MELCAYA

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

Grant Agreement: 101096667

D6.4 Precis-mel Initiation Package

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0.9	05.02.2024	UCSC	Revised draft
1.0	20.03.2024	FCRB	Final draft
2.0	30.09.2024	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 6 clinical study Precis-mel, which is divided in two separate sub-studies, Precis-mel 1 and Precis-mel 2. The document contains the final version of the study protocols and corresponding regulatory/ethics approvals by the ethical committee of the study sponsor (Fundació Clínic per a la Recerca Biomèdica/Hospital Clinic de Barcelona). The protocols include 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.

1. General information

1.1. Identification of the study

Title: Precision medicine for L/GCMN and melanoma 1 (Precis-mel 1)

Code or protocol identification number: NCT06608420 (*https://clinicaltrials.gov/*)

Version and date: v3 (19/12/2023)

1.2. Identification of the sponsor

Name: Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer

Address: Carrer del Roselló 149-153, 08036 (Barcelona, Spain)

1.3. Identification of site investigators

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

2. Justification

In a hackathon organized by Hospital Clínic de Barcelona in collaboration with the consulting company Accenture in 2019, several participants developed algorithms to predict prognosis in melanoma patients with a performance slightly better than the American Joint Committee on Cancers (AJCC) staging system in estimating individual risk. The company Athena Tech has been working in the last years with Hospital Clínic de Barcelona in refining precision medicine algorithms to predict the prognosis of melanoma patients using multilayer information including clinical, dermatoscopic and histopathological images as well as clinical information (age, sex, location, phenotypic characteristics and pathological information). The primary motivation of this study is to improve the prognosis and risk stratification processes for melanoma in children and young adolescents (CAYA) through the use of precision medicine and artificial intelligence algorithms. The study aspires to enhance clinical outcomes by improving the accuracy of diagnostics and prognostics, which, in turn, will contribute to more efficient clinical workflows, freeing up valuable time for healthcare professionals to focus on other critical aspects of patient care.

3. Study hypothesis

Our working hypothesis is that the risk stratification prognosis for CAYA patients may see incremental improvements through the utilization of machine learning models. These models, initially trained on adult patient data, would be fine-tuned using the limited data available from the CAYA cohort. Despite the limitations and challenges posed by the relative scarcity of pediatric data for melanoma, we hope to extract valuable insights by employing transfer learning techniques. Additionally, we plan to incorporate expert medical opinions to calibrate our prediction models, aiming to increase their reliability and relevance to the CAYA context. It is important to note that, while we aim to improve the prognosis process, due to the constraints

we face, significant enhancements may not be immediately achievable. Our goal is to make the best use of available resources to positively impact pediatric oncology prognosis and care.

4. Objectives and purpose of the study

The primary objective of this study is to create a highly multidimensional and multicentric database for melanoma that encompasses cohorts of children, adolescent and young adults. This database will be used to perform survival analysis and evaluate sentinel lymph node (SLNB) positivity in CAYA. The secondary objectives to be met are the following:

- **Adaptation and optimization of algorithms**: to adapt and optimize existing precision medicine algorithms, which are currently being utilized in adult patient care, for their application within pediatric and young adult populations.
- **Implementation of transfer learning**: given the limitations associated with pediatric and young adult data, we intend to utilize transfer learning techniques. The study will employ a sequential waterfall methodology, whereby machine learning models trained on adult patient data will be fine-tuned using the more limited data from younger cohorts.
- **Integration of expert medical opinion**: to integrate physicians' scientific domain knowledge into the decision support system. This will be facilitated through the comprehensive examination of existing literature, as well as the evaluation of variable risk contributions within each patient group.
- **AI-based prognostic models**: to develop artificial intelligence-based models for the quantitative prognosis of melanoma across the three age groups: adults, young adults, and children.

5. Study design

Precis-Mel 1 is a unicentric observational study using retrospectively collected data. The proposed procedure is to start using data including demographic and family data, genetic data, medical procedures and cancer treatment, cutaneous biopsy, etc. to build a multidimensional dataset and apply AI algorithms that can produce survival curves and sentinel lymph node (SLNB) positivity in CAYA. The approach to be used is presented in the following sub-sections:

5.1. Data engineering

The multidimensional dataset is meticulously integrated via DBT and SQL queries on a

PostgreSQL database. This results in a model-ready comprehensive table, maintaining the crucial temporal dimension of patient histories. Identifiers are assigned to maintain the integrity of the data trail and the connection between various patient events such as metastasis and death. Python-based transformations ensure that sequential patient events are contextually enriched by preceding occurrences. Operations include arithmetic aggregations, extremum calculations, and string manipulations. Events are discretized over a standardized temporal frame (1-3 months) for uniform staging reference, also serving to consolidate any misaligned data instances.

5.2. Model development

Our approach employs survival analysis to address the unique challenges of our dataset, particularly censoring, where an event of interest, like death, does not occur within the observation window. Based on our previous experience in modelling this problem, we prefer to use Gradient Boosting Survival Analysis (GBSA), a non-deep learning method, as it effectively addresses data scarcity issues. GBSA adapts the gradient boosting machine algorithm for survival analysis, particularly accommodating censored data. In survival analysis, patients are represented by a triplet (x_i, δ_i, T_i), where x_i is the feature vector, T_i is the time to event, and δ_i indicates whether the observation is censored. Our goal is to estimate the survival function $S(t)$, representing the probability of a patient surviving beyond time t, and the hazard function $\lambda(t)$, indicating the instantaneous probability of an event occurring at time t. To adapt it for the survival modelling domain, our model utilizes the gradient boosting approach with a modified loss function, the negative log partial likelihood. This allows us to effectively estimate the survival function.

5.3. Performance metrics

We measure model performance using the concordance index (*c-index*), a metric particularly suited for survival analysis. The c-index assesses the predictive accuracy of our model by comparing predicted and observed event times. A high *c-index* indicates that our model effectively predicts the order of patient hazard given its input features.

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. However, due to the scarcity of data in that age range, the model will be first trained with adult patients (over 18 years old) with histopathological confirmed melanoma.

6.2. Subject exclusion criteria

Not having a melanoma diagnosis or not having signed the informed consent. In order to mitigate data sparsity issues and ensure robustness of the models, records dating prior to the year 2012 will also be excluded. The field of oncology has undergone significant advancements in recent years, and as such, data prior to this cut-off date might not accurately reflect current practices and treatment outcomes. By setting these boundaries, we aim to maintain the integrity of our data and the subsequent models, ultimately leading to more reliable and effective outcomes.

7. Treatment and study calendar

Not applicable.

8. Statistics

8.1. Sample size

The training dataset will consist of N = 6000 adult melanoma patients while the adaptation dataset for CAYA will be of N = 120.

8.2. Statistical analysis

Comprehensive descriptive statistics will be generated to summarize the demographic and baseline characteristics of the patients. Continuous variables will be presented as mean ± standard deviation (SD) and categorical variables will be presented as frequencies and percentages. Given the study's focus on the causality of variables in the prognosis of melanoma patients, statistical tests (Mann-Whitney, Chi-squared, etc.) will be applied to assess the relationships or differences among variables. To control for potential confounding factors, multivariate analyses will be conducted. This will allow us to assess the impact of multiple variables on the outcome simultaneously. Missing or incomplete data will be handled using multiple imputation techniques. A complete-case analysis will also be conducted for comparison.

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 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) will be followed.

9.2. Communication of incidental/secondary findings

In the event that incidental/secondary findings 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 will be stored in a secured electronic database known as *Xarxa Melanoma* approved by the Ethical Committee of the Hospital Clínic de Barcelona on the 14/04/2015 (Reg. HCB/2015/0298). This database is routinely used by dermatology medical professionals of our hospital and complies with international standards on data protection and offers a consistent, auditable and integrated electronic database environment. Each institution involved in the study will have a local data protection officer (DPO) to advise on complex, sensitive, or large-scale data processing activities.

Upon completion of the study, data will be preserved for a minimum of 25 years to guarantee continued accessibility and data discovery. Personal data information will only be kept for updating follow-up by the local center investigator. The sponsors will only use the data collected

for other scientific purposes if participants have given prior consent and if the legal basis for processing is still in place (see section 9.1). After that, paper and electronic records will be destroyed or erased per institutional/University policy.

10.2. Data codification

Before uploading the collected patient data to the database, a codification procedure will be implemented at each local data source center. The procedure will be carried out in the following way: a researcher from our center will assign a code to the clinical information of each patient, which will be kept in a separated database to which only the Principal Investigator or authorized personnel in his research team will have access to. In that way, without knowledge of the respective assignment of code 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 data collection.

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

Not applicable.

13. Financing

Precis-Mel 1 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 dissemination of study findings, whether through scientific publications or presentations at academic gatherings such as congresses, conventions, and seminars, is subject to the written authorization of each principal investigator involved in the study.

- **Written authorization:** each principal investigator commits to compiling a comprehensive report of the study and takes responsibility for ensuring that the study's data are disseminated in a manner that is both responsible and coherent.
- **Independence of results:** the decision to publish or present the study data will be made independently of the results obtained. This emphasizes our commitment to scientific integrity and transparency.
- **Data anonymization:** all data that are transmitted or disseminated must undergo appropriate statistical analysis or be anonymized to protect study participants. This applies to all forms of data sharing, including contributions to multicentric studies.

By adhering to these policies, we aim to maintain the highest ethical standards while maximizing the study's reach and impact.

DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS

ANA LUCIA ARELLANO ANDRINO, Secretario del **Comité de Ética de la Investigación con medicamentos del Hospital Clínic de Barcelona**

Certifica:

Que este Comité ha evaluado la propuesta del promotor, para que se realice el estudio:

CÓDIGO:
DOCUMENTOS CON VERSIONES:

Tipo	Subtipo	Versión
Protocolo		v3 (19/12/2023)

TÍTULO: Precision medicine for L/GCMN and melanoma 1 (Precis-mel 1)
PROMOTOR:
INVESTIGADOR PRINCIPAL: SUSANA PUIG SARDÁ

y considera que, teniendo en cuenta la respuesta a las aclaraciones solicitadas (si las hubiera), y que:

- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles.
- La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.
- Que se han evaluado las compensaciones económicas previstas (cuando las haya) y su posible interferencia con el respeto a los postulados éticos y se consideran adecuadas.
- Que dicho estudio se ajusta a las normas éticas esenciales y criterios deontológicos que rigen en este centro.
- Que dicho estudio cumple con las obligaciones establecidas por la normativa de investigación y confidencialidad que le son aplicables.
- Que dicho estudio se incluye en una de las líneas de investigación biomédica acreditadas en este centro, cumpliendo los requisitos necesarios, y que es viable en todos sus términos.

Este CEIm acepta que dicho estudio sea realizado, debiendo ser comunicado a dicho Comité Ético todo cambio en el protocolo o acontecimiento adverso grave.

y hace constar que:
1º En la reunión celebrada el día 26/10/2023, acta 20/2023 se decidió emitir el informe correspondiente al estudio de referencia.
2º El CEIm del Hospital Clínic i Provincial, tanto en su composición como en sus PNTs, cumple con las normas de EMA/CHMP/ICH/135/1995

3º Listado de miembros:

Reg. HCB/2023/1033

Presidente:

- JOSEP MARÍA MIRÓ MEDA (Médico Enfermedades Infecciosas, HCB)

Vicepresidente:

- JULIO DELGADO GONZÁLEZ (Médico Hematólogo, HCB)

Secretario:

- ANA LUCIA ARELLANO ANDRINO (Médico Farmacólogo Clínico, HCB)

Vocales:

- JOSE RIOS GUILLERMO (Estadístico. Plataforma Estadística Médica. HCB)
- OCTAVI SANCHEZ LOPEZ (Representante de los pacientes)
- MARIA JESÚS BERTRAN LUENGO (Médico Epidemiólogo, HCB)
- JOAQUÍN SÁEZ PEÑATARO (Médico Farmacólogo Clínico, HCB)
- SERGI AMARO DELGADO (Médico Neurólogo, HCB)
- EDUARD GUASCH CASANY (Médico Cardiólogo, HCB)
- MARINA ROVIRA ILLAMOLA (Farmacéutico Atención Primaria, CAP Eixample)
- PAU ALCUBILLA PRATS (Médico Farmacólogo Clínico, HCB)
- JOSE TOMAS ORTIZ PEREZ (Médico Cardiólogo, HCB)
- ELENA CALVO CIDONCHA (Farmacéutica Hospitalaria, HCB)
- CECILIA CUZCO CABELLOS (Enfermera, HCB)
- PAULA MARTÍN FARGAS (Abogada, HCB)
- SALVATORE BRUGALETTA (Médico Cardiólogo, HCB. Miembro del CEA, HCB)
- XAVIER CANALS-RIERA (Ingeniero Telecomunicaciones)
- JOSEP DÍAZ CORT (Licenciado en Ciencias Físicas. Catedrático en Informática)
- GASPAR MESTRES ALOMAR (Médico, Angiología, Cirugía Vascular, HCB)
- MARTA FRANCH SAGUER (Abogada)
- ANNA MARÍA GUIJARRO PÉREZ (Servicio de Atención a la Ciudadanía, HCB)
- BEGOÑA ROMAN MAESTRES (Doctor en Filosofía)
- LINA LEGUIZAMO MARTÍNEZ (Médico Farmacólogo Clínico, HCB)
- MIREIA DALMASES CLERIES (Médico Neumólogo, HCB)

En el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, este se ausentará de la reunión durante la discusión del proyecto.

Para que conste donde proceda, y a petición del promotor,

Fecha: 2024.02.22
11:37:02 +01'00'

Barcelona, a 22 de febrero de 2024

Reg. HCB/2023/1033

HOSPITAL CLÍNIC DE BARCELONA
Villarroel, 170 - 08036 Barcelona (España)
Tel. 93 227 54 00 Fax 93 227 54 54
www.clinicbarcelona.org

1. General information

1.1. Identification of the study

Title: Precision medicine for L/GCMN and melanoma 2 (Precis-mel 2)

Code or protocol identification number: NCT06605443 (*https://clinicaltrials.gov/*)

Version and date: v2 (19.12.2023)

1.2. Identification of the sponsor/principal investigator

Name: Susana Puig Sardà

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

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1.3. Identification of site investigators

Researcher 1

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Researcher 2

Name: Teresa Torres Moral

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Researcher 3

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Researcher 4

Name: Jaume Bagué Companys

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Researcher 5

Name: Beatriz Alejo

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Researcher 6

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Researcher7

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Researcher 8

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Researcher 9

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Researcher 10

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

1.4. Identification of the principal investigators from participant centers

N/A

2. Justification

In children, sentinel lymph node biopsy (SLNB) can be used as a prognostic indicator for poorer outcomes being reported a melanoma-specific survival of 89 % for the positive SLNB in a study of 261 children, adolescent and young adults (CAYA) under 20 years old [1]. However, there are no specific indications about follow-up strategies in those CAYA with high-risk melanoma. Liquid biopsy, identifying BRAF and NRAS mutant copies in circulant free DNA has been recently investigated in the follow-up of high-risk melanoma patients and large/giant congenital melanocytic nevi (L/GCMN) [2], opening the possibility of minimally invasive methods in CAYA at risk of melanoma progression. However, further studies to implement these methods in clinical practice are needed. Volatile biomarkers have also been identified in melanoma [3] but they have never been used in a clinical setting for the follow-up of patients at high risk of melanoma relapse or progression. The proposed study will enable to develop an autonomous, real-time, non-invasive and inexpensive unequivocal melanoma detection system by identifying melanoma-specific volatile organic compounds profiles (VOCs, metabolites emitted by or as a result of infected cells) found in the exhaled breath and skin surface.

3. Study hypothesis

Previous H2020 EU projects making use of the same non-invasive devices for VOCs detection have shown promising results in the diagnosis of different diseases. For instance, a clinical study carried out in the project *Smart Phone for Disease Detection from Exhaled Breath (SNIFFPHONE)* [4] showed that people with gastric cancer have unique mixtures of chemicals in their breath compared to other diseases and healthy people [5]. These tests were based on the detection of VOCs patterns from exhaled breath using highly sensitive nanomaterial-based chemical sensors. Using a smartphone, the measurements were then sent via Bluetooth to a dedicated cloud platform for analysis by medical personnel. A different project known as *Skin wearable patches for detecting and monitoring infection (A-Patch)* [6] made use of a hybrid sensor patch array with multiplexed detection capabilities to detect irregularities in the volatile biomarkers pattern when placed on the skin. This sensor has been used for point-of-care diagnosis to discriminate

between active pulmonary tuberculosis patients and controls with a sensitivity above 90 % [7]. There is also a certain number of articles supporting the use of volatile biomarkers for melanoma detection. For instance, a study demonstrates that trained dogs can discern cases of invasive melanoma from disease-free controls [8]. Another study also corroborates, using gas chromatography, the use of volatile organic compounds (VOCs) to differentiate between melanoma cell cultures and healthy skin [9]. This study will build upon all these previous results and adapt the aforementioned non-invasive technologies (breath analyzer and skin patch) for the follow-up of patients at high risk of melanoma progression in the context of active surveillance.

4. Objectives and purpose of the study

The primary objective is to evaluate the possibility of using minimally and non-invasive technologies (skin patch and breath analyzer) based on the detection of volatile organic compounds (VOCs) for the early identification of metastases. The secondary objective is to evaluate the usability of these technologies in the follow up of high-risk melanoma patients.

5. Study design

This is a unicentric national prospective observational study aimed at evaluating the use of two devices (skin patch and breath analyzer) for the non or minimally invasive diagnosis of metastatic melanoma with a total duration of 24 months. The study will be based on the obtention of different patterns of volatile organic compounds using the aforementioned devices for melanoma patients with and without metastasis. The results will be compared with the standard procedures for the detection of metastatic melanoma (standard imaging techniques such as PET, MRI, etc.) and correlated with standard prognostic biomarkers (cfDNA mutations in BRAF, NRAS, etc.) obtained using liquid biopsy.

6. Participant selection

Adult population (over 18 years of age) diagnosed with melanoma or L/GCMN that are currently being treated at the Hospital Clinic de Barcelona or that are admitted before or at the time of the enrolment in the study.

6.1. Subject inclusion criteria

Patients of either sex over 18 years old with histopathological confirmed melanoma. We will

include patients with stage II, III or IV according to the American Joint Committee on Cancer (AJCC) staging. In the case of the L/GCMN cases, an individual must meet the following criteria: be over 18 years of age and present a congenital nevus with estimated size of 20 cm or more.

6.2. Subject exclusion criteria

Not signing the informed consent form and/or present other cancers or chronic diseases (such as diabetes, asthma, etc., which may affect the VOCs profiles).

7. Treatment and study calendar

The study will have a total duration of 24 months (from March 2024 to March 2026). A total of 30 adult patients (over 18 years of age) with L/GCMN and 70 patients admitted to the Hospital Clinic de Barcelona with histopathological confirmed melanoma will be recruited for the study with the breath analyzer and the skin patch.

The study will be developed in two phases:

Phase I: enrollment and baseline assessment

- Recruitment of patients who are eligible for the study.
- Categorization of patients into their respective groups: L/GCMN group or melanoma diagnosed group.
- Collection of baseline data on each patient, including any relevant medical history, physical examinations, initial biomarkers and diagnostic tests.

Phase II: follow-up and late assessment

- Annual follow-up for control patients.
- For those identified in the melanoma diagnosed group, follow-up according to internal protocols, every 3 months for the 2 years after diagnosis and every 6 months from 2 to 5 years. The follow-up includes blood test, ultrasonography, brain RMN the first 2 years, and CT or PET CT all period every 6 months.
- Metastatic melanoma subgroup will be established consisting of patients who show progression to metastatic melanoma. Approximately 30% of patients included, stage II-III, will progress in the follow-up period of 2 years.

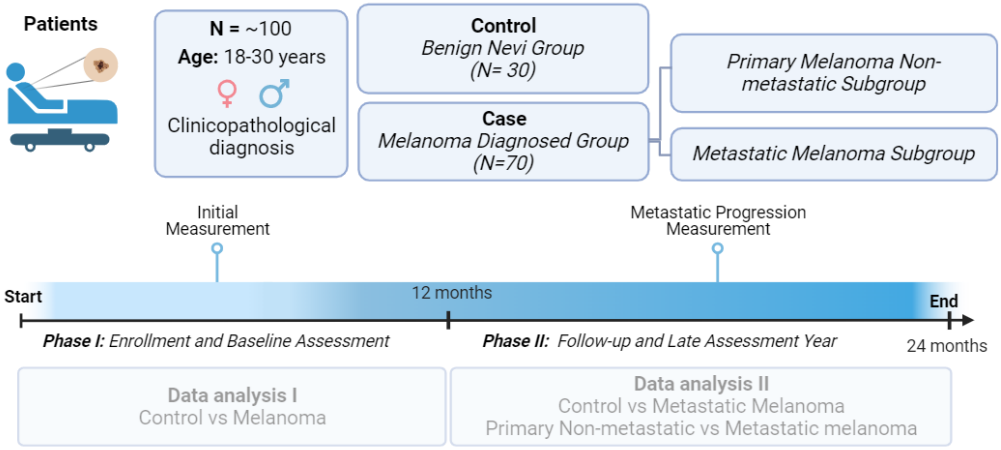

Figure 1 *Timeline for the Precis-Mel 2 study*

The patients will be informed 24 h before the time of the planned procedure (by telephone call or printed information sheets) about the following requirements:

- Fast for at least 12 hours.
- Refrain from coffee, tea and soft drinks for at least 12 hours.
- Refrain from smoking for at least 2 hours.
- Avoid alcohol for at least 24 hours.
- Do not clean teeth at least 2 hours before the procedure (no brushing, no mouthwash, no flossing if the floss has any aroma).
- Avoid chewing gum and any mouth fresheners for at least 12 hours.
- Refrain from using cosmetics/fragrances prior to the procedure on the day of test.
- Avoid excessive physical activity (gym, jogging, cycling, intense physical work) at least 2 hours prior to the test.

During the first visit, the patients will be also asked to fill different questionnaires including the following topics:

- Clinical questionnaire (previous cancers, chronic diseases, chemotherapy, etc.).
- Confounding factors (air quality, smoking, coffee, etc.).
- Medication intake questionnaire.
- Food recall for the last 24-hours.

The room location for sample collection should be registered with the patient data. If possible, the breath and skin samples will be collected in the same premises for all patients. Study staff being involved in the collection of samples should avoid using cosmetics or perfumes, eating or using disinfectants in the test room in order to avoid major sources of VOCs. When possible, only the sampling officer and the study subject should be present in the collection room. The room temperature should be kept between 20-25 ºC (samples taken at temperatures outside this range should be discarded).

The study subject will be advised to sit quietly for minimum 10 minutes prior the sampling to avoid temporal changes in levels of VOCs related to body movement or try to avoid abrupt changes in body posture. Then, he/she will be asked to blow in the breath analyzer in order to obtain the exhaled VOCs profile. After that, the skin patch will be placed in the anterior part of the arm for the obtention of the skin VOCs profile (estimated sampling time of around 1 h). These profiles will be recorded with a dedicated software and analyzed using standard statistical methods. This information will be compared to the monitoring clinical data routinely obtained from diagnostic tests based on liquid biopsy to detect mutations in BRAF and other prognostic genes. We will also compare the results with the usual medical monitoring tests to evaluate the presence of metastasis such as imaging (including RMN, CT, PET-CT) and sentinel lymph node biopsy.

8. Statistics

8.1. Sample size

Around 100 young adults' patients will be included in this study.

8.2. Statistical analysis

Continuous variables will be reported as mean and standard deviation, or median and range where appropriate. Categorical variables will be summarized as number and proportion of the total study population, and by subgroups where appropriate. Frequencies will be presented as n (%), with percentage calculated based on the total study population and by subgroups where appropriate. Proportions will include all patients in a specified group in the denominator and the number of these patients with an outcome of interest in the numerator. The corresponding 95% CI will be calculated using the Pearson-Clopper binomial proportion method. Non-parametric Mann-Whitney test will be performed to compare continuous variables with no

normal distribution. Categorical variables will be evaluated by Chi-squared analysis or Fisher's exact test were appropriate.

9. Ethical and legal aspects

9.1. Legal and ethical basis

As the study will gather new data during the clinical practice for research purposes, an explicit consent (article 9.2 (a) GPDR) will be required. The informed consent will explain to the subjects the purpose of the study as well as the nature and extent of their participation, complying with the rules set out in Regulation EU No. 536/2014. Subjects will be informed that participation in MELCAYA is completely voluntary, and that they can withdraw the consent at any time.

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 Harmonization of Good Clinical Practice (ICH GCP) 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 will be stored in a secured electronic database known as *Xarxa Melanoma* approved by the Ethical Committee of the Hospital Clínic de Barcelona on the 14/04/2015 (Reg. HCB/2015/0298). This database is routinely used by dermatology medical professionals of our hospital and complies with international standards on data protection and offers a consistent, auditable and integrated electronic database environment. Each institution involved in the study

will have a local data protection officer (DPO) to advise on complex, sensitive, or large-scale data processing activities.

Upon completion of the study, data will be preserved for a minimum of 25 years to guarantee continued accessibility and data discovery. Personal data information will only be kept for updating follow-up by the local center investigator. The sponsors will only use the data collected for other scientific purposes if participants have given prior consent and if the legal basis for processing is still in place (see section 9.1). After that, paper and electronic records will be destroyed or erased per institutional/University policy.

10.2. Data codification

Before uploading the collected patient data to the database, a codification procedure will be implemented at each local data source center. The procedure will be carried out in the following way: a researcher from our center will assign a code to the clinical information of each patient, which will be kept in a separated database to which only the Principal Investigator or authorized personnel in his research team will have access to. In that way, without knowledge of the respective assignment of code 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 data collection.

10.3. FAIR data

In the case of publishing the results, all data will be identified by a digital object identifier (DOI) to ensure that it is findable, made available and publicly accessible in 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, etc.) 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

Not applicable to this study.

13. Financing

Precis-Mel 2 study was conceived independently of any commercial organization and will be coordinated, managed and analyzed in 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

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DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS

ANA LUCIA ARELLANO ANDRINO, Secretario del **Comité de Ética de la Investigación con medicamentos del Hospital Clínic de Barcelona**

Certifica:

Que este Comité ha evaluado la propuesta del promotor, para que se realice el estudio:

CÓDIGO: R120904-090
DOCUMENTOS CON VERSIONES:

Tipo	Subtipo	Versión
Protocolo		v3 (01.02.2024)
Hoja Información de Paciente		v1.0 de 19.12.2023

TÍTULO: Precision medicine for L/GCMN and melanoma 2 (Precis-mel 2)
PROMOTOR:
INVESTIGADOR PRINCIPAL: SUSANA PUIG SARDÁ

y considera que, teniendo en cuenta la respuesta a las aclaraciones solicitadas (si las hubiera), y que:

- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles.
- La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.
- Que se han evaluado la compensaciones económicas previstas (cuando las haya) y su posible interferencia con el respeto a los postulados éticos y se consideran adecuadas.
- Que dicho estudio se ajusta a las normas éticas esenciales y criterios deontológicos que rigen en este centro.
- Que dicho estudio cumple con las obligaciones establecidas por la normativa de investigación y confidencialidad que le son aplicables.
- Que dicho estudio se incluye en una de las líneas de investigación biomédica acreditadas en este centro, cumpliendo los requisitos necesarios, y que es viable en todos sus términos.

Este CEIm acepta que dicho estudio sea realizado, debiendo ser comunicado a dicho Comité Ético todo cambio en el protocolo o acontecimiento adverso grave.

y hace constar que:
1º En la reunión celebrada el día 11/01/2024, acta 1/2024 se decidió emitir el informe correspondiente al estudio de referencia.
2º El CEIm del Hospital Clínic i Provincial, tanto en su composición como en sus PNTs, cumple con las normas de EMA/CHMP/ICH/135/1995

Reg. HCB/2023/1111

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Vicepresidente:

- JULIO DELGADO GONZÁLEZ (Médico Hematólogo, HCB)

Secretario:

- ANA LUCIA ARELLANO ANDRINO (Médico Farmacólogo Clínico, HCB)

Vocales:

- JOSE RIOS GUILLERMO (Estadístico. Plataforma Estadística Médica. HCB)
- OCTAVI SANCHEZ LOPEZ (Representante de los pacientes)
- MARIA JESÚS BERTRAN LUENGO (Médico Epidemiólogo, HCB)
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- MIREIA DALMASES CLERIES (Médico Neumólogo, HCB)

En el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, este se ausentará de la reunión durante la discusión del proyecto.

Para que conste donde proceda, y a petición del promotor,

Fecha: 2024.03.01
16:25:07 +01'00'

Barcelona, a 1 de marzo de 2024

Reg. HCB/2023/1111