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Toward a Miniature Ultrasound Device for Imaging TBI Under PFC Scenarios

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14. ABSTRACT
Tissue pulsatility imaging (TPI) of brain structure -- hence sTPI -- of individual moderate to severe TBI brains can (a) identify the presence of and quantify the spatial extent of epidural and subdural hematomas as well as (b) differentiate those brain injuries from others that arise due to closed-head trauma and from the brains of trauma/non-TBI patients, in a manner comparable to computed tomography (CT) imaging. The focus of our study is to develop and test on civilian patients a field-deployable (tablet-based) ultrasound imaging device for brain structure after moderate to severe TBI. We observed TBI features within sTPI images that correlate with the damage associated with TBI highlighted by corresponding CT or magnetic resonance (MR) images. After 3 years, we expect to deliver a prospectively tested (in the setting of a preclinical study) final sTPI ultrasound-data processing algorithm, deployed on a tablet-based and otherwise standard diagnostic ultrasound system. Aim 1: We are collecting sTPI of brains of moderate to severe TBI patients and of controls. Aim 2: We have made very significant progress in developing sTPI software and deploy on a tablet-based ultrasound system. We use trauma/non-TBI patients as controls.

15. SUBJECT TERMS
Tissue pulsatility imaging, Traumatic Brain Injury, epidural and subdural hematomas, Brain imaging, CT scans, Tablet based diagnostic ultrasound for brain injury.

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1. **Introduction.**

We seek to provide portable technology able to image abnormal brain structure after acute TBI as encountered at and near battlefields that lack on-site CT and MR imaging modalities. Our core technology consists of images of the pulsation of brain tissue: tissue pulsatility imaging (TPI) derived via novel analysis of standard diagnostic ultrasound. Since here we target imaging of abnormal brain structure we call this ‘structural TPI’ or sTPI. We will work with civilian patients with moderate and severe TBI. Successful completion of our proposed work will demonstrate that sTPI images of TBI yield diagnostically useful information comparable to that derived from CT images. Moreover, we will do so using a diagnostic ultrasound system with a form factor of a tablet. Of critical importance, this approach represents novel reinterpretation of standard B-mode diagnostic ultrasound imaging. Specifically, we work with the ultrasound data collected by standard diagnostic ultrasound imaging systems and process that data in a way different than that used to create gray-scale (B-mode) ultrasound images. Therefore, as we emphasize below, our anticipated tablet-based diagnostic ultrasound system can perform basic gray-scale imaging of the body – critical for Focused Assessment with Sonography in Trauma (FAST) analysis of potential intra-abdominal bleeding – as well as structural tissue pulsatility imaging of brain. Moreover, because our approach requires only modification of the software on extant diagnostic ultrasound systems, we anticipate that sTPI algorithms can embody rapidly into whatever portable diagnostic ultrasound imaging system the military targets for its use.

We therefore seek with this proposal to refine (Aim #2) structural tissue pulsatility imaging (sTPI) of moderate to severe TBI using retrospective analysis of images collected from civilian moderate to severe TBI patients (Aim #1) then (2) test prospectively, in a pre-clinical study, our sTPI algorithms deployed in a tablet-based form factor on moderate to severe TBI (Aim #3).

Objective: Tissue pulsatility imaging (TPI) of brain structure – hence sTPI – of individual moderate to severe TBI brains can [a] identify the presence of as well as quantify the spatial extent of epidural and subdural hematomas as well as [b] differentiate those brain injuries from others that arise due to closed-head trauma and from the brains of trauma/non-TBI patients, in a manner comparable to CT imaging.

2. **Keywords.**

Tissue pulsatility imaging, Traumatic Brain Injury, epidural and subdural hematomas, Brain imaging, CT scans, Tablet based diagnostic ultrasound for brain injury.

3. **Accomplishments.**

We first list the major and subtasks of this project. We then use the subtask number so the reader can correlate our description of our accomplishments to the subtask.

SPECIFIC AIM 1	***Timeline (months)***	***Participants***
Major Task 1.1: Collect sTPI of brains of TBI and control patients for retrospective analysis of sTPI algorithm. ***N = 200 TBI & 25 trauma/non-TBI & 50 Stroke*** ***= 275 patients.***	*1-42*	*Neurosurgery;* *Applied Physics Laboratory*
Subtask 1.1: Obtain UW IRB Approval for human studies.	*1-3*	*Neurosurgery*
Subtask 1.2: HRPO Review and Approval for human studies, including an IDE from the FDA by month 12 if necessary.	*4-12*	*Neurosurgery*
Subtask 1.3: enable desktop-based research ultrasound system and clinical ultrasound system. Purchase, setup, and calibrate desktop and clinical ultrasound systems.	*2-4*	*Applied Physics Laboratory*
Subtask 1.4: demonstrate, in vitro, capabilities of ultrasound systems from Subtask 3. Embody within the desktop and clinical systems sTPI software, with devices tested on tissue phantoms.	*3-5*	*Applied Physics Laboratory*
Subtask 1.5: train residents for image collection and interpretation duties.	*5-6*	*Neurosurgery;* *Applied Physics Laboratory*
Subtask 1.6: gather ultrasound and CT data from moderate/severe TBI patients and stroke patients. Collect ultrasound data from civilian patients with moderate to severe brain injury after closed-head trauma of two classes [1] epidural and subdural hemorrhage; [2] other e.g., subarachnoid or intraparenchymal hemorrhage or diffuse brain injury.	*7-42*	*Neurosurgery*
Subtask 71: gather ultrasound and CT data from trauma/non-TBI controls. Collect ultrasound and CT data from civilian patients who have experienced trauma but not TBI.	*7-42*	*Neurosurgery*
Subtask 1.8: produce sTPI images for moderate/severe TBI patients, for stroke patients, and for trauma/non-TBI controls.	*7-42*	*Applied Physics Laboratory*
Milestone 1.1: *local IRB Approval*	*3*	*Neurosurgery*
Milestone 1.2: *HRPO Approval*	*6*	*Neurosurgery*
Milestone 1.3: *production of sTPI images from moderate to severe TBI patients across two classes of damage types, from stroke patients, and from trauma/non-TBI controls.*	*42*	*Neurosurgery;* *Applied Physics Laboratory*
SPECIFIC AIM 2	***Timeline***	***Participants***

	(months)	
Major Task 2.1: Optimize sTPI software	7-42	Neurosurgery; Applied Physics Laboratory
Subtask 2.1: compare sTPI images with clinical CT images for TBI & for stroke patients. Compare, retrospectively and on a patient-by-patient basis, the size, shape, extent and other features of brain damage in sTPI of TBI patients with those in their CT images.	7-42	Neurosurgery; Applied Physics Laboratory
Subtask 2.2: compare sTPI images with clinical CT images for trauma/non-TBI control patients. Compare, retrospectively and on a patient-by-patient basis, the size, shape, extent and other features of brain damage in sTPI of trauma/non-TBI control patients with those in their CT images.	7-42	Neurosurgery; Applied Physics Laboratory
Subtask 2.3: perform retrospective comparison of diagnostic utility of sTPI versus CT of moderate to severe closed TBI. Here we will use the structural information from Subtasks 1 & 2 to differentiate between [1] epidural or subdural bleeds versus [2] other brain damage and versus [3] trauma/non-TBI brain, with CT images as the gold standard.	12-42	Neurosurgery: Applied Physics Laboratory
Subtask 2.4: Amend software as needed to optimize the ability of sTPI to capture diagnostically useful information regarding TBI.	18-42	Applied Physics Laboratory
Milestone 2.1: retrospective demonstration that sTPI of TBI offers diagnostic utility comparable to CT.	42	Neurosurgery; Applied Physics Laboratory
Milestone 2.2: production of optimized sTPI software ready for prospective testing.	42	Applied Physics Laboratory
Major Task 2.2: Deploy final sTPI software on a tablet-based ultrasound system.	36-42	Applied Physics Laboratory
Subtask 2.5: enable final sTPI software on tablet-based system._Purchase, setup, and calibrate final tablet-based ultrasound system.	36-42	Applied Physics Laboratory
Subtask 2.6: demonstrate in vitro the final tablet-based ultrasound system's capabilities. Embody within the final, tablet-based system optimized sTPI software, with device tested on tissue phantoms.	36-42	Applied Physics Laboratory
Milestone 2.3: tablet-based ultrasound system with optimized sTPI software ready for prospective testing.	42	Applied Physics Laboratory
SPECIFIC AIM 3	**Timeline (months)**	**Participants**
Major Task 3.1: Prospective studies of sTPI algorithm deployed on an ultrasound tablet. **N = 50 TBI & 15 trauma/non-TBI = 65**	42-48	Neurosurgery; Applied Physics Laboratory

Subtask 3.1: collect sTPI & CT images from TBI and trauma/non-TBI patients.	*42-48*	*Neurosurgery;* *Applied Physics Laboratory*
Subtask 3.2: compare, prospectively, ability of sTPI to detect epidural or subdural bleeds relative to other TBI sequela, validated with clinical CT.	*42-48*	*Neurosurgery;* *Applied Physics Laboratory*
Subtask 3.3: compare, prospectively, clinical utility of sTPI for epidural or subdural bleeds, validated with clinical CT images.	*42-48*	*Neurosurgery;* *Applied Physics Laboratory*
Subtask 3.4: For patients with brain injury other than epidural or subdural hematomas, produce prospective analysis of clinical utility of sTPI as compared to clinical CT images.	*42-48*	*Neurosurgery;* *Applied Physics Laboratory*
***Milestone 3.1**: Prospective demonstration that analysis of sTPI of TBI patients can differentiate those patients with epidural or subdural bleeds from those with other brain injuries associated with TBI, in a manner comparable to that of CT.*	*48*	*Neurosurgery;* *Applied Physics Laboratory*
***Milestone 3.2:** Prospective demonstration that analysis of sTPI of TBI patients can quantify the structural extent of epidural or subdural bleeds due to TBI, in a manner comparable to that of CT.*	*48*	*Neurosurgery;* *Applied Physics Laboratory*
***Milestone 3.3:** Prospective demonstration that sTPI of TBI patents with brain injury other than epidural or subdural hematomas has diagnostic utility comparable to that of CT.*	*48*	*Neurosurgery;* *Applied Physics Laboratory*
ADMINISTRATIVE	***Timeline (months)***	***Participants***
Major Task 4.1: Delivery of reports	*various*	*Neurosurgery*
Subtask 4.1: produce quarterly reports.	*quarterly*	*Neurosurgery*
Subtask 4.2: produce annual reports.	*annually, yrs 1-2*	*Neurosurgery*
Subtask 4.3: produce final report.	*Year 3*	*Neurosurgery*
***Milestone 4.1:** Production of quarterly reports.*	*quarterly*	*Neurosurgery*
***Milestone 4.2:** Annual reports approved.*	*annually, yrs 1-3*	*Neurosurgery*
***Milestone 4.3:** Final report approved.*	*Year 4*	*Neurosurgery*
Major Task 2.4: FITBIR submission.	*various*	*Neurosurgery*
Subtask 4.4: facilitate FITBIR data submission	*7-36*	*Neurosurgery*
Subtask 4.5: Submit data to FITBIR.	*quarterly*	*Neurosurgery*

Milestone 4.4: *Submission of all data to FITBIR completed.*	*Year 4*	*Neurosurgery*

Major goals and associated accomplishments for the time period covered by this report.

Subtask 1.6: gather ultrasound and CT data from moderate/severe TBI patients …

- We identify an average of ~one patient per day during the five days per week we can perform our study. We lose approximately a third of the patients we identify before we can approach them for reasons that include, primarily, the movement of the patients to the OR, or they die, consistent with the moderate to severe head injuries that we are studying. We successfully consent ~80% of the patients we approach. We have studied ~80% of the patients we have consented, with the drop off due to emergent patient procedures that arose after consent but before we arrived at Harborview to perform the study, or patient/family irritability after we arrive.
- In total, we have collected data from approximately 25% of the patients we identify, without any adverse events or unanticipated problems.
- This last quarter included a partial shutdown (mid-December through early February) while we waited for team members to get vaccinated.

human data	Identified	Approached	Consented	Studied	Data Sets Collected
Total	~350	154	109	83	83
This quarter (16Nov'20 - 15Feb'21)	~40	22	8	5	5

Subtask 1.7: gather ultrasound and CT data from trauma/non-TBI controls and stroke patients…

- We have started to collect data from the controls (two thus far).

Subtask 1.8: produce sTPI images ...

- We have generated such images using a wide range of techniques for all our data sets, with moderate success (some great success versus por results).

Subtask 2.1: compare sTPI images with clinical CT images for TBI patients …

- We have analyzed many of our ultrasound images and offer several representative ones at the end of this document.

Subtask 2.3: perform retrospective comparison of diagnostic utility of sTPI versus CT of moderate to severe closed TBI.

- For a given patient, we have the ability to define within the volume of CT data a plane that plausibly aligns with their ultrasound image plane. With this in hand we have projected the CT image information onto the ultrasound image plane that defines epidural or subdural bleeds, intra- parenchymal bleeds, ventricles (another fluid-filled space) and other anatomical structures. We have mixed results as to whether or not the pulsatility of brain tissue within these different structures differ from one another in a usefully sensitive and specific way, reviewed in the appendix.

Subtask 2.4: Amend software as needed to optimize the ability of sTPI to capture diagnostically useful information regarding TBI.

- This represents an on-going effort as we (a) collect more data and (b) learn more from that collected data and on-going analysis efforts.

Subtask 4.4: facilitate FITBIR data submission.

- We established a FITBIR account and started uploading data.

Opportunities for training and professional development for the time period covered by this report.

Cory Kelly has made quite and now ever-increasing contributions to the interpretation of the images we generate, as they begin to show some promise. He will likely go on to medical school in a year, so these experiences should help inform his eventual clinical practice.

Also, we have engaged several undergraduates into this project, who help in a mentorship scenario with a variety of the secondary efforts – not the detailed analysis that I've put in the hands of our lead scientists.

Results disseminated to communities of interest.

Nothing to report.

Plans for the next reporting period.

- We plan to collect data from as many IPH patients patients, and trauma/non-TBI patients as we can, subject to on-going, but loosening, COVID-19 restrictions (thanks to vaccinations of staff members).
- We will continue our analysis of the data to define at least one plausible sTPI algorithm.

4. **Impact**

What was the impact on the development of the principal discipline(s) of the project?
We can report that our colleagues from neurological surgery, from neurology, from critical care, and from emergency medicine are excited about the possibility of our device. We therefore anticipate that a hand-held device capable of rapidly determining the presence and grade of intracranial bleed will have a profoundly positive impact on the practice of civilian emergency medicine. We also see the possibility of using this device to quickly determine the presence of ischemic versus hemorrhagic stroke: if an ischemic stroke, the on-site medical providers can push drug-based therapies without fear of damaging the hemorrhagic stroke patient.

What was the impact on other disciplines?
We anticipate that we will develop novel algorithms beyond the state of the art tissue pulsatility algorithms in ways specifically applicable to brain. There exist a one group that use tissue pulsatility algorithms to study brain function, for example. We believe our advances will help them.

What was the impact on technology transfer?
We anticipate that, as above, we will develop novel algorithms beyond the state of the art tissue pulsatility algorithms in ways specifically applicable to brain. Commercial opportunities may include direct development of our tablet-based ultrasound system embodying sTPI. Terason, the privately held company from which we have purchased our clinical system and anticipate purchasing our tablet-based system has an interest in this possibility. More broadly, with its anticipated form factor and possibility of measuring brain *function* not just brain *structure*, we have some hope that our device will evolve into what one could call functional tissue pulsatility imaging (or fTPI).

What was the impact on society beyond science and technology?
We anticipate that a hand-held device capable of rapidly identifying and differentiating between different intracranial maladies will help reduce the cost of health care.

5. Changes/Problems

Changes in approach and reasons for change

None, though we are re-considering working with a local start-up company that can help us aim our ultrasound through use of projection of a patient's CT image onto the head of that patient using augmented reality.

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

We have had unseasonably mild winters hence a reduction in TBI, good for the general population, of course but not for our study. Also, COVID-19 spiked this winter (bad, of course) and vaccinations started (good, of course), so we postponed collection of new data until our people received their vaccinations. Note that this delay has not stopped analysis of existing data.

Changes that had a significant impact on expenditures

NA

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

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Significant changes in use or care of human subjects

We added more TBI patients (October 2020) to insure we get enough with intraparenchymal hemorrhage (IPH), either isolated ones (best for modeling) or in combination with other bleeds. We've added ischemic and hemorrhagic stroke patients (November 2020) because some traumatic brain injury can lead to ischemia (if a blood vessel dissects for example) or hemorrhage (if an internal blood vessel bleeds, which mimics IPHs). Finally, we added healthy test subjects (December 2020) to provide additional control data, easier to get and, we anticipate, with the same brain structure as trauma-non-TBI patients.

Significant changes in use or care of vertebrate animals.

NA

Significant changes in use of biohazards and/or select agents

NA

6. **Products**

Publications (journals; book chapters), conference papers, and presentations.

We have signed up for the DoD MHSRS under the topic of ‘point of care ultrasound in the expeditionary environment – from point of injury through (to) ‘out of theater evacuation’.

Websites or other internet sites.

Nothing to report.

Technologies or techniques

[a] an algorithm that corrects for the motion of the transducer relative to the patient’s head; [b] an algorithm that will at least identify the presence of a large lesion that warrants immediate surgery, if not also differentiates between extra-axial and intra-parenchymal bleeds, the former with better clinical outcomes if treated quickly as compared to the latter, a distinction that would drive triage decisions regarding those patients. We remain focused on providing [c] images that a medic could interpret, which would support the algorithm we’ve aimed for since the beginning of this study – a means of directly imaging various bleeds.

Inventions, patent applications, and/or licenses.

The previous section outlines what we anticipate we will try to commercialize, with Terason (our ultrasound device partner.

Other Products.

Nothing to report, yet.

7. **Participants and Other Collaborating Organizations**

Name. **Project Role.** **Nearest Person Month.** **Contribution to project.**	Pierre D. Mourad, PhD PI 33%/month leadership
Name. **Project Role.** **Nearest Person Month.** **Contribution to project.**	John Kucewicz, PhD Scientist/engineer 80%/month data-collection & analysis
Name. **Project Role.** **Nearest Person Month.** **Contribution to project.**	Nina LaPiana Scientist 100%/month Data collection and organization; attending to FITBIR
Name. **Project Role.** **Nearest Person Month.** **Contribution to project.**	Caren Marzban, PhD Mathematician 20%/month Data analysis
Name. **Project Role.** **Nearest Person Month.** **Contribution to project.**	Cory Kelly Scientist 50%/month Identifies candidate patients; interprets images
Name. **Project Role.** **Nearest Person Month.** **Contribution to project.**	Various undergraduates Neurobiology 30%/month Data organization/processing
Name. **Project Role.** **Nearest Person Month.** **Contribution to project.**	Jason Caucutt Research Coordinator 10%/month Informs/consents patients
Name. **Project Role.** **Nearest Person Month.** **Contribution to project.**	Dan Leotta, PhD Scientist/engineer 30%/month data analysis

8. Special Reporting Requirements

We have submitted a Quad Chart to eBRAP.

9. Appendices

Summary of analysis of representative images of intracranial bleeds. We have two approaches to providing help to medics seeking to triage patients after closed head injuries. Here we focus on one that shows the greatest promise for producing images. This approach uses a range of deep learning methods using match pairs of ultrasound-displacement & CT images (6-30 images per patient), with ‘skull’, ‘brain tissue’ and ‘blood’ each identified on the CT image. Here, we represent brain displacement as its Fourier transform, keeping anywhere from 3-7 components with a significant amount of data processing, such as normalizing each cardiac cycle to the same unit length then Fourier transforming each cardiac cycle. For all models, we ‘train’ the model based upon one data set, we ‘test’ the model on a second and independent data set, which leads the refinement of the training. When we feel we have converged on a model, we then validate its results on a third and independent data set. We have worked with various models and have not yet decided which one to use, because the model fails too often, though when it works, it works quite well.

We provide below some examples of successes, mixed successes, and failures.

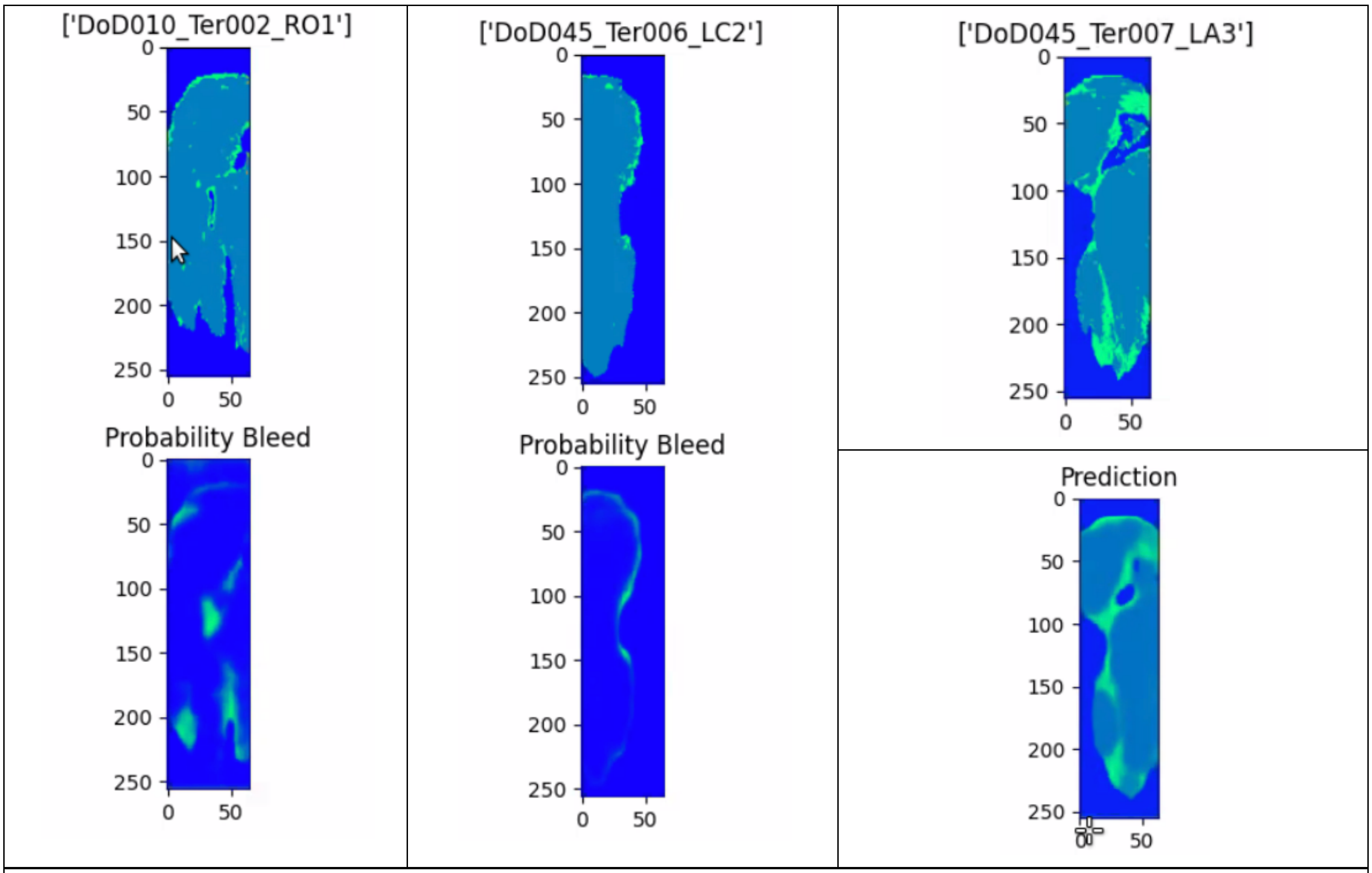

Figure 1 – three examples of success. The top figure shows the CT of a given patient with the color black denoting the extracranial space, the dark green denoting brain tissue and light green denoting blood. The bottom figure shows the prediction of bleed (light color).

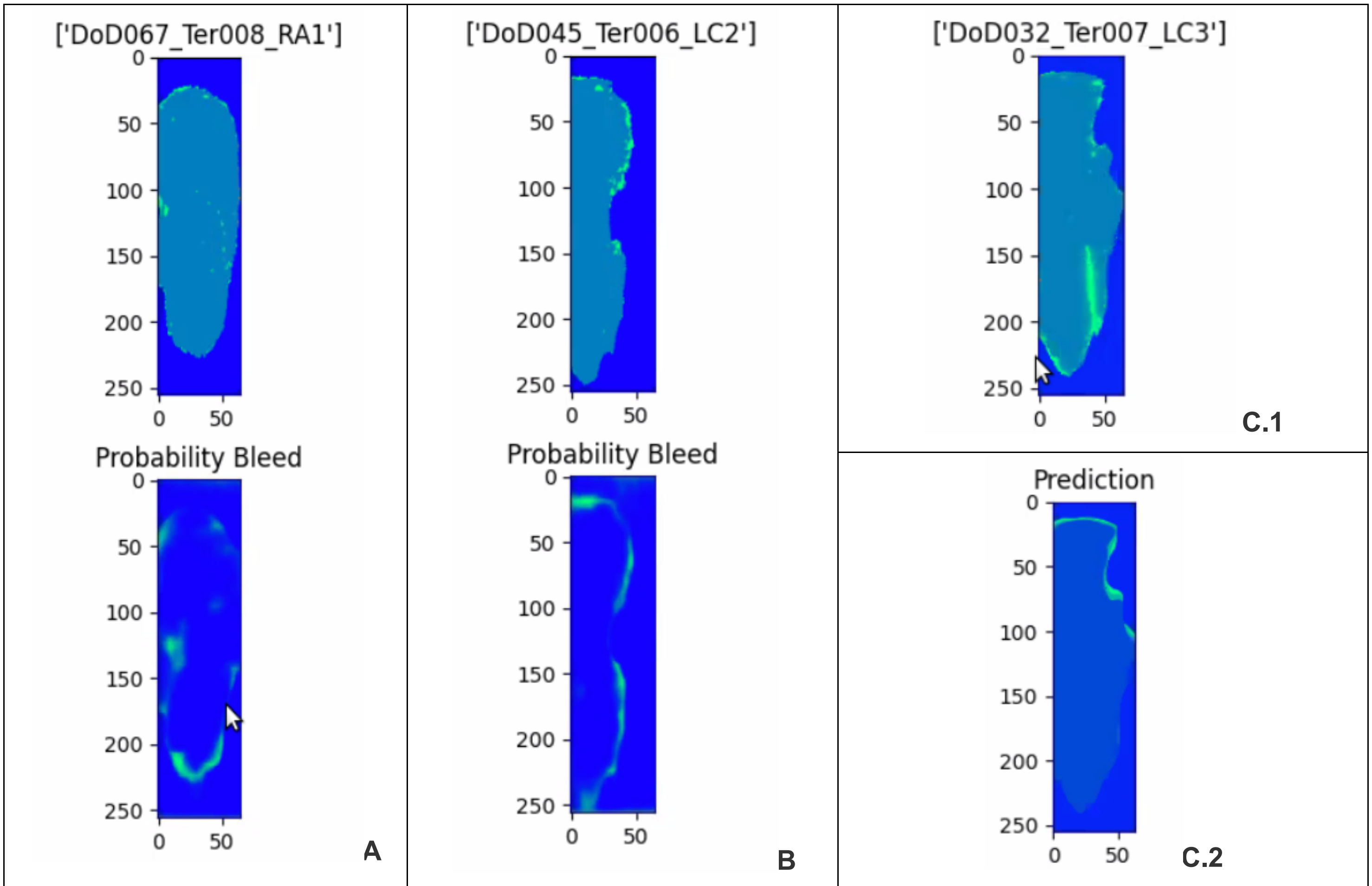

Figure 2 – three examples of mixed success. The figure pairs are the same as in Figure 1. In figure A, the model picks up some of the extra-axial bleed at the top and left-hand side of the CT image while missing a large extra-axial bleed t the bottom of the CT image. In Figure B each of the CT and predicted images highlight substantial extra-axial bleeds but the prediction misses the extra-axial bleed near the bottom of the CT image. In Figure C the prediction over-predicts the extra-axial bleed at the top of the CT image and completely misses the other bleeds.

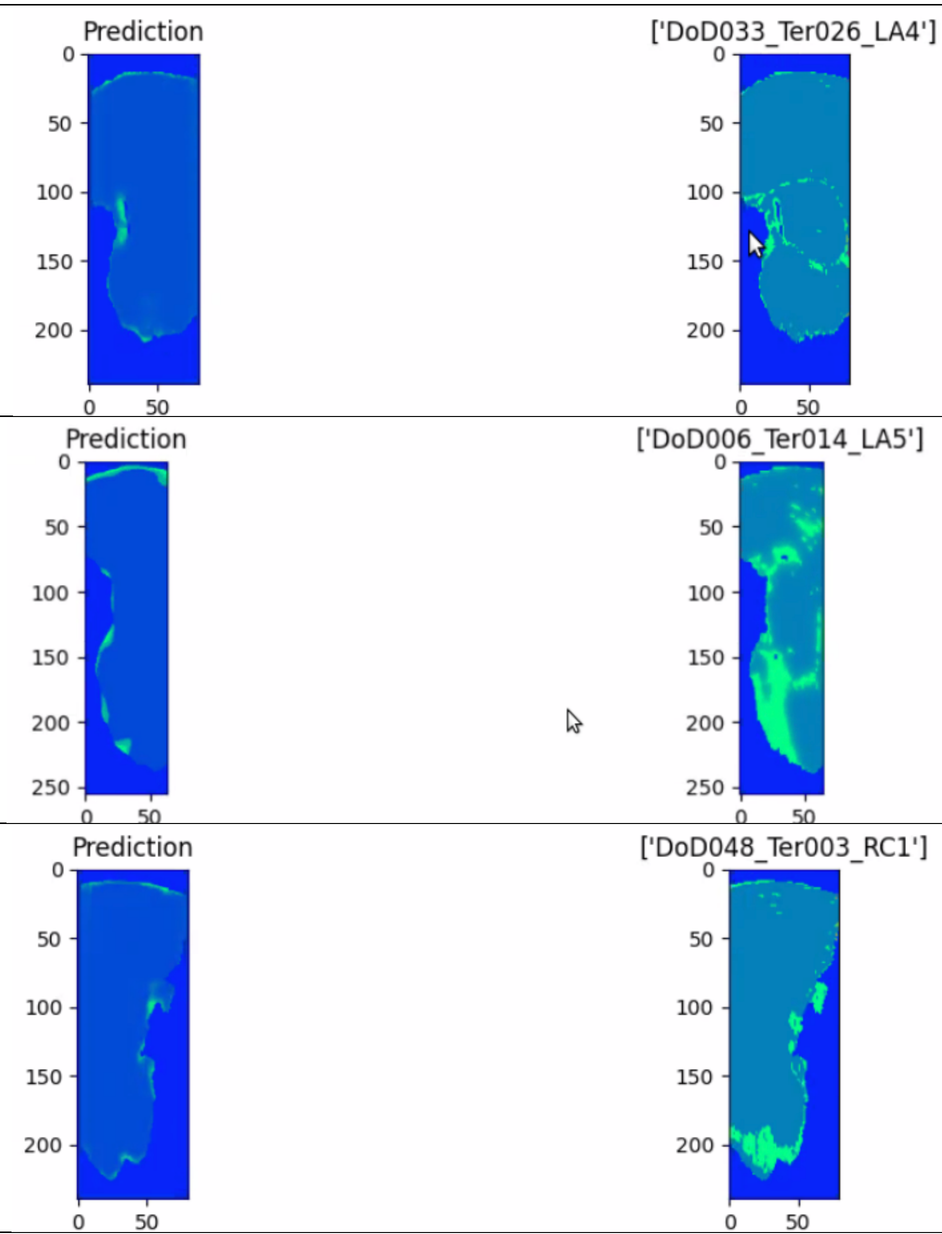

Figure 3 – three examples of model failures. The figure pairs are the same as in Figure 1. While there are some points of correct prediction, the model in each of these cases substantially missed the bleeds as imaged by the CT.