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

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CONTRACTING ORGANIZATION: Children's Hospital of Philadelphia

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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. Currently, we have completed Tasks 1, 2 and 3 (Aim 1) and Task 4-5 (Aim 2). The remaining tasks in Aim 3 as listed in the SOW were impacted by the COVID19 pandemic, but have been addressed and should readily be completed during our no cost extension. We continue to refine and analyze how we use the different MRI features to create our predictive algorithm. While we have produced some encouraging and supportive results, we do not want to publish these results until we can confirm we have done due diligence and complete the most rigorous analysis. Lastly, as the co-PI of the NF1-OPG natural history study (D3 and D4 cohorts), I can confirm will have a complete data set needed to complete the Aim 3 analysis during 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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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 ≤ 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 ≥ 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	90% 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	70% Completed	Dr. Avery	Dr. Linguraru
Milestone(s) Achieved: MRI-based prediction model of vision loss based on retrospective data	27	70% 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	60% Completed	Dr. Avery	
Subtask 3: Transfer dataset D4 (N=50, at least two time points per patient) to CNHS	12-32	70% Completed	Dr. Avery	
Milestone(s) Achieved: Full access to dataset D4	32	40% 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	50% Completed	Dr. Avery	Dr. Linguraru

Milestone(s) Achieved: Prospectively validated MRI-based prediction model of vision loss (PPV ≥ 80%)	36	50% 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 all manual segmentations as well as 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. During this analysis, we came across some striking findings compared to clinical findings. In the example below, a patient was called a treatment success as the primary portion of the tumor was decreased, however, other portions of the tumor got significantly larger (**Figure 1**). This highlights are previous results. Although this was supposed to be finished over the past year, we didn't want to complete this Task as we want to be VERY sure we have identified the best results to deliver rigorous results. 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.

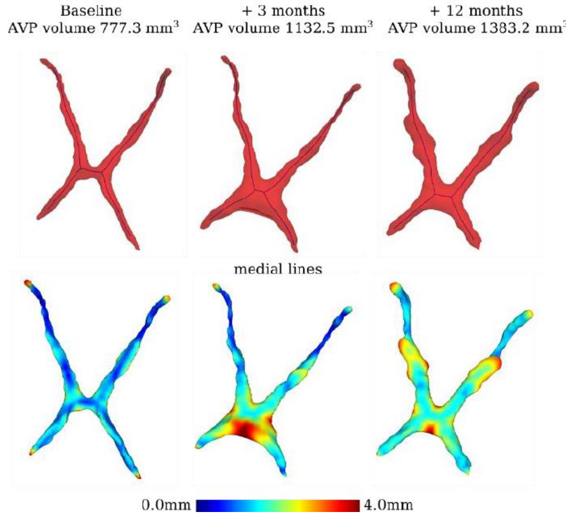

Figure 1 Longitudinal changes in volume using different techniques highlight that despite the center of the tumor getting smaller, the total tumor burden has increased.

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 on schedule and roughly 70% complete. Our analysis suggests that tumor volume remains the strongest predictor of vision loss, but we are exploring more dynamic and granular methods to determine which specific features of tumor shape and texture influence the model. **Table 1** shows the analysis from our current paper under review in Neuro-Oncology advances that received favorable reviews.

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		
	Abnormal (≥ 0.2 LogMAR)	Normal (<0.2 LogMAR)	*p*
Subjects	13	13	
Optic Nerve Diameter (mm)	6.85 ± 1.71	3.54 ± 0.97	<0.0001
Optic Nerve Volume (mm³)	1.00 ± 0.42	0.42 ± 0.94	0.0002
Optic Chiasm Width (mm)	17.67 ± 8.21	12.78 ± 5.87	0.08
Optic Chiasm Height (mm)	15.68 ± 7.32	14.581 ± 6.9	0.56
Optic Chiasm Volume (mm³)	1.14± 1.27	0.45 ± 0.89	0.13
Optic Tract Diameter (mm)	3.26 ± 1.48	2.77 ± 1.17	0.28
Optic Tract Volume (mm³)	0.44 ± 0.73	0.14 ± 0.05	0.21
Total Anterior Visual Pathway Volume (mm³)	3.63 ± 2.73	1.52 ± 0.97	0.0005
Total Brain Volume(mm³)	1446.39 ± 261.44	1497.5 ± 227.27	0.89

Table 1. MRI features identifying visual acuity loss from cross-sectional analysis.

A second aspect of this analysis is to look at the relationship between axonal damage via optical coherence tomography (OCT). This is an objective ocular imaging technique that avoids the variability of standard visual acuity measures. We have analyzed this compared to our data and found some very encouraging results (**Table 2, next page)**. This supported some previous data using this study cohort. While both positive and negative predictive values were strong, we are still working to make sure all of our other clinical variables like tumor location and time of vision loss are included. The impact of tumor location may be a confounding variable in this analysis and thereby decreasing the strength of our predictive values. Therefore, to maintain rigor, we will consider these more carefully on future tasks. As previously state we are very thoughtful of our analysis approach and trying to avoid over or underfitting our models.

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 is on track but was slowed significantly due to the COVID 19 pandemic. This significantly impacted all 25 site investigators on their ability to enroll and follow patients successfully. Furthermore, staffing issues have impacted the ability to obtain complete data sets and MRI images. Nonetheless, the study investigators have done an excellent job of returning to near pre-pandemic efficiency and we will have a complete data set to finish Aim 3 as planned.

Table 2. Diagnostic Accuracy of Tumor Measures to Detect a Decreased Circumpapillary Retinal Nerve Fiber Layer Thickness (< 80 microns) and Vision Loss for All Participants with Optic Pathway Gliomas Secondary to Neurofibromatosis Type 1.

	Abnormal cpRNFL			Abnormal VA	
	AVP volume > 1.75	Chiasm width >17mm		AVP volume > 1.75	Chiasm width >17mm
Sensitivity	80.0	46.1		85.0	57.1
Specificity	83.3	82.6		75.8	85.7
Positive Predictive Value	83.3	75.0		70.8	75.0
Negative Predictive Value	80.0	57.5		88.0	72.7

Table 2. Predictive values from basic MRI features identifying cpRNFL loss and visual acuity loss from cross-sectional analysis.

SA3/Major Task 8 Enable MRI-based comprehensive assessment of longitudinal OPG changes: Subtask 1 is marked as completed, but based on the data listed above, we are still considering multiple different variables to have the most robust model. As stated above, the COVID 19 pandemic impacted the data collection and analysis. Once the subjects finish their expected time points and the data is acquired, we will be able to complete the analysis relatively quickly. We believe this will be adequately powered, but as previously stated, we will be able to determine if additional subjects with or without vision loss will need to be included in the analysis to achieve statistical power (Major Task 7, subtask 3). Lastly, we have also developed a clinical algorithm using our predictive model that has been described in our numerous invited presentations which highlighted our CDMRP productivity (**Figure 2**). The ability of our MRI volumetrics to classify a child as "low risk for vision loss" will result in the reduced number of MRI scans and most notably the reduced exposures of the child to anesthesia. This will impact a majority of children with NF1-OPGs and provide demonstrable changes in improved quality of life along with better resource utilization. Next, those defined as "high risk vision loss" will permit improved and more focused monitoring in order to start chemotherapy at the earliest possible point in order to optimal treatment outcomes. Lastly, in the era of precision medicine and current therapies in the development pipeline, it is very conceivable our model will be used as a first-in-kind approach for preventative treatment to avoid vision loss all together. In summary, our clinical algorithm based on MRI volumetrics is positioned to dramatically improve the clinical care of all children with NF1-OPG.

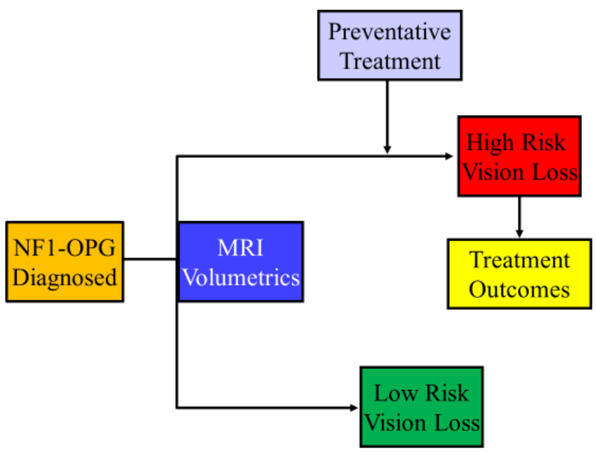

Figure 2 Clinical algorithm demonstrating how our MRI volumetric analysis developed by our CDMRP award will impact clinical care.

◦ **<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. In addition, we have an intern from George Washington University, who is spending the summer of 2022 doing an in person internship Children's National and learning about MRI image analysis and curation. The intern works with Dr. Linguraru and Dr. Zhang and is also learning about technical applications in pediatric oncology.

◦ **<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>?**

We have become much more facile with our online meetings and trouble-shooting over the past year, thus we will continue to follow this workflow as it has allowed us to accomplish our goals. If the COVID19 pandemic work standards change again (e.g., return to strict mitigation procedures) we are prepared to deal with these circumstances in order to achieve our study goals. On the other hand, we have been able to travel and have in person meetings.

<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.

<u>CHANGES/PROBLEMS</u>:

◦ **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**

▪ The COVID19 pandemic has slowed down different aspects of the study due to institutional safety guidelines. We created better work from home options with our laptops. We were able to utilize better data transfer modules from home that improve imaging transfer and data transfer timeliness and efficiency. Despite a decrease in typical in person interactions, we are operating at nearly our pre-pandemic efficiency.

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

There has been a modest carryover in expenditures as Dr. Tor Diez left urgently due to personal reasons and Dr. Zhang was not hired until September 2021.

◦ **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.**

Carlos Tor-Diez Antonio R. Porras, Roger J Packer, Robert A Avery, Marius George Linguraru. Multi-Platform MRI Quantification: Unsupervised MRI Homogenization: Application to Pediatric Anterior Visual Pathway Segmentation. In: Liu M., Yan P., Lian C., Cao X. (eds) Machine Learning in Medical Imaging. MLMI 2020. Lecture Notes in Computer Science, vol 12436. Springer, Cham. https://doi.org/10.1007/978-3-030-59861-7_19

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

Nothing to report.

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

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 (2022) (under review)

Invited Talks

Avery, R.A. Jiang, Z. Tor Diez, C. Collins, C.V. Stence, N. Foreman, N. Packer, R.J. Fisher, M.J. Linguraru, M.G.: Multi-Center Brain MRI: Implications for Quantitative Image Analysis as an Outcome in NF1-OPG Clinical Trials. In: Children's Tumor Foundation Neurofibromatosis Forum, 2022, (Avery)

New Horizons for the Management of Ophthalmic Manifestations of NF1", The 6th Annual Saudi Arabian Ophthalmology Society meeting, Riyahd, Saudia Arabia, 2022 (Avery)

"Optic Pathway Gliomas: Clinical Challenges." Division of Ophthalmology Ground Rounds, Boston Children's Hospital, 2021. (Avery)

Optic Pathway Gliomas: Current Management", Advanced course on Pediatric Ophthalmology and Strabismus of the Virgilio Galvis Eye Center and Santander Ophthalmology Foundation Bucaramanga, Colombia, 2022 (Avery)

"Ophthalmic Manifestations of NF1", NF Summit, Chicago, IL, 2022 (Avery)

"AI Challenges in Pediatric Imaging" at MRI Together, A Global Workshop on Open Science and Reproducibility organized by the European Society for Magnetic Resonance Imaging in Medicine and Biology, December 2021. (Linguraru)

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

Nothing to report.

◦ **Technologies or techniques**

Nothing to report.

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

Mansoor, A. Linguraru, M.G. Avery, R.: Apparatus and Method for Segmenting Complex Structures. US/62/470,728 PCT/US2017/065562

◦ **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.

SPECIAL REPORTING REQUIREMENTS

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.

APPENDICES: