Work Instruction UTI-191015-UtiMax GN ID/AST Clinical Testing Protocol
GeneFluidics Inc.

Revision History

Rev	Description	Date	Author	QA
0	Consolidation of current testing protocols	**10/15/19**	**JC**	**VG**

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1. SUBMITTER INFORMATION

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2. NAME OF THE DEVICE

Trade Name: UtiMax GN ID/AST

Classification Name: Cellular analysis system for multiplexed antimicrobial susceptibility testing

Review Panel: Microbiology (MI)

Regulation: 866.1650

Class: Class II

Product Code: TBD

3. EQUIVALENCE CLAIMED TO PREDICATE DEVICES

The UtiMax GN ID/AST is equivalent to the Accelerate PhenoTest BC Kit (DEN160032), manufactured by Accelerate, Inc.

4. REGULATORY HISTORY

This observational clinical testing plan describes a clinical performance study (with passing criteria, as applicable and defined within each section) to establish or confirm aspects of UtiMax GN1 ID/AST performance which cannot be determined by analytical performance studies, literature and/or previous experience gained by routine diagnostic testing.

	ProMax (Q171600)	**UtiMax** (Q171451)	**BsiMax** (Q-sub to be submitted soon)	**NicuMax** (Q172118)
Function	AST	ID/AST	ID/AST	ID/AST

Population	all	all	All (adult & pediatric) but neonates	NICU patients > 3 days old
Indication	Susceptibility	Urinary tract infection	Sepsis	Late onset sepsis, urinary tract infection and pneumonia
Specimen	Clinical isolates	Urine	Blood	Urine, tracheal aspirate & blood
System	ProMax	UtiMax	BsiMax	NicuMax

Table 1. GeneFluidics product development roadmap

5. INTENDED TO USE

UtiMax GN ID/AST is intended for use as an aid in the diagnosis of Gram-negative urinary pathogens and antimicrobial susceptibility testing directly from urine samples for prescription use only.

6. DEVICE DESCRIPTION

6.1 UtiMax Lab Automation System

The UtiMax Lab Automation System is a fully automated rapid diagnostic system to identify urinary pathogens directly from urine samples. Identification (ID) and antimicrobial susceptibility testing (AST) are performed by the UtiMax Lab Automation System with the reagent kit, AST strip well and disposable sensor array chip.

This information is used to demonstrate compliance with the relevant Essential Principles with respect to clinical performance.

We will demonstrate the effectiveness using clinical and contrived urine samples with various strains of target organisms. This Clinical Testing Protocol describes the detailed testing procedures that will be used to carry out the following aspects of the assay clinical validation:

- Sensitivity and specificity
- Reproducibility
- Positive predictive value (PPV) and negative predictive value (NPV)
- Limit of detection
- Categorical Agreement (CA) with minor error (min), major error (maj) and very major error (vmj)
- Interference
- Carryover

UtiMax GN ID/AST is an electrochemical-based sandwich hybridization test to quantify species-specific ribosomal 16S ribosomal RNA (rRNA) of Gram-negative organisms including *Escherichia coli* (EC), *Pseudomonas aeruginosa* (PA), *Klebsiella spp.* (KS) *and Enterobacter spp.* (ES), *Proteus mirabilis* (PM), *Citrobacter Freundii* (CF), *Morganella morganii* (MM), and *Serratia marcescens* (SM). Each sample is lysed chemically prior to hybridization at high stringency. A potentiostat reads the electrical current from the steady-state enzymatic cycling amplification: signal is proportional to the bound 16S rRNA content from lysate and reported as positive or negative.

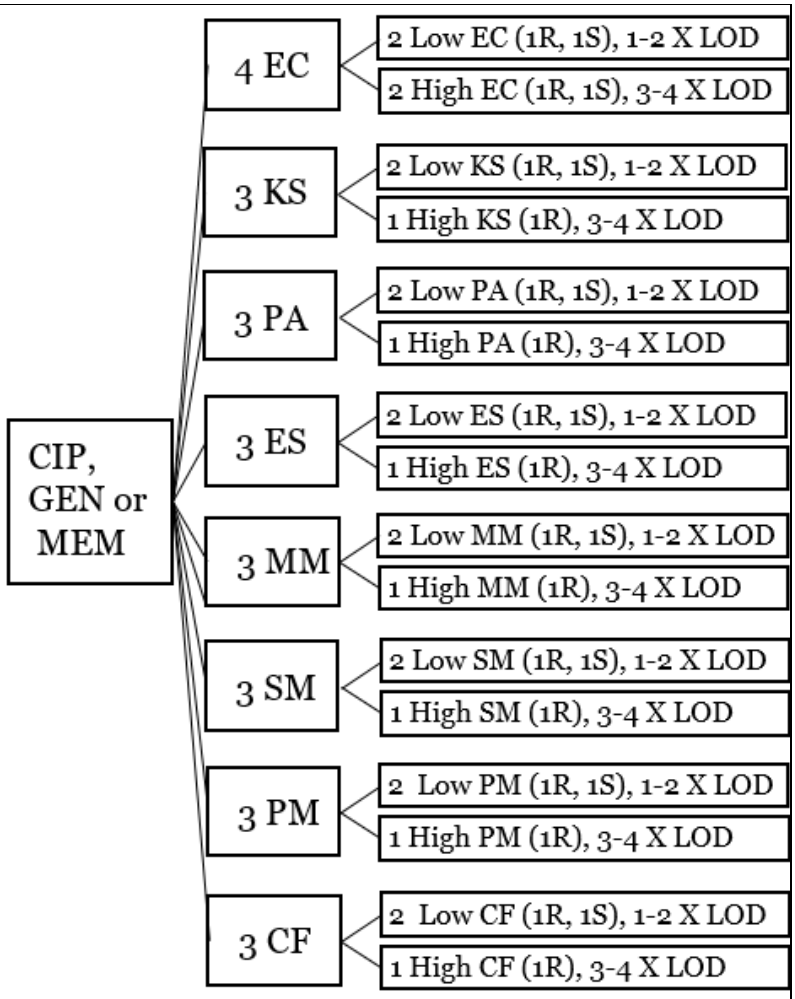
6.2 Indications for Use

The UtiMax GN1 ID/AST system can directly process urine samples and quantify the unique 16S rRNA nucleic acid sequence associated with the target uropathogen for identification (ID) and antimicrobial susceptibility testing (AST) for prescription use only. The UtiMax GN1 ID/AST test is intended for the *in vitro* presumptive identification of viable *Escherichia coli* (EC), *Pseudomonas aeruginosa* (PA), *Klebsiella spp.* (KS) *and Enterobacter spp.* (ES), *Proteus mirabilis* (PM), *Citrobacter Freundii* (CF), *Morganella morganii* (MM), *Serratia marcescens* (SM) and subsequent ciprofloxacin (CIP), gentamicin (GEN), and meropenem (MEM) antimicrobial susceptibility breakpoint reporting if tested positive. Subculturing of positive urine cultures is necessary to recover organisms for definitive identification and susceptibility testing.

7. ID/AS2 PROTOCOL SYNOPSIS

TITLE	UtiMax GN1 ID/AST Clinical Testing Protocol
SPONSOR	GeneFluidics
FUNDING ORGANIZATION	GeneFluidics
NUMBER OF SITES	3 (three independent sites including the Sponsor, GeneFluidics)
SAMPLE COLLECTION SITES	Clinical settings by healthcare professionals
SAMPLE TESTING SITES	Clinical microbiology labs in clinical settings or GLP labs
RATIONALE	Standard automated platforms (e.g., bioMerieux Vitek, BD Phoenix) are time consuming due to the need for a priori isolation of the pathogens from the samples before AST with overnight culture. Development of a compact platform capable of pathogen ID and AST directly from patients' urine samples can provide clinicians and healthcare providers with evidence-based information to start patient-specific antimicrobial

	treatment only when necessary. Faster susceptibility test results and informed modifications in the use of antibiotics, even short-term, have been found to favorably impact patient care and antibiotic resistance profiles.
STUDY DESIGN	This is a multi-center, clinical testing study.
PRIMARY OBJECTIVE	Demonstrate the Substantial Equivalence (SE) of UtiMax GN1 ID/AST to CLSI reference methods in pathogen identification and antimicrobial susceptibility testing
SECONDARY OBJECTIVES	Demonstrate that direct urine pathogen identification and subsequent antimicrobial susceptibility testing (AST) results can be streamlined in the UtiMax system.
NUMBER OF SUBJECTS	**Reproducibility Study**: 3 sites → 75 total contrived urine samples per antibiotic. A total of 225 tests (3 sites x 3 ABX x 25 samples) for the reproducibility study. Reproducibility study will use contrived urine samples with same preselected panel of on-scale microorganisms for all three sites.



Clinical Testing Study:
We will test prospectively collect clinical urine samples to cover target microorganisms with both resistant and susceptible strains at all three sites. The total number of clinical urine samples to be tested is (25+75) x 3 sites = 300 tested against three antibiotics for clinical testing. Clinical study will use contrived urine with prospectively collected clinical strains meeting the selection criteria as shown below at 3 clinical sites.

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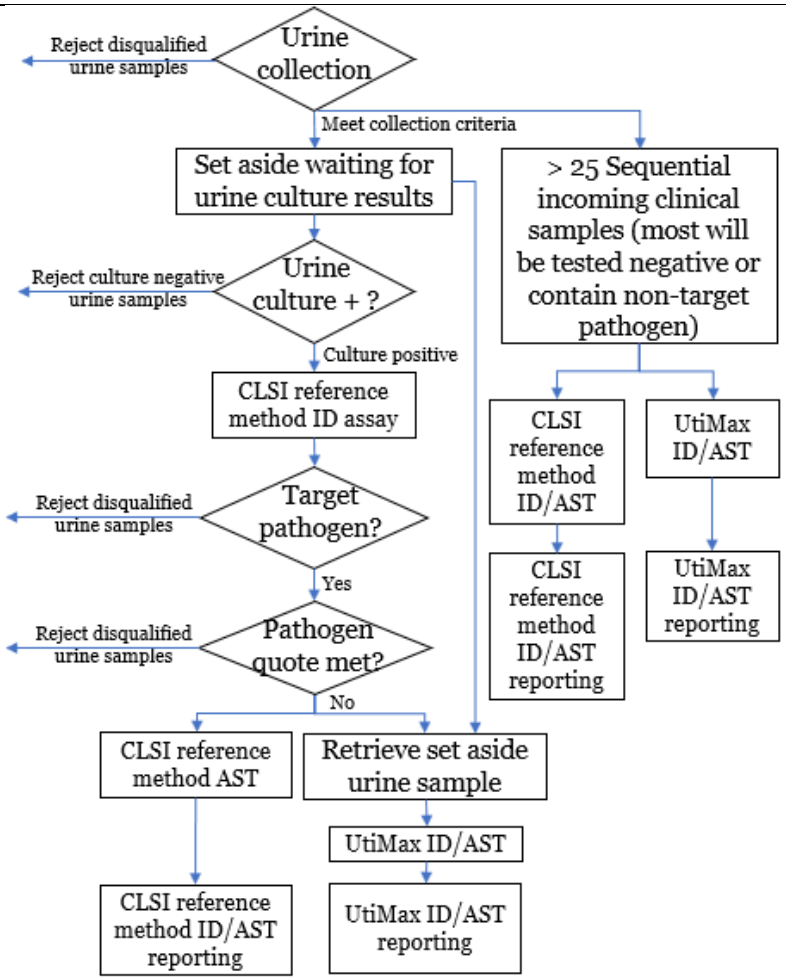

At least 25 sequential incoming urine samples will be tested along with CLSI reference methods, and most of these clinical urine samples are expected to be culture-negative samples.
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<td>INCLUSION AND EXCLUSION CRITERIA</td>
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Inclusion criteria:

Positive clinical urine samples must contain one of the target species listed in the Indications for Use

Exclusion criteria:

The clinical urine sample will be excluded if it is not collected, prepared, or stored according to the information on the Package Insert and at the discretion of the site PI and study director.
Each site will track the number of clinical urine samples with each target species tested as part of the clinical testing using the daily log sheet. If the number of target organisms of the indicated species tested reaches the number

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	needed, no more urine sample of that species will be tested until all required contemporary clinical isolates are completed. This is to ensure that a roughly even number of all indicated species are tested.
INVESTIGATIONAL DEVICE/INTENDED USE	The UtiMax GN1 ID/AST system is an electrochemical-based sandwich hybridization test used to determine qualitative pathogen identification and antimicrobial susceptibility of non-fastidious Gram-negative organisms directly from urine samples. It is intended for pathogen identification and *in vitro* antimicrobial susceptibility breakpoint reporting for the following organisms: *Escherichia coli* (EC), *Pseudomonas aeruginosa* (PA), *Klebsiella spp.* (KS), *Enterobacter spp.* (ES), *Proteus mirabilis* (PM), *Citrobacter Freundii* (CF), *Morganella morganii* (MM), *Serratia marcescens* (SM) These organisms are tested against the following antibiotic panel: - Ciprofloxacin (CIP) - Gentamicin (GEN) - Meropenem (MEM)
PRIMARY ENDPOINTS	-Confirmation of ≥95% accuracy of pathogen identification with sheep blood agar plate (BAP) methods as described in CLSI M35. Confirmation of ≥90% categorical agreement (CA) of the UtiMax GN1 ID/AST system with disk diffusion reference method as described in CLSI M02 -Very major error (vmj) rate ≤ 2% of "R" isolates -Major error (maj) rate ≤ 3% of "S" isolates -Growth failure rate <10% for all genus and species
SECONDARY ENDPOINTS	Reproducibility at each site and between-sites ≥95% pathogen identification accuracy and categorical agreement

INTENDED USER	Personnel who have passed the Proficiency Tests in the clinical microbiology lab for a clinical facility. The passing of a pre-clinical proficiency test (100% sensitivity with blood agar plating and 100% categorical agreement with disk diffusion results) is required for each operator to ensure the proper handling of samples, reagents, and sensor chips.
STATISTICS Primary Analysis Plan	Statistical analysis will be conducted against the reference standard results. Any runs which do not perform as expected will be deemed invalid and discarded from the categorical agreement analysis. However, these events will be reported separately in the final submission. ID accuracy and AST categorical agreement results will be presented as described in the Analytical Validation Plan. ID accuracy and categorical agreement for the clinical isolates per site and combined for all three sites will be analyzed separately. The challenge isolates independently and combined with the clinical isolates will be analyzed separately. When applicable, testing and statistical analysis methods are established according to: CLSI EP12-A2 "User Protocol for Evaluation of Qualitative Test Performance," FDA Recognition Number 7-152. FDA Guidance for Industry and Staff, "Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests."
STUDY POPULATION	Clinical urine samples from both adult and pediatric patients will be collected. However, no pediatric or sub-populations with different age groups will be specified.
TARGET POPULATION	No selection bias based on gender. No selection bias based on ethnicity. No selection bias based on age. Both adult and pediatric patient samples will be tested. Three different testing sites covering different geographical areas (GeneFluidics: Irwindale, CA; Johns Hopkins Hospital, Baltimore, MD; NYPH, Queens, NY). Clinical urine samples will be collected at the Clinical Microbiology Lab at Medical College of Wisconsin and shipped to GeneFludics within 72 hours of collection with refrigeration.

INFORMED CONSENT	Only remnant clinical urine samples collected will be used. No informed consent is needed. IRB approval is needed at each site.
CLINICAL PERFORMANCE CHARACTERISTICS TO BE EVALUATED IN THIS CLINICAL TESTING PLAN	ID accuracy Specificity Sensitivity Category Agreement (with breakpoints) Major Error (maj) rate Very Major Error (vmj) rate Minor error (min) Reproducibility Growth failure rate Matrix interference Carryover