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TITLE: MRI Volumetrics for Risk Stratification of Vision Loss in Optic Pathway Gliomas Secondary to NF1

PRINCIPAL INVESTIGATOR: Robert A. Avery, DO

CONTRACTING ORGANIZATION: Children's Hospital, Philadelphia, PA

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14. ABSTRACT

Our overall objective is to develop and validate a novel quantitative MRI analysis software application that will enable: 1) identifying children who are at the greatest risk for vision loss from their NF1-OPG; and 2) making treatment decisions based on accurate evaluation of disease progression and response to therapy. We have completed Tasks 1, 2 and 3 (Aim 1), Task 4-5 (Aim 2) and will present the results of Aim 3 in the summer of 2024 despite a majority of the data being analyzed. As previously mentioned, we will be presenting these findings in parallel to the clinical findings of NF1-OPG natural history study results for the very first time. These simultaneous presentation this summer ensures scientific rigor without altering the future study course. Lastly, as the co-PI of the NF1-OPG natural history study (D3 and D4 cohorts), we have the Aim 3 data set in our possession as promised for the NCE. We have not made any significant changes to our study plan.

15. SUBJECT TERMS
NF1, optic pathway glioma, vision

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TABLE OF CONTENTS

Introduction

Nearly 20% of children with Neurofibromatosis type 1 (NF1) will develop a tumor of the visual system. The tumor, called an optic pathway glioma (OPG), causes irreversible vision loss leading to permanent disability in about 50% of children who have NF1, typically between 1 to 6 years of age. For unknown reasons, the other 50% of children with NF1-OPGs will not lose vision. Unfortunately, doctors do not have a good way of identifying which children will lose vision and when the vision loss will occur. Given this uncertainty, some children will sustain lifelong disability from their vision loss, even despite receiving treatment for their tumor, likely because treatment is started only after the loss of vision occurs. Also, for these exact same reasons, doctors may unknowingly treat NF1-OPGs that would have never caused vision loss. To address these clinical challenges, we will develop a novel quantitative magnetic resonance imaging (MRI) application that will accurately identify which children with NF1-OPGs will lose vision, thereby providing an opportunity to provide early treatment and preserve their vision.

Keywords: Neurofibromatosis type 1 (NF1); Optic pathway glioma (OPG); Visual Acuity (VA), Magnetic Resonance Imaging (MRI);

Accomplishments

- **What were the major goals of the project?**

Specific Aim 1 *Enable accurate MRI volumetric measurements of NF1-OPGs and reaffirm the relationship between these measures and vision loss in two independent cohorts (N=100, retrospective).*	**Timeline**	**July 2021 Technical Report Completion**	**CHOP**	**CNHS**
Major Task 1: Data acquisition	Months			
Subtask 1: Acquire and curate dataset D1 (N=50) from CNHS	1-3	Completed		Dr. Linguraru
Subtask 2: Acquire and curate dataset D2 (N=50) from CHOP	1-6	Completed	Dr. Avery	
Milestone(s) Achieved: Acquired multi-institutional data (N=100)	6	Completed	Dr. Avery	Dr. Linguraru
Local IRB/IACUC Approval	3	Completed	Dr. Avery	IRB already approved
Major Task 2: Enable accurate MRI-base volumetric measurements of NF1-OPG from new independent cohorts				
Subtask 1: Ensure robustness to data protocols	1-9	Completed	Dr. Avery	Dr. Linguraru
Milestone(s) Achieved: Accurate volumetric analysis of NF1-OPG (error $\leq$ 0.65 mm)	9	Completed	Dr. Avery	Dr. Linguraru
Major Task 3: Reaffirm the relationship between OPG volumetric measures and vision loss in the new independent cohorts				
Subtask 1: Relation between MRI Volumetrics and Visual Acuity	6-12	Completed	Dr. Avery	Dr. Linguraru
Milestone(s) Achieved: Good correlation between NF1-OPG volumes and vision loss (r-squared $\geq$ 0.60)	12	Completed	Dr. Avery	Dr. Linguraru

Specific Aim 2: *Enable MRI-based comprehensive assessment of longitudinal OPG changes and determine which features are*	**Timeline**	**July 2022 Technical**	**CHOP**	**CNHS**

associated with vision loss in a large cohort of children (N= 100, retrospective).		**Report Completion**		
Major Task 4: Data acquisition				
Subtask 1: Access dataset D3 (N=100) from the NF1-OPG natural history study	3-12	Completed	Dr. Avery	
Subtask 2: Transfer dataset D3 (N=100) to CNHS	3-12	Completed		Dr. Linguraru
Milestone(s) Achieved: Full access to dataset D3	12	Completed	Dr. Avery	Dr. Linguraru
Major Task 5: Enable MRI-based comprehensive assessment of longitudinal OPG changes				
Subtask 1: Quantify the size, shape and texture of NF1-OPG with MRI	9-18	Completed	Dr. Avery	Dr. Linguraru
Subtask 2: Quantify longitudinal MRI changes of NF1-OPG	12-21	Completed		Dr. Linguraru
Milestone(s) Achieved: Tool for MRI comprehensive assessment of longitudinal OPG changes	21	Completed	Dr. Avery	Dr. Linguraru
Major Task 6: Design MRI-based prediction model of vision loss (PPV ≥ 90%)				
Subtask 1: Identify and evaluate the optimal set of MRI features that predict clinical outcomes	21-27	Completed	Dr. Avery	Dr. Linguraru
Milestone(s) Achieved: MRI-based prediction model of vision loss based on retrospective data	27	Completed	Dr. Avery	Dr. Linguraru
Specific Aim 3: *Prospectively validate the predictive model of vision loss in a cohort of subjects enrolled in a large NF1-OPG longitudinal study from 25 international NF1 clinics (N=50, prospective).*				
Major Task 7: Prospective data acquisition				
Subtask 1: Enroll new patients in dataset D4 (N=50) from the NF1-OPG natural history study	12-22	Completed	Dr. Avery	
Subtask 2: Assess patients in dataset D4 (N=50) at 1 year from enrollment	22-32	Completed	Dr. Avery	
Subtask 3: Transfer dataset D4 (N=50, at least two time points per patient) to CNHS	12-32	Completed	Dr. Avery	
Milestone(s) Achieved: Full access to dataset D4	32	Completed	Dr. Avery	Dr. Linguraru
Major Task 8: Enable MRI-based comprehensive assessment of longitudinal OPG changes				
Subtask 1: Validate the predictive model of vision loss at baseline	14-24	Completed	Dr. Avery	Dr. Linguraru
Subtask 2: Validate the predictive model of vision loss at 1 year	24-36	90% Completed	Dr. Avery	Dr. Linguraru

Milestone(s) Achieved: Prospectively validated MRI-based prediction model of vision loss (PPV ≥ 80%)	36	90% Completed	Dr. Avery	Dr. Linguraru

◦ **What was accomplished under these goals?**

SA2/Major Task 5: Enable MRI-based comprehensive assessment of longitudinal OPG changes and determine which features are associated with vision loss in a large cohort of children (N= 100, retrospective). Enable MRI-based comprehensive assessment of longitudinal OPG changes. We have completed the volumetric size analysis for this large cohort derived from 2 centers with two different MRI platforms. We have also analyzed data from the longitudinal cohorts. Our analysis of radiomic features (relevant to *SA2/Major Task 6 below)*, has improved our ability to predict vision loss (**Figure 1**). We believe this will be a landmark finding for the evaluation and management for these children and want to make sure our final results are correct for when they are published.

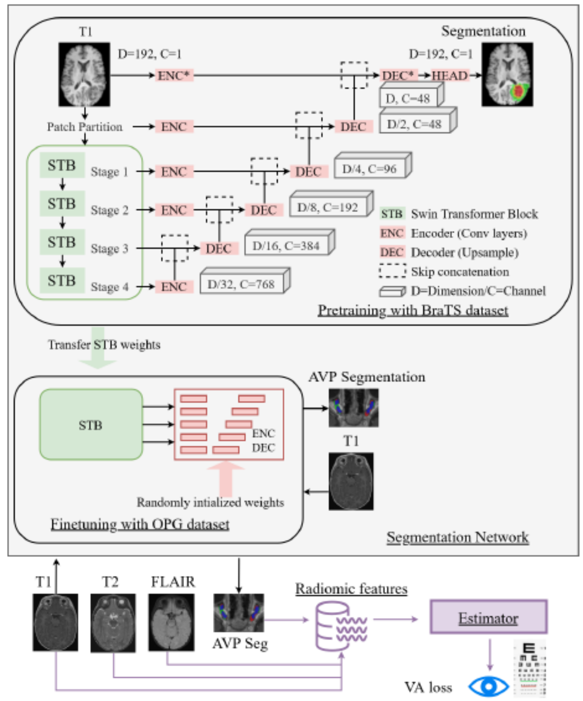

Figure 1 Our end-to-end framework for AVP ROI segmentation and VA loss prediction (Jiang et al., IEEE EBMC, 2023).

SA2/Major Task 6 Design MRI-based prediction model of vision loss (PPV ≥ 90%) by identifying and evaluating the optimal set of MRI features that predict clinical outcomes. This task is 100% complete and, as hypothesized, tumor volume remains the strongest predictor of vision loss. **Table 1** shows the analysis from our current paper published in Neuro-Oncology Advances (Avery et al., 2023) using a brand new cohort using an entirely different MRI platform. By validating these findings on two unique cohorts using two different MRI platforms, this confirms our approach and analysis can be scaled to other MRI platforms and more importantly included in clinical trials from a variety of clinical sites. Also, further confirming the relationship between axonal damage via optical coherence tomography (OCT) and MRI volume, we are reassured that our current path of investigation is rigorous and biologically meaningful. **(Table 2, next page)**.

Table 1. Comparison of Linear and Volumetric Measurements of Structures of the Anterior Visual Pathway for Participant with Normal and Abnormal Visual Acuity

	Visual Acuity		*P*
	Abnormal (≥ 0.2 LogMAR)	Normal (<0.2 LogMAR)	
Subjects	13	13	
Optic nerve diameter (mm)	6.85 ± 1.71	3.54 ± 0.97	<.0001
Optic nerve volume (ml)	1.00 ± 0.42	0.42 ± 0.94	.0002
Optic chiasm width (mm)	17.67 ± 8.21	12.78 ± 5.87	.08
Optic chiasm height (mm)	15.68 ± 7.32	14.581 ± 6.9	.56
Optic chiasm volume (ml)	1.14 ± 1.27	0.45 ± 0.89	.13
Optic tract diameter (mm)	3.26 ± 1.48	2.77 ± 1.17	.28
Optic tract volume (ml)	0.44 ± 0.73	0.14 ± 0.05	.21
Total anterior visual pathway volume (ml	3.63 ± 2.73	1.52 ± 0.97	.0005
Total brain volumE(ml)	1446.39 ± 261.44	1497.5 ± 227.27	.89
OCT average cpRNFL (microns)	48.00 ± 15.80	97.08 ± 12.19	<.0001
OPG Location [a]			
Nerve only	4	8	
Chiasm	2	3	
Tracts	7	2	

All values are mean ± standard deviation.
aDenotes most posterior location of the OPG.
Abbreviations: OCT, optical coherence tomography; cpRNFL, circumpapillary retinal nerve fiber layer; OPG, optic pathway glioma.

Table 1. MRI features identifying visual acuity validated using a new platform and patient cohort.

SA3/Major Task 7 Prospective Data acquisition: We have completed subtask 1 by enrolling the new patients in dataset D4 from the NF1 Natural History Study. Subject enrollment in the International NF1-OPG Natural History study has reached its study goal of 250 enrollees. We have a complete data set for Aim 3.

SA3/Major Task 8 Enable MRI-based comprehensive assessment of longitudinal OPG changes: Subtask 2 is marked as 90% completed, as we are awaiting some final time points to be completed by subjects and to enable simultaneous presentation with the NF1 Natural History study clinical data. We have recently published our supporting algorithms (see **Figure 2**). Once the subjects finish their expected time points. We believe we have adequately powered, this approach. As stated in last year's report, our clinical algorithm using our predictive model that has been described in our numerous invited presentations and publications (supported by the CDMRP) will undoubtedly improve the clinical care for all children with NF1-OPGs. The ability to now use MRI volumetrics to make evidence-based decisions will not allow physicians to apply more precision medicine approach to this young and vulnerable population. This will impact a majority of children with NF1-OPGs and provide demonstrable changes in improved quality of life along with better resource utilization. We have an unwavering goal to make our volumetric analysis available to all clinicians caring for children with NF1. Lastly, and as previously mentioned in last year's report, we are now in discussions to use or our volumetric analysis to test the very first "preventative" medication to avoid tumor growth and progression. Due to the CDMRP support, our volumetrics algorithm will be used this first-in-kind approach to children with NF1-OPG and, as far as we know, in all of pediatric brain tumros.

Table 5. Diagnostic Accuracy of Tumor Measures to Detect a Decreased Circumpapillary Retinal Nerve Fiber Layer Thickness (<80 microns) and Vision Loss for Subjects with Optic Chiasm With or Without Optic Tract Involving Optic Pathway Gliomas Secondary to Neurofibromatosis Type 1

	Abnormal cpRNFL		Abnormal Visual Acuity	
	AVP Volume > 1.75	Chiasm Width >17 mm	AVP Volume > 1.75	Chiasm Width >17 mm
Sensitivity	88.2	73.6	87.5	70.5
Specificity	66.6	77.7	60.0	77.7
Positive predictive value	83.3	87.5	77.7	85.7
Negative predictive value	75.0	58.3	75.0	58.3

Table 2. Diagnostic accuracy from MRI features identifying cpRNFL loss.

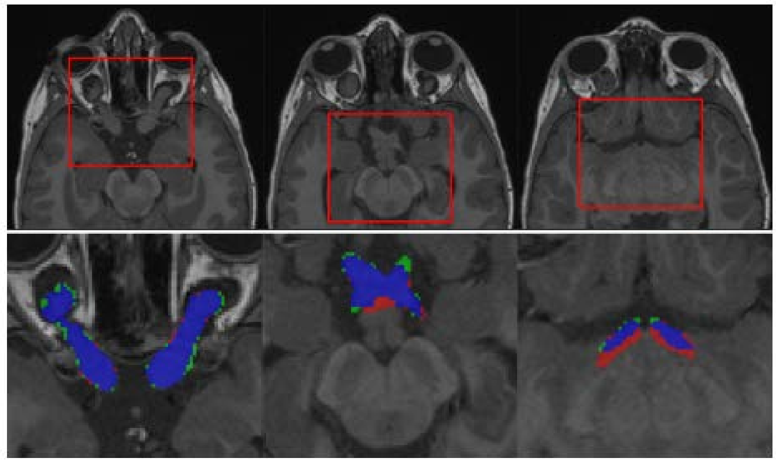

Figure 2 Segmentation of the AVP in order to define radiomic features and develop VA loss prediction models (Jiang et al., IEEE EBMC, 2023).

- **<u>What opportunities for training and professional development has the project provided</u>?**

We have provided technical and translational training to a postdoctoral fellows at Children's National Hospital. The training covers machine learning techniques for quantitative imaging as well as translational applications of imaging for children with NF1-OPG. The fellow also received career development support to transition to an independent research position, including resources for publications, funding and mentorship.

- **<u>How were the results disseminated to communities of interest</u>?**

Nothing to report.

- **<u>What do you plan to do during the next reporting period to accomplish the goals</u>?**

Our collaboration will continue as previously described.

<u>IMPACT</u>:

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

Nothing to report.

- **What was the impact on other disciplines?**

Nothing to report.

- **What was the impact on technology transfer?**

Nothing to report.

◦ **What was the impact on society beyond science and technology?**

Nothing to report.

CHANGES/PROBLEMS:

◦ **Changes in approach and reasons for change**

▪ There have been no significant changes to the objectives or scope.

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

▪ None

◦ **Changes that had a significant impact on expenditures**

▪ N/A

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

There have been no significant deviations, unexpected outcomes or changes to the protocol. The institutional review board (IRB) approved this protocol on January 24, 2018 and there is no study expiration date as determined by the rules of the 2018 Common Rule (see prior communications with CDMRP).

◦ **Significant changes in use or care of human subjects**

Nothing to report.

◦ **Significant changes in use or care of vertebrate animals.**

N/A.

◦ **Significant changes in use of biohazards and/or select agents**

N/A.

PRODUCTS:

◦ **Publications, conference papers, and presentations**

▪ **Journal publications.**

Avery, R.A. Mansoor, A. Liu, G.T. Trimboli-Heidler, C. Ying, G.S. Centrella, C.R. Packer, R.J. Fisher, M.J. Linguraru, M.G. Larger Tumor Volume is Associated with Visual Acuity Loss and Axonal Degeneration in Children with Optic Pathway Gliomas Secondary to Neurofibromatosis Type 1. Neuro-Oncology Advances, 5(1) 1-7, 2023.

Jiang Z, Parida A, Answar S.M, Tang Y, Roth H.R., Fisher M.J., Packer R.J., Avery R.A., Linguraru M.G. Automatic Visual Acuity Loss Prediction in Children with Optic Pathway Gliomas Using Magnetic Resonance Imaging. IEEE Medicine and Biology, 2023.

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

Nothing to report.

▪ **Other publications, conference papers, and presentations.**

Invited Talks

“NF Virtual Case Conference--Progressive Optic Pathway Gliomas", University of Alabama and Children's Tumor Foundation Master Class Symposium, 2023, (Avery).

"Current Diagnosis and Treatment Options for Children with Optic Pathway Gliomas", AAP and AAPOS Fall Conference, 2023 (Avery).

“Multimodal Imaging and Outcomes in Children with Optic Pathway Gliomas", American Neurologic Association Annual Meeting, Philadelphia. 2023 (Avery).

"Visual Outcomes in Decentralized Trials", NF Clinical Trials Consortium and REiNS Consortium Annual meeting, Baltimore, 2023 (Avery).

"MRI Shape and Intensity Features are Associated with Vision Loss in Children with NF1-OPG", Children's Tumor Foundation Annual Meeting, Scottsdale, 2023 (Linguraru).

"An Update on the NF1-OPG Natural History Study", Children's Tumor Foundation Annual Meeting, Scottsdale, 2023 (Avery).

"Harmonization Across Imaging Locations (HAIL): Implications of Image Harmonization for NF1-OPG Clinical Trials. Children's Tumor Foundation Annual Meeting, Scottsdale, 2023 (Linguraru).

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

Nothing to report.

- **Technologies or techniques**

Nothing to report.

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

- **Other Products**

Nothing to report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name: Robert Avery
Project Role: PI
Researcher Identifier: ORCID ID: 0000-0003-1453-7282
Nearest person month worked: 1.2
Contribution to Project: Dr Avery has coordinated the major activities of the project and has help gather and analyze the MRI and clinical data for specific aims 1, 2, and 3. Dr. Avery has worked closely with Dr. Linguraru (Qualified collaborator) through in person meetings and video conferences to ensure accuracy of all data acquisition and analysis. Dr. Avery supervised Ms Garcia (research coordinator).
Funding Support: N/A

Name: Marius Linguraru
Project Role: Qualified collaborator
Researcher Identifier: ORCID ID: 0000-0001-6175-8665
Nearest person month worked: 1.2
Contribution to Project: Dr. Linguraru has worked closely with Dr. Avery (PI) on coordinating the activities of the project. He leads the technical developments conducted at CNHS for quantitative imaging and volumetric analysis. Dr. Linguraru supervised Dr. Tor Diez and the technical analysis.
Funding Support: N/A

Name: Chandra Collins
Project Role: Research coordinator
Researcher Identifier: N/A
Nearest person month worked: 1.8
Contribution to Project: Ms Collins has been responsible for collecting and organizing subject's MRI, clinical data entry and regulatory compliance.
Funding Support: N/A

Name: Carlos Zifhan Zhang
Project Role: Postdoctoral research fellow
Researcher Identifier: ORCID ID: 0000-0003-3339-5777
Nearest person month worked: 6.0
Contribution to Project: Dr. Zhang has provided technical expertise to the project in the areas of automated image segmentation and quantification and machine learning. He has been the primary developer of the software and methodology to assess optic pathway gliomas after Dr. Tor Diez had to urgently leave his position due to personal reasons. Dr. Zhang has also supported the evaluation of the methodology and participates in dissemination processes.
Funding Support: N/A

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

Nothing to Report.

- **What other organizations were involved as partners?**

Nothing to Report.

<u>SPECIAL REPORTING REQUIREMENTS</u>

As the project PI, Dr. Avery involved Dr. Linguraru as a "Qualified Collaborator" on this project. The above report will be duplicative between investigators. As instructed, the tasks are clearly outlined in the SOW table for which investigator is responsible for the task. These assignments are applicable to all accomplishments listed in the above report.

<u>APPENDICES</u>:
-see attached publications