REPORT
25th SOCIAL RETURN OF THE RESEARCH
CANCER

# IMPLEMENTATION OF PERSONALISED MEDICINE IN MALIGNANT MELANOMA THROUGH ARTIFICIAL INTELLIGENCE

**Dr Josep Malvehy Guilera**
IDIBAPS Institut d'Investigació Biomèdica August Pi i Sunyer
**Dr Verónica Vilaplana Besler**
Escola Tècnica Superior d'Enginyeria de Telecomunicació de Barcelona - UPC
Universitat Politècnica de Catalunya

## 1. Summary of the project

At present, the prognostic evaluation of melanoma patients is based on an international guideline with several clinical limitations. This classification includes clinical data of the patient, histological data of the tumor, medical tests, the evaluation of the local regional lymph nodes, and distant metastasis. This information is used to predict the evolution and risk of relapse and death of the patient. However, the information used to perform this classification is often insufficient to provide a customized prognosis for each patient and makes it difficult to provide individualized treatment recommendations. Also, the systemic and surgical treatments offered to patients often involve significant toxicities and morbidities which impact their quality of life (i.e. sentinel node biopsy is not needed for 80% of the melanoma patients [Gershenwald, Jeffrey E., et al. (2017)], 50% of patients do not benefit from adjuvant treatment [Weber, Jeffrey, et al. (2017).]). Therefore, melanoma patients should benefit from a more precise risk classification.

The goal of this project was to provide an artificial intelligence tool to assess the risk of relapse, metastasis, and death of melanoma patients and to help to provide personalized treatment options for each patient. A new artificial intelligence algorithm based on clinical, socioeconomic, phenotypical, biochemical, pharmacological, genetic, and imaging data improved the AJCC staging system used in clinical management, leading to a more accurate prediction of metastasis/recurrence and death. A new patient stratification based on a larger subset of variables will lead to personalized treatment options.

This project was made possible by the collaboration of a multimodal team of clinical experts, mathematicians and engineers from two institutions at the Hospital Clinic of Barcelona and the IDIBAPS and the Image Processing Group of the Signal Theory and Communications Department at the Universitat Politècnica de Catalunya. BARCELONATECH. The two principal investigators were Josep Malvehy (Hospital Clinic of Barcelona) and Veronica Vilaplana (UPC).

The project included data from many patients from Catalan hospitals (more than 6,000,000 data entries of 14,000 patients) about the tumor and patient, tests, medications, genetics and others, at the time of the diagnosis and during the follow-up

visits. This information had been collected during the last decade in an research effort that was unprecedented in the world. The project research team analyzed and integrated the data usefully with the help of artificial intelligence and built a method that can help physicians around the world to improve the care of patients with melanoma.

**Objectives**

1. To create a survival analysis database for melanoma patients
2. To identify clinical, environmental, behavioral, socioeconomic, phenotypical, biochemical, pharmacological, genetic, and medical imaging melanoma-related features.
3. To pre-process and aggregate the patient variables adequately to create a survival analysis dataset for disease-free survival and melanoma survival.
4. To combine the variables in an artificial intelligence algorithm.
5. To construct and train a deep neural network to estimate the patient's risk of metastasis, relapse or death.
6. To provide interpretation to the outputs of the model
7. To use clustering and visualization techniques to create a new, statistically coherent stratification for melanoma patients
8. To provide a measure of uncertainty to the model's predictions
9. To create a tool called AID-MM (artificial intelligence-driven melanoma model) to make the trained model available to other physicians around the globe.
10. To develop an easy-to-use interface and interpretation toolbox for clinicians.
11. To validate the usability of the tool in clinical practice.
12. Dissemination of the results
13. Dissemination in scientific meetings and impact-factor journals
14. Dissemination to the general public

## 2. Results

In the project we identified clinical, environmental, behavioral, socioeconomic, phenotypical, biochemical, pharmacological, genetic and medical imaging melanoma-related features associated to prognosis of melanoma. A comprehensive data set was

built up by pre-processing of the structured patient variables and pre-processing of the medical images.

The variables were adequately created to create a survival analysis dataset for disease-free survival and melanoma survival.

A single modality algorithm was produced for structured data for survival analysis. In addition, single modality algorithms were constructed for medical imaging for survival analysis.

Integration of the single modality algorithms into a multimodal architecture was achieved and model interpretation modules were created for structured data and image data.

A clinical interpretation of the model's outputs and definition of a new stratification for melanoma patients was produced.

Finally, implementation and clinical validation of the AID-MM app were conducted in the last year of the project. To comprehensively assess the AID-MM app, 16 leaders in skin cancer from 13 referral melanoma centers in six European countries—Spain, Italy, Portugal, France, Germany, and the Czech Republic—participated in the clinical evaluation. Notably, these experts were affiliated with referral centers from the EADO (European Association of Dermato-Oncology) and EORTC (European Organisation for Research and Treatment of Cancer) scientific societies, signifying their prominence in the field. The clinical evaluation incorporated a multifaceted approach, combining a detailed project presentation, individual interviews with the experts, and a survey designed to capture their nuanced perspectives. The evaluation was conducted following established mHealth app implementation guidelines, with a specific focus on three key pillars: quality, usability, and expected impact on management practices.

To streamline the evaluation process, a heuristic questionnaire was meticulously designed. This questionnaire aimed to gather quantitative and qualitative insights from the experts, covering various dimensions crucial for assessing the app's performance. The questionnaire comprised five key items:

1. Accuracy of Predictive Models: This item focused on gauging the perceived reasonability of the results generated by the predictive models. Experts were required to rate this aspect on a scale from 1 to 5, ranging from Highly Unreasonable to Highly Reasonable.

2. Interpretability of Models: The questionnaire sought to understand how insightful the experts found the model interpretability diagrams in aiding their comprehension of predictions. Ratings ranged from Not Insightful to Extremely Insightful on a scale from 1 to 5.

3. Clinical Applicability with AJCC Guidelines: Experts were asked to express the extent to which they envisioned using the predictive models to complement the existing AJCC staging system in their clinical practice. Responses were rated on a scale from Definitely Would Not Use to Definitely Would Use, ranging from 1 to 5.

4. Usability and Format: This item delved into how well the format of the AID-MM tool integrated into the clinical workflow of the experts. Ratings ranged from Poorly Integrates to Seamlessly Integrates on a scale from 1 to 5.

5. Suggestions for Improvement: An open-ended question sought to gather qualitative feedback on potential enhancements for the tool's functionality, accuracy, and user experience.

Results of the questionnaire revealed overwhelmingly positive feedback from the skin cancer experts indicating a high level of satisfaction with the AID-MM app across critical dimensions. We had a strong consensus among the evaluators regarding the accuracy of predictive models, interpretability, clinical applicability, and the seamless integration of the tool into their clinical workflows.

This positive reception suggests that the AID-MM app successfully met the expectations of the skin cancer experts, demonstrating its effectiveness in providing reasonable predictions, offering insightful model interpretability, aligning with clinical practices, and the potential integration smoothly into existing workflows.

## 3. Relevance and possible clinical applicability of the final results

The artificial intelligence-driven melanoma model (AID-MM) represents a significant advance in skin cancer research, particularly in the management of melanoma, a serious and potentially deadly skin cancer. The practical implications of this project are broad and impactful, spanning clinical decision-making, patient care, global healthcare, and the field of oncology at large. The clinical validation in a clinical trial was not our goal considering the time frame and funding of the project. However, we can conclude that the results obtained will guide the implementation of multimodal predictive tools using AI in precision oncology in the future. The relevance and expected clinical applicability of the project can be summarized in the following aspects:

1. Enhanced Personalized Medicine:
The core strength of AID-MM lies in its ability to provide personalized medical recommendations. Traditional methods of melanoma treatment have often followed a 'one-size-fits-all' approach, but the AID-MM tool changes this by taking into account a wide array of patient-specific data. This includes not just clinical and genetic information, but also socioeconomic, behavioral, and environmental factors, which are often overlooked in traditional staging systems. By considering these diverse factors, AID-MM can help clinicians tailor treatment plans to the individual, potentially improving outcomes and reducing the risk of unnecessary treatments and their associated side effects.

2. Improvement in Prognostic Accuracy:
AID-MM's advanced AI algorithms can offer a more nuanced and precise understanding of a patient's prognosis. This is critical in a disease like melanoma, where early and accurate prediction of metastasis and recurrence can significantly alter the course of treatment and patient management. With better prognostic tools, clinicians can make more informed decisions about the aggressiveness of the treatment required, surveillance strategies, and the need for adjunct therapies.

3. Global Impact on Melanoma Care:
Given its design for accessibility, AID-MM has the potential to show a new way to standardize and elevate the quality of melanoma care. This is particularly important in regions where access to specialized oncological expertise is limited. By providing a

user-friendly interface and comprehensive decision-support system, AID-MM can assist healthcare providers of varying levels of expertise in making informed treatment decisions, thus democratizing high-quality melanoma care.

4. Contribution to Oncological Research:
This project serves as a model for how AI can be integrated into cancer care, paving the way for similar approaches in other types of cancers. The data-driven insights generated could inform future oncological research, contributing to a deeper understanding of cancer biology, treatment responses, and patient outcomes.

5. Education and Training:
AID-MM can also serve as an educational tool for medical professionals. By providing insight into how various factors contribute to melanoma prognosis and treatment efficacy, it can enhance the training of dermatologists, oncologists, and other healthcare professionals. This educational aspect is crucial for improving overall cancer care and keeping practitioners aware of the latest advances in personalized medicine.

6. Patient Engagement and Empowerment:
Finally, by providing clearer, more personalized information about prognosis and treatment options, AID-MM can help patients become more engaged in their care. Understanding the rationale behind treatment choices and what to expect can empower patients, reduce anxiety, and improve compliance with treatment plans.
In conclusion, the AID-MM project stands to significantly advance the field of melanoma treatment and cancer care as a whole. Its implications extend from individual patient care to global healthcare practices, research, education, and patient empowerment, illustrating the transformative potential of AI in medicine.

## 4. Publications, communications and training of personnel derived from this research

1. Bridging Machine Learning and Medical Expertise: Comparative Analysis and Interpretability of Survival Models in Melanoma Research. Carlos Hernández-Pérez,VerónicaVilaplana,SebastianPodlipnik,JosepMalvehy,JoanFicapal,Susana Puig

2. BCN20000: Dermoscopic Lesions in the Wild Carlos Hernandez-Perez, Veronica Vilaplana, Marc Combalia, Sebastian Podlipnik, Noel C. F. Codella, Veronica Rotemberg, Brian Helba, Ofer Reiter, Cristina Carrera, Alicia Barreiro, Allan C. Halpern, Susana Puig, and Josep Malvehy

3. Pachón-García C, Hernandez C, Delicado P, Vilaplana V. SurvLIMEpy: A Python package implementing SurvLIME. Expert Systems With Applications. 2024;237, Part C. Google Scholar BibTex

4. Hernandez C, Pachón-García C, Delicado P, Vilaplana V. Interpreting Machine Learning models for Survival Analysis: A study of Cutaneous Melanoma using the SEER Database. In: XAI-Healthcare 2023 Workshop at 21st International Conference of Artificial Intelligence in Medicine (AIME 2023). XAI-Healthcare 2023 Workshop at 21st International Conference of Artificial Intelligence in Medicine (AIME 2023). Portoroz, Slovenia; 2023. Google Scholar BibTex

5. Hernandez C, Combalia M, Puig S, Malvehy J, Vilaplana V. Contrastive and attention-based multiple instance learning for the prediction of sentinel lymph node status from histopathologies of primary melanoma tumours. In: Cancer Prevention through early detecTion (Caption) Workshop at 25th International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2022). Cancer Prevention through early detecTion (Caption) Workshop at 25th International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2022); 2022. Google Scholar BibTex

6. Hernandez C, Combalia M, Malvehy J, Vilaplana V. Sentinel lymph node status prediction using self-attention networks and contrastive learning from routine histology images of primary tumours. In: Medical Imaging with Deep Learning MIDL 2022. Medical Imaging with Deep Learning MIDL 2022.; 2022. Google Scholar BibTex

7. Combalia M, Podlipnik S, Hernandez C, García S, Ficapal J, Burgos J, Vilaplana V, Malvehy J. Artificial intelligence to predict positivity of sentinel lymph node biopsy in melanoma patients. In: European Association of Dermato Oncology (EADO 2022). European Association of Dermato Oncology (EADO 2022).; 2022. Google Scholar BibTex

8. Hernandez C, Vilaplana V, Combalia M, García S, Podlipnik S, Burgos J, Puig S, Malvehy J. Sentinel lymph node status prediction with self-attention neural networks using histologies of primary melanoma tumours. In: European Association of Dermato Oncology (EADO 2022). European Association of Dermato Oncology (EADO 2022).; 2022. Google Scholar BibTex

9. Podlipnik S, Hernandez C, Kiroglu A, García S, Ficapal J, Burgos J, Calbet N, Puig S, Malvehy J, Vilaplana V, et al. Personalized medicine in melanoma patients aided by artificial intelligence. In: Clinical Translation of Medical Image Computing and Computer Assisted Interventions (CLINICCAI) Workshop at MICCAI. Clinical Translation of Medical Image Computing and Computer Assisted Interventions (CLINICCAI) Workshop at MICCAI.; 2021. Google Scholar BibTex

10. Hernandez C, Kiroglu A, García S, Ficapal J, Burgos J, Podlipnik S, Calbet N, Puig S, Malvehy J, Vilaplana V, et al. Implementation of personalized medicine in cutaneous melanoma patients aided by artificial intelligence. In: 10th World Congress of Melanoma / 17th EADO Congress. 10th World Congress of Melanoma / 17th EADO Congress; 2021. Google Scholar BibTex

**Presentations in Congresses**

3.1. Congress: Challenging Melanoma (international Congress)). City: Lisbon.Date: 6th November, 2023. Author: Josep Malvehy; Title: The multiple faces of AI in melanoma (invited lecture in a symposium)

3.2. Congress: European Academy of Dermatology and Venereology (international Congress).City: Berlin. Date: October 11-14, 2023 Author: Josep Malvehy. Title: Applications of AI in Dermatology

3.3. Congress: MEL2023 (Symposium). City: Lisbon. Date: September 29, 2023. Author: Josep Malvehy. Title: AI in melanoma