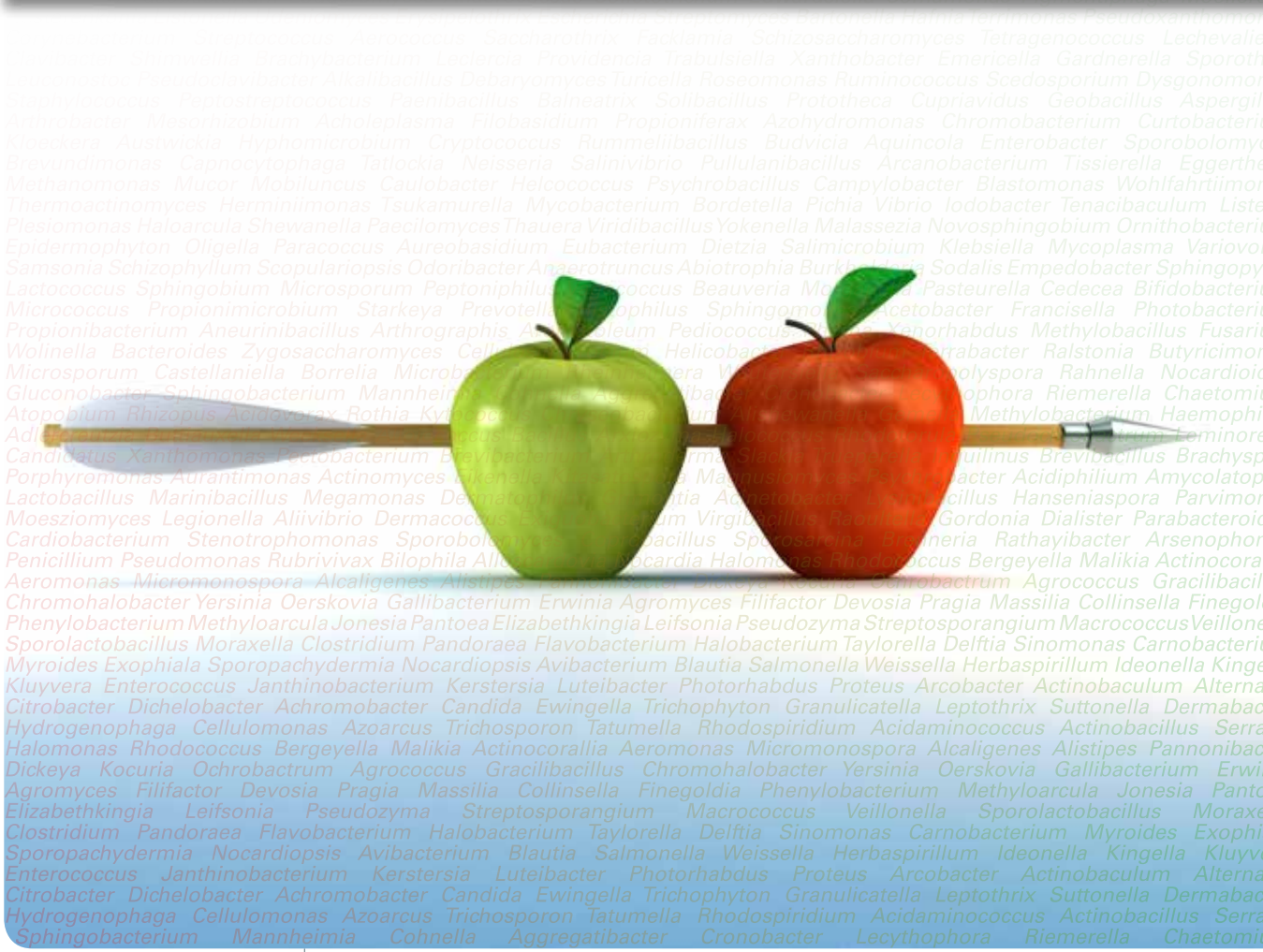
IVD



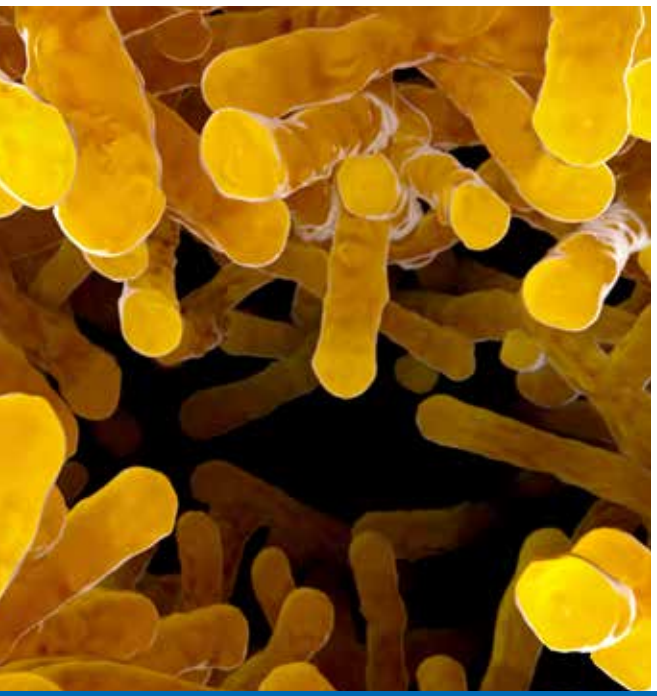
MBT Subtyping IVD Module

- Changing Microbiology

MALDI-TOF

Innovation with Integrity

Fast Microorganism Identification Combined with Instant Typing



Over the past decade, the implementation of Bruker's MALDI Biotyper® in many microbiology labs worldwide has entirely changed microorganism identification. Its high discriminatory power permits the identification of thousands of different species, but some species are still difficult to differentiate. Bruker has therefore developed the MBT Subtyping IVD Module, allowing for automated differentiation of some species which are typically very difficult to distinguish.

And there's more! The potential of MALDI-TOF mass spectrometry reaches beyond species identification and the MBT Subtyping IVD Module is the first IVD application exploring this potential. It combines the identification of important pathogens with subsequent detection of specific resistance markers in one automated workflow.

The principle

A prerequisite for the automated typing process is a high confidence identification of the bacterium in the MALDI Biotyper IVD workflow. For species differentiation, the MBT Subtyping IVD Module then looks for decisive peaks in the identified mass spectrum. For detection of specific resistance markers, the software searches for peaks associated with proteins related to antibiotic resistance and, if present, reports the respective bacterium as presumptive resistant.

Applications of the MBT Subtyping IVD Module

- Detection of KPC-producing *Klebsiella pneumoniae* and *Escherichia coli*
- *Bacteroides fragilis cfiA* subtyping
- Differentiation of *Mycobacterium chimaera* from *Mycobacterium intracellulare*

Seamless and Fast Workflow

Once the samples are transferred to the MALDI target plates for routine identification, no additional sample preparation is required to obtain a typing result. When the bacterium has been identified, the software automatically performs the typing and result reporting.

1 **Transfer sample and add matrix**

2 **Create project and start measurement**

3 **Spectrum instantly matched against IVD reference library to perform identification**

5 **Automated typing process after high confidence identification**

6 **Final review and validation**

An aid to diagnosis: Instant Resistance Marker Detection with MALDI Biotyper

Antibiotic resistant bacteria are on the rise and are a major global public health threat. Effective prevention and control are therefore of high importance to reduce the risk of infections associated with antibiotic resistant microorganisms. The MBT Subtyping IVD Module enables fast detection of specific resistance markers in an automated workflow, hence providing an aid to diagnosis.

Detection of KPC-producing *Klebsiella pneumoniae* and *Escherichia coli*

A significant increase of carbapenem resistant *K. pneumoniae* (CRKP) is observed in many countries worldwide, which is a major concern as infections result in high rates of morbidity and mortality.
The most important mechanism of resistance by CRKP is the production of the *K. pneumoniae* carbapenemase enzyme (KPC), encoded by the bla_{KPC} gene. This plasmid based resistance can easily be exchanged between bacteria by horizontal gene transfer, making it even more dangerous in healthcare settings.

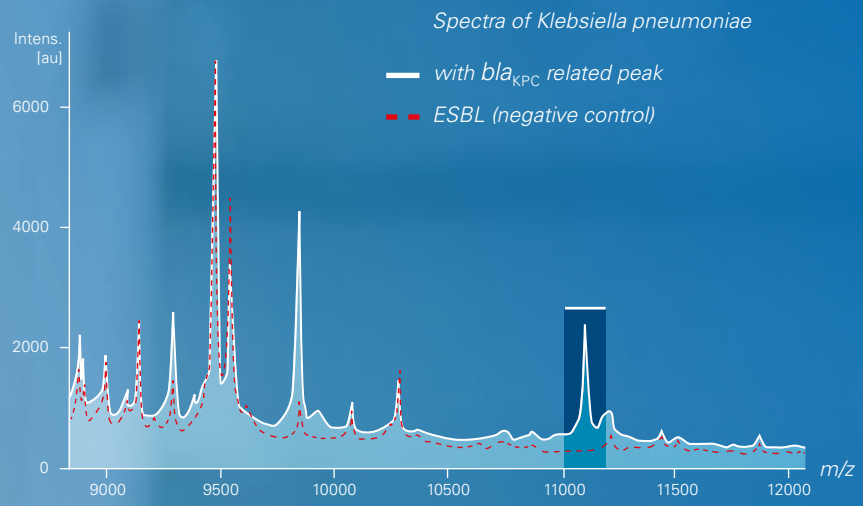
This mechanism and the fact that CRKP resistance could spread rapidly between patients - if not detected in time - demand efficient identification methods for laboratory testing, active surveillance and screening of patients.

Lau *et al.* (2014) discovered a peak in MALDI-TOF mass spectra of KPC-producing *K. pneumoniae*, related to the plasmid carrying bla_{KPC}. This specific peak at 11,109 m/z is clearly detectable in bacterial MALDI-TOF mass spectra.

Prerequisite for the automated detection process with the IVD MALDI Biotyper is the successful identification of the bacterium, i.e. the log(score) ID value must be ≥ 2.0. The MBT Subtyping IVD Module then looks for the bla_{KPC} related peak in the sample spectrum. And, if present, the software will report this sample as a KPC positive one. If no characteristic peak has been detected, nothing is mentioned.

Anna F. Lau *et al.*, Journal of Clinical Microbiology 2014:52(8):2804-2812. DOI: 10.1128/JCM.00694-14
Yung-Ho Youn et al., Journal of Clinical Microbiology 2016:54(1):35-42. DOI: 10.1128/JCM.01643-15

KPC detection of *K. pneumoniae* and *E. coli* includes only strains with a bla_{KPC} pKpQIL plasmid. If another resistance mechanism is present, it will not be identified by the MBT Subtyping IVD Module. Also, if the gene expression rate is low, there will be no characteristic peak and no KPC subtyping alert. Cultivation media and conditions might suppress or induce a signal at m/z 11,109 which is not related to a KPC resistance. Therefore, Columbia Agar with 5% sheep blood agar must be used for cultivation of *K. pneumoniae* and *E. coli*.



Bacteroides fragilis cfiA Subtyping

B. fragilis is the most frequently isolated anaerobic pathogen. Carbapenem resistance in *B. fragilis* is frequently associated with presence of the *cfiA* gene, encoding for a metallo-beta-lactamase conferring resistance to nearly all ß-lactam antibiotics. As a result, infections with *B. fragilis cfiA* positive strains are difficult to treat.

After successful identification, the MBT Subtyping IVD Module looks for specific peaks associated with respectively *cfiA* positive and *cfiA* negative *B. fragilis* strains. The best match for the respective sample will be reported as a *cfiA* positive or *cfiA* negative strain. Nothing is stated when the subtyping algorithm result is not reliable.

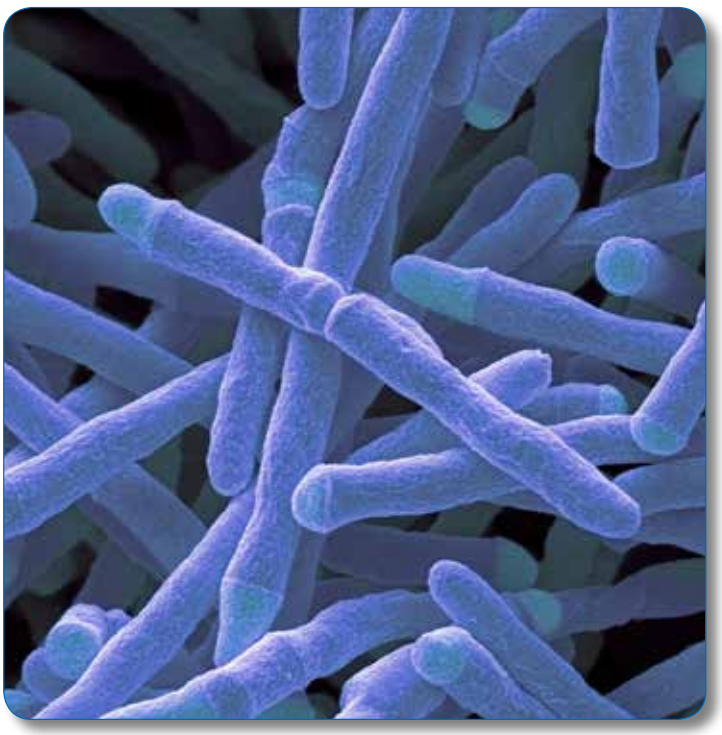
Ingrid Wybo et al., Journal of Clinical Microbiology 2011:49(5):1961-1964. DOI: 10.1128/JCM.02321-10
Elisabeth Nagy et al., Journal of Medical Microbiology 2011:60(11):1584-1590. DOI: 10.1099/jmm.0.031336-0

An Early Warning System

The MBT Subtyping IVD Module quickly detects bla_{KPC} expressing *K. pneumoniae* and *E. coli*, and *cfiA* positive/negative *B. fragilis* strains. Please note that negative results do not necessarily mean that these strains are susceptible but will require additional confirmation methods.

The final identification results must be assessed by a trained professional experienced in clinical microbiology.

Accurate Differentiation of *Mycobacterium chimaera* from *Mycobacterium intracellulare*



Mycobacterium chimaera very rarely causes infections in humans, but there have been reports about contamination of medical equipment used in heart surgery.
There was a risk that heater-cooler units used in open-heart surgery were contaminated with *M. chimaera* and that exposure of patients to these units in the operating theatre could lead to infections appearing months to years after surgery. Most reported infections were those of prosthetic valves or vascular grafts.

Routine identification using MALDI-TOF mass spectrometry is restricted to the identification of the *M. chimaera / intracellulare* complex because mass spectra of both species are very similar. Conventional identification methods suffer from the same limitation.

After successful identification of the *M. chimaera / intracellulare* complex by the IVD MALDI Biotyper, application of the MBT Subtyping IVD Module allows fast and accurate differentiation of both species by thorough comparison of characteristic mass spectrum peaks as described by Pranada et al. (2017). This differentiation will support further insights into the pathogenic role of *M. chimaera* and can contribute to epidemiological studies which might improve infection control in future.

Note: Prerequisite for successful identification and differentiation of Mycobacteria is an installed MBT Mycobacteria IVD Module.

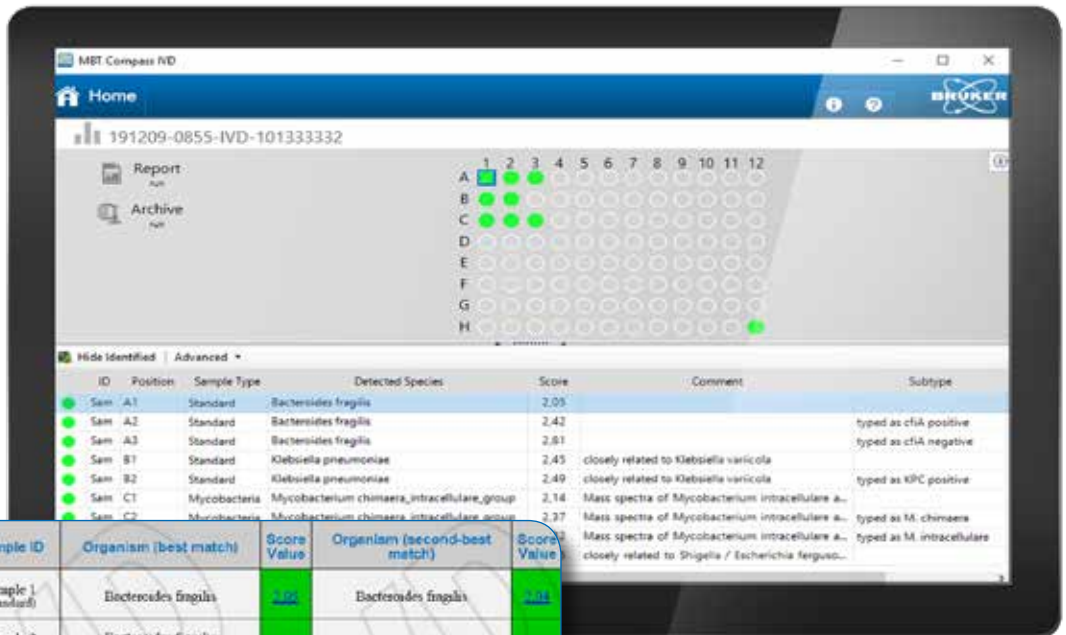
Mycobacterium avium / intracellulare complex includes several species and only *M. intracellulare* and *M. chimaera* can be subtyped.
Analysis of clinical samples, for example sputum, without any cultivation step does not form part of the intended use / intended purpose; a cultivation step is required.

Arthur B. Pranada et al., J Med Microbiol 2017:66:670-677. DOI: https://dx.doi.org/10.1099/jmm.0.000469

No additional work – A clear report

Besides the usual sample preparation for routine microbial identification by the IVD MALDI Biotyper, no additional work needs to be done to benefit from the MBT Subtyping IVD Module. No special kits are needed for using the MBT Subtyping IVD Module.
After high confidence identification of the bacterium in the MALDI Biotyper IVD workflow, the MBT Subtyping IVD Module automatically looks for decisive peaks in the identified mass spectrum and shows the typing results in both the MBT Compass IVD software and in the report.

- For KPC positive samples, the result identifier "typed as KPC positive" is displayed. If no characteristic peak has been detected, no typing result is mentioned.
- For *B. fragilis*, the subtyping result is reported as "typed as *cfiA* positive" or "typed as *cfiA* negative".
- For the Mycobacterium_chimaera_intracellulare_group, the result identifier "typed as M. intracellulare" or "typed as M. chimaera" is displayed.
- Nothing is stated if the subtyping algorithm result is not reliable.



Display:
The subtyping result is shown in the Subtype column of the result table in the MBT Compass IVD software.

Sample Name	Sample ID	Organism (best match)	Score Value	Organism (second-best match)	Score Value
A1	Sample 1 (standard)	Bacteroides fragilis	2.05	Bacteroides fragilis	2.04
A2	Sample 2 (standard)	Bacteroides fragilis typed as cfiA positive	2.42	Bacteroides fragilis	2.33
A3	Sample 3 (standard)	Bacteroides fragilis typed as cfiA negative	2.81	Bacteroides fragilis	2.71
B1	Sample 4 (standard)	Klebsiella pneumoniae	2.45	Klebsiella pneumoniae	2.33
B2	Sample 5 (standard)	Klebsiella pneumoniae typed as KPC positive	2.49	Klebsiella pneumoniae	2.43
C1	Sample 6 (Mycobacteria)	Mycobacterium chimaera intracellulare group	2.14	Mycobacterium chimaera intracellulare group	2.06
C2	Sample 7 (Mycobacteria)	Mycobacterium chimaera intracellulare group typed as M. chimaera	2.27	Mycobacterium chimaera intracellulare group	2.18

Report:
Identification results with subtyping results below the species name in the Organism (best match) column

Order Information

Part-No. 1866180
The MBT Subtyping IVD Module enables the automated detection of strain specific characteristics.

MBT Compass IVD software (Part-No. 1832771, build 4.2.100 or higher) is a prerequisite for the use of the MBT Subtyping IVD Module.

Differentiation of *Mycobacterium chimaera* from *M. intracellulare* needs an installed MBT Mycobacteria IVD Module (Part-No. 1850731).

Please contact your local representative for availability in your country. Not for sale in the USA.
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CE IVD