



Vector Smart™ Zika, dengue, and chikungunya (VZDC) Kit

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CO-DIAGNOSTICS, INC.

REF

VZDC-K-001

RUO



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1 INTENDED USE

The **Vector Smart™ Zika, dengue, and chikungunya (VZDC)** kit is a research use only multiplex test, based on real-time PCR (qPCR) technology, for the simultaneous qualitative detection of the Zika (ZIKV), dengue types 1-4 (DENV), and chikungunya (CHIKV) specific RNA in mosquitoes.

For research use only (RUO). Not for use in diagnostics procedures.

2 KIT COMPONENTS

Lid Color	Component	Symbol	Catalog Number	Description	Amount
Black	Vector Smart™ VZDC Master Mix	MM	VZDC-MM- 001	Proprietary blend of CoPrimers™ and PCR reagents	1x500µL (100 reactions)
Red	Vector Smart™ VZDC Positive Control	PC	VZDC-PC- 001	Proprietary blend of target templates	1x500µL (100 reactions)
Clear	Nuclease-Free Water	NTC	GEN-NF-001	DNase/RNase-free water	1x500µL (100 reactions)
Orange	Vector Smart™ VZDC Extraction Control	EC	VZDC-EC-001	Proprietary blend of the IPC template	1x500µL (100 reactions)

- Kit Catalog Number is VZDC-K- 001. Contact Sales at 801-438-1036 ext. 02 or at www.codiagnostics.com/contact/ to order.

3 VECTOR SMART™ VZDC STORAGE, HANDLING, & DISPOSAL

- The **Vector Smart™ VZDC** kit is shipped on dry ice. The components of the kit should arrive frozen. If one or more of the components are not frozen upon receipt, or are compromised during shipment, contact your distributor for assistance.
 - Upon receipt of kit, laboratory should follow internal procedures for quality control.
- All components should be stored below -20°C upon arrival to prevent degradation of reagents.



- Repeated thawing and freezing of components (more than four times) should be avoided, specifically the master mix, as this might affect the performance of the assay. The reagents should be frozen in multiple aliquots if they are to be used intermittently.
- Co-Diagnostics recommends storage between +2°C and +8°C should not exceed a period of 4 hours.
- If you work in an area prone to power outages, it is recommended to have a back-up generator for your freezer as well as a temperature data log system to ensure that the **Vector Smart™ VZDC** test kit remains frozen at -20°C.
- Protect **Master Mix** from light.
- Expired products should not be used, as the integrity of the components cannot be guaranteed.
- The product is not a biological waste. See Safety Data Sheets (SDS) for hazard classification. Disposal should be in accordance with applicable regional, national, and local laws and regulations.

4 WARNINGS AND PRECAUTIONS

WARNING!



Read this *Instructions for Use* carefully before using the product. Before first use check the components for:

- Integrity
- Frozenness upon arrival

Users should pay attention to the following:

- Use of this product should be limited to personnel instructed and trained in the techniques of real-time PCR.
- Samples should always be treated as infectious and/or biohazardous. Use standard precautions.
- Wear protective gloves, lab coat, and eye protection when handling samples. Always wear gloves when handling kit components.
- Always use DNase/RNase-free disposable pipette tips with filters.
- Use segregated working areas for sample preparation, reaction setup, and amplification/detection activities. The workflow in the laboratory should proceed in a unidirectional workflow. To prevent contamination, change PPE between areas.
- Store and extract positive materials (specimen, controls, and amplicons) separately from other reagents. Dedicate supplies and equipment to separate working areas and do not move them from one area to another.
- Consult appropriate Safety data Sheets (SDS) for safety. The SDS for the **Vector Smart™ VZDC** test kit is provided with the shipment. If not provided with shipment the SDS can be retrieved from Co-Diagnostics website at the link: <http://codiagnostics.com/resources/safety-data-sheets/>
- Do not open the reaction tubes/plates post amplification.



- Do not autoclave reaction tubes/plates after the PCR, since this will not degrade the amplified nucleic acid and will risk contaminating the laboratory area.
- Do not use components of the kit that have passed expiration date.
- Discard sample and assay waste according to your local safety regulations.

5 BACKGROUND INFORMATION

5.1 Zika virus (ZIKV)

- **About:** The Zika virus was first isolated in 1947 in monkeys found in the Zika Forest in Uganda. The first human cases were discovered in 1952 and since then outbreaks throughout Africa, the Americas, Asia, and the Pacific have been reported. Zika virus was not thought to be endemically transmitted in the Americas until the emergence in Brazil in 2015. There was a striking increase in reports of congenital microcephaly cases, which triggered a declaration of an international public health emergency (Araújo, et al., 2018). In this study Araújo et al. found direct correlation between microcephaly cases and Zika occurrences. Another study conducted in 2016 demonstrated that ZIKV infects and destroys human neuronal stem cells grown as neurospheres and brain organoids. These observations helped solidify the link between fetal ZIKV infection and the development of microcephaly (Relich & Loeffelholz, 2017). Due to these serious neurological sequelae found in 2018, the World Health Organization (WHO) issued the annual review of diseases where the priority for R&D investments for Zika has been raised (World Health Organization, 2018).
- **The virus:** is an enveloped, single-stranded (+) RNA virus part of the *Flaviviridae* family.
- **Transmission:** It is an arbovirus spread by the bite of infected mosquitos of the genus *Aedes*. *Aedes* mosquitoes usually bite during the day (early morning and late afternoon/evening). Zika virus is also transmitted from mother to fetus during pregnancy, through sexual contact, transfusion of blood and blood products, and organ transplant (Zika virus, 2018).

5.2 Dengue virus (DENV)

- **About:** According to the World Health Organization Severe dengue was first recognized in the 1950s during the dengue epidemics in the Philippines and Thailand. Today, severe dengue affects most Asian and Latin American countries and has become a leading cause of hospitalization and death among children and adults in these regions (Dengue and severe dengue, 2019). There are 4 known serotypes of dengue (DENV 1-4). Immunity is acquired for long periods for each type, although the immunity to one type does not prevent the infection from the other types, what may cause in hyperendemic areas infection of dengue virus as frequent as up to four times per individual. The illness spectrum varies from asymptomatic, classic dengue fever, and severe or hemorrhagic dengue fever, which can be fatal (Wilder-Smith & Gubler, 2008). There is no specific treatment for dengue or severe dengue, but early detection and access to proper medical care lowers fatality rates below 1%. In many countries dengue fever is a reportable disease and must be registered with the responsible authority.
- **The virus:** is an enveloped, single-stranded (+) RNA virus part of the *Flaviviridae* family.
- **Transmission:** Like Zika virus, dengue is an arbovirus spread by the bite of infected mosquitos of the genus *Aedes*. *Aedes* mosquitos usually bite during the day (early morning and late afternoon/evening). Humans who are already infected with the virus can transmit the infection



(for 4-5 days; maximum 12) via bite from uninfected *Aedes* mosquitoes after their first symptoms appear (Dengue and severe dengue, 2019).

5.3 Chikungunya virus (CHIKV)

- **About:** Chikungunya is a mosquito (mainly by *Aedes albopictus*) spread disease that leads to painful rheumatic symptoms. The lineages of chikungunya are divided into two branches: West African (WA) and East/Central/South African (ECSA). The West African strains are more related to small outbreaks locally in Africa. The strains from ECSA lineage are the ones that spread largely through the world (Silva & Dermody, 2017).
- **The virus:** is a small enveloped, single-stranded (+) RNA virus part of the *Alphavirus* genus of the family *Togaviridae*.
- **Transmission:** Like Zika and dengue virus, chikungunya is an arbovirus spread by the bite of infected mosquitos of the genus *Aedes*. *Aedes* mosquitos usually bite during the day (early morning and late afternoon/evening).

6 PRODUCT DESCRIPTION

The **Vector Smart™ VZDC** kit is a research use only multiplex test, based on real-time polymerase chain reaction technology. It tests for the presence or absence of ribonucleic acid (RNA) of the Zika, Dengue types 1-4, and Chikungunya viruses.

The **Vector Smart™ VZDC** test includes an internal control to identify possible qPCR inhibition, confirm the integrity of the reagents, and verify the quality of sample extraction. The **Vector Smart™ VZDC** test also includes a positive control which includes four synthetic nucleic acid molecules carrying sequences that are homologous to Zika (ZIKV), Dengue (DENV), and Chikungunya (CHIKV) viruses and the mosquito gDNA positive control sequence are targeted by this multiplex assay. Positive controls represent a source of cross-contamination. Precautions should be taken to prevent and minimize the risk.

CoPrimers™ included in the **Vector Smart™ VZDC** test are:

- CoPrimers™ that are targeting ZIKV are labelled with the FAM™ fluorophore
- CoPrimers™ that are targeting DENV are labelled with the CAL Fluor® Orange 560 fluorophore
- CoPrimers™ that are targeting CHIKV are labelled with the Quasar® 670 fluorophore
- CoPrimers™ that are targeting the Mosquito Enhancer of the Internal Positive Control (IPC) DNA are labelled with CAL Fluor® Red 610 fluorophore

7 MATERIALS AND DEVICES (REQUIRED BUT NOT PROVIDED)

- Appropriate 4-channel real-time PCR instrument, compatible with the fluorophores used in this test.
- Appropriate nucleic acid extraction system or kit, with associated equipment according to the manufacturer's protocol.
- Vortex mixer
- Centrifuge with a rotor for 2 mL reaction tubes
- Pipettes (adjustable)
- Pipette tips with filters (disposable)



- Powder-free gloves (disposable)
- Ice
- Biosafety cabinet, ideally BSL-2 facility
- Copper coated premium BB's (for extraction) or another sample homogenizer



All instruments should be properly installed, calibrated, and maintained according to the manufacturer's instructions and recommendations. Do **not** use instruments with outdated calibration.

8 PROCEDURE

8.1 Mosquito Collection

Mosquitos are typically collected using commercially available mosquito traps, such as the CDC miniature light trap Model 512. The mosquitoes collected from a single collection site are often called a pool. The pool of mosquitoes are sexed and speciated based upon the region and the target(s) being tested for.

After being sexed and speciated, the mosquitoes are either stored frozen or can go through the extraction process. After extraction, the mosquito extract can then be tested or stored frozen, preferably at -70°C for future testing.

8.2 Mosquito Preparation

The quality of the extraction of the RNA from the samples is essential for the performance of **Vector Smart™ VZDC**. The extraction protocol to be followed should be performed following manufacturer's instructions or an internally validated protocol. The suitability of the nucleic acid extraction procedure for use with **Vector Smart™ VZDC** must be validated by the user. Suggestions of extraction methods and systems include:

- QiAamp® Viral RNA Mini Kit (QIAGEN)
- MagMAX™ Viral RNA Isolation Kit (Applied Biosystems)
- MagMAX™ Viral Pathogen Nucleic Acid Isolation Kit (Applied Biosystems)
- Sbeadex Livestock Kit (LGC)

To prepare the mosquitoes before the extraction, place a pool of 10-50 mosquitoes in a 1.5 or 2.0 mL microcentrifuge tube, and add 10 µL per mosquito of (TE Buffer with 1% Triton X-100) to the tube (ex. 10 mosquitoes = 100 µL TE/Triton X mix added), and 1 copper coated premium BB (for 19 or less mosquitoes) or 2 BB's (for 20 or more mosquitoes). Vortex the tube for 7 minutes, and centrifuge at 21,380 x g for 10 minutes. Remove the supernatant and continue with the extraction process.



An important step to ensure that the extraction process is working is to add 5 µL of **Extraction Control**, after the lysis step or when instructed by the extraction kit, into every sample pool being extracted. Due to the variability of



mosquito populations, this will ensure that there is consistent amplification of the Mosquito Internal Positive Control (IPC).

For additional information and technical support regarding preparation please contact Technical support 801-438-1036 ext. 04 or at www.codiagnosics.com/contact/.



If your sample preparation system is using washing buffers containing ethanol, make sure to eliminate any traces of ethanol prior to elution of the nucleic acid. Ethanol is a strong inhibitor of real-time PCR.

The use of carrier RNA is crucial for extraction efficiency and stability of the extracted nucleic acid.

Do not use buffer from other products besides the buffer in the sample extraction kit. Products like the RAMP grinding buffer is known as a PCR inhibitor and should not be used (Burkhalter, Horiuchi, Biggerstaff, Savage, & Nasci, 2014).

8.3 Vector Smart™ VZDC Reagent Setup

- When preparing reagents, clean all working surfaces with appropriate cleaning solution that disinfects and degrades nucleic acids.
- All **Vector Smart™ VZDC** Master Mix, Positive Control (PC), no template control nuclease-free water (NTC), and sample tubes should be vortexed for 3 seconds, and briefly spun down before using to ensure properly mixed reagents, and to remove any condensation or residue from the lids.
- Thaw all reagents and samples on **ice**, or on a cold block, before starting setup.

8.4 Reaction Setup

- 8.4.1 Every reaction setup should include enough reaction wells for the number of samples and at least one positive and one NTC (**# samples + 2 = total reaction wells needed**). Example: 5 samples to test + 1 PC well + 1 NTC well = 7 total reaction wells.
- 8.4.2 All pipetting should be done on **ice**, if possible. Pipetting of PC and sample elution is recommended to be done in a separate area if possible, or at a separate time, than the Master Mix and NTC. Change pipette tips in-between sample elution and change pipette tips after pipetting each component. Pipet PC last if possible, to avoid contamination events.
- 8.4.3 Pipet 5 µL of **Master Mix** into each well being used in an appropriate optical plate or optical reaction tube (example: CoDx Box real-time PCR instrument uses 48-well reaction tubes).
- 8.4.4 Pipet 5 µL of sample (elution from nucleic acid extraction) or 5 µL of a control (**NTC** and **Positive Control**) to the appropriate well(s). At least one positive and one NTC control must be included in each run.
- 8.4.5 Seal the reaction plate with an optical adhesive film or the reaction tubes with appropriate lids.
- 8.4.6 Place plate or tubes into real-time PCR instrument in the correct orientation and start run.



8.5 PCR Instrument Setup

8.5.1 For basic information regarding setup and programming of the different real-time PCR instruments, please refer to the user manual of the respective instrument. For programming instructions questions regarding the use of other real-time PCR instruments please contact the Laboratory 801-438-1036 ext.04 or at www.codiagnosics.com/contact/.

8.5.2 If using a Co-Diagnostics Inc. CoDx Box, contact the Laboratory 801-438-1036 ext. 04 or at www.codiagnosics.com/contact/ for the template file for download. The template file comes pre-programmed with the settings described below. When not using a template, or using another device, use the settings outlined below to program the PCR instrument.

8.5.2.1 In order to achieve optimal performance from the test, it is important to make sure that the instrument is compatible with the conditions outlined below.

8.5.3 Define the following settings:

Reaction Volume	10 µL
Ramp Rate	Default
Passive Reference	None

8.5.4 Program PCR instrument with the cycling conditions below:

	Stage	Cycles	Temperature	Time
Reverse Transcription	Activation	1	45°C	15 minutes
	Initial Denaturation	1	95°C	2 minutes
Amplification	Cycling	50	95°C	3 seconds
			55°C	32 seconds

8.5.1 Ensure that PCR instrument being used is compatible with fluorophores below. Some devices may not have options for the quencher. If needing help or have questions, contact Co-Diagnostics Inc. technical support at 801-438-1036 ext. 04 or at: www.codiagnosics.com/contact/.

8.5.2 Define the fluorescence detectors (dyes):

Target	Detector Name	Reporter	Quencher
ZIKV specific RNA	ZIKV	FAM™	BHQ® - 1
DENV specific RNA	DENV	CAL Flour® Orange 560	BHQ® - 1
CHIKV specific RNA	CHIKV	Quasar® 670	BHQ® - 2
Mosquito Internal Positive Control	IPC	CAL Flour® Red 610	BHQ® - 2

➤ When the run is finished, ensure that the run file is saved.

9 DATA ANALYSIS

For basic information regarding data analysis on specific real-time PCR instruments please refer to the user manual of the respective instrument.



9.1 Validity of Test Runs

9.1.1 Valid Test Run

- Check to see that both the positive and no template control passed.

9.1.1.1 The following control conditions must be met:

Control Type	Control Name	Purpose of Control	ZIKV	DENV	CHIKV	Internal Positive Control
VZDC Positive Control	ZIKV (FAM™)	Verifies the performance of the master mix	+	+	+	+
	DENV (CF®560)					
	CHIKV (Q®670)					
	IPC (CF®610)					
No Template Control	Master Mix + Water	Verifies the reagents are free of contamination	-	-	-	-

- If controls pass, interpret the sample results.

9.1.2 Invalid Test Run

9.1.2.1 If any of the controls fail, the run is invalid. Document the run and initiate troubleshooting.

9.2 Interpretation of Results

Once the controls have passed, the unknown samples can be interpreted based on three possible outcomes:

- Positive
- Negative
- Inconclusive

A **Positive** result will show an amplification curve or cycle threshold value for ZIKV, DENV, or CHIKV. The cut off value should be determined by in house validation testing. However, internal studies have shown rare primer-dimer formation or other non-specific amplification at 45 cycles. This fact can be attributed to the nature of the CoPrimers™ (Satterfield, 2014) (Poritz & Ririe, 2014). The amplification of the IPC shows that the extraction was successful.

A **Negative** result will show no amplification for ZIKV, DENV, or CHIKV; The absence of a curve for VZDC indicates a negative result ONLY when the IPC marker is positive.

An **Inconclusive** result will result if any of the controls fail. See troubleshooting.



The interpretation of results can be translated to the following table:

Marker	ZIKV	DENV	CHIKV	Mosquito Internal Positive Control (NAM.18S)	Vector Smart™ Positive Control	No Template Control (NTC) Vector Smart™ Master Mix + Nuclease-Free Water	Result				
Instrument Reading	+	+	+	Pass			VZDC +				
	-	-	-				VZDC -				
	+	-	-				ZIKV + DENV- CHIKV-				
	-	+	-				ZIKV- DENV+ CHIKV -				
	-	-	+				ZIKV- DENV- CHIKV+				
	+	+	-				ZIKV+ DENV+ CHIKV-				
	-	+	+				ZIKV- DENV+ CHIKV+				
	+	-	+				ZIKV+ DENV- CHIKV+				
	Any Result						Fail	Pass		Inconclusive: See Troubleshooting	
							Pass	Fail	Pass		
Pass					Fail	Fail					
The cut off value will determine what results are to be considered positive or negative. It should be determined by the assay development.											

10 TROUBLESHOOTING

Co-Diagnostics Inc. values customer feedback and we would like to be informed of any issues with the **Vector Smart™ VZDC kit**, even if the recommended steps for troubleshooting solve the issue. To give feedback please fill out the Customer Feedback Form by visiting www.codiagnostics.com/contact/feedback/



10.1 Stability

Real-time and accelerated shelf-life and in-use stability studies are currently under testing. Presently, the expiration date of this product has been established as 12 months. It is not recommended to use expired kit reagents, doing so may lead to inaccurate results.

Always use the most recent version of this document for updates as more stability information will be added when studies are completed.

10.2 User Errors

Good Laboratory Practices for Molecular Biology Diagnostics (Viana & Wallis, 2011) are necessary for the use of this product. This product is not intended to be used by untrained personnel.

It is essential for the user to have some molecular biology experience and be familiar with proper pipetting technique to prevent errors, such as splashes, crossover contamination, and errors on volume selection. Pipette tips must be replaced after every pipetting. Gloves must be replaced often. Equipment, such as pipettes and real-time PCR instruments, should be calibrated when applicable.

90 minutes of online training for Good Laboratory Practices for Molecular Genetics Testing (Centers for Disease Control and Prevention, 2017) is available at the CDC website at the following link <https://www.cdc.gov/labtraining/training-courses/good-lab-practices-molecular-genetics-testing.html>

10.3 Invalid Results/Inconclusive Results

10.3.1 Vector Smart™ VZDC Positive Control not amplifying

No amplification from the PC could be the result of one or multiple factors, such as:

- Pipetting errors (pipetting control into the wrong well, missing a well, pipetting inadequate amount of reagent),
- Incorrect placement of plates or tubes into the real-time PCR instrument,
- **Vector Smart™ VZDC Master Mix** or **Vector Smart™ VZDC Positive Control** degradation (result of reagents being at temperatures above -20°C for an extended period),
- Use of expired reagents,
- or the wrong reagents being used.

Without further evidence, it is best to disregard the results from the samples and re-test by re-amplification. If the positive control fails again, then an investigation should be conducted to identify possible causes for error, and the test must be reprocessed from extraction or not, depending on the investigation results and risks identified in the process. If failure of the positive control happens a third time after re-extraction and re-amplification, open a new **Vector Smart™ VZDC Positive Control** or **Master Mix**, and retest. If still failing, please contact Co-Diagnostics Inc. technical support by calling 801-438-1036 ext. 04 visiting www.codiagnostics.com/contact/.

10.3.2 NAM. 18s Mosquito Internal Positive Control (IPC) not amplifying in samples

No amplification from the IPC channel could be the result of one or multiple factors, such as:

- Not enough nuclear material in the sample,
- PCR inhibitors such as: ethanol and heparin,
- the extraction was performed incorrectly,



- or the extraction kit used is not compatible or has a step that eliminates a crucial element for extraction.
- Sample origin not compatible to the test designed application.
- or the extraction kit used is not compatible or has a step that eliminate the mosquito DNA (e.g. a DNase Digestion step).

Negative results, without IPC amplification, cannot be trusted and re-testing by re-amplification should be performed. If the IPC fails again, then samples should be re-extracted and re-amplified. If it fails after a third time an investigation should be conducted to identify possible causes for error. If the cause for the error is clear, the test can either be signed out as **inconclusive** due to either PCR inhibitors being present or not enough nuclear material being present. If the cause for error is unclear, contact Co-Diagnostics Inc. technical support by calling 801-438-1036 ext. 04 or by visiting www.codiagnostics.com/contact/.

10.3.3 No Template Control showing amplification

- Amplification of VZDC in a No Template Control indicates contamination in one or more of the reagents, incorrect placement of plate or tube into the real-time PCR instrument, or pipetting errors.

None of the results can be trusted and re-testing by re-amplification should be performed. If the NTC fails again, then an investigation should be conducted to identify possible causes for error, and the test must be reprocessed from extraction or not, depending on the investigation results and risks identified in the process. If failure of the NTC, after re-extraction and re-amplification, happens a third time, open a new nuclease-free water and retest. If still failing, please contact Co-Diagnostics Inc. technical support by calling 801-438-1036 ext. 04 or by visiting www.codiagnostics.com/contact/.

11 LIMITATIONS

- This product is intended for research use only. Not intended for use in clinical diagnostics for its performance for diagnostic applications has not be established.
- Strict compliance with this document is required for optimal results. Please, always use the most recent version of this document. This can be downloaded for free at: www.codiagnostics.com/resources/instructions-for-use/ or by visiting www.codiagnostics.com/contact/.
- Use of this product is to be limited to trained and instructed personnel in real-time PCR techniques.
- Good laboratory practices are essential for the proper performance of this assay. It is also recommended that upon receipt of reagents a test run be performed to check the integrity, and performance of the reagents prior to testing on samples.
- Appropriate collection, transport, storage, and processing procedures of samples are required for optimal results.
- Do not use the **Vector Smart™ VZDC** kit components directly on the specimens collected. Perform an appropriate nucleic acid extraction prior to using this assay.
- The presence of PCR inhibitors may cause false negatives or invalid results.
- Potential mutations of the target regions of the ZIKV, DENV, and CHIKV genome covered by this test kit may result in failure to detect the presence of the pathogens.



12 QUALITY CONTROL

In accordance with the Co-Diagnostics Inc.'s ISO 13485-certified Quality Management System, each lot of **Vector Smart™ VZDC** kit is tested against predetermined specifications to ensure consistent product quality.

13 TECHNICAL ASSISTANCE

For technical assistance, please contact our Technical Support:

- Website: <http://codiagnostics.com/contact/>
- Email: info@codiagnostics.com
- Phone: 801-438-1036 ext. 04

14 REFERENCES

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15 TRADEMARKS AND DISCLAIMERS

Registered names, trademarks, etc. used in this document, even if not specifically marked as such, are not to be considered unprotected by law.

Product not available in all countries.



16 LEGEND OF PACKAGE SYMBOLS

	Catalog number
	Batch Code
	Cap color
	Component
	Content/Volume
	Number
	Use-by-date
	Contains sufficient for X tests/ reactions X = 20 sample size X = 100 regular size
	Protect from light
	Temperature limit
	Consult Instructions for Use
	Non-Sterile product – Do not sterilize
	Manufacturer
	Research Use Only