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Bead-Free Automated Cleanup and Size-Selection with INTip™ Solutions for NGS Library Preparation

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HIGHLIGHTS: Fully automated, fast, reproducible

NiX

INTRODUCTION

At present, automated next-generation sequencing (NGS) library preparation workflows predominantly rely on superparamagnetic beads and plate-based magnets for sample cleanup and fragment size-selection. A typical bead-based cleanup method requires six pipette tips per sample, a labware transport mechanism, and fine-tuning of pipetting heights to ensure complete supernatant removal from pelleted beads. DPX Technologies' NiXTips® contain immobilized silica media within robotic pipette tips and offer an automated bead-free alternative for cleanup and size-selection. The NiXTips workflow requires only two pipette tips per sample (**Figure 2**) and five fewer deck positions than bead-based methods. In this study, the performance of NiXTips was compared against beads in two NGS library preparation workflows, including downstream sequencing analysis. In all areas, NiXTips had equivalent or superior performance compared to beads, demonstrating the suitability of using NiXTips for NGS library preparation workflows.

MATERIALS AND METHODS

DNA recovery using NiXTips (DPX Technologies, NIX-HM300-96) was evaluated on a Hamilton VANTAGE liquid handler (**Figure 1**). A 1 kb Plus DNA ladder (Thermo, SM0311) diluted to 20 ng/µL (1 µg total input; n = 6 per condition) was used as the input sample. Samples were mixed with binding buffer (DPX, NIX-BB-001) at a 1:1 buffer-to-sample ratio and subjected to 5, 10, 20, or 30 NiXTips binding cycles. Tips were washed using two 100 µL aspirate/dispense cycles with 80% ethanol, then dried by four air-dry cycles consisting of a 1000 µL air gap blown through the silica media (**Figure 2**). DNA was eluted in 50 µL PCR-grade water at room temperature, and eluates were quantified using the Qubit BR dsDNA assay (Invitrogen, Q32853).

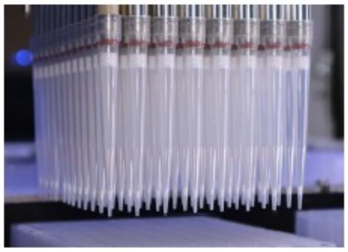
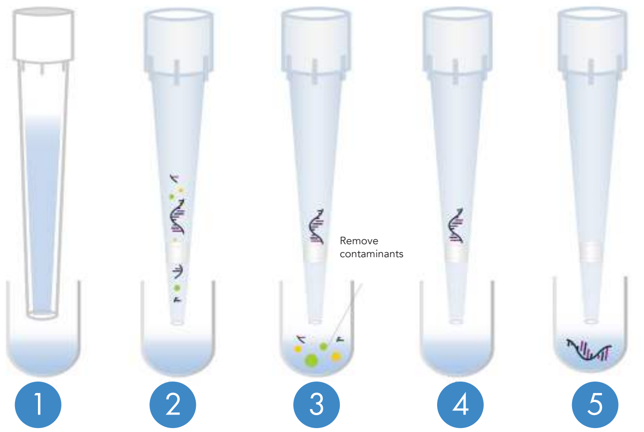


Figure 1. *NiXTips shown on Hamilton Robotics platform.*



1 Mix	Combine DPX NiX Binding Buffer with the nucleic acid sample at the selected ratio (e.g. 0.5:1) and mix by pipetting.
2 Bind	Aspirate and dispense the sample within the NiXTips to bind the nucleic acid sample to the silica media.
3 Wash	Aspirate and dispense 100 µL of wash reagent twice within the NiXTips to remove contaminants.
4 Dry	Aspirate 1 mL airgap, pickup the NiXTips, and blowout to dry the silica media four times.
5 Elute	Aspirate and dispense elution buffer to elute the sample in the desired volume.

Figure 2. *Schematic of the 1 mL NiXTips workflow for cleanup or size-selection of nucleic acid samples.*

NiXTips performance for size selection was evaluated using a 100 bp DNA ladder (Thermo, SM0242) at 20 ng/µL (1 µg total; n = 6). The workflow described above was repeated with modifications for size selection. The binding buffer-to-sample ratio was reduced to 0.5:1, and 30 binding cycles were performed. DNA was eluted in 25 µL water at room temperature and analyzed using D1000 ScreenTape (Agilent, 5067-5582).

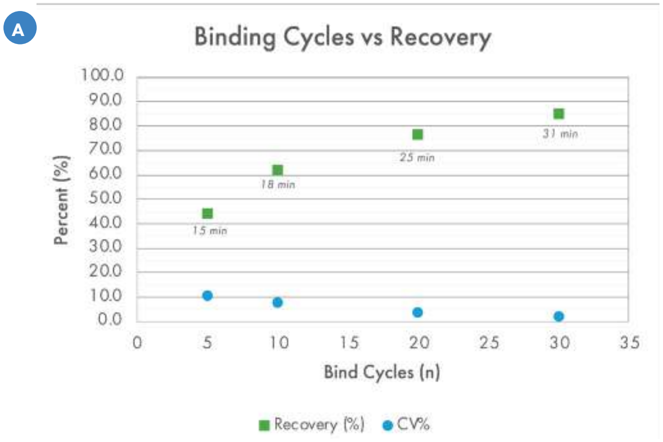
NiXTips were further assessed in targeted NGS library preparation using the Pillar Biosciences oncoReveal Essential MPN Panel (Pillar, HDA-MY-1002-48). Libraries were prepared according to the manufacturer's protocol on a Hamilton STARlet.

Contrived and wild-type samples were prepared at 2 ng/µL (n=2 each). Positive sample set one was generated using Myeloid Mutation DNA Mix (SeraCare, 0710-0408). Positive sample set two was prepared by mixing positive sample one and wild-type DNA at a 1:1 ratio. Wild-type samples contained human genomic DNA (Coriell, NA12878), and negative controls contained molecular-grade water. Prior to STARlet bead cleanup steps, replicate samples were transferred to a Hamilton VANTAGE for NiXTips-based cleanup in parallel with bead-based purification. Following cleanup, NiXTips-processed samples were returned to the STARlet to complete automated library preparation. Final libraries were quantified using the Qubit BR dsDNA assay and assessed by D1000 ScreenTape prior to sequencing on an Illumina NextSeq 2000. Sequence analysis was performed using Pillar's PiVAT platform to compare variant allele frequencies between NiXTips- and bead-purified libraries.

Finally, NiXTips were evaluated as a size-selection and cleanup method during whole-genome sequencing (WGS) library preparation. WGS libraries were prepared with Watchmaker Genomics' DNA with Fragmentation Kit (Watchmaker, 7K0019-096),15 µM Watchmaker FL-UDI adapters (Watchmaker, P1000307), and 100 ng human genomic DNA (Coriell, NA12878) according to the manufacturer's instructions. Enzymatic fragmentation was performed at 30°C for 8 minutes, followed by automated NiXTips- or bead-based cleanup on the Hamilton VANTAGE using a 0.5:1 binding ratio. After library amplification, a second automated cleanup was performed using NiXTips (0.5:1 ratio) or beads (1:1 ratio). Libraries (n = 3 per method) were sequenced on an Illumina NextSeq 2000, and sequencing metrics were analyzed using MultiQC to compare quality between NiXTips- and bead-prepared libraries.

RESULTS

DNA binding to the silica media within the NiXTips increased with the number of aspirate/dispense binding cycles (**Figure 3a**). Recovery improved progressively with additional cycles, reaching a maximum of 85.1% with a coefficient of variation (CV) of 2.0% at 30 cycles. For size selection, a 0.5:1 binding ratio effectively depleted shorter fragments, removing most DNA fragments <300 bp and approximately half of 400 bp fragments, while retaining fragments ≥500 bp (**Figure 3b**).



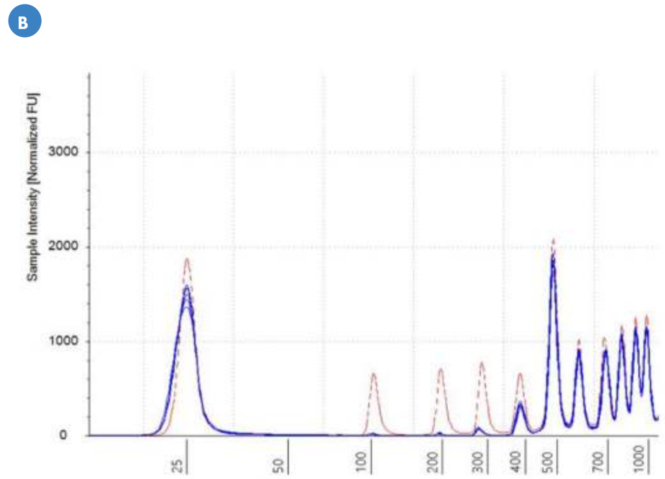
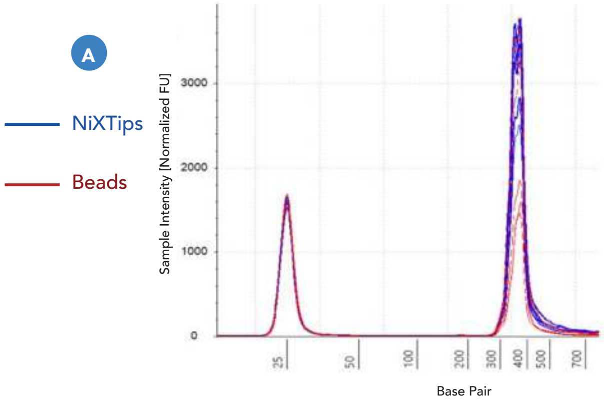


Figure 3. *NiXTips cleanup and size-selection performance characteristics.* **a**) *Recovery is improved and variability is reduced by increasing the number of NiXTips binding cycles.* **b**) *NiXTips size-selection will remove the majority of small fragments (<300 bp) at a 0.5:1 binding ratio which is ideal for WGS library preparation.*

Performance of NiXTips was further evaluated during targeted library preparation using the Pillar Biosciences oncoReveal Essential MPN Panel, which generates six 225 bp amplicons from CALR, JAK2, and MPL genes. Libraries prepared with either NiXTips or magnetic beads showed comparable size distributions (**Figure 4a**). However, NiXTips-based cleanup produced higher overall yields with reduced variability relative to bead-based purification (**Figure 4b**). Both workflows generated the expected variant allele frequencies (VAFs) in positive contrived samples, while no target mutations were detected in wild-type genomic DNA controls (**Figure 4c**).



B

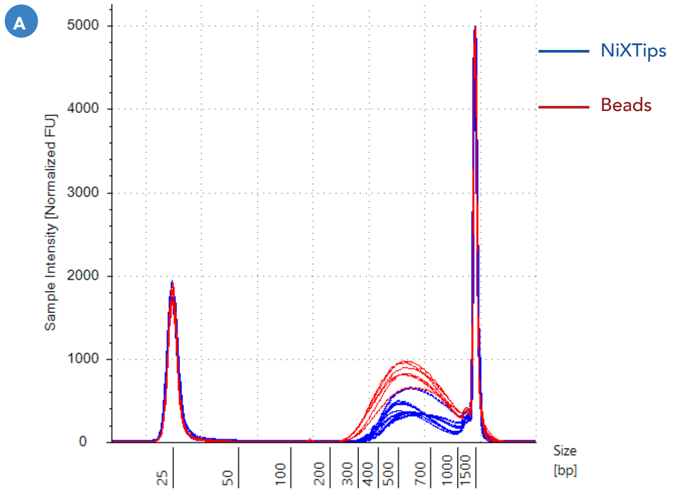
	Library (ng/µL)	CV%	Neg. Control (ng/µL)
Beads	10.73	38.8	0.09
DPX NiXTips	16.85	13.8	0.10

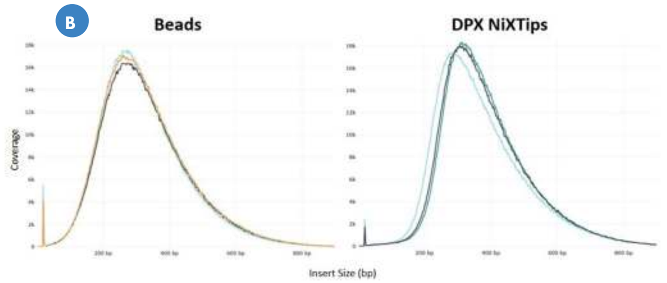
C

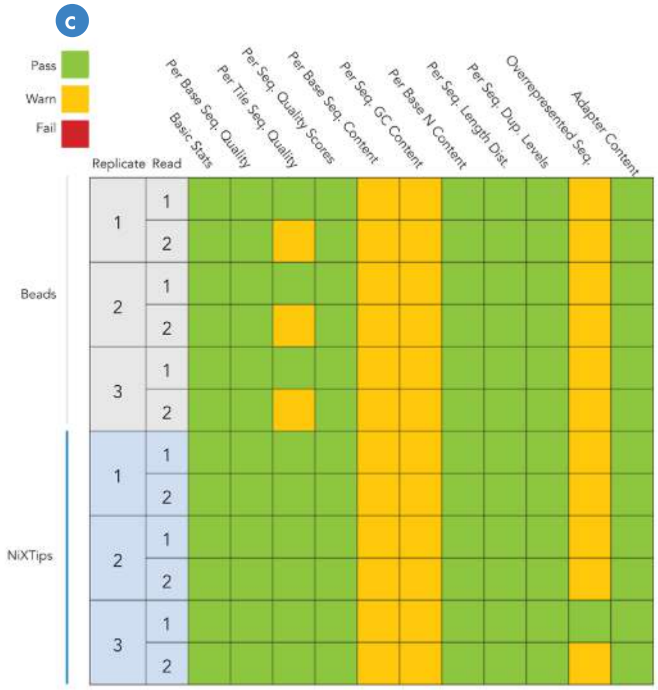
		Variant Allele Frequency (mean %)		
	GENE, mutation	Positive Sample Set 1 (+/+)	Positive Sample Set 2 (+/-)	Wild-Type (-/-)
Beads	JAK2, 1624_1629del	8.36	4.12	n.d.
	JAK2, 1849G>T	6.21	3.17	n.d.
	CLAR, 1099_1150del	5.14	2.77	n.d.
	MPL, 1544G>T	4.92	2.53	n.d.
NiXTips	JAK2, 1624_1629del	8.72	4.29	n.d.
	JAK2, 1849G>T	7.06	3.38	n.d.
	CALR, 1099_1150del	5.67	2.85	n.d.
	MPL, 1544G>T	4.77	2.65	n.d.

Figure 4. *Pillar Biosciences library preparation using NiXTips and magnetic bead cleanup methods.* **a**) *Libraries prepared with both NiXTips and magnetic beads resulted in the expected amplicon sizes.* **b**) *NiXTips delivered higher yields and less variability than magnetic beads.* **c**) *NiXTips and magnetic bead libraries both resulted in the expected variant allele frequencies in positive contrived samples. n.d. = not detected.*

NiXTips were also assessed during whole-genome sequencing (WGS) library preparation using the Watchmaker Genomics DNA with Fragmentation Kit. Fragment analysis showed similar mode library sizes for NiXTips- and bead-prepared libraries (543 bp and 562 bp, respectively; **Figure 5a**). MultiQC analysis indicated comparable sequencing performance between methods, with similar insert size distributions (**Figure 5b**) and equivalent quality metrics including sequence duplication levels, genome coverage, Phred quality scores, per-sequence GC content, and adapter content. No failing quality control metrics were observed for either workflow (**Figure 5c**).







Pass 🟩 Warn 🟨 Fail 🟥

	Replicate	Read	Basic Stats	Per Base Seq. Quality	Per Tile Seq. Quality	Per Seq. Quality Scores	Per Base Seq. Content	Per Seq. GC Content	Per Base N Content	Per Seq. Length Dist.	Per Seq Dup. Levels	Overrepresented Seq.	Adapter Content
Beads	1	1	🟩	🟩	🟩	🟩	🟨	🟨	🟩	🟩	🟩	🟨	🟩
		2	🟩	🟩	🟨	🟩	🟨	🟨	🟩	🟩	🟩	🟨	🟩
	2	1	🟩	🟩	🟩	🟩	🟨	🟨	🟩	🟩	🟩	🟨	🟩
		2	🟩	🟩	🟨	🟩	🟨	🟨	🟩	🟩	🟩	🟨	🟩
	3	1	🟩	🟩	🟩	🟩	🟨	🟨	🟩	🟩	🟩	🟨	🟩
		2	🟩	🟩	🟨	🟩	🟨	🟨	🟩	🟩	🟩	🟨	🟩
NiXTips	1	1	🟩	🟩	🟩	🟩	🟨	🟨	🟩	🟩	🟩	🟨	🟩
		2	🟩	🟩	🟩	🟩	🟨	🟨	🟩	🟩	🟩	🟨	🟩
	2	1	🟩	🟩	🟩	🟩	🟨	🟨	🟩	🟩	🟩	🟨	🟩
		2	🟩	🟩	🟩	🟩	🟨	🟨	🟩	🟩	🟩	🟨	🟩
	3	1	🟩	🟩	🟩	🟩	🟨	🟨	🟩	🟩	🟩	🟩	🟩
		2	🟩	🟩	🟩	🟩	🟨	🟨	🟩	🟩	🟩	🟨	🟩

Figure 5. *Watchmaker DNA WGS library preparation using NiXTips and magnetic bead methods.* **a**) *Libraries prepared with both NiXTips and magnetic beads resulted in mode library sizes of 543 bp and 562 bp, respectively.* **b**) *Insert size distribution from libraries prepared with beads or NiXTips.* **c**) *QC analysis metrics showed that NiXTips performed similarly to beads, demonstrating the suitability of NiXTips for WGS library preparation.*

CONCLUSIONS

DPX NiXTips incorporate immobilized silica media within a pipette tip format, enabling automated nucleic acid cleanup and size selection without the need for magnetic beads or magnets (**Figure 2**). Using a 1:1 binding buffer-to-sample ratio and 30 binding cycles, NiXTips achieved 85.1% DNA recovery with low variability (2.0% CV) using room-temperature elution (**Figure 3a**). This level of recovery and reproducibility supports consistent downstream library preparation. Recovery may be further improved with heated elution, which could benefit applications that require low-input or dilute samples. In addition, fragment size selection was easily adjusted by modifying the binding buffer ratio, allowing selective removal of small fragments commonly excluded from sequencing workflows (**Figure 3b**).

In the Pillar oncoReveal Essential MPN panel workflow, NiXTips-based cleanup generated higher library yields with reduced variability compared to magnetic bead purification (**Figure 4b**), while maintaining equivalent fragment size distributions (**Figure 4a**). Variant allele frequencies were consistent between methods, indicating that NiXTips do not introduce bias during cleanup (**Figure 4c**). No mutations were detected in wild-type samples or negative controls, and no cross-contamination was observed. Together, these results demonstrate that NiXTips provide performance equal to or better than beads for targeted amplicon library preparation.

For whole-genome sequencing, both NiXTips- and bead-based workflows produced libraries within the desired 500–600 bp size range (**Figure 5a**). Compared to beads, a lower NiX binding ratio was used during the post-amplification size selection to remove smaller library fragments (<300bp) and ligated adapters. NiXTip size selection is tunable by altering the binding buffer ratio and is highly reproducible once the optimum ratio is determined for a specific application. Sequencing quality metrics, including insert size distribution, duplication rate, coverage, Phred quality scores, GC content, and adapter content, were comparable between methods, and no failing QC metrics were observed (**Figure 5b–c**). These findings confirm that NiXTips deliver sequencing-ready libraries without compromising data quality.

Beyond analytical performance, NiXTips offer clear workflow advantages over magnetic beads (**Figure 2**). The tip-based format reduces consumable use, requiring only two tips (one transfer tip and one NiXTip) per sample compared to six for bead workflows, which lowers plastic waste and decreases tip consumption by approximately 66%. Fewer deck positions are required when using NiXTips, magnets and transport hardware are not needed, and tips can be stored at room temperature. The workflow also avoids low-clearance pipetting steps associated with bead pellets, simplifying automation setup and reducing method optimization. Collectively, these features streamline liquid handling workflows and improve overall laboratory efficiency.

Overall, NiXTips combine high recovery, reproducible size selection, and sequencing performance comparable to magnetic beads with a simpler and more efficient automated process, making them a practical and scalable solution for both targeted and whole-genome NGS library preparation.