An update on research priorities in hydrocephalus: overview of the third National Institutes of Health–sponsored symposium “Opportunities for Hydrocephalus Research: Pathways to Better Outcomes”

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Building on previous National Institutes of Health–sponsored symposia on hydrocephalus research, “Opportunities for Hydrocephalus Research: Pathways to Better Outcomes” was held in Seattle, Washington, July 9–11, 2012. Plenary sessions were organized into four major themes, each with two subtopics: Causes of Hydrocephalus (Genetics and Pathophysiological Modifications); Diagnosis of Hydrocephalus (Biomarkers and Neuroimaging); Treatment of Hydrocephalus (Bioengineering Advances and Surgical Treatments); and Outcome in Hydrocephalus (Neuropsychological and Neurological). International experts gave plenary talks, and extensive group discussions were held for each of the major themes.

The conference emphasized patient-centered care and translational research, with the main objective to arrive at a consensus on priorities in hydrocephalus that have the potential to impact patient care in the next 5 years. The current state of hydrocephalus research and treatment was presented, and the following priorities for research were recommended for each theme. 1) Causes of Hydrocephalus—CSF absorption, production, and related drug therapies; pathogenesis of human hydrocephalus; improved animal and in vitro models of hydrocephalus; developmental and macromolecular transport mechanisms; biomechanical changes in hydrocephalus; and age-dependent mechanisms in the development of hydrocephalus. 2) Diagnosis of Hydrocephalus—implementation of a standardized set of protocols and a shared repository of technical information; prospective studies of multimodal techniques including MRI and CSF biomarkers to test potential pharmacological treatments; and quantitative and cost-effective CSF assessment techniques. 3) Treatment of Hydrocephalus—improved bioengineering efforts to reduce proximal catheter and overall shunt failure; external or implantable diagnostics and support for the biological infrastructure research that informs these efforts; and evidence-based surgical standardization with longitudinal metrics to validate or refute implemented practices, procedures, or tests. 4) Outcome in Hydrocephalus—development of specific, reliable batteries with metrics focused on the hydrocephalic
As reported in the priorities from the 2005 National Institutes of Health (NIH) hydrocephalus workshop and presented at the 2009 NIH-sponsored workshop in Baltimore, Maryland, the clinical and scientific perspective of hydrocephalus has shifted from the oversimplified view of hydrocephalus as a “plumbing problem” that is adequately managed with a shunt to that of an exceptionally complex, multifactorial disorder involving novel and poorly understood injury and recovery mechanisms. The white paper generated from the 2005 NIH hydrocephalus symposium provided a broad overview of the priorities within the hydrocephalus community and set the framework for the last several years in terms of research focus and funding initiatives both within NIH and within nongovernmental funding agencies.

The most recent conference, “Opportunities for Hydrocephalus Research: Pathways to Better Outcomes,” held in Seattle, Washington, July 9–11, 2012, was organized to review the current state of the field and to identify which areas of research could produce short-term clinical progress and which would require a longer-term strategy. Clearly, both efforts would benefit from multidisciplinary approaches, so an additional goal of the conference was to foster collaborations and data sharing.

Presenters were invited based on the initial review and acceptance of an NIH U13 Conference grant (1U13NS080503–01) and recommendations from the Steering Committee, which consisted of experienced investigators in all aspects of clinical and basic research in hydrocephalus, a program director at NIH, and the CEO of the Hydrocephalus Association. The Hydrocephalus Symposium Expert Panel (see Appendix) also provided input on who should present. The registration to the symposium was open to any attendees. Thus, a diverse group of 65 active investigators in hydrocephalus participated.

This report will summarize the research priorities generated by the conference attendees in four broad categories: 1) causes of hydrocephalus; 2) diagnosis of hydrocephalus; 3) treatment of hydrocephalus; and 4) outcome in hydrocephalus. The remaining discussion is organized to highlight the background information presented at the meeting and to summarize the consensus discussion that resulted in the summary research priority recommendations. The references cited highlight the presentations and discussion and are not intended to be a comprehensive review of the field. It is important to note that all of the participants in this conference had an opportunity to express their opinions, especially in the plenary group discussions. Numerical rankings of responses from the entire audience were obtained during the final discussions and were used to identify consensus priorities in this report. Nevertheless, this work reflects the opinions of the experts who attended this conference rather than a systematic, balanced review of the literature or the field. The goal of the paper is to present the conclusions from the conference to the larger neurosurgical and medical community, rather than to serve as a comprehensive review of hydrocephalus research, a topic that could fill an entire volume. Additional objective international perspectives on hydrocephalus research can be found in reviews by Stagno et al., McAllister, Andreason and Juhrer, and Robinson. The scientific program agenda, conference structure, meeting objectives, list of attendees, conference leadership, and slides for each presentation are available on the website of the Hydrocephalus Association (http://www.hydroassoc.org/2012-seattle-conference-program/).

Theme 1: Causes of Hydrocephalus

Genetics

Judging from the plethora of information on the underlying genes in human and mouse hydrocephalus, the genetic basis of hydrocephalus appears to be a daunting problem. Early pattern formation genes such as SHH, ZIC2, PAX6, and WNT1, neuronal path-finding genes such as L1CAM, genes related to cortical development such as POMT1, and those related to growth regulation such as PIK3CA and AKT3 have been implicated. Developmental disorders presenting with hydrocephalus include neural tube disorders, forebrain and hindbrain developmental disorders, brain growth disorders, and cortical malformations. Alterations in the choroid plexus, ependyma, aqueduct, ventricles, and extraxial spaces can also lead to hydrocephalus. The study of known human genetic syndromes that have hydrocephalus as a component of the disease represents a pathway to understand the complex polymorphisms that lead to hydrocephalus.

Abnormal neurogenesis in fetal-onset hydrocephalus in both humans and animal models represents an avenue for stem cell therapy. It was suggested that a common pathogenetic mechanism involving junctional complexes starts early in embryonic life with disruption of the neural stem cells (NSCs) and neural precursor cells (NPCs) forming the ventricular zone (VZ) and subventricular zone (SVZ), respectively. NSCs and NPCCs have been collected from the CSF of hydrocephalic human fetuses and mutant HTx rats and grown into neurospheres. The cells forming these neurospheres express pathological features, thus becoming a valuable tool to study cellular and molecular defects in animal and human neurogenesis and providing a platform for future drug studies in hydrocephalus.

Models of the disrupted VZ demonstrate that repair mechanisms are present in hydrocephalic animals and humans. In congenital hydrocephalus, reactive astrocytes replace absent ependymal cells at the ventricular border. The role of these astrocytes in the production of
proinflammatory and neuroprotective factors is currently under study. In animal models, the reactive astrocytes can be involved in the production of tumor necrosis factor–α (TNFα) that could have a role in hippocampal and neocortical impairment. Thus, TNFα and transforming growth factor–β (TGF-β) may be suitable biomarkers for diagnosis and prognosis in different forms of hydrocephalus.

Pathophysiological Modifications

A cardinal feature of ventriculomegaly is that it leads to the gradual destruction of periventricular white matter axons through hypoxic, ischemic, and mechanical stress mechanisms. Metabolic disturbances contribute to reversible dysfunction, but the clinical syndrome of hydrocephalic brain dysfunction may be due predominantly to a subcortical disconnection syndrome. Possible causes of ventricular dilation include obstructed CSF flow with associated increased CSF pulsatility. Small forces repeatedly applied to the brain can lead to ventricular enlargement. Reduced cerebral blood flow occurs in children and adults with hydrocephalus but improves after shunt placement and normalization of intracranial pressure (ICP). Metabolic dysregulation may lead to oligodendroglial and axonal damage. Calcium-related proteolysis and cell death occur analogous to injury cascades seen in brain ischemia and trauma. In the developing brain, hydrocephalus can lead to delayed or reduced myelination, and adverse effects on periventricular germinal matrix tissue have the potential to impair brain development. The degree and type of damage are related to the age at the time of insult, the rate of ventricular enlargement, and the associated rise in ICP with decrement in cerebral perfusion pressure. Some changes are reversible with ventricular shunt placement and reduction in ICP. If axonal destruction has already occurred, improvements are less likely with shunt placement. Targets of pharmacological interventions aim at reducing CSF production, enhancing CSF flow and absorption, decreasing neuroinflammation, providing neuroprotection, and improving recovery/regeneration of damaged tissues.

Recurrence hypoxia-ischemia is common in critically ill preterm infants, but maturation of oligodendrocytes affords increased resistance to this condition. In the setting of cerebral palsy, the declining burden of necrosis in white matter injury raises the question of whether myelination failure is from selective loss of precursor oligodendroglia (PreOL) that are required to generate mature oligodendroglia and myelin. PreOLs are selectively damaged by oxidative stress, and surviving PreOLs can fail to generate myelin in chronic lesions. PreOL maturation arrest is correlated with astrogliosis; glial scars contain high CD44 expression that blocks PreOL differentiation and prevents remyelination. Thus, as the brain matures, PreOL-rich chronic white matter lesions may retain persistent susceptibility to hypoxia-ischemia. Furthermore, high-field MRI permits unprecedented resolution of white matter injury previously not detected clinically at lower field strengths, raising the possibility that therapies directed at myelin regeneration and repair could be monitored over time in preterm survivors.

Lysophosphatidic acid (LPA) is prominent during hemorrhage where high concentrations, as well as hypoxia, can overactivate LPA receptors present on prenatal NPCs. Studies in animals have identified altered LPA signaling that disrupts the normal development of NPCs, suggesting that therapeutic intervention targeting LPA receptors could provide medical treatments for some forms of hydrocephalus.

Areas of Promise and Recommendations for Causes of Hydrocephalus in the Next 5 Years

The consensus of the attendees strongly favored the need for more research in CSF absorption, production, and related drug therapies (Table 1). Two topics are especially important: 1) pathogenesis of human hydrocephalus, including CSF physiology, and 2) improved animal and in vitro models of hydrocephalus. Moderate interest was also shown in developmental and macromolecular transport mechanisms, biomechanical changes in hydrocephalus, and age-dependent mechanisms in the development of hydrocephalus.

Theme 2: Diagnosis of Hydrocephalus

From a clinical perspective, the diagnosis of hydrocephalus has remained a relatively simplistic endeavor, encompassing both clinical signs and symptoms and basic neuroimaging modalities. This theme brought forward new concepts, ideas, and technology that have the potential not only to advance our ability to diagnosis hydrocephalus, but also to track meaningful metrics of diagnostic and treatment success.

Biomarkers

Few biomarkers accomplish the goal of measuring and evaluating normal biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions cleanly or individually. The use of complementary biomarkers within a single disease is likely to provide a more comprehensive assessment of the disease and its course.

Molecules and other predictors of outcome represent an important focus for future research in biomarkers. Normal pressure hydrocephalus (NPH) remains an under-treated diagnosis based on clinical symptoms and knowledge of ICP in association with basic imaging modalities. While clinical consensus guidelines have been advanced, the method of diagnosis is invasive, often requiring external lumbar drainage trials. Various investigations have examined CSF peptides, neurotransmitters, metabolites, and proteins as potential biomarkers. The most promising biomarkers to date include Tau protein, amyloid-β, TNF, lactate, sulfatide, and neurofilament triple protein.

A possible solution to the difficulty of interpreting these results is the use of ratios and/or panels of biomarkers and recording CSF production rate. Similarly, the methods of collection and storage of samples are critical. The ability to follow biomarkers across cohorts, stratify risk factors, and, someday, personalize care is among the translational benefits biomarkers afford in the diagnosis and care of patients with NPH.

CSF proteomics offer the ability to characterize the CSF proteome, identify candidate diagnostic biomark-
ers of hydrocephalus or therapeutic efficacy, identify biomarkers that predict cognitive outcome, elucidate the mechanisms underlying developmental delay, and identify target genes for genetic analysis quickly. NumerouNPH is a two-hit disease, i.e., benign external head proteins involved in nervous system development and function have been identified in CSF, including neural cadherin, neural cell adhesion molecules, neurocan, and neuroserpin. Alterations in CSF proteomic profiles have been noted in patients with impaired cognition. Human ventricular CSF may contain a protein signature that could be used to predict outcome in hydrocephalus patients. Future goals include 1) sharing samples between clinical and experimental research centers to validate techniques and findings; 2) developing guidelines for sample storage, mass spectrometry, and data end points; and 3) supporting these overall goals with governmental and nongovernmental funding allocation.

Neuroimaging

Challenges arise within the standard uses of imaging when determining whether NPH is the result of ventricular enlargement or cerebral atrophy. Neuroimaging is essential to the diagnosis of NPH, but visual inspection without advanced techniques is subjective, with limited power to distinguish NPH from other conditions. Nevertheless, a recent study has shown that diffusion tensor imaging (DTI) can differentiate among NPH, Alzheimer disease, and Parkinson disease. Advanced MRI methodologies can also guide the development of pharmacological treatments by providing quantitative measures of treatment.

MRI findings suggest that in some patients idiopathic NPH (iNPH) is a two-hit disease, i.e., benign external hydrocephalus in infancy followed by deep white matter ischemia in late adulthood. Patients with iNPH have larger than normal intracranial volumes and increased apparent diffusion coefficients in the white matter, supporting the possibility that at least partial CSF outflow occurs through extracellular spaces. Phase-contrast MRI can quantify aqueductal CSF flow and, along with other imaging correlates such as CSF flow voids, can predict shunt responsiveness in NPH.

What is often missing in development and validation of diagnostic and prognostic imaging techniques is the link between these techniques and the underlying mechanisms responsible for any imaging changes. Various MRI techniques, such as phase-contrast MRI, DTI, and elastography, hold great promise in identifying hydrocephalus pathophysiology, guiding clinical management, and developing alternative therapies. Cerebral blood flow represents an important marker that can be assessed with a variety of techniques, including PET, SPECT, and MRI. Standardization of techniques is also critical for multiple centers to correlate various outcome measures.

Areas of Promise and Recommendations for the Diagnosis of Hydrocephalus in the Next 5 Years

The two most important issues in diagnoses are implementation of a standardized set of protocols and a shared repository of technical information (Table 2). Nearly as important are prospective studies with multimodal techniques (e.g., MRI and CSF biomarkers to test potential pharmacological treatments), and quantitative and cost-effective assessment techniques (e.g., CSF diagnosis). The interest in a shared repository with standardized samples was driven largely by the technical and experimental progress made recently in the evaluation of CSF biomarkers. This initiative would require identification of consensus priorities for coordinated and focused biomarker development, validation of promising biomarkers through multi-institutional networks to accelerate clinical implementation, and advocacy for funding to support technology and provide resources for biomarker discovery.

Likewise, the potential that newer noninvasive MRI techniques could bring to the diagnosis of hydrocephalus was clearly apparent. It is encouraging that noninvasive phase-contrast MRI has the ability to calculate ICP indirectly; this advancement could dramatically reduce the need for invasive measurements of ICP, which are not routinely performed currently in North America because of ethical concerns.

Theme 3: Treatment of Hydrocephalus

The continuing high complication rates and new advances prompted a renewed focus on better treatments. In addition, previous conferences have not included bioengineering advances, which are fundamental to the development of optimal surgical devices.

Bioengineering Advances

Despite many advances in the design of the CSF shunt, there have been few improvements in the rate of shunt malfunction, with greater than 40% of first-time shunts failing within 2 years. Shunt obstruction remains a critical challenge and represents the most common point of failure in patients with shunt-dependent hydrocephalus. Current options for solving this problem include the use of improved catheter geometry, the use of antifouling coatings, and active methods to fight in-growth or remove growth after it occurs. Despite various attempts to alter the proximal catheter geometry, none have proven superior. Similarly, catheter coatings have been tried as a means to reduce obstruction, but these prototypes have not been tested clinically. Little to no activity has occurred to address the problem of valve obstruction. Models of flow dynamics, an understanding of cellular and tissue responses to implanted catheters and valves, and the development of novel bioengineering solutions are the pathways to improve upon the recalcitrant problem of obstruction-based device failures.

Improved diagnostics save the clinician from determining device failure by clinical signs/symptoms and rudimentary imaging studies. Opportunities exist to incorporate pressure and flow sensors into devices. The most advanced technologies in this arena have used cutaneous diagnostics to assess shunt function by using CSF flow. Issues arise related to the low range of ICP values needing to be registered, accuracy, resolution, and drift.

Smart shunts represent another area that could provide tangible benefits to patients with hydrocephalus. The common vision of a “smart” shunt includes incorporated sen-
on the bench and in vitro. Models of CSF dynamics are needed to test smart shunts with appropriate algorithms for controlling such devices. Advanced implantable devices that do not drift, and importantly, appropriate low-power draw components, pressure sensors that are suitable for hydrocephalus emphasizes the need for partnership between the scientist, engineer, clinician, and industry. Experience with the development of the Delta sensors (flow or pressure), a pump or valve to regulate flow of CSF, installed electronics to drive a controlling algorithm, the ability to measure various parameters, two-way communication, and implanted power sources such as a battery. Described in concept and detail decades ago (reviewed by Lutz et al. 25), the technological hurdles include low-power draw components, pressure sensors that are implantable with little to no drift, and importantly, appropriate algorithms for controlling such devices. Advanced models of CSF dynamics are needed to test smart shunts on the bench and in vitro.

A perspective on business development pathways related to hydrocephalus emphasizes the need for partnership between the scientist, engineer, clinician, and industry. Two important factors have caused innovation to stagnate in this market sector: 1) The small market relative to other neurological disorders and insertion site have been asserted to improve venous reflux and suture-less connectors. Nevertheless, there is great potential for the development of antifouling and self-cleaning catheters, “smart” valves with telemetry and pressure sensors that do not drift, reinforced kink-resistant catheters, and suture-less connectors.

**Surgical Advances**

For more than 10 years, accurate catheter placement and insertion site have been asserted to improve ventriculoperitoneal shunt (VP) shunt survival. Freehand insertions show that only 50% are placed with high accuracy, but the value of costly navigation systems remains in question. A randomized controlled trial (RCT) faces obstacles including surgeon agreement to randomize when adjunct technology is known to be more accurate for catheter placement.

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<tr>
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<th>Areas of Promise</th>
<th>Recommendations</th>
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<tr>
<td>Genetics</td>
<td>• Determine whether fetal hydrocephalus is a stem cell pathology</td>
<td>• Support multicenter studies that correlate genetic changes in animal models of congenital hydrocephalus with those found in clinical hydrocephalus</td>
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<td>• Determine the pathogenetic roles that VZ and SVZ disruption play</td>
<td>• Promote pathogenetic studies that focus on clinically relevant forms of congenital human hydrocephalus</td>
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<td>• Identify genetic factors in primary and secondary hydrocephalus</td>
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<td></td>
<td>• Identify epigenetic factors in all forms of hydrocephalus</td>
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<td>Pathophysiological</td>
<td>• Identify/clarify the multifactorial injury mechanisms underlying the pathogenesis of hydrocephalus, including the pathophysiology of white matter in hydrocephalus and other neurological disorders</td>
<td>• Support experimental and clinical studies that identify both normal and abnormal CSF production, flow, and absorption</td>
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<td>Modifications</td>
<td>• Improvements in the identification and collaborative use of preclinical models of hydrocephalus</td>
<td>• Support translational studies on the pathogenesis and pathophysiology of human hydrocephalus</td>
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<td>• Pharmacological interventions to supplement surgical treatments for preventing neuronal injury and promoting recovery of function in all forms of hydrocephalus</td>
<td>• Promote experimental studies (both in vivo and in vitro) on improved (translational) models of hydrocephalus</td>
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<td>• Promote studies on the development of pharmacological therapies for all forms of hydrocephalus</td>
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**TABLE 1. Areas of promise and recommendations for hydrocephalus research on causes of hydrocephalus in the next 5 years**

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<tr>
<th>Theme</th>
<th>Areas of Promise</th>
<th>Recommendations</th>
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<tr>
<td>Biomarkers</td>
<td>• Many centers have the ability to collect CSF and tissue from pediatric and adult hydrocephalic patients; this capacity could produce excellent multicenter studies if standardized protocols are followed</td>
<td>• Implementation of a standardized set of acquisition protocols and a shared repository for CSF and tissue from all types of hydrocephalic cases</td>
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<td>• Improved quantitative and cost-effective assessment techniques for evaluating CSF and tissue now allow excellent data analyses</td>
<td>• Support for multidisciplinary and multimodal (neuroimaging and proteomics) studies coupled with outcome analyses</td>
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<td>• Development of home-based diagnostics</td>
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<td>Neuroimaging</td>
<td>• Collaborations to develop a standard set of imaging protocols and a shared repository of neuroimaging data</td>
<td>• Implementation of a standard set of imaging protocols and a shared repository of neuroimaging data</td>
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<td></td>
<td>• Prospective studies using multimodal techniques including MRI and CSF proteomics to test potential pharmacological agents</td>
<td>• Support methodological studies that standardize neuroimaging devices and procedures</td>
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<td>• Prospective multicenter studies comparing the accuracy of MRI techniques</td>
<td>• Support multidisciplinary studies that correlate neuroimaging data with both cellular and biochemical alterations, and to correlate these data with clinical outcomes</td>
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<td>• Formulate evidence-based guidelines for the use of quantitative MRI, such as phase-contrast MRI</td>
<td>• Support studies that validate noninvasive MRI techniques to monitor critical physiological parameters</td>
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<td></td>
<td>• Validation of noninvasive MRI techniques to indirectly measure ICP and compliance</td>
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**TABLE 2. Areas of promise and recommendations for hydrocephalus research on diagnosis of hydrocephalus in the next 5 years**
The Hydrocephalus Clinical Research Network (HCRN) implementation of a shunt infection protocol demonstrated that compliance with the protocol reduced shunt infection rates significantly.54 The study and institution of quality improvement methodologies in the context of multicenter studies has provided a framework to advance care across the broader pediatric neurosurgical community.

Similarly, patient registries can provide very large numbers of patients to study relatively rare events; an example is the analysis of antibiotic-impregnated shunts. The involvement of multiple centers reduces issues related to generalizability of data or techniques. The HCRN has been an example of this vision, with 10 centers and more than 2500 patients enrolled and almost 5000 procedures tracked (http://www.hcrn.org). Networks such as the HCRN provide the infrastructure to conduct nested prospective cohort studies and RCTs.

Critical to the discussion of surgical treatment for pediatric hydrocephalus is the use of combined endoscopic third ventriculostomy (ETV) and choroid plexus cataractomy (CPC). In a large cohort of Sub-Saharan patients, most of whom presented with infectious hydrocephalus, CPC significantly increased the success of ETV in infants.125–129 ETV/CPC procedures are safe with low morbidity and mortality, and long-term ETV/CPC failure and infection rates were lower than for shunts in a study in East Africa, with success rates ranging from 62% to 82%.130 ETV success scores can be highly predictive of which patients will benefit or should have a standard shunt implanted as the principal intervention. Ongoing studies coordinated by the HCRN will help determine if these results can be translated to the broader pediatric neurosurgery population, whether the procedure has long-term durability, whether ultimate cognitive outcomes are similar to those of VP shunts, and whether removal of homeostatic and trophic factors secreted by the choroid plexus have consequences later in life.49,50

As noted, VP shunt survival has remained constant regardless of the hardware used.17 Thus, strategies to reduce proximal catheter revision rates are important. Although it may play a role in improving accuracy, the financial costs of image guidance and whether it is needed in routine cases must be evaluated. Advances in proximal catheter design have been minimal and have not been tested in RCTs. Many factors may influence proximal catheter dynamics including catheter material, number of holes, hole sizes, and other confounders such as adjuncts (flanges). Novel catheter designs are desired and should undergo RCTs to show efficacy before widespread clinical implantation.

Areas of Promise and Recommendations for Treatment in Hydrocephalus in the Next 5 Years

Bioengineering advances hold promise for the development of more physiological valve mechanisms and for reducing catheter obstruction by preventing cell and tissue adhesion (Table 3). Across both the pathophysiology section (Theme 1) and within treatment (Theme 3), a better understanding of the biological basis of catheter obstruction was needed to better guide engineering advances based on the most common causes of shunt failure. The ability to provide on-demand diagnostics in the physician’s office was a voiced priority, as was the development of improved ventricular catheters and the need for improved partnership with industry.

It was a uniform recommendation that the efficacy, safety, generalizability, and longitudinal outcome of ETV/CPC should be studied and the opportunity for a randomized trial of ETV/CPC versus VP shunting should be considered. The standardization of surgical technique and optimization of various aspects of the current practice of shunt implantation should be a priority.

Theme 4: Outcome in Hydrocephalus

Neuropsychological Outcomes

Variability is a hallmark of neuropsychological outcomes in congenital and acquired hydrocephalus.26,37,38,105 Outcome assessments should include traditional neuropsychological assessments as well as interview-based measures of adaptive behavior and rating scales.2 Adaptive behavior assessments do not simply duplicate cognitive performance assessments but can directly indicate the level of independent functioning in multiple domains.

Spina bifida with or without hydrocephalus is an important condition-related variable that influences neuropsychological outcome in children with obstructive hydrocephalus.38 It remains important to look beyond IQ to functional relevance and self-management outcomes46 and appreciate the malformations that underlie hydrocephalus in this patient population.15 The context of the evaluation must be considered, including the emotional and family dynamics. Living with congenital brain disorders involving hydrocephalus for 30–50 years involves not only cognitive challenges originating in childhood but also new challenges emerging in adult life. Various alterations in brain morphology are implicated, including changes in frontal lobe development, thinning of white matter pathways, and issues related to memory structures within the mesial temporal lobe. While the effect is unclear in children, VP shunt revisions in adults negatively affect functional numeracy, memory function, independent living, and employment.105

Treatment of the reversible neuropsychological deficits of iNPH is a focus of study.9,12,21,32,35,78,119 Studies show an improvement in neurocognitive measures after treatment, including verbal memory, psychomotor scores, mental tracking speed, attention, independent living, and caregiver scores.62 Postshunting cognitive changes can precede functional recovery and may be sensitive and early markers of NPH outcome. The durability of the improvement is influenced by many factors such as shunt survival and complications, and distinguishing worsening due to progressive iNPH or other comorbidities such as vascular dementia and Alzheimer disease.77

Neurological Outcomes and Quality of Life

Focus on the quality of life in children with hydrocephalus includes the general concepts of measuring health-related outcomes in children and the specific challenges in improving these outcomes.59,63,121 The major self-identified issues related to quality of life in children with hydrocephalus include cognitive difficulties, behavioral difficulties,
and headaches. Quality-of-life concerns that follow into adulthood include depression, inability to live independently, inactivity to drive, unemployment, substance abuse, and denial of health care. Areas in which health care providers and surgeons can influence current and future quality of life include reducing operative complications such as infections, improving access to community-based services, and improving transition into adulthood.

Intraventricular hemorrhage interrupts normal brain development, resulting in “encephalopathy of the preterm infant” and a unique neurodevelopmental phenotype of prematurity.42–44,47,99,109 The potential for additional damage to the developing brain as well as the impact of hydrocephalus on neurodevelopment of the preterm infant most certainly impact functional outcome. Outcomes are likely related to extent of initial injury, gestational age at injury, and the timing of intervention. Currently used outcome measures are linked to major outcomes that represent just a rudimentary overview so there is a need to develop more robust, granular functional outcome measures.

Changing the paradigm from “eminence-based” to “evidence-based” care requires a focus on the value of high-quality evidence and its impact on patient care.5,56,108,123,134 Appropriate sample size has been a major issue, with 50% of general surgical trials being underpowered.31,107 Within surgical specialties, RCTs are less common because of the surgical research culture, the difficulty of conducting surgical RCTs, limited RCT expertise among surgeons, limited infrastructure, and limited funding. In the last 20 years, the quality of surgical research is rated as very low to poor quality in more than 60% of studies. Clearly, improved surgical research calls for randomization, blinding outcomes, objective outcome measures, complete follow-up, limiting differential expertise, and enrolling sufficient patient numbers.

### Areas of Promise and Recommendations for Outcomes in Hydrocephalus in the Next 5 Years

The recommendations in Table 4 apply broadly to children and adults with hydrocephalus. Specific, reliable batteries with metrics focused on the patient need to be developed and validated. Measurements of neurocognitive outcome and quality of life should be adaptable, trackable across the growth spectrum, and applicable cross-culturally. With INPH, developing comparisons against normative age-based data and sensitive screening tools would be especially valuable in early diagnosis.30,82,94 An important issue is the need for a better understanding of the incidence and prevalence of hydrocephalus within both pediatric and adult populations and to compare aging patterns in adults with hydrocephalus against normal aging patterns.

### Summary

Consensus priorities in four major areas of hydrocephalus research (causes, diagnosis, treatment, and outcomes) that have the most potential to impact patient care in the next 5 years emphasize patient-centered care and translational research. Areas of promise included evaluation of the genetics of hydrocephalus, development of models to improve our understanding of the disease, use of multidisciplinary opportunities and standardized protocols, emphasis on novel bioengineering designs, improved surgical trials, and developing validated metrics of outcome. These priorities should serve as guidelines for the hydrocephalus community at large as well as governmental and nongovernmental funding agencies in the future.

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**Table 3. Areas of promise and recommendations for hydrocephalus research on treatment of hydrocephalus in the next 5 years**

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<th>Theme</th>
<th>Areas of Promise</th>
<th>Recommendations</th>
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<tr>
<td>Bioengineering Advances</td>
<td>• Obstruction-resistant shunts (both proximal catheter and valve)</td>
<td>• Provide incentives for novel ventricular catheter design, materials</td>
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<td>• In vitro biological models for preclinical testing</td>
<td>engineering, and antifouling technologies</td>
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<td></td>
<td>• Implantable sensors for monitoring CSF pressure and flow plus pertinent physiological data</td>
<td>• Support collaborative efforts between clinicians, scientists, and engineers via program projects and/or center grants; expand NIH support of STTR and SBIR grants to enhance translational research.</td>
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<td>• Improved understanding of desirable algorithms for CSF drainage</td>
<td>• Support advances in several engineering categories, including implantable pressure and flow sensors</td>
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<td>• “Smart” shunts with diagnostics, advanced control, and maintenance</td>
<td>• Support development of realistic and reliable testing platforms (bench-top and in vitro models) to advance and reduce the cost of testing implantable devices.</td>
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<td>Surgical Advances</td>
<td>• Refinement of surgical shunting procedures to improve survival and reduce infection rates</td>
<td>• Improved animal models would be valuable for pre-IDE device development and testing</td>
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<td>• Determination of optimal ventricular catheter placement</td>
<td>• Refine mathematical modeling of CSF dynamics; pair with in vivo knowledge of CSF dynamics</td>
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<td></td>
<td>• Understanding the generalizability and outcome of ETV and/or CPC procedures within North American populations</td>
<td>• Develop exquisitely controlled shunting devices</td>
</tr>
</tbody>
</table>

IDE = investigational device exemption; SBIR = Small Business Innovation Research; STTR = Small Business Technology Transfer.
TABLE 4. Areas of promise and recommendations for hydrocephalus research on outcome in hydrocephalus in the next 5 years

<table>
<thead>
<tr>
<th>Theme</th>
<th>Areas of Promise</th>
<th>Recommendations</th>
</tr>
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</table>
| Neuropsychological Outcomes    | • Refinement of neuropsychological testing for both pediatric and adult hydrocephalus patients to determine which of the battery of tests are most expedient and reliable  
  • Determining which neuropsychological measures have robust correlation between alterations in brain structure/morbidity or functions that can be imaged with fMRI or DTI  
  • Determining whether various preoperative neuropsychological tests can predict postoperative outcome reliably  
  • Increased efforts to record and design metrics of quality-of-life measures  
  • Correlation of neurobiology with neuropsychological assessments, i.e., to identify physiological correlates (ICP, CSF genomics/proteomics, etc.) that lead to discrete neuropsychological deficits | • Undertake a concerted funding effort to support improved outcomes metrics in hydrocephalus research  
  • Implement multidisciplinary efforts whereby neuropsychologists are paired with clinicians, basic scientists, and imaging researchers to more broadly correlate outcome with treatment interventions and basic science findings  
  • Prioritize funding of longitudinal studies of outcomes data  
  • Provide incentives for development of hydrocephalus-specific, expedient, and reliable cross-cultural neuropsychological testing batteries |
| Neurological Outcomes and Quality of Life | • Development of appropriate outcome metrics to longitudinally follow quality-of-life measures  
  • Implementation of more granular outcome measures in patient tracking  
  • Expanded multicenter networks to provide enough power within the context of outcome studies  
  • Increased efforts to bring forward appropriately powered RCTs within hydrocephalus and NPH  
  • Improved tracking and potential standardization of the timing of surgical treatment in premature IVH and its relationship to outcome measures | • Support funding for RCTs within hydrocephalus  
  • Support collaborations and mentorship both within and outside of the hydrocephalus arena  
  • Foster multidisciplinary efforts to integrate appropriate outcome metrics into all facets of hydrocephalus research  
  • Identify long-term funding opportunities to support longitudinal studies of outcome |

fMRI = functional MRI; IVH = intraventricular hemorrhage.

Appendix

The Hydrocephalus Symposium Expert Panel

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References


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