AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report

Priority Area 06: Developmental Delays, ADHD, and Autism

Potential High Impact Interventions Report

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA29020100006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual Topic Profiles are developed for technologies and programs that appear to be closer to diffusion into practice in the United States. Drafts of those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify those interventions that experts deem, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually, and topics included may change depending on expert comments received on interventions issued for comment during the preceding six months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in the horizon scanning, assessing the leads for topics, or provide opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor target technologies and innovations in health care and to create an inventory of target technologies that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is the analysis of the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future utilization and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 7,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0 to 4 years of potential diffusion (e.g., in phase III trials for pharmaceuticals or biotechnologies or in phase II or a trial with some preliminary efficacy data on the target population for devices and programs) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling a profile on topics and issuing topic profile drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COI).

Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the high impact potential designation. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as potential high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the six topics for which (1) preliminary phase III data were available; (2) information was compiled by November 2011 in this priority area; *and* (3) we received six to eight sets of comments from experts between February 2011 and November 1, 2011. (A total of 25 topics in this priority area were being tracked in the system as of November 2011.) For purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present 4 summaries on 4 topics (indicated below by an asterisk) that emerged as potential high impact on the basis of experts' comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 06: Developmental Delays
1. CM-AT enzyme replacement therapy for children with autism
2. CM-4612 enzyme replacement therapy for attention-deficit hyperactivity disorder
3. *Device (Q Sensor) to signal impending emotional meltdown in children with autism
4. *Functional MRI for differentiating autism spectrum disorders from bipolar disorder in children
5. *Hyperbaric oxygen therapy for autism
6. *Interactive robotic dolls to improve social skills of children with autism

Discussion

Autism spectrum disorders (ASDs), also sometimes referred to as pervasive developmental disorders, are a wide continuum of associated cognitive and neurobehavioral disorders, including, but not limited to, three core-defining features: impairments in socialization, impairments in verbal and nonverbal communication, and restricted and repetitive patterns of behaviors. While all children with ASDs demonstrate similar core features, the severity of impairments, age of onset, and associations with other disorders (e.g., mental retardation, specific language delay, epilepsy) vary considerably. ASD diagnoses have been increasing, and recent estimates place the prevalence at about 1% of children in the U.S., with occurrence in males being more than 4 times as common as in females.

Treatment for early intervention includes any or several of the following: behavioral and communication therapies (including, but not limited to, applied behavior analysis) and dietary, medication, and complementary therapies.

The paucity of leads and innovations identified by the horizon scanning system on diagnosis, treatment, and services for developmental disorders such as autism spectrum disorders implies a lack of progress in basic understanding of these disorders. Nonetheless, some researchers are trying new uses of existing tools (e.g., hyperbaric oxygen therapy [HBOT]), and others are developing new tools to mitigate the effects of the disorders and aid behavior treatment programs that have been shown to work to some extent. Early diagnosis of autism is thought to be important because, many believe, the earlier the intervention, the more opportunity for improvement in a child's cognitive development and social functioning.

Device to Signal Impending Emotional Distress in Individuals with ASDs

- **Key facts**: The Q Sensor (Affectiva, Inc., Waltham, MA) is a wireless device intended to measure emotions by recording skin conductance as a function of sympathetic nervous system activity. The device is used in research study applications, but also has been proposed to monitor electrodermal-activity fluctuations to purportedly signal caregivers of individuals with autism or other developmental or learning disabilities of severe possible impending emotional distress in the person wearing the device. The relationship between autonomic reactivity and behavioral responses to auditory stimulation in high-functioning children with autism and typically developing children was studied, and findings suggested that high arousal levels may underlie some behavior problems that autistic children experience in reaction to auditory stimuli in natural environments. The device is placed around the child's wrist and secured with a Velcro strap, and a caregiver can monitor the signals which are sent wirelessly to a lap-top computer with software that records and analyzes the data. The computer displays the information According to the manufacturer, the device became available in a prerelease version in November 2010 and was released in commercial version (Q 2.0 version) in May 2011 at a cost of $2,000 per unit. The device cost is borne by the user.
- **Key Expert Comments**: Experts commenting on this topic agreed that management of emotional distress in ASD is a continuing challenge for family and professional caregivers. They thought that the device has potential to improve quality of life for children and their families and to aid caregivers in addressing needs of children with ASDs. However, experts opined that it is not clear whether other symptoms of ASDs would benefit from this type of early, proactive intervention for diffusing emotional disturbances.
- **Potential for High Impact**: Lower range of high impact

Functional Magnetic Resonance Imaging for Differentiating Autism from Bipolar Disorder in Children

- **Key facts**: According to the Autism Society, no imaging tests to aid diagnosis of autism exist. Diagnosis is usually based on observation of the child's communication, behavioral, and developmental levels. Array-based comparative genomic hybridization testing (a blood test) is sometimes used to determine (through clinical examination) whether a child believed to be affected by autism has genetic markers thought to be associated with ASDs. Suspected ASD can also sometimes mimic bipolar disorder symptoms. Investigators theorize that functional magnetic resonance imaging (fMRI) techniques could be used to

differentiate abnormalities in the cerebellum that have been associated with severe neuropsychiatric disorders such as bipolar disorder from those associated with ASD. A noninvasive brain-imaging technique that indirectly measures neural activity by detecting local changes in cerebral blood flow, fMRI can be used to study brain function and to map active brain regions in awake humans during specific tasks such as speaking, moving, feeling, and remembering.

- **Key Expert Comments**: Experts commenting on this topic agreed on the potential of fMRI as an adjunctive diagnostic tool for ASD. However, they expressed concern about the high cost (3 tesla MRI is required), limited availability (i.e., to regional research centers), and uncertainty about how it could really affect health outcomes because of its early stage of investigation for this application.
- **Potential for High Impact**: Lower range of high impact

Hyperbaric Oxygen Therapy for Autism

- **Key facts**: Recent research suggests that some individuals with autism have decreased cerebral perfusion, evidence of neuroinflammation, and increased markers of oxidative stress. Evidence of decreased blood flow in the brain, neuroinflammation, and oxidative stress in autistic children has prompted some researchers to consider HBOT, which has been used to treat various other conditions for more than 40 years, as adjunctive treatment for children with ASDs. Treatment involves placing the patient in a compression chamber, increasing the environmental pressure within the chamber, and administering 100% oxygen for respiration. Basing their theories on previous studies showing that HBOT has some antiinflammatory effects and appears to reduce oxidative stress, investigators hypothesize that HBOT offers a means of improving symptoms in individuals with autism. However, in pediatric populations, barotrauma (i.e., injuries caused by pressure as a result of an inability to equalize pressure between an air-containing space and the surrounding environment) has been reported as one of the more frequently seen injuries caused by HBOT, so the treatment is controversial not only on the basis of efficacy, but on safety. HBOT chambers are available, and this use is not subject to regulatory approval processes, so a clinician could use the chamber at his or her discretion for myriad clinical applications. Thus, HBOT could diffuse for this application without going through regulatory hurdles. Reported charges for its use in autism range widely by treatment center from one hundred to several hundred dollars per session, or several thousand dollars for a course of treatment delivered over a number of weeks. The treatment is not covered by most third-party payers that publish their policies publicly.
- **Key Expert Comments**: Experts commenting on this intervention expressed concern about the underlying theory and safety risks, but noted that parents' frustration with current treatments could promote demand for HBOT as an adjunct treatment for ASD. They believe that some parents are willing to pay out of pocket, despite lack of reimbursement and coverage. However, other experts countered that the number of available HBOT chambers, high cost of therapy, and lack of reimbursement could limit access and wider diffusion for ASD treatment. Clinical experts expressed concerns about potential adverse effects, such as oxygen poisoning, barotrauma, and blurred vision, despite very preliminary results showing some efficacy.
- **Potential for High Impact**: Lower range of high impact

Interactive Robotic Dolls to Improve Social Skills of Children with Autism

- **Key facts**: Popchilla (Interbots, Pittsburgh, PA), a robotic doll, is being investigated for children in whom ASD has been diagnosed who have limited or nonverbal communication. Developers at Carnegie Mellon University (Pittsburgh, PA) are using robotic doll prototypes to study whether they reduce behavioral frustrations by promoting communication and understanding of the child's internal feelings. The underlying theory for study of use of robotic dolls arises from research studies suggesting that children with ASD who interact with android or humanoid forms may improve function in the area of social communication, and robotic movements may elicit visual motor priming in children with autism. Popchilla's developers suggest that children with ASDs are more likely to interact with an endearing and "human-like" robotic doll because it appears less threatening than human interactions. Computer programmers at Interbots are also pursuing development of an iPad application intended to allow therapists to direct sessions and eventually allow the children to control the robot and identify emotions.
- **Key Expert Comments**: Experts indicated that cost of the intervention is relatively low—an estimated $150 for the robotic doll. Thus, they thought it would likely be a very accessible device that could be easily integrated into behavior therapy programs for children with autism. Experts also noted that clinicians using the dolls with children with ASD would require training on how to effectively integrate it into therapy programs.
- **Potential for High Impact**: Moderately high

Autism Interventions

Intervention

Device to signal impending emotional distress in children with autism

According to the National Research Council, despite strong and consistent commonalities among children with autism spectrum disorders (ASDs), no single behavior can be attributed to all children with an ASD.[1] Additionally, no particular behavior automatically excludes an individual child from diagnosis of symptoms of ASD.[1] For patients receiving a diagnosis of autism or ASDs, detecting impending severe emotional distress could be critical to more effective management and increased safety for the patient and caregiver. The Q Sensor™ (Affectiva, Inc., Waltham, MA) is a wireless device worn on the wrist and is intended to measure emotions by recording skin conductance as a function of sympathetic nervous system activity.[2] The sensor is intended to monitor electrodermal-activity (EDA) fluctuations to signal a caregiver, researcher, or clinician who is monitoring the readouts of those signals on a computer about indicators of the emotional status of the wearer. The idea is to signal possible or impending severe emotional distress in children with ASDs or other learning or disabilities, such as attention deficit disorder. The device became commercially available in May 2011 and did not require regulatory clearance from the U.S Food and Drug Administration (FDA) for use.

EDA has been recognized by some as a sensitive index of sympathetic nervous system activity.[3] The sensor uses minute electrical signals to measure a wearer's EDA. The device is placed around the wrist and secured with a Velcro strap.[2] To measure and record data from the device, software must be downloaded from the manufacturer's Web site onto a computer. According to the manufacturer, up to 3 months of data from the device can be logged on the program and the device is priced at $2,000.[4]

In 2009, Chang investigated the relationship between autonomic reactivity and behavior responses to auditory stimulation in 22 high-functioning children with autism and 10 typically developing children. Investigators measured EDA at rest and in response to two auditory stimuli. Findings reported from this study suggested that high arousal levels might underlie some behavior problems that children with autism experience in reaction to auditory stimuli in natural environments.[5] EDA has been used to test psychophysiology of children with ASDs.[6] In laboratory settings, children with ASD have shown increases in skin conductance (sweat release) when presented with images of faces that they cannot recognize.[7] Individuals with a diagnosis of ASD are known to experience states of emotional or cognitive overload. This type of overload is measured as autonomic nervous system activation.[8] Emotion-communication technologies such as the Q Sensor have been proposed as an opportunity for learning, to better understand and serve the needs of persons with ASDs.[8]

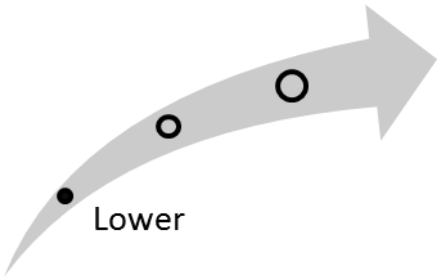
The manufacturer recommends the following indications and contraindications: Use of the device on small children should occur only under adult supervision; the device should be kept away from other devices that may cause electromagnetic interference of any nature; for children with sensitive skin, the device should be removed at least 1 hour every 24 hours; and exposure to fluids and use of the sensor in water, is strongly discouraged.[2] In patients with pacemakers, or with conditions sensitive to electrical signals, consultation with their physicians before wearing the device is recommended.[2]

Clinical Pathway at Point of This Intervention

ASDs can sometimes be detected at 18 months of age or younger, but usually a diagnosis is made at about age 2 years.[9] A screening for developmental delays and disabilities is done during regular well-child visits at 9-, 18-, 24- or 30-month intervals. If signs and symptoms indicate, developmental pediatricians and other specialists then conduct a comprehensive evaluation. After diagnosis, a treatment plan for early intervention includes any or several of the following: behavioral and communication therapies (including, but not limited to, applied behavior analysis [ABA]) and dietary restrictions, medication, and complementary therapies.[10]

The Q Sensor has the potential to assist clinicians and caregivers to proactively address and possibly avert adverse emotional reactions in children with ASDs as part of an overall treatment approach.

Figure 1. Overall High Impact Potential: Device to signal impending emotional distress in children with autism



Experts providing comments on this topic agreed that management of emotional distress in ASD is a continuing challenge for family and professional caregivers. These experts thought the device has potential to improve quality of life for children and their families and to aid caregivers in addressing needs of children with ASDs. However, the experts noted that it is not clear if other symptoms of ASDs would benefit from this type of early, proactive intervention for emotional disturbances. Based on this input, our overall assessment is that this intervention is in the lower end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.[11-17]

Six of seven experts agreed that the unmet need of early intervention to head off extreme emotional distress in children with ASDs is important. One clinical expert indicated behavior problems and managing the emotional distress in ASD are continuing challenges for caretakers. An expert with a research perspective indicated there is a need to enhance caregivers' effectiveness by means of early warnings. Comments regarding the certainty about the intervention's underlying mechanism were mixed. Some experts believe the theory is reasonable, as one put it, that "clinicians are currently able to track through an EEG or an EKG various responses of the brain and the heart" and that "this innovation brings an additional resource tool for treatment in the medical diagnostic process by evaluating galvanic responses and by improving the clinical education of the care team to promote patient safety."[15] Several other experts were not as convinced about the intervention's mechanism of action, expressing concerns that the Q Sensor might not accurately detect the cause of arousal in the child. One expert with health systems and health administration perspectives stated, "Although it has been shown that a Q sensor (a device to measure skin's conductivity) can detect how well children with autism can recognize faces as well as how much children with autism were aroused by various sensory stimuli (sight, sound, smell, and vestibular), it has not been shown if the sensor could indicate whether the children enjoyed any of the sensory stimulations."[16] Ultimately, the experts who remain unconvinced of the underlying mechanism believe that it might not be feasible for Q Sensor to distinguish negative arousal from positive arousal.

Three experts had a definite opinion about the potential effect of this intervention on health outcomes in children with ASDs. An expert with a research perspective thought the device could be important, but would not likely change outcomes. An expert with health systems and administration perspectives was uncertain about the potential in assisting providers and parents to mitigate emotional meltdowns. A clinical expert thought the device could improve knowledge and understanding about ASDs, which could lead to improving health outcomes.

Several of the experts believe that patients would be accepting of the Q Sensor device, believing it would be a noninvasive tool with no significant risks that could more readily detect early signs of emotional meltdown in a child with autism. However, other experts believed that this intervention

might meet patient resistance; three thought that patients might not want to wear a wristband and would not comply if it were placed on them. Two experts, one with a health systems and one with a clinical perspective, agreed this device could shed light on clinical processes used to treat ASDs. An additional expert with health systems administration experience indicated the device could potentially address the need to detect levels of arousal and changes in arousal to sensory stimuli in children with ASDs. A researcher indicated this device could potentially address the need to improve existing services.

Intervention

Functional MRI for differentiating autism from bipolar disorder

According to the Autism Society, no medical tests for diagnosis of autism exist. Diagnosis is usually based on observation of the child's communication, behavioral, and developmental levels. Input from parents and caregivers and a developmental history are important components of an ASD diagnosis, but suspected ASD can also sometimes appear as bipolar disorder.[18] Investigators theorize that functional magnetic resonance imaging (fMRI) techniques could be used to differentiate abnormalities in the cerebellum that have been associated with severe neuropsychiatric disorders such as bipolar disorder from those associated with ASD.

A noninvasive brain-imaging technique, fMRI indirectly measures neural activity by detecting local changes in cerebral blood flow. It can be used to study brain function and to map active brain regions in awake humans during specific tasks such as speaking, moving, feeling, and remembering. When applied for differentiating autism from bipolar disorder in children, fMRI's ability to highlight correlations between brain and behavior measures is studied by researchers.[19] The hypothesis for using fMRI this way is based on observations in which severe neuropsychiatric disorders in childhood have been associated with abnormalities in brain development. Researchers theorize that it might be possible to detect neuroanatomic features indicative of such abnormalities with the use of fMRI.[19]

Although many fMRI studies have been performed using 1.5 tesla (T) MRI scanners (used in most clinical settings), optimal fMRI conditions require higher magnetic field strength scanners (3 T), rapid-acquisition techniques (echo-planar imaging), and postprocessing. The most common form of fMRI uses blood oxygen level-dependent (BOLD) contrast, which does not require the injection of exogenous contrast agents. The BOLD contrast signal is based on changes in the ratio of oxygenated to deoxygenated hemoglobin that occurs during brain activity. Currently, the only FDA-approved clinical application for fMRI is neurosurgical planning.[20]

Supporting the hypothesis for possible applications in autism are studies involving fMRI techniques in which abnormalities in the cerebellum were found in children with ASDs. Diffusion tensor imaging (which allows for the determination of directionality as well as the magnitude of water diffusion) has been used to study abnormalities in connectivity and microintegrity in brains of children in whom ASD has been diagnosed.[21] MRI also was used to determine severity of ASD and its association with alterations in white-matter development.[22] Regarding initial observations of an above-average head circumference and ASD, using structural MRI studies, researchers observed increased total brain volume and early rapid brain overgrowth in individuals with ASD. Consistent abnormalities in cortical gray- and white-matter volume in ASDs were also found.[23] One imaging study observed age-related changes in gray-matter volume and cortical thickness associated with symptoms of severity in children with autism.[24]

Because the magnetic field can move implanted medical devices, possibly causing fatal injuries, MRI is contraindicated for patients with certain implanted devices. In general, patients with any electrically, magnetically, or mechanically activated implants (e.g., pacemakers, neurostimulators, infusion pumps, cochlear implants) could be adversely affected by the magnet.

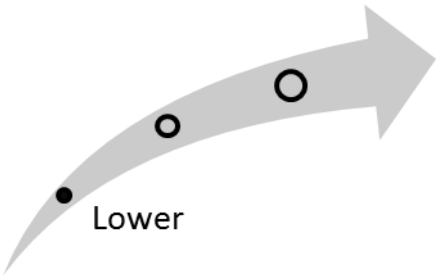
FDA classifies MRI systems as class II devices subject to special controls. Thus, MRI manufacturers have gained marketing clearance for their systems under the 510(k) substantial equivalence process. FDA has granted 510(k) marketing clearance for several 3 T MRI scanners, including systems from General Electric Co. (Fairfield, CT), Siemens AG (Munich, Germany), and Royal Philips Electronics (Amsterdam, The Netherlands). FDA does not specify the indications for which these scanners may be used. Thus, no fMRI system has a labeled indication for screening or

testing children for ASDs or psychiatric disorders. It is unlikely that a manufacturer would seek a specific labeled indication for this use.

Clinical Pathway at Point of This Intervention

ASDs can sometimes be detected in individuals at 18 months of age or younger, but diagnosis is usually made by age 2 years[25] using screening questionnaires and clinical examination for developmental delays and disabilities during well-child pediatrician visits at 9-, 18-, 24- or 30-month intervals. ASDs and bipolar disorder can exhibit similar signs and symptoms in children. fMRI would be intended as an adjunct to assess suspected signs and symptoms suggestive of either ASD or bipolar disorder and differentiate one from the other so that an accurate diagnosis can be made and appropriate treatment can be initiated.[10]

Figure 2. Overall High Impact Potential: Functional MRI for differentiating autism from bipolar disorder



Experts agreed that the need for early diagnosis of ASDs to initiate early intervention is well established, as is the ability to differentiate it from bipolar disorder, which can exhibit similar symptoms in children. Experts agreed on the potential of fMRI as a adjunctive diagnostic tool for ASD. However, they expressed concern about the high cost, limited availability (i.e., limited to regional research centers), and uncertainty about how it could really affect health outcomes because of its early stage of investigation for this application. The cost and limited access would make it have a lower overall impact. Based on this input, our overall assessment is that this intervention is in the lower end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.[26-32] Most experts agreed fMRI addresses an important unmet need in the ability to diagnose ASDs. However, one expert with a clinical perspective stated, "Screening and identification of individuals who meet criteria for an ASD has been THE area of greatest progress in recent years, and this is not currently a major problem."[32] Regarding this intervention's underlying theory, most experts agreed it might be plausible to associate distinctive brain activity patterns with certain conditions. One clinical expert indicated that fMRI might provide researchers with evidence of correlations between brain and behavior measures needed to differentiate between autism and bipolar disorder/psychiatric disorders. However, two other experts with clinical perspectives were pessimistic about fMRI's ability to detect brain activity specific to ASDs.

The effect of fMRI on current care models when used as a diagnostic tool for ASDs would depend on access, cost, reimbursement, and demand from families. An expert with a research perspective indicated that if significantly large numbers of children undergo fMRI for early diagnosis, major disruptions in current care models could occur because the technology has limited availability and is very expensive. A clinical expert viewed the costs associated with fMRI as prohibitive to widespread use and therefore did not think it had potential to disrupt current care models.

Regarding how well this intervention could address the unmet need to accurately diagnose ASD and distinguish it from bipolar disorder in children, most experts agreed that it would need to provide a definitive diagnosis of ASD to be seen as worthwhile. An expert with a health systems perspective thought fMRI has some promise in being able to identify structural and connectivity deficiencies but

asserted it would be many years before its use could translate to differentiating ASD from bipolar disorder. An expert with a research perspective indicated the potential to address unmet needs in differentiating ASDs from bipolar disorder depends on the capacity of fMRI to correlate brain patterns with clinical assessments. Given that no gold standard for diagnosing ASD and differentiating it from bipolar disorder exists, this will be difficult to demonstrate.

Experts agreed that fMRI would likely create health disparities if adopted as part of a diagnostic pathway because access would be limited by its limited availability and high costs. Experts generally believe that the per-patient cost of diagnosis would increase significantly with this intervention, with one expert stating that "this would cause a huge increase in per-patient costs, especially because it wouldn't eliminate the need to perform [an] ADOS/ADI [autism diagnostic observation schedule/autism diagnostic interview] also."[32]

Intervention

Hyperbaric oxygen therapy for autism

Experts indicate that no single treatment is effective for all individuals with autism spectrum disorder (ASD), and even combinations of treatment may not sufficiently address the behaviors and functioning of children and adults affected by ASDs.[18] De Maistre and colleagues (2010) indicate that decreased blood flow in the brain, neuroinflammation, and oxidative stress findings in autistic children have prompted researchers to consider hyperbaric oxygen treatment (HBOT) as an adjunctive treatment for children with ASDs.[33]

HBOT refers to intermittent treatment of the entire body with 100% oxygen at greater-than-normal atmospheric pressures. Treatment involves placing the patient in a compression chamber, increasing the environmental pressure within the chamber, and administering 100% oxygen for respiration. This form of therapy is intended to improve the cellular oxygen supply by raising the tissue-cellular diffusion gradient.[34] Over the past 40 years, HBOT has been used to treat a wide variety of medical conditions, including autism, brain injury, cerebral palsy, multiple sclerosis, stroke, and wound healing. Recent research suggests that some individuals with autism exhibit decreased cerebral perfusion, evidence of neuroinflammation, and increased markers of oxidative stress. Basing their theory on previous studies showing that HBOT has some antiinflammatory effects and appears to reduce oxidative stress, researchers hypothesize HBOT can be a means of improving symptoms in individuals with autism.[34]

Granpeesheh and colleagues (2010) reported the following results from a randomized, double-blind, placebo-controlled trial that compared HBOT delivering 24% oxygen at 1.3 atmospheric pressure (n = 18) to placebo (n = 16) in children with ASD. Direct observational measures of behaviors symptomatic of autism and standardized psychological assessments were used to evaluate the effects of the treatment. No differences were detected between HBOT and placebo groups across any of the outcome measures. According to Granpeesheh, the study demonstrated that HBOT delivered at 24% oxygen at 1.3 atmospheric pressure did not result in a clinically significant improvement of the symptoms of autistic disorder.[35]

In 2009, Rossignol and colleagues reported results from a multicenter, randomized, double-blind controlled trial on the efficacy of HBOT for autism. Sixty-two children with autism aged 2 to 7 years were recruited from 6 centers and randomly assigned to 40 hourly treatments of either HBOT at 1.3 atmosphere and 24% oxygen (treatment group, n = 33) or slightly pressurized room air at 1.03 atmosphere and 21% oxygen (control group, n = 29). The children with HBOT were reported to have significant improvements in overall functioning, receptive language, social interaction, eye contact, and sensory/cognitive awareness compared with children who received slightly pressurized room air.[36] These results have piqued some interest in the intervention.

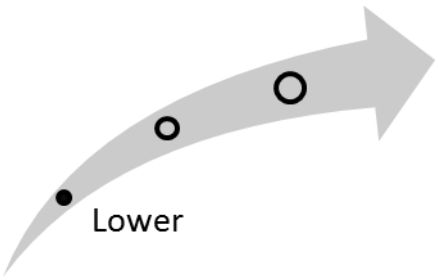
However, in pediatric populations, barotrauma (i.e., injuries caused by pressure as a result of an inability to equalize pressure between an air-containing space and the surrounding environment) has been reported as one of the more frequently seen injuries caused by HBOT. Hyperthermia and middle ear barotrauma are also considerations in pediatric populations.[37] HBOT chambers are widely available and may be used at a clinician's discretion for myriad clinical applications; thus, HBOT can currently be employed for use in children with ASDs without being subject to any regulatory pathway. To receive FDA marketing clearance in the United States, HBOT devices must meet American Society of Mechanical Engineers pressure vessels standards for human occupancy, National Fire Protection Association standards, and FDA good manufacturing practice class I and class II devices qualifications.[38] Although searches of coverage policies of third-party payers indicated that the therapy

is not reimbursed because it is considered experimental or investigational for this indication, it might be pursued by some parents of children with autism, choosing to pay out of pocket for the procedure, especially if therapies they have tried for their children are not working to their satisfaction. Reported charges for its use in autism range widely by treatment center from one hundred to several hundred dollars per session, or several thousand dollars for a course of treatment delivered over a number of weeks.

Clinical Pathway at Point of This Intervention

ASDs can sometimes be detected at 18 months of age or younger, but usually a diagnosis is made by age 2 years.[25] Once a diagnosis is made, a treatment plan for early intervention includes behavioral and communication therapies (such as ABA) and dietary, medication, and complementary therapies).[18] The potential antiinflammatory effects of HBOT would be considered complementary to the above programs for treatment of autism.

Figure 3. Overall High Impact Potential: Hyperbaric oxygen therapy for autism



Experts noted that parents' frustration with current treatments could promote demand for HBOT as an adjunct treatment for ASDs, especially because the treatment is available and not subject to an FDA regulatory pathway. However, the number of available HBOT chambers, cost of therapy, and lack of reimbursement may limit the impact of this intervention. Concern about potential adverse effects, such as oxygen poisoning, barotrauma, and blurred vision, despite very preliminary results showing some efficacy, are also likely to lower its overall impact. Based on this input, our overall assessment is that this intervention is in the lower end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.[39-45] These experts agreed on the importance of the unmet need that HBOT purports to address. One clinical expert noted the rising number of children in whom ASD is being diagnosed and that expansion of treatment modalities are needed to mitigate this number in the future. Experts indicated that few medical and behavior treatments are totally effective at managing adverse behavior and communication challenges in children with ASDs.

Most, but not all, experts agreed on the theoretical basis by which HBOT might provide improvements in ASD symptoms. However, one clinical expert argued that there seems to be no true theory to this treatment modality, stating "being generally 'anti-inflammatory' is not a theory."[45] One expert with a research background primarily in autism indicated that more studies are needed to prove HBOT's underlying theory, and these should replicate data presented so far in early HBOT clinical trials. This expert also indicated that the feasibility of the treatment's underlying theory could be negatively affected by allowing participants' parents or primary caregivers to provide input on a study's evaluative methods. The expert indicated the intervention may pose safety issues in patients with otitis media and asthma, as well. Safety concerns, the closed environment of the HBOT chamber (which could cause claustrophobia), and inconvenience could affect both parent and patient acceptance of the therapy. Conversely, two experts with research and health systems perspectives thought that, given some preliminary limited positive results thus far, the therapy seems to have some potential to improve health outcomes. The expert with a health systems background suggested that families'

frustration with current treatments could motivate them to try the intervention, regardless of the scientific validity or potential safety issues. Similarly, another expert with a research perspective indicated that despite HBOT costs and potential side effects, some parents might be willing to try it as a last resort if other interventions have not worked and their child is severely disabled by ASD. An expert with a health systems background also expressed HBOT time per treatment could affect parent and patient acceptance.

According to experts, the overall impact on unmet need depends on several factors. For example, four experts with a research background suggested HBOT could have a great impact on the unmet need, but more information about the frequency of treatments and efficacy is needed. One expert with a health systems background considered HBOT cost the main factor associated with the overall impact of this intervention on addressing unmet needs in ASDs. A clinical expert stated that if HBOT was deemed a successful intervention for patients with ASD, this could improve the relationship between clinician and patient/family because current treatment modalities for this patient population seem to create a schism in this relationship. However, this same expert warns that this treatment might further divide the relationship between clinician and patient/family because in-home therapists may potentially be removed from the treatment paradigm.

Intervention

Interactive robotic dolls to improve social skills of children with autism

ASDs refer to a wide continuum of associated cognitive and neurobehavioral disorders, including, but not limited to, three core-defining features: impairments in socialization, impairments in verbal and nonverbal communication, and restricted and repetitive patterns of behaviors.[46] Experts indicate no single treatment is effective for all individuals with an ASD.[18] Treatment options for ASD include behavioral and communication therapies (such as ABA) and dietary, medical, and complementary interventions.[18]

Popchilla, a robotic doll, is being investigated for children in whom ASD has been diagnosed who have limited or nonverbal communication. Developers hope the robotic doll can reduce behavioral frustrations by promoting communication and understanding of the child's internal feelings.

Recent studies on robotic dolls have focused on social relationships between people and robots and shown potential for robotic doll platforms as therapy tools for children with autism.[47] Popchilla is a small, emotionally expressive interactive robot developed by Interbots, a spin-off company of Carnegie Mellon University, Pittsburgh, PA. Interbots' goal is to develop a robot that can interact with children with autism who are nonverbal or have emerging verbal skills. The underlying theory for study of use of robotic dolls arises from research studies suggesting that children with ASD who interact with android or humanoid forms may improve function in the area of social communication,[48] and robotic movements may elicit visual motor priming in children with autism.[49] Popchilla's developers suggest that children with ASDs are more likely to interact with an endearing and "human-like" robotic doll because it appears less threatening than human interactions. According to its developers, the robotic doll's attributes could facilitate the teaching of verbal and emotional skills that the children could apply in everyday life. The development of Popchilla-based computer applications could allow therapists and clinicians to work with the robot to teach children various skills.[50]

Popchilla moves its head and rabbit-like ears, changes the color of its eyes, and expresses a variety of emotions, including happiness, sadness, anger, confusion, surprise, and embarrassment. A "puppeteer" remotely directs where Popchilla is looking and what emotion it displays. A microphone in the remote control lets the puppeteer speak for Popchilla. Potentially, a therapist "puppeteer" could provide an opportunity to stimulate imitation by the child. Research suggests that imitation can be used to enhance autonomous adaptive actions in children with autism.[51] Developers see the interactive toy robot as an alternative that could help children who have difficulties focusing on another human.

Computer programmers at Interbots are also pursuing development of an iPad application intended to allow therapists to direct sessions and eventually allow the children to control the robot and identify emotions.

In theory, as children master the control of Popchilla, they would find opportunities in its use that would allow them express their own emotions. This feature could help children proactively play with the robot and develop social skills. Proactive play with robots in children with autism has been associated with higher levels of play, increased reasoning skills related to the robot, and shows of affection towards the robot.[52]

Interbots (Pittsburgh, PA) makes the Popchilla robotic doll. It is not subject to FDA regulatory processes.

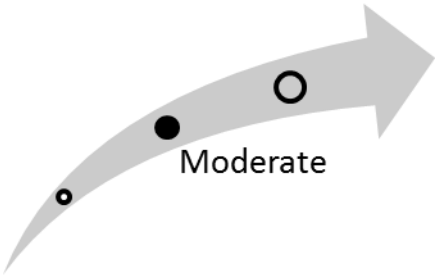
Clinical Pathway at Point of This Intervention

ASDs can sometimes be detected at 18 months of age or younger, but usually a diagnosis is made by age 2 years.[25] A screening for developmental delays and disabilities is done during regular well-

child visits at 9-, 18-, 24- or 30-month intervals. If signs and symptoms indicate, developmental pediatricians and other specialists then conduct a comprehensive evaluation. Once the diagnosis has been made, a treatment plan for early intervention includes any or several of the following: behavioral and communication therapies (such as ABA) and dietary, medical, and complementary therapies.[10]

Popchilla, a character-assisted therapy robot, is intended to assist therapists trained in ABA in addressing behavior and communication issues of children with ASD.

Figure 4. Overall High Impact Potential: Interactive robotic dolls to improve social skills of children with autism



Experts agreed that there is a significant unmet need to identify interventions that could improve nonverbal communication and social functioning and interactions of children with autism. Currently interventions such as this humanoid robotic doll are in an early phase of development and implementation, and experts indicated that efficacy data are needed to ascertain its impact on communication outcomes and quality of life in children with ASDs and their families. The cost of the intervention is relatively low—an estimated $150 for the robotic doll. Thus, it would likely be very accessible as a device that could be integrated into behavior-therapy programs for children with autism. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.[53-59]

Four experts with health systems, clinical, and health administration perspectives indicated the need for this specific robotic doll could be affected by the availability of other humanoid robots in development, but that the overall unmet need for interventions to improve social skills and human interactions of children with autism is significant. An expert with a research background in human robotics in autism thought that this intervention's impact would be affected by its efficacy and features relative to other humanoid robots in development.

Regarding the certainty of the underlying theory, an expert with research experience in humanoid robots in children with autism suggested that trained animals have also been known to foster uniquely social interactions among children with autism. According to this researcher, use of humanoid robots has produced results that are similar or better and with a wider range of children. For example, the researcher indicated that independently conducted studies have shown that children with autism respond uniquely well to social interaction with humanoid robots in many different ways, such as eye gaze, initiation of speech/conversation, spontaneous speech/babbling, displays of positive affect, use of and understanding of joint attention, and desire to share robotic experiences with other people. An expert with a health systems perspective suggested the intervention's theory is plausible because, according to this expert, children with autism might become overwhelmed by actual human interaction and might be more responsive and feel less fear and anxiety when interacting with robotic dolls with an inherently limited sensory stimulation range. A clinical expert echoed this sentiment, adding that children diagnosed with ASD tend to refrain from human interaction and more commonly rely on nonhuman/semi-human relationships.

Regarding the potential to improve health outcomes, two experts with research backgrounds indicated that patients with autism who are nonverbal might benefit from this type of intervention. One expert suggested the intervention could improve health outcomes by bridging the difficulties these children have in expressing emotions to peers and adults. An expert with a health systems background suggested that findings from previous research indicate this intervention has potential to improve health outcomes.

The need for additional data on this intervention's impact on unmet need was cited by all of the experts commenting on this intervention; however, most experts expressed optimism in the potential success of this therapy to address the unmet need in this patient population. One clinical expert noted that interactive robotic dolls might serve as a significant complement to current treatment modalities for children receiving a diagnosis of ASD.

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