Discontinuation of the Applied Biosystems™ 7500 Fast Dx Real-Time Polymerase Chain Reaction (PCR) Instrument and Strategic Selection of Future PCR Platforms

Summary Report

OCTOBER 2022

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES®

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EXECUTIVE SUMMARY

The Association of Public Health Laboratories (APHL) is a non-profit, membership organization working to strengthen laboratory systems serving the public's health in the United States and globally. APHL represents the laboratories that work to protect the health and safety of the public by acting as a liaison between the member laboratories and federal and international agencies. Along with the US Centers for Disease Control and Prevention (CDC), APHL works collaboratively to support state and local public health laboratories to respond to biological, chemical, radiological threats, infectious diseases, and other public health emergencies. APHL and CDC are responsible for the strategic selection of instrumentation, evaluation of platforms, and technology transfer to these laboratories.

Polymerase Chain Reaction (PCR) has been the "gold standard" for detection of biological threats in the Laboratory Response Network for Biological Threats Preparedness (LRN-B), Influenza Virus Testing Programs, and the Department of Homeland Security BioWatch Program. These programs standardize instrumentation to ease training burden, reduce costs, increase redundancy for surge testing, improve regulatory compliance, and satisfy quality assurance needs.

The Applied Biosystems™ (ABI) 7500 Fast Dx Real-Time PCR instrument is currently, and has been for a number of years, used in the LRN-B, influenza and BioWatch testing. This PCR instrument is one of the few instruments approved for testing across all three programs and represents the highest percentage of PCR instruments in state and local public health laboratories. In February 2022, Thermo Fisher Scientific announced the discontinuation of the ABI 7500 Fast Dx Real-Time instrument. This announcement has significant impacts on the ability of state and local public health laboratories to rapidly detect threats.

In March 2022, APHL and CDC co-facilitated two conference calls with 14 LRN-B Advanced Reference Laboratories. Participants included Laboratory Directors, LRN-B staff, influenza staff and coronavirus disease (COVID-19) testing leads. LRN-B Advanced Reference Laboratories support the LRN-B program with assay development, evaluation of new technologies, proficiency testing remediation and high throughput surge capacity. The purpose of the calls was to gather information on:

1. Current and alternative PCR platforms to replace the ABI 7500 Fast Dx;
2. Future platform priority specifications (e.g., size, cost, throughput capabilities);
3. Instrument evaluation studies laboratories have performed on alternative platforms.

Key Findings and Conclusions

- The platform(s) should be standardized across all programs (i.e., LRN-B, influenza, BioWatch).
- Multiple platforms, from different manufacturers, should be selected to create diversity and prevent reliance on one vendor.
- Platforms need to offer flexibility in throughput capacity, should be open platforms, and be US Food and Drug Administration 510(k) cleared.
- Instrument size is important to accommodate variations in laboratory spaces as well as the need for initial testing of high risk pathogens in Biosafety Level 3 (BSL-3) suites.
- Purchase and maintenance costs are key factors, particularly because laboratories will be replacing multiple instruments.

INTRODUCTION

Association of Public Health Laboratories

The Association of Public Health Laboratories (APHL) is a non-profit, membership organization working to strengthen laboratory systems serving the public's health in the United States and globally. APHL represents the laboratories that work to protect the health and safety of the public by acting as a liaison between the member laboratories and federal and international agencies. Membership consists of local, state, country, and territorial public health laboratories; environmental, agricultural, and veterinary laboratories; and corporations and individuals interested in public health laboratory science. One aspect of assisting public health laboratories with their work is collaborating with partners to provide guidance on laboratory procedures, testing, and instrumentation.

Laboratory Response Network for Biological Threats Preparedness (LRN-B)

The Laboratory Response Network (LRN) was established in 1999 by APHL, CDC, and the Federal Bureau of Investigation (FBI). At its inception the primary objective was to create a system for responding to biological threats. Today the LRN has expanded to form a network of state and local public health, federal, military, and international laboratories capable of responding to biological, chemical, radiological, and other public health threats, such as emerging infectious diseases. By linking state and local public health laboratories and clinical laboratories to other key LRN stakeholders, including first responders, clinical laboratories, and international partners, the LRN provides an expert and efficient response to a variety of public health threats. The ABI 7500 Fast Dx instrument is approved for use in LRN-B screening and confirmatory assays.

Influenza Testing Program

State and local public health laboratories provide testing for diagnosis, routine surveillance, and novel virus detection. Their testing informs local, national, and international influenza surveillance systems by providing data used for vaccine virus selection. Through testing, public health laboratories are also able to provide information on circulating viruses, including location, and potential mutations the virus may undergo. The collected data from testing and surveillance is submitted to CDC and National Influenza Surveillance Reference Centers. The ABI 7500 Fast Dx instrument has been approved by CDC for influenza testing in state and local public health laboratories.

BioWatch Program

The Department of Homeland Security (DHS) BioWatch Program was established in 2003 by DHS to provide early warnings of biological threat attacks in more than 30 major metropolitan areas across the country. The program operates a network of air-monitoring collectors at multiple locations within a jurisdiction. BioWatch laboratories a co-located within, state and local public health laboratories who process and analyze filter samples to determine the presence of select biological agents. If the laboratory determines the presence of a biological agent on a filter, federal and jurisdictional notifications are activated. BioWatch laboratories perform LRN-B confirmatory assays utilizing the ABI 7500 Fast Dx instrument.

Polymerase Chain Reaction (PCR) Technology

Polymerase Chain Reaction (PCR) has been the "gold standard" for detection of biological threats in the Laboratory Response Network for Biological Threats Preparedness (LRN-B), Influenza Testing Programs, and the Department of Homeland Security BioWatch Program. These programs standardize instrumentation to ease training burden, reduce costs, increase redundancy for surge testing, improve regulatory compliance, and satisfy quality assurance needs. In February 2022, Thermo Fisher Scientific announced the discontinuation of the ABI 7500 Fast Dx Real-Time PCR instrument. New production of the instrument will cease in May 2022, sale of existing stock will end in December 2022, and technical support would be phased out by 2027. This announcement has significant bearing on many public health programs that have utilized the instrument for over 10 years. As previously mentioned, programs such as the LRN-B, Influenza Testing, and BioWatch, all use the ABI 7500 Fast Dx on a daily basis for testing. Further, because these programs utilize the same instrument, they provide redundancy in the event or a surge event. This PCR instrument is

one of the few instruments approved for testing across all three programs and represents the highest percentage of PCR instruments in state and local public health laboratories.

Analysis of Alternative PCR Platforms

In collaboration with CDC, APHL facilitated a conference call in March 2022 to address rising concerns about the discontinuation of the ABI 7500 Fast Dx and gather more information on potential replacement PCR platforms. Participants included CDC, APHL, Public Health Laboratory Directors, LRN-B staff, influenza staff, and COVID-19 testing leads. The purpose of the calls was to gather information on:

1. Current and alternative PCR platforms to replace the ABI 7500 Fast Dx;
2. Future platform priority specifications (e.g., size, cost, throughput capabilities);
3. Instrument evaluation studies laboratories have performed on alternative platforms.

As the strategic selection of future PCR platforms continues, CDC wants to ensure public health laboratory input is captured and their needs are addressed. This meeting and others that will be taking place in the coming months is to gather enough information to make an informed decision on one or more platforms to support all public health programs utilizing real-time PCR technology.

ALTERNATIVE PLATFORMS

Each conference call included a session discussing real-time PCR platforms that laboratories either (1) currently utilize for testing or (2) are aware of their existence on the market. These instruments did not need to be specifically used for LRN-B, influenza, or BioWatch testing.

Real-Time PCR testing is a fast and inexpensive method to detect DNA in a variety of sample types. As such, the technology and capabilities have expanded greatly since inception. The conference call discussion categorized PCR technology in three types noted in Table 1. Small and efficient instruments usually have the lowest throughput, fastest turnaround time, and can be used for routine testing. Standard instruments have higher throughput capabilities,

Figure 1. Model and Number of Real-Time PCR Instruments Utilized in State and Local Public Health Laboratories

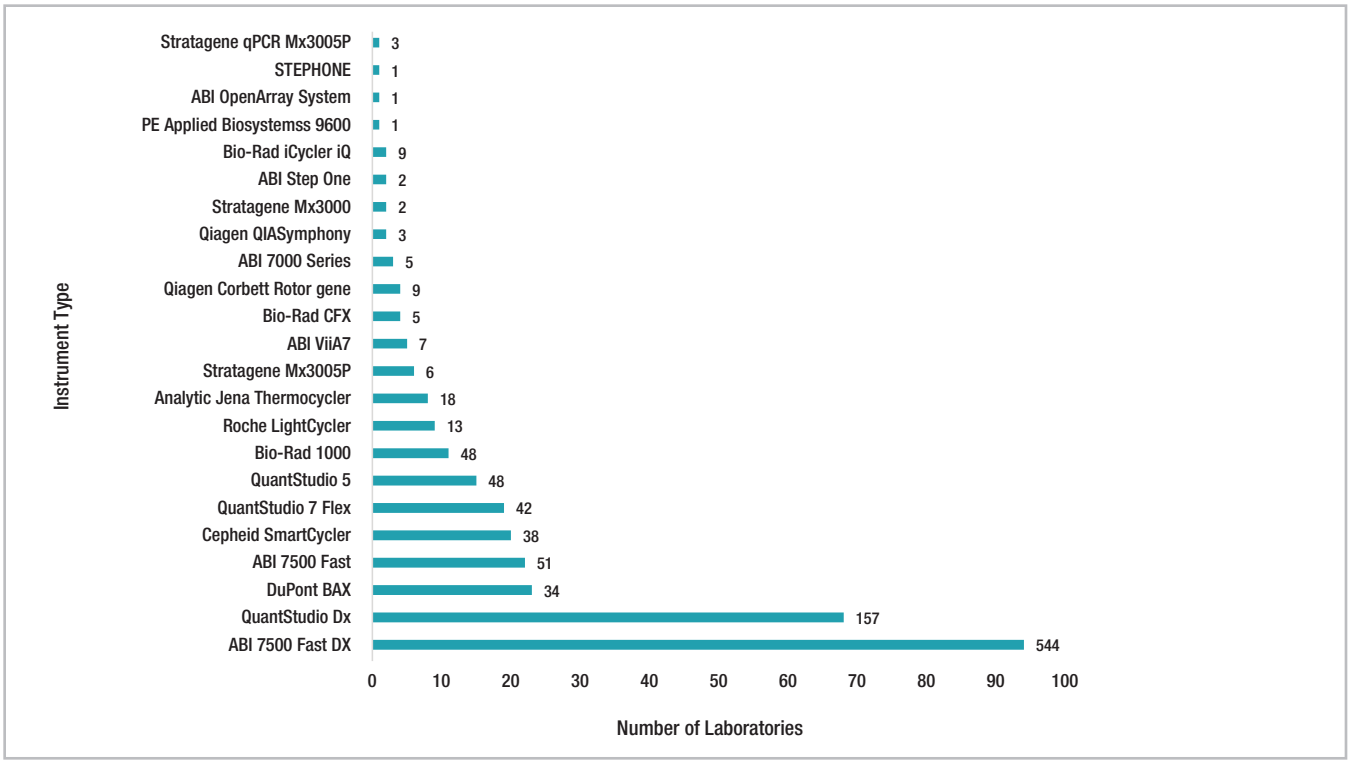

Table 1. Alternative Real-Time Polymerase Chain Reaction (PCR) Instruments.*

Type	Manufacturer	Instrument
Small/Efficient Instruments may have the lowest throughput, faster turnaround time, and be used for routine testing.	Luminex	Aries
	BioFire	FilmArray
		Torch
	BD	BD Max
	GenMark	E-Plex
	DiaSorin	Liaison MDX
	Cepheid	GeneXpert
Standard Instruments have standard throughput capabilities, turnaround time, can be used for routine and surge testing.	Thermo Fisher Scientific	Applied Biosystems 7500
		Applied Biosystems 7500 Fast
		QuantStudio 3
		QuantStudio Dx
		QuantStudio 5
		QuantStudio 5 Dx
		QuantStudio 6 Pro
		QuantStudio 7 Pro (Dx)
		QuantStudio 12K
	Roche	LightCycler 480
		LightCycler 1536
	Bio-Rad	CFX 96
		CFX 384
		CFX Opus
	Qiagen	Rotor-Gene
		QIAQuant
	Analytic Jena	Q Towers
Highly Automated Instruments with the highest throughput, automation and most practical for surge testing.	Hologic	Panther
		Panther Fusion
	Qiagen	NeumoDx
	Roche	Cobas 5800
		Cobas 6800
		Cobas 8800
	Abbott	Alinity M
	Cepheid	Infinity

*The list is not all-inclusive. Certain instruments may no longer be in production and being replaced with alternatives by the manufacturer.

average turnaround times, and because of their throughput, can be used either for routine or surge testing. Highly automated instruments tend to have the highest throughput, have built-in automation, and are generally considered most practical for surge situations. Attendees were asked to comment on real-time PCR instruments their laboratories utilize, experience with the instruments, experience with the manufacturers, and any other pertinent information. The instruments and manufacturers discussed are displayed in the **Table 1** (on page 6).

APHL has collected data on overall PCR instrument usage across its member public health laboratories. A previously conducted survey of 100 public health laboratories asked which make and model instruments laboratories used overall to perform testing. The number of laboratories utilizing each instrument as well as the total quantity of each instrument in all laboratories (i.e., the total number of instruments is indicated by a number at the end of each bar) are listed in **Figure 1**. However, the list developed does not include all instruments or manufacturers, and instead is a snapshot of PCR instruments used in state and local public health laboratories.

Manufacturers and Instruments

Not all instruments in **Table 1** were discussed in detail. The following is specific feedback on manufacturers and instruments provided by attendees.

Becton, Dickinson, and Company (BD)

One of the benefits of the BD Max is its capability to integrate with Laboratory Information Management Systems (LIMS). BD has also been noted as a manufacturer that is open to working with public health laboratories on laboratory developed tests (LDTs) and making their cartridges compatible. In testing, the sensitivity of the instrument has been found comparable to the ABI 7500 Fast Dx. Alternatively, the BD Max is more costly than a manual PCR-based assay and has a rather large footprint.

Bio-Rad

Bio-Rad's CFX Touch 96-well and 384-well systems are well-liked among those who use them. However, they are soon to be discontinued and replaced with the CFX Opus which provides similar performance standards as its predecessors. The Opus also has a Dx option which may be more appealing to laboratories.

Hologic

The company's Panther Fusion is an open access system that allows for multiple targets to be tested in one reaction. The Panther line of instruments have also been utilized in testing for SARS-CoV-2 during the pandemic. Despite its benefits, the colossal size of the instrument remains its greatest challenge. The Fusion can also do LDTs and rapidly deployed manufactured assays with specific primes/probes paired with Hologic enzymes. Furthermore, its ability to streamline nucleic acid extraction with PCR amplification and detection makes it promising.

Qiagen

Qiagen's NeumoDx instrument is favored by several laboratories for its assays and LIMS integration. Like the Panther Fusion, it is also capable of streamlining nucleic acid extraction with PCR amplification and detection.

Roche

The Cobas 6800 has open development channel for LDTs. The instrument is an exceptionally large system, and its size may be an issue for some laboratories. Furthermore, the service contract cost is great enough to cause difficulties in maintain service on more than one instrument.

Thermo Fisher

The QuantStudio line appears to meet many of the needs of the laboratories, but members have expressed that the multiple versions cause confusion, makes it more difficult to align with various Food and Drug Administration (FDA) package inserts. This line includes instrument with In Vitro Diagnostic (IVC) clearance and some with smaller footprints and networking capabilities. Of this line, the most prominent in laboratories is the QuantStudio Dx. This model looks to be an adequate transition instrument but presents several challenges that make it less favorable to the laboratories. Members have difficulty with the instrument software and consider it not user-friendly, leading to some complications transitioning certain assays to the QuantStudio Dx. The size of the instrument also presents an issue as it is considered

too large, and the location of the tray on the side as opposed to the front, makes it more difficult to work with unless robotics is integrated. The cost of the service contracts also presents issues, particularly for smaller public health laboratories where funding is more limited.

PRIORITIES FOR THE NEXT PLATFORM(S)

Subsequent to discussing alternative platforms, attendees were asked to provide feedback on laboratories' needs and priorities for the next platform(s). Below is a summary, including comments and recommendations from members on considerations for moving forward. Primary factors of concern for the laboratories included instrument size, technical specifications/capabilities, device and maintenance costs, customer service, and instrument/consumable production capacity during surge events (e.g., COVID-19). It was noted to consider selecting multiple platforms to be used depending on the situation (e.g., routine versus surge).

Instrument Size and Facility Requirements

Alternate platforms must be of a size all laboratories can comfortably accommodate, particularly if any facility requires more than one instrument. Depending on testing requirements there may be significantly more space in a BSL-2 environment versus testing that is required to be conducted in smaller, BSL-3 spaces. At least one chosen instrument should be small enough to be used in BSL-3 spaces. At the same time, instruments must have large enough capacity to accommodate appropriate testing.

Other considerations include infrastructure requirements such as the need for a floor drain or high-quality water. Finally, the electricity usage of the instrument will matter as the laboratories will need appropriate uninterruptible power supplies in the event of power outages.

Technical Specifications

Real-time PCR instruments vary greatly in their technical specifications. While there may be no one ideal instrument that can accommodate every factor, some technical specifications should be considered higher priorities as specified by the laboratories. There are several technical specifications laboratories seek to be included in the next platform(s) to better serve their work. Some are features currently in the ABI 7500 Fast Dx, while others are additional requirements requested by laboratories. Ideally the platform selected should have (in no particular order):

- At least as many fluorophore channels as the ABI 7500 Fast Dx, ideally supporting the same wavelengths.
- Capability to switch between singleplex and multiplex capabilities.
- User-friendly software support and data export functions.
- Block flexibility to analyze single or multiple samples to increase throughput depending on the situation.
- Laboratory Information Management System (LIMS) software integration.
- Potential for automation. If multiple platforms are selected, at least one platform should have some automation to increase efficiency.
- An open platform although this is not necessarily a requirement for all laboratories.
- Capability to link multiple instrument (i.e., daisy chain to increase throughput efficiency).
- US Food and Drug Administration 510(k) clearance.

Manufacturing

Manufacturing capabilities and availability of proprietary consumables is a concern for the laboratories. This was especially relevant during COVID-19 response when there was a consumable shortage. It should also be considered that if programs all switch to a new platform at once, manufacturers should be able to accommodate a significant increase in platform production. A solution to this issue would be to select more than one platform from different manufacturers so laboratories will not be competing for instruments and consumables in surge situations. The need for a mature supply chain can be addressed by (1) utilizing more than one manufacturer, (2) ensuring the existence of a national stockpile for resources, and (3) working closely with manufacturers to safeguard their ability to upscale production. In addition, the communication ability and responsiveness of the manufacturer is important.

Cost

Manufacturing and cost will also play key role in laboratories' selecting platforms. Budgets vary across public health laboratories and a transition to a completely new instrument will take a significant amount of planning. As cost is a major factor for laboratories to consider, it would be important for a vendor to support public health pricing not just for the purchase of the instrument and its consumables, but also for the service contracts. Many laboratories will be looking to purchase more than one instrument, making the price of the instrument and its service contract a significant priority. Highly automated systems have significantly higher service contract costs and make the addition of more than one instrument to a laboratory is expensive. In addition, highly automated instrument use significantly more consumables, increasing cost and supply needs during surge events.

INSTRUMENT EVALUATION STUDY STRATEGIES

The final discussion focused on instrument evaluation studies currently underway at laboratories. The purpose of the discussed was to gain insight on usefulness of current instruments being used by laboratories. Few laboratories have performed validation studies and have data on new PCR platforms, so information was limited. The New York State Department of Health - Wadsworth Center has performed a side-by-side comparison study of the QuantStudio 6 and the ABI 7500 Fast Dx, which included both LRN-B assays and LDTs. They have also performed isolated evaluation studies for instruments such as the Panther Fusion, NeumoDx, and GeneXpert for diseases such as influenza and COVID-19. The Arizona Department of Health Services have conducted their own evaluations, but such studies are limited to a few instruments and assays.

Evaluation studies will be extremely important prior to selecting the next platform. Before laboratories can invest in a new instrument for testing, its functionality and repeatability must be tested in Multicenter Evaluation Studies (MCEs) to confirm that it will produce the same results under the same conditions, regardless of where the test is performed. While several evaluation studies on various instruments and assays have been completed thus far, there is currently not enough data to properly identify alternate platforms. Additionally, there are limitations to what can be performed based on software availability for some assays and instruments.

RECOMMENDATIONS AND CONCLUSIONS

The discussions regarding the next potential PCR platform are ongoing and should continue until enough data is available to make an informed decision. Collaboration and dialogue with other impacted groups such as BioWatch and Influenza Testing are important as they can offer insights not previously considered. While each group may have different priorities for the next platform(s), any that are stated by more than one group should be given significant attention. While many key factors should be considered, the following are highlights:

- The platform(s) should be standardized across all programs (i.e., LRN-B, influenza, BioWatch).
- Multiple platforms, from different manufacturers, should be selected to create diversity and prevent reliance on one vendor.
- Platforms need to offer flexibility in throughput capacity, should be open platforms, and be US Food and Drug Administration 510(k) cleared.
- Instrument size is important to accommodate the varying size of laboratory testing space, including testing Biological Safety Level 3 (BSL-3) facilities.
- Purchase and maintenance costs are key factors, particularly because laboratories will be replacing multiple instruments.

Communication between the laboratories and CDC will be instrumental in this effort, as understanding the challenges faced when performing the evaluations is extremely helpful in bringing together resources and data for a more well-informed decision. It would also benefit the effort for CDC and laboratories to work with the manufacturers to evaluate the instruments, thereby eliminating the burden of finding laboratories that already have the instrument or having to procure the instrument for evaluation studies. Guidance and insights on potential evaluation strategies from the APHL

Laboratory Systems and Standards Committee may also help the various groups who currently use the ABI 7500 Fast Dx and must address its sunset. It would benefit the decision-making process to develop a list of candidate PCR platforms that can then be further evaluated for their suitability. CDC and APHL should consider utilizing the LRN Operational Workgroup to further narrow down the available platforms. Once a shortlist of instruments is made available, MCEs can be conducted in a coordinated effort among programs.

Time is of the essence as the search for new platform(s) continues. Although technical support for the ABI 7500 Fast Dx is confirmed for five years and may extend to seven years, the transition to new instruments will be a significant overhaul that needs to happen quickly. Both manufacturers and laboratories will need time to plan for budgets, production, training, and validation. The process of choosing, validating, and implementing new instruments and technology is one that may take years to finalize.

Association of Public Health Laboratories

The Association of Public Health Laboratories (APHL) works to strengthen laboratory systems serving the public's health in the US and globally. APHL's member laboratories protect the public's health by monitoring and detecting infectious and foodborne diseases, environmental contaminants, terrorist agents, genetic disorders in newborns and other diverse health threats.

This project was 100% funded with federal funds from a federal program of $2,189,261. This publication was supported by Cooperative Agreement #NU60OE000104 from the US Centers for Disease Control and Prevention (CDC). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC.

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