CMTA

Comprehensive Molecular Tumor Analysis

The certified molecular tumor diagnostics from Alacris Theranostics (ISO DIN EN 15189:2014) for an individualized approach to cancer therapy

The CMTA is a unique comprehensive molecular tumor diagnostics designed to identify the best treatment options for your patients.

Based on next-generation sequencing (NGS) of the exome and transcriptome of the tumor, the CMTA analyses all cancer-relevant genes and transcripts to generate a detailed personalized report of the tumor profile with the associated therapy options.

This information package contains all relevant information for the attending physician: service description, sample requirements, requisition form and a check list of the required documents.

If you have any questions, please contact us at:

Phone: +49 30 8431 2250
Email: cmtanalysis@alacris.de

Content

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ALACRIS THERANOSTICS GMBH … the systems medicine company

CMTA

Comprehensive Molecular Tumor Analysis

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… the systems medicine company

Innovative diagnostics for precision oncology

Alacris offers advanced solutions in personalized oncology. The CMTA translates our long-standing expertise in genome and transcriptome research into an innovative, high-precision, clinical tumor diagnostics solution.

Every patient is unique, every tumor is different. To capture this individuality, the CMTA technology integrates two layers of sequence data, DNA (genome/exome) and RNA (transcriptome), for a comprehensive scoring of the clinically-relevant alterations in every tumor .

The CMTA enables the unbiased identification of key tumor features (gene fusions, overexpressed oncogenes, immune microenvironment, etc.), in addition to mutations and chromosome copy number alterations, providing essential information for the evaluation of best treatment choice.

Starting from a tumor biopsy, our end-to-end CMTA process generates the NGS data and deploys advanced bioinformatics analysis pipelines to deliver a tumor profiling report with associated therapeutic options.

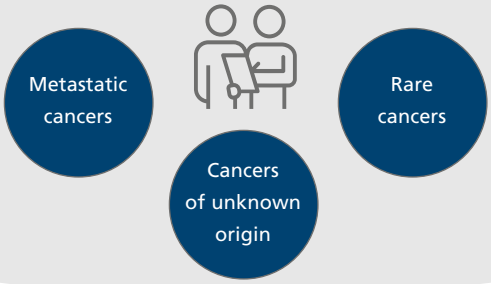
The CMTA is a medically certified diagnostics test (ISO DIN EN 15189:2014) offering a versatile solution for every tumor type. The list of genes explicitly mentioned in the accreditation can be found on our website.

Why adopt the CMTA ?

- → Holistic, accurate, sensitive tumor molecular profiling with a single analysis
- → Enables precision oncology for all cancer types, including tumors of unknown origin and rare tumors
- → Flexible solution, customizable to specific requirements
- → High-dimensional, high-quality molecular data for clinical trials and research

Clinical consultation

Background & benefits of CMTA

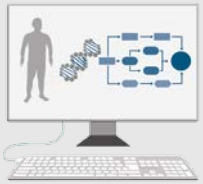


Data generation workflow

Whole exome and transcriptome

NGS integrative analysis

Advanced bioinformatics pipelines



Expert curated patient report

Key molecular findings & treatment options

One combined report with all key information

- Mutations
- Expressed variants
- Tumor Mutation Burden (TMB)
- Copy number variants (CNVs)
- Loss of heterozygosity (LOH)
- Gene fusions
- Oncogenic splice variants
- Prognostic signatures
- Immune microenvironment
- Biomarker expression

Informing on personalized therapeutic options

~3 weeks From sample reception to final report

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Data Security

Zertifiziert nach DIN EN ISO 9001:2015

Accreditated to DIN EN ISO 15189:2014

A. Laboratory Analysis Components

1. Isolation of genomic DNA and total RNA from the tumor sample
2. Isolation of genomic DNA from blood/control tissue
3. Preparation of sequencing libraries:
   - **whole-exome libraries** from tumor and blood DNA (Twist Bioscience)
   - **RNA libraries** (ribo-depleted, strand specific) from tumor total RNA
4. Next Generation Sequencing (NGS):
   - **whole exome libraries:** paired-end sequencing, 12-24 Gb (100-150x mean coverage) of filtered data per library
   - **RNA libraries**: paired-end sequencing, ca. 10-12 GB (100 Mio reads) of filtered data per library

B. Bioinformatics Analysis Components

1. Mutational burden (TMB) of the tumor (number of mutations per Megabase), graphical representation of the TMB of the patient in comparison to a cohort from a similar tumor type
2. Somatic variants: mutations (SNVs and Indels) and expressed mutations
3. Mutational signatures
4. Chromosomal copy number changes (including amplifications, deletions, regions of loss of heterozygosity-LOH)
5. Gene fusions
6. Oncogenic splice variants
7. Integrative gene expression profiling: (a) dysregulated genes of clinical interest (b) gene expression of disease related marker genes (c) gene expression signatures (e.g. signalling pathways, drug response, drug resistance, cell types: dependent from the availability of signatures for a particular tumor type)
8. Estimation of the immune microenvironment content.

C. Patient Report

Generation of a comprehensive patient report summarizing the integrative molecular tumor analysis with clinically relevant annotations and potential targeted treatments.

Terms and conditions

Alacris AGBs are valid for this offer and are available on the company's webpage: **http://www.alacris.de/terms-and-conditions/**

Note

If the quantity or quality of the samples (e.g. below 30% tumor content) is insufficient, the analysis cannot be performed appropriatley. This only becomes apparent during quality controls of the work processes. If the quantity or the quality of the samples is not sufficient, only the services provided up to that point will be invoiced.

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Genetic Investigation Requisition

ALACRIS THERANOSTICS GMBH
… the systems medicine company

Patient

Surname

First name

Date of Birth

Gender ☐ female ☐ male

Street

City, Postcode

Country

Telephone

E-Mail

Doctor / Clinic

Institution

Doctor

Street

City, Postcode

E-mail

Stamp and signature of responsible medical person:

Samples

☐ FFPE tumor sample ☐ FROZEN tumor sample ☐ EDTA blood (1 x 0,5 ml)

other

Diagnosis - Tumor type/ICD-10 code

Tumor purity (%) Tumor sample location

I hereby authorise Mr / Mrs .....

(responsible medical person, in accordance with the German Gene Diagnostics Act)

to conduct a genetic investigation, the sampling required for this and to analyse the transcriptome and exome of the sample for the purpose of a molecular examination of the tumor in relation to normal tissue.

I will bear the associated costs as listed in the attached appendix "Service Description", regardless of a possible reimbursement provided by my health insurance.

Date, Signature .....

(Patient)

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Declaration of Consent

With my signature I hereby give my informed consent according to German Gene Diagnosis Act (for content and scope see below) to undergo a genetic investigation and the associated required sampling. I have had the opportunity to ask questions and I am aware of my right to revoke. I agree that samples used for the genetic investigation are given to Alacris Theranostics GmbH and in this respect the responsible medical person is released of his or her duty of confidentiality.

I have been informed about the nature, significance, implications and implementation of genetic testing, possible result-based treatment options and the risks involved, according to §9 of the German Gene Diagnosis Act, on the basis of the attached information sheet, which was given to me and explained.

With regards to the storage and use of study samples and analysis results for scientific purposes in anonymised form I:

agree ☐ do not agree ☐

.....

In rare cases, medical findings not related to the investigation mandate can become apparent. Regarding these findings I would:

not ☐ in every case ☐ or in certain cases ☐

like to be informed.

.....

I agree that findings from the genetic investigation can be sent to other doctors/persons (as indicated below).

yes ☐ no ☐

1. Name, Address, Email: .....

2. Name, Address, Email: .....

3. Name, Address, Email: .....

.....

I am aware that my participation in this investigation is voluntary and I may withdraw consent at any time. I acknowledge that a sufficient reflection period was given between being provided with relevant information and providing my consent. I also had the opportunity to ask additional questions.

Date, Signature .....
(Patient)

Date, Signature .....
(Responsible medical person)

Dear Patient,

There is a possibility you or a family member may have a hereditary disease, or you are considering prenatal diagnostics or cancer has been diagnosed. Many genetic changes can now be detected by examining an appropriate sample.
Before any genetic test is performed your doctor must inform you about its nature, meaning and scope (obligation to inform). In the case of investigations involving cancer patients (spontaneous or hereditary cancer) genetic counselling should be offered; however, you may waive this counselling, in writing, if you have previously been informed about the counselling content. The information below therefore provides an explanation of what happens during genetic counselling and what can be achieved through this process.
Genetic counselling is offered to help you to answer questions regarding how a possible hereditary condition or genetic disease impacts you (or your family) and correctly assess potential consequences (risks) for your life- and family planning. How far it can actually be useful depends on the particular disorder and your personal questions. Both determine what is discussed in the context of genetic counselling and the accuracy of statements about genetic risks.

Genetic counselling routinely includes

- clarifying your personal questions and the objectives of the counselling
- assessment of your personal and family medical history
- evaluation of available medical findings and diagnostic reports
- as accurate as possible genetic diagnosis
- detailed information regarding diseases or disabilities in question
- assessment of specific genetic risks
- description of the common genetic risks
- a detailed consultation regarding the possible meaning of the information above, where appropriate, for your health and wellbeing, as well as life- and family planning.

Genetic counselling sometimes includes

- a physical examination of you or family members
- sample taking (e.g., blood, saliva, amniotic fluid, etc.).

If during the course of the consultation it turns out that there are some additional risks so far unknown to you, you would be informed about it. You can, however, determine if and to what extent you want to be informed and whether you want to undertake further medical-genetic examinations. Genetic tests would not be performed without your positive decision to do so.
During the process of genetic testing, abnormalities may be revealed, which according to the current medical knowledge, are not known to cause adverse health effects. In such cases you will only be notified about these abnormalities if deemed a necessary part of the requested investigation. A comprehensive overview and diagnosis of all aberrations is not possible, as often the cause is not known. Nor is it possible to exclude any risk of illness for yourself or your family, including your children. In some cases, no exact guidance on the probability of occurrence of a particular disease or disability is possible; even if only a low risk of recurrence is given, this means that an occurrence is possible.
The most important points arising from the consultation will be documented and summarised for you in writing. You decide which doctors are informed. Your blood/tissue samples may be analysed in different laboratories. In such cases everyone involved is subject to all legal requirements of doctor-patient confidentiality and, in particular, data protection compliance.

For further information please do not hesitate to contact us.

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Sample Requirements & Shipping Guidelines: blood and tissue samples

Please note: *For successful molecular characterisation of tumors, high quality nucleic acids are essential. This can only be ensured by proper handling and shipment of samples. Please read the guidelines carefully and send samples only after consultation with an Alacris representative.*

Sample types required:

1. tumor tissue for exome and transcriptome sequencing **(with at least 30% tumor purity)**
2. blood (or healthy tissue) sample for healthy (control) exome sequencing.

The best material for molecular characterisation of tumors is fresh tumor tissue, isolated during OP, immediately frozen on dry ice and shipped to Alacris on dry ice. If there is no fresh tissue available, we can also use FFPE tumor material for analysis.

General note for shipping samples:

Before shipping samples, please contact Alacris to clarify date and type of shipment. If necessary, Alacris can also organise delivery of samples via a courier service. For dry ice shipment, inform the courier *two days prior to shipment date*.

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Sample transport containers:

Alacris can supply (free-of-charge) the appropriate consumables required for blood collection, sample transport and storage. If self-supplied consumables are used, please ensure that sample tubes can withstand snap-freezing in liquid nitrogen/dry ice.

Important notes about samples

Fresh tumor sample

Equipment: -80 °C freezer (for sample storage before shipment), liquid nitrogen, Styrofoam box (or equivalent), dry ice

- Optimal tissue size: (2 mm x 2 mm). **Minimum tumor purity is 30%.**
- Transfer the tissue to a cryotube and immediately freeze on dry ice; when immediate freezing is not possible, the sample can be kept on ice for a maximum of 5 min.
- Store the tubes at -80 °C prior to shipping.
- For shipment, put tubes in in a sealed plastic bag, and place in a Styrofoam box (or equivalent) with dry ice (at least 10 cm of dry ice is required above and below the sample tubes).

Important: The completed *Tumor Sample(s) Description* form should be sent along with the sample.

➔Sheet 2

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Sample Requirements & Shipping Guidelines: blood and tissue samples

FFPE tumor sample

- FFPE block with an ideally 2 cm^2 x 3 mm piece of tissue with a tumor content of at least 30%.
- FFPE block in a sealed plastic bag
- Slide with a section of the FFPE block corresponding to the tumor, on which the tumor region is marked.
- Shipment in a padded envelope
- Note. ***If no block but only sections can be provided, please contact us in advance for technical specifications.***

Important: The completed *Tumor Sample(s) Description* form should be sent along with the sample.

Blood sample

We need one tube with 0,5 ml blood. Use only EDTA as anticoagulation agent. Samples with heparin cannot be processed.

- Fill EDTA tube with 0,5 ml blood and mark with unique patient number.
- Let the tube stand for 30 min at room temperature before proceeding to *Blood shipment variant 1* or *Blood shipment variant 2*.

Blood shipment variant 1: frozen

Equipment: -80 °C freezer (for sample storage before shipment), Styrofoam box, dry ice

- Freeze the EDTA/blood tubes on dry ice
- Store the tubes at -80°C prior to shipping.
- For shipment, put tubes in in a sealed plastic bag and place in a Styrofoam box (or equivalent) with dry ice (at least 10 cm of dry ice is required above and below the sample tubes).

Blood shipment variant 2: cooled

Equipment: Styrofoam box (or equivalent), +4°C cool blocks

- Put the EDTA/blood tubes in a sealed plastic bag and place in a Styrofoam foam box with +4°C cool blocks.
- Send immediately, DNA should be isolated within 24 hours.
- Select a "handle with care" shipment option, shaking should be avoided.

Important: Inform Alacris at least two days before you plan to ship the non-frozen blood.

Please note: *If multiple samples from the same tumor are sent to Alacris, only one sample will be processed, unless otherwise agreed. If information about tumor content in the samples is available, the sample with the highest tumor percentage will be processed. From equivalent samples, the sample for processing will be selected randomly. Samples may also be combined to obtain sufficient quantities of DNA and RNA for genetic analysis.*

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Tumor sample(s) description

Please fill-in and send to Alacris along with the sample(s) for analysis.

Patient

Name

Date of birth

Gender ☐ female ☐ male

Contact person

Name

Institution

Telephone

Email

Tumor sample(s)

Sample(s) obtained on [DD/MM/YYYY]

Pathology report(s) ☐ enclosed ☐ will be sent by [DD/MM/YYYY]

For FFPE sample(s) only: ☐ slide(s) with stained tissue sections & marked tumor area is/are included.

Nr.	Sample ID (e.g. FFPE block number)	Tissue type	Tumor content * in [%]	Type of sample e.g. FFPE, frozen, etc.	Comments

* estimation of the tumor content in the sample is essential for the analysis

For multiple tumor samples only:

The samples were obtained:

☐ from different parts of **the same** tumor region ☐ from different **independent** tumor regions

Comments:

Important! *If multiple samples from the same tumor are sent to Alacris, only one sample will be processed, unless otherwise agreed. If information about tumor content in the samples is available, the sample with the highest tumor percentage will be processed. From equivalent samples, the sample for processing will be selected randomly. Samples may also be combined to obtain sufficient quantities of DNA and RNA for genetic analysis.*

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Checklist of the documentation required by Alacris

Please note: *Processing of sample(s) cannot be started until all listed forms and information are supplied to Alacris.*

The patient was given the 'Patient Information Sheet: Genetic Counselling before genetic investigations in accordance with the Gene Diagnostics Act - GenDG, and duly informed ☐

Order / Contract

'Genetic Investigation Requisition' and 'Declaration of Consent' to genetic investigation in accordance with the German Gene Diagnostics Act *(form attached)* signed by ☐

the doctor ☐ and the patient ☐

Patient information

Information on disease and treatment history ☐

Information about previous genetic tests performed on the patient and their results ☐

Sample information

Pathology report(s) on the sample(s) ☐

Tumor Sample Description *(form attached)* ☐

Documentation is complete ☐

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