Langerhans cell histiocytosis (LCH) – Brief information

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1. General disease information

Langerhans cell histiocytosis (LCH) usually occurs in childhood and adolescence and is classified as a malignant disease. According to current knowledge, LCH originates from certain precursor cells of the white blood cell series in the *bone marrow* and can affect almost any organ or region of the body.

The most commonly involved organs are the skeleton (in 80% of cases), the skin (30% of cases) and the *pituitary gland* (with up to 25%). Bone involvement can be present in almost all parts of the skeleton; however, the skull and long bones are most commonly affected. Other relatively commonly affected organs are the liver, spleen, hematopoietic system, and lungs (with 15% each). In addition, the *lymph nodes* (5–10%) and the *central nervous system* (2–4%) can also be involved.

LCH can have different degrees of severity and also vary in terms of the course of the disease. In this context, the decisive factor is whether only one or more organs or organ systems are affected and which ones they are. Patients in whom only one organ / organ system is affected – for example, only the bone or only the skin (so-called monosystemic LCH) – usually have a more favorable *prognosis* than patients in whom several organs / organ systems are affected (multisystemic LCH).

Good to know: Some patients do not require treatment, while others need chemotherapy; the treatment decision is determined by the location and spread of the disease (*see chapter "Treatment"*).

2. Incidence

Langerhans cell histiocytosis (LCH) is a rare disease. It accounts for far less than 5 % of all malignant diseases in childhood and adolescence. It is estimated that around 80 to 100 children and adolescents aged younger than 18 years (3 to 5 per million) are diagnosed with LCH in Germany per year. However, due to possible spontaneous recoveries, the number of reported new cases probably does not correspond to the number of cases that actually occurred.

Though LCH may occur at any age, it is mainly diagnosed in childhood, most frequently in infants and toddlers up to the age of four. The frequency of the dise-ase decreases with increasing age. Overall, boys are affected slightly more often than girls (gender ratio: 1.3:1).

3. Symptoms

Since Langerhans cell histiocytosis (LCH) can affect almost any organ or region of the body (*see chapter "General disease information"*), the range of possible signs of disease (*symptom*s) is wide. They depend primarily on the location and extent of the disease.

Some patients are symptom-free and the diagnosis is based on an incidental finding, as it is sometimes observed with individual foci of disease (lesions) on the skull bone. Other patients have skin changes of varying degrees (individual skin lesions to extensive or whole-body rashes), while others have a severe clinical presentation with multi-organ involvement.

The possible symptoms include:

- **if the bones are affected:** bone pain, sometimes swelling and/or restricted movement (e.g. limping); protrusion of the eyeball (*exophthalmus*) (if the bony eye socket is affected)
- **if the skin is affected:** persisting skin changes/rashes (exanthema) of various kinds (e.g. nodular, scaly, weeping, ulcer-like or crust-forming), for example on the scalp, in the diaper area or on the arms, legs and torso; also possible: small punctiform skin bleedings, discharge of secretions from the ear or polyps in the ear canal
- **in case of involvement of the mucous membranes:** mucous membrane changes in the mouth and external genital area, such as swelling, ulcers
- **if the lungs / respiratory truct** are/is affected: breathing difficulties such as coughing, shortness of breath, chest pain
- **in case of involvement of the liver, spleen and/or lymph nodes:** enlargement of the affected organs / organ systems, which are noticeable, for example, by a extended abdomen and/or (very rarely) lymph node swelling
- **in case of pituitary gland involvement:** hormonal deficiencies, which can be noticed, among other things, by severe thirst and frequent urination (indication of *diabetes insipidus*) or by growth disorders / disorders of sexual development (*puberty*)
- **if the hematopoietic bone marrow is affected:** *infection*s, pallor and/or signs of bleeding
- **if the central nervous system is affected:** *neurological* symptoms such as visual and/or hearing disorders, impaired gait, concentration and/or behavioural disorders

Good to know: The symptoms of LCH can vary greatly from patient to patient. It is also important to know that the occurrence of one or more of above-mentioned symptoms does not necessarily mean that they are caused by LCH. Many of these symptoms also occur in benign diseases that have nothing to do with LCH. Nevertheless, it is strongly recommended to have the child or teenager see a paediatrician as soon as possible in case such symptoms persist or progress.

4. Causes

The causes of Langerhans cell histiocytosis (LCH) are still largely unclear. It is known that the disease is caused by the modification of a certain (myeloid) precursor cell of white blood cells and its subsequent replication. The altered cells sometimes make up less than 10% of all cells in the LCH tumour foci, which otherwise consist mainly of normal inflammatory cells of the *immune system* (*T lymphocytes*, *granuloytes* and so-called multinuclear giant cells).

In LCH cells, certain *genetic* deviations (mutations) in the genetic material are often observed. For example, in about two-thirds of the diseased patients, *gene* changes in certain signaling pathways of the LCH cells can be detected, which are important for the control of cell growth, cell development and cell survival. The gene changes in the LCH cells are mainly the so-called *BRAF V600E mutation*, less often a *MAP2K1* mutation. Both mutations cause a permanent activation of the above-mentioned signal transmission pathways and promote the development of the disease by disrupting cell function.

Good to know: Finding such mutations has not only contributed to a better understanding of the disease, it also opens up completely new diagnostic and therapeutic approaches for the future (*see chapter "Treatment – New therapy options"*). LCH needs more research. However, it is important to know that such mutations occur spontaneously, i.e. they are not inherited or hereditary.

5. Diagnosis

If the paediatrician suspects Langerhans cell histiocytosis (LCH) based on the patient's medical history (*anamnesis*) and *physical examination*, he will, depending on the type of finding, either first recommend *imaging* procedures, such as an *X-ray examination*, an *ultrasound* examination (sonography) or *magnetic resonance imaging* (MRI), or first arrange for a tissue sample to be taken (*biopsy*). The latter is usually done by sampling from easily accessible areas, such as the skin.

In order to confirm the *diagnosis*, the removal and examination of tissue is required in any case, and the subsequent precise determination of the spread of the disease (staging) requires specific imaging procedures. The paediatrician will therefore refer the patient to a hospital specialising in cancer and blood disorders in children and adolescents (Clinic for Paediatric Oncology/ Haematology) for any subsequent examinations and potential therapeutic management.

The various diagnostic procedures are then explained in more detail. Whether and in what order these examinations are carried out depends on the specific situation and on any existing findings.

5.1. History and physical examination

Both a specific medical history and a complete, specific *physical examination* are crucial after the diagnosis has been confirmed (primarily by tissue sampling, *see below*). The examining physician will pay particular attention to pain, swelling, impaired range of motion, rashes and mucosal changes, discharge from the ear, fever, loss of appetite, vomiting, diarrhea, weight loss or failure to thrive. In addition, attention is paid to abnormalities regarding drinking behaviour (extremely large

amount of drinking) and/or urine formation (extremely high urine production), signs of shortness of breath and *neurological* abnormalities.

5.2. Blood tests and imaging diagnostics

Specific blood serum markers that provide indications of LCH or may serve to monitor the course of the disease have not yet been identified. The diagnosis of the disease and the assessment of its potential spread ("staging") is therefore carried out, in addition to various standard blood test, primarily by *imaging* procedures (radiological *diagnostics*) at the time of diagnosis (and later also for progress assessment and follow-up).

As part of the routine blood work, the blood cell counts, liver and kidney function and coagulation parameters are examined. The imaging procedures include an *ultrasound* examination of the abdomen and an *X-ray examination* of the lungs or skeletal system, because LCH preferably affects the bones. In order to keep *radiation exposure* as low as possible, many clinics use whole-body MRI; however, if there are uncertainties regarding the evaluation, an X-ray or *computed tomography* (CT) is sometimes necessary.

In addition to these basic diagnostic procedures, additional examinations may be necessary for special *indication*s, i.e. in some disease situations, such as an eye test, a hearing test (*audiogram*), a lung function test, *hormone* tests, certain MRI examinations or an *endoskopy*.

5.3. Tissue sampling (biopsy) to secure diagnosis

The final diagnosis of LCH is based on microscopic examination of tissue from the area(s) affected by the disease using a conventional *light microscope* and on the *immunhistochemic* detection of special *molecule*s (so-called markers) on the surface of the LCH cells (CD1a *antigen* and/or langerin (CD207)).

An additional *molecular genetic* examination with regard to common *gene* changes (mutations), such as *BRAF V600E*, is recommended especially for patients with multisystem involvement, but is not initially necessary for therapy planning. The diagnosis of LCH is usually confirmed by another expert (so-called reference assessment); however, this is not always necessary (for example, in the case of clear results).

If tissue sampling (biopsy) poses a risk to the patient due to the location of the tumour focus (for example, in the area of the second cervical vertebra or in the pituitary stalk) or if sufficient tissue material cannot be obtained, the treatment team carefully weighs up the benefit-risk ratio for the respective patient. If a *biopsy* is not performed, it is particularly important to ensure careful follow-up.

Good to know: Not every patient needs the complete check-up. On the other hand, tests might be added that haven't been mentioned here, depending on the individual situation of the patient. Your caregivers will inform you and your child, which diagnostic procedures are individually required in your situation and why.

6. Therapy planning

After the diagnosis has been confirmed and subsequent staging of the disease (*see above*) has been completed, therapy is planned. In order to provide a therapy that is specifically designed for the patient's individual situation (risk-adapted therapy), the doctors will take into consideration certain factors that have been shown to have an impact on the *prognosis*[*] (so-called risk factors or prognostic factors).

Important *prognostic factors* in patients with LCH are the extent of the disease (monosystemic, multisystemic, unifocal, multifocal) and the type of organs affected by the disease (taking into account so-called risk organs and the exact location of the disease in an organ, *see below*). In addition, the response of the disease to treatment (especially chemotherapy) also plays a role in the patient's prognosis.

6.1. Classification of LCH according to the degree of spread and type of organ affected

According to international studies, the classification of Langerhans cell histiocytosis (LCH) first takes into account whether only one organ / organ system is affected by the disease or whether the disease involves two or more organs / organ systems. The former is referred to as a single-system LCH (SS-LCH), the latter as a multi-system LCH (MS-LCH).

6.1.1. Monosystemic LCH

If monosystemic LCH is present, it is important for therapy planning whether the organ / organ system is affected in only one area (unifocal) or in multiple ones (multifocal). For example, in the case of bone involvement, unifocal bone foci ("single bone") are distinguished from multifocal bone disease (more than one bone), whereby the location of the bone involvement and the size of the foci of disease also play a role (*see section "Organ involvement – Special Sites"*). In addition to bones, monosystemic LCH can also affect the skin, lungs, the pituitary-*hypothalamus* region, the *central nervous system* and other organs (such as the thyroid gland, *thymus gland*).

6.1.2. Multisystemic LCH

In case of multisystemic LCH (infestation of two or more organs / organ systems), it is taken into account whether so-called "risk organs" are affected by the disease or not. The haematopoietic system as well as the spleen and liver are considered to be risk organs. As (therapy) studies have shown that an involvement of these organs is associated with a less favourable prognosis than the involvement of other organs and, therefore, must be taken into account regarding therapy and, in particular, the assessment of the response to therapy. The lungs, which used to be considered a risk organ, are no longer defined as such in the international LCH studies.

Lymph node involvement is considered to be a separate organ involvement if the lymph node(s) are not located in the drainage area of another LCH foci and are therefore not directly related to it.

6.1.3. Organ involvement – „special sites“

Regardless of whether monosystemic or multisystemic LCH is present, foci of the disease in very specific organs or organ locations are considered so-called *"special sites"* that are considered separately. These are foci of disease that, due to their location or size, are either difficult or inaccessible for surgical intervention (e.g. a large lesion in load-bearing bones), pose a threat to life (e.g. if certain vertebral bodies are affected) or, according to older study data, are associated with a higher risk of hormonal disorders, such as *diabetes insipidus*. The latter applies, for example, to certain facial or skull bones. If such "special sites" are affected in LCH disease, *systemic* therapy, i.e. *chemotherapy*, is recommended.

7. Treatment

Treatment of children and adolescents with Langerhans cell histiocytosis (LCH) should only be carried out in centres that are familiar with the disease and its treatment. This is usually a children's hospital with a paediatric oncology/haematoloy program. In such a treatment centre, highly experienced and qualified staff (doc-tors, nurses and many more) is guaranteed, since they are specialised and focus on the diagnostics and treatment of children and teenagers with cancer according to the most advanced treatment concepts. The doctors (such as oncologists, radiologists, surgeons) in these centres collaborate closely with each other. Together, they treat their patients according to treatment plans (protocols) that are continuously optimised.

Depending on the spread and severity of the disease, there are different therapeutic approaches. The possible procedure for children with LCH depends, among other things, on whether one or more organ systems (e.g. skin, bones, liver, spleen) are affected and whether – in the case of bone involvement – one or more sites are affected and in what position (*see chapter "Therapy planning"*). It is also important whether it is a first diagnosis of the disease or a relapse of LCH.

Depending on the criteria mentioned, the following procedures are possible in principle:

- "Watch-and-wait“ strategy
- Local therapy
- Systemic therapy

Due to possible long-term damage of healthy tissue, *radiotherapy* is generally no longer recommended as a suitable therapeutic measure.

7.1. "Watch-and-wait" strategy

In the "watch-and-wait" strategy ("look/observe and wait"), a wait-and-see attitude is carried out under close follow-up checks and no treatment for the time being. This can be an option, for example, in the case of a single bone focus or an isola-ted skin lesion, among other things, because spontaneous regression is possible in such cases. In the follow-up checks, careful care is taken to

detect the progression of a localized disease or the development into a multisystemic disease as early as possible. This is very important, especially in very young patients.

7.2. Local therapy

Local therapy can be considered for patients presenting with skin involvement only as well as in patients with unifocal bone involvement and without the involvement of other organs.

Patients who are only receiving local therapy should be closely monitored during therapy – as in the case of a "watch-and-wait" strategy – in order to detect pro-gression of the disease or a change to a multisystemic disease as early as possible.

Often, tissue removal (biopsy) is already considered as a local treatment, as the surgical procedure often leads to a spontaneous regression at that site of the disease. Complete removal or extensive surgery of the lesion is usually not recommended. In case of bone involvement, such a procedure could actually increase the bone defect, delay the healing process and thus cause permanent bone damage.

7.3. Systemic therapy

For many LCH patients, *chemotherapy* is necessary due to the location and spread of the disease. This generally applies for multisystemic disease, but may also be necessary in patients with monosystemic LCH, unless (for example) there is a single local skin lesion or a unifocal bone lesion without any involvement of other organs (*see chapter "Local therapy"*).

In chemotherapy, drugs (so-called cytostatics) are used that inhibit cell growth and thus contribute to the destruction of LCH cells. Since this therapy affects cells throughout the body, it is also known as *systemic* therapy. In order to destroy as many LCH cells as possible, chemotherapy usually involves a combination of different cell growth-inhibiting drugs (*cytostatics*) that have proven particularly effective in combating this disease.

In the context of chemotherapy for LCH treatment, a distinction is made between first-line therapy and second-line therapy. Second-line therapy is only used if the first-line therapy is not efficient.

7.3.1. First-line therapy

First-line therapy for patients with LCH consists of two major phases of therapy: induction and maintenance therapy. In both phases, the drugs vinblastine (VBL) and prednisone are used.

The current standard therapy involves a six-week course of chemotherapy, consis-ting of six doses of the cytostatic drug vinblastine (once a week) and daily predni-sone administrations. Following the six-week treatment, the response of the disease to therapy (therapy response) is examined. If the treatment works well, induction therapy is ended. If, on the other hand, there is only a partial response to therapy and, in particular, there is still an involvement of high-risk organs, another six-week course of chemotherapy is generally recommended. In this second course, the drugs vinblastine and prednisone are used again: vinblastine is administered once a week, a total of six times, prednisone on days 1–3 of the six-week treatment period.

After the end of the induction therapy, which lasts six or twelve weeks, maintenance therapy follows, if there is sufficient response to therapy. It consists of vin-blastine/prednisone doses administered every three weeks on days 1–5.

The current total duration of therapy according to the standard of care (induction and maintenance therapy) is six months for patients with monosystemic LCH ("single-system LCH"), i.e. for example with unifocal or multifocal bone involvement. For patients with multi-system LCH, the standard therapy is twelve months in total. Both the optimal duration and the optimal intensity of maintenance therapy are currently being investigated in studies.

7.3.2. Second-line therapy ("Salvage“ therapy)

If, at the time of the sixth week of treatment, the response to therapy is not satis-factory or the disease is even progressing in organs at risk, an early change in therapy to "salvage" therapy should be considered, especially in patients with involvement of the haematopoietic system or the liver. These patients should be treated in a specialised centre.

Possible treatment options include chemotherapy drugs such as vincristine (VCR), cytarabine (Ara-C), clofarabine, a combination of 2-chlorodeoxyadenosine (2-CDA) and cytarabine (Ara-C), and/or a blood *stem cell transplantation* (haematopoietic blood stem cell transplant). The use of newer drugs such as *inhibitor*s is currently being investigated (*see below*).

7.3.3. New therapeutic approaches

Due to the increasing characterisation of disease-activating signaling pathways in the altered cells (e.g. *BRAF* or *MAPK2K1* gene changes, *see chapter "Causes"*), there is a growing interest in the research and use of drugs that block these signaling pathways (so-called checkpoint inhibitors). In observational studies (*case series*), *checkpoint inhibitor*s in children show very promising results.

However, these treatment strategies and the optimal duration of therapy with these substances are still unclear, and in the majority of patients, the disease returns when the drugs are discontinued. For this reason, studies are currently being designed to test a combination of signaling pathway blockers with chemotherapy.

Since the long-term side effects of such drugs are still unclear on the one hand and chemotherapy works well in most patients on the other, these drugs should initially only be used in acutely life-threatening situations or in the absence of a response to conventional therapy. Also, any additional procedure should be discussed with experts.

8. Treatment for relapse of LCH

At present, all therapy recommendations in case of disease *recurrence* are based on experience from clinical practice as well as on expert opinions. The therapeutic decision depends on the time of relapse and the spread of the disease.

If only one organ / organ system is affected, the decision on the appropriate treatment strategy is based on similar criteria as for the initial disease. Even if the recurrence affects more than

one organ / organ system after the first-line therapy has been completed, a resumption of treatment with vinblastine and steroids (prednisolone) may be successful within the framework of the chemotherapy required in this case (*see chapter "Treatment"*).

In the case of relapses in the bone area, smaller case series with LCH patients also have found indomethacin or *bisphosphonates* to be effective treatment options, although these strategies have not yet been tested in randomised trials [see *randomisation*]. In the event of therapy failure or a relapse during ongoing therapy, the further course of action is decided on an individual basis. The study director can support the treating institution with therapy recommendations.

9. Therapy optimising trials and registries

In order to continuously improve the treatment options for children and adolescents with Langerhans cell histiocytosis (LCH), all patients with LCH should be included in an ongoing (therapy optimising) study or registry.

Therapy optimising trials are standardised and controlled clinical trials that aim at continuously developing and improving treatment concepts for patients based on the current scientific knowledge. Patients who cannot participate in any study, for example because none is open for them at that time or since they do not meet the required inclusion criteria, respectively, are often included in a so-called **registry**.

Until recently, the LCH-REG-DE 2013 registry was available in Germany for patients with LCH, but it was closed for administrative reasons; the registry is scheduled to be reopened as LCH-REG-DE 2025 at the end of 2025.

All LCH patients under the age of 18 can then be included in the **"LCH-REG-DE 2025" registry** – as was previously the case in the LCH-REG-DE 2013 registry (which was available at the end of 2022 after patient enrolment in the therapy optimising trial "LCH IV-G 2016" had been completed). This applies to patients with initial LCH disease as well as to patients with relapse of the disease.

The registry primarily serves to scientifically accompany the therapy of patients and to obtain answers to various questions. There are no therapy specifications within the framework of the registry; patients receive standard treatment tailored to their form of disease. If necessary, the LCH study group advises the treating physicians on the selection of the optimal diagnostics and therapy in each case.

The LCH study group is headed by Prof. Dr. Thomas Lehrnbecher at the University Hospital Frankfurt (Main), Germany. Further members of the study centre are PD Dr. Konrad Bochennek and Dr. Anke Barnbrock as well as the neuroradiologist Prof. Dr. Luciana Porto.

10. Prognosis and course of the disease

Langerhans cell histiocytosis (LCH) is a diverse clinical condition that can be associated with different disease courses and prospects of recovery (prognosis). Both the course and the *prognosis* of disease depend largely on the degree of spread of the disease and its response to therapy. On

the one hand, there are courses of the disease that can be accompanied by spontaneous healings. On the other hand, LCH can also keep recurring or, rarely, even rapidly progress to a fatal outcome.

As a rule, the prognosis for patients with monosystemic LCH is very good – in the older studies, such as the international study LCH III, all children survived –, while in multisystemic LCH up to 10% of patients still pass away. However, these are almost exclusively small children (under 2 years of age) in whom important organs (liver, spleen, bone marrow) are affected and whose disease has responded poorly or not at all to the initial treatment (induction). It remains to be seen to what extent the use of inhibitors can improve this. The majority of patients, however, respond well to conventional treatment and then remain disease-free.

In about one third of patients, a relapse of the disease occurs after a disease-free phase (of varying duration). LCH relapses are mainly limited to bones, skin and *pituitary gland* and are therefore usually not life-threatening. However, they can be accompanied by protracted (chronic) problems (long-term effects). Late effects of the disease are observed in 30–40% of patients, and a chronic course of the disease significantly increases the risk of those (*see our information on "Late sequelae"*).

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Glossary

anamnesis	medical interview, a patient's history, development of signs of illness; the type, onset and course of the (current) symptoms as well as any risk factors (e.g. hereditary diseases) are evaluated during a medical interview.
antigen	substance that appears foreign to the body; it stimulates the immune system to produce antibodies against it and can trigger an allergic reaction.
audiogram	hearing test; graphical representation of the subjective hearing ability of sounds; the audiogram records a persons hearing sensitivity in different frequency ranges. The examination is carried out with the help of the patient. By audiogram, the severity, type and cause of a hearing disorder can be determined. A separate audiogram is created for each ear, usually by the ear-nose-throat-(ENT) specialist. An audiogram that deviates from the norm suggests a disease of the ear. The audiogram is one of many methods used to examine hearing (audiometry).
biopsy	removal of a tissue sample for subsequent (mainly microscopic) examination; this can be done, for example, by puncture with a hollow needle, with the use of special instruments (such as forceps, punching instruments, probes) or surgically with a scalpel.
bisphosphonates	substances that inhibit bone resorption, thereby maintaining bone structure and strength; they are often used to treat benign bone diseases, such as osteoporosis.
bone marrow	site of blood formation; spongy tissue with a strong blood supply that fills the cavities inside many bones (e.g., vertebrae, pelvic and thigh bones, ribs, sternum, shoulder blade, and collarbone); in the bone marrow, all forms of blood cells develop from blood progenitor cells (blood stem cells).
case series	a type of observational study; it is used to evaluate various substances in some cases with very small numbers of patients, without any special measures being taken within the scope of the study, e.g. study-specific therapy (non-interventional study).
central nervous system	comprises the brain and spinal cord and is separated from the so-called peripheral nervous system; as a central organ of integration, coordination and regulation, it serves to process

	external sensory impressions as well as stimuli produced by the organism itself.
checkpoint inhibitor	drug (monoclonal antibody) that activates the bodys own immune response against tumour cells; is used specifically as immunotherapy in cancer treatment. The effect of checkpoint inhibitors is based on the blocking of certain switching points of the immune system, so called immune checkpoints. These are surface proteins on immune cells (T lymphocytes) that ensure that an immune reaction is terminated on time. This checkpoint control usually serves to ensure that the immune system does not react too strongly or is directed against the bodys own tissue (autoimmune reaction). Cancer cells can also activate these checkpoints and thus slow down the bodys immune response. By blocking these switching points, checkpoint inhibitors reactivate the immune cells, thereby initiating an immune response against the tumour cells.
chemotherapy	here: use of drugs (chemotherapeutic agents, cytostatics) for the specific inhibition of tumor cells in the organism
computed tomography	imaging, X-ray diagnostic procedure; it produces an image by computer-controlled evaluation of a large number of X-rays from different directions. This makes it possible to produce sliced images of body parts (tomograms, transverse or longitudinal sections of the human body)
diabetes insipidus	increase in urine excretion with urine volumes of several litres per day; as the body loses a lot of water, the body and mucous membranes dehydrate and patients feel very thirsty. The cause is usually a disorder in the posterior lobe of the pituitary gland and/or diencephalon resulting in decrease or lack of antidiuretic hormone (ADH) function.
diagnostics	methods / measures for the detection of a disease
exophthalmus	pathological protrusion of the eyeball from the eye socket on one or both sides;
gene	unit of genetic information in the genome of living organisms; a gene contains the genetic information – the blueprint – for a specific gene product (protein or RNA). In most organisms, the entirety of all genes, the genome, is present as a deoxyribonucleic acid chain (DNA), which forms the chromosomes in the cell nucleus. The information of a gene is mediated by a certain

	sequence of the nucleic acid building blocks adenine, guanine, cytosine and thymine.
genetic	concerning the (level of) inheritance or genes; inherited
hormone	chemical signaling substances (proteins) that are produced in different body glands and have different tasks (for example: thyroid hormone, growth hormone, sex hormones).
hypothalamus	part of the diencephalon and supreme control organ of the endocrine system; the hypothalamus controls numerous vegetative body functions (e.g. blood pressure and heart rate) and is the overarching center of homeostasis. It controls, among other things, the wake-sleep rhythm, appetite and thirst, body temperature and sex drive, and it processes the sensation of pain and temperature. It also controls the pituitary gland and stimulates it to release hormones.
imaging	diagnostic procedures generating images of the inside of the body, such as ultrasound and X-ray examination, computed tomography, magnetic resonance imaging, and scintigraphy
immune system	the bodys own system for maintaining a healthy organism by defending against foreign substances and destroying abnormal body cells (e.g. cancer cells); the immune system has the ability to distinguish between self and foreign or dangerous and harmless; mainly the organs of the lymphatic system as well as cells distributed throughout the body (e.g. leukocytes) and molecules (e.g. immunoglobulins) are involved.
indication	reason for the use of certain diagnostic procedures and treatment methods that are evidence-based regarding the respective disease and which require a patient’s consent
infection	penetration of the smallest organisms (e.g. bacteria, viruses, fungi) into the body and subsequent multiplication within it. Depending on the characteristics of the microorganisms and the immune system of the infected person, various infectious diseases can occur after infections.
inhibitor	the term derives from „inhibition“ (= hindering); a substance that influences one or more biochemical reactions thereby slowing it down or completely preventing it
light microscope	a microscope that uses light to produce highly magnified images of small objects, thus allowing the detection of structures that are

	not visible to the naked eye; magnification is done by exploiting the refraction of light on the microscopes lens system.
lymph nodes	small lenticular to bean-shaped organs that are part of the bodys immune system and are located in many parts of the body; they serve as filter stations for the tissue water (lymph) of a region of the body and contain cells of the immune system.
magnetic resonance imaging	diagnostic imaging method; very precise, radiation-free examination method for the visualization of structures inside the body; with the help of magnetic fields, cross-sectional images of the body are generated, which usually allow a very good assessment of the organs and many organ changes.
molecular genetic	referring to structure, formation, development, function and interactions of cells and cell building blocks (e.g. nucleic acids, proteins) at the molecular level; the focus is on the analysis of the genetic information stored in the nucleic acids (DNA and RNA) and its processing in the context of protein synthesis as well as gene regulation.
molecule	chemical compound of two or more atoms joined together
mutation	alteration of genetic material; it can arise without any identifiable external cause (so-called spontaneous mutation) or be caused by external influences (induced mutation). External influences include, for example, ionizing radiation or certain chemical substances (mutagens). If somatic cells are affected, it is referred to as a somatic mutation, and if germ cells are affected, it is referred to as a generative mutation. Somatic mutations are not heritable, while germ cell mutations can lead to hereditary damage. Depending on the extent of the change (single or multiple genes, larger chromosome segments or complete chromosomes), a distinction is made between point and block mutations as well as numerical and structural chromosomal aberrations.
neurological	referring to the function of the nervous system / nerve tissue
physical examination	an important part of diagnostic examinations; includes palpation and listening to certain body organs as well as testing reflexes to obtain indications of the nature or course of a disease.
pituitary gland	endocrine gland inside the skull; together with the hypothalamus, it plays a central role in the regulation of hormones in the body. The pituitary hormones stimulate the production and secretion of hormones in the various hormone glands of the body (such as

	thyroid, mammary glands, ovaries, testicles). For example, they control growth prior, during and after puberty, promote the growth of internal organs and the development of germ cells in the ovaries or testicles and have an influence on metabolism.
prognosis	prediction of the course and outcome of a disease / prospect of recovery
prognostic factors	factors that allow an approximate assessment of the further course of the disease (i.e. the prognosis);
puberty	the process of sexual maturation; the period during which adolescents reach sexual maturity and become capable of reproduction
radiation exposure	the dose of ionising radiation to which humans are exposed from natural, civilised or artificial sources of radiation; natural sources of radiation include cosmic, terrestrial and natural radioactive substances produced by the decay of natural radioactive substances, which are absorbed into the body with drinking water, food and breathing air. Artificial sources include radiation produced by the technical and medical use of nuclear and atomic forces, such as X-rays.
radiotherapy	controlled use of ionizing (high-energy) radiation for the treatment of malignant diseases
randomisation	(statistical) random distribution of patients to treatment and control groups in a study; the strict random distribution is intended to eliminate systematic errors in the evaluation of therapy studies.
recurrence	relapse, recurrence of a disease after recovery
stem cell transplantation	transfer of haematopoietic stem cells after conditioning chemotherapy, radiation or immunosuppression of the recipient; the stem cells can be obtained either from the bone marrow or from the bloodstream. In the first case, the procedure of their transfer is called bone marrow transplantation, in the second case peripheral stem cell transplantation. Depending on the type of donor, a distinction is made between two forms of SCT: allogeneic SCT (stem cells from a foreign donor) and autologous SCT (own stem cells).
symptom	sign of illness
systemic	covering/includiing the entire body
T lymphocytes	subtype of lymphocytes (a form of white blood cells); they develop in the thymus gland and are responsible for the so-called cellular

	immune response; T lymphocytes play an important role in the direct defense against viral and fungal infections and control the activities of other immune cells (e.g. granulocytes).
thymus gland	organ belonging to the lymphatic system below the thyroid gland; part of the bodys own defence system and significantly involved in the development of the immune system, especially during childhood; from puberty onwards, it loses its size and importance.
ultrasound	an imaging technique used to examine organs, in which ultrasound waves are sent through the skin into the body; at tissue and organ boundaries, the sound waves are reflected back, picked up by a receiver (transducer) and converted into corresponding images with the help of a computer.
X-ray examination	imaging procedure that uses X-rays to visualize organs or parts of organs