Ref. Ares(2024)6945954 - 01/10/2024

MELCAYA

NOVEL HEALTH CARE STRATEGIES FOR MELANOMA IN CHILDREN, ADOLESCENETS AND YOUNG ADULTS

Grant Agreement: 101096667

D5.4 AI-MEL Initiation Package

Funded by
the European Union

Document Information

Deliverable number:	D5.4
Deliverable title:	AI-MEL initiation package
Deliverable version:	v2.0
Work package number:	WP5
Work package title:	Image analysis and machine learning for early diagnosis and risk prediction
Due date of delivery:	31.10.2023
Actual date of delivery:	31.10.2023
Dissemination level:	Public (PU)
Type:	R – Document, report
Author(s):	Titus Brinker (DKFZ) Tabea Bucher (DKFZ) Sara Laiouar-Pedari (DKFZ)
Contributor(s):	-
Reviewer(s):	Adrián López (FCRB)
Project name:	Novel health care strategies for melanoma in children, adolescents and young adults
Project acronym:	MELCAYA
Project starting date:	01.12.2022
Project duration:	48 months
Rights:	MELCAYA consortium

Document history

Version	Date	Beneficiary	Description
0.1	25.04.2023	DKFZ	First draft version
0.2	17.05.2023	FCRB	Revised draft
0.3	30.05.2023	DKFZ	Revised draft
1.0	19.10.2023	FCRB	Final draft
2.0	01.10.2024	FCRB	Revised final draft

Executive Summary

The purpose of this deliverable is to present all the documentation necessary for the initiation of the MELCAYA work package 5 clinical study AI-MEL. It contains the final version of the study protocol and corresponding regulatory/ethics approval by the ethical committee of the study sponsor (German Cancer Research Center). The protocol includes an introduction in which a review on relevant literature, the objectives of the study, the design and study procedures are presented. Details on data collection and management are also discussed, as well as ethical considerations such as how incidental or secondary findings will be communicated or how personal data will be processed. The documents presented in this deliverable will be subsequently used by the other clinical sites for approval in their respective ethical committees.

1. General information

1.1. Identification of the study

Title: Image analysis and machine learning for early diagnosis and risk prediction in children, adolescents and young adults (AI-MEL)

Code or protocol identification number: NCT06621810 (*https://clinicaltrials.gov/*)

Version and date: v1 (01/08/2023)

1.2. Identification of the sponsor/principal investigator

Name: Titus Brinker

Institute and department: German Cancer Research Center (Digital Biomarkers for Oncology group)

Address: Im Neuenheimer Feld 223, 69120 (Heidelberg, Germany)

1.3. Identification of site investigators

Researcher 1

Name: Sara Laiouar-Pedari

Institute and department: German Cancer Research Center (Digital Biomarkers for Oncology group)

Address: Im Neuenheimer Feld 223, 69120 (Heidelberg, Germany)

Researcher 2

Name: Tabea Bucher

Institute and department: German Cancer Research Center (Digital Biomarkers for Oncology group)

Address: Im Neuenheimer Feld 223, 69120 (Heidelberg, Germany)

1.4. Identification of the principal investigators from participant centers

Researcher 1

Name: Susana Puig Sardá

Institute and department: Hospital Clínic de Barcelona (Dermatology department)

Address: Carrer de Villaroel 170, 08036 (Barcelona, Spain)

Researcher 2

Name: Ines Brecht

Institute and department: Eberhard Karls Universitaet Tuebingen (Pediatric Oncology and Hematology department)

Address: Hoppe-Seyler-Straße 1, 72076 (Tübingen, Germany)

Researcher 3

Name: Stephan Forchhammer

Institute and department: Eberhard Karls Universitaet Tuebingen (Pediatric Oncology and Hematology department)

Address: Hoppe-Seyler-Straße 1, 72076 (Tübingen, Germany)

Researcher 4

Name: Daniela Massi

Institute and department: University of Florence (Department of Health Sciences)

Address: Viale Pieraccini 6, 50139 (Florence, Italy)

Researcher 5

Name: Filippo Ugolini

Institute and department: University of Florence (Department of Health Sciences)

Address: Viale Pieraccini 6, 50139 (Florence, Italy)

2. Justification

Melanoma in childhood and adolescence is under-studied, lacking adequate preventive, diagnostic, and therapeutic strategies. The incidence of melanoma is reported to be about 1.5 per million in children under 15 years of age and 15 per million in 15-19 years old, with increasing incidence in adolescents by 4 % annually since 1997 [1,2]. As benign melanocytic lesions develop in nearly every child and are present in over 1 % at birth, the diagnostic accuracy of melanoma is very low in this age group. A large number of benign lesions are unnecessarily excised (593.8 benign nevi per melanoma under 20 years of age [3]). Furthermore, lower sensitivity than in adults [4] results in late diagnosis with poorer outcomes, when children, adolescents and young adults (CAYA) patients, particularly the children, could show a 90 % 10-year survival rate from stage I/II disease. Thus, melanomas in CAYAs represent a medical challenge.

Numerous studies have shown that the analysis of medical images through algorithms based on artificial intelligence can provide important information. In oncology, a classic use case is the analysis of pigmented skin lesions by deep learning algorithms, in particular by Convolutional Neural Networks (CNNs), for early melanoma detection. However, the accuracy of deep learning algorithms is only given on data sets whose distribution corresponds to the images with which the algorithm was trained. The diagnostic accuracy of the deep learning algorithms cannot be guaranteed on so-called out-of-distribution datasets, which, for example, originate from other hospitals and were thus generated with different imaging devices, or whose demographic distribution differs from the distribution of the dataset used to develop the model.

Fitting on data sets with a different distribution, in the case of this project fitting on a different age cohort, can be done by means of transfer learning. In this case, the deep learning algorithms trained on the data of the original cohort are adapted to the new data set, for example, by retraining only the last layers of the neural networks. In the case of very few data in the out-of-distribution domain, Few-Shot Learning approaches can be applied, where technical methods are used for adaptation via only a few new data points. Deep neural networks as classifiers are essentially black-box systems. Especially in the medical domain, additional methods are therefore essential to explain the classifier decisions. For example, the XAI methods CAM, GradCAM, and Integrated Gradients can be used to visualize examination regions in the image as a heat map [5,6]. Alternatively, textual explanations can be output, for example by training an additional concept activation vector that can quantify the sensitivity of the classification model with respect to a concept (a well-known example here would be the concept "stripes" in a classifier that is supposed to recognize zebras). In addition, similar and/or counterfactual examples can be identified with content-based image retrieval (CBIR) systems. In addition, post-hoc XAI methods can be applied to the trained models to detect and avoid model bias during the development phase.

3. Study hypothesis

Currently available deep learning algorithms have been trained with images from open source and proprietary databases that mostly contain melanomas from patients after the age of 60 (e.g., International Skin Imaging Collaboration (ISIC) archive 4/2022: only 111 of 5734 melanomas from patients up to 30 years of age). Furthermore, 60 % of melanoma in children aged < 10 years and 40 % of adolescents did not meet the traditional ABCDE clinical criteria of melanoma [4]. Therefore, it is unlikely that the existing diagnostic tools will show optimal performances if challenged with images of pigmented skin lesions in adolescents and young adults.

Some groups, including the Brinker group leading this study, have already developed accurate deep learning-based image classifiers for melanomas and other skin lesions. Most of these classifiers were trained on clinical or dermatoscopic images, but first classifiers based on histological images were also generated. However, performance of these classifiers specifically on CAYA lesions or optimization of classifier performance on CAYA lesions has not been reported. Moreover, to our knowledge, specific classifiers for spitzoid lesions have not been generated yet. Classifiers for skin age are advertised by several companies that specialize in skin care products, but these are not open source and not intended as skin cancer risk predictors**.** In one of our previous studies, we have already shown that the prediction of patient age using skin images is feasible by separating patients into two age groups.

4. Objectives and purpose of the study

The research goal of this study is to develop supportive diagnostic deep learning algorithms to distinguish melanoma from nevi or other benign pigmented skin lesions, especially in young patients. The University Hospitals of Tübingen, Florence and Barcelona will contribute the data that will be used to train and test the classifiers. Data from open-source databases will also be used. One of these algorithms will be based on macroscopic or dermatoscopic images and will be targeted to skin cancer screening in vulnerable populations. The other tool will be based on histological images and is intended to be used by pathologists on the lesions that are still suspicious of melanoma after dermatologic assessment.

We will also implement explainability methods (XAI) to enable users of such diagnostic assistance tools to comprehend the systems' decisions, avoid biases and increase trust in these applications. In the long term, these deep learning algorithms could be used to improve melanoma early detection in young patients by reducing the number of unnecessary biopsies on the one hand and by minimizing the number of melanomas that are overlooked. In addition, we aim to develop a skin age classifier that could determine melanoma risk in CAYA patients.

5. Study design

5.1. Data acquisition

AI-Mel is a multicenter observational study using retrospectively collected data. Dermatoscopic and histological images with associated metadata will be acquired from participating clinics in the current project. In addition, macroscopic and histopathologic images collected during the Skin Classification Project (SCP2) in the Brinker lab and those collected during previous projects by Susana Puig (Hospital Clinic de Barcelona) will be used. These data include data from the CAYA cohort and data of patients over 30, which will be used to build the adult model. We will also obtain histopathological images of the CAYA cohort from the *Clinical* Registry for Rare Pediatric Tumors (STEP) of the Institute of Pathology of the University of Tübingen. The Institute of Pathology of the University of Florence provides histopathological tissue images of the CAYA and adult cohorts, and specifically adult spitzoid lesions to create a classifier for spitzoid lesions. Moreover, open source dermatoscopic images from the International Skin Imaging Collaboration (ISIC) archive (e.g., HAM10000 or BCN20000) and a few histological images from the Cancer Genome Atlas Program (TCGA) melanoma cohort from patients below the age of 30 will be collected.

To train the macroscopic skin aging classifier, we will use open-source images obtained from healthy patients with or without benign skin lesions including the patient age. These will be tested on skin sections from macroscopic CAYA melanoma images. In addition, we plan to use normal skin images collected from participating clinics. In order to achieve a high data quality, we limit ourselves in this project to images with a highly reliable labelling. All data will be provided in digital format. Data augmentation by rotating and flipping images as well as other modifications such as altering the zoom or brightness will also be tested. Tumor regions will be annotated manually. For hand-crafted features, the pathology program QuPath will be trained to detect specific cells, in particular melanocytic cells and lymphocytes.

5.2. Development of classifiers

In order to obtain an accurate classifier for the rare occurrences of pigmented skin lesions in young patients, the existing model for adults will be adapted to the new cases by fine-tuning, an established method to make use of a neural network trained on abundant data to a related task with limited data availability. This is necessary because the estimated number of cases that can be included in the project is rather small due to the rarity of childhood, adolescent, and young adult melanoma.

We will optimize the fine-tuning by comparatively "freezing" most of the parameters learned in the first adult model and retraining only some of the parameters in the final layers of the neural network or, alternatively, retraining all of the parameters, limiting the variances of the parameters. Also, in the first case, the ideal number of "frozen" layers can be determined using hyperparameter tuning. Similarly, we will use the higher absolute number of available spitzoid lesions in older adults to adapt our existing classifier or to train a spitzoid lesion-specific classifier on the collected adult data. This classifier can then in turn be fine-tuned using spitzoid lesions from children and CAYAs from participating clinics.

We will mostly rely on lesion-containing images to train the skin age classifier. If necessary, we will remove the lesions using image segmentation or only use patches of normal skin derived from those images. However, we will at least test the classifier on images with and without benign lesions collected from the participating clinics. Importantly, we will only use images from healthy (non-melanoma) patients to avoid biases like the sun damage that is more prevalent in melanoma patients. Importantly, we must take different Fitzpatrick skin types into account, since melanomas will be more prevalent in the light-skinned population. It may be necessary to create separate classifiers for different skin types. Once the classifier is established, we will test it against skin images from young melanoma patients to find out whether age is systematically overestimated in these patients, indicating accelerated skin aging as a risk factor and possible biomarker for melanoma development.

CNNs or other deep learning architectures will be trained by supervised, semi-supervised and unsupervised training to generate binary melanoma/nevus classifiers. For that purpose, data will be split into training/validation and test sets, including at least one external test set per classifier, i.e., a test set comprised of out-of-distribution data from another cohort/clinic. The whole slide images will have to be split into tiles (= patches) because of image size. For whole slide image classification, tile-level and slide-level approaches will be tested. The multiclass dermatoscopic skin age classifier will be trained using images from patients of all age groups. Patients with confirmed melanoma will be excluded, since it is expected that many of these patients have experienced a high amount of UV damage, which will have aged their skin more strongly than usual

In addition to an CNN-based image classification algorithm, we will also investigate whether quantifiable hand-crafted features can be identified together with dermatologists and pathologists that might be helpful to distinguish melanomas from nevi in young patients and younger from older skin, e.g., such as wrinkles or pigmented spots for the dermatoscopic images and cell densities or features connected to solar elastosis on histological slides.

5.3. Addition of explainable artificial intelligence (XAI) methods to the classifiers

Deep neural networks as classifiers are essentially black box systems. Particularly in the medical domain, additional methods to explain the classifier decisions are thus indispensable. For instance, regions of interest can be visualized as a heatmap in the picture using CAM, GradCAM, and Integrated Gradients [5-7]. Alternatively, textual explanations can be provided, for example by training an additional concept vector identifier [8] that can quantify the sensitivity of the classification model with respect to a concept (a well-known example here would be the concept "stripes" in a classifier that is supposed to recognize zebras) Moreover, similar and/or counter-factual examples can be identified with content-based image retrieval (CBIR) systems.

In addition, post-hoc XAI methods will be applied to the trained models to detect and avoid model biases during the development phase. If the generated explanations indicate bias, for instance if the models use artifacts such as rulers on dermoscopic images for shortcut learning, the data will be balanced towards equal artefact distribution per class. Alternatively, the artifacts will be removed from the data or the classifier's objective function for training is adjusted accordingly.

The selection of the explainability method will be based on the outcome of current studies within the Brinker group, where the influence of different XAI methods on AI-supported classification accuracy as well as acceptance of such systems by the dermatologists and pathologists is currently investigated. The XAI methods selected for dermatologists and pathologists will be implemented on top of the final classifiers. They will be tested for fidelity and robustness before final approval. A suitable user interface will be chosen and implemented to allow the physicians to evaluate the CNN prediction, the explanation and uncertainty estimate.

5.4. Evaluation of the results in cooperation with dermatologists and pathologists

By help of a questionnaire including the respective images, dermatologists and pathologists, respectively, will be asked to classify the lesions themselves. Subsequently, they will be presented with the results of the classifier(s) including the results of the XAI. The human experts will then be asked whether these results would influence their diagnostic decision and why, or why not. Thereby, the potential impact of an IA-based diagnostic assistance system for the CAYA cohort in routine dermatological and pathological practice will be determined. Using the results of the XAI, human experts will also try to identify recognizable features that the algorithm is likely to use, and evaluate whether these features could also be used by the experts themselves without the aid of the assistance system (train the dermatologist/pathologist approach).

6. Participant selection

6.1. Subject inclusion criteria

The focus of this study is to develop deep learning algorithms for melanoma early diagnosis and risk prediction in children, adolescents and young adults (CAYA). Therefore, data from patients under and including 30 years of age will be primarily included in this study. Data from adults will be used to develop algorithms for spitzoid lesions or the skin-age classifier. In addition, only macroscopic images of lesions suspicious for melanoma that can be assigned to the diagnosis of melanoma or nevus after biopsy verification will be included. For histopathologic images, the pathologic diagnosis of melanoma or nevus is the determining factor for inclusion in the study database.

6.2. Subject exclusion criteria

Patients without a melanoma or nevus diagnosis will not be considered for the diagnostic classifiers of this study. In addition, images with insufficient image quality will be excluded. For post-training of diagnostic classifiers, dermatoscopic and histologic images of patients under and including 30 years of age, will be used. For these classifiers, the base model will be trained on older patients. The algorithms for spitzoid lesions and the multiclass classifier for dermatoscopic skin age are trained with images from patients of all ages. Patients with confirmed melanoma will be excluded for training of the skin age classifier.

7. Treatment and study calendar

Not applicable.

8. Statistics

8.1. Sample size

A precise case number planning of the data is only possible to a limited extent for this study. For the part of the data that we will obtain from databases, the case numbers for each age group are as follows: for the International Skin Imaging Collaboration (ISIC) database: age > 30 = 5329 images, age 18-30 = 445 images, age 15-18 = 3 images, age < 15 = 0 images; for the Skin Classification Project (SCP2) database: age > 30 = 1900 images, age 18-30 = 130 images; and for the Cancer Genome Atlas Program (TCGA) database: age > 30 = 450 images, age 18-30 = 25 images, age 15-18 = 1 image, age < 15 = 0 images.

Since melanomas in CAYAs are basically very rare, we have to expect that partner hospitals (UT, UNIFI and FCRB) can only provide us with a limited amount of data. In this case, case number planning is not useful as we will collect as many images as possible to ensure a sound data basis for training the classifiers.

8.2. Statistical analysis

The evaluation of the adapted diagnostic classifiers is performed on internal and external test datasets. Internal test datasets follow the same distribution as the training dataset. In contrast, an external dataset should be unknown to the model, for example, by being collected from a clinic whose data were not used to develop the model. This allows a better assessment of the generalization ability of the models. Sensitivity, specificity, accuracy weighted by class ("balanced accuracy"), and area under the receiver operator curve (AUROC) are measured. Accuracy metrics of both the base models for the adult cohort and the adjusted classifiers are calculated. For the adjusted classifiers, the evaluation is performed exclusively on data from the CAYA cohort, in case of sufficient numbers of cases also separately for sub-age groups children (up to and including 15 years of age), adolescents (16-20) and young adults (from 21 to 30 years of age). As expected, there will be more cases for the cohort of young adults than for children and adolescents due to the incidence.

For the skin risk classifier, we will systematically assess whether there is an overestimation of skin age in young melanoma patients. Therefore, in the first step, the accuracy of the classifier on healthy skin will again be assessed using internal and external test data sets. A Wilcoxon Mann-Whitney U-test will be used to test the hypothesis of systematic overestimation of skin age in the presence of a malignancy.

To determine the usefulness of the final classifiers as assistive systems, they will be evaluated with pathologists as well as dermatologists. The participating clinicians will diagnose the same cases with sufficient time interval once without and once with AI assistance. Pairwise significance tests using the two-sided paired t-test will be performed to determine the effect of the system on diagnostic sensitivity, specificity, and accuracy. The metrics as well as the statistical tests will be calculated using the Python programming language.

9. Ethical and legal aspects

9.1. Legal and ethical basis

The partners have a lawful basis for the re-use of health data for scientific purposes under specified conditions and with adequate safeguards i.e., legitimate interests (article 6.1 (f) GDPR), combined with 'scientific research' article 9.2 (j) GDPR. In the cases that the subjects could be re-identified, the guidelines on registry-based studies (EMA/426390) will be followed to ensure that access and use of the proposed data poses minimum to no risk to the study subjects or their fundamental rights and freedoms. In the cases where pre-existing ethics approvals are currently not in place, an authorization (or an amendment in the case of existing approval) to access and use this data will be requested from each partner's respective local ethics committee or national competent body prior to study start-up.

All study materials, including clinical and laboratory protocols, will be submitted to pertinent Institutional Review Boards (IRBs) for review and approval. Approval of the study protocol will be obtained prior to participant/case selection. Any changes to the study protocol, materials, etc. will be subjected to ethics review and approval before the changes are implemented into the study. All participating institutions will comply with international ethical standards regarding principles for medical research involving human subjects and data (Declaration of Helsinki, 2013). In the particular case of Hospital Clínic de Barcelona, compliance at the Spanish level with the Ley 14/2007 de 3 de julio, de Investigación biomédica will be ensured. On top of that, the guidelines set out in the International Conference on Harmonisation of Good Clinical Practice (ICH GCP) and the EMA/426390/2021 (Guideline on registry-based studies) will be followed.

9.2. Communication of incidental/secondary findings

In the event that incidental/secondary finding occur during the study, the researcher is expected to inform an officer from his or her local Ethics Committee and coordinate a consultation with the medical professionals involved in the study from their participating institution to review and evaluate if the finding is relevant and how it should be communicated to the participant. In case of doubt, consultation can be made with other medical experts within the consortium. Contact with the patient would be done through the practitioner that generally attends the patient, using the available data recorded in the clinical history (if any). For minors, the general practitioner would contact with the parents or legal representatives (signatory of the informed consent). Ideally, a medical appointment would be scheduled when sharing this information to reassure the patient and avoid unnecessary stress.

The general conditions that must be always met to communicate an incidental/secondary finding are the following:

- It may affect a participant's health and welfare.
- It is scientifically and clinically valid.
- Ethical approvals have been obtained and the participant or their legal representative has opted in to receiving such results through their clinician(s) in the informed consent form.

Incidental and secondary findings will not be communicated:

- When the clinical information is anonymized, as it will be justifiably impractical or impossible to contact the research participant.
- When the participant has indicated that he/she does not want to be informed about such findings.

9.3. Supervision of legal-ethical issues

The institutions involved in this study will establish an Ethical Monitoring Board (EMB) that will act as liaison between them and local competent IRBs. This will be done to ensure that data collection methods and clinical aspects of the study protocol are efficacious and in agreement with competent IRBs policies and procedures, as well as to oversee the process of obtaining scientific advice and regulatory guidance from the appropriate regulatory agencies. In addition, access to regulatory expertise will be ensured through each institution ethics committee. Communication between the partners and competent IRBs will be continuous in order to verify that the study is in compliance with European and national regulatory guidelines.

10. Data management

10.1. Data storage

All data and datasets (collection of dermatoscopic and histological images) will be stored in a digital form in a database provided by the German Cancer Research Center. Data transfer will take place on the legal basis of bilateral Data Transfer Agreement contracts via the HIFIS (Helmholtz Federated IT Services) system Filesender. The German Cancer Research Center IT department provides this system to ensure secure, encrypted data upload. Via an authentication and role system, designated persons of the partner institutes are granted access to the data upload, which is only possible in encrypted, password-protected form due to system restrictions. At the German Cancer Research Center, the data will then be downloaded by the authenticated Data Scientist and transferred to an HD-SATA hard drive, which will be connected to the Data Scientist's local workstation for development.

10.2. Data pseudoanonymization

Before sharing the collected images to the HIFIS system, pseudoanonymization procedures will be implemented at each local data source center. Pseudonyms are character strings of defined length that are used instead of personally identifying data for linking different types of data of a study participant. Pseudonymization of data is an essential step in maintaining a high level of data protection, as it prevents re-identification of patients. In some cases, the data may already be stored under a pseudonym without the patients’ identifying data (IDAT) being available. If available, patients’ identifying data are documented at the local source centers. Each study participant is assigned a randomly selected pseudonym. Local patient lists are additionally maintained, which store the assignment of IDAT or local identifiers to pseudonyms. Both the local patient lists and the patient consents forms are stored locally and separately from the medical data at each source center. Without knowledge of the respective assignment of pseudonym and patient, no re-identification of individual persons is possible. Data processing will be carried out exclusively by persons who had no direct patient contact during the data collection. Furthermore, the IDAT of the study participants will not be used for any purpose, but only the pseudonymized data of the study database.

10.3. FAIR data

All publishable data resulting from this study will be identified by a digital object identifier (DOI) to ensure that it is findable and made available through scientific publications and publicly accessible data repositories such as Zenodo. Priority will be given to open access high impact journals. The Directory of Open Access Journals or a similar index will be used to determine the most appropriate one for submission of the study data and results to ensure immediate and unrestricted access to new knowledge. Open data formats (such as XML, PNG, HTML) will be used to increase data interoperability. The data will be released under an open access license, for instance, Creative Commons Attribution International Public Licence (CC BY) or similar. This will facilitate the reuse of data and ultimately maximize the overall impact.

11. Treatment of data, record keeping and data confidentiality

The processing, communication and transfer of personal data of all participants shall comply with Regulation EU 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of data and the Organic Law 3/2018 of December 5 on the Protection of Personal Data and guarantee of digital rights. The legal basis that justifies the processing of your data is the consent you give in this act, in accordance with the provisions of article 9 of EU Regulation 2016/679. The data collected for these studies will be only identified by a code, so no information will be included that would allow to identify the participants. Only the study physician and his collaborators with the right to access the source data (medical history) could relate the collected data with the patient's medical history. The identity of the participants will not be available to any other person except for a medical emergency or legal requirement. Health authorities, Research Ethics Committee and personnel authorized by the study sponsor may have access to the identified personal information when necessary to verify data and procedures of the study, but always maintaining confidentiality in accordance with current legislation.

Only the encrypted data will be transferred to third parties and other countries, which in no case will contain information that can directly identify the participant (such as name and surname, initials, address, social security number, etc.). In the event that this transfer was to occur, it would be for the same purpose of the study described and guaranteeing confidentiality. If encrypted data is transferred outside the EU, whether to entities related to the hospital where the patient participates, to service providers or collaborating researchers, the data of the participants will be protected by safeguards such as contracts or other mechanisms established by the data protection authorities.

Data processing will be done in accordance with EU Regulation 2016/679. As a result, a record of all the processing activities will be kept and a risk assessment of those activities will be performed to know what measures will be needed and how to implement them. In addition to the rights already provided for in the previous legislation (access, modification, opposition and cancellation of data, deletion in the new Regulation), participants can now also limit the processing of data collected for the project that is incorrect, request a copy or transfer them to a third party (portability). To exercise these rights, they should contact the principal investigator of the study or the Data Protection Officer of the Hospital Clínic de Barcelona through protecciodades@clinic.cat. Likewise, they have the right to contact the Data Protection Agency if they are not satisfied. Data cannot be deleted, even if a patient leaves the study, to ensure the validity of the research and comply with legal duties and drug authorization requirements. The Investigator and the Sponsor are obliged to keep the data collected for the study for at least 25 years after its completion. Subsequently, personal information will only be retained by the health care facility and by the sponsor for other scientific research purposes if the patient has consented to do so, and if permitted by applicable law and ethical requirements.

12. Management of biological samples

An exchange of human material in the form of tissue samples is not necessary in this study.

13. Financing

AI-MEL study was conceived independently of any commercial organization and will be coordinated, managed and analyzed in an independent form. The costs related to the analyses envisaged on the samples, for research purposes only, will be supported by research fundings of MELCAYA project (HORIZON-MISS-2021-CANCER-02, proposal number: 101096667).

14. Publication policy

The transmission or dissemination of the data, through scientific publications and/or presentation in congresses, conventions, and seminars, may be carried out only after each Principal Investigator’s written authorization. Accordingly, the Principal Investigator of the study undertakes to produce a report on the study, publish all data collected as described in the protocol and ensure that the data are reported responsibly and coherently. In particular, the publication of the data deriving from this study will be independent of the results obtained. The transmission or dissemination of data, through scientific publications and/or presentation in congresses, conventions and seminars, participation in multicentric studies, will take place only following a purely statistical elaboration of the same, or otherwise in anonymous form.

15. References

[1] Pappo, A. S. Melanoma in children and adolescents, Eur. J. Cancer 39, 2651–2661 (2003)

[2] Ferrari, A. et al. Defining and listing very rare cancers of pediatric age: consensus of the Joint Action on Rare Cancers in cooperation with the European Cooperative Study Group for Pediatric Rare Tumors, Eur. J. Cancer 110, 120–126 (2019)

[3] Moscarella, E. et al. Excised melanocytic lesions in children and adolescents - a 10-year survey. Br. J. Dermatol. 167, 368–373 (2012)

[4] Cordoro, K. M., Gupta, D., Frieden, I. J., McCalmont, T. & Kashani-Sabet, M. Pediatric melanoma: results of a large cohort study and proposal for modified ABCD detection criteria for children. J. Am. Acad. Dermatol. 68, 913–925 (2013)

[5] Zhou, B., Khosla, A., Lapedriza, A., Oliva, A. & Torralba, A. Learning deep features for discriminative localization. in 2016 IEEE Conference on Computer Vision and Pattern Recognition (CVPR) 2921–2929 (IEEE, 2016)

[6] Selvaraju, R. R. et al. Grad-CAM: Visual explanations from deep networks via Gradient-based localization. arXiv [cs.CV] 618–626 (2016).

[7] Sundararajan, M., Taly, A. & Yan, Q. Axiomatic Attribution for Deep Networks. in Proceedings of the 34th International Conference on Machine Learning (eds. Precup, D. & Teh, Y. W.) vol. 70 3319–3328 (PMLR, 06--11 Aug 2017)

[8] Kim, B. et al. Interpretability Beyond Feature Attribution: Quantitative Testing with Concept Activation Vectors (TCAV). in Proceedings of the 35th International Conference on Machine Learning (eds. Dy, J. & Krause, A.) vol. 80 2668–2677 (PMLR, 10--15 Jul 2018)

MEDIZINISCHE
FAKULTÄT
HEIDELBERG

Ethikkommission der Med. Fak. HD | Alte Glockengießerei 11/1 | 69115 Heidelberg

Herrn Dr. med. Titus J. Brinker
Deutsches Krebsforschungszentrum
Nachwuchsgruppe Digitale Biomarker
für die Onkologie
Im Neuenheimer Feld 223
69120 Heidelberg

Universität Heidelberg
Ethikkommission der
Med. Fakultät

Alte Glockengießerei 11/1
69115 Heidelberg

Tel. +49 6221 56264-60 (Zentrale)
Fax +49 6221 56264-80
ethikkommission-I@med.uni-heidelberg.de

www.medizinische-fakultaet-hd.uni-heidelberg.de/einrichtungen/zentrale-einrichtungen/ethikkommission

Vorsitz:
Prof. Dr. med. Dr. h.c. Thomas Strowitzki

Stellv. Vorsitz:
Prof. Dr. med. Klaus Herfarth

Geschäftsleitung:
Dr. med. Verena Pfeilschifter

eFeedback
Scan or click

399893 QM 15

BIC SOLADEST600
IBAN DE64 6005 0101 7421 5004 29

MF
HD

21.06.2023
ts-sn/bw

BERUFSRECHTLICHE BERATUNG

Unser Zeichen: **S-329/2023 (Bitte stets angeben)**
Titel: **AI-MEL: Bildgebende Verfahren und maschinelles Lernen für die Melanom-Frühdiagnose und Risikovorhersage bei Kindern, Jugendlichen und jungen Erwachsenen**

Sehr geehrter Herr Dr. Brinker,

die Ethikkommission hat Ihr Forschungsvorhaben in der Sitzung am 19.06.2023 beraten.

Die Ethikkommission hat keine Bedenken gegen die Durchführung der Studie.

Sie gibt jedoch folgende Empfehlungen bzw. Hinweise:

Allgemein:

1. Der Kommission ist die Rechtslage in Spanien und Italien nicht bekannt. Es obliegt der Verantwortung des Studienleiters, die einschlägigen Rechtsvorschriften zu beachten. Dies betrifft insbesondere die wirksame (insbesondere auch freiwillig erteilte) Einwilligung der Patienten zur Verwendung der angefertigten Bilddaten im Rahmen des hier vorliegenden Forschungsvorhabens.
2. Bei den teilnehmenden Partnern (Universität Florenz (UNIFI-Università degli Studi di Firenze, Public University, Italy), Universität Tübingen (UT), dem Institut für biomedizinische Forschung in Barcelona (FCRB-Fundació Clínic per a la Recerca Biomèdica))) und deren europäischen Partnerkliniken werden im Rahmen der Routine die Proben entnommen und Bilder der Läsionen angefertigt. Die Aufnahmen werden anschließend nach Heidelberg transferiert. Es liegt im Verantwortungsbereich der teilnehmenden Partner, dass für die Datenweitergabe eine entsprechende Rechtsgrundlage vorliegt. Es wird dringend die Einbindung der jeweiligen Datenschutzbeauftragten empfohlen.
3. Es wird darauf hingewiesen, dass sich im Rahmen der Studiendurchführung an anderen Kliniken und/oder Arztpraxen beteiligte Ärzte jeweils zusätzlich auch von der für sie zuständigen Ethikkommission berufsrechtlich beraten lassen müssen (vgl. § 15 Abs. 1 BOÄ BW), sofern das nicht bereits erfolgt ist.

Wir wünschen Ihnen bei der Durchführung der Studie viel Erfolg.

Bitte leiten Sie das Ergebnis der berufsrechtlichen Beratung und die studienrelevante Korrespondenz allen teilnehmenden Ärzten in unserem Zuständigkeitsbereich weiter.

Mit freundlichen Grüßen

Digital unterschrieben von Dr. Thomas Strowitzki
DN: c=DE, cn=Dr. Thomas Strowitzki, title=Dr., givenName=Thomas Franz, sn=Strowitzki, serialNumber=DTR210096304P0001
Datum: 2023.06.22 11:08:43 +02'00'

Prof. Dr. med. Dr. h.c. Thomas Strowitzki
Vorsitzender

Anlagen
Anhang

Allgemeine Hinweise:

- Änderungen in Organisation und Ablauf der Studie sind der Kommission, zusammen mit einer Bewertung der Nutzen-Risiko-Relation, umgehend mitzuteilen. Sowohl die **Antragsnummer** als auch die **geänderten Passagen** sollten in den betreffenden Unterlagen **deutlich gekennzeichnet** sein, da anderenfalls keine zügige Bearbeitung möglich ist.
- Es ist **kontinuierlich und eigenverantwortlich** eine **Nutzen-/Risiken-Abwägung** in Bezug auf die derzeitige **Covid-19-Pandemie** durchzuführen. Dabei ist der Nutzen der Studiendurchführung während der aktuellen Pandemie dem Risiko von Neuinfektionen (der Studienteilnehmer und des Studienpersonals sowie indirekt auch weiterer Personen) gegenüberzustellen. Das Infektionsrisiko z.B. durch studienbedingte Kontakte der Beteiligten oder durch studienbedingten Reiseaufwand ist dabei stets gemäß der aktuellen Pandemiesituation zu bewerten. Sollte die Studie regelmäßige Maßnahmen erfordern (regelmäßige Visiten, regelmäßige Behandlung/Verabreichung von Arzneimitteln o.Ä.), ist auch zu bedenken, ob und ggfs. inwieweit diese Maßnahmen während der Pandemie zuverlässig durchgeführt werden können. Dabei sind auch mögliche Vorkehrungen zur Risikominimierung zu treffen. Sofern aufgrund der aktualisierten Nutzen-/Risiken-Bewertung pandemiebedingt Maßnahmen eingeleitet werden müssen und es dadurch zu Änderungen bei der Studiendurchführung kommt, sind diese Änderungen (insbesondere an Prüfplan und Informationsschrift bzw. Einwilligungserklärung) der Ethikkommission gemäß § 10 Abs. 1 GCP-V als nachträgliche Änderung vorzulegen. Es wird ausdrücklich darauf hingewiesen, dass alle Studienteilnehmer über alle für sie relevanten Änderungen im Studienablauf schriftlich und ohne Verzug informiert werden müssen. § 11 der GCP-V regelt die ggfs. unverzüglich zu ergreifenden Maßnahmen zum Schutz vor unmittelbarer Gefahr. Es empfiehlt sich, alle Abweichungen vom Prüfplan, die auf die Pandemiesituation zurückzuführen sind, zu dokumentieren. Zusätzlich sind immer die Informationen des Arbeitskreises Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland e.V. unter www.ak-med-ethik-komm.de zu beachten.
- Jedes Forschungsvorhaben, an dem Versuchspersonen beteiligt sind, ist vor der Rekrutierung der ersten Versuchsperson in einer öffentlich zugänglichen Datenbank zu registrieren.
- Innerhalb von einem Jahr nach Studienende sollte die Studienleitung der Kommission einen Abschlussbericht vorlegen, der eine Zusammenfassung der Ergebnisse und Schlussfolgerungen der Studie enthält, unabhängig davon, ob diese vollständig abgeschlossen oder vorzeitig beendet wurde. Dafür ist die auf der Homepage der Kommission abrufbare Mustervorlage „Abschlussbericht“ zu verwenden (Pfad: → Sonstige Studien → Vorlagen).
- Datenschutzrechtliche Aspekte von Forschungsvorhaben werden durch die Ethikkommission grundsätzlich nur kursorisch geprüft. Dieses Votum / diese Bewertung ersetzt mithin nicht die Konsultation des zuständigen Datenschutzbeauftragten. Die Einhaltung der einschlägigen Datenschutzgesetze sowie die Umsetzung des Datenschutzkonzeptes liegen in der Verantwortung des Studienleiters/Prüfers bzw. Sponsors.
- Die Ethikkommission geht davon aus, dass im Falle von Videovisiten die Vorgaben gemäß Anlage 31b Bundesmantelvertrag eingehalten werden und die Visiten mittels eines zertifizierten Anbieters durchgeführt werden.
- Mit dem Urteil des Europäischen Gerichtshofs vom 16. Juli 2020 [Aktenzeichen C-311/18] stellen die Regelungen des EU-US-Privacy Shield insbesondere vor dem Hintergrund des Clarifying Lawful Overseas Use of Data Act (CLOUD Act) bzw. des Foreign Surveillance Act (FISA) keinen geeigneten Rechtsrahmen mehr dar. Es sollte daher seitens der Verantwortlichen im Einzelfall geprüft werden, inwieweit personenbezogene/personenbeziehbare Daten (also auch i.S.d. Art. 4 Abs. 5 DSGVO pseudonymisierte Datensätze) rechtssicher entweder auf Basis geeigneter Garantien (etwa verbindlicher Unternehmensregeln, Standardvertragsklauseln oder auf Basis einer ausdrücklichen Einwilligung nach erfolgter Risiko-Aufklärung nach Art. 49 Abs. 1 lit. a) DSGVO) übermittelt werden können. Es empfiehlt sich v.a. hinsichtlich der Standardvertragsklauseln die Auswirkungen des Urteils und die voraussichtlich folgenden regulatorischen Leitlinien seitens der zuständigen Behörden aufmerksam zu verfolgen.
- Die Ethikkommission der Medizinischen Fakultät Heidelberg arbeitet gemäß den nationalen gesetzlichen Bestimmungen und den ICH-GCP-Richtlinien. Ihren Beratungen liegt die Deklaration des Weltärztebundes von Helsinki in der jeweils aktuellen Fassung zugrunde.
- Unabhängig vom Beratungsergebnis macht die Ethikkommission Sie darauf aufmerksam, dass die ethische und rechtliche Verantwortung für die Durchführung einer Studie beim Leiter der Studie und bei allen teilnehmenden Ärzten liegt.

Anhang

Liste der eingereichten Unterlagen

Primär eingereichte Unterlagen:

Anschreiben vom 30.05.2023
Zusammenfassung
Checkliste Sonstige Studien
Formular für Erstantrag
Kostenübernahmeerklärung vom 30.05.2023
Studienprotokoll Version 2.0 vom 30.05.2023
CV Dr. med. Titus J. Brinker vom 26.04.2023 (unsigniert)
Barcelona_Informed Consent (adolescents) zur Studie *„Caracterización fenotípica-molecular de síndrome de nevus congénito gigante y su impacto psicoemocional. Identificación de patrones clínicos y genéticos relacionados con melanoma”* Version 3 vom 29.06.2018 (mit gelbmarkierten Textpassagen)
Barcelona_Informed Consent (adults) zur Studie *„Caracterización fenotípica-molecular de síndrome de nevus congénito gigante y su impacto psicoemocional. Identificación de patrones clínicos y genéticos relacionados con melanoma”* Version 3 vom 29.06.2018 (mit gelbmarkierten Textpassagen)
Barcelona_Informed Consent (children) zur Studie *„Caracterización fenotípica-molecular de síndrome de nevus congénito gigante y su impacto psicoemocional. Identificación de patrones clínicos y genéticos relacionados con melanoma”* Version 3 vom 29.06.2018 (mit gelbmarkierten Textpassagen)
Barcelona_Informed Consent Biobank Version 1.3 vom 15.06.2022 (mit gelbmarkierten Textpassagen)
Barcelona_Informed Consent Xarxa Melanoma Version 1.0 vom 12.03.2015 (mit gelbmarkierten Textpassagen)
Barcelona_Translation Informed Consents
Florenz_InfoEinwilligung_Erziehungsberechtigte zur Studie *„Novel health care strategies for melanoma in children, adolescents, and young adults. Histological, computational, and molecular pathology for improved diagnosis (Mol-Mel)”* Mod. C2 Version vom 20.12.2019 (mit gelbmarkierten Textpassagen)
Florenz_InfoPatienteneinwilligung_Alter 7-13Jahre zur Studie „*Mol-Mel*“ Mod. C3 Version vom 20.12.2019 (mit gelbmarkierten Textpassagen)
Florenz_InfoPatienteneinwilligung_Alter 14_18 Jahre zur Studie „*Mol-Mel*“ Mod. C4 Version vom 20.12.2019 (mit gelbmarkierten Textpassagen)
Florenz_InfoPatienteneinwilligung_Erwachsene zur Studie „*Mol-Mel*“ Mod. C1 Version vom 20.12.2019
Florenz_Uebersetzung INFO_ Einwilligungserklaerung zur Studie „*Mol-Mel*“
SCP Mannheim Patienteninformation und -Einwilligung Version 1.5 vom 09.02.2021
UK Tübingen Info_Einverständnis TAAs - Kontrolle erwachsene Patienten zur Studie „*Umfassende genetische Charakterisierung von pädiatrischen Patienten mit Melanom*.“ (ohne Versionsnummer, undatiert, mit gelbmarkierten Textpassagen)
UK Tübingen Info_Einverständnis TAAs - Kontrolle minderjährige Patienten zur Studie „*Umfassende genetische Charakterisierung von pädiatrischen Patienten mit Melanom*.“ (ohne Versionsnummer, undatiert, mit gelbmarkierten Textpassagen)
UK Tübingen Patienteninformation und Einwilligung zur Studie *„STEP“* Version 01 vom 2023
Stellungnahme der Ethik-Kommission an der Medizinischen Fakultät der Eberhard-Karls-Universität und am Universitätsklinikum Tübingen zur Studie *„STEP“* vom 24.01.2013
Antrag zur Studie *„STEP“* an die Ethik-Kommission der FAU Tübingen vom 17.10.2012
Stellungnahme der Ethik-Kommission an der Medizinischen Fakultät der Eberhard-Karls-Universität und am Universitätsklinikum Tübingen zur Studie *„STEP“* vom 20.12.2023
Stellungnahme der Ethik-Kommission an der Medizinischen Fakultät der Eberhard-

Karls-Universität und am Universitätsklinikum Tübingen zur Studie *„STEP“* vom 11.01.2023
„Ethical and legal aspects clinical protocols“ (Anhang zum Projekt: *AI-MEL*) Version 01 vom 11.04.2023
Grant agreement Project 101096667 — MELCAYA HORIZON-MISS-2021-CANCER-02

Formelle Nachreichung:	Nachreichung vom 05.06.2023: Vollmacht Studienkorrespondenz CV Dr. med. Titus J. Brinker vom 05.06.2023