Version 1.4; 07.03.2026 – MaximALL

Study protocol

“MaximALL“

More than just X-Rays - Imaging of chemotherapy-induced morphological and functional cardiovascular and lung changes after childhood ALL and other cancers - a monocentric late effects study (MaximALL)

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2. Study title, version number, version date

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Version
Version 1.4

Version date
07.03.2026

Protokollversionen

Date	Version	Status	Changes
01.12.2024	1.0	Draft	
15.12.2024	1.1	Draft	
02.01.2026	1.2	Draft	Inclusion of DLCO, CH
26.01.2026	1.3	Draft	Inclusion of radiological parameters
07.03.2026	1.4	Formal revisions according to Ethics Committee	

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3. Project summary

With increasing cure rates of childhood cancer there is growing recognition of late effects of treatments. However, there is a lack of non-invasive and child-friendly procedures that can indicate possible late damage. In a previous project (MinimALL study, ClinicalTrials.gov number, NCT06093334), we demonstrated the great benefit of free-breathing phase-resolved functional low-field (PREFUL) magnetic resonance imaging (MRI) for the detection of subclinical pulmonary damage after treatment for childhood acute lymphoblastic leukemia (ALL) and Hodgkin's disease (HD). Based on the observations in this pilot study, we now present this follow-up project to investigate possible subclinical organ damage after oncological treatment in childhood and adolescence and young adults through the use of various diagnostic tools.

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5. Scientific background

As cure rates of childhood cancer have increased in the last 20 years, there is growing evidence that children diagnosed with cancer have an increased risk of late effects even years to decades after completing treatment.[1] Contemporary systemic and local treatment regimens are less intensive than previous therapies, they are still associated with diverse general and specific, acute and chronic organ toxicities such as cardiac dysfunction, osteonecrosis, neurocognitive impairment, and second malignant neoplasms[2]. Studies show that 7,3% of the occurring late effects affect the pulmonary system and 8,6% the cardiovascular system.[3]

Improved therapy concepts and cure rates have led to a greater awareness regarding late effects of childhood cancer. As a result, a number of guidelines for long-term follow-up (LTFU) after childhood cancer therapy have been proposed.[4]

Echocardiography remains the only functional imaging routinely applied according to the current protocols for general long term follow up.[5] It appears conceivable that minor organ alterations at an early stage could be missed. Thus, there is an urgent need for more sensitive and non-invasive diagnostic tools for the detection of organ damage before clinical symptoms develop.

Symptomatic pulmonary dysfunction often presents with cough or dyspnea, especially on exertion. As there is a large functional pulmonary reserve, clinical symptoms may occur only with a substantial decline in pulmonary function.[6]

Childhood Cancer Survivors are significantly more likely to take medications for hypertension, dyslipidemia, or diabetes, and the risk of cardiovascular disease with premature mortality rate is 5–10 times more common. Vascular toxicities are a very

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[1] Oeffinger, K. C., Mertens, A. C., Sklar, C. A., Kawashima, T., Hudson, M. M., Meadows, A. T., Friedman, D. L., Marina, N., Hobbie, W., Kadan-Lottick, N. S., Schwartz, C. L., Leisenring, W., Robison, L. L., & Childhood Cancer Survivor Study (2006). Chronic health conditions in adult survivors of childhood cancer. *The New England journal of medicine*, *355*(15), 1572–1582. https://doi.org/10.1056/NEJMsa060185

[2] Silverman LB. Balancing cure and long-term risks in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2014;2014(1):190-7. Epub 2015/02/20. doi: 10.1182/asheducation-2014.1.190. PubMed PMID: 25696854.

[3] Gebauer J, Rieken S, Schuster S, et al.: Multidisciplinary Late Effects Clinics for Childhood Cancer Survivors in Germany – a Two-Center Study. Oncol Res Treat 2018; 41 (7–8): 430–6.

[4] Gebauer J, Baust K, Bardi E, Grabow D, Stein A, van der Pal HJ, et al. Guidelines for Long-Term Follow-Up after Childhood Cancer: Practical Implications for the Daily Work. Oncol Res Treat. 2020;43(3):61-9. Epub 2020/01/14. doi: 10.1159/000504200. PubMed PMID: 31931503.

[5] S. Schuster, B. Hahn, J. D. Beck, G. Calaminus, B. Timmermann, A. am Zehnhoff-Dinnesen, J. Gebauer , T. Langer Langzeit - Nachsorge von krebskranken Kindern, Jugendlichen und jungen Erwachsenen – Vermeiden, Erkennen und Behandeln von Spätfolgen

[6] Otth, Maria et al. "Recommendations for surveillance of pulmonary dysfunction among childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group." EClinicalMedicine vol. 69 102487. 20 Feb. 2024, doi:10.1016/j.eclinm.2024.102487

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common cause of death in long-term cancer survivors.[7] There is an unmet need and lack of screening methods in early detection of vascular changes.

Long-term survivors of childhood and adolescent cancer are at increased risk for therapy-related late effects that resemble conditions typically observed in older age. In particular, pulmonary dysfunction and vascular damage are well-recognized consequences of cancer therapy and represent important predictors of long-term morbidity and mortality.

Within the maximALL project, these clinically relevant late effects are systematically and prospectively assessed. Clinical data generated in maximALL include detailed parameters of lung toxicity (e.g. functional and imaging-based pulmonary measures), cardiac abnormalities (e.g. functional and imaging-based assessment of the heart function and myocardial fibrosis), as well as markers of vascular damage. These outcomes constitute core components of the maximALL study and provide a unique clinical framework to investigate mechanisms of accelerated biological aging in cancer survivors.

In parallel, molecular biomarkers have emerged as promising tools to capture biological aging processes. Epigenetic aging markers, alterations in telomere biology, and clonal hematopoiesis (CH) have been associated with age-related diseases and increased long-term morbidity. Importantly, cancer survivors show a higher prevalence of CH with a distinct, therapy-related mutational spectrum, which has been linked to adverse clinical outcomes. [8,9,10]

[7] Herrmann, J. Vascular toxic effects of cancer therapies. *Nat. Rev. Cardiol.* 2020, *17*, 503–522. Meacham, L.R.; Chow, E.J.; Ness, K.K.; Kamdar, K.Y.; Chen, Y.; Yasui, Y.; Oeffinger, K.C.; Sklar, C.A.; Robison, L.L.; Mertens, A.C. Cardiovascular risk factors in adult survivors of pediatric cancer—A report from the childhood cancer survivor study. *Cancer Epidemiol. Biomark. Prev.* 2010, *19*, 170–181

[8] Hagiwara K, Natarajan S, Wang Z, Zubair H, Mulder HL, Dong L, Plyler EM, Thimmaiah P, Ma X, Ness KK, Li Z, Mulrooney DA, Wilson CL, Yasui Y, Hudson MM, Easton J, Robison LL, Zhang J. Dynamics of Age- versus Therapy-Related Clonal Hematopoiesis in Long-term Survivors of Pediatric Cancer. Cancer Discov. 2023 Apr 3;13(4):844-857. doi: 10.1158/2159-8290.CD-22-0956. PMID: 36751942; PMCID: PMC10070170.

[9] Nachun D, Lu AT, Bick AG, Natarajan P, Weinstock J, Szeto MD, Kathiresan S, Abecasis G, Taylor KD, Guo X, Tracy R, Durda P, Liu Y, Johnson C, Rich SS, Van Den Berg D, Laurie C, Blackwell T, Papanicolaou GJ, Correa A, Raffield LM, Johnson AD, Murabito J, Manson JE, Desai P, Kooperberg C, Assimes TL, Levy D, Rotter JI, Reiner AP, Whitsel EA, Wilson JG, Horvath S, Jaiswal S; NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. Clonal hematopoiesis associated with epigenetic aging and clinical outcomes. Aging Cell. 2021 Jun;20(6):e13366. doi: 10.1111/acel.13366. Epub 2021 May 29. PMID: 34050697; PMCID: PMC8208788.

[10] Belsky DW, Caspi A, Corcoran DL, Sugden K, Poulton R, Arseneault L, Baccarelli A, Chamarti K, Gao X, Hannon E, Harrington HL, Houts R, Kothari M, Kwon D, Mill J, Schwartz J, Vokonas P, Wang C, Williams BS, Moffitt TE. DunedinPACE, a DNA methylation biomarker of the pace of aging. Elife. 2022 Jan 14;11:e73420. doi: 10.7554/eLife.73420. PMID: 35029144; PMCID: PMC8853656.

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Within maximALL, peripheral blood samples will be obtained from adult survivors following comprehensive written and oral informed consent. Samples will be pseudonymized, biobanked, and used for analyses of clonal hematopoiesis, epigenetic aging markers, and telomere biology. The resulting molecular data will be directly correlated with the clinical data collected within maximALL, particularly measures of pulmonary toxicity and cardiovascular damage, enabling integrated analyses of therapy exposure, biological aging processes, and clinically relevant late effects.

The subproject with a focus on clonal hematopoiesis, epigenetic aging markers, and telomere biology will be conducted in collaboration with the Department of Human Genetics of the University of Oldenburg and the Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation of the University Hospital Aachen. In the long term, this integrative approach aims to improve risk stratification and to support the development of personalized long-term follow-up strategies for childhood cancer survivors.

In recent years Low field-strength MRI has proven to be a sensitive and non-invasive technique for the illustration of pulmonary ventilation/perfusion mismatches in asymptomatic patients.[11]

In a previous pilot study (MinimALL study), we were able to detect early limitations in pulmonary ventilation and perfusion after oncological treatment in childhood and adolescence for the first time using low-field MRI. In addition, the subjects showed abnormal parameters in echocardiography and spiroergometry. With the present project proposal, we would like to confirm our hypothesis of an early onset of organ changes after oncological treatment in a larger patient population and at a greater time interval from initial therapy. Furthermore, we want to expand the imaging protocol with cardiac MRI sequences in order to assess potential myocardial dysfunction and fibrosis. In addition, we would like to expand the screening for possible microangiopathic changes with further non-invasive tools and with blood samples to enable integrated vascular phenotyping and correlation with molecular biomarkers.

[11] Dierl A, Hinsen M, Wild EM, Bayerl N, Heiss R, Nagel AM, Schmidt S, Grimm R, Vogel-Claussen J, Voskrebenzev A, Naumann-Bartsch N, Anderheiden F, Huber F, Mueller N, Schoeffl I, Woelfle J, Uder M, Regensburger AP, Knieling F, Karow A. Free-breathing phase-resolved functional lung (PREFUL) low-field magnetic resonance imaging (LF-MRI) of pulmonary dysfunction after surviving childhood cancer. Commun Med (Lond). 2026 Jan 22. doi: 10.1038/s43856-025-01365-w. Epub ahead of print. PMID: 41571877.

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The results of this trial could contribute to the implementation of further investigation techniques in future standardized, structured and individualized LTFU care.

Beyond physical late effects, childhood cancer survivors may experience long-term psychosocial consequences related to cancer-related decision-making and coping with the disease. Evidence from pediatric and young adult oncology suggests that limited age-appropriate involvement in treatment decisions and insufficient information may contribute to decision regret later in life, whereas trustful communication and perceived support act as protective factors.[12,13,14] At the same time, many survivors report posttraumatic growth (PTG), describing positive psychological changes such as increased personal strength, altered life priorities, and improved interpersonal relationships, despite persistent health-related challenges.[15,16]

Within the maximALL framework, psychosocial outcomes will therefore be assessed alongside clinical and biological parameters. Health-related quality of life, decision regret, and posttraumatic growth will be evaluated using standardized questionnaires and a short, survivor-adapted decision regret instrument. Integrating psychosocial data with cardiopulmonary, vascular, and molecular biomarkers aims to provide a more comprehensive understanding of long-term survivorship, including the interaction between physical late effects, accelerated biological aging, and psychological adaptation after childhood cancer.

6. Study aims

Determination of the frequency of morphological and functional lung parenchymal changes using low-field MRI (LF-MRI), and assessment of cardiopulmonary health using diffusion capacity of the lung for carbon monoxide (DLCO), spiroergometry, echocardiography, and LF-MRI. In addition, results from imaging and functional assessments will be correlated with biological parameters, including clonal hematopoiesis, epigenetic aging markers, and telomere attrition. Mental health and psychosocial outcomes after therapy will be assessed using standardized

[12] Benedict C, Thom B, Kelvin JF. J Adolesc Young Adult Oncol. 2015;4(4):213-218. doi:10.1089/jayao.2015.0002

[13] Mack JW et al. Pediatrics.2019;143(5):e20182800. doi:10.1542/peds.2018-2800

[14] Keij SM et al. Patient Educ Couns. 2023;111:107677. doi:10.1016/j.pec.2023.107677

[15] Zhang S, Liu CY, Wang F, Ni ZH. Post-traumatic growth among childhood cancer survivors: A qualitative meta-synthesis. Eur J Oncol Nurs. 2023;63:102289. doi:10.1016/j.ejon.2023.102289

[16] Bolliger C, Holmer P, Dehler S, Roser K, Michel G. Posttraumatic growth and illness perception in survivors of adolescent and young adult cancer. Discov Oncol. 2023;14(1):194. Published 2023 Oct 30. doi:10.1007/s12672-023-00810-3

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questionnaires (EORTC SURV100 and PPR) and a questionnaire specifically developed to assess decision regret in childhood cancer survivors, in collaboration with Survivor Deutschland e.V.

Hypotheses:

- Oncological treatment in childhood and adolescence can cause organ damage like vascular toxicity, microangiopathy and decreased heart function.
- These vascular changes show a temporal progression after completion of the therapy but do not necessarily have to be accompanied by clinical symptoms.
- Reduced cardiopulmonary function can be assessed by echocardiography, spiroergometry and pulmonary diffusion capacity (DLCO).
- LF-MRI is capable of detecting perfusion and ventilation defects of the lungs as well as myocardial fibrosis and functional impairment of the heart.
- Survivors of childhood cancer show signs of accelerated biological aging
- Accelerated biological aging correlates with blood(-based) biomarkers, including clonal hematopoiesis, epigenetic aging markers, and telomere attrition.
- Psychosocial outcomes, including decision regret and posttraumatic growth, are associated with health-related quality of life in long-term survivors of childhood cancer.
- Psychosocial outcomes are associated with clinical late effects and markers of accelerated biological aging.

Primary Objective:

- To determine the frequency of morphologic and functional lung parenchymal changes in healthy individuals and patients after oncological treatment in childhood and adolescence using LF-MRI.
- To determine the frequency of myocardial dysfunction and fibrosis in healthy individuals and patients after oncological treatment in childhood and adolescence using LF-MRI.

Secondary Objectives:

- Determination of the anamnestic frequency of clinical respiratory symptoms

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- Assessment of pulmonary gas exchange capacity using DLCO
- To assess pulmonary function by spirometry
- To assess functional cardiopulmonary exercise capacity by spiroergometry
- To assess myocardial function by echocardiographic strain and strain-rate imaging
- To collect peripheral blood samples for the analysis of molecular biomarkers of accelerated biological aging and to correlate these findings with clinical outcomes
- To assess decision regret, posttraumatic growth, and health-related quality of life using standardized questionnaires (EORTC SURV100, PPR) and a questionnaire specifically developed to assess decision regret in childhood cancer survivors.
- To explore associations between psychosocial outcomes, cardiopulmonary and vascular late effects, and molecular biomarkers of accelerated biological aging.

Study type

Prospective, monocentric, diagnostic study

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7. Target variables

Primary target variables:

LF-MRI	Morphological lung changes Functional lung parameters (Ventilation match/mismatch, Perfusion match/mismatch, combined defects) Quantitative cardiovascular changes Functional cardialvascular parameters

Secondary target variables:

Pulmonary testing	DLCO (absolute value) DLCO (% predicted) VA (Alveolar Volume) KCO (DLCO/VA) KCO (% predicted) Spirometry (VC%, FEV1%)
Cardiopulmonary testing	Oxygen uptake (VO_2) peak oxygen uptake (VO_2max) Respiratory exchange ratio (RER) Ventilatory anaerobic threshold (VT2) Carbon dioxide output (VCO_2) Heart rate (HR) Heart Rate Reserve (HRR) Breath rate at VAT Breath rate reserve (BRR) minute ventilation (VE) O_2 Pulse Heart rate variability (HRV) Exercise capacity (Borg Scale) Capillary blood gases and lactate Myocardial function by echocardiographic strain and strain-rate imaging
Clinical parameters	Age* Gender* Weight*

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	Ethnicity* Time from therapy initiation/Interval until study day Current medication* Secondary diagnoses* Clinical examination* Blood pressure measurement
Questionnaire regarding psychosocial aspects	EORTC-SURV100 PPR (Posttraumatische Persönliche Reifung) Adapted Decision Regret questionnaire for childhood cancer survivors
blood samples	Presence of clonal hematopoiesis (CH) Type of CH-associated gene mutations (e.g. DNMT3A, TET2, DDR genes) Clone size / variant allele frequency (VAF) Epigenetic aging markers (e.g. epigenetic age acceleration measures) Telomere biology parameters (e.g. telomere length–related measures) biomarkers for long-term pulmonary dysfunction (WFDC2, TNFR1, MMP2, SPD[17])

*Standard procedures/parameters routinely available in follow-up care

[17] Small IS, Cheng PC, Rahrig AL, Rowan CM. Potential Early Risk Biomarkers for Reduced Forced Expiratory Volume in Children Post-Hematopoietic Cell Transplantation. Pediatr Blood Cancer. 2026 Jan 2:e70024. doi: 10.1002/1545-5017.70024. Epub ahead of print. PMID: 41482572.

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8. Study design

Monocentric / multicentric
This is a monocentric study

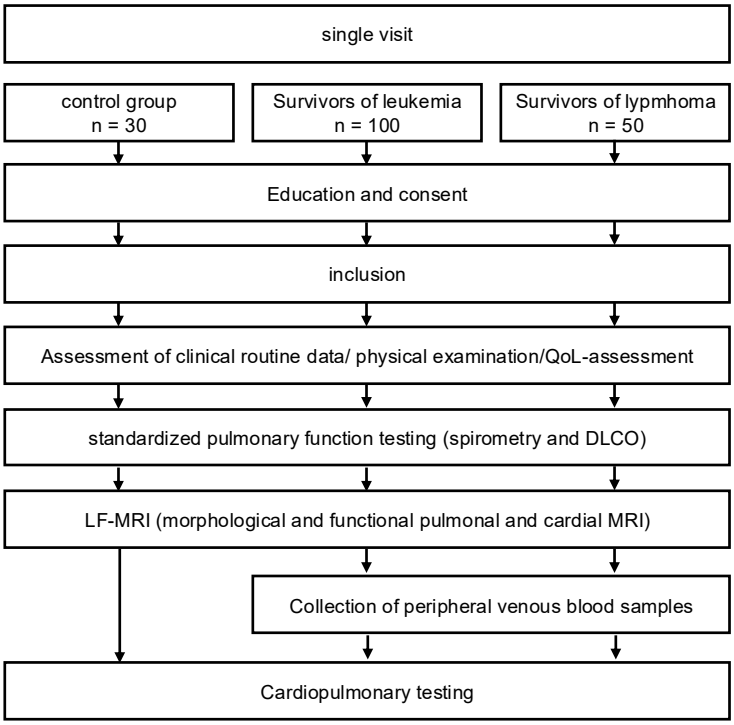
Study arms: intervention/control
Patients fulfilling the inclusion criteria will be examined, receive an MRI scan of the lungs and heart, undergo pulmonary and cardiopulmonary testing, provide peripheral blood samples for molecular analyse and will be handed out a questionnaire.
Healthy individuals in the control group will receive an analysis of their cardiopulmonary health using MRI of the lungs and heart and performing pulmonary and cardiopulmonary testing (spiroergometry, spirometry and DLCO)

Randomization
Randomization is not planned

Blinding
Blinding to the study is not possible. Blinding of patients/subjects is not necessary. The responsible radiologist does not receive any information about the affiliation of the participant to the control or study group.

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Graphical design of study flow



Kommentiert [1]: Müssen wir dann noch anpassen

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9. Study population

This study aims to achieve a broad and even distribution across age groups, focusing on the time after the end of therapy. Based on the experience gained from our previous pilot project, it is usually possible to perform lung MRI scans in children aged 3 years and older without the use of sedatives. This age typically coincides with the first peak age for ALL (between 2 and 5 years). Based on our experience at our oncology center, the shortest treatment time for ALL or lymphoma is 6 months. Therefore, it seems reasonable to us to enroll patients in our study from this age onwards. Each examination will be conducted in an age-appropriate manner. For young children, we schedule more time for each examination to avoid putting extra time pressure on families and participants. During each examination, at least one parent can remain in the child's immediate vicinity. Sedatives will not be used, and the examination will be stopped if the child becomes too anxious.

In- and exclusion criteria

Control Group	Survivors of ALL	Survivors of Lymphoma
Planned number of patients		
N=30	N=100	N=50
Inclusion criteria		
- no cancer diagnosis - no lung diseases - no vascular diseases - No subjective reduction in physical performance - age >/= 18 years	- Completed therapy for ALL - age >/= 3 years	- Completed therapy for lymphoma (Hodgkin or non-Hodgkin lymphoma) - age >/= 3 years
Exclusion criteria		
- Pregnancy, Lactation - Known pleural or pericardial effusion - Critical condition (requiring respiratory support, ventilation, oxygen, shock,	- Pregnancy, Lactation - Known pleural or pericardial effusion - Critical condition (requiring respiratory support, ventilation, oxygen, shock,	- Pregnancy, Lactation - Known pleural or pericardial effusion - Critical condition (requiring respiratory support, ventilation, oxygen, shock,

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symptomatic heart failure) - Marked thoracic deformities/malformations - Previous lung surgery - Injuries that do not allow physical stress diagnostics - Rejection of MRI imaging - General contraindications for MRI examinations (e.g. electrical implants such as cardiac pacemakers or perfusion pumps, copper IUD etc.)	symptomatic heart failure) - Marked thoracic deformities/malformations - Previous lung surgery - Injuries that do not allow physical stress diagnostics - Rejection of MRI imaging - General contraindications for MRI examinations (e.g. electrical implants such as cardiac pacemakers or perfusion pumps, copper IUD etc.)	symptomatic heart failure) - Marked thoracic deformities/malformations - Previous lung surgery - Injuries that do not allow physical stress diagnostics - Rejection of MRI imaging - General contraindications for MRI examinations (e.g. electrical implants such as cardiac pacemakers or perfusion pumps, copper IUD etc.)

Recruitment channels and measures

Patients and parents for participants under 18 years of age will be informed about the possibility to participate in the study in public notices and announcements on the homepage of the cooperating hospitals as well as when visiting the pediatric or aftercare clinics for hematology and oncology (including its outpatient clinics). If patients and their parents are interested in participating, they can contact us by email (ki-nachsorge@uk-erlangen.de) or telephone. They will be fully informed about the aims and methods, about the scientific/explorative nature of the study, the benefits and risks and the revocability of participation in the study before giving their consent prior to study initiation. Patients in childhood and adolescence are additionally informed and educated about the study and its procedure in an age-appropriate manner.

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10. Study procedures

Procedures for informing and obtaining Consent

Patients can only be enrolled in the study after written informed consent has been obtained. The written informed consent requires an oral and written explanation to the patients/subjects, as well as their parents or legal guardians, about the aims and methods (incl. scientific-explorative character of the study), benefits and risks as well as the revocability of the study participation. Children and adolescents are informed by means of age-appropriate, comprehensible patient information sheets. By giving written informed consent, the patients/participants as well as their parents/guardians declare that they agree with the collection and storage of study-relevant data and their review by monitoring or authorities. It must be clearly conveyed to the study participant that withdrawal of consent is possible at any time and without any disadvantage. Furthermore, all study participants/subjects and parents/guardians are informed that this study is a purely scientific study without any current diagnostic or therapeutic benefit.

Participants and, where applicable, their legal representatives will be informed of the study results after the evaluation is completed. The results will be explained in an understandable format by physicians involved in the study who will answer any questions and address any concerns.

In case of incidental findings, the study participants/test persons and parents/guardians will be informed and further clarification will be initiated if indicated.

The original consent form will be kept in the study folder at the study site. The patient/proband and parent/guardian will be given a copy of the patient information and consent form. The patient information and informed consent form can be found in the appendix of this study protocol.

Study procedures

As the majority of participants will be traveling from outside the region, possible contraindications for participation will be determined in advance by personal contact by telephone or E-Mail. After informing the patient/proband and parents/guardians and receiving their oral and written consent, clinical data and peripheral blood samples are collected. This includes the latest laboratory analyses, which are routinely performed in these patients.

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After appropriate education of parents/guardians/patients, the patients will be included in the study. First, participants undergo standardized pulmonary function testing, including spirometry and assessment of the diffusing capacity of the lung for carbon monoxide (DLCO) using a single-breath technique in accordance with established clinical guidelines. The test involves controlled breathing maneuvers under medical supervision and provides quantitative measures of pulmonary ventilation and alveolar–capillary gas exchange. The total duration of lung function testing is approximately 10 minutes. Next, a native MRI examination (MRI examination without contrast medium administration) is performed. The duration is about 30 minutes. This is performed exclusively without sedation. Patients can remain in a lying position during the examination. During the examination, patients are protected by hearing protection from the noise generated. To enable the patient to make himself/herself heard, he/she is given a bell button shortly before the examination begins; during the examination planning, communication is possible by means of an intercom system. In addition, the presence of a parent in the scanner room is possible during the entire examination time. The examination in the new 0.55 T MRI system does not differ in procedure and especially with regard to contraindications for an MRI examination from an examination in routinely used 0.55, 1.5 or 3T devices. There is no intravenous administration of contrast medium and the images produced are not evaluated diagnostically.

During spiroergometry, the participants are subjected to a step test using treadmill spiroergometry. Spiroergometry is a non-invasive test method. The subject then has to put on a mask during the examination, has ECG electrodes attached to the thorax and has to run for a period of around 10 minutes at increasing speed up to the limit. Time schedule and study duration for the individual subjects: approx. 60 minutes per spiroergometry. Spirometry is also performed at rest. We plan 5-10 minutes for this.

Cardiopulmonary testing will also include echocardiographic strain and strain-rate imaging. This is a non-invasive method for the assessment of myocardial function defined as shortening or lengthening of the myocardium. This examination will take around 15 minutes. The patients lie quietly on an examination table without further measures being carried out or required.

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Psychosocial outcomes, including health-related quality of life, posttraumatic growth, and decision regret, will be assessed using standardized questionnaires (EORTC SURV100, PPR) and a questionnaire specifically developed to assess decision regret in childhood cancer survivors. The questionnaires will be provided digitally via a QR code and completed as an online survey using the epilot platform (ISO/IEC 27001 certified, encrypted and GDPR-compliant data storage). Completion of all questionnaires will take approximately 20 minutes.
In addition, venous blood samples will be taken for the analysis of molecular biomarkers. Blood sampling will be performed by trained medical personnel using standard venipuncture techniques and will take approximately 5 minutes. The samples will be pseudonymized immediately after collection and stored in the Central Biobank Erlangen (CeBE) and thus in accordance with applicable data protection regulations.
After informing the proband, healthy individuals in the control group will receive an analysis of their cardiopulmonary health using MRI of the lungs and performing cardiopulmonary testing (spiroergometry, spirometry and DLCO) in the same way as the survivors of ALL or Lymphoma. No venous blood samples will be taken.

Time schedule and duration of the study for the individual subjects/patients
For the individual patient, the duration of study participation is 170 minutes. This includes approximately 30 minutes for education, consent of study participants/parents/guardians, 20 minutes for completing the questionnaire and taking the blood samples, 30 minutes for DLCO, 30 minutes for spirometry and MRI as well as 60 minutes for cardiopulmonary testing.

Total duration of the study
According to the number, the expected total duration of the study until inclusion of the last patient is approximately 18 months.

11. Benefit-risk assessment

All study-related risks

Magnetic resonance imaging
Unlike computed tomography, MRI does not use ionizing radiation, so no permanent side effects are expected. More than 1 million MRI examinations at higher field

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strengths (1.5/3T) are performed annually in Germany. Provided that the general contraindications for MRI examinations are observed, no serious side effects occur. MRI is therefore one of the safest examination procedures.
The risks associated with an MRI examination emanate from the three main components of the MRI system.

Static magnetic field

The static magnetic field exerts forces and torques on ferromagnetic objects that can be so strong that the (mostly ferromagnetic) objects fly uncontrollably toward the magnet and can hit patients and staff (missile effect). The magnetic forces are proportional to the field strength B and the field change with location (dB/dz). These risks are lower with the low-field MRI system. Risks are further minimized by providing safety training to operators and excluding patients with ferromagnetic implants from the study.

The gradient system

Gradient switching can cause the appearance of magnetic phosphenes and nerve and muscle cell stimulation. Fast switched gradients produce high magnetic field changes per time (dB/dt), which induce voltages in the body. If a current flows through the tissue via nerve endings, for example, this can result in so-called peripheral nerve stimulation. However, the manufacturer of the gradient system guarantees compliance with the limits for gradient switching times and amplitudes recommended in the IEC 60601-2-33 guidelines. Thus, nerve stimulation effects need not be considered further in the risk assessment of this study.

Another safety-relevant effect of gradient fields is noise caused by gradient circuits due to current- and field-strength-dependent Lorentz forces in the gradient tube. These often unpleasant loud knocking noises occur especially during fast imaging processes where high currents flow through the gradients. Noise levels can rise up to 115dB for 1.5T tomographs (background noise: approx. 78dB). Due to the lower magnetic forces at 0.55T, we expect lower noise levels. In addition, patients always wear hearing protection during the examination, so that the noise exposure remains well below the legal limit of 99 dB.

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The high-frequency system

During the MR measurement, radiofrequency (RF) fields are sent into the human body, which are partially absorbed by the tissue and can lead to an increase in body temperature. The thermoregulatory response of human tissue to RF pulses has now been studied for 50 years. For example, using conservation of energy, it has been calculated that the body temperature of lightly clothed patients with undisturbed thermoregulation at room temperature increases by up to 0.6 °C when exposed to RF at 4 W/kg (63 MHz, 1.5 Tesla). The assumed specific absorption rate (SAR) of 4 W/kg body tissue corresponds to the so-called "controlled mode first level" (IEC safety guideline), which is also used as an upper limit in routine clinical imaging. The magnitude of the actual temperature rise is generally smaller because skin cooling was not considered in the calculations (worst case scenario).

The body's energy production at rest is about 1.2 W/kg - equivalent to the energy conserved when wearing a thin sweater. Most healthy people are capable of compensating for 15 times this resting energy, and only a minimal increase in core body temperature occurs. Studies at 1.5 T have shown that RF absorption in humans leads only to the expected cardiac adaptation and does not cause adverse health effects. Theoretically, a 63 kg person is even capable of emitting 1296 W to the environment through the skin by cardiac adaptation (i.e., maximum increase in blood flow) - this would correspond to a SAR of 20.6 W/kg.

The same limits are observed with the 0.55 Tesla MRI system. At 0.55 Tesla, the wavelength of the radio waves used is significantly longer, so that the spatial distribution of the energy emission is more homogeneous and thus the risks tend to be lower.

The spiroergometry

If the infection is unknown, cardiopulmonary exertion can lead to inflammation of the heart muscles. A precise anamnesis regarding the constellation of infection as well as a clear explanation of the risks is therefore essential before exposure. A doctor is present at every examination. In addition, a risk of falling during treadmill ergometry cannot be ruled out with absolute certainty. To safely avoid injuries, the participants are secured with a safety rope.

The spirometry

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During this non-invasive test, the subject must breathe against resistance through a mouthpiece. The test does not involve any major safety risks.

Echocardiographic strain and strain-rate imaging

This ultrasound-based non-invasive measurement will take about 15 additional minutes, during which the patient lies on an examination table. Further procedures are not required through this method. There is no additional risk associated with this method.

The DLCO measurement

DLCO measurement is a non-invasive pulmonary function test. Possible risks are minimal and may include transient dizziness, shortness of breath, or coughing due to the breathing maneuvers required during the test. The examination is performed under medical supervision, and participants can stop the procedure at any time if discomfort occurs.

The Questionnaires

All study-related risks associated with the completion of questionnaires are considered minimal and are limited to possible transient emotional discomfort when reflecting on past experiences; participants may skip any question or discontinue the questionnaires at any time without consequences.

The blood sampling

Blood sampling is associated with minimal risks, including transient pain at the puncture site, minor bleeding, bruising, or, rarely, infection. Blood collection is performed by trained medical personnel using standard sterile techniques to minimize these risks.

Benefits associated with the study

The data obtained in the studies may provide essential insights into the long-term effects of chemotherapeutics after treatment in childhood and adolescence. Therefore, the study may influence future clinical management and therapeutic regimes and improve LTFU.

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Discontinuation Criteria

Discontinuation criteria for the individual participant:

Particularly in light of the inclusion of pediatric and adolescent participants, study participation will be discontinued if MRI cannot be performed without sedation.

Study discontinuation for the individual participant will occur if:

- an event occurs that may lead to endangerment of the patient or the staff,
- the patient withdraws consent to participate in the study, or withdraws,
- the patient does not comply with the instructions of the investigators and the operating personnel.

The patient can stop the examination at any time without giving any reason. For this purpose, a so-called bell button is available to the patient during the MRI examination, the activation of which gives a signal with which the patient can draw the attention of the physician/examiner to him/herself, even while the measurement is in progress. Furthermore, the patient is in contact with the examiner via microphone and headphones between the individual measurements and can thus also verbally request the termination of an examination. In addition, the presence of a parent in the scanner room is possible during the entire examination time. Study participants may also discontinue the study at any time before, during, and after all other study-related examinations without providing a reason.

<u>Dropout criteria for the entire study:</u>

There is no provision for discontinuation of the entire study.

<u>Termination criteria for spiroergometry:</u>

Here we follow the termination criteria of the German Spiroergometric Society or DGSP (German Society for Sports Medicine and Prevention):

• Reaching the maximum heart rate (200/min)
• No reserve of breathing available
• RER > 1.15
• Breath Equivalent > 35
• VO2 plateau despite increasing exertion (O2 rise < 150 ml/min. over 30 sec.)
• After exertion, idling for 2 minutes.
• Abnormalities in blood pressure (> 2.5 hrs above 50th percentile, sudden drop or rise)
• In treadmill ergometry with ECG: ST depression, ventricular extrasystoles

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Statement on medical justifiability

The examinations will be performed exclusively on an approved MRI device using approved techniques. As the only significant difference to routinely applied MRI diagnostics, part of the data analysis will be performed with a novel software which is not yet applied in clinical practice and has not yet received the Conformité Européenne (CE) marking. The field strength used is significantly lower than the 1.5T and 3T scanners mostly used in clinical routine to date. The risks are low as described above, especially since no measures such as contrast agent application are foreseen.

Spiroergometry is an accepted and recognized method for examining cardiopulmonary capacity in athletes and patients and is widely used even in individuals with severe cardiac or pulmonary disease. It is an integral part of preoperative diagnostics to assess surgical fitness in older patients. Spiroergometry represents a harmless and non-invasive method for estimating cardiopulmonary capacity and is therefore also suitable for use in children.

Measurement of DLCO is a standard, non-invasive pulmonary function test used routinely in clinical practice. The risks are minimal and may include transient dizziness, shortness of breath, or coughing during the breathing maneuvers required for the examination. DLCO testing is performed under medical supervision and can be stopped at any time at the participant's request.

Peripheral venous blood sampling is a routinely applied medical procedure with low risk. Possible adverse effects include transient pain at the puncture site, minor bleeding, bruising, or, rarely, local infection. Blood sampling will be performed by trained medical personnel using standard sterile techniques, and samples will be pseudonymized immediately after collection.

The overall findings may help to estimate and minimize therapeutic risks for survivors of acute lymphoblastic leukemia (ALL) and lymphoma and to improve long-term follow-up (LTFU) strategies.

The personal benefit of the study for each participant is to receive information about their individual physical (cardiopulmonary and vascular) resilience and potential secondary harm related to previous chemotherapeutic treatments. As the study aims

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to establish innovative diagnostic methods such as PREFUL MRI a control group is required to differentiate pathological from non-pathological findings in these novel imaging modalities.

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12. Biometry

Explorative, hypothesis-generating study

Power calculation

Based on the observations in our pilot study, an N=150 is considered reasonable (50 survivors after treatment of lymphoma, 100 patients after treatment for ALL). Furthermore, 30 measurements (MRI/cardiopulmonary testing) of healthy individuals are planned.

In more detail:

An a priori power analysis was conducted using G*Power [1] to determine the required sample size. Based on preliminary data, the smallest observed effect size (Cohen's d = 0.67 for QDP) was used as the minimal expected effect. Observed effect sizes ranged from d = 0.67 (QDP) to d = 1.2 (V/Q match) and d = 1.3 (VDP). The analysis was based on an ANOVA (planned analysis for primary objectives) with four groups, an alpha level of 0.05, and a desired power of 0.95. The estimated optimal total sample size was n = 160. Due to different incidences regarding ALL, HD and NHL the group sizes were chosen differently, but the total sample size we are aiming is with 150 close to optimal sample size result of the the power calculation.

Statistical Methodology

Continuous variables are reported as mean with standard deviation, categorical variables as numbers with percentages if necessary. The occurrence of morphological MRI changes is reported as a percentage of the study population, functional deficits are quantified as a percentage of the parenchymal tissue. All analyses were performed using GraphPad Prism (version 7.00 or later, GraphPad Software, La Jolla, CA, USA), RStudio (version 1.1.456 or later, RStudio Inc., Boston, MA, USA), or IBM SPSS Statistics (version 24 or later, IBM Corp., Armonk, NY, USA). The results of the rank correlation measurement are reported as Spearman's rho. Independent sample t-test is used to determine significant differences between two groups. In cases of violated normal distribution the Mann-Whitney U-Test is applied. In all statistical analyses, $P < 0.05$ is considered to indicate statistically significant difference in all analyses.

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13. Data management and data protection

Data acquisition, storage

All raw data, such as patient records, represent source documents. Their availability is ensured for routine monitoring. Participation of individual patients or subjects in the study is documented, and the study director maintains an independent list to identify participating patients. This list included name and date of birth as well as study date and pseudonymization abbreviation of the patients and subjects. The study director is responsible for the quality of data collection and storage. Data storage (total data) is performed on computers or specially designated network drives at Erlangen University Hospital. Comparable to routine, imaging data are transferred to the protected PACS (Picture Archiving and Communication System).

Pseudonymization

Prior to any scientific analysis of the materials and data of this study, all information will be pseudonymized according to the guidelines of the German Data Protection Act.

Data transfer

The data will be shared in a pseudonymised form with Survivor Deutschland e.V. (patient advocacy organisation) for the purpose of conducting a quality-of-life survey, and with the University Hospitals of Aachen and Oldenburg for the analysis of molecular biomarkers.

Study results may be published in an anonymised manner, and it will not be possible to infer the identity of individual participants. All data will be stored for 10 years and subsequently destroyed.

Revocation, data deletion

In case of revocation of the declaration of consent, data collected up to this point can be taken into account. The patient has the right to demand their destruction, provided that legal regulations do not prevent the destruction.

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14. Handling of biomaterial

Peripheral venous blood samples will be obtained during the study visit in addition to capillary blood samples collected as part of pulmonary testing. Capillary blood samples will be used for routine laboratory analyses (e.g., blood count, liver enzymes, and renal retention parameters), which represent standard parameters in follow-up care and are routinely determined in conjunction with pulmonary assessments. . In addition, approximately 10 ml of peripheral venous blood (1 EDTA- and 1 serum tube) will be collected for future research on late effects after pediatric cancer therapy including clonal hematopoiesis, epigenetic aging markers, and parameters of telomere biology. These samples will also be stored in the Central Biobank Erlangen (CeBE). All blood samples will be pseudonymized immediately after collection and stored in the Central Biobank Erlangen (CeBE) in accordance with applicable data protection regulations. Samples intended for molecular analyses will be stored under controlled biobank conditions and used for the purposes defined in this study as well as for future ethically approved analyses within the same research context. Storage of samples in the CeBE biobank requires separate information and written informed consent. Participation in the present study is possible without consent for biobanking, and refusal to store samples will not affect participation in the study. No additional biomaterials beyond blood samples will be obtained.

15. Insurance for participants

Patient insurance is provided for arrival and departure as well as examinations on the study day.

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16. Signatures

Erlangen, 07.03.2026



Dr. med. Eva-Maria Wild



Dr. med. Alexander Dierl



PD Dr. med. Axel Karow



PD Dr. med. Ferdinand Knieling



Dr. med. Nadine Bayerl



Dr. med. Maximilian Hinsen

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