (Bard Medical Max Core; Bard Medical) employed in routine urologic practice at our institution was used to obtain two sets of sextant biopsy specimens ex vivo from 30 prostatectomies performed for prostate carcinoma, eight cystoprostatectomies performed for bladder carcinoma, and 10 prostate specimens obtained from autopsy cases in patients who died of unrelated causes. For each specimen, a pair of biopsy specimens was obtained at near-identical locations (<1 mm apart) from bilateral base, middle, and apex portions of the gland to duplicate physical and morphologic similarity. One set was processed in accordance with the standard protocol (SP) employed in our institution, and the other was processed using a multiplex chip (MC) protocol (MCP). In the SP, each tissue core was swiped onto a moist filter paper and fixed in separate site-designated formalin containers. These were routinely grossed by forceps extraction, examined, described, and placed between sponges into separate tissue cassettes. After the standard tissue-processing steps for dehydration, clearing, and paraffin infiltration, the cores were embedded in molten paraffin using forceps to create six tissue blocks. These were then microtome sectioned at three levels, placed on separate slides, H&E stained, and cover-slipped for microscopic examination. The second set of biopsy specimens was processed using the MCP. The multiplex BxChip (Lumea), costing $12, is a sectionable 22-mm-long proprietary biomimetic matrix with six 0.8-mm-wide grooves separated by three differently colored partition ridges. The MC is preplaced between formalin soaked sponges in a standard tissue cassette. The six biopsy cores were directly transferred from the needle into the site-designated (by color codes) MC grooves via capillary action and gentle in-axis rotation **Figure 1**. The cassette was placed in a formalin container after which gross examination and description were performed by examining the tissue in the MC in situ. The single cassette containing the six biopsy cores was then subject to routine tissue processing.

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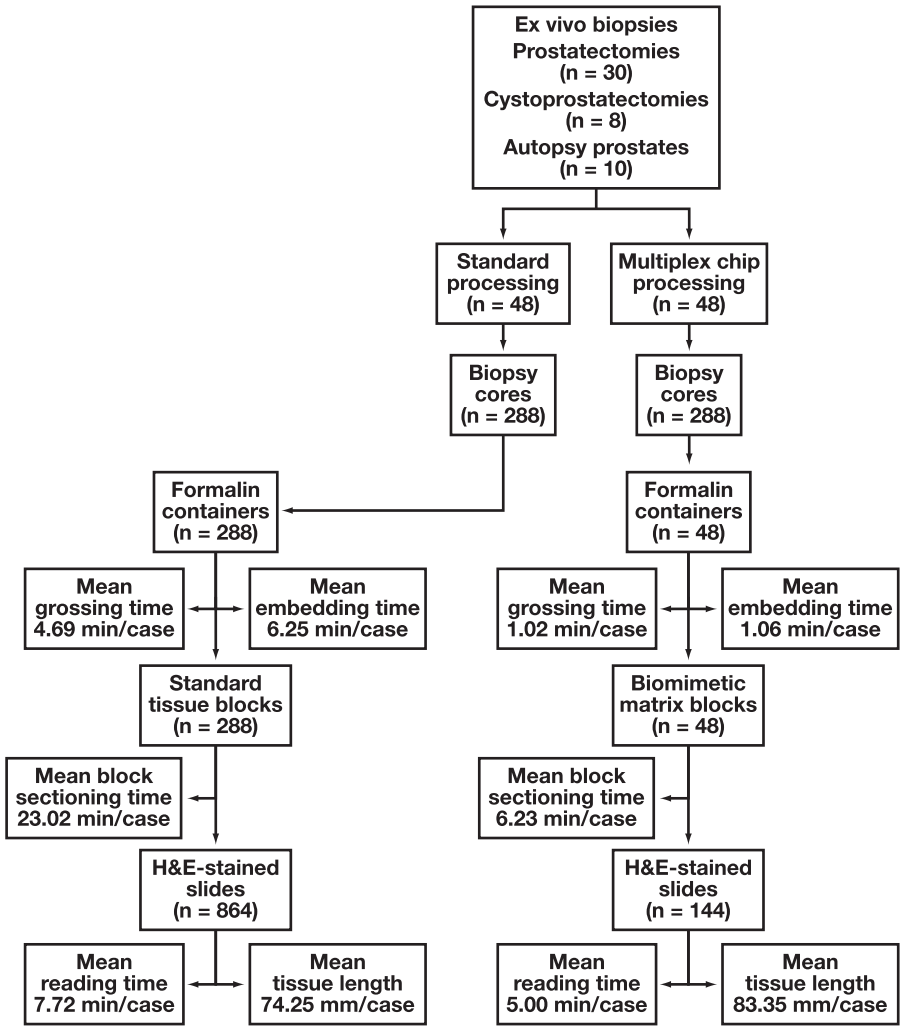

Figure 2 Study methodology depicting major processing steps, quantity of material involved, and key analytical parameters.

Embedding was performed by placing the MC as a whole in molten paraffin without tissue handling. The MC, along with the tissue cores, was sectioned at three levels and placed on three separate slides, H&E stained, and cover-slipped for microscopic examination Figure 2.

Outcome measures included mean processing time (grossing, embedding, sectioning), sample quality (tissue fragmentation, total tissue length, total cancer length), reading time, and cost. Fragmentation was measured as linear vs nonlinear. Linear fragmentation was defined as a more than 2-mm in-line separation of the core fragments. Nonlinear fragmentation was defined as a more than 2-mm out-of-line/plane separation of the core fragments that typically causes considerable challenge in ascertaining which core the fragments belong to. The microscopic examination was performed on both the standard and MC material by an expert genitourinary pathologist (P.M.). The reading time involved routine examination of all levels of the biopsy tissue and, where applicable, cancer quantification by length, percentage core involvement, and Gleason scoring.

A comparative cost analysis of prostate biopsy specimens processed by the two protocols was conducted, and a per-case cost estimate was calculated. This included the cost of materials (MC, formalin containers, tissue cassettes, slides, etc), pathologist assistant/histology technician time, and pathologist time. A two-tailed paired *t* test was used for statistical analysis of the various process metrics, with significance marked by a *P* value of less than .05.

Results

The use of the MC allowed an organized, multiplexed processing of prostate needle biopsy specimens. It eliminated tissue manipulation and handling, a staple of the standard protocol, thereby limiting tissue fragmentation

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Table 1

Comparison of Pre- and Postanalytical Parameters Between Standard and Multiplex Chip Prostate Biopsy-Processing Protocols

Per Case	Standard Protocol, Mean	Multiplex Chip Protocol, Mean	*P* Value
Gross time, min	4.69	1.02	.0001
Embed time, min	6.25	1.06	.0001
Section time, min	23.02	6.23	.0001
Linear fragments	1.146	1.40	.3571
Nonlinear fragments	2.19	0	.0001
Tissue length, mm	74.25	83.35	.0001
Cancer length, mm	5.14	5.67	.3161
Cores with cancer	1.19	1.13	.4971
Reading time, min	7.72	5	.0001

Table 2

Comparison of Tissue Length and Cancer Length in Benign and Malignant Cores Between Standard and Multiplex Chip Protocols[a]

	Standard Protocol		Multiplex Chip Protocol	
Characteristic	Benign Cores	Malignant Cores	Benign Cores	Malignant Cores
Tissue length, mm, range (mean)	61-108 (75.4)	62-96 (73.2)	65-109 (87)	50-98 (80)
Cancer length, mm, range (mean)		0.5-47 (9.9)		0.5-37.5 (10.9)
Percentage cancer, %		13.5		13.6

[a]No significant difference between the benign and malignant core lengths were noted in either of the two methods (standard protocol, $P = .50$; multiplex chip protocol, $P = .07$). However, a significant increase was noted in the benign as well as malignant core lengths in the multiplex chip protocol compared with their standard protocol counterparts (benign, $P = .004$; malignant, $P = .04$). Neither the percentage of cancer nor the cancer length ($P = .75$) was significantly different between the two methods.

and loss. Nonlinear fragmentation was entirely absent with the MCP due to the cores being held linear, constrained, and separate in their designated grooves. In contrast, the SP produced a mean of 2.19 (interquartile range [IQR], 0-4) nonlinear fragments per biopsy core ($P = .0001$). Linear fragmentation was noted with the MCP and was not significantly different from the SP ($P = .32$). The biopsy tissue core length increased from a SP mean of 74.25 mm (IQR, 65.5-81.5) to an MCP mean of 83.35 mm (IQR, 74.5-94), resulting in an average increase of 9.10 mm ($P = .0001$) per case. The cancer length increased by an average of 0.5 mm in the new processing method ($P = .54$). No significant difference in the number of cores with cancer or Gleason score was observed between the two methods **Table 1**. A comparison of tissue length and cancer length in benign and malignant cores between SP and MCP is depicted in **Table 2**.

In addition to improvements in tissue quality, significant reductions in time required for tissue processing were also observed. A greater than fourfold reduction ($P = .0001$) in preanalytical time was observed using MCP. As expected, this improvement resulted from processing one tissue matrix compared with six individual tissue cores. Grossing time was reduced from a mean of 4.69 minutes (IQR, 4-5) to 1.02 minutes (IQR, 1-1) per case while embedding time was reduced from a mean of 6.25 minutes (IQR, 5.5-7) to 1.06 minutes (IQR, 1-1). In particular, a marked reduction, from a mean of 23.02 minutes (IQR, 19-27.5) to 6.23 minutes (IQR, 5-7), was noted in sectioning time. Furthermore, the organization of the cores in the MC reduced the slide microscopic examination time by 2.72 minutes per case (Table 1).

Use of the MCP was associated with an overall cost savings. A comparison of pathology assistant, histology technician, and pathologist time per case and material costs between the two protocols projected savings in excess of $10 per case **Table 3** without including potential reduction in immunohistochemistry and processing reagents expenditure. The use of the MC also resulted in a sixfold reduction in storage space of tissue blocks and slides.

Discussion

The diagnosis and management of prostate cancer is a significant burden on health care systems across the world, given the high incidence and wide prevalence of the disease. Both diagnostic and active surveillance strategies involve systematic TRUS-guided biopsies wherein at least 12 core needle biopsy specimens (modified sextant procedure) are performed per procedure according to current guidelines.[2-5,9] Additional targeted sampling aided by multiparametric magnetic resonance imaging (MRI) studies is progressively more prevalent as well.[10] For one standard case, this typically results in 18 to 42 slides when two or one core(s) per part respectively are submitted. Considerable time, effort, and experience are involved in accurately embedding, sectioning, mounting, and reading the corresponding number of blocks and

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Table 3
Comparison of Cost Between Standard and Multiplex Protocols for a Six-Core Prostate Biopsy Case

Item	Cost per Unit, $	Number Required		Total Cost, $	
		SP	MCP	SP	MCP
Multiplex chip	12	0	1	0	12
Formalin jar	0.35	6	1	2.1	0.35
Tissue cassette	0.18	6	1	1.08	0.18
Biopsy sponge	0.18	12	0	2.16	0
Glass slide and cover slip	0.15	18	3	2.7	0.45
Pathology assistant time (per minute)	0.75	4.69	1.02	3.52	0.77
Histotechnologist time (per minute)	0.41	29.27	7.29	12	4.92
Pathologist time (per minute)	2.15	7.72	5	16.6	10.75
Total cost per case, $				40.16	29.42

MCP, multiplex chip protocol; SP, standard protocol.

slides. Furthermore, accurate Gleason grading and quantification of percentage and number of cores involved by carcinoma are critical determinants of patient management and mandatory requirements for prostate biopsy reporting.[11-13] Evaluating intact, unfragmented tissue cores is of considerable importance in this regard. Unfortunately, fragmentation is a common byproduct of standard biopsy processing,[6-8] since the delicate <0.1-cm diameter prostate tissue cores are subject to physical stressors at various points of tissue handling, including transfers from biopsy needle to filter paper, formalin container to tissue cassettes, and during tissue embedding. This is especially pronounced in cores that are inherently fragile due to higher volume and/or grade of cancer as a result of diminished stromal support. Such fragmentation can compromise diagnostic accuracy through errors in cancer quantitation or Gleason scoring **Figure 3**, thereby resulting in potential patient mismanagement.[9] When translated to ~1,000 cases or more per year for busy urologic practices, the large number of specimens per case and the possibility of tissue fragmentation place a substantial burden on anatomic pathology laboratories and pathologist workload, especially in the face of diminished reimbursement rates. Hence, a pressing need for process innovation exists.

Our study demonstrated that the multiplex chip protocol offered an effective solution to these issues, demonstrating a significant process improvement. The MC used in our study is a custom-made tissue array that can accommodate six prostate needle biopsy cores in a single scaffold. It is constructed using a proprietary biomimetic material that allows processing and sectioning using standard protocols. The MC can be used at the point of care where the biopsy procedure is performed. The chip is preplaced in a standard tissue cassette between biopsy pads and the needle cores from each location are directly transferred from the biopsy gun into site-designated grooves by capillary action (Figure 1). The cores are examined in situ at the grossing station without need for forceps extraction. Similarly, the chip is directly embedded without disturbing the cores. Both these modifications prevent the possibility of traumatizing the delicate tissue. Grossing, embedding, and sectioning one block instead of six saves considerable time and material and offers a clear advantage over standard processing. In addition, the cores are supported in a single plane, thus making sectioning easier and preventing tissue loss by block facing when poorly oriented tissue cores are encountered.[14] Moreover, the capillary action of the flanking ridges stretches the tissue and increases the diagnostic surface area. Since nonlinear fragmentation and misalignment are obviated by using the MC, the time required to decipher tissue orientation and cancer quantification is conserved. In this regard, it should be noted that although a diagnosis of "cancer involving multiple fragmented cores" is acceptable practice, such an interpretation is less than ideal for patient care and should be considered only when accurate quantification is impossible. In addition, especially in cases with multiple benign cores, the reading time is much quicker, analogous to diagnosing a prostatectomy case on whole-mount sections compared with standard sections. Thus, compared with SP specimens, our study showed an average increase of total biopsy core length by 9.10 mm (P = .0001) with absence of nonlinear fragmentation, thus mitigating factors that reduce diagnostic yield and accuracy. Our study also demonstrated that the use of the MCP resulted in greater than fourfold reduction (P = .0001) in preanalytical time and significant reduction of the slide microscopic examination time.

In addition to reduced storage space for blocks and slides, a factor that is of import in the long run for high-volume laboratories, other apparent advantages of the MC approach may be observed in the following contexts.

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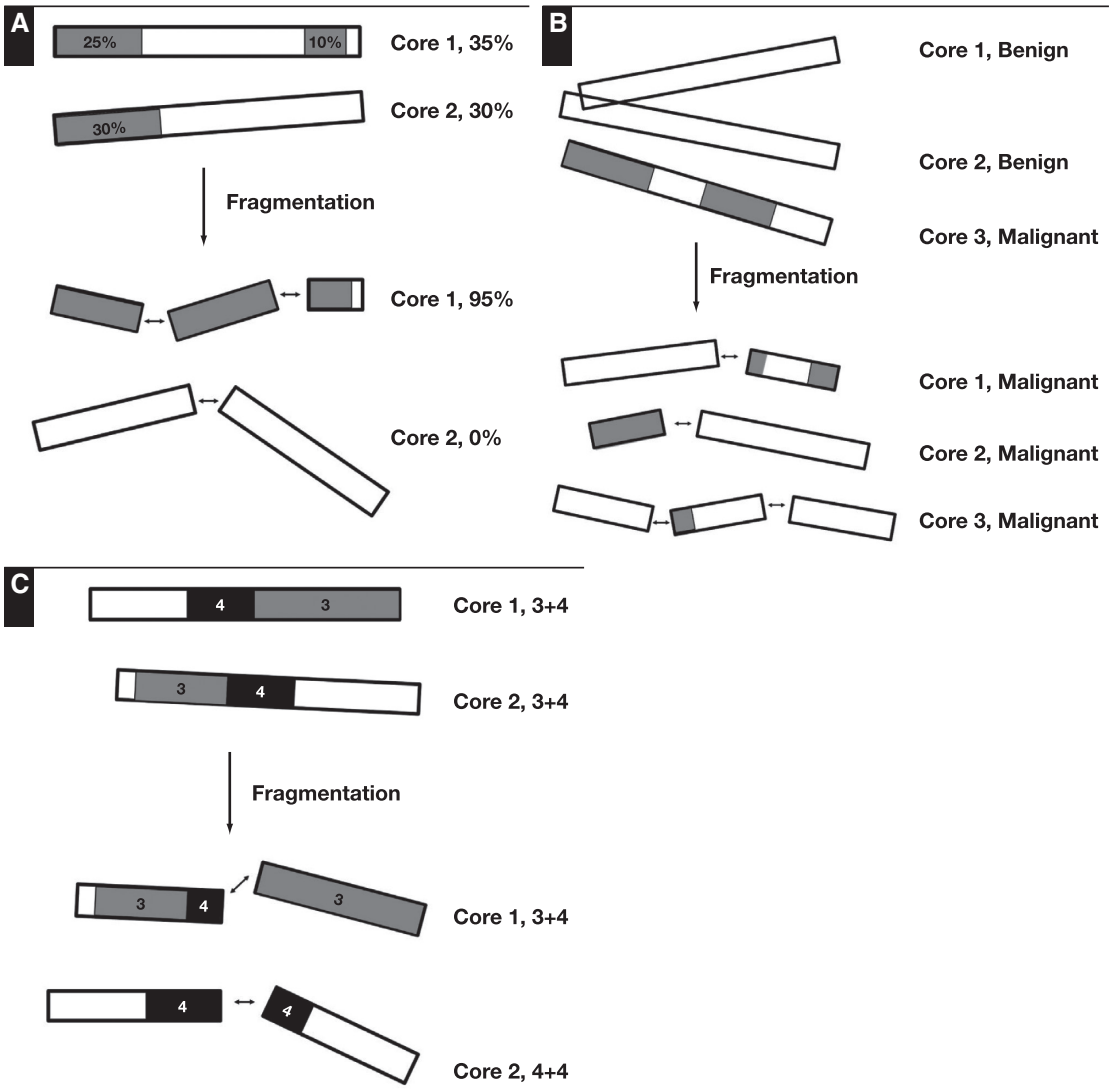

Figure 3 Examples of potential diagnostic errors due to fragmented and misaligned tissue. **A**, Error in calculating percentage involvement: two cores, each with less than 50% involvement by carcinoma, may be misrepresented as one core involved by more than 50% tumor. **B**, Error in determining the number of cores with cancer: one of three cores involved by carcinoma presenting as three of three cores positive for tumor. **C**, Error in determining Gleason score when each core is scored separately: two cores, each with Gleason 7(3 + 4) carcinoma, fragmented and misaligned to falsely depict Gleason 8(4 + 4) carcinoma in a core.

1. Multiplex immunohistochemistry (IHC) stains are routinely used in prostate biopsy diagnosis to support the morphologic impression. The impact of the MC in this regard is underscored in cases where IHC is required for more than one part. The chip array offers the benefit of performing IHC on a single section that covers six tissue cores (similar to tissue microarray sections), in contrast to multiple separate standard protocol sections. Not only does this conserve expensive IHC reagents, but it also offers the distinct advantage of being able to evaluate the IHC features of all tissue cores in the chip in addition to the ones queried. This increases diagnostic accuracy without driving up the cost of testing. Furthermore, correlation of lesional foci between the H&E and IHC stains is precise since block facing due to plane misalignment is absent and multiple identical duplicates can be obtained. This conserves invaluable tissue for research and genetic testing as well.
2. At present, there is burgeoning interest and research in multiparametric MRI-based detection and targeted biopsies for prostate cancer. A critical aspect of these studies involves stereotactic correlation of tissue diagnosis with the imaging findings to help validate and

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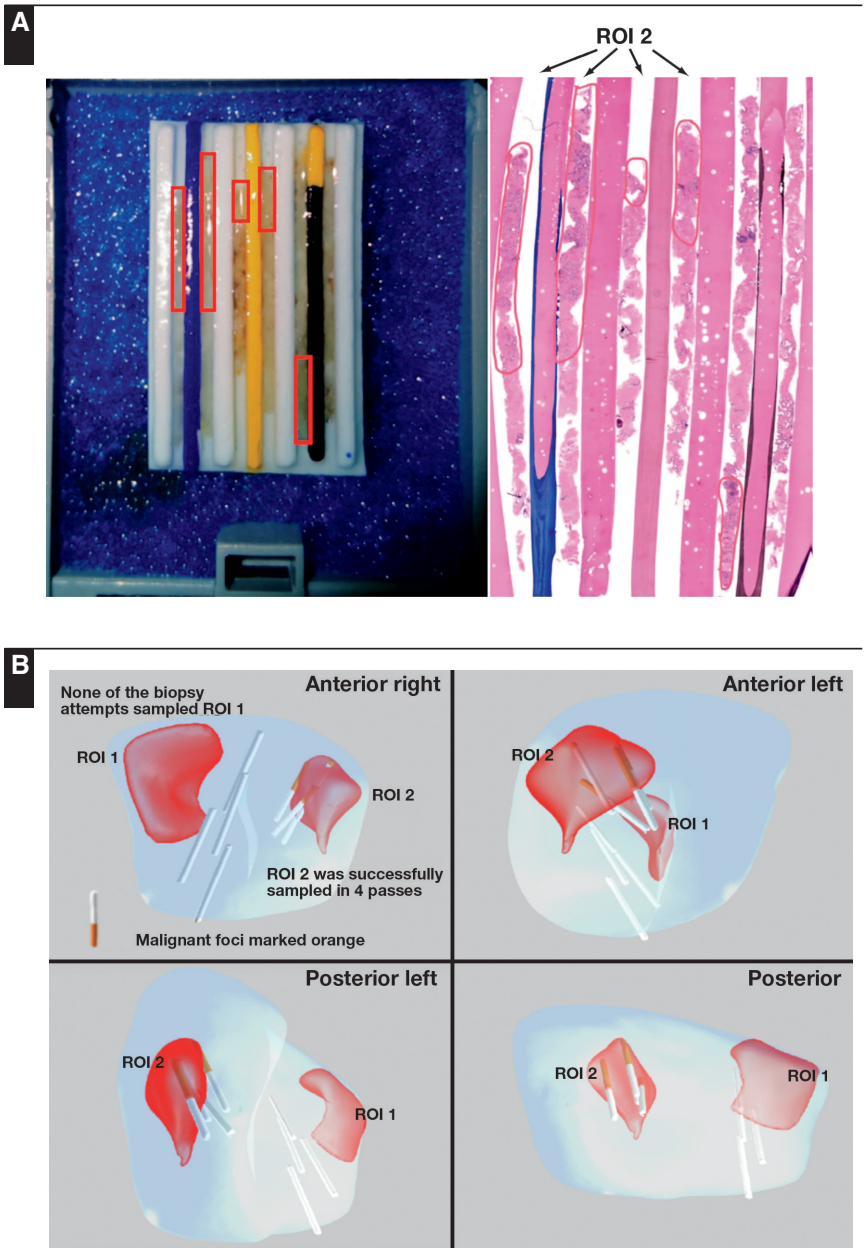

Figure 4 Radiology-pathology correlation from targeted biopsy specimens. **A**, Standardized, oriented placement of biopsy cores in the MC and digital pathology annotation from designated region of interest (ROI)–2 (malignant areas in red). **B**, Radiology-pathology fusion images depicting carcinoma sampled from ROI-2.

thus increase the accuracy of MRI assessment. The MC matrix layout allows for specific orientation and organization of the biopsy specimens, which can then be digitally annotated for the location and extent of the carcinoma. This can be accurately extrapolated with the MRI images to create a radiology-pathology fusion image that serves as an invaluable correlation tool Figure 4.

3. Whole-slide imaging and digital pathology are expected to play a central role in pathology diagnosis in the near future. Currently, we are in the early days of diagnostic automation using artificial intelligence (AI) platforms. Prostate cancer is at the forefront of these attempts given the fact that it has well-structured grading and quantification schemes.[15] The standardized organization of the cores in the MC matrix will allow AI algorithms to effectively quantify and qualify carcinoma.

Several techniques have been explored in the past for improving efficiency of prostate biopsy specimen processing, but the need for a universally adaptable solution is

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unmet. Multiplexing tissue for histologic examination and immunohistochemical studies using tissue microarray[16] and similar technology are well established. However, these pertain to archived paraffin blocks and are typically confined to the research domain. Multicompartment cassettes for prostate biopsy specimens also have been used,[17] but despite reducing the number of blocks and slides, this method amplifies the other described challenges. Solutions for reducing tissue handling and maintaining orientation, especially by avoiding the embedding process, have been explored in the past, albeit without widespread acceptance. The common denominator in these methods are synthetic sectionable tissue holders. One of these, a proprietary resin cassette (Tissue-Tek Paraform) manufactured by Sakura Finetek USA, offers a multiplex solution for biopsy cores. However, the design of this cassette renders its adaption for prostate biopsy specimens challenging and has thereby not gained widespread acceptance.[18] Researchers have previously reported at conference proceedings their observations on the MC used in our study.[19-22] In concurrence with our results, they have reported significant processing time and cost savings, increased core length, increased cancer detection rate, absence of nonlinear fragmentation, decreased storage space, and increased tissue preservation in the block for ancillary testing. However, these reports could not demonstrate a difference in reading time since the biopsy specimens compared were from different sets of patients and could not be controlled for the presence of carcinoma.

Limitations of our study include the fact that our study design was simplified for logistic purposes and thus sampled only one core per part. Although some urologists do submit specimens in this manner, there are several who sample two cores per part. It is highly probable that the advantages of the MC we observed would be enhanced in the latter scenario due to increased likelihood of tissue fragmentation and misalignment.[8] The other limitation is that one must be vigilant in making sure the MC material does not completely dry out during loading or grossing as this can cause the matrix to become brittle and cause breakage or difficulty during sectioning or result in the cores sliding out. In our experience, the skill required to transfer the biopsy tissue from the needle to the MC is easily mastered after a short learning curve. However, a potential limiting factor could be the initial buy-in from clinical staff responsible for loading the chip in the biopsy suite. While this study was mainly performed to demonstrate a proof of principle, we acknowledge as limitations that the microscopic review was performed by a single genitourinary pathologist and that the possibility of making errors while examining a single slide with multiple cores could potentially be higher than separately reviewing individual cores on a slide.

In conclusion, our study prospectively analyzed various sample processing and quality metrics between the standard histologic processing protocol and a multiplex method that eliminates tissue handling and allows simultaneous processing of prostate biopsy specimens. The latter not only reduced processing time, reading time, and cost but also allowed for potential improvement in diagnostic accuracy by minimizing tissue loss and nonlinear fragmentation. The MC method could also play a foundational role in current and future advancements in prostate cancer detection and diagnosis.

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