
HYDROCEPHALUS ASSOCIATION STRATEGIC RESEARCH PLAN 2010-2014

1 PROCESS/BACKGROUND

1.1 PRIOR TO 2010

In September of 2005, the Hydrocephalus Association (HA) was instrumental in the first ever NIH-sponsored workshop on Hydrocephalus entitled "*Hydrocephalus: Myths, New Facts, and Clear Directions*". From those workshops a white paper was written outlining priorities for hydrocephalus research. The white paper was titled "*Priorities for hydrocephalus research: report from a National Institutes of Health-sponsored workshop*" and was published in the Journal of Neurosurgery in November 2007. In May of 2008, HA held a research strategy workshop "Accelerating Hydrocephalus Research" with respected scientists and peer cure research nonprofits to review the landscape of research against the 2007 priorities white paper from the NIH conference and decide if and how to incorporate research funding into HA's mission. In early 2009, HA's board changed its mission to include funding research and developed a research funding initiative. HA raised \$500K of funds and launched its first round of funding. The first funding initiative was to provide grants to mentored young investigators (MYIs) to stimulate new researchers to study hydrocephalus.

1.2 DURING 2010 - 2011

In February 2010, HA's research committee (RC) invited an advisory group of noted hydrocephalus and brain researchers to Washington DC for a research strategy retreat. Specific research targets and possible mechanisms were recommended by the advisors as the RC contemplated its research strategy.

Two important outcomes from that meeting followed in May and June of 2010. The CEO met with the device manufacturers in May to share our general direction and seek support. The RC convened a research strategy retreat in June with experts in the area of cognitive and behavioral development to seek their input on research priorities related to hydrocephalus.

From July-October 2010 the RC has discussed the recommendations from the two strategy retreats in 2010 and developed briefs on the targets (and likely mechanisms) along with help from advisors. This plan represents the strategies and priority investments developed by the RC

for review by the HA board of directors for HA's November 2010 board meeting in Washington DC.

In early 2011, Research Committee members began to reach out to various constituents for feedback. The RC has garnered feedback from members of the National Institutes of Health's Working Group on Hydrocephalus. In addition, HA's members of HA's Scientific and Medical Research Advisory Committee have provided feedback. Throughout the rest of 2011, HA board members contacted members of the hydrocephalus community to get their feedback on the Research Initiative Strategic Plan. This plan represents the culmination of that process and sets our direction for fundraising and research through 2014.

2 DESIRED HIGH LEVEL OUTCOMES OF HA'S RESEARCH STRATEGY

HA Mission: The mission of the Hydrocephalus Association is to eliminate the challenges of hydrocephalus.

HA Research Mission: The specific mission of the Hydrocephalus Association's research program is to stimulate and fund innovative research that improves the quality of life for people living with hydrocephalus and, ultimately, to find a cure.

HA Research Strategy: Desired High Level Outcomes

1. Research funded and stimulated by HA's investments will have positive clinical and quality of life outcomes on the lives of those who suffer from this condition.
2. More scientists will be studying this condition and trying to unlock its mysteries and improve our understanding so that we might better diagnose and treat it.
3. HA will be respected as an effective leader in driving a hydrocephalus research agenda.
4. HA's strategy will generate significant additional financial resources – both those it raises itself and those it stimulates through its research investments - dedicated toward hydrocephalus research.
5. The hydrocephalus research agenda will be better coordinated and communicated across all stakeholder groups: donors, government, scientists, clinicians, partner NGOs and patients. HA will be seen as the critical bridge between all of these groups.

3 HYDROCEPHALUS RESEARCH PROBLEM STATEMENTS

The following problems are the most important issues to be addressed by the HA Research Initiative in the near term:

1. There are inadequate resources - money, people, and infrastructure - devoted to hydrocephalus research.
2. The complexity of hydrocephalus - its multiple etiologies, symptoms and sequelae - leads to: (1) a lack of consensus on treatments and outcome measures for a patient's clinical and developmental health, and on measures for their quality of life; and (2) significant challenges to the high-level organization, coordination, and direction of independent research efforts, hampering progress toward a better collective understanding of hydrocephalus. The complexity of the condition also creates barriers to entry for new investigators and for established investigators seeking to turn their tools and approaches to the problems of hydrocephalus
3. Variation in clinical diagnosis and treatments or interventions indicates substantial room for improvement in patient safety, clinical outcomes, and cost of treatment.

4. Shunts are, and will continue in the near term to be, the primary treatment for hydrocephalus, yet their use has unacceptably high and frequent negative consequences such as shunt failure and numerous attendant complications and costs.

4 HA'S HIGH LEVEL PRIORITIES TO ADDRESS RESEARCH PROBLEMS

The Hydrocephalus Association's Research Committee has considered the problems associated with hydrocephalus research and have recommended these strategic priorities. The high-level priorities below are focused on making progress in *all* the problem areas. Under each priority we list possible investments HA could make to advance our research mission. In the section 5, we recommend a specific list of research investments in the near term.

Priority 1: Stimulate the hydrocephalus research ecosystem

The hydrocephalus research ecosystem is the set of institutions (public and private) and individuals that are studying this condition. It includes patients who are part of studies. Due in large part to HA's concerted efforts to raise funds and awareness for research, the current ecosystem is more robust than even five years ago. Nevertheless, much more attention and effort - is required to "move the needle" on improving the outlook for those unfortunate enough to be suffering from hydrocephalus. Public and private investments combined are less than \$10MM a year for hydrocephalus as of 2010.

HA proposes to stimulate the ecosystem to drive more attention and funding.

- Fund forums, consensus conferences and research workshops to coordinate and organize researchers working on problems relating to hydrocephalus and encourage multi-center and interdisciplinary collaborative research
- Encourage cross-disciplinary collaboration
- Incentivize younger, early career investigators to choose hydrocephalus research problems and pair them with senior hydrocephalus research mentors
- Support mid-career investigators who are actively working on hydrocephalus problems
- Fund studies that can lead to pilot data that might prove useful in submitting compelling grants to the NIH
- Encourage application of cutting-edge techniques and approaches to hydrocephalus research
- Fund tissue banks and registries to provide sufficient data sources for investigators interested in studying problems that require such infrastructure

Priority 2: Identify and improve clinical best practices, reduce common problems associated with shunting, and develop consensus in the scientific and clinical community on common clinical assessments and outcome measures.

There is clear evidence from a number of sources that the management of patients with hydrocephalus varies from surgeon to surgeon, and center to center. This variation does not seem to be based on the underlying condition, or the severity of the hydrocephalus, but rather (at least to some extent) the local habits and training of the people doing the treatment. Some of this variation is unavoidable and reasonable, but there is considerable evidence that minimizing variation has significant impacts on clinical outcomes, efficiency of care, and cost of care. With rapidly expanding knowledge and technology, and a health care system that performs far below acceptable levels for ensuring patient safety and needs, it is becoming increasingly important that front-line health care professionals understand the basics of quality improvement methodologies and terminology. The fundamentals of quality improvement provide a starting point for improvement projects, and stimulate further inquiry into the quality improvement methodologies currently in use, such as plan-do-study-act, six-sigma, and lean strategies. This area is a high yield area for funding support. It does not depend on "new discoveries" or prolonged multicenter trials. It is adaptable to academic and private practice and is more of an iterative process in which care is improved based on incoming data. This methodology is broadly applicable to many areas of care. It is currently being applied in pediatrics in an attempt to reduce infection rates. The benefit of this type of research is directly to the patient. The cost is low compared to other types of clinical research.

- Support multicenter clinical research networks for pediatrics and adults by funding shared datacenter infrastructure (note: such a strategy provides a shared infrastructure and patient population for clinical and translational research).
- Fund clinical registries built on the multicenter research network's data centers
- Fund clinical quality improvement studies and randomized control trials.
- Encourage participation by clinicians and sites in clinical and translational research studies in multicenter network studies

Shunt failure remains a difficult problem with a one year failure rate (after implantation) in the 30-40% range, at least in the pediatric population (the failure rate is lower in adults). The ultimate benefits of reducing shunt failure are reduced shunt-surgery-related complications such as bleeding and infection that can cause additional damage to an already compromised nervous system, reduced hospitalization, reduced cost of care and improved quality of life.

Complications that reduce shunt survival include shunt malfunction, and shunt failure. In addition, shunt infection is a significant problem that can significantly impact the health of a patient of any age implanted with a shunt. Shunts fail when they disconnect, become blocked (obstructed), infected, or when the functional characteristics no longer meet patient needs. The shunt failure rate is relatively high. Of approximately 40,000 shunt surgeries performed annually in the U.S., only about 30% are a patient's first surgery and the norm is that patients require multiple shunt revisions within their lifetime. Shunt malfunction may be difficult to diagnose. Diagnostic tests specific for shunt failure include CT, plain x-rays, nuclear medicine studies. Also, there is a woeful ignorance of many physicians, including neurologists and neurosurgeons, regarding the functioning of shunts and how to manage shunt failure.

Improving shunt treatments is a critical component of improving near term prospects for patients who have or need shunts.

- Fund clinical studies that seek to reduce shunt failure rates
- Fund clinical studies that seek to reduce complications from shunting (e.g. infection)
- Fund basic science pilot studies that develop novel ways to identify or eliminate the major problems associated with shunting (e.g. clogging, infection, and invasive and irradiating diagnosis and monitoring)

Assessment of life quality, including cognitive-behavioral functioning (strengths and weaknesses) of children and adults with hydrocephalus, is essential to the development of appropriate individualized educational and life plans. It is also a vital component of research examining the development, response to medical/clinical treatments and educational interventions, and well-being of individuals with hydrocephalus. Although some measures do exist, quality of life outcome assessments are not widely used in practice, nor are they widely accepted. There is no standard for which assessment methods and tests are most appropriate for individuals with hydrocephalus. As a result, clinicians, physicians, researchers, and educators must make their best guesses about what assessments to conduct, leading to rampant inconsistencies in our knowledge base about the quality of life and cognitive-behavioral functioning of individuals with hydrocephalus.

- Fund a consensus conference to develop an accepted core battery of cognitive and behavioral assessments
- Fund studies that develop and validate quality of life models and measures, and fund consensus conference to adopt said studies.

Priority 3: Improve our understanding of hydrocephalus etiology/etiologies to ultimately aid in diagnosis and treatment of the condition, and improve quality of life.

There are a multitude of known causes of hydrocephalus. It is a poorly understood and complex set of interactions in the brain. For example, irregular CSF production and/or absorption in the brain are believed to be mechanisms causing brain injury, yet little is known about what constitutes "regular" CSF flow. Having a better understanding of hydrocephalus' root causes, and validated scientific tests and tools to identify them, will go a long way to improving diagnoses, designing treatments/interventions, and measuring the effectiveness of treatments.

- Fund basic research to better understanding CSF flow and absorption
- Fund research on possible biologic/pharmacologic interventions
- Fund research on possible biomarker identification
- Fund basic research on identification of possible structural genetic variations and phenotypes of hydrocephalus
- Fund research on brain injury and recovery mechanisms

5 HA'S SHORT TERM PRIORITY INVESTMENTS AND OBJECTIVES

Investment Framework:

We propose a set of research investments for FY2011-2014 to advance all five of our priorities. Not only do these investments address the problems outlined in this document, they also create a framework with enough breadth to enable HA and donors and strategic partners to evaluate and proposed new initiatives and to evolve our priorities based on progress.

5.1 PRIORITY INVESTMENTS 2011-2014

Priority Investments:

Priority 1: Stimulate the hydrocephalus research ecosystem

- A. **(\$50-\$200K per year)**; In order to drive and coordinate the research agenda, the RC recommends funding research forums and conferences to stimulate multi-disciplinary collaboration within and across institutional teams on *critical research areas*. HA's past investments in helping to set the agenda have influenced a 10X increase in NIH investments in Hydrocephalus. *Critical areas for research collaboration include investigating causes and complications of shunt failure; investigating practice variation; achieving consensus on a core battery of cognitive and behavioral assessments; beginning discussions about how to set up shared tissue and fluid banks, and shared data; beginning discussions on possible biomarker avenues; beginning discussion on CSF dynamics; beginning discussion of possible areas for identifying structural genetic variations that lead to hydrocephalus.* **3 Year Objective:** collaborative efforts catalyzed by the forums and conferences that result in pilot studies that buttress effective NIH research study applications, which ultimately result in NIH funding hydrocephalus at \$15M (2x what they are funding today).
- B. **(\$220,000 per year)** Catalyze new research and researchers through career development and education grants. These investments will incentivize researchers to work in *critical areas* mentioned in priority 1. These investments could be mentored young investigator awards and mid-career awards. **3 Year Objective:** 50% of our funded PI's secure NIH funding in hydrocephalus topics in 3 years.

Priority 2: Identify and improve clinical best practices, reduce common problems associated with shunting, and develop consensus in the scientific and clinical community on common clinical assessments and outcome measures.

- A. **(\$250,000 per year)** Fund a multi-center clinical research network data center for pediatric and adult hydrocephalus participating institutions. As part of this investment, fund the development and accrual of data into a patient registry. **NOTE:** *This expense is based on HA's funding of a long term relationship with the Hydrocephalus Clinical Research Network (HCRN) to provide cost effective clinical research to improve outcomes and treatments for hydrocephalus. HCRN is an established collaboration of seven hospitals and their clinicians that treat hydrocephalus. HCRN pools its patient data in a registry and conducts multiple simultaneous studies across its network population. Current studies include shunt infection, management of post hemorrhagic hydrocephalus, ultrasound guided shunt placement, imaging and neurological outcomes, efficacy of Endoscopic Third Ventriculostomy, and biomarkers for Post Hemorrhagic Hydrocephalus. Currently HCRN is focused on a pediatric population but it is expected that there will be synergies for pediatric and adult networks – and that the pediatric network will share knowledge to help the adult network get launched.* **3 Year Objective:** detailed clinical treatment and outcome histories for 5,000 patients by the end of 2013.
- B. **(\$100,000 per year)** Fund scientific studies that seek to understand shunt failure and reduce infection rates associated with shunt treatments. **NOTE:** *The HCRN is currently conducting a QI study aimed at reducing shunt surgery infection rates.* **3 Year Objective:** 50% reduction in infection rates at participating centers with a published protocol to leverage these benefits at other institutions (**NOTE:** *The HCRN has already accomplished a 35% reduction*); 25% reduction in failure rate of shunts in the first year.
- C. **(\$100,000 per year)** Fund scientific studies that seek to understand and reduce clinical practice variation. **3 Year Objective:** complete 3 studies of variation.

Priority 3: Improve our understanding of hydrocephalus etiology/etiologies to ultimately aid in diagnosis and treatment of the condition, and improve quality of life.

- A. **(\$50,000 per year)** The development of tissue, fluid, animal models and image databanks to aid in testing research hypotheses. **3 Year Objective:** data obtained from the banks facilitates the proposal and piloting of new studies in hydrocephalus resulting in 2 high quality grants submitted to NIH.
- B. **(\$230,000 per year)** Fund basic and translational scientific research investments. These investments should consist of pilot studies to find biomarkers, pilot studies to better understand CSF regulation, pilot studies investigation possible biological or pharmacological interventions, and studies that investigate the possibility of genetic variations in populations experiencing/exhibiting hydrocephalus. **3 Year Objective:**

for each of these studies, the goal would be to have one to two researchers successfully secure NIH funding in this area.

5.2 INVESTMENT PRIORITIES BY DOLLARS RAISED

The following priority table would delineate the projects that got funded as investment levels were reached.

HA will invest in its top priorities by raising money to support a one year or multi-year commitment, depending on the RFA, before funding the next priority. So while a commitment to run a conference is a per year commitment which will receive the first \$50K of money raised, a two year commitment to two young investigators will require \$220K to be raised before seeking to commit to a network and registry.

	Yr1	Yr2	Yr3	Total
Conferences	\$50,000	\$50,000	\$50,000	\$150,000
Career	\$220,000	\$220,000	\$220,000	\$660,000
Network/Registry	\$250,000	\$250,000	\$250,000	\$750,000
Shunt Failure	\$100,000	\$100,000	\$100,000	\$300,000
Practice Variation	\$100,000	\$100,000	\$100,000	\$300,000
Banks/Animal Models	\$50,000	\$50,000	\$50,000	\$150,000
Basic Science Investments	\$230,000	\$230,000	\$230,000	\$690,000
	\$1,000,000	\$1,000,000	\$1,000,000	\$3,000,000

APPENDIX: RESEARCH INVESTMENT PHILOSOPHIES AND GUIDING PRINCIPLES

The mission of the Hydrocephalus Association is to eliminate the challenges of hydrocephalus by stimulating innovative research and providing support, education and advocacy for individuals, families and professionals dealing with hydrocephalus.

The specific mission of the Hydrocephalus Association's research program is to stimulate and fund innovative research that improves the quality of life for people living with hydrocephalus and, ultimately, to find a cure.

5.3 INVESTMENT PHILOSOPHIES

HA will follow these philosophies when making grants:

- We will seek to fund high quality, meritorious research.
- We want to be fast and urgent about our mission and so we will grant quickly and change course quickly if we find things are not working.
- We will encourage collaboration and information sharing in research we fund.
- We will encourage interdisciplinary science in research we fund.
- Our basic science funding will be directed toward science that is likely to be translated into clinical applications.
- We will grant using a venture philanthropy model – we will “give with strings.” Continuing funding will be contingent on meeting pre-determined progress milestones.
- Where possible, we will encourage a “center” based approach to interdisciplinary research.
- We will encourage the development of new scientists to study this condition, while continuing to support the careers of those with experience in studying hydrocephalus.
- We will establish an expense ratio informed by standards of excellence and meet that expense ratio by year three.

5.4 GUIDING PRINCIPLES

1. HA will seek to strategically balance investments in basic science, translational, and clinical based hydrocephalus research across the range of causes of hydrocephalus.
2. In its initial phase, HA's priority will be to fund research oriented toward building preliminary data (i.e., pilot studies, etc.) in support of increasing the researcher's odds for success in acquiring government and other research funding for follow-on pivotal trials.
3. HA will employ a venture philanthropy approach to grant making.

4. HA Research will develop an “opportunity map” to provide guidance to investigators about what we are interested in funding.
5. The HA opportunity map will include clinical research, bench science and translational research.
6. HA will seek to attract new research talent into the field through various pipeline and early career development mechanisms.
7. HA will seek to fund researchers that are committed to collaboration.
8. HA Research will establish itself as a central clearinghouse for all hydrocephalus research such that most researchers will see significant benefit in keeping HA in the loop of their work, funding status and grant writing.
9. HA will seek to create a complementary research funding story in conjunction with existing private research funding organizations.
10. HA's role is as a funder of research and will not conduct research itself.
11. HA Research will work with HA Advocacy to establish funding for critical infrastructure elements of a healthy research ecosystem such as a registry, tissue data banking, etc.
12. HA will be a timely strategic conduit for funding but raising and giving money away each year with consideration to an endowment when appropriate.
13. In addition to its own funding criteria and process, HA Research will utilize existing scientific evaluation processes to vet grant proposals.
14. HA will consider supporting research that could significantly benefit hydrocephalus even if the research does not directly concern hydrocephalus (e.g., CSF production rates and sources, CSF drainage mechanisms, etc.)