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Automated Multiplex Simultaneous Gene-Related Testing System: Verigene® Bloodstream Infection Testing Panels

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Abstract

The Verigene® bloodstream infection testing panels are an automated system for genetic testing. It can simultaneously detect both bacteria and drug-resistance genes. This is useful for identifying appropriate therapeutic options for patients with sepsis. These testing panels were introduced for sale in 2016 and received insurance coverage in June 2017. The Verigene® system is 24–48 hours faster than the conventional method in terms of identifying major bacteria and detecting drug-resistance genes. This enables faster and more effective and appropriate antibacterial drug selection in the treatment of sepsis.

Keywords

Verigene®
Sepsis
Antimicrobials

1. Introduction

Genetic testing generally offers higher detection sensitivity and the ability to produce results in a shorter timeframe compared to conventional culture and antigen tests. Among these, multiplex simultaneous gene testing offers the advantage of detecting multiple infectious factors all at once, allowing for the detection of numerous factors in a single test.

A survey conducted by the Infectious Diseases Genetic Testing Committee of the Japanese Society of Infectious Diseases in 2018 [1] on infectious disease genetic testing showed that although there is a need for a fully automated genetic testing system, it is yet to be introduced due to factors like laboratory environment, cost and infrastructure, and lack of insurance coverage. Unlike other countries, insurance in Japan does not cover genetic tests for all infectious diseases. Therefore, more effort is needed from academic societies and the Ministry of Health, Labor, and Welfare to ensure early insurance coverage and the expansion of coverage.

When utilizing the test within their facilities, clinical laboratory technicians have expressed viewpoints, for example: “It is not feasible to assess all samples using costly reagents,” “Collaboration with infectious disease experts is crucial for choosing test specimens and interpreting outcomes,” and “How

should test findings be communicated to healthcare professionals?" Concerning result interpretation, pertinent guidance is available in the "Guidelines for the Implementation of Multi-Parameter Genetic-Related Tests," [2] jointly crafted by the Japanese Society of Infectious Diseases and the Japanese Society for Clinical Microbiology. This guidance emphasizes that, in severe infectious ailments like sepsis, the involvement of infectious disease or clinical laboratory specialists is vital to accurately evaluate results. It is evident that expertise is indispensable for result assessment. Furthermore, clinicians often commence empirical therapy for infectious diseases, necessitating promptness. Swift and appropriate data acquisition is essential for transitioning to suitable antimicrobials based on test outcomes. In other words, the key is how quickly appropriate treatment can be initiated in collaboration with the laboratory, the infectious disease specialist, and the clinician. In the future, appropriate and effective operation of tests based on a good understanding of the characteristics of the products will be required given these issues.

2. Introduction to the Verigene® bloodstream infection testing panels

The Verigene® bloodstream infection testing panels are used as a diagnostic aid for pathogenic and drug-resistant bacterial infections in the bloodstream. There are two types of panels, BC-GP (for gram-positive bacteria) and BC-GN (for gram-negative bacteria). BC-GP is used to identify nucleic acids and detect drug-resistance genes in gram-positive bacteria, while BC-GN is used to identify nucleic acids and detect drug-resistance genes in gram-negative bacteria. No sample preparation is required for either type.

2.1. Composition

The Verigene® system consists of dedicated equipment and reagent kits (panels) (**Figure 1**).

装　置

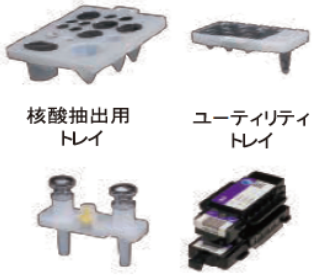
Verigene®
リーダー

Verigene®
プロセッサーSP

装置構成*		Verigene®リーダー	Verigene®プロセッサーSP
同時処理数		1検体	1検体
処理時間		約5分以内/検体	2～2.5時間/検体
接続数		1台	1～32台 (リーダー1台に対して)
外形寸法(WxHxD)		298x316x521mm	194x475x582mm
質量		11.3kg	17.3kg
電源	電圧・周波数	AC 100V, 50/60Hz	AC 100V, 50/60Hz
	最大消費電力	40W	200W

*リーダーとプロセッサーSPは個別販売です。

試薬キット



核酸抽出用
トレイ

ユーティリティ
トレイ

チップ
ホルダー

テスト
カートリッジ

試薬キット構成	用途
核酸抽出用トレイ	検体からの核酸抽出
ユーティリティトレイ	コントロールなどを格納
チップホルダー	試薬などの分注
テストカートリッジ	標的核酸の捕捉

Figure 1. Verigene® system and its reagents

2.1.1. Equipment

The instrument consists of a processor and a reader. The processor is an automated reaction device with functions such as nucleic acid extraction, nucleic acid amplification, and hybridization reactions of specimens. The reader is an automated detection and analysis device with functions such as system control and scattered light detection and analysis. One processor can process one specimen at a time, but if multiple specimens are to be processed simultaneously, up to 32 processors can be connected to one reader.

2.1.2. Reagents

All consumables required for testing are provided in the reagent kit. The reagents in the reagent kit contain all reagents and internal controls required for the reaction. All items are measured in one test and the entire process is controlled by an internal control.

2.2. Reagents to be measured

The reagents used in this system measure the main causative organisms of bloodstream infections and drug-resistant genes (**Table 1**), with BC-GP being able to detect 15 items (12 bacteria and 3 drug-resistant genes) and BC-GN also being able to detect 15 items (9 bacteria and 6 drug-resistant genes).

One of the characteristics of the Verigene® system is the large number of drug-resistant genes that can be detected. In BC-GP, it is possible to detect *mecA* carried by methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE), as well as *vanA* and *vanB* carried by vancomycin-resistant *enterococci* (VRE). In BC-GN, it is possible to identify drug-resistant genes such as CTX-M and IMP, as well as KPC, NDM, VIM, and OXA, which are frequently found in causative bacteria of bloodstream infections in Japan.

Table 1 Parameters measured by the Verigene® system

Type	BC-GP	BC-GN
Bacteria	*Staphylococcus*	*Acinetobacter*
	Staphylococcus aureus	*Citrobacter*
	Staphylococcus epidermidis	*Enterobacter*
	Staphylococcus lugdunensis	*Proteus*
	Streptococcus	*Escherichia coli*
	Streptococcus pneumoniae	*Klebsiella pneumoniae/Klebsiella variicola*
	Streptococcus pyogenes	*Klebsiella oxytoca*
	Streptococcus agalactiae	*Pseudomonas aeruginosa*
	Streptococcus anginosus	*Serratia marcescens*
	Enterococcus faecalis	*Acinetobacter*
	Enterococcus faecium	
	Listeria	
Drug-resistant genes	*mecA, vanA, vanB*	CTX-M
		KPC, NDM, VIM, IMP, OXA

For instance, when considering one of the prominently emphasized drug-resistant bacteria, the ESBL-producing bacteria (Extended-spectrum β-lactamase-producing bacteria), various types are observed both domestically and internationally, with many of them being CTX-M. Among the major subgroups, Groups 1, 2, and 9 collectively make up over 90% of the total [3].

In the case of carbapenemase-producing *Enterobacterales* (CPE), IMP is the most common type detected in Japan. On the other hand, KPC and OXA are frequently reported overseas. With the increasing number of people traveling abroad nowadays, there is a growing demand for the broad detection of drug-resistant genes. In this context, the Verigene® bloodstream infection panel is capable of detecting drug-resistant genes that are considered mainstream both domestically and internationally.

2.3. Principle and mechanism of measurement

The measuring principle is a microarray method in which target nucleic acids are captured by hybridization using the reaction properties of complementary nucleic acid sequences on a glass array substrate (**Figure 2**).

Multiple target nucleic acids (genes) relating to bacteria, viruses, and drug resistance are captured simultaneously and rapidly on a single array substrate. The captured target nucleic acid sequences are sensitized by gold and silver nanoparticles, and the scattered light is detected with high sensitivity.

2.4. Main mechanism from extraction to determination of nucleic acids

(1) Extraction, purification, and fragmentation of nucleic acids.
(2) Capture of target nucleic acids by hybridization (on the array substrate).
(3) Hybridization of the captured target nucleic acids with gold nanoparticle-labeled probes via mediator oligonucleotides.
(4) Coating of gold nanoparticles with silver ions (silver sensitization).
(5) Irradiation of 634 nm light from an LED light source and measurement of the scattered light.
(6) Determination of the presence or absence of target nucleic acids according to a determination algorithm.

3. Usefulness of Verigene®

When this system is implemented, the main bacteria names and drug resistance gene information can be

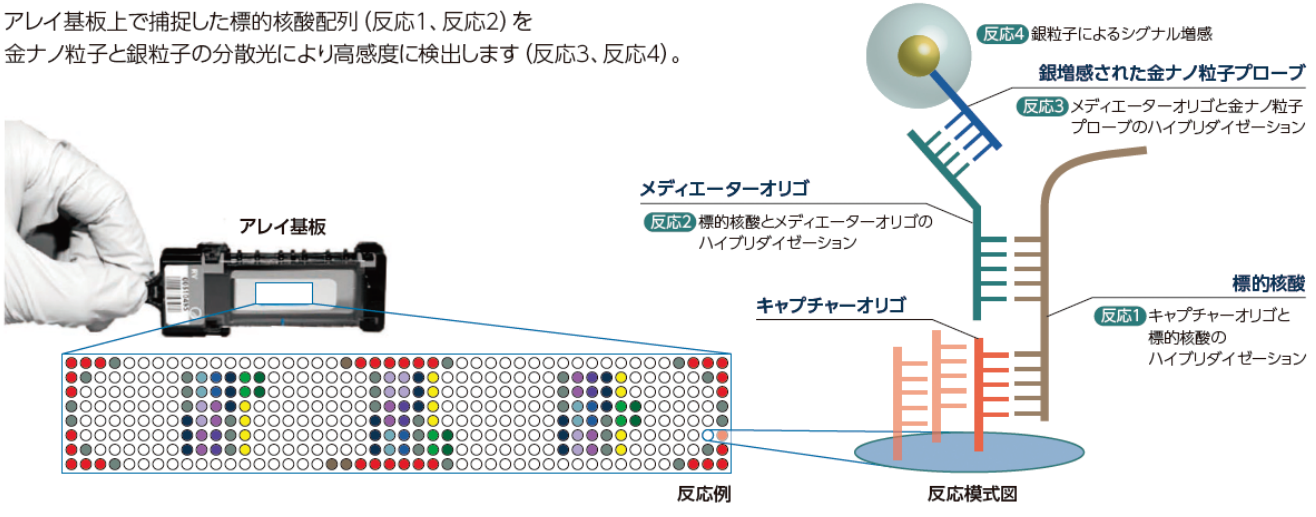


Figure 2. The measurement principle of the Verigene® system

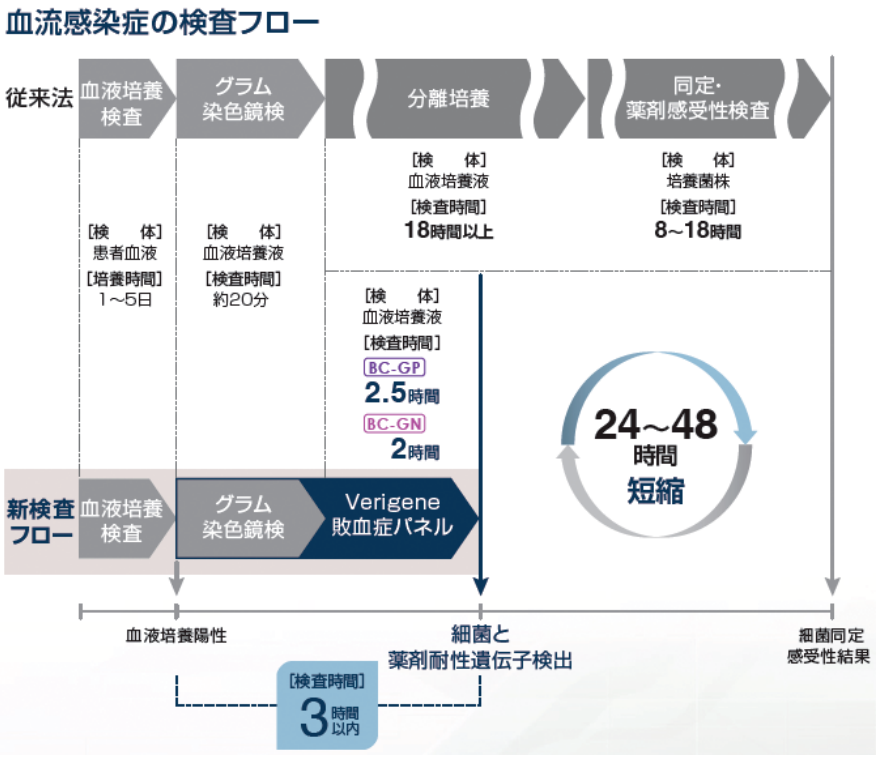


Figure 3. Position of the Verigene® system in the inspection workflow

reported to the clinical site within about three hours after a positive blood culture test, together with a Gram stain test (**Figure 3**).

In comparison to the conventional method, this system can reduce the time taken to report results by one or two days. In cases of bloodstream infections like sepsis, delays in administering antimicrobial treatment can significantly impact patient survival. Hence, providing appropriate and effective antimicrobial therapy for patients with drug-resistant (or multidrug-resistant) infections is of paramount importance. Swift transition to suitable antimicrobials is also crucial for controlling nosocomial infections, as it prevents the emergence of drug-resistant bacteria due to prolonged use of inappropriate antimicrobials. In an intervention study conducted in Japan, comparing Verigene® bloodstream infection detection with conventional methods, the time for test results was shortened from an average of 3.84 days to 21.7 hours, starting from the initiation of blood culture testing. Consequently, the cost of antimicrobials dropped by approximately half, from ¥8,505 to ¥3,618 per patient, and the 30-day mortality rate reportedly decreased from 13% to 3%, roughly a quarter of the previous rate [4].

4. Conclusion

Verigene® bloodstream infection testing panels are an incredibly useful diagnostic test for identifying causative microorganisms and detecting drug-resistance genes in sepsis treatment. The introduction of the sepsis panel allows for test results to be delivered 1 to 2 days earlier than conventional methods. Anticipated benefits include the ability to switch to effective narrow-spectrum drugs. Additionally, in cases where drug-resistance genes are detected, there is the option to switch to drugs that the microorganisms are susceptible to. As a result, it is believed that this approach can contribute to early improvement of the patient's medical condition, a reduction in mortality rates, and the control of drug-resistant bacterial infections. From a medical-economic perspective, it is also expected to lead to cost savings in terms of medication expenses, treatment, and hospitalization fees.

Disclosure statement

The author declares no conflict of interest.

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