AWARD NUMBER: W81XWH-21-1-0819

TITLE: Risk Prediction Models for Rare Melanomas

PRINCIPAL INVESTIGATOR: Marc Hurlbert, Ph.D.

CONTRACTING ORGANIZATION: Melanoma Research Alliance Foundation, Washington, DC

REPORT DATE: October 2022

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2022	Annual	05Sep2021-04Sep2022

4. TITLE AND SUBTITLE

Risk Prediction Models for Rare Melanomas

5a. CONTRACT NUMBER
W81XWH-21-1-0819

5b. GRANT NUMBER
ME200118

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER
0011638991-0002

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release, Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

We hypothesize that unique clinical, environmental, and genetic risk factors confer risk of acral, mucosal, and uveal melanoma among Veteran and civilian populations. Aims:1) Identify clinical and environmental risk factors for each of the rare melanoma subtypes; 2) Integrate germline genetic factors for each rare melanoma risk model; and 3) Interrogate rare melanomas risk prediction model performance in two independent civilian cohorts. A nested case-control study based within the VA Corporate Data Warehouse (CDW) will be used to examine the association of clinical and environmental risk factors with rare melanoma risk. Cases will be identified by pulling all melanoma reports, identified by histology ICD morphology code, and then we will use natural language processing to identify anatomical site. We will ascertain information regarding deployment together with clinical, genetic, and administrative data (e.g., age, race-ethnicity, co-morbidities, medication, environmental exposures). Similar approaches will be used to pull a civilian case-control cohort from the MGH Research Patient Data Registry. Next, we will test the risk algorithms in prospective cohorts/patient registries. Identifying and targeting individuals at high-risk for rare melanomas can direct prevention efforts, enable early-intervention studies and ultimately reduce mortality.

15. SUBJECT TERMS

Rare melanoma risk, acral melanoma, mucosal melanoma, uveal melanoma, skin cancer, veterans, civilians

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	32	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

Risk of rare melanomas (defined as acral, mucosal, and uveal) among military personnel compared with the general population is unknown. Risk factors for these rare and uncommon melanoma subtypes have not been identified and comprehensively validated. This ongoing project aims to narrow these gaps by identifying clinical, environmental, and genetic risk factors associated with rare melanoma susceptibility among military personnel, and to test the validity of these models in the civilian population. The findings of the study will be used to develop an individualized risk stratification and scoring system for each rare melanoma subtype (acral, mucosal, and uveal). The specific aims being addressed include: 1) Identify clinical and environmental risk factors for each of the rare melanoma subtypes; 2) Integrate germline genetic factors for each rare melanoma risk model; and 3) Interrogate rare melanomas risk prediction model performance in two independent civilian cohorts. A nested case-control study based within the VA Corporate Data Warehouse (CDW) is being used to examine the association of clinical and environmental risk factors with rare melanoma risk. We will ascertain information regarding deployment together with clinical and administrative data (e.g. age, race-ethnicity, co-morbidities, medication, environmental exposures). Next, we plan to integrate existing germline data from the Million Veteran Program (MVP) cohort and refine environmental factors to ascertain whether addition of genomic risk prediction tool performance. Lastly, we will validate the risk models in two civilian cohorts: MGB Research Patient Data Registry and the MRA Rare Melanoma Registry.

2. KEYWORDS:

Skin cancer, melanoma, rare melanomas, acral, mucosal, uveal; clinical, environmental, genetic risk factors; veterans, civilians; individualized risk scoring system

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Launch Team Collaboration
Major Task 1: Assemble team, agreement, and contracting
Major Task 2: Finalize study protocol, data dictionary

Specific Aim 1: Develop risk prediction tools for acral, mucosal, and uveal melanomas based on clinical and environmental risk factors from VA CDW
Major Task 1: Identify study participants from VA CDW
Major Task 2: Select variables for inclusion in risk prediction models
Major Task 3: Develop clinical risk prediction models

Specific Aim 2: Integrate germline genetic information on rare melanoma susceptibility loci and additional environmental information from MVP into models developed in Aim 1 to assess improvements in performance of risk prediction models.

Specific Aim 2 (continued):
Major Task 1: Identify study participants from VA MVP
Major Task 2: Perform GWAS to identify SNPs associated with each of the rare melanoma subtypes
Major Task 3: Add genetic data to risk prediction models

Specific Aim 3a: Validate rare melanoma risk assessment tools that incorporate polygenic risk score with clinical risk factors in an independent civilian cohort (Mass General Brigham Research Patient Data Registry, RPDR).
Major Task 1: Identify study participants in RPDR
Major Task 2: Test clinical risk prediction model in RPDR cohort
Major Task 3: Test integrated genetic and clinical risk prediction model in RPDR cohort

Specific Aim 3b: Validate rare melanoma risk assessment tools that incorporate polygenic risk score with clinical risk factors in a patient-centered prospective cohort of patients with rare melanomas.
Major Task 1: Test clinical risk prediction model in MRA registry cohort
Major Task 2: Test genetic and clinical risk prediction model in MRA registry cohort

What was accomplished under these goals?

Launch Team Collaboration
Major Task 1: Assemble team, agreement, and contracting

Subtask 1: Kick-off meeting, assign tasks, establish schedule for monthly meetings & annual in-person mtg

- Team PIs and key personnel met August 4, 2021 to discuss an upcoming official kick-off meeting and launch of project, distribution of tasks, and assembling external advisory board (including patients and researchers).
- It was determined that project leads would be Marc Hurlbert for MRA, Rebecca Hartman and Nate Fillmore for VA sites, and Eugene Semenov for Mass General Brigham. These four, and their respective peers and junior staff, would meet monthly or as needed.
    - The MRA team joins approximately bi-weekly meetings for the VA sites and weekly meetings for the MGB site.
- Formal Kickoff Meeting, including External Advisors, was held October 14, 2021.
    - Drs. Hurlbert, Asgari, and Weinstock led the discussion and welcomed external advisors (see Subtask #4 below for details about advisors).
    - Hartman and Fillmore provided an update on the VA site IRB protocol. The team began assessing a variety of approaches to identify cases and controls (e.g., ICD, SNOMED codes). Note that normal formal cohort has NOT yet been pulled as we await OHRO (previously called HRPO) final approval to start project.

What was accomplished under these goals? (continued)

- Semenov and team provided an update on MGB site protocol. The team was also assessing how best to identify cases and controls from the MGB RPDR database.
- The groups decided it is best for the Hartman and Semenov teams to harmonize approach(es) to identifying cases and controls (all pending OHRO approvals to pull formal VA-CDW and MGB-RPDR cohorts).
- In lieu of an annual meeting as the project awaits OHRO approval, the full team reconvened on May 6, 2022 via Zoom to discuss OHRO protocols and updates to identifying cases and controls.

Subtask 2: Finalize site-specific non-key research personnel and on-board

- Year 1 site-specific non-key research personnel include (see Appendix 1):
  - **MRA:** Joan Levy, Ph.D., Senior Director; Isabel Ryan, Science Intern, Nico Starink, Science Intern (George Washington University MPH student)
  - **Providence VA:** Rachel Lim (Brown University student)
  - **Boston VA:** Nicole Trepanowski (Boston University School of Medicine MS4)
  - **Mass General Brigham:** Bonnie Leung, BS; Nga Nguyen, MD, MPH; and Ahmad Rajeh, MS

Subtask 3: Submit addendums to IRB and HRPO applications, and new IRB and HRPO as required

- Each of sites 1, 2, 3 and 4 have IRB protocols for studies separate from, but related to, the proposed work in this Team Science project. Thus, site-specific protocols had to be harmonized and submitted for approvals.
- The table below summarizes the status of harmonized proposal submission and IRB and OHRO statuses.
- As of September 19, 2022, Ocean State has OHRO letter noting allowance to start Aim 1 of the project. We await OHRO confirmation that Site 4 (Boston VA) can start Aim 1.

Protocol: ***Risk Prediction Models for Rare Melanomas***					
Site	**Site 1: MRA**	**Site 2: Ocean State**	**Site 3: Mass General Brigham**	**Site 4: Boston VA**	**Site 5: Harvard School of Public Health**
Project IRB submitted	10/30/2021	1/10/2022	6/16/2022	6/24/2022	N/A – advisory only
Project IRB approval	11/12/2021	4/21/2022	7/25/2022	8/4/2022	N/A – advisory only
OHRO submitted (most recent submission)	8/15/2022	9/7/2022	8/15/2022	9/14/2022	N/A – advisory only
OHRO approval	pending	9/19/2022 for Aim 1	pending	pending	N/A – advisory only

Subtask 4: Assemble formal patient advisory board

- It was determined when the team convened in August 2021 to assemble an external Patient and Researcher Advisory Board. Initially we had only planned on patient advisors.
- The Patient and Research Advisory Board was assembled, and the members joined the official kick-off on October 14, 2021.
- Project Advisory Board members include:
    - Chris C. patient advocate for acral melanoma
    - Amy J. patient advocate for acral melanoma
    - Jamie M. patient advocate for uveal melanoma
    - Teresa M. patient advocate/caregiver for uveal melanoma
    - Jonathan S. patient advocate for mucosal melanoma
    - Richard Carvajal, MD, Columbia University
    - Priya Nagarajan, MD, PhD, University of Texas MD Anderson Cancer Center
- See Appendix 2 for Advisory Board member biographies.
- A *Patient Advisory Board – Quarterly Participation Form* has been established for tracking patient advisors time and effort; however time and effort has been minimal in Year 1 as we await OHRO approval.

Subtask 5: Finalize communication and sharing platform (Microsoft Teams, Slack, Handzin or Citavi)

- The team decided Microsoft Teams and SharePoint would be the only platform each entity could access based on individual institutional policies. Before we could develop a shared MS Teams/SharePoint site, the Initiating PI Site (Site 1: Melanoma Research Alliance) needed to complete an upgrade and transition of the entire organization to Office 365, which was completed July 15, 2022.

Subtask 6: Execute institutional agreements

- MRA subaward to Mass General Brigham executed on 2/3/2022.
- MRA subaward to Harvard School of Public Health executed on 12/12/2021.
- Ocean State subaward to BVARI pending VA Boston IRB approval as of 9/30/2022.

Milestone(s) Achieved: We launched the project with a kick-off call with external advisors, including patient and researcher advisors. Advisory input has shaped our approach to identifying cases in the various cohorts for this project, as well as the variables being studied in the data dictionary and risk algorithms. The teams have met periodically on a monthly, or semi-monthly, basis as we negotiated sub-award contracts, and drafted IRB protocols and OHRO submission forms. Harmonization of IRB protocols across multiple sites has been a lengthy and time-consuming process. As of September 19, 2022, we have received OHRO approval for one site (Providence VA) to begin work on Aim 1.

Launch Team Collaboration (continued)

Major Task 2: Finalize study protocol, data dictionary

Subtask 1: Develop study operation manual

Subtask 2: Develop data dictionary

Milestone(s) Achieved: Finalized study protocol, study operations manual and data dictionary for CDW, MVP, RPDR data extractions

A preliminary draft data dictionary of patient, tumor, clinical management, environmental risk factors, and genomic characteristics has been created and will be finalized prior to start of study pending OHRO approvals. See Appendix 3. This will be finalized in the coming weeks.

Specific Aim 1: Develop risk prediction tools for acral, mucosal, and uveal melanomas based on clinical and environmental risk factors from VA CDW
Major Task 1: Identify study participants from VA CDW
Major Task 2: Select variables for inclusion in risk prediction models
Major Task 3: Develop clinical risk prediction models

Specific Aim 1 has not started as of this report, pending OHRO approvals. Hartman and colleagues have, however, made progress in developing the methodology for identifying melanoma cases within the VA system.

Briefly, Hartman and colleagues initially tested methodology similar to *Asgari MM et al, Prognostic factors and survival in acral lentiginous melanoma, BJD 177:428-435, 2017*. A trial test for identifying acral lentiginous melanoma (ALM) cases was conducted using ICD-O-3 codes from pathology reports accessed through the VA Corporate Data Warehouse. Note this trial test run was conducted under a separate, institution only IRB while we are developing and finalizing the protocol for this project.

ICD03 codes 8744/2 (ALM in situ), 8744/3 (ALM), and 8745/3 (Melanoma, Acral Lentiginous desmoplastic or amelanotic) can be utilized to identify acral melanoma cases (See Appendix 4). To identify uveal and mucosal melanoma cases, will have to review possible cases as 'disease site' might be listed in a separate field in the database from the ICD-O-3 codes. Thus, using only ICD-O-3 codes may miss a sizeable percentage of reports.

A second approach to identifying cases is also being tested, to develop natural language processing (NLP) and use NLP on reports themselves to identify sites. For the NLP annotations, the team is going to pull all melanoma reports, identified by histology ICD morphology code, and then will use NLP to annotate the site. Any ICD morphology code with the word melanoma is included, except four listings were removed that were dysplastic nevus or atypical melanocytic hyperplasia. In the NLP algorithm, we will annotate whether a melanoma is present or not as a confirmatory step. All of the pathology reports identified will need to be reviewed by a dermatologist, similar to Asgari MM BJD 2017.

The team will refine and finalize the case-identification approach to be utilized upon OHRO approval to start this team science project. Case-identification approaches will be harmonized across the VA and MGB sites.

Specific Aim 2: Integrate germline genetic information on rare melanoma susceptibility loci and additional environmental information from MVP into models developed in Aim 1 to assess improvements in performance of risk prediction models.
Major Task 1: Identify study participants from VA MVP
Major Task 2: Perform GWAS to identify SNPs associated with each of the rare melanoma subtypes
Major Task 3: Add genetic data to risk prediction models

Specific Aim 2 has not started as of this report, pending OHRO approvals.

Specific Aim 3a: Validate rare melanoma risk assessment tools that incorporate polygenic risk score with clinical risk factors in an independent civilian cohort (Mass General Brigham Research Patient Data Registry, RPDR).
Major Task 1: Identify study participants in RPDR
Major Task 2: Test clinical risk prediction model in RPDR cohort
Major Task 3: Test integrated genetic and clinical risk prediction model in RPDR cohort

Specific Aim 3a has not started as of this report, pending OHRO approvals. However, Semenov and colleagues have made progress with obtaining access to cancer databases within MGB for future identification of study participants for this Team Science project. The team is coordinating with the VA sites for alignment with the method for identification using ICD-O-3 codes, melanoma location, and morphology as outlined in Appendix 4.

In addition, they have made progress, through a separate site-specific IRB, in developing methodologies for identifying projected cancer cases from MGB RPDP and a large retrospective cohort, the TriNetX Diamond Network (Tang K et al, JAMA Dermatology 2022 and Tang K et al, JNCI 2022). TriNetX is a possible alternative large retrospective cohort to identify rare melanoma cases, should the number of cases in the MGB RPDR prove insufficient as we conduct this current study.

- Tang K, et al., Association of cutaneous immune-related adverse events with increased survival in patients treated with anti-PD1 and anti-PD-L1 therapy. JAMA Dermatology 158(2):189-193, February 2022
- Tang K, Tiu BC, Wan G, Zhang S, Nguyen N, Leung B, Gusev A, Reynolds KL, Kwatra SG, Semenov YR. Pre-Existing Autoimmune Disease and Mortality in Patients Treated with Anti-PD-1 and Anti-PD-L1 Therapy. J Natl Cancer Inst. 2022 Aug 8;114(8):1200-1202. doi: 10.1093/jnci/djac046. PMID: 35188215; PMCID: PMC9360452

For a separate study, Semenov and team have developed methods that can identify cutaneous immune related adverse events in immunotherapy at a high level of accuracy using ICD codes(Chen 2022). This process can be effectively applied to TriNetX cohort for identification of rare melanoma study participants. Semenov and colleagues also published 2 studies which detail how machine learning algorithms predicted melanoma recurrence in an MGB cohort using predefined clinical and histopathologic characteristics. (Wan et al, JAAD International 2022 and Wan et al, NPJ Precision Oncology 2022). This pipeline can be effectively applied in the future to genetic data to generate risk prediction models for this Team Science project.

- Wenxin Chen, Guihong Wan, Nga Nguyen, Bonnie Leung, Jun Wen, Michael R. Collier, Shawn G Kwatra, Yevgeniy R. Semenov, Identification of Cutaneous Immune-Related Adverse Events by International Classification of Diseases Codes and Medication Administration, JAAD International. 2022.
- Guihong Wan, Bonnie Leung, Nga Nguyen, Mia S. DeSimone, Feng Liu, Min Seok Choi, Diane Ho, Valerie Laucks, Stacey Duey, Ryan Sullivan, Genevieve Boland, Nicole LeBoeuf, David Liu, Alexander Gusev, Shawn G. Kwatra, Peter K. Sorger, Kun-Hsing Yu, Yevgeniy R. Semenov, The Impact of Stage-Related Features in Melanoma Recurrence Prediction: A Machine Learning Approach. *JAAD International*. 2022.
- Wan GC, Nguyen N, Liu F, DeSimone MS, Leung BW, Rajeh A, Collier MR, Choi MS, Amadife M, Tang K, Zhang S, Phillipps P, Jairath R, Alexander NA, Hua Y, Jiao M, Chen W, Ho D, Lacks V, Duey S, Németh IB, Marko-Varga G, Valdés JG, Liu D, Boland G, Gusev A, Sorger PK, Yu KH, Semenov YR. Prediction of Early-Stage Melanoma Recurrence Using Clinical and Histopathologic Features. NPJ Precision Oncology, *provisionally accepted*, September 2022.

Specific Aim 3b:
Specific Aim 3b has not started as of this report, pending OHRO approvals.

What opportunities for training and professional development has the project provided?

Site 1: MRA
MRA's Rachel Fischer post-doctoral fellow on this project has received training in understanding the management of a multi-site team award and in the development of an IRB protocol. In addition, Rachel has mentored two post-baccalaureate interns: Isabel Ryan, BS and Nicolas Starink, BS (an MPH candidate). Rachel, Isabel and Nico have participated in professional development through the Health Research Alliance and its ongoing peer 'Registry and Biobank' working group semi-annual meetings. This professional development has allowed for refinement of the MRA Rare Melanoma Registry that is key to Aim 3b of this proposal. Dr. Fischer attended ASCO (June 2022) with MRA senior scientific and leadership team and had the opportunity to engage with several industry partners interested in the Rare Melanoma Registry. Dr. Fischer will represent MRA and present a poster (on an unrelated project) at the upcoming Society for Melanoma Research Conference (October 2022). Both interns Isabel and Nico attending weekly science team meetings and weekly full staff meetings. As a part of each of their respective internship projects, each made a formal presentation to MRA all staff about their internship projects and progress made – both related to rare melanomas. Isabel has been key to programming the surveys for the forthcoming Rare Registry, while Nico has conducted a landscape analysis about the published literature on risk factors for acral, mucosal, and uveal melanomas.

Site 2: Ocean State
Rachel Lim, BS (medical student): Rachel Lim conducted an in-depth literature review to identify putative risk factors for rare melanomas that should be included in our data dictionary and future analysis of cases within the VA cohort. Rachel attends weekly meetings with Dr. Weinstock.

Site 3: Mass General Brigham
Bonnie Leung, BS; Nga Nguyen, MD, MPH; and Ahmad Rajeh, MS attend weekly team melanoma meetings. They manage cancer registry data at MGB and define variables from the registry that can be utilized in the future for the data dictionary for rare melanoma identification. Bonnie has attended the Society of Investigative Dermatology (May 2022) and published articles (Wenxin 2022) (Wan 2022) with applicable methodologies to this project as outlined in Aim 3 above.

Site 4: Boston VA Research Institute
Nicole Trepanowski – Nicole Trepanowski has conducted an in-depth literature review to examine and identify nomenclature for identifying relevant rare melanoma cases for case ascertainment. She also has reviewed VA pathology data to identify data categories relevant to case identification. Nicole attends weekly lab meetings with Drs. Hartman and Fillmore.
Rebecca Hartman – Dr. Hartman has worked closely with bioinformatics experts at VA Boston to understand the pathology database at the VA to identify relevant melanoma cases. She has worked closely with this team to organize the reports and design an NLP annotation schema to create an NLP algorithm to identify relevant cases. Through this process, she has gained additional knowledge about NLP and the VA dataset. She attends the aforementioned weekly lab meetings.
Nathanael Fillmore – Dr. Fillmore has worked closely with Dr. Hartman and Nicole on case ascertainment and through this work, has expanded his content knowledge about melanoma staging and melanoma pathology reports. He also attends the aforementioned weekly lab meetings.

Site 5: Harvard T.H. Chan School of Public Health
n/a during this reporting period.

How were the results disseminated to communities of interest?

Nothing to report. The primary components of this project have not started as we await OHRO approval.

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

As we make progress identifying case-control cohorts and developing the risk prediction algorithms in Aim 1, we intend to submit team abstract(s) to relevant conferences and to quickly submit our preliminary cohort analyses for publication. Concurrent with presentation at a conference or publication, the Team intends to hold a public facing 'Research Update' webinar to update large cohorts of several hundred active patient advocates from the acral, mucosal, and uveal melanoma communities that are following the work of the Team award.

4. **IMPACT:**

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report. The primary components of this project have not started as we await OHRO approval.

What was the impact on other disciplines?

Nothing to report. The primary components of this project have not started as we await OHRO approval.

What was the impact on technology transfer?

Nothing to report. The primary components of this project have not started as we await OHRO approval.

What was the impact on society beyond science and technology?

Nothing to report. The primary components of this project have not started as we await OHRO approval.

5. CHANGES/PROBLEMS:

The only challenges to report are the delays in harmonizing IRB protocols and approvals across all sites. IRBs have been approved at each site (except site 5, which is not applicable). We await OHRO approval to move forward with the project.

Actual or anticipated problems or delays and actions or plans to resolve them

The overall project is delayed as we await OHRO approval. The team is poised and ready to go to make rapid progress on case-control identification and begin risk algorithm development once approvals received.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report. Awaiting OHRO approvals to start.

Significant changes in use or care of vertebrate animals
Significant changes in use of biohazards and/or select agents

N/A

6. PRODUCTS:

- **Publications, conference papers, and presentations**
  Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Site 1: Melanoma Research Alliance (MRA)
Name: Marc Hurlbert, Ph.D.
Project role: PI
ORCID ID: 0000-0003-3301-3572
Nearest person month worked: 1.2
Contribution to Project: Dr. Hurlbert has led the team calls and steered the IRB and OHRO approval processes.
Funding Support: MRA general funds and this award (no funds yet drawn down from CDMRP).

Name: Rachel Fischer, Ph.D.
Project role: Post-Doctoral Fellow
ORCID ID: 0000-0003-4123-800X
Nearest person month worked: 0.6
Contribution to Project: Dr. Fischer has led the team calls and steered the IRB and OHRO approval processes.
Funding Support: MRA general funds and this award (no funds yet drawn down from CDMRP).

Name: Kris'tina Ackerman
Project role: Administrative Assistant
ORCID ID: n/a
Nearest person month worked: 0.6
Contribution to Project: Ms. Ackerman has managed administration of subawards, invoice management and payments to MGB and Harvard.
Funding Support: MRA general funds.

What individuals have worked on the project? (continued)

Site 1: Melanoma Research Alliance (MRA) (continued)
Name: Isabel Ryan, B.S.
Project role: Science Intern
ORCID ID: none
Nearest person month worked: 1.2
Contribution to Project: Ms. Ryan helped develop the surveys to support IRB protocol for the Rare Melanoma Registry core protocol.
Funding Support: MRA general funds.

Name: Nicolas Starink, B.S.
Project role: Science Intern
ORCID ID: none
Nearest person month worked: 1.2
Contribution to Project: Mr. Starink conducted a literature review on the putative risk factors for each of the rare melanoma subtypes: acral, mucosal, and uveal.
Funding Support: MRA general funds.

Site 2: Ocean State Research Institute
Name: Martin Weinstock, M.D., Ph.D.
Project role: Partnering PI
ORCID ID: 0000-0001-5445-142X
Nearest person month worked: 1.2
Contribution to Project: Led the VA team sites; drafted and finalized IRB protocol for the VA sites, helps lead overall team across sites.
Funding Support: N/A (this award)

Name: Rachel K. Lim
Project role: Student
ORCID ID: 0000-0001-7711-3095
Nearest person month worked: 1.2
Contribution to Project: Rachel performed a literature review on melanoma risk factors and coordinated with the BVARI and MGB sites in case identification strategies and developing the draft data dictionary.
Funding Support: None (medical student)

Site 3: Massachusetts General Brigham (MGB)
Name: Maryam Asgari, MD, MPH
Project role: Partnering PI
ORCID ID: none
Nearest person month worked: 0.1
Contribution to Project: Dr. Asgari has helped lead the overall team across sites; and serves as a mentor to both Hartman (BVARI) and Semenov (MGB).
Funding Support: N/A (this award)

What individuals have worked on the project? (continued)

Site 3: Massachusetts General Brigham (MGB) (continued)
Name: Yevgeniy ('Eugene') Semenov, MD, MA
Project role: Early-stage Investigator / Co-PI
ORCID ID: 0000-0002-7387-3094
Nearest person month worked: 0.5
Contribution to Project: Led MGB team and coordinated with MRA/VA team for alignment of factors for identification of study participants.
Funding Support: N/A (this award)

Site 4: Boston VA Research Institute
Name: J. Michael Gaziano
Project role: Co-Investigator
ORCID ID: 0000-0002-5384-9767
Nearest person month worked: 0
Contribution to Project: Dr. Gaziano has provided expertise on the VA database and pathology domains.
Funding Support: Other awards and clinical and administrative duties.

Name: Rebecca Hartman, MD, MPH
Project role: Early-stage Investigator
ORCID ID: 0000-0001-5559-9100
Nearest person month worked: 0
Contribution to Project: Dr. Hartman has provided content expertise on melanoma pathology report structure and melanoma staging and case identification via various methods (clinical ICD codes, ICD pathology codes, and NLP annotation). Dr. Hartman is now annotating pathology reports for case identification via NLP.
Funding Support: Other awards and clinical duties.

Name: Nathanael Fillmore, PhD
Project role: Collaborator
ORCID ID: 0000-0002-8058-3423
Nearest person month worked: 0
Contribution to Project: Dr. Fillmore has provided expertise on NLP as well as the VA database and pathology domains.
Funding Support: Other awards.

Name: Kelly Cho, PhD, MPH
Project role: Collaborator
ORCID ID: 0000-0003-1727-7076
Nearest person month worked: 0
Contribution to Project: Dr. Cho has provided expertise on the VA database and pathology domains.
Funding Support: Other awards.

What individuals have worked on the project? (continued)

Site 4: Boston VA Research Institute (continued)
Name: Nicole Trepanowski, BA
Project role: Fellow
ORCID ID: 0000-0001-5885-1009
Nearest person month worked: 0
Contribution to Project: Nicole performed a literature review on melanoma case identification strategies, including clinical ICD codes, pathology ICD codes, and SNOMED codes. She also reviewed VA melanoma pathology reports to identify domains that can assist with case identification.
Funding Support: None (medical student).

Site 5: Harvard T.H. Chan School of Public Health
Name: Peter Kraft
Project role: Co-Investigator
ORCID ID: 0000-00002-4472-8103
Nearest person month worked: 0.6
Contribution to Project: Dr. Kraft serves as a co-investigator and an advisor to the Team project. He has helped the team begin to think about strategies for Aim 2, the integration of germline genetic data to the clinical and environmental risk factors that will be identified in Aim 1. He participates in meetings of the entire team and provided guidance to Hurlbert, Semenov and Hartman.
Funding Support: N/A (this award)

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Hurlbert and Levy et al received the CDMRP Rare Cancer Research Program, Resource Community Development Award, entitled *Building a Community for Patients with Acral Melanoma*, from 8/1/2022 – 7/31/2025 [no budgetary overlap].

Semenov received the Dermatology Foundation Career Development Award (CDA), entitled *Predictive Modeling of Cutaneous Immunotherapy Toxicities*, 7/1/2022 – 6/30/2025 [no overlap].

Hartman has received the VA Career Development Award; pending IRB approval, in the 'Just in Time' phase. [no overlap]

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

Summary:

We have made progress assembling this multi-site Team focused on identifying risk factors for rare melanoma subtypes in a VA case-control cohort, which will be tested in two civilian case-control cohorts. We have assembled an external patient and expert advisory panel over the first year of the project. Both the VA and MGB teams have developed methodologies that will be used for identifying cases of rare melanomas. Briefly, the team is going to pull all melanoma reports, identified by histology ICD morphology code, and then will use NLP to annotate the anatomical site of melanoma. The team has not yet pulled the cases or controls for this study as we do not have OHRO approval to start the project. The biggest challenge in Year 1 has been to harmonize IRB protocol across sites, and to secure OHRO approval. Once the team receives OHRO approval, we are poised to make rapid progress on this Team award and advance knowledge about potential risk factors for rare melanoma subtypes including acral, mucosal, and uveal melanoma.

Appendices

Appendix 1 – Non-key personnel bios or biographical sketches (Joan Levy, Isabel Ryan, Nico Starink) (Rachel Lim) (Nicole Trepanowski)(Nga Nguyen, Bonnie Leung, Ahmad Rajeh)

Appendix 2 – Advisory Board Biographies – Patient and Researcher Advisory Board

Appendix 3 – Working Data Dictionary and Risk Factors List

Appendix 4 – ICD-O-3 codes in pathology reports

Appendix 1 – Non-key personnel biographies

- **Site 1: MRA** - Joan Levy, Isabel Ryan, Nico Starink
- **Site 2: Providence VA -** Rachel Lim
- **Site 3: BVARI -** Nicole Trepanowski
- **Site 4: MGB –** Nga Nguyen, Bonnie Leung, Ahmad Rajeh

Site 1: MRA - Joan Levy, Isabel Ryan, Nico Starink

Joan Levy, PhD, serves as the Senior Director of Special Projects for the Melanoma Research Alliance. In this role she is responsible for building and leading a drug and target discovery and validation program for acral melanoma and other rare melanomas. Joan has more than 30 years of experience in oncology research in academic, pharmaceutical, and disease foundation settings with extensive knowledge spanning from therapeutic target identification and preclinical drug screening approaches to driving the results into clinical studies.

Isabel Ryan, BA, is a Science Intern at the Melanoma Research Alliance working in several aspects of the RARE Melanoma Registry that is necessary for Aim 3b of this project. Isabel joined MRA in 2021 for a one-year internship following her graduation with a BA in neuroscience and creative writing from Washington and Lee University.

Nico Starink, BS, is a Science Intern at the Melanoma Research Alliance working in several aspects of the RARE Melanoma Registry that is necessary for Aim 3b of this project. Nico is a candidate in the MPH, Global Health Policy program at The George Washington University – Milken Institute School of Public Health. Nico joined MRA during his master's education program. He holds a BS in Global Health & Economics from The University of British Columbia.

Site 2: Providence VA - Rachel Lim

Rachel Lim, BA, is medical student at The Warren Alpert Medical School of Brown University. Rachel holds a BA from Brown University in a double major in Economics and Biology. She was instrumental in identifying risk factors for rare melanomas in the published literature.

Site 3: BVARI - Nicole Trepanowski

Nicole Trepanowski, BS, is a fourth-year medical student at the Boston University School of Medicine. Nicole holds a BS in biochemistry from Northeastern University. Nicole has been instrumental in developing methodologies for case-identification for rare melanomas in the VA cancer registry system.

Site 4: MGB – Nga Nguyen, Bonnie Leung, Ahmad Rajeh

Nga Nguyen, MD, MPH is a resident physician at SUNY Upstate Medical University. She received her BS in chemical engineering from North Carolina State University, MD from University of North Carolina at Chapel Hill, and MPH from the UNC Gillings School of Public Health. She has previously worked as an engineer in the pharmaceutical industry and was a research fellow for the Semenov Dermatology Clinical Informatics Laboratory. Her research is focused on machine learning and healthcare advances, particularly within the dermatologic space.

Bonnie Leung, BS is a medical student at University of Texas Southwestern. She received her BS in finance from the Wharton School at the University of Pennsylvania. She has worked previously in the financial services industry. During medical school she has undertook a longitudinal research fellow in the Semenov Dermatology Clinical Informatics Laboratory at Harvard Medical School.

Ahmad Rajeh, M.S., is a medical student at the University of Missouri – Columbia and a research fellow at MGH in the Semenov Dermatology Clinical Informatics Laboratory. He received his B.S. in Computer Science and master's in computational biology from Saint Louis University. He is interested in driving genomic medicine in the field of dermatology.

Appendix 2 – Advisory Board Biographies – Patient and Researcher Advisory Board

Christopher C., Patient Advisor – Chris is a patient living with acral melanoma. He is an advocate for raising awareness about melanoma in Black and African American populations, as well as advocate for health equity and access to care for all cancer patients.

Amy J., Patient Advisor – Amy is a patient living with acral melanoma. She is an active advocate in the melanoma, pancreatic cancer and other communities. Amy is passionate about advancing research, especially into rare cancer subtypes without many treatment options.

James M., Patient Advisor – James is a patient living with uveal melanoma and a veteran. James is an advocate for advancing research on uveal melanoma. He is also an avid advocate for the study of rare cancers among the veteran population.

Teresa M., Patient Advisor/Caregiver– Teresa is a caregiver for a patient living with uveal melanoma. She is passionate about advancing research on uveal melanoma and in providing support and education for family members and caregivers affected when a loved one faces a rare cancer diagnosis.

Jonathan Swingle, Patient Advisor – Jonathan is a patient living with mucosal melanoma for >10 years. Jonathan is passionate about advancing population studies and research on mucosal melanoma. He is also passionate about advancing research on 'long term survivors' that have lived much longer than peers diagnosed with similar stage of an advanced cancer diagnosis.

Richard Carvajal, MD; Columbia University Herbert Irving Comprehensive Cancer Center – Dr. Carvajal is an oncologist and physician-scientist. He is expert in melanoma, with a particular research and clinical emphasis on helping patients with rare melanomas. He leads an international academic registry focused on uveal melanoma and serves as a lead advisor on two direct-to-patient registries: one focused on uveal melanoma, and the MRA registry focused on acral and mucosal melanoma.

Priyadharsini Nagarajan, MD, PhD; University of Texas MD Anderson Cancer Center – Dr. Nagarajan is a Dermatopathologist and clinician scientist. Her primary research interests include advancing research on rare melanoma subtypes, with a particular expertise on mucosal melanoma.

Appendix 3 – Working Draft Data Dictionary and Risk Factors List

Data Dictionary - CDMRP Team Science Award [ME200118 - Risk Prediction Models for Rare Melanomas]

Patient Characteristics

Demographics

Age
Sex (assigned at birth)
Gender
Race

Skin color or Fitzpatrick skin type
Ethnicity
Rurality (Highly rural, rural, urban, unknown)
Region (continental, Midwest, north Atlantic, pacific, southeast)
Income ($0-$24,999; $25,000-$74,999; >=$75,000)
Education (HS or less, any college, beyond college, advanced degree)
Eye Color
SPT
Military History (Air Force, Army, Coast Guard, Marine Corps, Navy, Space Force)
Conflict (Korean, Vietnam, Persian Gulf War, World War II, Other)
Years of Active Service (median, IQR or mean, SD)
Age of melanoma diagnosis
Height
Weight
BMI
Vital status
Date of death
Personal history of cancer
Personal history of melanoma
Family history of cancer
Family history of melanoma

Tumor Characteristics (see Swetter, JAAD 2019;80:208-50

Type of melanoma (acral, mucosal, uveal)
Histologic subtype (ALM, NM, SSM, LMM)
Anatomical site
Acral - Upper limb and dorsal v prone
Uveal
Acral - Lower Limb dorsal v prone
Mucosal
Acral - Subungual
Macroscopic satellites
Clinical photograph
TNM classifications at presentation
TNM classifications - FINAL
Size of specimen (<1mm, >=1, unknown)
Breslow depth, nearest 0.1mm
Ulceration
Dermal mitotic rate
Lymphovascular invasion
Perineural invasion
Tumor infiltrating lymphocytes
Regression
Associated precursor nevus
Peripheral and deep margin status
Microsatellitosis
Extent of disease at presentation (in situ, localized, regional/distant)
Tumor mutation (BRAF, etc.) status

Clinical Management Characteristics (see Asgari 2017 Br J Derm)

Medical comorbidities (Charlson, NCI Comorbidity Index)
Immune status (HIV, organ transplant, immune suppression)
Menopausal status
Pregnancy history
Medication use (photosensitizers, immunosuppressants, dopamine agonists, hormone replacement therapy)
Inflammatory disease
STD history (e.g. HPV)
Wound and injury history
Tumor stage
Tumor treatments
Lymph node exploration (Yes: negative; Yes: positive; Not done; Unknown)
Radiation (Yes, No) (To site of primary, regional lymph nodes metastasis or sites of distant metastasis and gamma knife surgery in brain)
Vaccine therapy (Yes, No)
Chemotherapy (Yes, No)
Targeted therapy (BRAF/MEK) (Yes, No)
Immunotherapy (Yes, No)

Adverse events (was the therapy stopped due to severity of side effects)?
Clinical trial

Environmental Characteristics	
Occupational (service branch exposures)	(e.g., pilot, welder, etc.)
Agent orange exposure	
Alcohol use history	(Never, Former, Current)
Chemical exposure	(agent orange, asbestos, chemical other)
Smoking history	(Never, Former, Current)
Tobacco history	(Never, Former, Current)
Personal history of severe sunburns	(Yes/No)
UV / sun exposure (Would try to include something about 'overall sun exposure', use of sunscreen. Contributory in conjunctival melanoma and to a smaller extent in acral melanomas developing on the dorsal aspect.)	
Medication exposure	(Photosensitizers, dopamine agonists)
Surgical history	(Prior conjunctival surgery)
Personal history	(choroidal nevus, tumor thickness, subretinal fibrosis, etc.)
Family history	NMSC, melanoma, ocular melanoma, atypical mole and melanoma syndrome
Genomic Characteristics	
Genetic Testing for Inherited Cancer Risk	
Germline mutations	ACD, ATM, BAP1, BRCA1, BRCA2, CDKN2A, CDK4, CHEK2, MDM2, MITF1, POT1, PTEN, TERT, TP53, XP, other
Tumor Biomarker Testing	BRAF, NRAS, NF1, KIT, GNAQ/GNA11, other
Somatic mutations	
Copy number alterations	
Deletions	

Appendix 4 – ICD03 Morphology Codes

SNOMED_Morphology	Morphology	Count_Morph
87222	1-LENTIGO MALIGNA	3
663049	663049	5
87202	87202	28
87203	87203	8
87442	ACRAL LENTIGINOUS MELANOMA, IN	3
87443	ACRAL LENTIGINOUS MELANOMA, MA	9
87443	ACRAL LENTIGINOUS MELANOMA,MAL	2
87303	AMELANOTIC MELANOMA	91
87306	AMELANOTIC MELANOMA, METASTATI	5
87223	BALLOON CELL MELANOMA	9
87668	BORDERLINE FOR IN SITU MELANOM	1
87453DM	DESMOPLASTIC MELANOMA	3
87453	DESMOPLASTIC MELANOMA, MALIGNA	2
87700	EPITHELIOID AND SPINDLE CELL N	420
87713	EPITHELIOID CELL MELANOMA	17
663036	INTRAEPITHELIAL MELANOCYTIC NE	26
663037	INVASIVE MELANOCYTIC NEOPLASIA	120
87423	LENTIGO MALIGNA	8
87323	LENTIGO MALIGNA MELANOMA	43
87423	LENTIGO MALIGNA MELANOMA	192
87423A	LENTIGO MALIGNA MELANOMA	5
87423	LENTIGO MALIGNANT MELANOMA	281
87203	MALIGNANT MELANOMA	53707
87613	MALIGNANT MELANOMA IN GIANT PI	116
87423	MALIGNANT MELANOMA IN HUTCHINS	2064
87403	MALIGNANT MELANOMA IN JUNCTION	210
87413	MALIGNANT MELANOMA IN PRECANCE	193
523029	MALIGNANT MELANOMA IN SITU	381
525001	MALIGNANT MELANOMA IN SITU	40
631029	MALIGNANT MELANOMA IN SITU	3
87201	MALIGNANT MELANOMA IN SITU	573
87202	MALIGNANT MELANOMA IN SITU	325

87212	MALIGNANT MELANOMA IN SITU	5
87402	MALIGNANT MELANOMA IN SITU/JUN	146
87202	MALIGNANT MELANOMA IN-SITU	440
87203A	MALIGNANT MELANOMA IN-SITU	417
87282	MALIGNANT MELANOMA IN-SITU	237
87413	MALIGNANT MELANOMA IN-SITU	140
AP53914	MALIGNANT MELANOMA IN-SITU	183
87202	MALIGNANT MELANOMA, CARCINOMA	34
87202	Malignant Melanoma, In situ	240
87202	MALIGNANT MELANOMA, IN-SITU	598
87206	MALIGNANT MELANOMA, METASTATIC	447
8720602	MALIGNANT MELANOMA, METASTATIC	5
87206	MALIGNANT MELANOMA, METASTIC	1
87207	MALIGNANT MELANOMA, RECURRENT	4
87233	MALIGNANT MELANOMA, REGRESSING	2
87209	malignant melanoma, uncertain	13
87233	MALIGNANT MELANOMA,REGRESSING	2
5200159	MELANOMA	20
57212	MELANOMA IN SITU	334
636X014	MELANOMA IN SITU	214
66892	MELANOMA IN SITU	97
693M112	MELANOMA IN SITU	13
6950056	MELANOMA IN SITU	66
87202	MELANOMA IN SITU	912
87321	MELANOMA IN SITU	358
87422A	MELANOMA IN SITU	211
87612	MELANOMA IN SITU IN GIANT PIGM	2
5200125	MELANOMA IN SITU, MALIGNANT	97
87202	MELANOMA IN-SITU	1370
87203A	MELANOMA IN-SITU	1686
87209	MELANOMA IN-SITU	24
87273	MELANOMA IN-SITU	521
87700	MELANOMA IN-SITU	712
663049	MELANOMA IN-SITU	541
548015	MELANOMA SUPERFICIAL SPREADING	17
87443	MELANOMA-IN-SITU	7

87453	MELANOMA, ACRAL LENTIGINOUS	1122
YY863	MELANOMA, ACRAL LENTIGINOUS	10
87453	MELANOMA, DESMOPLASTIC MALIGNA	4
87453	MELANOMA, IN SITU	96
87202I	MELANOMA, INVASIVE	32
87206	MELANOMA, MALIGNANT, METASTATI	62
87203	MELANOMA, MALIGNANT, NOS	729
187203	MELANOMA, METASTATIC	16
523031	MELANOMA, METASTATIC	37
87203A	MELANOMA, METASTATIC	86
87206	MELANOMA, METASTATIC	223
87206	MELANOMA, METASTATIC MALIGNANT	122
87203	MELANOMA, NOS	303
87206	MELANOMA,METASTATIC	118
87206	METASTATIC MALIGNANT MELANOMA	508
87206A	METASTATIC MALIGNANT MELANOMA	24
87206	METASTATIC MELANOMA	384
87206	METASTATIC MELANOMA, NOS	28
87726	METASTATIC SPINDLE CELL MELANO	1
87206	METASTIC MELANOMA	26
87473	MINIMAL DEVIATION MELANOMA	9
YY873	MINIMAL DEVIATION MELANOMA	1
87753	MIXED EPITHELIOID AND SPINDLE	5
87213	NODULAR MELANOMA	1055
87212	NODULAR MELANOMA, IN SITU	1
87412	PRECANCEROUS MELANOSIS	509
87412	PRECANCEROUS MELANOSIS/MELANOM	902
87723	SPINDLE CELL MELANOMA	245
87733	SPINDLE CELL MELANOMA, TYPE A	2
87743	SPINDLE CELL MELANOMA, TYPE B	6
87202SP	SPREADING MELANOMA	5
87433	SUPERFICIAL SPREADING MELANOMA	2475