

# User manual

## Check-MDR Carba

Rapid Molecular Detection of carbapenemase genes

**REF** 14-0041 & -0051  96 or 24

### ABI 7500

For use with the ABI 7500 real-time PCR system (Applied Biosystems, CA, USA) in combination with the TaqMan® Universal PCR MasterMix (Applied Biosystems, CA, USA)



041-03 & 051-03

### Key to symbols used



For *In Vitro* Diagnostic Use



Catalog number



Batch code



Instructions for use number



Use before YYYY-MM



Consult instructions for use



Temperature limitation



Contains sufficient for < n > tests



Manufacturer

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## Intended use

Check-MDR Carba is designed for the rapid molecular detection of the clinically important carbapenemase genes in gram-negative bacteria: KPC, NDM, OXA-48, VIM and IMP. Check-MDR Carba generates definitive results within 4.5 hours, compared to the 24 hours necessary for analysis with conventional phenotypic methods.

## Introduction

In the last decade various carbapenemases have been reported which cause elevated or complete resistance against carbapenem antibiotics when produced by bacteria. Strains carrying genes encoding such enzymes are generally resistant to all  $\beta$ -lactam antibiotics. They often contain additional  $\beta$ -lactamase genes and genes for resistance against quinolones and aminoglycosides. The carbapenemase genes detected with Check-MDR Carba include: 1) **KPC**, *Klebsiella Pneumoniae* Carbapenemase, an Ambler class A carbapenemase first identified in *K. pneumoniae* isolates in North America and now found in many countries worldwide in various other enterobacterial species including *E. coli*; 2) **NDM**, New Delhi Metallo- $\beta$ -lactamase (NDM) first reported in 2009 in Sweden in both *K. pneumoniae* and *E. coli*, nowadays regularly found in various European countries and quite prevalent in India and Pakistan; 3) **OXA-48** carbapenemase, a class D  $\beta$ -lactamase originating from *Shewanella* species, and regularly found in Europe, North Africa and Turkey in fermenting Enterobacteriaceae like *E. coli* and *Klebsiella*; and 4) **VIM & IMP** carbapenemases, metallo- $\beta$ -lactamases first reported in *Pseudomonas aeruginosa* (VIM-1 in Verona in 1997 and an IMP-1 in Japan in 1990), and since then transferred to *E. coli* and *K. pneumoniae* and many other Enterobacteriaceae. Many gene variants of VIM and IMP exist of which the DNA sequences may differ significantly and, therefore, VIM and IMP should be regarded as two separate gene families of homologous gene variants.

Conventional methods for detection of  $\beta$ -lactamases rely on phenotypic identification which is time-consuming, frequently inconclusive and not applicable to all species. Check-MDR Carba is a rapid molecular test for the detection of the most prevalent carbapenemase genes.

## Principle of the method

Check-MDR Carba is based on specific molecular recognition of target sequences by DNA probe ligation followed by real-time PCR detection. The recognition step uses two specific oligonucleotides (ligation probes) that are joined by a DNA ligase only when they match perfectly with the target DNA. In addition to target-specific sequences, the DNA probes contain two universal primer binding sites as well as a DNA segment that is complementary to a molecular beacon. Subsequent real-time amplification with universal primers is used to detect the connected probes, and their accumulation is visualized by fluorescence of a molecular beacon

## Kit contents (for 96 or 24 reactions)

Components (Mat. No.)	Description	Storage conditions
Solution A (9-0050)	1 tube (purple cap ●) 600 $\mu$ l	- 20°C
Solution P Carba (9-0052)	1 tube (green cap ●) 250 $\mu$ l	- 20°C
Solution R (9-0053)*	1 tube (yellow cap ●) 1000* or 250** $\mu$ l	- 20°C, <b>store in the dark</b>
Internal control (9-0054)	1 tube (transparent cap ●) 500 $\mu$ l	- 20°C
Positive control Carba (9-0056)	1 tube (white cap ○) 500 $\mu$ l	- 20°C
Manual (9-0058)	Leaflet – download from website	Not critical

\* Volume provided for 96 reactions. \*\*Volume provided for 24 reactions.

## Shelf life, Storage and Handling

The components of the kit must be stored at -20°C. Solution R has to be stored in the dark. Reagents stored at the appropriate storage conditions can be used until the expiration date. Please visually inspect the box upon initial opening to ensure that its content is intact. Do not use when damaged. Please contact the Check-Points office at [support@check-points.com](mailto:support@check-points.com) if you have any questions or in case shipping has taken more than 2 days.

## Materials required but not supplied with the kit

	Pre-PCR	Post-PCR
Equipment	<ul style="list-style-type: none"> <li>• Thermocycler*</li> <li>• Vortex mixer</li> <li>• Mini-centrifuge</li> <li>• PCR plate spinner</li> </ul>	<ul style="list-style-type: none"> <li>• Real-Time PCR instrument*</li> </ul>
Supplies	<ul style="list-style-type: none"> <li>• TaqMan®Universal PCR MasterMix</li> <li>• DNA extraction procedure**</li> <li>• Disposable laboratory (powder-free) gloves</li> <li>• Pipettes &amp; disposable (filter-) tips for volumes of 1 to 1000 µl</li> <li>• 1.5 ml tubes (“Eppendorf tubes”)</li> <li>• 10 ml tubes (for large volumes)</li> <li>• 96-well PCR plate</li> <li>• PCR plate seal</li> <li>• PCR tubes/strips</li> </ul>	

\*contact your local representative for specifications.

\*\*see Protocol, section 1

## Good laboratory practices

### Recommendations for best results

The quality of the results depends on strict compliance with the following good laboratory practices, especially concerning PCR:

- The test must be performed by adequately trained personnel.
- Spinning down for a few seconds is done in the various steps to ensure that all material is collected at the bottom of the tubes.
- Do not use reagents after their expiration date.
- Before use, thaw frozen reagents completely at room temperature and vortex briefly to obtain a homogeneous solution. After vortexing briefly, spin down the solution to avoid contamination when opening the lid. Avoid unnecessary freeze-thawing of the kit content.
- Periodically, verify the accuracy and precision of pipettes, as well as correct functioning of the instruments.
- **Keep Solution R (yellow cap ●) in the dark** to avoid photo-bleaching of the dyes.

## Prevention of contaminations

PCR produces a very high quantity of DNA amplification products (amplicons) even from minute quantities of starting material. Check-MDR Carba may therefore yield unreliable results if samples become contaminated with amplicons from previous amplification reactions prior to the PCR. Preventive measures to minimize the risk of amplicon contamination must be taken. Please read carefully and follow the instructions outlined below.

**Use separate rooms:** a pre-PCR room and a post-PCR room.

- Sample preparation, DNA recognition (step A) and preparation of the amplification step (step B) is carried out in the pre-PCR room.
- Incubation in the real-time PCR thermocycler of step B is carried out in the post-PCR room.
- Never bring the reaction products of step B to the pre-PCR room.
- Never prepare the ligation and/or amplification steps in the post-PCR room.

**To keep laboratory free of PCR product contamination:**

- Use pipettes with hydrophobic filter tips.
- Make sure to always use a new pipette tip when adding solutions or samples to a reaction tube to avoid contamination.
- Follow proper pipette-dispensing techniques to prevent aerosols.
- Use separate equipment, pipettes, thermocyclers, sample holders, lab coats, gloves, disposables and reagents, that are assigned to these rooms. Never transfer items from the post-PCR room to the pre-PCR room.
- Wear a clean lab coat and clean gloves during all steps of the test.
- Wear clean gloves and a clean lab coat not previously worn while handling amplified PCR products or during sample preparation.
- Change gloves whenever you suspect that they are contaminated.
- Keep the tubes of all kit components and samples closed as much as possible.
- Clean the lab benches and all equipment regularly with a 0,5% sodium hypochlorite solution.

## Protocol

**It is strongly recommended that the full protocol is read before using the test.**

The protocol consists of the following steps:

1. DNA extraction from bacterial cells
2. DNA recognition step A
3. Real-time probe amplification step B

### 1. DNA extraction from bacterial cells

Important points before starting:

- DNA extraction is completely carried out in the pre-PCR room.
- Make sure to always use a new pipette tip when adding solutions or samples to a reaction tube to avoid contamination.
- Clinical specimens should first be incubated on nutrient agar plates. Use bacterial cells from these agar plates for DNA extraction. Typical growth media include blood agar, MacConkey agar and Tryptic Soy agar.

Procedure:

1. Check-MDR Carba has been validated with the following extraction methods for bacterial cells:

- **NucliSENS® easyMAG®** (bioMérieux, France) automated DNA extraction procedure for bacterial cells. Follow the manufacturer's protocol for bacterial cells and use 200 µl cell suspension of McFarland 0,5 – 1,0 or OD<sub>600</sub> 0,08 – 0,12 (this may vary between spectrophotometers). Add 2,5 µl of the Internal Control solution (IC, transparent cap ●) to the cell suspension and start the DNA extraction. DNA is eluted in 110 µl elution buffer. DNA extracts can be stored at -20°C or +4°C for up to 6 months.
- **DNeasy Blood & Tissue Kit** (QIAGEN, CA, USA) DNA extraction procedure for bacterial cells (manual extraction or QIAcube automated system). Follow the manufacturer's protocol for gram-negative bacteria. Prepare 1 ml cell suspension of McFarland 1,2 – 1,8 or OD<sub>600</sub> of 0,16 – 0,24 (this may vary between spectrophotometers) and centrifuge at 14000 rpm for 10 minutes. Discard the supernatant and add 5 µl of the IC solution (transparent cap ●) to the pellet. Start the DNA extraction with the pelleted cells using either the manual procedure or the QIAcube automated procedure. DNA is eluted in 200 µl elution buffer. Store DNA extracts at -20°C or +4°C for up to 6 months.

- **MagNA Pure system** (32 samples) (Roche, CH) for DNA extraction procedure for clinical specimens. Use 200 µl of cell suspension in PBS, Phosphate buffered saline, McFarland 0,5 – 1,0 or OD<sub>600</sub> 0,08 – 0,12 (this may vary between spectrophotometers). Add 2,5 µl of the IC solution (transparent cap ●) to the cell suspension and start the DNA extraction. DNA is eluted in 100 µl elution buffer. DNA extracts should be stored at +4°C only, for up to 6 months.
2. Use the DNA solution directly and continue with “step A” or store as specified until use.

### 2. DNA recognition step A

Important points before starting:

- Step A is completely carried out in the pre-PCR room.
- Make sure to always use a new pipette tip when adding solutions or samples to a reaction tube to avoid contamination.
- It is advised to perform a positive and negative control reaction. The positive control (white cap ○) is supplied with the kit; for the negative control we recommend to perform a DNA extraction as specified earlier (with IC solution) for a sample known to be negative for the test in use (*i.e.*, Carba negative sample, elution buffer, clean water).
- Use a thermocycler located in the pre-PCR room to perform the step A reaction. Use PCR tubes that are suitable for the type of thermocycler used.

Procedure:

1. Determine the number of reactions. Thaw all reagents (*i.e.* Solution A, DNA samples If kept at -20°C, and positive control), mix well and keep on ice.
2. Prepare the ligation reaction mix as described in table 1 and include 10% surplus to ensure that you have enough ligation reaction mix. Mix well and spin down.
3. To each tube add 7,5 µl of ligation reaction mix and 10 µl of sample DNA or controls (see table 2).
4. Close the tubes, mix well (by tapping or vortexing) and spin down briefly. The solutions should have a uniform blue color.
5. Place the tube(s) in the thermocycler and run the Probe ligation program, see table 3 (total sample volume ~ 18 µl).

**Table 1:** Ligation reaction mix.

Component	Volume per reaction
Solution P Carba (green cap ●)	2,5 µl
Solution A (purple cap ●)	5 µl
<b>Total volume of ligation reaction mix</b>	<b>7,5 µl</b>

**Table 2:** Ligation reaction setup.

Reaction Type	Component	Volume per reaction
Test sample	Sample DNA	10 µl
Positive control	Carbapenemase positive (white cap O)	10 µl
Negative control	Negative sample extracted with the IC	10 µl

**Table 3:** Probe ligation cycling parameters.

Step	Temperature	Time	Cycles
1.	95°C	3 min	1
2.	65°C	120 min	1
3.	98°C	2 min	1
	4°C	hold	

**Note:**

- It is recommended to mix Solution P and Solution A first in a separate tube for x number of samples (including controls and 10% surplus) and then add 7,5 µl of this mix to each reaction tubes. Prepare this mix shortly before step A is started and use immediately. Do not store this mix and dispose after use.
- Close the PCR tube(s) carefully: excessive pressure may distort the cap and lead the sample evaporation during step A.

### 3. Real-time probe amplification step B

Important points before starting:

- The preparation of the reaction mix for step B is carried out in the pre-PCR room.
- Step B was developed for the real-time PCR **ABI 7500** instrument, therefore ABI 7500 PCR 96-well plates and corresponding adhesive seals should be used or alternatively adapted 8-Tube strip and optical 8-Cap strip (Applied Biosystems, CA, USA).
- Step B requires the **TaqMan® Universal PCR MasterMix** (Applied Biosystems, CA, USA).

Procedure:

- Briefly spin down the reaction mixtures from step A.
- Take Solution R (yellow cap ●) from the freezer. Thaw completely at room temperature **protecting from exposure to light**. Mix well and spin down briefly.
- Prepare the real-time PCR (qPCR) reaction mix as described in table 4 and include 10% surplus to ensure that you have enough qPCR reaction mix.

- Add 25 µl of qPCR master mix and 5 µl of each step A reaction to each well of the 96-well plate. Use a new pipette tip for each step A reaction sample added.
- Seal the plate, mix by tapping the plate on the bench and spin down briefly using a centrifuge with 96-well plate adapters.
- Transfer the plate to the post-PCR room.
- Following the manufacturer's instructions, start and set up the run of the real-time PCR ABI 7500 instrument using the following parameters, see also table 5 and 6:
  - Run mode: Standard 7500 - Standard ramp speed
  - Reaction volume: 30 µl
  - ROX™ passive reference dye: Included in the real-time PCR buffer
  - TaqMan® Reagents
  - Experiment: Quantitation – Standard Curve
- Without delay, place the plate or strips into the real-time PCR instrument and start the run with the cycling conditions presented in table 6. When the run is completed, discard the plate according to local regulations.

**Table 4:** qPCR-reaction mix.

Component	Volume per reaction
Solution R ( yellow cap ● )	10 µl
TaqMan® Universal PCR MasterMix	15 µl
<b>Total volume of master mix</b>	25 µl

**Table 5:** Real-time PCR Plate Setup.

Target	Detector	Reporter / Quencher
Carbapenemase	FAM (520nm)	FAM / none
Internal Control	Cy5 (662nM)	Cy5 / none

**Table 6:** Real-time cycling parameters – ABI 7500 default profile.

Step	Temperature	Time	Cycles	Data Collection	Ramp Rate
1.	50°C	2 min	1	OFF	100%, standard
2.	95°C	10 min	1	OFF	100%, standard
3.	95°C 60°C	15 sec 60 sec	40	ON	100%, standard

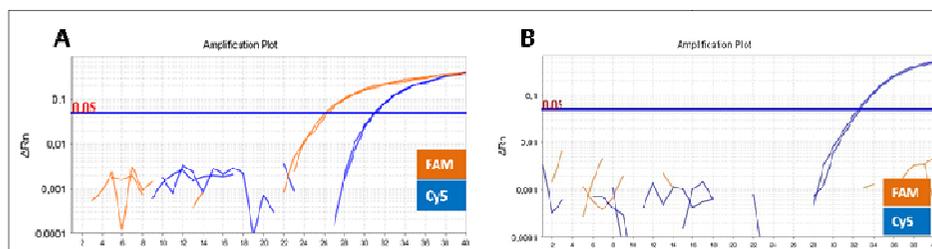
## Data analysis and interpretation

### ABI 7500 real-time PCR instrument

For a detailed description on how to operate the ABI 7500 instrument and how to analyze data, please refer to the *ABI 7500 real-time PCR system getting started guide*.

#### 1. Data analysis

1. In the *Analysis Settings* use the automatic baseline setting and **set the threshold manually at 0,05**, in the middle of the exponential phase (check on the Amplification plot). This process is described in the the real-time PCR instrument user guide.
2. Open the *Analysis* menu and check *Amplification Plots*. Figure 1 shows typical amplification plots of carbapenemase positive and negative samples.
3. Export  $C_T$  values for both FAM and Cy5 targets.



**Figure 1:** Typical real-time amplification plots of: A carbapenemase positive sample and B carbapenemase negative samples. The internal control curve (Cy5) may be absent or at a higher  $C_T$  in positive samples (7500 Software v2.0.5).

#### 2. Data interpretation

Interpret results (positive, negative or inconclusive) with the  $C_T$  values obtained for the samples following the guidelines outlined below and summarized in table 7 and 8.

1. The relevant columns in the results table are “Sample Name”, “Target Name”, “Reporter” and “ $C_T$ ”. All other columns may be ignored or removed from the table.
2. Verify that the real-time PCR run is valid before data analysis and interpretation of the results. Table 7 shows criteria for a valid real-time Check-MDR Carba run.

1. Positive carbapenemase samples will show a lower FAM  $C_T$  value than the internal control (IC) Cy5 signal. The FAM positive signal is expected at  $C_T < 32$ .
2. Negative carbapenemase samples will show a higher FAM  $C_T$  value than the IC Cy5 signal. The IC Cy5 signal is expected between  $33 \pm 2$ , and the FAM signal is expected at  $C_T > 36$ .
3. Samples with a FAM  $C_T$  between 32 and 36 and a  $C_T$  for the IC Cy5 at  $33 \pm 2$  are considered inconclusive. Please repeat the whole procedure with a new DNA extract of the bacterial culture. If still inconclusive the sample can be regarded neither positive nor negative.
4. In samples with a FAM  $C_T > 36$  or undetermined and an IC Cy5  $> 36$  or undetermined the assay has not worked well and should be repeated with a new DNA extract of the bacterial culture.

**Table 7:** Criteria for a valid run with Check-MDR real-time assay.

Reaction/Sample Type*	Carba (FAM) $C_T$ values	Internal Control (Cy5) $C_T$ values
Positive control	$28 \pm 3$	Undetermined
Negative sample (extracted with IC)	$C_T > 36$ or Undetermined	$33 \pm 2$

\* IC: internal control; If  $C_T$  values are not as expected, see FAQ

**Table 8:** Data interpretation guidelines.

Carba (FAM) $C_T$ values	Internal Control (Cy5) $C_T$ values	Interpretation
$< 32$	$\geq 31$	Positive sample
$> 36$ or Undetermined	$33 \pm 2$	Negative sample
$32 < C_T < 36$	$33 \pm 2$	Inconclusive
$> 36$ or Undetermined	$> 36$ or Undetermined	Sample failed*

\* see FAQ.

## Frequently asked questions (FAQ) & Troubleshooting

### 1. How important is the amount of input cells for DNA extraction?

Check-MDR Carba has been optimized using a well-defined amount of cells. A deviation of 20% in the amount of cells will have no major consequences. Larger deviations will not give optimal results.

### 2. May other DNA extraction methods be used with Check-MDR Carba?

Check-MDR Carba test has been optimized using DNeasy Blood & Tissue Kit (QIAGEN, CA, USA), NucliSENS® easyMAG® (bioMérieux, France), and MagNA Pure system (Roche, CH) extraction methods. Check-Points does not guarantee the performance of the test with extraction methods other than those recommended in this manual.

### 3. The thermocycler states an error in step A.

Please contact Check-Points Technical Support: [support@check-points.com](mailto:support@check-points.com)

### 4. During the step A the sample(s) have (partly) evaporated.

Reaction tubes may not have been closed properly. Please restart the procedure from step A.

### 5. I have left Solutions (A, P, R, Internal control or Positive control) out of the -20°C (-4°F) storage.

These reagents must be stored at -20°C (-4°F) for proper performance of the test. The performance of the product cannot be fully guaranteed if these solutions were left out of -20°C (-4°F) for more than 24 hours.

### 6. May I change the C<sub>T</sub> threshold when analyzing my real-time PCR data?

The Check-MDR Carba assay was developed using a manual threshold of 0,05 to analyze the data. We therefore strongly advise to use this threshold for data analysis. Please refer to the tutorial *Data Analysis on the ABI® 7500 PCR System: Setting Baselines and Thresholds* for more information on setting thresholds.

### 7. What does it mean if the real-time results show no C<sub>T</sub> values or interpretation concluded that the sample failed?

Such results may have multiple explanations:

- The sample DNA was not added to the assay in step A.
- The sample DNA tested with Check-MDR Carba is negative and the internal control was not added prior to DNA extraction.
- The DNA extraction failed since the internal control was not detected.
- The sample DNA contains contaminants inhibiting the reactions. Please repeat the DNA extraction.
- Solution P and/or Solution A was not added in step A. Please repeat the test.
- Solution R and/or TaqMan® Universal PCR MasterMix was not added to the assay. Please repeat the test.
- TaqMan® Universal PCR MasterMix may have expired.

### 8. What does it mean if the real-time results show no C<sub>T</sub> values for the positive control or interpretation concluded that sample is inconclusive?

Such results may have multiple explanations:

- The positive control solution was not added to its reaction tube in step A.
- Solution P and/or Solution A was not added in step A. Please repeat the test.
- Solution R or TaqMan® Universal PCR MasterMix was not added to the assay. Please repeat the test.
- TaqMan® Universal PCR MasterMix may have expired.

### 9. Duplicate DNA samples tested with Check-MDR Carba test do not yield identical results.

C<sub>T</sub> values of identical samples may vary slightly between individual reactions. Larger variations, > 2 C<sub>T</sub> values, suggest pipetting errors or other differences between the duplicate samples.

### 10. May the assay be interrupted after step A and continued at a later time?

Reaction mixtures from Step A can be kept at hold at +4°C for up to 2 hours. For further inquiries, please contact Check-Points Technical Support: [support@check-points.com](mailto:support@check-points.com).

## Limitations

Check-MDR Carba uses a range of specific DNA markers to detect the presence of the carbapenemase genes KPC, NDM, OXA-48, VIM and IMP, which currently represent the clinically most prevalent carbapenemases. The test detects all presently known variants of KPC, NDM, OXA-48 and VIM, except VIM-7, a rare variant only found in *Pseudomonas aeruginosa*. IMP is the most diverse carbapenemase gene family, and the test detects the clinically most important IMP-variants in *Enterobacteriaceae*, including IMP-1, -3, -4, -5, -6, -7, -8, -10 and -13. It should be noted that other rare carbapenemase gene families are not detected.

Check-MDR Carba requires DNA purified from a colony or bacterial culture. Clinical specimens cannot be tested directly. The quality of the input DNA is an important factor for obtaining reliable results with Check-MDR Carba. DNA must be extracted from cultured bacteria using the extraction methods validated with Check-MDR Carba and described in this manual (page 4). The assay has been tested extensively with purified DNA from gram-negative bacteria, such as *Escherichia*, *Salmonella*, *Klebsiella*, *Enterobacter*, *Citrobacter* and *Pseudomonas*, with excellent results. However, it may never be excluded that other Gram-negative bacteria or certain strains of the above species will yield poor results. Check-MDR Carba cannot and does not make any representation or warranty that it is capable of correctly detecting the carbapenemase genes in all gram-negative species, subspecies or type or in any clinical sample source. Results may need to be confirmed by additional methodologies in specific cases (e.g. for regulatory samples). Due to the high variability of bacterial genomes it is possible that certain subtypes might not be detected. The test reflects the state of knowledge of Check-Points Health B.V.

The presence of multiple bacterial species in a sample may hamper the interpretation of the test. As with other diagnostic assays, the results of this test may only be interpreted in combination with additional laboratory and clinical data available to the responsible person. Use of this assay is limited to appropriately qualified personnel, well-trained in performing DNA-based molecular detection methods.

Despite the utmost care in the development and preparation of the protocol Check-Points cannot take any responsibility for errors, omissions and/or future changes herein.

**Literature Citation:** When describing a procedure for publication using this product, please refer to it as the *Check-MDR Carba*.

**Notice to Purchaser:**

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