Title

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Journal

Seminars in Neurosurgery, 85(1)

ISSN

2193-6331

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Publication Date

2024-02-01

DOI

10.1055/a-1978-9380

Peer reviewed

The RAPID Consortium: A Platform for Clinical and Translational Pituitary Tumor Research

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J Neurol Surg B Skull Base 2024;85:1–8.

Abstract

Objectives Pituitary tumor treatment is hampered by the relative rarity of the disease, absence of a multicenter collaborative platform, and limited translational–clinical research partnerships. Prior studies offer limited insight into the formation of a multicenter consortium.

Design The authors describe the establishment of a multicenter research initiative, Registry of Adenomas of the Pituitary and Related Disorders (RAPID), to encourage quality improvement and research, promote scholarship, and apply innovative solutions in outcomes research.

Methods The challenges encountered during the formation of other research registries were reviewed with those lessons applied to the development of RAPID.

Setting/Participants RAPID was formed by 11 academic U.S. pituitary centers.

Results A Steering Committee, bylaws, data coordination center, and leadership team have been established. Clinical modules with standardized data fields for nonfunctioning adenoma, prolactinoma, acromegaly, Cushing's disease, craniopharyngioma, and Rathke's cleft cyst were created using a Health Insurance Portability and Accountability Act-compliant cloud-based platform. Currently, RAPID has received institutional review board approval at all centers, compiled retrospective data and agreements from most centers, and begun prospective data collection at one site. Existing institutional databases are being mapped to one central repository.

Conclusion The RAPID consortium has laid the foundation for a multicenter collaboration to facilitate pituitary tumor and surgical research. We sought to share our

Keywords
- pituitary adenoma
- craniopharyngioma
- Cushing's disease
- Rathke's cleft cyst
- registry
- consortium

received
July 10, 2022
accepted after revision
September 7, 2022
accepted manuscript online
November 15, 2022
article published online
December 30, 2022

DOI https://doi.org/10.1055/a-1978-9380.
ISSN 2193-6331.

experiences so that other groups also contemplating this approach may benefit. Future studies may include outcomes benchmarking, clinically annotated biobank tissue, multicenter outcomes studies, prospective intervention studies, translational research, and health economics studies focused on value-based care questions.

Introduction

Research into pituitary tumors has traditionally been done at individual, typically high-volume centers. This approach has been successful in slowly developing rough standards and basic concepts for treatment but tends to lack large case numbers to provide meaningful, statistically significant conclusions and has resulted in limited study of the molecular/genetic underpinnings of pituitary disease. The wide applicability of most findings in the field are limited by the lack of multicenter validation or collaboration. We aimed to develop a skull base research consortium—the Registry of Adenomas of the Pituitary and Related Disorders (RAPID)—to address these and other challenges.

The U.S. National Committee on Vital and Health Statistics describes clinical/surgical registries as "organized system[s] for the collection, storage, retrieval, analysis, and dissemination of information on individual persons who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects."[1,2] There has been continued interest in establishing surgical registries in neurosurgery, with some of the best examples in spine,[3,4] pediatric hydrocephalus,[5] radiosurgery,[6] neurovascular surgery,[7] syringomyelia, and Chiari I malformations,[8] and more recently, tumor[4] research. One group evaluating a variety of topics is comprised of neurosurgical trainees.[9] Prior publications regarding registry structure, best practices, and pitfalls have been immensely helpful for other research teams forming their own consortiums.[3,4]

Surgical registries may be powerful tools for studying neurosurgical patients that have advantages over traditional randomized clinical studies, single-center studies, or administrative databases. These advantages can include: (1) the ability to track practice changes over time, (2) involvement of multiple experts and incorporation of practice variation, (3) acquisition of sufficient sample sizes earlier than in traditional studies, (4) study of the impact of practice changes or bundles, (5) acquisition of prospective data, (6) evaluation of quality-improvement initiatives, and (7) lower cost than traditional multicenter clinical trials. When properly designed, registries can reduce study bias and loss of follow-up, which improves data fidelity.

A limited number of registry-based studies have evaluated pituitary adenomas and demonstrate the potential strength of such an approach. Saeger et al[10] described the findings of the German Registry of Pituitary Tumors, which identified 4,122 sellar cases from 1996 through 2005. This effort was primarily driven by the German Society of Endocrinology. Among the 3,489 identified pituitary adenomas, this group identified some of the histological features that correlate with tumor invasiveness. The same group also evaluated acromegaly, specifically enrolling 1,543 patients from 2003 through 2005.[11] These impressive efforts have undoubtedly shed light on the epidemiology of pituitary adenomas; however, limitations of their work include the relative exclusion of imaging, surgical, and perioperative factors from analysis, a lack of clinical outcomes studied, and a relatively low number of publications despite an impressive data set.

The creation of a research consortium in skull base neuro-oncology is opportune because of the rarity of many pathologies, the limited number of centers performing high volumes of cases, and significant practice variation depending on surgeon experience. A consortium can adapt to the ongoing research needs via a surgical registry but also serve as a source for technology development and testing, patient education and advocacy, and grant writing. Registries have only been explored in skull base surgery to a limited extent[10,12,13]; however, multicenter studies in skull base surgical neuro-oncology, such as the TRANSSPHER,[14–18] I-MiND,[8,19–22] and POET[23] studies, have shown that the work of a consortium is both feasible and impactful.

The purpose of this article is to describe the formation and structure of the RAPID consortium. This multicenter group of 11 academic centers aims to generate a large retrospective and prospective database for exploring pituitary adenomas and other neuroendocrine tumors (►**Fig. 1**). The rationale for RAPID is to improve and transform the care of pituitary patients by monitoring current practice patterns and trends, promoting value-based outcomes research, developing high-impact clinical protocols, disseminating best practices, improving the validity of data, and accelerating research studies (►**Fig. 2**). Other important goals are to foster collegiality in skull base research, provide professional development opportunities for junior faculty, and plan future multicenter studies.

Formation of RAPID

RAPID was formed by the Barrow Clinical Outcomes Center (BCOC) at the Barrow Neurological Institute (BNI) as a clinical outcomes platform for its internal use (►**Fig. 3**). The first clinical module developed targeted acromegaly outcomes. BCOC also coordinates internal BNI registries for spine, neurovascular lesions, vestibular schwannomas, radiosurgery, and gliomas. Initial pilot data for acromegaly, including clinical, surgical, imaging, and pathological variables in addition to patient quality-of-life (QOL) metrics, were

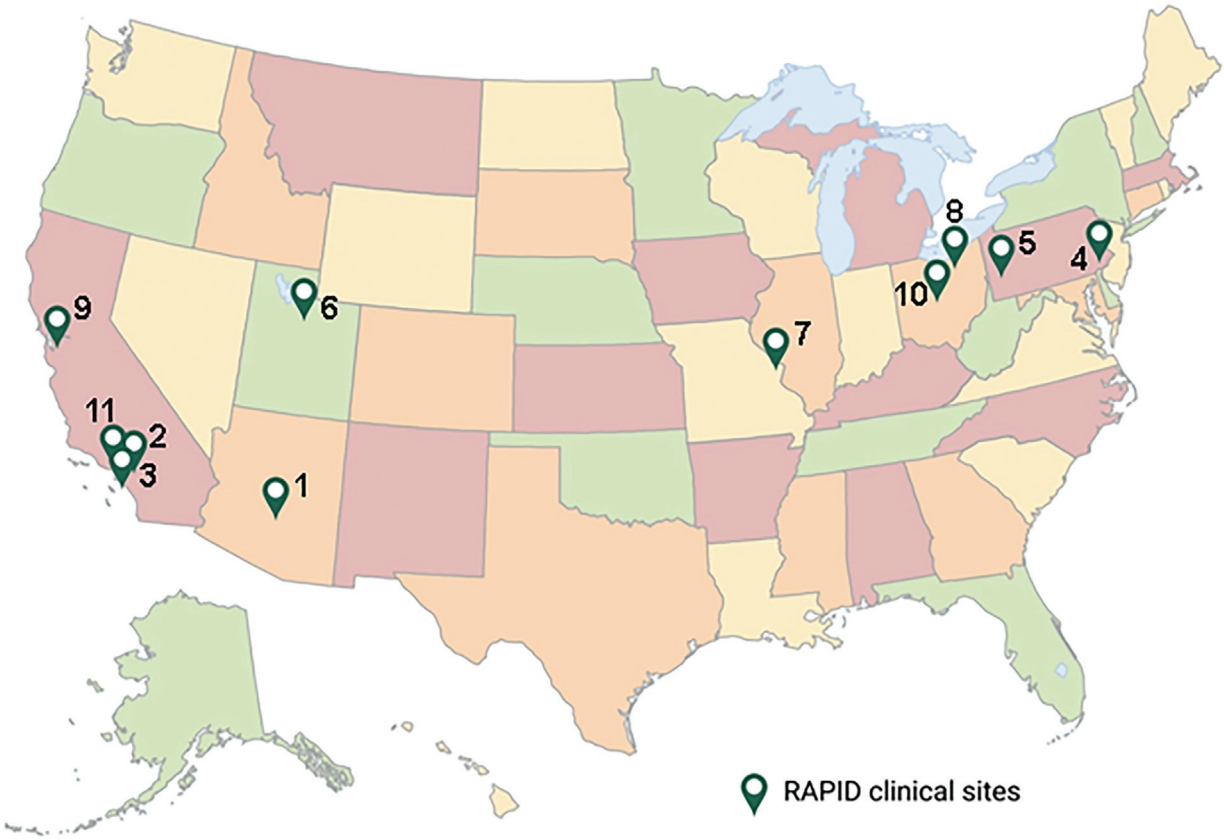

Fig. 1 Map of institutions participating in Registry of Adenomas of the Pituitary and Related Disorders (RAPID). (1) Barrow Neurological Institute, St. Joseph's Hospital, and Medical Center, Phoenix, AZ; (2) Ronald Reagan UCLA Medical Center, Los Angeles, CA; (3) University of Southern California, Los Angeles, CA; (4) Jefferson Hospital for Neuroscience, Philadelphia, PA; (5) University of Pittsburgh Medical Center, Pittsburgh, PA; (6) University of Utah Medical Center, Salt Lake City, UT; (7) Washington University, St Louis, St. Louis, MO; (8) Cleveland Clinic, Cleveland, OH; (9) Stanford University, Stanford, CA; (10) The Ohio State University, Columbus, OH; (11) Providence St. Johns Medical Center, Santa Monica, CA. Map created with biorender.com and freevectormaps.com.

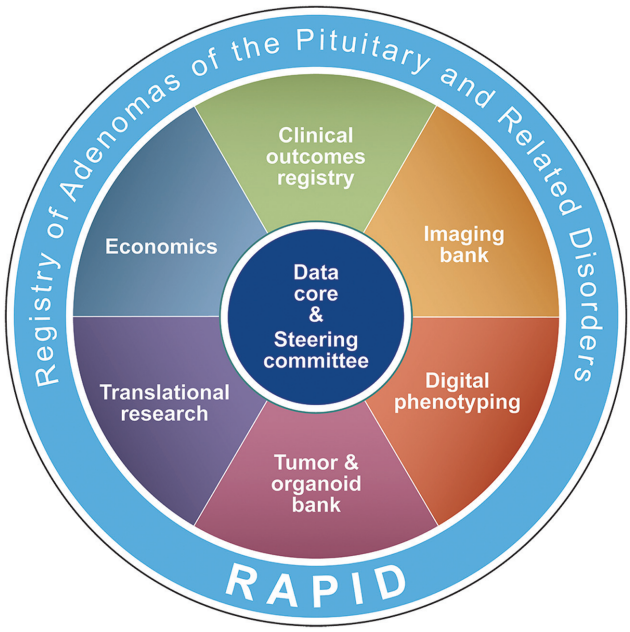

Fig. 2 Organizational structure of Registry of Adenomas of the Pituitary and Related Disorders (RAPID). Various avenues of potential research with RAPID are listed. Currently, the steering committee has aimed to drive the scientific direction of the work. Future potential study avenues are listed.

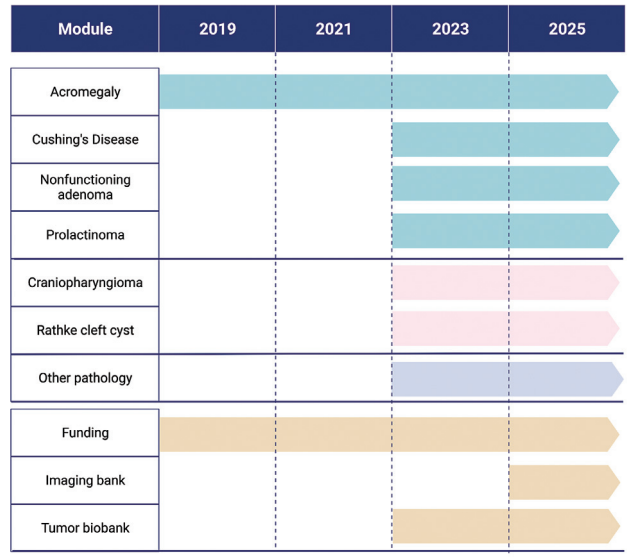

Fig. 3 Timeline of clinical and funding roadmap for Registry of Adenomas of the Pituitary and Related Disorders (RAPID). A development timeline of current and future disease modules in pituitary adenoma (green), craniopharyngioma and Rathke's cleft cyst (pink), and other pathologies (purple) are shown. Other plans for funding and development of imaging and tumor banks (yellow) are also shown. Created with biorender.com.

acquired at two sites beginning in 2019. Data were acquired prospectively, and data auditing was implemented. The Visiontree Optimal Care (VTOC) cloud-based system was used to provide data collection via a Health Insurance Portability and Accountability Act-compliant database (www.visiontree.com). Because it is a cloud-based platform, Visontree will scale to accommodate partner institutions. Numerous patient-reported QOL instruments are available in VTOC, and the RAPID team created several pituitary-specific and site-specific instruments. Visiontree allows for the generation of digital patient intake forms, automated prompts, and data importing. In the initial validation, a total of 600 surgical adenoma patients were screened, with 50 acromegalic patients enrolled in the registry.

RAPID Expansion to Multicenter Collaboration

Soon after the feasibility of RAPID was established, a multicenter group of 11 U.S. academic pituitary centers (►**Fig. 1**) gathered to discuss expansion of clinical modules for other functional tumor types (e.g., Cushing's disease, prolactinoma), nonfunctional tumors, craniopharyngiomas, and Rathke's cleft cysts (►**Fig. 4**). A steering committee was established to form bylaws governing the onboarding and participation. The use of teleconferencing was immensely helpful to the relatively quick involvement of multiple national sites in RAPID, allowing for monthly meetings that may be more impactful than a single large annual follow-up. Teleconferencing with legal counsel during the formation of bylaws and institutional agreements allowed for quicker, direct turnaround. Monthly teleconferencing as well as meetings at the major neurosurgical society conferences and at the annual North American Skull Base Society have allowed open discussion and development of the RAPID consortium. Collaboration at individual sites among various stakeholders in other departments (e.g., neuroendocrinology, otolaryngology, neuroradiology) has allowed for improved structuring of various clinical modules. Creating a framework to allow multidisciplinary input is critical. Currently, we have several endocrinologists and otolaryngologists from different institutions who have contributed input to the development of surgical variables and identification of key research questions to explore. In time, diversification of the steering committee and formation of a multidisciplinary advisory board will be essential to growth. The recruitment of appropriate specialists on a project-by-project basis will improve collaboration and development of the consortium. In addition, this approach leverages the strengths of each institution by recruiting the most interested specialists regardless of site location.

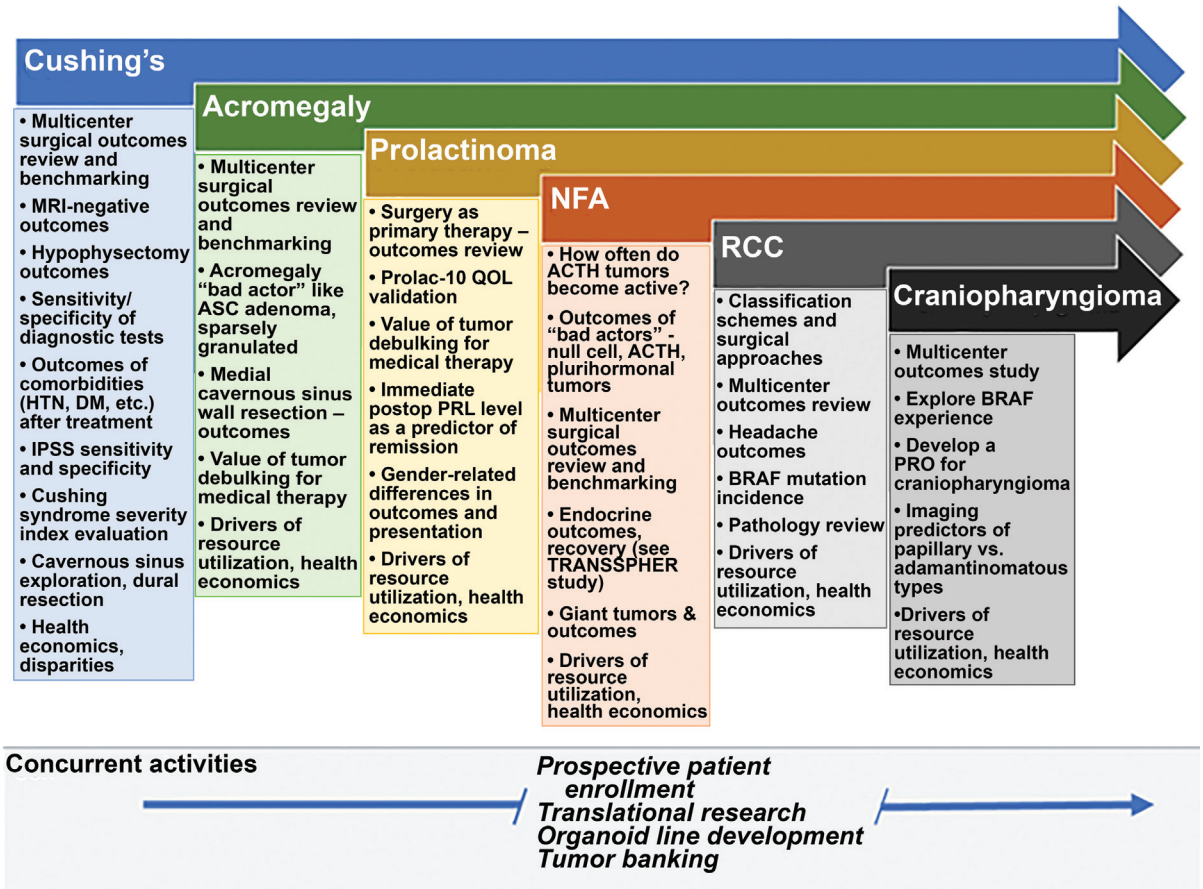

Fig. 4 Scientific roadmap. Sequencing of retrospective clinical studies and concurrent activities planned at the October 2021 virtual scientific session.

Regulatory Approval

Institutional board review (IRB) approvals for retrospective data sharing and prospective data collection were the first major challenge. Each joining clinical site had variability in IRB requirements. Completion of IRB protocols at the leading institution (i.e., BNI) aided the addition of other clinical sites by having an established and approved entity. An IRB waiver of consent was permissible for retrospective data sharing, but informed consent was deemed necessary by all participating institutions for prospective data collection. Agreements for data sharing required legal review, approval from each institution, and individual review of any process where protected health information was being managed. This process took significant time where unanticipated hurdles required completion. An established study protocol with clear guidance on the scope and structure of the consortium was key to inform other parties. Completion of paperwork and regulatory requirements without real scientific discussion was a major challenge to overcome.

Steering Committee and Bylaws

Development of consortium bylaws and establishment of leadership was key to identify and overcome challenges. Bylaws helped to define (1) the consortium scope and purpose, (2) the structure of the steering committee, (3) the scientific direction of the group, (4) new clinical site requirements and onboarding, (5) the protocol for research proposals, (6) authorship criteria and the publication process, and (7) data accessibility. The roles and term limits of consortium president, secretary, treasurer, and scientific lead were established. Monthly meetings among the representatives of the participating institutions with an established agenda and minutes as well as a shared project cloud drive helped with organization. The steering committee outlined potential avenues for future exploration (►**Figs. 2** and **3**).

Data Sharing and Collaboration

Data-sharing processes and authorship were important points of discussion. Individual data were determined to belong to each institution, but once aggregated could be used for investigation approved by site members. Authorship was based on individuals meeting all three of the criteria provided by the International Committee of Medical Journal Editors[24]: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, statistical expertise, or obtaining funding; (2) drafting the publication or revising it critically for important intellectual content; and 93) approval of the final version to be published.

Funding Roadmap

The data hub is funded by the BNI and philanthropic support from grateful patients and the Lodestar Foundation. Each participating site is self-funded. Future financial support will depend on executing the RAPID mission and demonstrating value for patients and surgeons. Our goal is to develop a track record of productivity that will serve as a foundation for competing for extramural government funding and industry partners. Previously successful registries such as the pediatric Hydrocephalus Clinical Research Network (hcrn.org) have used a variety of philanthropic and foundation funds before obtaining Patient-Centered Outcomes Research Institute funding.[5] Alternatively, the NeuroPoint QOD Spine Registry (neuropoint.org/registries/qod/), American Spine Registry (neuropoint.org/asr/), and International Spine Study Group (issgf.org) use significant industry funding for support.[3,4] A multicenter registry to study intraoperative magnetic resonance imaging (MRI) in neuro-oncology also uses industry funding.[8,19–22] The National Institutes of Health has a track record of funding registries, but the focus tends to be on disease pathophysiology and epidemiology with limited room for surgical outcomes. Ultimately, the path for funding will be defined by the goals, timeline, and stakeholders of the consortium. Emphasis of the public health and health economic aspects of surgical care will be key for successful funding. A formalized subcommittee under the treasurer will identify potential funding sources for the submission of proposals. Foundational and industry partners will be identified that can be used to expand the scope of RAPID.

Study Variables

Establishment of a data dictionary was important to answer clinically meaningful questions. Data modules for each tumor subtype were planned; the process of development of the clinical modules was divided among different clinical sites to compile the appropriate variables and construct the database. At least 385 variables were planned for the study and customized to the different pituitary tumor subtypes, namely acromegaly, Cushing's disease, nonfunctioning adenoma, prolactinoma, craniopharyngioma, and Rathke's cleft cyst (►**Fig. 3**). The members of the consortium agreed to include specified QOL instruments, including the 36-Item Short Form Health Survey, Acromegaly Quality of Life (ACRO-QoL) questionnaire, Cushing's disease QOL questionnaire, Sino-nasal Outcome Test 22 (SNOT-22), and Visual Function Index (VF-14). Variables were then reviewed by all clinical sites to ensure all desired variables were being captured. Automated data entry from electronic medical records to a separate database is not currently possible in most U.S. academic medical centers. Instead, data will need to be entered by established site coordinators. Thus, establishing internal data audits will be critical to reduce the risk of erroneous data collection. Audits of entered data, screened patients, and accuracy of data will be performed for each clinical site. The BCOC administrators will review data integrity and perform randomized audits for each clinical site on a continual basis. The BCOC team will hold monthly meetings with all clinical site study coordinators to troubleshoot issues, monitor progress, and facilitate data auditing.

Imaging Bank

The consortium will incorporate imaging information into the Visiontree database via the Ambra PACS system (https://ambrahealth.com/) at a future date. This will allow an imaging

database that correlates with clinical and pathological information. Images can be stored for future radiomics analysis.

Tumor Biobank

Initial discussions within the consortium determined the standard needed for biobanking, including storage of paraffin-embedded tissue and flash-frozen tissue. Each clinical site determined their own protocol for consenting patients and preserving tissue. Sites without a prior protocol were able to adopt the best practices of other sites. Tissue can be preserved for future genomic analysis. Additional guidelines for biobanking cryopreserved tissue depending on anticipated cell line needs, blood/serum for cell-free deoxyribonucleic acid study, and xenograft modeling of tumors will be established in stages. These tissues will be housed at each individual institution and incorporated into future research projects, which reduces upfront infrastructure needs and ensures longer-term specimen preservation. For example, recent unpublished work from Little et al demonstrated the potential to generate pituitary adenoma organoid models that could be used for study of molecular mechanisms and high-throughput drug testing. We also anticipate establishing a living biobank with pituitary adenoma organoids to facilitate future translational research.

Study Proposals

Multiple committee meetings organized around disease modules were used to outline retrospective and prospective studies. In addition, a virtual scientific retreat in October 2021 helped to identify study priorities. Study proposals reviewed the available literature, assessed the feasibility of study questions, and generated an analysis plan. Many study questions, such as the natural history of pituitary adenomas, could not be feasibly performed because of the long timeline required and sample size. Instead, analysis of treatment variation, surgical outcomes, and improved prospective data were strengths of a registry approach. Ultimately, retrospective data would be limited in accuracy and subject to bias but could be helpful in identifying research ideas for future study. Prospective patient data collection at 1, 3, 6, and 12 months postoperatively, and then annually, will be planned.

New study proposals generated by participating sites will be submitted to the steering committee, which would review in a timely fashion and provide a priority score, based on potential scientific impact, soundness of methodology, practicality (e.g., study timeline and resources necessary), and overall assessment. Studies with low priority score or methodological concerns would receive feedback from the steering committee and encouraged to resubmit ideas thus supporting the collaboration. All sites are encouraged to submit proposals regardless of whether the site is a lead on development of the clinical module. In addition, it is a goal of RAPID that all sites be a champion for at least one project and that relative priority would be given to proposals from sites that are not currently leading a project. Although participating sites may submit study proposals requiring sites to collect additional data not already built into the clinical modules, the steering committee plans to limit the number of these types of studies at any given time to avoid overburdening data collection processes at participating sites.

Future Directions

The scientific roadmap was developed at the virtual scientific session in October 2021 and has been continually developed. Clinical modules will be prioritized as follows: Cushing's disease, acromegaly, prolactinoma, nonfunctioning adenoma, Rathke's cleft cyst, and craniopharyngioma (►**Fig. 3**). The initial work will focus on retrospective studies to achieve early "wins" and demonstrate a track record of success. For example, in Cushing's disease, we will review surgical outcomes benchmarks, MRI-negative outcomes, and diagnostic utility of biochemical testing. The breadth of these studies will expand as the prospective data collection matures. Implementation and study of patient care pathways are planned. Identification of institutional variation and comparison of adequately powered outcomes would be the initial step before implementing a system-wide practice change. Certain potential avenues of standardizing patient perioperative care could include which preoperative laboratory tests or imaging are required for surgery or in postoperative follow-up, which postoperative management pathways offer the best outcomes, and which follow-up time points offer the most benefit. The consortium can also be a mechanism to study standardized training and protocol to improve patient care. Generation of a simulation training based on feedback from individual sites can be a deliverable for other surgeons to learn.[25] Simulation training can also help generate checklists for best practices (e.g., carotid injury on an endonasal procedure, management of cerebrospinal fluid leak).[26–28]

Plans to continue expanding RAPID to other topics and institutional sites have been proposed. Additional topics will require involvement and agreement from different clinical sites. Success from initial work will be key to continue expansion to other skull base research topics. Additional sites will be added via a structured approach if they are able to demonstrate a commitment to clinical research, potential to contribute to the team, and institutional structure to support a role in the consortium. The success factors for participating centers are a track record of academic productivity, availability of internal funding, multidisciplinary practice environment, an eager collaborator who will attend to the work of the consortium, and support from the department chair.

Patient recruitment is anticipated to be one of the strengths of the consortium. Results from the TRANSSPHER trial showed recruitment of 530 patients with pituitary adenoma among 7 centers between February 2015 and June 2017. We anticipate approximately 360 recruited patients with pituitary adenomas annually among the 11 centers, as well as additional patients with other pathologies. We also anticipate sufficient heterogeneity of cases to allow for the planned subgroup analysis.

Conclusion

Surgical consortia can potentially aid in the treatment of neurosurgical patients by establishing care pathways,

sharing best practices, and adjusting to surgical practice changes. Significant collaboration is needed to organize, develop, and maintain a surgical consortium. Our goal with the development of a neuroendocrine consortium is to improve patient outcomes, establish benchmarks for procedures, and develop multicenter collaboration. Skull base pathologies remain rare enough that they are challenging to study in single-center studies. In addition, significant surgical nuance and various institutional-specific perioperative pathways are used in the treatment of these lesions, which makes external validation of study findings difficult to interpret. Evaluation of pituitary adenoma outcomes will be helpful as an initial step, which can then be broadened to other pathologies. A framework for developing a consortium as well as the challenges faced in doing so have been described here. More important than a finalized structure, a framework for continually developing the collaboration, modifying its intention, and adding future clinical sites are key.

Funding
This study is funded by Barrow Clinical Outcomes Center, Barrow Women's Board, individual member institutions/departments, and Lodestar Foundation.

Conflict of Interest
A.L. received grant from Barrow Foundation. P.G. received consulting fee from Spiway, LLC; A.L. from BK Medical, Spiway; V.K. from Integra and Stryker and J.J.E. from Mizuho. D.H. received honoraria from Varian Siemens 2022. A.L. also has a leadership role in Kogent.

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