Cepheid GeneXpert Carba-R assay

General Limitations

• The Xpert Carba-R Assay detects *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{OXA-48}$, and *bla*$_{IMP}$ from rectal swab specimens or pure colonies, and is not for bacterial identification. Detection of these gene sequences does not indicate the presence of viable organisms.

• The Xpert Carba-R Assay is not a sub-typing tool and does not report variants of the *bla*$_{IMP}$, *bla*$_{VIM}$, *bla*$_{NDM}$, *bla*$_{KPC}$, or *bla*$_{OXA-48}$ genes.

• Certain bacterial species, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* have been shown to exhibit resistance to carbapenems due to intrinsic resistance mechanisms.

• The detection of other OXA-carbapenemase genes, besides *bla*$_{OXA-48}$ and *bla*$_{OXA-181}$, has not been evaluated in the study.

• The *in silico* analyses used to predict variants detected by the assay were based on a comparison of target gene sequences available in GenBank to the Xpert Carba-R Assay primer/probe oligonucleotides and amplicon sequence for each gene target. BLAST searches for *in silico* analysis were performed in 2014-2015. *In silico* analysis of new variant gene sequences deposited into the database after 2015 for the five target genes have not been performed.

• Mutations or polymorphisms in primer or probe binding regions may affect detection of current, new or unknown *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{OXA-48}$, and *bla*$_{IMP}$ variants, resulting in a false negative result.

• The Xpert Carba-R Assay will generate a negative IMP result when testing samples containing IMP-7, IMP-13, or IMP-14 gene sequences.

• Performance of the Xpert Carba-R Assay with non-target carbapenemase genes, other than *bla*$_{SPM}$, *bla*$_{SME}$, and *bla*$_{IMI}$, is unknown.

• As the detection of *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{OXA-48}$, and *bla*$_{IMP}$ gene sequences is dependent on the number of organisms present in the sample, reliable results are dependent on proper sample handling and storage.

• Testing with the Xpert Carba-R Assay should be used as an adjunct to other available methods.

• Xpert Carba-R Assay results may sometimes be **INVALID** due to a failed SPC control, or result in an **ERROR** or **NO RESULT**, and require retesting that can lead to a delay in obtaining final results.

Rectal Specimen Limitations

• The performance of the Xpert Carba-R Assay has not been evaluated with rectal swab specimens from pediatric patients.

• Analytical studies using combinations of two bacterial populations on contrived swab specimens indicate that when one carbapenemase-producing bacterial species is inoculated near the LoD and another carbapenemase-producing bacterial species is present at concentrations equal or greater than 5×10^6 CFU/swab, the low concentration target may not be detected. Co-colonization with two or more carbapenemase-producing organisms has been reported with Xpert Carba-R Assay, but is rare. Lack of detection of a second target should have minimal impact on patient management since isolation procedures would be instituted for patients showing any positive result for a carbapenemase-producing organism.

• Interference with the Xpert Carba-R Assay may be observed with barium sulfate at > 0.1% w/v, and Pepto-Bismol at > 0.01% w/v in tests with rectal swab matrix samples.

• In rectal swab samples containing the VIM target, interference may occur if fecal fat is present at a concentration of 0.25% w/v, resulting in delayed cycle threshold values.

• In addition to *Pseudomonas aeruginosa* and *Acinetobacter baumannii* groups tested in the contrived study, other non- *Enterobacteriaceae* were also evaluated: *Pseudomonas stutzeri* (1), *Pseudomonas oryzihabitans* (1), *Pseudomonas putida* (2), and *Empedobacter brevis* (1). The performance of the Xpert Carba-R Assay with other non-*Enterobacteriaceae* besides these six species has not been evaluated and is therefore unknown.

• The Xpert Carba-R Assay showed reduced positive percent agreement (PPA of 55.6%) for detection of the bla_{VIM} gene sequence in *Pseudomonas aeruginosa.* Four (4) false negative results were observed with the assay in specimens in which *Pseudomonas aeruginosa* containing the bla_{VIM} sequence was recovered by the reference method.

• The Xpert Carba-R Assay showed reduced positive percent agreement (PPA of 85.7%) for the detection of the bla_{IMP} gene sequence in *Acinetobacter baumannii* during the Contrived Study. In addition, a low % total agreement (86.1%) across sites for the Reproducibility Study was observed with samples containing low concentrations of organism harboring the bla_{IMP} gene sequence.

• Carbapenem-resistant anaerobes potentially present in fecal specimens have not been evaluated by the Xpert Carba-R Assay.

• The detection of bla_{KPC}, bla_{NDM}, bla_{VIM}, $\text{bla}_{\text{OXA-48}}$, and/or blaI_{MP} from rectal specimens may be from organisms other than *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter baumannii.*

• The performance of the Xpert Carba-R Assay with susceptible isolates bla_{NDM}, bla_{KPC}, bla_{VIM}, $bla_{\text{OXA-48}}$, and/or bla_{IMP} gene sequences has not been fully evaluated.

Pure Colonies Limitations

• For pure colonies, the performance of the Xpert Carba-R Assay with bacteria other than Enterobacteriaceae, Pseudomonas aeruginosa, or Acinetobacter baumannii has not been evaluated. Organisms should be identified, and carbapenem nonsusceptibility status should be determined prior to testing on Xpert Carba-R Assay.

• Erroneous test results might occur from improper culture techniques, failure to follow the recommended procedure to prepare the 0.5 McFarland suspension, handling and storage procedures, technical error, sample mix-up, or because the number of organisms in the specimen is too low to be detected by the test. Careful compliance with the instructions in this insert is necessary to avoid erroneous results.