Director, Operational Test and Evaluation

Next Generation Diagnostic System (NGDS)

Operational Test and Evaluation Report

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Director

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Next Generation Diagnostic System Operational Test and Evaluation Report

Executive Summary

This report provides the Director, Operational Test and Evaluation (DOT&E) evaluation of the Next Generation Diagnostic System (NGDS) in support of a Full-Rate Production decision. This is an update to the June 2017 Early Fielding Report in which DOT&E assessed the NGDS to be operationally effective and suitable in providing land-based deployable medical units with timely clinical sample analysis to support the diagnosis and treatment of symptomatic patients.[1]

Based on testing conducted since June 2017, the NGDS is also operationally effective for use aboard Navy ships and for the analysis of environmental samples to confirm the presence of biological warfare agents (BWAs). Analytical laboratories equipped with the NGDS are able to prepare and analyze environmental samples to provide timely and accurate information to support commanders' situational awareness and make force protection decisions. The NGDS meets the user requirement for sensitivity in aerosol samples and most of the other sample types used in testing.[2] The system demonstrated a false identification rate of 1 percent in operationally realistic samples. NGDS provides a measurable improvement in capability over the Joint Biological Agent Diagnostic System (JBAIDS) that it replaces.

The NGDS is operationally suitable. The system exceeds user reliability and availability requirements. The NGDS is easy to use, requires less operator hands-on time, and has a smaller logistics footprint than the system it replaces.

The NGDS is survivable against cyber threats. The Services do not plan to connect NGDS to computer networks at this time. Testing identified cyber vulnerabilities that can be exploited to make the system unstable or change the analytical results. Operators are able to detect system anomalies and follow procedures to restore operational capability.

The Program Office should:

- Complete Sentinel Panel shelf-life testing and provide periodic updates to the Services that accept the Sentinel Panel for use in the interim.
- Make the required changes to NGDS to prevent reliability failures associated with vibration during wheeled-vehicle transport and verify resolution of the failure modes.
- Address identified cyber vulnerabilities and verify that they have been resolved.

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1 Next Generation Diagnostic System Early Fielding Report, Director Operational Test and Evaluation, June 2017.

2 The Services use filter systems to collect aerosol samples. The sample is extracted using a liquid buffer solution. The buffer solution containing aerosol particles is sent to environmental laboratories for analysis.

System Overview

Army, Navy, and Air Force units equipped with the NGDS analyze clinical and environmental samples to identify the presence of BWAs and infectious diseases to aid in medical diagnosis and provide situational awareness to support force protection decisions. The Services intend for NGDS to replace the currently fielded JBAIDS, which is becoming obsolete.

Mission Description and Concept of Employment

The Army, Navy, and Air Force plan to employ the NGDS Increment 1 at facilities with existing microbiology laboratories equipped with a Class II Biosafety Cabinet, refrigerator, line power sources, lighting, and appropriately trained personnel. Clinical laboratories will receive blood or sputum samples from symptomatic patients for analysis. Environmental laboratories will receive samples (air, soil, vegetative, surface, food, liquid, and/or aerosol) collected by units conducting chemical and biological defense monitoring, survey, or site assessment missions. Upon receipt of the sample at the laboratory, a trained technician documents the receipt and prepares and analyzes the sample using the NGDS. The technician documents the results and provides them to the laboratory officer for review and transmission to the requesting unit or medical provider for use in supporting medical treatment, force health protection, and operational decisions. The remaining sample may be sent to another laboratory for more definitive analysis.

System Description

The NGDS is a U.S. Food and Drug Administration (FDA) cleared commercial off-the-shelf (COTS) diagnostic device manufactured by BioFire Defense, LLC. Figure 1 depicts the system components. The NGDS laptop and FilmArray® analyzer are connected via Ethernet; the barcode scanner and a printer (not included in the system) can be connected via USB. Operators use the FilmArray® software to control the analyzer function and store data. FilmArray® software on a single laptop is capable of controlling up to eight FilmArray® analyzers for analysis of multiple samples at once. Two consumable panels are available for use with the NGDS. Medical laboratory technicians use the Warrior Panel to identify the presence of BWA in clinical samples. Four additional commercial clinical panels are available for the analysis of clinical samples for use in diagnosing common diseases. Technicians at environmental laboratories utilize the Sentinel Panel to identify the presence of BWA in environmental samples such as air, soil, liquid, surface swaps, insects, and animal blood. Appendix A contains tables which list the clinical diagnostic capability of the Warrior Panel and the BWAs and associated samples types that can be identified using the Sentinel Panel.

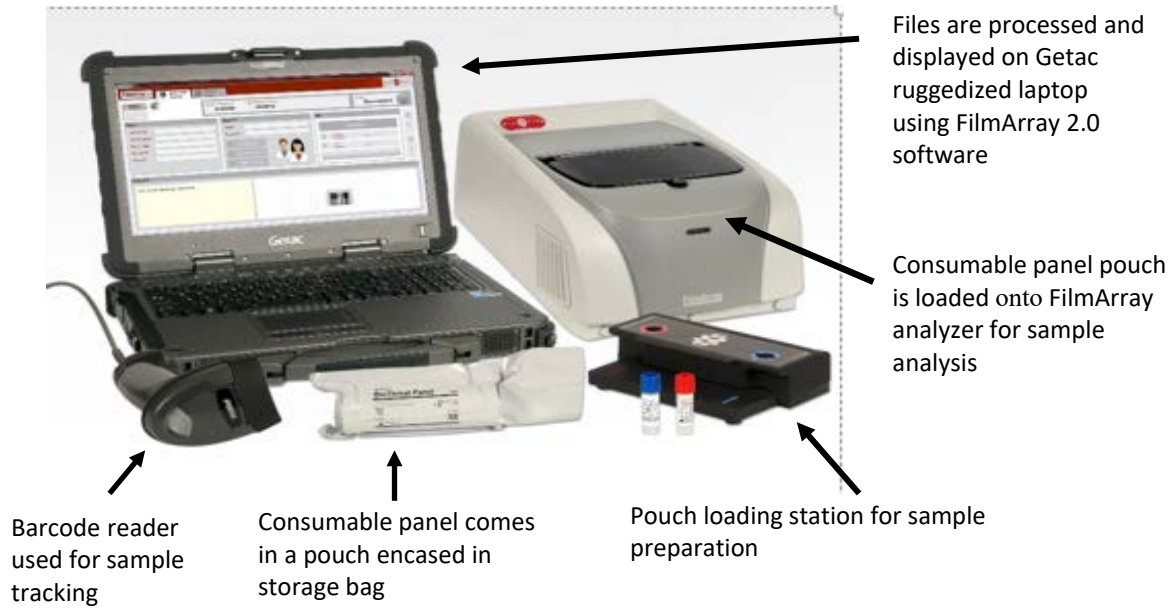

Figure 1. NGDS includes FilmArray® 2.0 Polymerase Chain Reaction analyzer, barcode scanner, ruggedized Getac laptop, sample preparation equipment and consumables, and consumable panels

Test Adequacy and Limitations

The NGDS test program was adequate to assess operational effectiveness, operational suitability, and survivability for both clinical and environmental sample analysis. Testing was conducted in accordance with the DOT&E-approved test plans. DOT&E approved modifications to the Initial Operational Test and Evaluation (IOT&E) plan due the need for ships and personnel to deploy in response to hurricane activity in September 2017.

DOT&E is unable to adequately assess Sentinel Panel shelf-life. One of the three lots of Sentinel Panels used in testing demonstrated the required 12-month shelf-life. The Program Manager halted Sentinel Panel shelf-life testing after the other two production lots failed to meet shelf-life requirements. BioFire Defense determined that a print head used in manufacturing the panel became misaligned during production. BioFire has corrected the problem and instituted additional quality control steps to prevent occurrence in the future. The Program Manager completed verification and authorized Sentinel Panel shelf-life testing to begin again in late April 2018. The Navy requires panels to have a 12-month shelf-life for use in shipboard laboratories to support deployment schedules. This will result in a delay in fielding NGDS to shipboard laboratories.

The Navy Commander, Operational Test and Evaluation Force (COTF) conducted the IOT&E pier-side in Norfolk, Virginia, aboard the USNS *Comfort* hospital ship, the USS *Gerald R. Ford*, and at the Navy Environmental and Preventive Medicine Unit. A senior Navy medical officer directed the prioritization of samples for analysis when multiple samples were received at the same time. A naval laboratory technician prepared the samples, conducted analysis using the NGDS, and reported the results to the senior medical officer. The senior medical officer made

decisions on medical treatment and recommended force health protection measures to a command officer.

The Army Medical Research Institute of Infectious Disease and Battelle Memorial Institute conducted combined developmental/operational live agent laboratory testing to determine the performance of the NGDS Sentinel Panel against the required BWAs in operationally realistic environmental sample types to determine the system's limits of identification and sensitivity. Table 1 lists the test events that form the basis for this evaluation of NGDS to support analysis of environmental samples and shipboard clinical and environmental sample analysis.

Table 1. Test Events Supporting Evaluation

Test Phase	Dates	Location	Samples Analyzed
Dedicated OT&E			
OA	May 17 – 25, 2016	Camp Bullis, TX	506
IOT	August 21 – September 9, 2017	USNS *Comfort* - Norfolk, VA USS *Gerald R. Ford* – Norfolk, VA Navy Environmental and Preventive Medicine Unit – Norfolk, VA	80
Combined Developments/Operational Testing			
DT/OT Live Agent Testing – Sentinel Panel	April 2017 – February 2018	Battelle Eastern Science and Technology Center, Aberdeen, MD U.S. Army Medical Research Institute of Infectious Disease, Frederick, MD	3,673
Cybersecurity Testing			
Cooperative Vulnerability Penetration Assessment	July 11 – 13, 2017*	Fort Sam Houston, San Antonio, TX	
Adversarial Assessment	July 31 – August 4 2017	Fort Sam Houston, San Antonio, TX	

OA – Operational Assessment; IOT – Initial Operational Test; DT/OT – Developmental Test/Operational Test

* Initial cybersecurity operational testing was conducted on a Microsoft Windows-based NGDS laptop. Subsequent to this testing, BioFire Defense LLC upgraded the system to run on a Windows 10 laptop. Cybersecurity testing in July and August 2017 was conducted using an NGDS operating in a Windows 10 environment.

Operational Effectiveness

The NGDS is operationally effective for the analysis of environmental samples to confirm the presence of BWAs. Forward deployed environmental laboratories on land and aboard naval vessel are able to employ the NGDS to analyze environmental samples to provide timely and accurate information to improve situational awareness and support force protection decisions. The DOT&E June 2017 Early Fielding Report found the NGDS to be operationally effective in providing land-based deployable medical units with timely clinical sample analysis to aid in the diagnosis of anthrax, plague, tularemia, Q fever, and the hemorrhagic fevers caused

by Ebola and Marburg viruses, in response to a suspected or confirmed bioterrorism event or outbreaks.

During IOT&E, Navy laboratories were able to employ the NGDS to provide timely and accurate information to officers to support force protection decisions in each of the five scenarios. The laboratories received 82 clinical or environmental samples, some of which were spiked with the DNA of BWAs. Laboratory technicians used the NGDS with Warrior and Sentinel Panels to correctly identify 81 out of 82 aerosol collection buffer, soil, swabs, fleas, sputum, and blood samples with and without BWAs. The single false negative result was a soil sample containing smallpox DNA. The false negative result did not affect mission success because the laboratory had received multiple samples that were positive for smallpox in addition to the sample which was incorrectly identified as negative.

The NGDS with the Sentinel Panel met the user requirement for sensitivity in aerosol samples extracted from a filter into an aerosol buffer solution.[3] The NGDS was able to identify concentrations of agent at or below the infectious dose level. For most other sample types, the NGDS met the user requirement for sensitivity but was less sensitive than in aerosol collection buffer, depending on the agent and sample type. For some agents in some sample types (i.e. soil and sand), the NGDS did not meet the user requirement with statistical confidence. Appendix B provides the NGDS Sentinel Panel sensitivity data by agent and sample type in comparison to the user requirement.

The NGDS Sentinel panel exceeds the 90 percent requirement for specificity, the ability to correctly determine that an agent is not present. Appendix C identifies test results for specificity by agent.

Table 2 compares the NGDS performance demonstrated during testing to the operational requirements.

Table 2. Comparison of NGDS Performance to Operational Requirements

Performance Attribute	Requirement	Demonstrated Performance
Sensitivity	85% probability of identification of: 1,000 cfu/ml for bacteria 10,000 pfu/ml for viruses	See Appendix B
Specificity – Sentinel Panel	90%	99-100%[A]
System Set-up Time	45 minutes	< 5 minutes
Time to results	90 minutes[B]	62-70 minutes based on sample type

cfu/ml – colony forming units per milliliter; pfu/ml – plaque forming units per milliliter

[A] Appendix C provides more detail on specificity test results.

[B] The requirement for NGDS results within 90 minutes is intended to enable a laboratory to prepare and complete analysis of 16 individual samples within a 24-hour period using one NGDS identifier.

[3] Appendix B contains the user sensitivity requirements for the Sentinel Panel and an analysis of test results.

At the end of the operational test event, test operators and laboratory officers participated in focus groups to discuss the ability of the NGDS to support laboratory operations. Overall, both technicians and laboratory officers viewed the system positively. Some of the survey respondents expressed concern over the ability of the NGDS to support the sample processing workload due to the inability to analyze multiple samples at a time.

The current NGDS basis of issue plan calls for most units to receive a single NGDS. The NGDS software can support up to eight analyzers connected to the same laptop. A single NGDS system may not be able to provide timely analysis of the large number of sample analysis requests related to a disease outbreak or for missions requiring analysis of a large number of environmental samples.

Comparison to Legacy System

The NGDS provides significant improvements over the currently fielded JBAIDS. The NGDS supports diagnosis of BWA-related illnesses and infectious diseases with similar initial symptoms, which may contribute to more rapid recognition of a BWA-related event. The NGDS provides shorter, simpler sample preparation and the ability to test a single sample against a large number of agents simultaneously. Table 3 summarizes the key differences between NGDS and JBAIDS.

Table 3. JBAIDS and NGDS Comparison

System Characteristic	JBAIDS	NGDS
Sample preparation time	20-40 minutes per sample (Platinum Path extraction kit)	5 minutes per sample
Total time to result	60-80 minutes	62-72 minutes
Samples analyzed per run	32 samples per run (including controls)	1 sample (including controls)
Number of agents analyzed per run	Max 10 targets - Operator must choose agent assay	14-27 depending on panel – All tests run simultaneously
Types of agents analyzed	Biological Warfare Agents, Influenza	Biological Warfare Agents, many common infectious disease agents

Cybersecurity

The NGDS is survivable against cyber threats. The system is not vulnerable to external cyberattacks due to the Services' plans to not connect NGDS to computer networks at this time. Testing identified cyber vulnerabilities that can be exploited by someone with physical access to the system to cause system instability or change analytical results. Operators are able to detect system anomalies and follow procedures to restore operational capability. A list of specific NGDS cyber vulnerabilities identified during testing has been provided to the program manager for resolution.

Operational Suitability

The NGDS is operationally suitable for shipboard use and to support clinical and environmental sample analysis. The DOT&E June 2017 Early Fielding Report found the NGDS to be operationally suitable for land-based clinical diagnostic use. The system exceeded mission reliability and operational availability requirements. The NGDS requires less ancillary support equipment resulting in a reduction in the operational footprint of the system and the associated logistics and support requirements than the system it replaces. NGDS is easy to operate, requiring minimal operator hands-on time for sample preparation and analysis. Table 4 compares the demonstrated NGDS performance to key user suitability requirements.

Table 4. NGDS Performance Compared to Suitability Requirements

Performance Attribute	Requirement	Demonstrated Performance
Mission Reliability (probability of completing 5 analytical analyses without an operational mission failure)	94.4%	98.6%*
Availability	85%	98% (98% - 99%)*
Warrior Panel Shelf-Line	12 months	15 Months
Sentinel Panel Shelf-Life	12 months	Unable to assess

* 80 percent lower confidence bound.

Reliability

The NGDS demonstrated 98.6 percent reliability during testing. The most common NGDS failure mode was a consumable assay panel internal control failure. Panel internal controls ensure the Polymerase Chain Reaction (PCR) is working correctly. When a control fails, the operator is not alerted until the end of the analysis run. The sample must be prepared and analyzed a second time with a new consumable panel, resulting in a delay of about an hour in results reporting. BioFire Defense advertises an internal control failure rate of 3 percent. During NGDS testing, the internal control failure rate was approximately 1.5 percent. The single hardware failure that occurred during testing occurred during developmental/operational testing. One NGDS system had to be replaced because of difficulty properly seating the consumable panel in the analyzer to begin analysis.

Army testers identified damage to the NGDS transit case, internal NGDS components, and the AC power adapter after composite wheeled-vehicle vibration developmental testing designed to replicate ground transportation on a typical 500-mile mission. The Program Manager has indicated that implementation of fixes to resolve the problem are expected in late 2018. Until the fixes are implemented, verified, and fielded, the Program Office should alert receiving units to the potential for damage during ground transportation that may result in the need to replace the NGDS.

Maintainability

The NGDS vendor is responsible for maintaining configuration control as an FDA-approved medical device. As a result, there are limited operator-level maintenance tasks such as rebooting the analyzer or laptop. In the event of an NGDS hardware failure, the unit must return the system to BioFire Defense for repair. The Services plan to maintain spare systems at depots and other pre-positioned sites to deploy replacement systems as needed while systems are with the vendor for repair,

NGDS Training

Operator training includes 44 hours of hands-on equipment time, lectures, homework, and exams. Overall, test participants rated NGDS training positively and felt it prepared them to use NGDS in the field. At this time, the Services do not have a plan to familiarize forward deployed medical providers and public health officers on NGDS capabilities that could aid in the rapid diagnosis of BWA-related illness to support force health protection decision-making. The Services should provide education to medical providers on NGDS to support medical diagnostics and force health protection.

Recommendations

The Joint Program Manager for Medical Countermeasures should:

- Complete Sentinel Panel stability shelf-life testing and provide periodic updates to the Services that accept the Sentinel Panel for use prior to demonstrating the required operational shelf-life.
- Make the required changes needed to the NGDS to prevent reliability failures associated with vibration during wheeled-vehicle transport and verify the changes resolved the failure modes.
- Address identified cyber vulnerabilities and verify that they have been resolved.

Appendix A

Table A-1 lists the clinical diagnostic capability of the Warrior Panel.

Table A-1. Warrior Panel Agent and Clinical Sample Types

Pathogen	Sample Types		
	Blood Culture	Whole Blood	Sputum
Bacillus anthracis	✓	✓	
Yersinia pestis	✓	✓	✓
Francisella tularensis		✓	✓
Coxiella burnetii		✓	
Ebola Virus		✓	
Marburg Virus		✓	

Table A-2 lists the BWAs and associated samples types that can be identified using the Sentinel Panel.

Table A-2. Sentinel Panel Agents and Environmental Sample Types

Pathogen	Sampe Types								
	Culture Medium	Aerosol Collection Buffer	Surface Water	Soil	Sand	Surface Swab	Powders	Vectors	Animal Blood
Bacillus anthracis	✓	✓	✓	✓	✓	✓	✓		✓
Yersinia pestis	✓	✓	✓	✓	✓	✓		✓ (Flea)	✓
Francisella tularemia	✓	✓	✓	✓	✓	✓		✓ (Tick)	✓
Coxiella burnetii		✓	✓	✓	✓	✓		✓ (Tick)	
Brucella (4 strains)	✓	✓	✓	✓	✓	✓			✓
Burkholderia mallei	✓	✓		✓	✓	✓			✓
Burkholdieria pseudomallei		✓		✓	✓	✓			
Rickettsia-prowazekii		✓				✓		✓ (Louse)	
Eastern Equine Encephalitis Virus	✓	✓				✓		✓ (Mosquito)	
Venezuelan Equine Encephalisits Virus (2 strains)	✓	✓				✓		✓ (Mosquito)	
Western Equine Encephalitis Virus	✓	✓				✓		✓ (Mosquito)	
Smallpox (Orthopox and Variola major)	✓	✓	✓	✓	✓	✓	✓		
Ebola Virus (5 strains)	✓	✓				✓			
Marburg Virus (4 strains)	✓	✓				✓			
Clostridium botulinum (parent agent gene)		✓							
Ricinus communis (parent agent gene)*		✓							

* *Clostridium botulinum* and *Ricinus communis* are the biological agents that produce Botulinum toxin and Ricin, which are biological threats.

Appendix B

Users require the NGDS provide an 85 percent probability of accurately identifying biological warfare agents (BWAs) in environmental samples when greater than 1,000 colony forming units of bacteria per milliliter or 10,000 plaque forming units per milliliter are present. The sensitivity number in Table B-1 are colony forming units for bacteria and 10,000 plaque forming units per milliliter for viruses. The numbers in the body of the table show the concentration at which there is an 85 percent probability of identification. The numbers in parentheses reflect the 80 percent confidence intervals. The numbers in red indicate that the agent/sample type combination does not meet the NGDS requirement.

Table B-1. Sentinel Panel Sensitivity for All Agent/Sample Type Combinations

Agent	Disease	Culture Media	Aerosol Collection Buffer	Surface Water	Soil	Sand	Swab	Powder	Animal Blood	Vector
***Bacillus anthracis* spores**	**Anthrax**	N/A	30 (<90)	90 (50-210)	123 (72-301)	70 (30-200)	2 (<70)	50 (20-140)	N/A	N/A
***Bacillus anthracis* vegetative**	**Anthrax**	100 (90-110)	N/A	20 (15-40)	N/A	N/A	10 (5-20)	N/A	1 (<10)	N/A
Yersinia pestis	**Plague**	<20	40 (20-80)	50 (30-110)	70 (40-170)	30 (10-80)	20 (10-70)	N/A	50 (30-110)	10 (<40)
Francisella tularensis	**Tularemia**	110 (1-250)	280 (170-540)	120 (<300)	540 (350-990)	890 (600-1340)	180 (70-390)	N/A	350 (220-630)	70 (<240)
Coxiella burnetii	**Q Fever**	N/A	40 (30-60)	<15	<30	30 (10-60)	<20	N/A	N/A	<20
Brucella abortus	**Brucellosis**	220 (60-490)	280 (150-650)	160 (<410)	580 (340-1390)	510 (290-1250)	410 (240-920)	N/A	440 (250-1100)	N/A
Brucella melitensis	**Brucellosis**	N/A	80 (50-140)	N/A	N/A	N/A	N/A	N/A	110 (80-190)	N/A
Brucella ovis	**Brucellosis**	N/A	5 (2-20)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Brucella suis	**Brucellosis**	270 (190-410)	200 (110-340)	160 (60-280)	350 (250-510)	380 (260-580)	180 (80-300)	N/A	640 (250-510)	N/A
Burkholderia mallei	**Glanders**	N/A	390 (240-670)	N/A	1210 (800-1960)	910 (560-1650)	628 (395-1080)	N/A	N/A	N/A
Burkholderia pseudomallei	**Meliodosis**	N/A	4 (<160)	N/A	540 (330-1210)	70 (<260)	20 (<190)	N/A	N/A	N/A

Agent	Disease	Culture Media	Aerosol Collection Buffer	Surface Water	Soil	Sand	Swab	Powder	Animal Blood	Vector
Ricketssia prowazekii	**Typhus**	N/A	2 (1-3)	N/A	N/A	N/A	3 (2-4)	N/A	N/A	1 (1-2)
Eastern Equine Encephalitis	**Viral Encephalitis**	20 (>10)	20 (>5)	N/A	N/A	N/A	<15	N/A	N/A	<10
Venezuelan Equine Encephalitic 1C	**Viral Encephalitis**	30 (<340)	40 (<400)	N/A	N/A	N/A	60 (<380)	N/A	N/A	<160
Venezeulan Equine Encephalitis 1AB	**Viral Encephalitis**	40 (20-60)	60 (40-90)	N/A	N/A	N/A	20 (1-40)	N/A	N/A	<10
Western Equine Encephalitis	**Viral Encephalitis**	30 (10-160)	10 (<60)	N/A	N/A	N/A	<10	N/A	N/A	<20
Vaccinia Virus	**N/A**	<20	<20	<20	<20	<20	<20	<20	N/A	N/A
Smallpox DNA	**N/A**	N/A	210 (120-1540)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Clostridium botulinum	**N/A**	N/A	460 (>85)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ricinus communis	**N/A**	N/A	710 (>460)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ebola Virus (Sudan)	**Ebola**	<20	<20	N/A	N/A	N/A	<20	N/A	N/A	N/A
Ebola Virus (Bundibugyo)	**Ebola**	<20	<20	N/A	N/A	N/A	<20	N/A	N/A	N/A
Ebola Virus (Reston)	**Ebola**	<20	<20	N/A	N/A	N/A	<20	N/A	N/A	N/A
Ebola Virus (Zaire)	**Ebola**	<20	<20	N/A	N/A	N/A	<20	N/A	N/A	N/A
Marburg Virus (ci67)	**Marburg**	<20	<20	N/A	N/A	N/A	<20	N/A	N/A	N/A
Marburg Virus (RAVN)	**Marburg**	<20	<20	N/A	N/A	N/A	<20	N/A	N/A	N/A
Marburg Virus (Musoke)	**Marburg**	<20	<20	N/A	N/A	N/A	<20	N/A	N/A	N/A
Marburg Virus (Angola)	**Marburg**	<20	<20	N/A	N/A	N/A	<20	N/A	N/A	N/A

Appendix C

Table C-1. NGDS Sentinel Panel Specificity Test Results[A]

Agent Assays	Number of False Positive Agent Identifications	Number of True Negative Results[B]	Specificity[C]
Bacillus anthracis	2	2345	0.99
Brucella	8	2188	0.99
Burkholderia mallei	0	2439	1.0
Burkholderia pseudomallei	0	2453	1.0
Yersinia pestis	9	2375	0.99
Coxiella burnetii	0	2261	1.0
Francisella tularensis	1	2373	0.99
Rickettsia	0	2474	1.0
Ebola	0	2374	1.0
Marburg	0	2350	1.0
Ricinis communis	0	2531	1.0
Clostridium botulinum	0	2531	1.0
Smallpox (gblock)	0	2520	1.0
VEE	1	2337	0.99
WEE	3	2445	0.99
EEE	0	2448	1.0
Vaccinia	0	2415	1.0
Bacillus thurigensis	0	2537	1.0
Saccharomyces cerevisiae	12	2537	0.99
Bacillus globigii	1	2537	0.99
TOTAL	**37**	**2718**	**0.99**

A The limit of identification is defined as the agent concentration at which the system identifies agent with 85 percent probability at the 80 percent confidence level

B Includes samples spiked with other agents and blanks

C True Negatives/(True Negatives + False Positives)