AWARD NUMBER: **W81XWH-20-1-0798**

TITLE: **Improving the Diagnosis of Melanoma and Precursor Lesions Among Veterans: Developing AI Techniques and Teledermatopathology**

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CONTRACTING ORGANIZATION: **University of Washington;**
University of California, Los Angeles

REPORT DATE: SEPTEMBER 2021

TYPE OF REPORT: Annual Progress Report

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
SEPTEMBER 2021	Annual Progress Report	15AUG2020 - 14AUG2021

4. TITLE AND SUBTITLE

Improving the Diagnosis of Melanoma and Precursor Lesions Among Veterans: Developing AI Techniques and Teledermatopathology

5a. CONTRACT NUMBER
W81XWH-20-1-0798

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

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

In year 1, Aim 1 pilot sites and expert dermatopathologists were invited to take part in the teledermatopathology pilot study, as well as submission of a proposal to seek VA approval for a Quality Improvement project. Aim 2 analyses are ongoing, utilizing archived cases of melanocytic skin lesions to develop computer aided tools. Finall IRB approval has been obtained at the Puget Sound VA to create an Aim 3 data repository of melanocytic skin lesions. The scientific work involved in Aims 1-3 will ultimately accelerate our understanding of pathologists' interpretation of melanoma and lead to the development of computer aided tools to improve diagnostic accuracy. The development and implementation of a VA Teledermatopathology system will be a transformative clinical resource to enhance the level of care for VA patients.

15. SUBJECT TERMS					
NONE LISTED					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERS
a. REPORT	b. ABSTRACT	c. THIS PAGE	Unclassified	16	USAMRMC
Unclassified	Unclassified	Unclassified			19b. TELEPHONE NUMBER *(include a code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Our work aims to improve the clinical care provided to our Veterans by improving the reproducibility and accuracy of the diagnosis of melanoma and related melanocytic skin lesions. The project includes three aims: 1) Development of a VA teledermatopathology system that will immediately provide diagnoses of skin biopsies by experienced dermatopathologists; 2) Improvement of our scientific understanding of pathologists' viewing behavior, to guide future implementation of AI, and 3) Usage of AI /machine learning to investigate associations between viewing behaviors and regions of interest. The field has struggled for decades to diagnose skin biopsies based on the image features by human pathologists. We will leverage insights into machine learning and teledermatopathology to improve the diagnosis of melanoma and its precursor lesions, to ultimately improve the clinical care provided to our Veterans.

2. KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

Melanoma, Melanocytic skin lesions, Skin cancer, Artificial intelligence, machine learning, diagnostic accuracy, teledermatopathology, dermatopathology, histopathology, regions of interest, computer-aided detection

3. ACCOMPLISHMENTS: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific Aim 1: Virtual VA dermatopathology consulting network.
Major Task 1: Establish a Teledermatopathology Network System for the VA. Dr. Oliver Chang has identified expert board certified dermatopathologists in the VA system, and is finalizing pilot sites to perform technical preparation of cases (80% completion). The VA IRB has suggested we get this project approved as a Quality Improvement project. The QI project has been signed off by Dr. Chang's Service Line Leader, and is currently on the desk of the Chief of Staff for signature (50% completed). A new scanner and Aperio eSlide manager software upgrade has been funded by the Puget Sound VA and is awaiting acquisition and installation from the VA IT department, and we anticipate it will be installed for use in Fall, 2021 (50% complete). Major Task 2: Develop VA Acquisition System for digitized whole slide images. A research data repository for melanocytic skin lesions has been IRB approved at the Puget Sound VA IRB (100% complete; Aug. 2021), and is additionally being reviewed by the R&D committee.

Specific Aim 2: Analyze Pathologists' viewing behaviors. Major Task 3: Characterize Pathologist Visual Search patterns. Professor Linda Shapiro, along with her graduate students at UW, have received IRB approval at UW/UCLA for all specific Aim 2 projects, involving 240 archived skin biopsy cases of melanocytic lesions. They have calculated time spent on each pathologists' viewport scene, converted tracking data to extract viewing behavior variables, and performed preliminary analyses (100% completed). Ongoing analytic strategy and writing up/submitting results is ongoing (30% completed). Major Task 4: Evaluate pathologist and case characteristics. Dr. Shapiro, along with her graduate students, has merged pathologist and case characteristics from raw data, and performed correlational and ANOVA analyses (100% completed). Ongoing regression analytic strategy and writing up/submitting results is ongoing (30% completed). Major Task 5: Determine relationship between regions pathologists marked and diagnostic accuracy. Dr. Shapiro, along with her graduate students, has extracted the viewports that intersect with the consensus ROI and defined ROI-related variables to assess how pathologists interact with the consensus ROI and how this affects their diagnostic accuracy. (100% completed). Writing up the results is ongoing (30% completed), with the ultimate goal of submitting for publication.

Specific Aim 3: Investigate Associations between viewing behaviors and ROI's. Major Task 6: Develop a ROI classifier. IRB has approved this task through UW/UCLA, using 240 archived M-Path skin biopsy cases, and a classifier is to be developed for detecting regions of interest along with their probabilities in whole slide images of melanoma biopsies using simple features (color histograms and texture histograms. Three factors (Zoom Peaks, Slow Pannings and fixations) are considered to extract pathologists' ROI, to be used as labels to train the classifier – (50% completed). Major Task 7: Use multiple features and advanced classifiers to try to separate consensus ROI's from distractor regions. This work will involve additional cases from the VA, and will be performed in years 2 and 3 of the project (next reporting periods).

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Major activities for Aim 1: Dr. Chang has secured funding from the VA to purchase a new Puget Sound VA digital slide scanner, including the most current Aperio software (eSlide Manager), allowing for efficient case organization and ability to triage/assign cases between VA hospitals and dermatopathologists.

Approval has been initiated at the VA to conduct Aim 1 as a Quality Improvement project. IRB approval has been obtained to develop a Data Repository for melanocytic skin lesions, allowing

for another resource of cases for AI/Machine learning. Final R&D committee review will allow us to begin compiling cases.

Dr. Chang has networked within the VA system to identify VA dermatopathologists willing to serve as experts in the teledermatopathology pilot, as well as VA facilities to provide cases for the teledermatopathology pilot.

Items in process include soliciting bids for hardware upgrades to slide scanners (including the potential for FDA-approved primary diagnostic impression on scanned slides) and acquiring IT/BioMed approval for inter-facility sharing of scanned slides.

Major activities for Aim 2: IRB approval was obtained from UW/UCLA for this aim, and the proposed work is ahead of schedule.

Analysis is underway to **assess pathologists' viewing behaviors** (regions of interest where they look or mark) to support future human-computer centered development of AI/machine learning tools. Preliminary findings are available, although analytic plans are ongoing:

- To characterize pathologists' visual search patterns using data from computer screen viewports (e.g., to use screen data such as location, time stamp, zoom level to characterize their behavior as scanning versus drilling) and assess the accuracy of these search patterns.

- To evaluate the association of the above viewing patterns with pathologist and case **characteristics** (e.g., pathologist characteristics such as clinical experience, fear of malpractice and case characteristics such as type of biopsy, extent of solar elastosis in the lesion)

- To determine the relationship between areas that pathologists indicated as diagnostic regions of interest (ROIs) on whole slide digital images and their diagnostic accuracy.

Major activities for Aim 3: IRB approval was obtained from UW/UCLA to develop a classifier for detecting regions of interest, along with their probabilities in whole slide images (for the 240 M-Path skin biopsy cases).

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist

others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Fatemah Ghezloo is a PhD student in the Department of Computer Science at the University of Washington. She is being mentored by our research team and is working closely with Drs. Shapiro and Elmore to analyze pathologists' viewing behaviors and the associations between viewing behaviors and ROIs, which will culminate into manuscripts that will be submitted to peer reviewed journals.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report at this time.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

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

During the next reporting period, we aim to:

Aim 1 – receive approval from the VA Puget Sound to set up the teledermatopathology service as a Quality Improvement project, create profiles of expert dermatopathologists in Aperio eslide manager web portal, begin digitizing whole slide images, and begin pilot of teledermatopathology interpretations

Aim 2 – complete analyses and drafting of manuscript; submit for publication/conference presentation. This work will improve our understanding of pathologists' viewing behavior and regions on the biopsy images that they identify as regions of interest.

Aim 3 – receive IRB approval at VA Puget Sound to give UW access to the melanocytic lesion data repository through an IRB modification form to the VA Melanocytic Skin Lesion Data Repository, as well as a data use agreement; use multiple features and advanced classifiers to try to separate consensus ROIs from distractor regions; attempt to characterize the ROIs further by using a large set of image features including 75 texture features. We will also report ROIs on the M-Path set of skin biopsy images as relevant to an accurate diagnosis, versus distractor regions that led pathologists to give the wrong diagnosis and compare their features. Ultimately, this work will produce ground truth data that allows us to use machine learning techniques to evaluate the images and develop tools to educate pathologists as to what region is a clinically useful ROI.

4. IMPACT: D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report at this time.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report at this time.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report at this time.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

As described in an email update from Lisa Reisch (UW) to Emma Gentry (DoD) on May 20 and May 26, 2021, our original VA IRB application for this grant was re-worked to suit the preferences of the IRB committee at the Puget Sound VA.

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

None to report

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Rather than including all aims in the IRB application, the VA IRB preferred that we separate the aims into separate IRB approaches. They requested we first receive approval to create a data repository of melanocytic skin lesion cases at the VA Puget Sound (IRB approval received, R&D committee sign-off pending). They requested that we pursue Quality Improvement project approval for the Aim 1 teledermatopathology service (approval pending). They requested UW/UCLA approval ONLY for Aim 2 work, since the cases utilized do not include Veteran cases (approved at UW/UCLA). Finally, they requested we seek approval for Aim 3 work through a modification form to the VA IRB, as well as a data use agreement with Dr. Shapiro's UW team. Given this adjustment to the IRB approval strategy, work on Aim 1 has been slightly delayed. As described in the aforementioned May 2021 email correspondence to Emma Gentry (see Appendix 1), we have focused more of our efforts in Year 1 on Aim 2 work, and are therefore ahead of schedule with that aim. This will afford more time in Year 2 for our research team to complete the goals of Aim 1 (in essence, the order of the aims have been switched to complete the entirety of the project by the end of Year 3).

The SARS-CoV-2 pandemic obviously added unexpected challenges in year 1 of this project. At UCLA we had a hiring freeze and thus have unexpected carryforward funds. At UW, winter quarter release for one of our key personnel was taken by sick leave funding for surgery recovery.
Additionally, due to Covid travel issues, some travel expenses from Year 1 were not used. These remaining year 1 funds will be used to support staffing in Years 2 and 3 to assure we successfully complete all major tasks of this project.

reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

None to report

Significant changes in use or care of vertebrate animals

NA

Significant changes in use of biohazards and/or select agents

NA

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report at this time.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report at this time.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report at this time.

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

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report at this time.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report at this time.

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

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report at this time.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Name: *Fatemeh Ghezloo*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): *0000-0003-3888-2793*
Nearest person month worked: *12*

Contribution to Project: *Ms. Ghezloo has performed work to achieve the goals for Aim2. She has utilized the 240 M-Path skin biopsy cases to create necessary variables and perform relevant analyses. She has also begun analytic work for Aim 2 , and is currently drafting a manuscript to report findings. She has also performed some work toward finding Pathologists' Regions of Interest for Aim3.*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Dr. Elmore has received a new subcontract award from the CDC to study long-COVID; this new award does not impact Dr. Elmore's effort on the DoD project. There are no other changes in support for the co-PIs.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*