

Sample processing

# Multidrop Combi+ Reagent Dispenser workflow solutions

## A workflow solution to help increase throughput, reproducibility, and speed

### Improving high-throughput workflows

The cost of high-throughput sample processing is an expense that most labs cannot afford. Automated liquid handlers (ALHs) are becoming bigger and better, but with an expensive price tag. Scientists at Thermo Fisher Scientific have recently developed a workflow for automating their samples, incorporating the smaller footprint of a Thermo Scientific™ Multidrop™ Combi+ Reagent Dispenser, instead of an ALH. This workflow is designed to save costs and improve the number of samples processed per week. This workflow can also be applied to multiple workflow applications as a way for labs to implement high-throughput testing at potentially lower costs.

The Applied Biosystems™ GeneTitan™ Multi-Channel (MC) Instrument was developed to improve sample processing and increase automation in the microarray workflow. The GeneTitan instrument combines a hybridization oven, fluidics station, and imaging device in a single instrument with less than 30 minutes of hands-on time. However, the sample preparation and target preparation steps still require a long, intensive process. The current workflow uses ALHs to increase automation and decrease sample prep time. When utilizing the Multidrop Combi+ Reagent Dispenser, throughput can be significantly increased from 768 samples (eight 96-well plates) per week to 2,784 samples (twenty-nine 96-well plates) per week per system, a factor of ~3.6 more.



**Figure 1. The high-throughput Multidrop Combi+ Reagent Dispenser workflow.** In the revised workflow, the Multidrop Combi+ dispenser replaces the aspiration and dispense step. In the mixing step, a pipette is replaced by sealing the microplate, shaking for ~30 seconds, and spinning for ~30 seconds. With the dispensing speed of the Multidrop Combi+ dispenser and the 4 plate positions of the Thermo Scientific™ Digital Microplate Shaker, labs can process 4 plates per reagent faster than it would take using an ALH.

The high-throughput Multidrop Combi+ Reagent Dispenser workflow increases throughput in labs by dedicating one Multidrop Combi+ dispenser to one specific reagent (Figure 1). By assigning each reagent in the protocol to its own Multidrop Combi+ dispenser and cassette, this allows for faster filling of plates. Once plates are filled with a reagent, rather than using a pipette to mix the sample, the plates are sealed with a microplate heat sealer. Next, the sealed plate is shaken for 30 seconds and then spun for an additional 30 seconds. Once this step is completed, the sealing film is removed, and the plate is placed in the next Multidrop Combi+ dispenser with the next reagent and the process is repeated.

After target preparation is completed in 96-well plates using the Multidrop Combi+ Reagent Dispenser workflow, array plates are processed on the GeneTitan instrument (Figure 2).

### Reduce time

To highlight the speed of the high-throughput Multidrop Combi+ Reagent Dispenser workflow, we compared the workflow using several different dispense volumes, with the same workflow using an alternative ALH. The Multidrop Combi+ dispenser time was the total time needed to dispense the appropriate volume for 4 plates, heat seal each plate (2 seconds per plate), and shake and spin plates (30 seconds each). The alternative ALH time was the total time needed to load tips, move tips into position above liquid, aspirate the liquid, move tips into position over microplate,

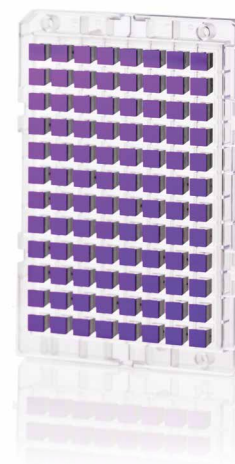


Figure 2. Array plate for GeneTitan instrument.

dispense the liquid, mix 3 times, and unload tips (4 plates total). The high-throughput Multidrop Combi+ Reagent Dispenser workflow timings are significantly less in comparison to the tested ALH (Table 1).

Furthermore, if more than 3 mixes are needed, this would increase the time for the ALH, thus further increasing the difference in the amount of time the ALH requires in comparison to the Multidrop Combi+ Reagent Dispenser workflow. It is also important to note that for higher dispense volumes, i.e., 660  $\mu$ L, most ALHs don't have tips large enough for this volume. Therefore, multiple aspirations and dispenses are required. An additional benefit of using multiple Multidrop Combi+ dispensers is the potential time saved during equipment downtime. ALHs need frequent maintenance and, whether for maintenance or repairs, can be unavailable for use for days at a time. With multiple Multidrop Combi+ dispensers on hand, if one requires maintenance or repair, another may be substituted in its place providing a continuous workflow.

Table 1. Decreased processing time with the high-throughput Multidrop Combi+ Reagent Dispenser workflow.

Dispense volume ( $\mu$ L)	Mix volume ( $\mu$ L)	Multidrop Combi+ dispenser time (seconds)	Alternative ALH (seconds)
20	10	80	129.28
35	10	83.6	131.44
60	15	90	132.8
80	20	95.2	138.4
105	20	102	141.4
130	40	108	147.56
150	50	113.6	151.88
220	100	130.6	169.76
230	100	134	203.6
660	100	242.4	246.12

10x



**Figure 3. Ten Multidrop Combi+ units can be purchased for the price of one ALH.** The units are compact and stackable, which helps to maximize bench space.

### Reduce cost and plastic waste

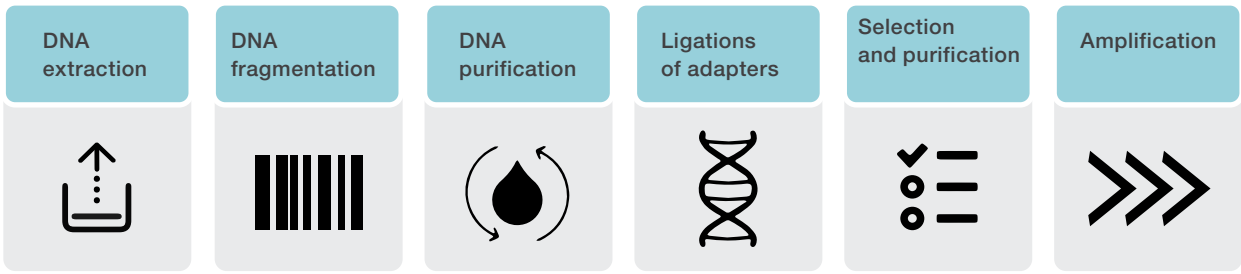
Many laboratories struggle to break into high-throughput genotyping because of the high cost. To make a lab truly high throughput, some type of automation must be implemented. The obvious answer is an ALH; however, the base unit with 2 robotic arms can start at around \$300,000. Any customization and additional tools needed can significantly increase the price. When comparing costs of an ALH to the high-throughput Multidrop Combi+ Reagent Dispenser workflow, 10 Multidrop Combi+ units can be purchased along with an automated microplate sealer, a 4-position digital microplate shaker, and a centrifuge and rotor for less (Figure 3, Table 2). Switching to the high-throughput Multidrop Combi+ Reagent Dispenser workflow can also help labs save on cost and help reduce the number of plastic consumables needed. When using an ALH, new pipette

tips are needed for each reagent and after each mixing step per each plate. If a workflow has 16 different reagents, then this means using 16 tip magazines/racks per plate. With the high-throughput Multidrop Combi+ Reagent Dispenser workflow, Multidrop Combi+ cassettes can be cleaned daily and reused. The cassettes can be used to dispense approximately 28.8 L before needing to be replaced, or 1,500 plates when dispensing a 200 µL volume per plate. When comparing costs of one Multidrop Combi+ cassette to 1,500 racks of tips, the cassette is significantly less expensive. Even if a lab bought 10 cassettes, one for each reagent in a workflow, the cost of the cassettes would be less than the cost of 1,500 racks of tips.

**Table 2. Estimated savings when using the high-throughput Multidrop Combi+ Reagent Dispenser workflow.**

Equipment needed	Cost of ALH workflow*	Cost of the high-throughput Multidrop Combi+ Reagent Dispenser workflow*	
Base ALH unit	\$300,000		
Multidrop Combi+ dispenser		\$23,025	x 10 = \$230,250
Sealer		\$43,127	
Shaker		\$1,160	
Centrifuge		\$14,400	
Microplate rotor		\$7,090	
<b>Equipment total</b>	<b>\$300,000</b>	<b>\$88,802</b>	<b>\$296,027</b>
ALH tips	\$14.1 (per rack) x 1,500 = \$21,150		
Multidrop cassette		\$753	x 10 = \$7,530
<b>Consumables total</b>	<b>\$21,150</b>	<b>\$753</b>	<b>\$7,530</b>

\* Prices based on estimated values.

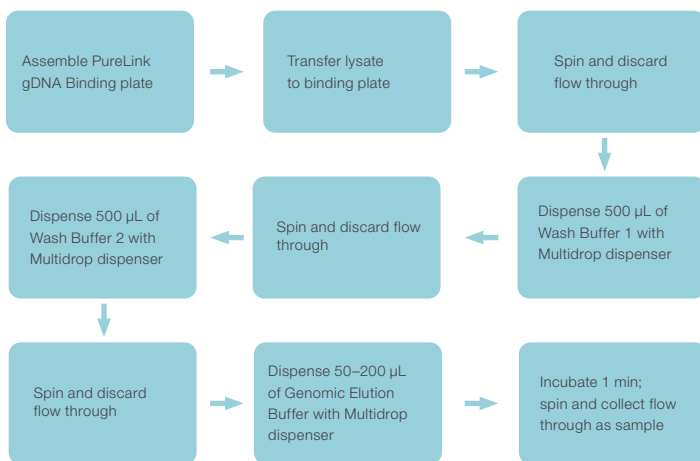


**Figure 4. Next-generation sequencing (NGS) sample prep workflow.** NGS is a multistep and multiday process. This process can be sped up and improved using the high-throughput Multidrop Combi+ Reagent Dispenser workflow.

**Applicable for many workflows**

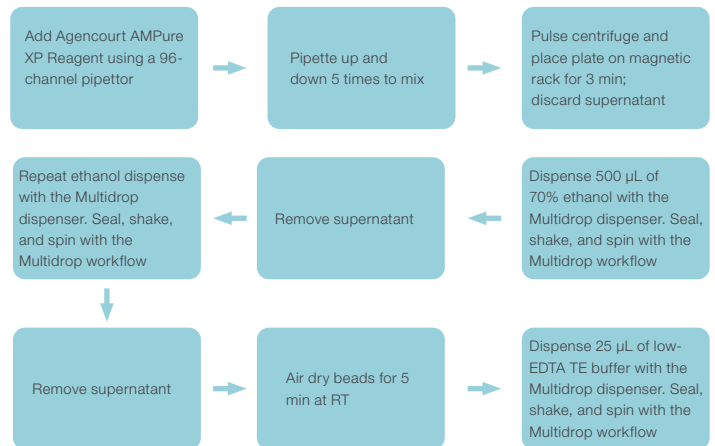
The high-throughput Multidrop Combi+ Reagent Dispenser workflow was originally developed for use with microarray sample prep workflows. However, it can be applied for use with many other laboratory workflows, such as next-generation sequencing (Figure 4). While the Multidrop Combi+ dispenser can't be used for sample transfer, it can be used for any assay that contains reagent-dispensing steps.

After transferring samples to a 96-well plate, the high-throughput Multidrop Combi+ Reagent Dispenser workflow can be used in the NGS workflow during the DNA extraction steps (Figure 5). Products like the Invitrogen™ PureLink™ gDNA Binding Plate use a 96-well SLAS format that fits seamlessly with the Multidrop Combi+ dispenser. After transferring the lysate, the Multidrop Combi+ Dispenser can be incorporated into any reagent dispense steps to make it a faster and higher-throughput solution: 3 Multidrop Combi+ dispensers would be used with this workflow example.



**Figure 5. DNA extraction using the high-throughput Multidrop Combi+ Reagent Dispenser workflow.**

Additionally, the full high-throughput Multidrop Combi+ Reagent Dispenser workflow can be applied in the DNA purification process (Figure 6). After the addition of Agencourt™ AMPure™ beads with a 96-channel pipettor, like the Thermo Scientific™ Versette™ Liquid Handler, the high-throughput Multidrop Combi+ Reagent Dispenser workflow can again be applied. Reagents are dispensed with the Multidrop Combi+ dispenser, and then the mixing step is replaced with a plate seal, shake, and spin. For the DNA purification workflow, 2 Multidrop Combi+ dispensers would be used.



**Figure 6. DNA extraction using the high-throughput Multidrop Combi+ Reagent Dispenser workflow**

**Table 3. Benefits of workflow solution.**

Feature	Benefit
Faster than an ALH or hand pipetting	More samples processed in a week
Less expensive than buying an ALH instrument	Lab costs kept at a minimum
Smaller instrument footprint	Multidrop dispensers can be stacked to save bench space
Cassettes are cleaned daily for reuse	Saves money
Fewer consumables used	Reduces environmental footprint
Reduced downtime due to machine services and maintenance	Keeps project on track and helps meet deadlines
Applicable for many workflows	Enables a variety of uses and flexibility if project changes

### Conclusion

Using the high-throughput Multidrop Combi+ Reagent Dispenser workflow offers many potential benefits compared to high-throughput sample processing (Table 3). By incorporating many Multidrop Combi+ dispensers into a workflow, labs can save time and money while increasing the amount of samples processed. Furthermore, the dispenser's compact size and ability to be stacked helps reduce the footprint, freeing up valuable benchtop space. The ability to substitute another dispenser in the place

of one that may require service provides continuous sample processing without downtime. Although this workflow was originally designed for microarray workflows, it can be used in many applications including NGS.

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### Ordering information

Product	Quantity	Cat. No.
Multidrop Combi+ Reagent Dispenser	1 unit	5840330
Multidrop Combi Smart+ Reagent Dispenser	1 unit	5840340
ALPS5000 Automated Plate Heat Sealer	1 unit	AB-5000
Digital Microplate Shaker	1 unit	88882005
Sorvall X4 Pro-MD Centrifuge	1 unit	75009506
HIGHPlate 6000 Microplate Rotor	1 unit	75003606

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