
Medical Policy



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***Current Policy Effective Date: 3/1/19**
(See policy history boxes for previous effective dates)

Title: PCR Panel Testing for Gram-Negative Bacillus Antimicrobial Resistance Genes

Description / Background

Antibiotic resistance is evolving as a result of use and overuse of antibacterial agents. Characterizing the molecular mechanisms of antimicrobial resistance can be helpful to explain unusual phenotypic susceptibility profiles or for epidemiologic purposes. The impact is startling when seen through statistics from the US Centers for Disease Control and Prevention (CDC). CDC reports that highly resistant bacterial infections cause an estimated 23,000 deaths and 2 million illnesses in the United States annually.

A myriad of beta-lactamase enzymes may be found in gram-negative bacteria; these enzymes hydrolyze (break down) the beta-lactam ring of beta-lactam antibiotics, destroying their antibacterial activity. A single bacterial isolate may carry 1 or more genes that code for the production of a beta-lactamase enzyme. Beta-lactamases can be on the chromosome or on plasmids and may be classified as extended-spectrum beta-lactamases (ESBLs), AmpCs, and carbapenemases, among other types.

Carbapenemases show general resistance to all beta-lactam antibiotics including the beta-lactam-beta-lactamase inhibitor combinations and elevated or complete resistance against carbapenem antibiotics. In addition, isolates harboring carbapenemases often have additional beta-lactamase genes and genes for resistance to quinolones and aminoglycosides.

-*Klebsiella pneumoniae* Carbapenemase (KPC) is a plasmid-encoded carbapenemase first identified in *Klebsiella pneumoniae* isolates in North America. KPC has since spread to many parts of the world and can be found in several species of the *Enterobacteriaceae*.

ESBLs are beta-lactamases with an expanded substrate profile and are typically plasmid-borne. They are capable of hydrolyzing first-, second-, third- and fourth-generation cephalosporins, penicillins, and monobactams. *TEM*, *SHV*, and *CTX-M* genes are the most clinically prevalent. *TEM* and *SHV* subtypes are derived from the parental sequences by point

mutations resulting in amino acid substitutions, which allow the enzymes to hydrolyze a wide range of beta-lactam antibiotics. *CTX-M* genes originate from *Kluyvera* species and can be separated into 5 different groups based on their amino acid sequence: *CTX-M-1*, *CTX-M-2*, *CTX-M-9*, *CTX-M-8*, and *CTX-M-25*. *-VEB*, *PER*, *BEL*, and *GES* genes are less common.

AmpC cephalosporinases hydrolyze almost all beta-lactam antibiotics including penicillins, cephalosporins, and monobactams and may be chromosomally- or plasmid-encoded. Several *Enterobacteriaceae* carry a chromosomal copy of an AmpC gene.

<u>AmpC Gene</u>	<u>Origin of Chromosomal Gene</u>
CMY II	Citrobacter freundii
DHA	Morganella morganii
FOX	Aeromonas caviae
ACC	Hafnia alvei
ACT/MIR	Enterobacter cloacae and Enterobacter asburiae
CMY/MOX	Aeromonas hydrophilia

Plasmid-encoded AmpC genes may be shared among bacteria. Plasmid-encoded AmpC genes may produce a higher amount of beta-lactamase as compared to chromosomally-encoded AmpC genes; knowing the mechanism may be useful in assessing treatment. An AmpC gene detected in a species that does not have a chromosomal AmpC (see table above) suggests that the gene is plasmid-encoded.

Carbapenemase Genes:

GES (Carbapenemase)	OXA-24 like
GIM	OXA-48 like
IMP	OXA-58 like
KPC	SPM
NDM	VIM
OXA-23 like	VIM

ESBL Genes:

BEL	GES (ESBL)
CTX-M1 Group	PER
CTX-M2 Group	SHV
CTX-M9 Group	TEM
CTX-M8/25 Group	VEB

AmpC Genes:

ACC	CMYII
ACT/MIR	DHA
CMY MOX	FOX

Regulatory Status

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements.

Medical Policy Statement

The peer reviewed medical literature has not demonstrated the clinical utility of PCR panel testing for gram-negative bacillus antimicrobial resistance genes for treatment of an individual patient's drug-resistant infection. This testing was developed for determining the molecular mechanisms of antimicrobial resistance in gram-negative bacilli to explain unusual phenotypic susceptibility profiles and for epidemiologic research purposes. Therefore, this service is experimental/investigational for testing an individual patient's drug resistance to a gram-negative bacillus infection.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

0004U

Rationale

Routine evaluation of carbapenem resistance by the clinical laboratory is not necessary for patient care, as clinical breakpoints best predict response. However, evaluation for carbapenemase is integral to infection control efforts, and laboratories should have the capacity to do such testing, either in house or by submitting isolates to a reference laboratory.¹⁰

According to Banach et al (2014), Carbapenem-Resistant Enterobacteriaceae (CRE) are increasingly common causes of healthcare-associated infections for which limited therapeutic options exist. Active surveillance—identifying and implementing infection control measures for asymptomatic carriers—has been included in successful multifaceted CRE control programs¹ and is one of several interventions recommended in current Centers for Disease Control and Prevention guidance for CRE control.¹

Richter & Marchaim state that the global spread of carbapenem-resistant Enterobacteriaceae (CRE) has been fostered by the lack of preemptive screening of patients in healthcare facilities that could prevent patient-to-patient transmission. Outbreaks of CRE infections have led some institutions to implement rigorous screening programs, although controlled comparative data

are frequently lacking. Resource limitations and uncertainty regarding the optimal approach has kept many facilities from enacting more active routine surveillance policies that could reduce the prevalence of CRE. The ideal population to target for screening, the frequency of testing, and the preferred test method are components of surveillance programs that remain open to debate. This review discusses the rationale for different screening policies in use and the performance characteristics of laboratory methods available to detect CRE carriage.²

Antimicrobial susceptibility testing (AST) thus far has relied on phenotypically testing bacteria isolated. Although these phenotypic susceptibility testing techniques are relatively simple, they require bacterial isolation, and hence the result is often not available until 2 days after treatment has started. Other shortcomings of the phenotypic approach of susceptibility testing includes the tests being highly dependent on experimental conditions and the fact that more than one method needs to be performed to obtain an accurate susceptibility profile. They also highlighted the fact that different bacterial species have different susceptibilities to the same antibiotic, and that there is no international agreement on breakpoints for interpretation of antimicrobial susceptibility tests.³

To increase the speed and reliability of resistance testing, the use of a genotypic approach has been advocated recently, and numerous DNA – based assays have been developed for detection of bacterial resistance genes. Although this approach has been described as a true revolution, it does require a good understanding of resistance mechanisms and the genes involved. There are some limitations to this approach, as clinical studies will be required to validate the genotypic approach to testing for resistance, the presence of a resistance gene may not always be indicative of resistant bacteria, and conversely, if a gene coding for resistance to an antibiotic is not detected, it may not mean that the bacteria are susceptible to that particular agent.³

Check MDR CT103 Test

Cuzon et al (2012) evaluated the Check MDR CT103 array test. This test employs highly specific DNA markers to identify the β -lactamase genes of ESBLs (TEM, SHV and CTX-M, and discriminates between ESBL and non-ESBL TEM and SHV variants), of pAmpC (CMY-2-like, DHA, FOX, ACC-1, ACT/MIR and CMY-1-like/MOX) and of carbapenemases (KPC, OXA-48, VIM, IMP and NDM). One-hundred-and-eighty-seven well-characterized Gram-negative bacilli isolates possessing different bla genes were tested. Total DNAs were extracted using a Qiagen DNA mini kit. The Check MDR CT103 array was used as recommended by the manufacturer. The system correctly identified representatives of the three ESBL gene families tested, including differentiation between non-ESBL and ESBL TEM and SHV variants. All bla(CTX-M) genes were classified into the appropriate family group (i.e. CTX-M-1 group, CTX-M-2 group, CTX-M-9 group and CTX-M-8/25/26 group). In addition, the clinically relevant plasmid-encoded cephalosporinase and carbapenemase genes were also reliably detected. Specificities and sensitivities of 100% were recorded for most bla genes. The authors concluded that the Check-MDR CT103 array is a powerful high-throughput tool for rapid identification of ESBL, pAmpC and carbapenemase producers in culture. Because of its rapid performance, this platform is a valuable tool for epidemiological or infection control studies.⁴

Willemsen et al (2016) performed a validation study of the Check MDR CT103 (Check-Points, Wageningen, Netherlands) in 2013, an OXA-48-like carbapenemase gen was identified in two isolates that were previously obtained from a patient with non-Hodgkin lymphoma in 2007. Whole-genome sequencing (WGS) and subsequent BLAST Ringe Image Generator (BRIG)

analysis were performed to establish the presence of OXA-48 carbapenemase encoding plasmids and their similarity. This case report describes the first documented OXA-48-producing *Klebsiella pneumonia* (ST648) and *Escherichia coli* (ST866) in the Netherlands. A similar IncL/M plasmid was identified in both strains, suggesting within-patient horizontal transfer. This case illustrates that OXA-48-carbapenemase-producing Enterobacteriaceae can be unnoticed without adequate laboratory detection procedures. Our observation stresses the importance of uniform and adequate laboratory methods for the timely and accurate detection of important antimicrobial resistance.⁵

Cunningham et al (2016) evaluated the Check MDR CT103 and CT103XL tests. Using a rapid bacterial lysis method, the Check MDR CT103 and CT103 XL microarrays demonstrated accuracies of 98.1% and 94.2%, respectively, for detection of known resistance genes in 108 multidrug-resistant Gram-negative bacilli. In 45 isolates, 49 previously unrecognized extended-spectrum β -lactamase or plasmid AmpC targets were detected and confirmed by conventional PCR. The author concluded the results demonstrate the high accuracy of a microarray-based approach for resistance mechanism characterization in multidrug-resistant Enterobacteriaceae (MDRE). Despite the high cost compared to that of real-time or conventional PCR and phenotypic methods, the additional information provided by such arrays may be helpful for infection prevention and control, and potentially, antimicrobial stewardship and patient care.⁶

SUMMARY OF EVIDENCE

Outbreaks of extended-spectrum gram-negative bacilli have occurred in hospitals around the world. Detecting these resistance mechanisms may be important for identifying, stopping, and preventing such outbreaks. The peer reviewed medical literature has not demonstrated the clinical utility of PCR panel testing for gram-negative bacillus antimicrobial resistance genes for treatment of an individual patient's drug-resistant infection.

SUPPLEMENTAL INFORMATION

Ongoing and Unpublished Clinical Trials

A search on www.clinicaltrials.gov did not show any current trials that may influence this review.

Practice Guidelines and Position Statements

There are no practice guidelines or position statements for PCR panel testing gram-negative bacillus.

Government Regulations

National:

There is no national coverage determination on this testing.

Local:

There is no local coverage determination on this testing.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

References

1. Banach DB, Francois J, Blash S, Patel G, et al. Active surveillance for carbapenem-resistant enterobacteriaceae using stool specimens submitted for testing for clostridium difficile. *Infect Control Hosp Epidemiol*. January 2014;35(1):82-84
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3. Wheat P. History and development of antimicrobial susceptibility testing methodology. Mast Laboratories Merseyside, UK. July 2001.
4. Cuzon G, Naas T, Bogaerts P, et al. Evaluation of DNA microarray for the rapid detection of extended-spectrum β -lactamases (TEM, SHV and CTZ-M), plasmid-mediated cephalosporinases (CMY-2-like, DHA, FOX, ACC-1, ACT/MIR and CMY-1-like/MOX) and carbapenemases (CPC, OXA-48, VIM, IMP and NDM). *J Antimicrob Chemother*. August 2012;67(8):1865-1869.
5. Willemsen I, Hille L, Vrolijk A, et al. Evaluation of a commercial real-time PCR for the detection of extended spectrum β -lactamase genes. *Journal of Medical Microbiology*. 2014;63:540-543.
6. Cunningham SA, Vasoo S, Patel R. Evaluation of the Check-Points Check MDR CT103 and CT103 LX microarray kits by use of preparatory rapid cell lysis. *Journal of Clinical Microbiology*. May 2016;54(5):1369-1371.
7. Mayo Clinic; Mayo Medical Laboratories. Test ID information. Test ID: GNRG. Gram-Negative Bacillus Antimicrobial Resistance Genes, PCR Panel. Available at <http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/64721> (Accessed 6/16/17).
8. Nijhuis R, Zwet A, Stuart J, et al. Rapid molecular detection of extended-spectrum β -lactamase gene variants with a novel ligation-mediated real-time PCR. *Journal of Med Microb*. 2012;61: 1563-1567
9. Lutgring JD, Limbago BM. The problem of carbapenemase-producing carbapenem-resistant-enterobacteriaceae detection. *Journal of Clinical Microbiology*. March 2016;54(3):529-534.
10. Miller S and Humphries RM. Clinical laboratory detection of carbapenem-resistant and carbapenemase-producing Enterobacteriaceae. *Expert Rev Anti Infect Ther*. 2016 Aug;14(8):705-17.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through June 2018, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/17	8/15/17	8/15/17	Joint policy established
11/1/18	8/21/18	8/21/18	Routine policy maintenance, no change in policy status.
3/1/18	12/11/18		Code 0004U deleted as of 1/1/18, no replacement code. Recommend retirement of policy.

Next Review Date: This policy is no longer subject to routine review.

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: PCR PANEL TESTING FOR GRAM-NEGATIVE BACILLUS ANTIMICROBIAL
RESISTANCE GENES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not Covered
BCNA (Medicare Advantage)	Not Covered
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.