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OVERSIGHT HEARING ON TRAUMATIC BRAIN INJURY (TBI): PROGRESS IN TREATING THE SIGNATURE WOUNDS OF THE CURRENT CONFLICTS

HEARING

BEFORE THE

COMMITTEE ON VETERANS' AFFAIRS
UNITED STATES SENATE

ONE HUNDRED ELEVENTH CONGRESS

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OVERSIGHT HEARING ON TRAUMATIC BRAIN INJURY (TBI): PROGRESS IN TREATING THE SIGNATURE WOUNDS OF THE CURRENT CONFLICTS

WEDNESDAY, MAY 5, 2010

U.S. SENATE,
COMMITTEE ON VETERANS' AFFAIRS,
Washington, DC.

The Committee met, pursuant to notice, at 9:30 a.m., in room 418, Russell Senate Office Building, Hon. Daniel K. Akaka, Chairman of the Committee, presiding.

Present: Senators Akaka, Murray, Tester, Brown of Massachusetts, Begich, Burr, and Isakson.

OPENING STATEMENT OF HON. DANIEL K. AKAKA, CHAIRMAN, U.S. SENATOR FROM HAWAII

Chairman AKAKA. This hearing will come to order. Aloha and welcome to all of you here today.

Today we will be discussing the progress that has been made in providing care and services to veterans with Traumatic Brain Injury. Differences in tactics, such as the use of IEDs, and significant advances in battlefield medicine and protective equipment from prior wars have resulted in an unprecedented number of servicemembers sustaining and surviving TBIs, making this the signature physical wound of the conflicts in Iraq and Afghanistan. It is estimated that up to 360,000 servicemembers have sustained a brain injury in Iraq or Afghanistan. The Government must do all it can to treat these wounded veterans.

In 2007, in response to this trend, I convened a hearing of this Committee on diagnosing and treating TBI. That hearing led to the introduction and ultimate passage of legislation I authored to enhance TBI services in VA. Today we revisit this topic to determine how completely that law is being implemented and how effective the steps we have taken have been in making sure veterans with TBI are receiving necessary and appropriate care.

Today, we will explore the relationship between VA and outside entities in providing treatment and rehabilitation services for TBI. I have visited the Richmond, Virginia, polytrauma center, and was very impressed with what I saw, but I believe that there is a need to expand the geographic availability of care. It is a burden for family members to have to travel several hours to visit their loved ones in the hospital or to take them to rehabilitation appointments.

In addition to partnering with community and other non-VA providers, VA must do more to involve family members in providing care for their wounded veterans. We must recognize and support family members appropriately, as they are our partners in this shared mission.

The Legislation I authored to provide a comprehensive program of services and support to family members who wish to care for their veterans at home, instead of placing them in an institution, is to be signed by President Obama this afternoon. This caregiver program will be another tool we can use to provide a seamless and effective continuum of care for veterans with TBI.

I am pleased to have witnesses from both VA and the Department of Defense here today. Effectively addressing the issue of TBI requires the full efforts of both Departments; neither can do it alone. I encourage both Departments to continue to break down barriers in their processes and find new ways to work more seamlessly, which ultimately results in the best outcomes for servicemembers and veterans.

One of the most critical challenges remaining is properly diagnosing mild and moderate TBI. Reliance on self-reporting, the misdiagnosing of symptoms, and sometimes the lack of an easily identifiable traumatic event are all elements that make it more difficult to get the proper care to these veterans and servicemembers. An aggressive and proactive approach to screening using the latest innovations is necessary.

I thank our witnesses for being here today, and I look forward to your testimony. Veterans suffering with TBI have demonstrated courage on the battlefield, and they continue to do so in their recovery. Together we can improve the care and services available to them.

Thank you very much, and now I ask our Ranking Member, Senator Burr, for his statement. Senator Burr.

STATEMENT OF HON. RICHARD BURR, RANKING MEMBER, U.S. SENATOR FROM NORTH CAROLINA

Senator BURR. Aloha, Mr. Chairman.

Chairman AKAKA. Aloha.

Senator BURR. Thank you for calling this hearing. I want to take a moment, if I can, to recognize several North Carolinians who are in attendance at the hearing today. They each have important stories, and one will share that story with us.

First, we have on our second panel Jonathan Barrs. Jonathan retired from the Marine Corps last year after two tours in Iraq. He experienced two improvised explosive device blasts in 1 week while serving as a turret gunner in his Humvee and was later diagnosed with a TBI in 2008. Jonathan, thanks for agreeing to share your story with these Members and this panel today and, more importantly, for your service to the country.

Also joining us is Mason Poe and his wife, Kristen. Mason was in a coma for 1 month following an IED blast in Iraq. Thirty surgeries later, he is walking and has started his own small business. Both Mason and his wife have submitted testimony for the record today.

[The prepared statements of both Mr. and Mrs. Poe are in the Appendix.]

Senator BURR. Next, Vincent Gizzerelli served two tours in Iraq before his separation from service last year. He took shrapnel in his leg and has moderate to severe TBI following an IED blast in 2004. Vincent, thank you for being here.

Last, I want to acknowledge two individuals that are not here, Mr. Chairman, and I had hoped they would have been—Sarah and Ted Wade—for their work within the Wounded Warrior Project. Ted sustained a severe brain injury while in Iraq, and Sarah has been at his side ever since. Later today, the President will sign into law a bill that will direct the creation of a program of assistance for family caregivers. Without the bravery and support of loved ones like Sarah, many of our wounded warriors would be forced to live in nursing home settings. Sarah and Ted have submitted testimony for the record today, and they have already been an invaluable asset in helping Congress, the VA, and the Department of Defense on new ways to improve and coordinate care and its delivery to our servicemembers and veterans with TBI. Their efforts were critical in shaping the family caregiver legislation that the President will sign.

[The prepared statement of Mrs. Sarah Wade is in the Appendix.]

Senator BURR. To all of you, I thank you for your service to our country. I thank you for your willingness to continue that service by working with us to improve the system of care and the benefits for all our servicemembers.

Mr. Chairman, just over 3 years ago, the Committee held a hearing on VA's ability to respond to the health care needs of returning servicemembers, the care provided to what is known as the signature wound of the current war. TBI was the main focus. What we learned from that hearing led to provisions enacted within the 2008 Defense Authorization Act. Specifically, the law directed or authorized actions on the following points: one, providing to each of our TBI wounded an individual plan of rehabilitation and reintegration into the community; two, using rehabilitation services outside of VA where appropriate, particularly for newly injured veterans; three, research on the diagnosis and treatment of TBI; four, providing assisted living services in veteran communities; and, finally, the provision of age-appropriate nursing care to younger veterans with severe TBI whose needs are vastly different than a typical nursing home patient.

I hope to learn from both VA and DOD the progress they have made in each of these areas.

Furthermore, I am interested to learn whether one of the key recommendations of the Dole-Shalala Commission, the creation of Federal recovery coordinators, is helping servicemembers and their families navigate systems of care and benefits that in many cases are overwhelming. From those who work or do research on TBI issues on a day-to-day basis, I hope to learn how we might continue to improve our past efforts.

Mr. Chairman, our Nation faces extraordinary domestic challenges, but we must never forget the sacrifices our men and women and their families make in the defense of our freedom. Meeting

their needs is our highest priority as a Nation. I remain committed to work with you and with this entire Committee to fulfill our obligation to them. I am confident we can do better than we have.

I thank the Chair.

Chairman AKAKA. Thank you very much, Senator Burr.

Senator Tester?

STATEMENT OF HON. JON TESTER,
U.S. SENATOR FROM MONTANA

Senator TESTER. Thank you, Mr. Chairman. I want to thank you for holding this hearing today. I also want to welcome the witnesses, especially Karen Bohlinger, of Helena, MT. Karen is the wife of Montana's lieutenant Governor, but first and foremost, she is the mother of an American soldier. Her son, Jeremy, has been in a VA polytrauma network site for nearly 5 years. During that time, she has been one of the most vocal, passionate advocates for veterans and their families that I have ever met. She is going to talk about Jeremy's story in great detail, so I am not going to steal her thunder, except to say that she has a powerful story to tell about what the VA is doing right and what the VA is doing wrong. So, Karen, I want to thank you so very, very much for being here today. You have a critically important story to tell, and we all look forward to hearing it.

Much is made of how Traumatic Brain Injury is the signature wound of the Iraq and Afghanistan conflicts. By now, many of us know the statistics and the challenges facing the doctors and nurses in the DOD facilities and VA hospitals who have been tasked with treating hundreds of thousands of men and women. These are gut-wrenching, life-changing challenges, and it is critical that the spouses and the parents are a meaningful voice in patient care and treatment.

But all too often, I hear about folks who have a loved one that come into the DOD health system or the VA with serious TBI. The parents and the spouses of these servicemembers then have to wage a battle against the bureaucracy when someone that they care about is not getting the treatment that they deserve.

I met with a number of folks from Montana who have come through Walter Reed and Bethesda Naval. Most of them have been fortunate to have a spouse or a parent who has been able to drop everything and fight full time for their soldier or Marine. One of the things that I have heard frequently was that the individual care from doctors and nurses was outstanding, but fighting with the bureaucracy to schedule an appointment with a doctor or to have medications changed is nothing short of a full-time job.

What happens to a soldier or a veteran when he does not have a full-time advocate? What happens when a young person from rural Montana is brought to Seattle or Minneapolis with serious TBI? Who is looking out for that young woman or man? This is the area where we need to do better.

Mr. Chairman, I know we have got a busy agenda, but I want to say one more thing. Recently, I joined Senator Murray on a letter to the Secretary of the Army asking some questions about the Army's Warrior Transition Units. I have been told that most of these questions are beyond the scope of this Committee's jurisdic-

tion. I do believe that we should consider another round of joint hearings with our friends from the Armed Services Committee to find out about what we can do to make sure the WTUs work better for the soldier who will eventually become a veteran and, thus, will be in our jurisdiction.

With that, thank you again, Mr. Chairman, for the hearing. I look forward to the testimony from our participants.

Chairman AKAKA. Thank you very much, Senator Tester.

Senator Brown, your statement, please.

Senator BROWN OF MASSACHUSETTS. Thank you, Mr. Chairman. It is a pleasure to be here again. Being from Massachusetts, we have, Mr. Chairman, a statewide head injury program that we have implemented, for which we receive State funds. Obviously, it is funded by the State, and there are some Federal grants tied into it. It is an issue that we have identified and tried to work with the appropriate treatment authorities.

As you know, Mr. Chairman, I am in the Guard as a JAG. I notice regularly the transformation from a soldier who is raring to go to somebody who is not functioning quite right. Before, we never really knew why, and I think we have identified it through the research and treatment opportunities in Massachusetts and throughout the country. It is something that I want to thank you for holding another hearing about. Being new, it is something that we have taken very seriously back home because we are trying to find out how to help, you know, what types of tools and resources do we need to provide our men and women who are serving to get better and get back to their families and be the person they once were.

So I am going to defer. I look forward to the testimony though I will be bouncing back and forth to the Armed Services Committee. And, Senator Tester, I am happy to work with you on that letter and move that through the food chain. So thank you.

Chairman AKAKA. Thank you very much, Senator Brown.

Now I want to welcome our witnesses. Would you please come up to the dais? First we have Dr. Lucille Beck, who is Chief Consultant for Rehabilitation Services at the Department of Veterans Affairs. She is accompanied by Dr. Karen Guice, the Director of the Federal Recovery Coordination Program; Dr. Joel Scholten, Associate Chief of Staff for Physical Medicine and Rehabilitation at the Washington, DC, VA medical center; and Dr. Sonja Batten, Deputy Director of the Department of Defense Center of Excellence for Psychological Health and Traumatic Brain Injury.

We also have Col. (Dr.) Michael Jaffee, National Director of the Defense and Veterans Brain Injury Center. Katherine Helmick, Interim Senior Executive Director for TBI at the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury, is sitting there.

I thank you all for being here this morning. Your testimony will appear in the record. Dr. Beck, will you please proceed with your statement?

STATEMENT OF LUCILLE B. BECK, PH.D. CHIEF CONSULTANT, OFFICE OF REHABILITATION SERVICES, OFFICE OF PATIENT CARE SERVICES, VETERANS HEALTH ADMINISTRATION, U.S. DEPARTMENT OF VETERANS AFFAIRS; ACCOMPANIED BY KAREN GUICE, M.D., DIRECTOR, FEDERAL RECOVERY COORDINATION PROGRAM; JOEL SCHOLTEN, M.D., ASSOCIATE CHIEF OF STAFF FOR PHYSICAL MEDICINE AND REHABILITATION, WASHINGTON, D.C., VA MEDICAL CENTER; AND SONJA BATTEN, PH.D., DEPUTY DIRECTOR, U.S. DEPARTMENT OF DEFENSE CENTER OF EXCELLENCE FOR PSYCHOLOGICAL HEALTH AND TRAUMATIC BRAIN INJURY

Ms. BECK. Yes, thank you. Good morning, Mr. Chairman, Ranking Member Burr, and Members of the Committee. Thank you for inviting me here to update the Committee on VA's progress in implementing the wounded warrior provisions in the Veterans Traumatic Brain Injury and Health Programs Improvement Act of 2007. I would like to thank the Committee for its work, which has enabled VA to establish landmark programs and initiatives to meet the provisions of the Wounded Warrior Act.

I would also like to thank the members of the second panel for their advocacy on behalf of severely injured veterans. We appreciate these opportunities where we can listen to our stakeholders because they know the system and they can help us improve.

Polytrauma is a new phenomenon, and, unfortunately, medicine has not yet caught up in every regard. At the outset of the current conflicts, it is fair to say we were unprepared for the complexity of injuries we were seeing because servicemembers would not have survived these types of injuries in previous conflicts. While VA had established TBI centers, Traumatic Brain Injury centers, in 1992, it was in 2005 that we established the Polytrauma System of Care and the four Polytrauma Rehabilitation Centers. We know there were challenges during those early days in providing seamless care that could treat all of the veterans' needs. Care for complex injuries was limited to the four polytrauma centers. Some veterans with severe TBI were not regaining consciousness, and care was not optimally coordinated.

Today the Polytrauma System of Care has direct patient care available at 108 locations across the country. There are 48 polytrauma points of contact at other facilities who can refer veterans and family members to the specialists they need. Twenty Federal Recovery Coordinators support the transition and care of the severely injured. We worked with 1,573 facilities and providers in the private sector to provide care for more than 3,700 veterans at a cost of more than $21 million in fiscal year 2009. We have an Emerging Consciousness treatment approach that we developed after consulting with the best clinicians across the country that sees better than 70 percent of patients recover.

VA provided more than $23 million in fiscal year 2010 to support 106 research projects related to TBI, and we are screening every OEF/OIF veteran who comes to us for care for Traumatic Brain Injury. We have the systems in place and the resources we need to care for our veterans. In addition, we have made our programs veteran centric. We have modified the physical environment at our Polytrauma Rehabilitation Centers to be family friendly, and we

have added liaisons at the major military treatment facility to improve patient transfers. We use teams of clinicians to achieve our goal of returning veterans to the maximum level of independence and functionality.

Let me provide you with an example of how this benefits veterans. A 28-year-old servicemember was injured in a blast in 2007. He sustained moderate TBI, eye injuries, burns, and fractures in his hands. Within 12 hours, he was flown to Landstuhl for surgery and stabilization, and within 72 hours, he was sent to Walter Reed.

Ten days after the injury, the Richmond Polytrauma Rehabilitation Center was on a videoconference receiving a medical update and information about the family. Eleven days after that, the family toured the Richmond PRC with a case manager from Walter Reed. Less than a week later, 4 weeks from his injuries, the servicemember was admitted to the Richmond Rehabilitation Center and was recovering from his burns and fractures.

By the 120th day following his injuries, we were transferring him to the Polytrauma Transitional Rehabilitation Program, and he was also receiving services from blind rehabilitation and community rehabilitation. On the 210th day after his injuries, he returned home. VA continues providing outpatient care through the polytrauma network site as well as vocational rehabilitation and family counseling. Today he is living at home with his spouse, exploring work and volunteer opportunities, and continuing close case management with VA. This is one of many stories that we are proud of, and this Committee should also take pride in helping to make it possible.

Although we have accomplished much since we established these programs, we recognize that there are still challenges to overcome. For example, we need to improve the availability of services in rural areas. One way we are pursuing this goal is through the use of telemedicine. Four of our facilities, including Denver, now offer TBI screening and evaluation to veterans in rural areas. In addition, we are always looking to establish new relationships with high-quality local care providers and strengthen the more than 300 local agreements that are already in place.

In closing, let me thank you again for your support and the opportunity to appear before you today. I look forward to our continued partnership on this issue. Thank you.

[The prepared statement of Ms. Beck follows:]

PREPARED STATEMENT OF LUCILLE B. BECK, PH.D., CHIEF CONSULTANT, REHABILITATION SERVICES AND THE DIRECTOR OF THE AUDIOLOGY AND SPEECH PATHOLOGY PROGRAM, VETERANS HEALTH ADMINISTRATION, U.S. DEPARTMENT OF VETERANS AFFAIRS

Good morning, Mr. Chairman, Ranking Member Burr, and Members of the Committee. Thank you for inviting me here to update the Committee on the Department of Veterans Affairs' (VA) progress in implementing the wounded warrior provisions in the Veterans Traumatic Brain Injury and Health Programs Improvement Act of 2007. I would like to thank the Committee for its work in passing important legislation, which has enabled VA to establish landmark programs and initiatives to meet the provisions of the title XVI, referred to as the Wounded Warrior Act, and title XVII of Public Law 110–181.

I am accompanied today by Dr. Karen Guice, Director of the Federal Recovery Coordination Program; Dr. Joel Scholten, Associate Chief of Staff for Physical Medicine and Rehabilitation at the Washington, DC, VA Medical Center; and Dr. Sonja Batten, Deputy Director at the Department of Defense (DOD) Centers of Excellence for

Psychological Health and Traumatic Brain Injury. I will describe the current state of VA care and services for Veterans and Servicemembers with Traumatic Brain Injury (TBI), as well as discuss the interagency collaborations with DOD to improve the care, management and transition of recovering Servicemembers.

BACKGROUND

VA has developed and implemented numerous programs that meet legislative requirements and ensure the provision of world-class rehabilitation services for Veterans and active duty Servicemembers with TBI. VA has enhanced its integrated nationwide Polytrauma/TBI System of Care. The VA Polytrauma/TBI System of Care consists of four levels of facilities, including 4 Polytrauma Rehabilitation Centers, 22 Polytrauma Network Sites, 82 Polytrauma Support Clinic Teams, and 48 Polytrauma Points of Contact. The System offers comprehensive clinical rehabilitative services including: treatment by interdisciplinary teams of rehabilitation specialists; specialty care management; patient and family education and training; psychosocial support; and advanced rehabilitation and prosthetic technologies.

In 1992, VA designated four lead TBI Centers as part of the Defense and Veterans Brain Injury Center (DVBIC) collaboration to provide comprehensive rehabilitation for Veterans and active duty Servicemembers. In 1997, VA designated a TBI Network of Care to support care coordination and access to services across VA's system. In recognition of the high survival rate of severely injured Servicemembers in Iraq and Afghanistan, Congress passed two laws that underscored the need for a specialized system of care that meets the complex rehabilitation needs of Servicemembers and Veterans injured in combat: Public Law 108–422, the Veterans Health Programs Improvement Act of 2004, and Public Law 108–447, the Consolidated Appropriations Act, 2005 (in accompanying Reports S. Rep. 108–353 and H.R. Rep. 108–792 (Conf. Rep.)). These laws directed VA to ensure that severely injured Veterans would benefit from the best of both modern medicine and integrative therapies for rehabilitation. In addition, these laws furthered the development of specialized, interdisciplinary rehabilitation programs to handle the complex medical, psychological, and rehabilitative needs of these individuals. In 2005, VA expanded the scope of services at existing VA TBI Centers, and accordingly renamed them Polytrauma/TBI Rehabilitation Centers, to establish an integrated, tiered system of specialized, interdisciplinary care for polytrauma injuries and TBI.

"Polytrauma" is a new word in the medical lexicon that was termed by VA to describe the complex, multiple injuries to multiple body parts and organs occurring as a result of blast-related injuries seen from Operation Enduring Freedom (OEF) or Operation Iraqi Freedom (OIF). Polytrauma is defined as two or more injuries to physical regions or organ systems, one of which may be life threatening, resulting in physical, cognitive, psychological, or psychosocial impairments and functional disability. TBI frequently occurs in polytrauma in combination with other disabling conditions such as amputation, auditory and visual impairments, spinal cord injury (SCI), Post Traumatic Stress Disorder (PTSD), and other medical problems. Due to the severity and complexity of their injuries, Servicemembers and Veterans with polytrauma require an extraordinary level of coordination and integration of clinical and other support services.

The VA Polytrauma System of Care currently provides specialty rehabilitation care across 108 VAMCs to create points of access along a continuum, and integrating services available at 4 regional Polytrauma/TBI Rehabilitation Centers (PRC), 22 Polytrauma Network Sites—one in each Veterans Integrated Service Network (VISN) and one in San Juan, Puerto Rico—and 82 Polytrauma Support Clinic Teams.

PRCs provide the most intensive specialized care and comprehensive rehabilitation care for Veterans and Servicemembers with complex and severe polytrauma. PRCs maintain a full staff of dedicated rehabilitation professionals and consultants from other specialties to support these patients. Each PRC is accredited by the Commission on Accreditation of Rehabilitation Facilities, and each serves as a resource to develop educational programs and best practice models for other facilities across the system. The four regional Centers are located in Richmond, VA; Tampa, FL; Minneapolis, MN; and Palo Alto, CA. A fifth Center is currently under construction in San Antonio, TX, and is expected to open in 2011.

VA's Polytrauma System of Care strongly advocates family involvement throughout the rehabilitation process, and VA strives to ensure that patients and their families receive all necessary support services to enhance the rehabilitation process while minimizing the inherent stress associated with recovery from TBI and polytrauma. VA offers multiple levels of clinical, psychosocial and logistical support to ensure a smooth transition and continuous care for patients and their families. VA

assigns a dedicated case manager to each patient and family at a PRC. These case managers maintain workload levels of six patients each. Families can access this case manager for assistance 24 hours a day, 7 days a week.

Since 2007, VA has placed Polytrauma Nurse Liaisons at Walter Reed Army Medical Center and National Naval Medical Center (at Bethesda, MD) to support coordination of care, patient transfers, and shared patients between DOD and VA PRCs. Whenever an injured Veteran or Servicemember requires specialized rehabilitative services and enters VA health care, the Polytrauma Nurse Liaison maintains close communication with the admissions nurse case manager at the VA PRC, providing current and updated medical records. Before transfer, the Center's interdisciplinary team meets with the DOD treatment team and family by teleconference as another way to ensure a smooth transition.

The four VA Centers typically have between 12- and 18-inpatient beds staffed by specialty rehabilitation teams that provide acute interdisciplinary evaluation, medical management and rehabilitation services. Occupancy rates at these Centers fluctuate over time and location. The average length of stay is currently 30 days, but the average for the most severely injured is 67 days. Upon discharge from a VA PRC, patients may be transferred to another facility, although over 70 percent are discharged to their home.

VA ACCOMPLISHMENTS

A total of 1,736 inpatients with severe injuries have been treated at these Centers from March 2003 through December 2009; 879 of these patients have been active duty Servicemembers, of which 736 were injured in OEF or OIF. VA continues following these patients after their discharge from a VA PRC to assess their long-term outcomes. Data available for 876 former patients indicate:

- 781 (89 percent) are living in a private residence;
- 642 (73 percent) live alone or independently;
- 413 (47 percent) report they are retired due to age, disability or other reasons;
- 206 (24 percent) are employed;
- 90 (10 percent) are in school part-time or full-time; and
- 59 (7 percent) are looking for a job or performing volunteer work.

As patients recover and transition closer to their homes, the Polytrauma/TBI System of Care provides a continuum of integrated care through 22 Polytrauma Network Sites, 82 Polytrauma Support Clinic Teams, and 48 Polytrauma Points of Contact, located at VAMCs across the country.

The Polytrauma Network Sites develop and support a patient's rehabilitation plan through comprehensive, interdisciplinary, specialized teams; provide both inpatient and outpatient care; and coordinate services for Veterans with TBI and polytrauma throughout the VISN.

In 2008, the Polytrauma Support Clinic Teams expanded to 82 VA facilities. These interdisciplinary Teams of rehabilitation specialists provide dedicated outpatient services closer to home and manage the long-term or changing rehabilitation needs of Veterans. These Teams coordinate clinical and support services for patients and their families, conduct comprehensive evaluations of patients with positive TBI screens, and develop and implement rehabilitation and community reintegration plans.

VA Polytrauma Points of Contact are available at 48 VAMCs without specialized rehabilitation teams. These Points of Contact, established in 2007, are knowledgeable about the VA Polytrauma/TBI System of care and coordinate case management and referrals throughout the system.

Throughout the Polytrauma/TBI System of Care, we have established a comprehensive process for coordinating support efforts and providing information for each patient and family member. Specialized rehabilitation initiatives at the PRCs include:

- In 2007, VA developed and implemented Transitional Rehabilitation Programs at each PRC. These 10-bed residential units provide rehabilitation in a home-like environment to facilitate community reintegration for Veterans and their families, focus on developing standardized program measures, and investigate opportunities to collaborate with other entities providing community-based reintegration services. Through December 2009, 188 Veterans and Servicemembers have participated in this program spending, on average, about 3 months in transitional rehabilitation. Almost 90 percent of these individuals return to active duty, or transition to independent living.
- Beginning in 2007, VA implemented a specialized Emerging Consciousness care path at the four PRCs to serve those Veterans with severe TBI who are slow to recover consciousness. Patients with disorders of consciousness (e.g., comatose) require

high complexity and intensity of medical services and resources in order to improve their level of responsiveness and decrease medical complications. To meet the challenges of caring for these individuals, VA collaboratively developed this care path with subject matter experts from DVBIC and the private sector. VA and DVBIC continue to collaborate on research in this area, and incorporate improvements to the care path in response to advances in science. From January 2007 through December 2009, 87 Veterans and Servicemembers have been admitted in VA Emerging Consciousness care. Approximately 70 percent of these patients emerge to consciousness before leaving inpatient rehabilitation.

• In October 2008, all inpatients with TBI at VA PRCs began receiving special ocular health and visual function examinations based upon research conducted at our Palo Alto PRC. To date, 840 inpatients have received these examinations.

• In April 2009, VA began an advanced technology initiative to establish assistive technology laboratories at the four PRCs. These facilities will serve as a resource for VA health care, and provide the most advanced technologies to Veterans and Servicemembers with ongoing needs related to cognitive impairment, sensory impairment, computer access, communication deficits, wheeled mobility, self-care, and home telehealth.

• VA continues to optimize its Polytrauma Telehealth Network to facilitate provider-to-provider and provider-to-family coordination, as well as consultation from PRCs and Network Sites to other providers and facilities. Currently, about 30 to 40 videoconference calls are made monthly across the Network Sites to VA and DOD facilities. New Polytrauma Telehealth Network initiatives in development include home buddy systems to maintain contact with patients with mild TBI or amputation, and remote delivery of speech therapy services to Veterans in rural areas.

• The PRCs have been renovated to optimize healing in an environment respectful of military service. Military liaisons located at the centers help to support active duty patients and to coordinate interdepartmental issues for patients and their families. Working with the Fisher House Foundation, we are also able to provide housing and other logistical support for family members staying with a Veteran or Servicemember during their recovery at one of our facilities.

• In fiscal year (FY) 2009, 22,324 unique outpatients had 83,794 total clinic visits across the Polytrauma Support Clinic Team sites; an increase of over 30 percent from FY 2008.

In addition to improvements in the Polytrauma/TBI System of Care, VA developed and implemented the TBI Screening and Evaluation Program for all OEF/OIF Veterans who receive care within VA. From April 2007 through February 2010:

• 397,904 OEF/OIF Veterans have been screened;

• 54,675 who screened positive have been evaluated and received follow-up care and services appropriate for their diagnosis and their symptoms;

• 29,819 have been confirmed with a diagnosis of having incurred a mild TBI;

• Over 90 percent of all Veterans who are screened are determined not to have TBI, but all who screen positive and complete a comprehensive evaluation are referred for appropriate treatment.

VA developed and implemented a national template to ensure that it provides every Veteran receiving inpatient or outpatient treatment for TBI, who requires ongoing rehabilitation care, an individualized rehabilitation and community reintegration plan, as required by section 1702 of Public Law 110–181 (38 U.S.C. § 1710C). VA integrates this national template into the electronic medical record, and includes results of the comprehensive assessment, measurable goals, and recommendations for specific rehabilitative treatments. The patient and family participate in developing the treatment plan and receive a copy of the plan. Since April 2009, 8,373 of these plans have been completed and documented for Veterans who receive ongoing rehabilitative care in VA.

Section 1703 of Public Law 110–181 (38 U.S.C. § 1710E) permits VA, in implementing and carrying out § 1710C of title 38, to provide hospital care and medical services through cooperative agreements with appropriate public or private entities that have established long-term neurobehavioral rehabilitation and recovery programs. VA continues to increase collaborations with private sector facilities to successfully meet the individualized needs of Veterans and complement care in cases when VA cannot readily provide the needed services, or cases where the required care is geographically inaccessible. VA medical facilities have identified private sector resources within their catchment area that have expertise in neurobehavioral rehabilitation and recovery programs for TBI. In FY 2009, 3,708 enrolled Veterans with TBI received inpatient and outpatient hospital care and medical services from public and private entities, with a total disbursement of over $21 million.

VA has developed, and continues to enhance, policies regarding comprehensive long-term care for post-acute TBI rehabilitation that includes residential, community and home-based components utilizing interdisciplinary treatment teams. In 2007, VA chartered the Polytrauma Rehabilitation and Extended Care Task Force, to address the long-term care needs of seriously injured OEF/OIF Veterans, including rehabilitative care. As a result of this Task Force, VA developed approaches to meet the long-term care needs of Veterans with TBI through enhancements to the current spectrum of long-term care programs and services. Changes implemented include expansion and age-appropriate modifications in Home-Based Primary Care (HBPC) and Adult Day Health Care, development of volunteer home respite, geographic expansion and staff training for HBPC, implementation of Medical Foster Home for Veterans with TBI, and integration of home Telehealth. Last, TBI was a Select Program in VA's budget request, as directed in H.R. Report No. 110–775, accompanying Pub. L. 110–329, and VA has noted Congress' direction to continue this designation. In FY 2010, $231.9 million has been programmed for TBI care for all Veterans; $58.2 million is programmed for OEF/OIF Veterans.

VA/DOD COLLABORATIONS

VA and DOD have shared a longstanding integrated collaboration in the area of TBI through the Defense and Veterans Brain Injury Center (DVBIC). Since 1992, DVBIC staff members have been integrated with VA Lead TBI Centers (now Polytrauma Rehabilitation Centers) to collect and coordinate surveillance of long-term treatment outcomes for patients with TBI. Other significant initiatives that have resulted from the ongoing collaboration between VA and DVBIC include: developing collaborative clinical research protocols; developing and implementing best clinical practices for TBI; developing materials for families and caregivers of Veterans with TBI; developing integrated education and training curriculum on TBI, and joint training of VA and DOD heath care providers; and coordinating the development of the best strategies and policies regarding TBI for implementation by VA and DOD.

In addition to the longstanding affiliation with DVBIC, since 2007, VA has collaborated with DOD to develop implementation plans for Defense Centers of Excellence (DCoE) and the associated injury registries, including Centers for Psychological Health and Traumatic Brain Injury, Extremity Injuries and Amputation, Hearing Loss and Auditory System Injuries, and Vision. VA has assigned personnel at the Center for Psychological Health and TBI, and at the Vision Center. VA continues to be involved in working groups with DOD representatives to assist in developing concepts of operations and plans for the Hearing Loss and Auditory System Injuries Center and the Center for Extremity Injuries and Amputation.

VA has also collaborated with DOD to develop and implement several unprecedented initiatives that are improving care and services for those with TBI. VA, in collaboration with DOD and DVBIC, implemented a 5-year pilot program to assess the effectiveness of providing assisted living (AL) services to Veterans with TBI, as required by section 1705 of Public Law 110–181. The AL-TBI pilot program is being administered through contracts with brain injury residential living programs that provide individualized treatment models of care to accommodate the specialized needs of patients with TBI. Currently, four Veterans with moderate to severe TBI have been placed in private facilities that specialize in providing rehabilitation services for TBI (residing in Virginia, Wisconsin, Kentucky and Texas). Up to 26 Veterans are projected to be enrolled in the program in FY 2010 and 14 more in FY 2011. We are collecting and assessing outcome data on health information, functional status, satisfaction with care, and quality of life. VA will submit a final report to Congress at the conclusion of the program in 2013.

VA, in collaboration with DVBIC, developed a uniform training curriculum for family members in providing care and assistance to Servicemembers and Veterans with TBI: "Traumatic Brain Injury: A Guide for Caregivers of Servicemembers and Veterans." The final version of the curriculum was approved by the Defense Health Board, and dissemination of the curriculum is pending final approval from the Secretaries of DOD and VA. In 2009, VA and DOD collaboratively developed clinical practice guidelines for mild TBI and deployed this to health care providers, as well as recommendations in the areas of cognitive rehabilitation, drivers' training, and managing the co-occurrence of TBI, Post Traumatic Stress Disorder (PTSD), and pain.

In 2009, the VA-led collaboration with DOD and the National Center for Health Statistics produced revisions to the International Classification of Diseases, Clinical Modification (ICD–9-CM) diagnostic codes for TBI, resulting in significant improvements in the identification, classification, tracking, and reporting of TBI and its associated symptoms.

Finally, VA maintains ongoing collaborations with other Federal agencies to leverage resources and collective efforts in advancing the care and services for those with TBI. The most recent notable collaborations include:

• In 2009, VA began collaborating with the National Institute on Disability and Rehabilitation Research TBI Model Systems to collect and benchmark VA rehabilitation and longitudinal functional outcomes and establish a TBI Veterans Health Registry, as required by section 1704 of Public Law 110–181.

• Since 2009, VA has collaborated with the Centers for Disease Control (CDC), National Institutes of Health (NIH), and DOD in accordance with section 3(c) of Public Law 110–206 (42 U.S.C.A. § 280b–1d), the Traumatic Brain Injury Act of 2008 to: (1) determine how best to improve the collection and dissemination of information on the incidence and the prevalence of TBI among persons who were formerly in the military; and (2) make recommendations on the manner in which CDC, NIH, DOD, and VA can further collaborate on the development and improvement of TBI diagnostic tools and treatments. A report to Congress is being prepared regarding this collaborative effort.

THE FEDERAL RECOVERY COORDINATION PROGRAM

The Federal Recovery Coordination Program (FRCP) serves an important function in ensuring that severely injured Veterans and Servicemembers receive access to the benefits and care they need to recover. Beginning in 2008, FRCP has helped coordinate and access Federal, state and local programs, benefits and services for severely wounded, ill and injured Servicemembers, Veterans, and their families through recovery, rehabilitation, and reintegration into the community. The Program is a joint program of DOD and VA, with VA serving as the administrative home.

The Program has grown since enrolling the first client in February 2008. Not every individual referred to the Program meets enrollment criteria or needs the full services of FRCP. Some individuals are enrolled for a period of time and then determine that they no longer need the Program's services. Currently, 513 clients are enrolled and another 41 individuals are being evaluated for enrollment, and another 451 have received assistance. Anyone can return for re-enrollment or additional assistance if the problems are not resolved or if new problems develop.

Recovering Servicemembers and Veterans are referred to FRCP from a variety of sources, including from the Servicemember's command, members of the interdisciplinary treatment team, case managers, families or clients already in the Program, Veterans Service Organizations and other non-governmental organizations. Generally, those individuals whose recovery is likely to require a complex array of specialists, transfers to multiple facilities, and long periods of rehabilitation are referred.

FRCP outreach efforts include brochures, a presence on VA's OEF/OIF Web site, participation and presentations at local, state and national events. Our 1–800 number, new in April 2009, provides another avenue for referral or assistance. When a referral is made, a Federal Recovery Coordinator (FRC) conducts an evaluation that serves as the basis for problem identification and determination of the appropriate level of service.

FRCs coordinate benefits and services for their clients through the various transitions associated with recovery and return to civilian life. FRCs work with military liaisons, members of the Services' Wounded Warrior Programs, Service recovery care coordinators, TRICARE beneficiary counseling and assistance coordinators, VA vocational and rehabilitation counselors, military and VA facility case managers, VA Liaisons, VA specialty care managers, Veterans Health Administration (VHA) and Veterans Benefits Administration (VBA) OEF/OIF case managers, VBA benefits counselors, and others.

Each enrolled client receives a Federal Individual Recovery Plan (FIRP). The FIRP, based on the goals and needs of the Servicemember or Veteran and upon input from their family or caregiver, is designed to efficiently and effectively move clients through transitions by identifying the appropriate services and benefits. The FRCs, with input and assistance from interdisciplinary team members and case managers, implement the FIRP by working with existing governmental and non-governmental personnel and resources.

FRCP staffing has grown to meet the Program's needs. Eight FRCs were initially hired in January 2008. We are adding 5 additional FRCs to the 20 current positions in order to meet the growth, and success, of the Program. Most of these new hires will be placed at VA PRCs adding additional support for severely wounded, ill and injured Servicemembers and Veterans. The table below shows the current locations, as well as the locations for the new FRCs.

Facility Name and Location	Total FRCs
Walter Reed Army Medical Center, Washington, DC	3
National Naval Medical Center, Bethesda, MD	3
Brooke Army Medical Center, San Antonio TX	4
Naval Medical Center, San Diego, CA	3
Camp Pendleton, CA	1
Eisenhower Army Medical Center, Augusta, GA	2
James A. Haley VAMC, Tampa, FL	1
Providence VAMC, Providence, RI	1
Michael E Debakey VAMC, Houston, TX	1
USSOCOM Care Coalition, Tampa, FL	1
Richmond VAMC Polytrauma, VA	2 (new hire)
Palo Alto VAMC Polytrauma, CA	2 (new hire)
Navy Safe Harbor, DC	1 (new hire)
Total (FRC) FTE	25

Administrative staff includes an Executive Director, two Deputies (one for Benefits and one for Health), an Executive Assistant, an Administrative Officer and two Staff Assistants.

The FRCP is VA's lead for the National Resource Directory (NRD), an online partnership of the U.S. Departments of Defense, Labor and Veterans Affairs for wounded, ill or injured Servicemembers, Veterans, their families, caregivers, and supporting providers. The NRD is a comprehensive online tool available worldwide with over 10,000 Federal, state and local resources organized into nine easily searchable topic areas including: benefits and compensation, families and caregivers, employment, education and training, health care, housing, transportation and travel, and homeless assistance. The NRD has an average of 1,500 visitors a day where they access an average of 15,000 page views. Over 300,000 other Web sites now link to the NRD.

FRCP's success rests in its extraordinary and well-trained problem solving professional staff. We have learned a great deal over the past 2 years and have been able to respond quickly to developing needs or problems. We are looking forward to the results from a current Government Accountability Office program evaluation and those from our satisfaction survey. This input will guide the Program's future development and adaptation.

CONCLUSION

In conclusion, thank you again for the opportunity to speak about VA's efforts to support injured transitioning Servicemembers and Veterans. This concludes my prepared statement.

RESPONSE TO POST-HEARING QUESTIONS SUBMITTED BY HON. DANIEL K. AKAKA TO LUCILLE B. BECK, PH.D., CHIEF CONSULTANT, REHABILITATION SERVICES, U.S. DEPARTMENT OF VETERANS AFFAIRS

Question 1. The Institute of Medicine's (IOM) Preliminary Assessment on the Readjustment Needs of Veterans, Servicemembers and their families notes that there is a critical shortage of health care specialists. Given that the Mohonk Report on Disorders of Consciousness (DoC) notes that some 40% of persons with DoC are misdiagnosed, and that there are few rehabilitation facilities in the U.S. that specialize in the assessment and treatment of patients with DoC, how is the VA able to educate and train TBI specialists to provide accurate diagnosis and appropriate treatment?

Response. VA proactively maintains capacity for the treatment of Veterans and Servicemembers with TBI, including development of the health care specialists who serve this population. Steps taken to achieve this goal include establishment of Emerging Consciousness (EC) Programs at the four Polytrauma Rehabilitation Centers (PRC), collaborations with specialists from DOD, academia, and the private sector to develop the EC programs and clinical guidance, and ongoing efforts to educate and train current and future clinicians.

VA partnered with specialists from the Defense and Veterans Brain Injury Center and from academia to develop the EC care pathways at the PRCs. This is a clinical algorithm that details the main elements of the specialized medical, nursing, ther-

apy, technology, and family education and support services deployed for the care of patients in an emerging consciousness state. Participating in the development of the care pathways were some of the main authors of the Mohonk Report, including Dr. John Whyte, Director Moss Rehabilitation and Research Center, and Dr. Joseph Giacino, Spaulding Rehabilitation Network. More recently, the EC Programs have partnered with the VA Neurology Service to perform diagnostics and active monitoring of brain activity during the recovery phase. The care pathways and technologies are continually updated in response to advances in science.

EC Programs at the PRCs maintain the highest standards of accreditation and certification for rehabilitation facilities awarded by the Commission on Accreditation of Rehabilitation Facilities (CARF). CARF is an independent, nonprofit accreditor of health and human services in the area of medical rehabilitation, and VA EC programs are CARF accredited for Brain Injury Rehabilitation. CARF accreditation certifies that the provider meets internationally recognized standards and is committed to continually improving services through the quality, value, and optimal outcomes of services that are delivered.

VA is also a proven leader in recruiting, education, and training of healthcare providers. VA has made great strides in attracting and retaining high quality clinicians and researchers with specialization in such areas as diagnosis, rehabilitation, and treatment of Traumatic Brain Injury and disorders of consciousness. VA's recruitment efforts include hiring incentives, school loan forgiveness plans, performance based advancement opportunities, ample opportunities for professional growth, and strong ties with the academic and research communities.

Specifically, in the area of emerging consciousness, VHA's Office of Rehabilitation Services organizes yearly conferences dedicated to this topic and invites clinicians from the PRCs and experts from academic programs to share knowledge and experience. Clinicians have the opportunity to attend grand rounds and continuing education programs to stay current with new developments in the field. Rehabilitation specialists at the PRCs actively train the next generation of health professionals (i.e. fellows and allied health professionals) through the EC Program. The leadership of the EC Programs confer at least monthly about consistency of clinical care, outcomes management, and research projects. In conjunction with the non-VA EC Consortium, the VA EC Programs work on the latest innovations of the Mohonk Report and on planning ongoing collaborations in this area of expertise.

Question 2. How many Veterans with severe TBI are currently being treated in the Polytrauma sites and how many Veterans with TBI are currently living in VA Community Living Centers?

Response. Through the second quarter of Fiscal Year (FY) 2010, the Polytrauma Rehabilitation Centers (PRC) treated 145 patients in their inpatient bed units; 40 patients are currently being treated at the PRCs. Through the second quarter of FY 2010, 376 Veterans with TBI were served in one of the VA Community Living Centers (CLC); 26 of those were Veterans of Operation Enduring Freedom or Operation Iraqi Freedom (OEF/OIF). At the end of Q2 FY 2010, 9 Veterans with TBI were treated in a CLC bed unit; none of those were OEF/OIF Veterans.

Additionally, during the first five months of FY 2010, 11,376 unique outpatient Veterans had 30,720 total clinic visits for interdisciplinary outpatient rehabilitation services across the Polytrauma Support Clinic Team sites.

Question 3. The Secretary's report notes that the VA developed an Emerging Consciousness Program at the four Polytrauma centers. How many Veterans have been served? What have the outcomes been?

Response. Beginning in 2007, VA implemented a specialized Emerging Consciousness (EC) clinical care pathway at the four PRCs to serve those Veterans with severe TBI who are slow to recover consciousness. From January 2007 through December 2009, 87 Veterans and Servicemembers were treated in the VA EC Programs. Approximately 70 percent of these patients emerged to consciousness before leaving inpatient rehabilitation. Of the remaining 27 patients, 5 emerged at a later date and 5 are deceased. The majority of the patients (70.3 percent) continue to receive services in the VA; 11 Veterans are at home with family and home health support; 4 are in VA Community Living Centers; and 5 are hospitalized in rehabilitation facilities (2 at the PRCs, and 3 at the Kessler Institute).

Question 4. What is the status of the research being conducted on neutral adaptation for Emerging Consciousness?

Response. The study centered at the Hines VA in Illinois is active and still accruing patients. Since the study is still ongoing, no data analysis have been performed.

Question 5. What is the status of the research on the effectiveness of methylphenidate therapy during early TBI recovery?

Response. The existing research knowledge on the early use of methylphenidate (brand name Ritalin) in individuals with moderate to severe TBI reveals that it has no demonstrable effect on individuals with a DoC, but it does improve specific areas of cognitive functioning (attention, arousal) in individuals who have emerged from coma. Methylphenidate is used commonly, but judiciously, in the VA polytrauma system of care at both the early and late phases of recovery after TBI. VA is collaborating through the Defense and Veterans Brain Injury Consortium on a randomized, controlled trial of the effect of methylphenidate in individuals with early TBI, which will be continuing for at least the next 2–3 years.

Question 6. There have been reports in the media about research and new findings about the value of functional imaging techniques to improve communication and rehabilitation for persons with DoC. Has the VA used these techniques?

Response. Functional neuroimaging for TBI, particularly for individuals with DoC, remains a research tool. Advances in technology, technique and knowledge have greatly added to our understanding of brain injury. However, the specific clinical correlation of functional neuroimaging to real world activities is not well defined. There is no specific functional neuroimaging technology that has been used to enhance communication in individuals with a TBI/DOC. An ongoing VA Rehabilitation Research & Development research project utilizes functional neuroimaging (fMRI) as an outcome tool to assess the impact of "familiar voice" (repeated spoken paragraphs by family members) on Veterans with a DOC; results are not anticipated for at least 2 to 3 years.

Question 7. Please provide information, including the name and address, on local contract providers or VA medical centers which provided neuropsychological evaluations for Veterans claiming service-connected compensation due to TBI during FY 2009.

Response. In order to collect the information requested, VHA will survey the field facilities. We estimate that the time to survey the field and to consolidate responses will require additional time and we will provide this information later in July.

Question 8. Please provide data on the number of Veterans who received a VHA or VHA local contract compensation and pension examination for TBI and the number of those who received a neuropsychological evaluation and testing at each location during FY 2009 and the first two quarters of FY 2010.

Response. In order to provide the data requested, VHA will need additional time and will provide this information also in July .

Question 9. What is the status of VA's transformational activities pertaining to improving age-appropriate care in the Community Living Centers (CLC)?

Response. VA has and continues to embed the provision of age-appropriate care in all major VA CLC conferences and education. VA has and will continue to work with all CLC disciplines in facilitating the design of care plans and activities to accommodate the specific interests and needs of the younger Veteran. For example, the care planning process itself has changed to what is known as the "I Care Plan". This has been implemented in many VA CLCs and was recently a major presentation at a CLC education conference. In this approach, the Veteran is identified by name, age, and interests prior to the discussion of the Veteran's medical diagnosis. The plan of care then, is designed around personal preferences for sleep/wake cycles, food preferences, times for personal care, and includes the resident and family in the formulation of care goals.

Question 10. What additional resources does VA require in order to improve the quality or availability of TBI care and rehabilitation?

Response. VA has adequate resources to meet the needs of Veterans with TBI, and TBI continues to be a Select Program in VA budget submissions. In FY 2010, $231.1 million has been programmed for TBI care for all Veterans and $58.2 million is programmed for OEF/OIF Veterans. There are three specific areas where VA can benefit from support to improve TBI care and rehabilitation. This does not require "additional resources", as much as a better understanding and support of VA in its current collaborations and initiatives:

- An increased utilization of the VA Telehealth Network to allow for advanced access to a greater number of Veterans, in particular those from rural areas.
- Continued efforts to proactively provide education on Post Deployment issues including TBI, mild TBI, polytrauma (including amputation), and Co-Morbid conditions such as pain, Post Traumatic Stress Disorder, and other mental health issues. Ongoing support to educate clinicians across VA on advances in care, as well as training new VA clinicians, is necessary.
- VA must sustain the TBI treatment and rehabilitation capabilities that have been developed in recent years by continuing to develop its future workforce. Reha-

bilitation clinicians are necessary to support expanded efforts to provide timely evaluations and needed ongoing rehabilitation care for the wide range of symptoms commonly seen following TBI and polytrauma.

Question 11. What is the average daily census for the Polytrauma facilities or network sites, and are there wait times for admission to the facilities?

Response. Occupancy rates at the four Polytrauma Rehabilitation Centers (PRC) fluctuate over time and location. The occupancy rate across the PRCs was 68 percent for FY 2009. The four VA Centers operate between 12- and 18-inpatient beds staffed by specialty rehabilitation teams that provide acute interdisciplinary evaluation, medical management and rehabilitation services.

At no time since the beginning of conflicts in Afghanistan or Iraq has there been a "wait time" for admission to the VA Polytrauma Centers. Capabilities and capacity is maintained, and patients are admitted immediately upon medical referral and consistent with the patient's medical condition.

Question 12. What progress has been made on the proposed VHA Handbook 1172.02 Physical Medicine and Rehabilitation Transitional Bed Section, which was originally scheduled to be released in March 2010?

Response. The VHA Handbook 1117.02 Physical Medicine and Rehabilitation Transitional Bed Section was signed and issued by VA Under Secretary for Health on May 14, 2010. The document has been published on both the VHA Intranet and Internet Web sites.

Question 13. What is the status of the report required to be submitted to Congress, on the pilot program for assessing the feasibility of assisted living services for Veterans with TBI?

Response. The report to Congress on the Assisted Living Pilot for Veterans with TBI is due August 30, 2013. In anticipation of this report, VA continues to enroll eligible Veterans into the Pilot. These Veterans have TBI and require supervision and assistance with activities of daily living in order to enhance their rehabilitation, quality of living and community re-integration. Veterans are being placed in brain injury residential living programs in the private sector near their home communities. These programs provide individualized treatments to accommodate the specialized needs of patients with TBI. Case management services are provided by VA case managers with expertise in TBI. Outcome data are being collected that include demographic and health information, functional status, quality of life and satisfaction indices, and cost of care.

RESPONSE TO POST-HEARING QUESTION SUBMITTED BY HON. SHERROD BROWN TO LUCILLE B. BECK, PH.D., CHIEF CONSULTANT, REHABILITATION SERVICES, U.S. DEPARTMENT OF VETERANS AFFAIRS

Question. What is VA doing regarding the Eye Trauma Registry and when can we expect it to be up and functional?"

Response. VA and DOD continue to develop a Joint Defense and Veterans Eye Injury and Vision Registry (DVEIVR). VA has completed development of a data store to collect clinical data on Veterans with eye injuries and visual symptoms related to TBI. Initial testing was completed March 2010. DOD will implement a project similar to the VA functional data store by the end of the third quarter of FY 2010. This will be accomplished through use of the Joint Theater Trauma System.

Approval was granted to begin the acquisition phase for development of the DVEIVR Phase 1 Pilot in May 2010. The DVEIVR is expected to be operational by June 2011.

Chairman AKAKA. Thank you. Thank you very, very much.

Now we will hear from Colonel Jaffee.

STATEMENT OF COL. MICHAEL S. JAFFEE, M.D., NATIONAL DIRECTOR, DEFENSE AND VETERANS BRAIN INJURY CENTER (DVBIC), TRAUMATIC BRAIN INJURY PROGRAM, U.S. DEPARTMENT OF DEFENSE; ACCOMPANIED BY KATHERINE HELMICK, INTERIM SENIOR EXECUTIVE DIRECTOR FOR TBI, DEFENSE CENTERS OF EXCELLENCE FOR PSYCHOLOGICAL HEALTH AND TRAUMATIC BRAIN INJURY

Colonel JAFFEE. Mr. Chairman, Members of the Committee, thank you for the opportunity to discuss the progress that has been

made in the diagnosis and treatment of Traumatic Brain Injury (TBI), and the highly collaborative and fruitful relationship between the Department of Defense and the Department of Veterans Affairs.

The high rate of TBI and blast-related concussion events are felt within each branch of the service and throughout both the DOD and VA health care systems. We have been providing acute management for the entire spectrum of Traumatic Brain Injury—mild, moderate, and severe. The vast majority of the Traumatic Brain Injuries in the Department of Defense are mild TBIs, also known as concussion. Almost 90 percent of individuals who sustain mild TBI will have a complete resolution of their symptoms within days or weeks of the incident. We have focused a lot of effort on the appropriate, safe management of these patients to avoid recurrent injuries during their recovery.

Both the DOD and the VA have dedicated significant resources for the prevention, early detection, treatment, and rehabilitation of servicemembers and veterans with TBI. I will describe our efforts in these areas and how they support the direction of this Committee and the Veterans Traumatic Brain Injury and Health Programs Improvements Act of 2007.

Prevention of TBI is a critical component of our overall strategy. Central to the preventative approach is the continued development of state-of-the-art personal protective equipment, along with a broad-based awareness campaign to provide servicemembers with strategies to mitigate risks both in a deployed location and at home.

After prevention, we ensure our early detection efforts are directed at identifying potential TBI as close to the time of injury as possible. Mandatory concussion screening occurs at four levels: in-theater; at Landstuhl Regional Medical Center in Germany for all medically evacuated personnel; during the post-deployment health assessments and reassessments; and at VA facilities where veterans present for treatment.

DOD has developed and proliferated—with the input of VA and civilian subject matter experts—a systematic method for conducting these screenings. The Military Acute Concussion Evaluation, or MACE, has been used for in-theater screening following an incident. DOD and VA also jointly developed and are using a screening tool in the post-deployment health assessment and reassessment and the VA's TBI clinical Assessment. Both of these tools have been recommended to the DOD by the Institute of Medicine.

Once TBI is identified, DOD, in collaboration with VA subject matter experts, developed guidelines for the management of concussion in mild TBI in-theater. These initiatives have been adapted by several of our NATO allies.

For providers delivering care in the combat theater, we have introduced an electronic consult service for use by all service providers that connects them with a TBI expert—jointly manned by DOD and VA specialists. For care in the U.S., the DOD and VA partnered to develop evidence-based guidelines for the management of mild Traumatic Brain Injury. The Defense and Veterans Brain Injury Center, DVBIC, a congressionally-mandated collaboration between the DOD and VA, has facilitated or led a number of

TBI conferences, including focused approaches to managing minimally-conscious TBI patients, TBI patients with other clinical conditions to include PTSD, and efforts at cognitive rehabilitation.

We have worked with the VA on the Assisted Living for Veterans with TBI project, and we helped establish a pilot age-appropriate TBI-specific assisted living program at one of nine State-owned comprehensive rehabilitation facilities. Simply put, the DOD and VA collaboration could not be stronger and more results oriented than what we have accomplished in this area. An independent article published by the *Journal of Head Trauma Rehabilitation* cited that DVBIC collaboration between DOD and VA as the most fully-developed system of care in the U.S. for brain injury. Still, much remains unknown about the short- and long-term effects of blast injury on the brain, and so our research continues.

Last year, DVBIC published the largest randomized-controlled trial of cognitive rehabilitation for moderate to severe patients. The DOD is leveraging the latest advances in stem cell regenerative medicine through a collaboration between the Uniformed Services University and NIH. The DOD has been recognized for innovative research utilizing the latest advances in neuroimaging. The DOD is leveraging national expertise and resources in TBI research through more than $200 million allocated through the congressionally directed Medical Research Program.

Servicemember and family outreach is an equally strategic element of our educational efforts. At Congress' direction, we assisted the development of a Family Caregiver Program to meet the needs of family members, and this included a panel with members from the VA and civilian subject matter experts. We have developed a number of award-winning multi-media educational initiatives to include partnerships with public television, Brainline.org. Finally, we have established a National Care Coordination Network identifying all personnel with TBI who have been evacuated from theater. They get regular follow-ups upon their return home, and this program is closely linked with the VA's Polytrauma Federal Care Coordination System.

We have had the benefit over the past several years of significantly increasing the number of civilian providers who are eligible to care for patients in our TRICARE network. We have been implementing a number of pilot initiatives to enhance our telemedicine projects in the rural outreach.

The DOD, VA, and our civilian colleagues have performed extraordinary work across this country to advance our understanding of TBI, particularly as it relates to the unique nature of combat. Substantive progress has been made to implement the provisions of the 2007 law, and we are very pleased to have worked with the VA as colleagues in this endeavor.

Mr. Chairman, Members of the Committee, I want to again thank you for your steadfast support of our Military Health System and your ongoing investment in Traumatic Brain Injury research and care. I look forward to your questions.

[The prepared statement of Colonel Jaffee follows:]

PREPARED STATEMENT OF COL. MICHAEL S. JAFFEE, M.D., NATIONAL DIRECTOR, DEFENSE AND VETERANS BRAIN INJURY CENTER (DVBIC), TRAUMATIC BRAIN INJURY PROGRAM, U.S. DEPARTMENT OF DEFENSE

Mr. Chairman, Members of the Committee, Thank you for the opportunity to come before you today to discuss progress made in the diagnosis and treatment of Traumatic Brain Injury (TBI), and the highly collaborative and fruitful relationship between the Department of Defense (DOD) and the Department of Veterans Affairs (VA) in this vital area of medical research and treatment. Accompanying me today is Ms. Katherine Helmick, Interim Senior Executive Director for TBI at the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE).

I am honored to be able to represent DOD, and the men and women who serve in our Military Health System. I am the National Director of the Defense and Veterans Brain Injury Center (DVBIC), a congressionally mandated collaboration between DOD and VA which is organized as a network of excellence across 17 DOD and VA sites with more than 225 professionals representing more than 20 different clinical disciplines. For the past two and a half years, the DVBIC has also operated as the primary operational TBI center of DCoE. Through these collaborations, I have been fortunate to work closely and collaboratively with our colleagues across DOD and VA for the last several years. I am proud of what we have accomplished together to advance the prevention, diagnosis, and treatment of Servicemembers and veterans with TBI.I am confident in our organization's ability to serve as a national asset for helping Servicemembers and veterans maximize their functional abilities and decrease or eliminate their TBI-related disabilities.

The high rate of TBI and blast-related concussion events resulting from current combat operations directly impacts the health and safety of individual Servicemembers and subsequently the level of unit readiness and troop retention. The impacts of TBI are felt within each branch of the Service and throughout both the DOD and VA health care systems. Since January 2003, over 134,000 Servicemembers have been identified within our surveillance system as having sustained a clinician-confirmed TBI, most of which are considered mild TBI or a concussion (mTBI). It is important to note almost 90 percent of individuals who sustain mTBI will have complete resolution of their symptoms within days or weeks of the incident. Our in-theater management guidelines for TBI emphasize safety and prevention of recurrent injuries until recovery has occurred.

With the support of Congress, both Departments have dedicated significant resources to the prevention, early detection, treatment, and rehabilitation of Servicemembers and veterans with TBI. Ongoing medical research continues to contribute to our understanding of each of these activities. I will describe our efforts in these areas. I will also highlight the comprehensive professional medical education and family outreach undertaken to ensure our military and VA practitioners and the families who must help with managing this condition are aware of the most current findings and tools to assess and treat TBI. All of these activities support the direction of this Committee as reflected in the Veterans Traumatic Brain Injury and Health Programs Improvements Act of 2007.

PREVENTION

Prevention of TBI is a critical component of our overall strategy. Central to the preventative approach is the continued development of state-of-the-art personal protective equipment (PPE). The army combat helmet/light weight helmet was developed for today's battlefield environment, and a next generation enhanced combat helmet is under development. The Headborne System—a joint Service future initiative—is being engineered to provide added protection from blast injury.

Along with PPE investments, the Department has engaged in a broad-based awareness campaign to provide Servicemembers with strategies to mitigate risks both in a deployed location and at home to include ballistics protection and adherence to use of seatbelts.

EARLY DETECTION

Our early detection efforts are focused on identifying potential TBI as close to the time of injury as possible. Mandatory concussion screening occurs at four levels to maximize treatment opportunities for Servicemembers who may have sustained a concussion: in-theater; at Landstuhl Regional Medical Center, Germany (for all medically evacuated personnel); during Post Deployment Health Assessments and Reassessments; and at VA facilities when veterans are treated.

DOD has developed and proliferated—with the input of the Services, VA, and civilian subject matter experts—a systematic method for conducting these screenings

with the appropriate tools. The Military Acute Concussion Evaluation (MACE) has been used for in-theater screening following an incident. This evaluation tool has been independently reviewed by the Institute of Medicine and recommended for continued use in assessing combat-related TBI. We continue a cycle of process improvement for in-theater screening and management. The latest proposed guidelines include a transition to mandatory evaluation of all Servicemembers involved in an incident considered associated with risk of concussion. DOD and VA jointly developed and are using a screening tool in the Post-Deployment Health Assessment and Reassessment and the VA TBI Clinical Reminder. This tool is an adaptation of the Brief TBI Screen and has been recommended to DOD by the Institute of Medicine for this purpose.

TREATMENT

DOD has published clinical practice guidelines for both in-theater and CONUS-based management of mTBI ("Mild TBI Clinical Guidelines in the Deployed Setting" and "Mild TBI Clinical Guidance"), and developed tailored algorithms for use by medics/corpsmen, an initial evaluation, and a more comprehensive evaluation. NATO countries have used adaptations of the MACE and DOD clinical guidelines as a template for their own militaries.

For providers delivering care in the combat theater, we have introduced an electronic consult service for use by all Service providers to connect them with a TBI expert—jointly manned by DOD and VA specialists. This consult service has proven to be a useful tool to deployed medical staffs.

DOD and VA worked closely on developing and issuing evidence-based CONUS guidelines for management of mTBI. We issued these guidelines in April 2009, to providers in both organizations, assisting them with patients having subacute or chronic (more than 90 days) mTBI. These guidelines allow Servicemembers to receive care from their primary care providers, closest to home and family support. When required, referrals are made to TBI specialists at designated facilities.

For more severe categories of TBI, we have disseminated several guidelines for use in theater, and have sponsored the development of specialist guidelines such as those from the American Association of Neuroscience Nurses. We have also provided consultation in the development of civilian guidelines such as those developed by the American College of Emergency Physicians.

To advance our understanding of changes in neurocognitive abilities, we have implemented a program of baseline, pre-deployment cognitive evaluation. Introduced in 2008, this baseline test better informs return-to-duty determinations in theater following a concussion injury.

The DVBIC also facilitated a consensus conference on programs for minimally conscious TBI patients which included DOD, VA, and civilian subject matter experts. This conference was instrumental in helping inform further development of relevant programs to manage this population.

Finally, our clinical guidelines recognize there are often co-morbidities with TBI cases, to include depression, post-traumatic stress and substance use disorders, and other extremity injuries. To better understand this, the DVBIC co-sponsored with the Congressional Brain Injury Task Force, an international symposium on behavioral health and TBI. TBI case management demands an interdisciplinary endeavor that must incorporate and meld various clinical elements including neurology, neurosurgery, psychiatry, neuropsychology, and physical medicine and rehabilitation. DOD and VA have worked to ensure our TBI clinical guidelines represent the input from this diverse set of medical specialists.

An independent article published by the Journal of Head Trauma Rehabilitation cited the DVBIC collaboration between DOD and VA as the most fully developed system of care in the United States for brain injury.

REHABILITATION/RECOVERY/REINTEGRATION

Rehabilitation is an essential component of our TBI program, with a focused approach on cognitive rehabilitation. In 2009, we hosted the leading experts in this country—from DOD, VA, and the civilian sector—to develop and issue clinical guidance for cognitive rehabilitation programs based on available evidence. Fourteen DOD military treatment facilities will use these guidelines in a controlled, step-wise process to assess the effectiveness of these guidelines on patient outcomes.

The DVBIC has worked with VA on the Assisted Living for Veterans with TBI project. We have collaborated with VA in their exploration of means to contract with civilian facilities to serve veterans. We helped establish a pilot age-appropriate TBI-specific assisted living program with multidisciplinary rehabilitation and assistive technology at one of nine state-owned comprehensive rehabilitation facilities. I was

pleased to see VA issuance of a Request for Information from the industry just last month to continue to move forward with this initiative.

ONGOING RESEARCH

The short and long-term effects of blast injury on the brain are still not completely known. DOD has made important contributions to the medical literature with our own research, to include a history of published, successful randomized-controlled clinical trials and several awards from national professional organizations.

The Medical Research and Materiel Command and DVBIC convened a consensus conference with 75 experts identifying scientific evidence supporting the importance of blast injury. Last year, DVBIC published the largest randomized controlled trial of cognitive rehabilitation for moderate-severe patients. The Department's TBI research contributions were recognized in the external technical report on mTBI in DOD conducted by the Survivability/Vulnerability Information Analysis Center which stated in its conclusion:

> "Even within the limited existing literature, it is evident that researchers are now making use of screening criteria, instruments, and other resources developed and made available through DVBIC. The DVBIC now plays a central role in performing and advancing research that will directly benefit military Servicemembers and veterans with TBI."

With the support of Congress, DOD is leveraging national expertise and resources in TBI research through the Congressionally Directed Medical Research Program by investing more than $200 million to academic researchers after a process of scientific and programmatic review that included our VA colleagues.

We are working on innovative ways to enhance our system to fast-track promising research initiatives and findings, and rapidly identify gaps such as the paucity of research findings regarding clinical outcomes from cognitive rehabilitation in the concussion population, as well as direct resources to address these gaps.

DOD and VA are collaborating further with other Federal agencies on translational biophysics, proteomics, and other blast-related projects.

PROFESSIONAL EDUCATION & PATIENT OUTREACH

DOD and VA have worked closely to ensure our research into best practices and evidence-based medical guidance is rapidly distributed to the field. Since 2007, we have held annual conferences to educate our providers on the most current research and evidence-based clinical care guidelines for TBI. Our most recent conference in 2009, was attended by over 800 DOD and VA clinicians. In addition, DOD and VA have developed a series of educational modules for providers of all skill levels, which is accessible via our internal web-based educational platform, MHS Learn.

Servicemember and family outreach is an equally strategic element of our educational efforts. DOD has developed TBI education modules appropriate for all Servicemembers, and include self-help materials for dealing with a range of post-concussive symptoms. At Congress' direction, DVBIC facilitated a panel of the Defense Health Board to oversee development of a Family Caregiver Program to meet the needs of family members, providing them with consistent health information and tools to cope with daily challenges of caregiving.

A recent RAND report recognized DOD and DVBIC educational products for their clinical accuracy and effective risk communication.

Brainline.org is a multimedia project that provides information on preventing, treating, and living with TBI. Funded by DVBIC and delivered by WETA, the public radio and television network in Washington, DC, Brainline.org has reached a very broad audience of TBI patients and families. Additionally, we are using social networking media to connect family members with others who have gone through similar experiences.

Finally, DVBIC has established a national care coordination network, identifying all personnel with TBI who have been evacuated from theater. A care coordinator contacts the Servicemember at 3, 6, 12, and 24 months following injury, and determines what, if any, additional resources are needed to meet the Servicemember's needs. DVBIC Regional Care Coordinators (RCCs) work to ensure optimal care and recovery for Servicemembers and veterans with TBI whose rehabilitation and return to community do not always follow a strict linear path, or whose injury may result in cognitive, social, behavioral, or physical deficits which prevent them from accessing available systems of care. RCCs also follow Servicemembers and veterans with TBIs longitudinally to help avert poor outcomes and improve our understanding of the many factors related to outcome following TBI. This program is linked with the VA Polytrauma Federal Care Coordination System and with DCoE's Outreach Cen-

ter, providing 24 hours a day/7 days per week support to patients, family members, and providers.

OTHER FEDERAL COLLABORATION

While our brain injury collaborative efforts with VA have spanned two decades, we have worked across the Federal health sector on important national efforts to advance our research base. We worked closely with the Centers for Disease Control and Prevention (CDC) to select the appropriate International Classification of Disease codes for TBI surveillance. We are also working with the CDC to extend our education to rural and medically underserved areas for providers in these communities who may be treating Guard and Reserve members.

DOD, VA, and the Department of Education's TBI Model Systems of the National Institute for Disability Rehabilitation Research are collaborating to coordinate the important TBI registry initiatives we have underway. DOD is collaborating with the Department of Labor's "America's Heroes at Work" initiative providing education to employers enhancing incorporation of veterans with TBI into the workforce.

CONCLUSION

DOD, VA, and civilian colleagues have performed extraordinary work across this country to advance our understanding of TBI, particularly as it relates to the unique nature of combat.

DOD and VA experience has been one of intense collaboration—typified by open, fact-driven analysis, research, and dissemination of evidence-based findings. I am proud the DVBIC has been at the center of this collaboration—facilitating and deepening our joint efforts, inspired by the sacrifices of the Servicemembers, veterans, and families we serve. We are developing a system that allows for a more rapid and proactive approach to optimizing our systems of care for our wounded warriors with TBI.

Substantive progress has been made to implement the provisions of the 2007 law, and we are pleased to work with our VA colleagues in this endeavor.

Mr. Chairman, Members of the Committee, I want to thank you again for your steadfast support of our Military Health System and your ongoing investment in Traumatic Brain Injury research and care. I look forward to your questions.

RESPONSE TO POST-HEARING QUESTIONS SUBMITTED BY HON. DANIEL K. AKAKA TO COL. MICHAEL S. JAFFEE, M.D., NATIONAL DIRECTOR, DEFENSE AND VETERANS BRAIN INJURY CENTER, U.S. DEPARTMENT OF DEFENSE

EARLY DIAGNOSIS AND TREATMENT

Question 1. Early diagnosis and treatment is key to having positive outcomes after TBI. What is DOD doing to enforce adherence to the screening and rest standards after a servicemember is exposed to a TBI causing event.

Response. The Department of Defense currently does not enforce adherence to screening and rest standards. However, DOD must continue improving our processes to ensure that every Servicemember exposed to a TBI event received the appropriate diagnosis and treatment. To this end, we will continue to review how we can best enforce standards across Services and in theater.

DOD is currently re-evaluating revisions to current guidelines, originally developed in 2006, for the acute management of concussion/mild Traumatic Brain Injury in the deployed setting to reinforce the importance of early diagnosis and treatment as well as a recovery period to prevent further injury. Currently, the Department conducts baseline cognitive tests used to inform post-concussion evaluations. DOD employs evidence-based tools for concussion screening acutely following injury and during mandatory post-deployment evaluation. Current screening tools assess multiple symptoms in addition to cognition and the assessments are incorporated into the Post Deployment Health Assessment and the VA TBI Clinical assessments.

We are also developing clinical practice guideline for rest standards for those who are diagnosed with any symptoms concussion or TBI. While guidelines are not adequate to enforce adherence, we are educating and training Servicemembers, including the medical community and line leadership, regarding approaches to screening and treatment for concussion/mild TBI.

DOD DATA SHARING WITH VA

Question 2. How is DOD making data, such as predeployment cognitive baseline screenings, available to VA for use in their treatment of servicemembers and veterans?

Response. DOD will provide TBI data, such as predeployment cognitive baseline screenings, to VA for use in their treatment of Servicemembers and veterans by December 2010. To date, more than 500,000 multiservice baseline assessments have been collected using the Automated Neuropsychological Assessment Metrics, a Government off-the-shelf product, to collect baseline cognitive data on deploying Servicemembers. According to the VA, they will begin implementing technical solutions to enable VA providers to view DOD neuropsychological assessment data by June 30, 2011.

COMORBIDITIES ASSOCIATED WITH TBI

Question 3. Multiple comorbidities are associated with TBI, including vision impairment, hearing loss and tinnitus, and the frequency with which servicemembers suffer amputations or other severe extremity injuries. Despite substantial funding provided for the purpose, why has there been virtually no discernable progress in establishing the vision, amputation and extremity injury, and hearing loss centers of excellence, as mandated by the FY 2008 and FY 2009 NDAAs?

Response. The Department has made progress in establishing the vision, traumatic extremity injury and amputation, and hearing loss centers of excellence (COE). Although progress toward establishing these centers of excellence has been slow, the Department has never lost its focus on the care of the wounded warriors. Working in coordination with our VA and private-care partners, we continue to provide high quality care for wounded warriors in multiple clinical centers in the US and overseas. Milestones for establishment of the centers of excellence are provided below:

- Feb 2010—Deputy Secretary of Defense delegated authority to Under Secretary of Defense (Personnel & Readiness) to establish centers of excellence.
- May 2010—Under Secretary of Defense (Personnel & Readiness) established the centers and assigned each center to lead Service Component:
  - Vision—Navy
  - Hearing—Air Force
  - Traumatic extremity Injuries/Amputations—Army
- In May 2010, the VCE sponsored Vision Research Program awarded $10M for Vision Research primarily focused on the management of visual dysfunction with TBI.
- In April 2010, $1.86M was provided to the Hearing COE to be used for contracts, equipment and information management solution to electronic networking. The Hearing COE is also focusing on developing the Joint Hearing Registry with VA and the Services. The Registry will used for the tracking of the diagnosis, surgical intervention or other operative treatment for each case of hearing loss and auditory system injury incurred by a member of the Armed Forces while serving on active duty.
- The Traumatic Extremity Injuries and Amputations COE had not received funding in FY 2009 or FY 2010. However, in collaboration with the VA, DOD is fully engaged with continuing the DOD and VA programs for extremity injuries and amputations.
- Funding profile for each of CoEs provided in table below:

Center of Excellence (CoE)	FY 2009	FY 2010
Vision CoE		
DOD O&M	$3.00M	$6.84M
VA O&M	$0.38M	$1.10M
DOD MILCON	$4.05M	
O&M /MILCON Total	$7.43M	$7.94M
Hearing CoE		
DOD O&M	$0.00M	$1.86M
Traumatic Injuries/Amputations		
DOD O&M	$0.00M	$0.00M

Chairman AKAKA. Thank you very much, Colonel Jaffee.

Colonel, one Marine who returned from Afghanistan in December 2009 was in a lightly armored vehicle that struck an IED. The incident was fatal for other occupants of the vehicle and amputated the legs of the turret gunner. The Marine in question was knocked unconscious.

After seeking treatment from his corpsmen, having the incident documented in his medical record, and making the proper indication on his PDHA, he has since received no follow-up care. He has not been contacted by anyone about his PDHA. He has even sought care from several different military medical sites and has been turned away.

Can you comment on what the Department is doing to ensure servicemembers actually receive the treatment that is outlined in the policy?

Colonel JAFFEE. Thank you, Mr. Chairman. There are a couple of ways that we are trying to increase the penetration and ensure that people get the appropriate treatments, one of which is we are in the process of transitioning our system for evaluations from a subjective, voluntary approach where a servicemember would have to raise their hand and say that they have a problem and access care, to one in-theater, which is more of a mandatory—if you have been involved in an incident that is associated with a blast, even if you are being stoic and denying that you have symptoms, you would still receive a mandatory evaluation. And the current protocol for that also includes that that gets appropriately documented in-theater, which can help facilitate further follow-up. And your particular case mentioned assuring more robust care and follow-up in the post-deployment aspects throughout all of the facilities.

One of the things that is very important to the Department of Defense is providing the appropriate education and resources to all of our primary care providers in the military health care system on the systems and resources and guidelines that are in place to care for this very important population. To that end, we have been investing a lot of resources in providing appropriate education to all members of our military health care system. This includes having instituted for the past 3 years annual training events, which have trained more than 800 DOD and VA providers to make them aware of these newer developments and guidelines.

We have put in a system, a network of education coordinators throughout the country. We have 14 of these people throughout the country whose job is outreach to make sure that they are providing appropriate education and resources to our primary care providers at all of our military facilities. We recently are very pleased by the collaboration that we have with our line commanders.

So the medical community does not feel like we are doing this alone in the military, we have the unmitigated support of our line commanders who want to help us get the appropriate education out to all of our servicemembers. Part of that education campaign includes not just education to the patients, not just the providers and the family members, but actually involves the commanders and the line, so that if they are aware that one of the servicemen or servicewomen under their command is not getting the appropriate services, they will have an awareness of the types of resources avail-

able and can also assure that they will get the appropriate referrals and treatments.

The other aspect that we have is that immediate screening, that post-deployment health assessment. And we are aware that some people may not have problems that develop until several months after they return home. To address that challenge, we have implemented the post-deployment health reassessment, which occurs 90 to 100 days after they return home. We have found that that system can sometimes identify individuals with problems that were not identified initially, which also helps expedite getting them transitioned to the appropriate care network.

Chairman AKAKA. In this particular case where this person has claimed that he has been turned away, what alternative does this person have?

Colonel JAFFEE. There is a number—we have a network of those regional care coordinators who can certainly reach out and help facilitate—assuring that that individual can get to a facility that can provide the appropriate resources, be it a Federal facility or a local facility within the TRICARE network. That is the purpose of that program, to try and reach out to individuals like that, because the goal is to keep anyone from falling through the cracks.

Chairman AKAKA. Thank you.

Dr. Beck, as you know, Congress recently passed legislation I introduced that would create a comprehensive program of caregiver support services. If you could make any changes you wanted, how would you implement this program for veterans with TBI?

Ms. BECK. Thank you. We at the VA are very pleased that Congress has recognized the significant sacrifices that are made by caregivers and that there is support and legislation for the expansion of benefits and services to meet their needs.

The additional benefits outlined in the legislation will be of great value to families and to veterans with Traumatic Brain Injury who require a primary caregiver in the home. VA looks forward to working with Congress and other key stakeholders on the implementation of the plan. We think the legislation is comprehensive and will address the needs that our caregivers have.

Chairman AKAKA. Dr. Beck, the Secretary's March 23, 2010, report to the Committee says that, and I quote, "Collaborations with private sector facilities are regularly used to successfully meet the individualized needs of veterans and complement VA care."

Can you cite examples of private facilities providing care for veterans with the most severe TBIs?

Ms. BECK. Yes, sir. I would think first of hospitals like Kessler Hospital in New Jersey, Casa Colina in California, the Rehabilitation Institute in Chicago, Spaulding Hospital in Boston, Marianjoy in Wheaton, the National Rehabilitation Hospital here in the District of Columbia. I am aware of active-duty servicemembers who have been treated or where we have shared treatment with those facilities.

I would also like to point out that at the military treatment facilities, our servicemembers have a choice. They may choose the private sector at the military treatment facility. That is their choice. Some of them do use the private sector, but many of them choose to transfer to Polytrauma Rehabilitation Centers. And since

the beginning of conflicts in Afghanistan and Iraq, our polytrauma centers have been available to take patients. We have not denied admission, and we have had rehabilitation services available to the servicemembers and their families.

Chairman AKAKA. Thank you very much.

Senator Burr, your questions.

Senator BURR. Colonel, I heard you mention that every servicemember who might be exposed to a blast has a mandatory evaluation. Let me just ask you, is Severe Traumatic Brain Injury pretty identifiable?

Colonel JAFFEE. Yes.

Senator BURR. What we are really concerned with is people on the margins. Even with a mandatory evaluation, how in the world are we going to catch it if we do not have a baseline to compare? I think you are talking about a quiz that we send servicemembers through, and yet we know that this is a problem that is going to affect a lot of people. Why aren't we taking a baseline on these folks before they are deployed so we have got some comparison?

Colonel JAFFEE. Well, sir, I am happy to report that actually the DOD does have a program to do cognitive baselining. To date, since that program was implemented, we have baselined more than 500,000 servicemembers prior to their deployment. The purpose of that program is that we can better inform and make the safest determination for when it is safe to return them to duty in theater following an injury so that we can access that baseline information and compare it to their post-injury evaluation when we think we are preparing to send them back into the fight.

Senator BURR. So how does that baseline follow that servicemember from medical facility to medical facility or in-theater?

Colonel JAFFEE. Well, the baseline is meant to help inform those decisions in-theater, so currently it is in a system which the in-theater providers reach back to a help desk to access, and we are in the process of enterprising the execution of a system through our Defense Health Information Management System to tie those results directly into the theater computer systems where the providers there can directly access it from their computer.

Senator BURR. And do you know how many people in-theater know that that exists?

Colonel JAFFEE. I know that there has been a steady increase in utilization of that help desk since it was implemented.

Senator BURR. OK. Dr. Beck, Dr. Gans with the Kessler Institute appeared 3 years ago, and 3 years ago he sort of brought to the Committee's attention that we were doing little to reach outside. Now, you quoted all these places that we go, but let me quote from Dr. Gans' testimony today. "It appears that little has changed since 2007 regarding the use of local care providers for TBI care." Would you like to comment on that?

Ms. BECK. Yes, sir. Thank you. As I noted in my testimony, during fiscal year 2009 the VA treated 3,700 veterans in the private sector and spent over $21 million. There were 1,500, approximately, either facilities or individuals who provided that care to the Nation's veterans.

Senator BURR. What is the VA's criteria for determining whether you use a local provider?

Ms. BECK. The criteria are that the care is either—number 1, that we cannot provide the care at the VA; we do not have the services available at the VA.

Senator BURR. But define that for me. If the nearest VA facility is 90 miles away and they provide the care, is that their point of delivery?

Ms. BECK. What we do in those cases is, we have a geographically accessible statement, and that is a medical decision that is made by our physicians who manage the care, and that is related to distance from the facility, condition, and the specialty care needs. So the geographic accessibility decision is implemented based on those three conditions under the direction of a physician.

Senator BURR. What is the DOD criteria, Colonel?

Colonel JAFFEE. Basically it is up to the—if a certain resource or specialty is available at the military treatment facility, then that is where the servicemember would receive their treatment. If a particular specialty or need is not available, then we would go to the TRICARE network looking at the number of facilities and providers.

Senator BURR. Do you also have a geographical area for the DOD facility?

Colonel JAFFEE. This is done more local and regional by the facility, so it is at the facility itself, if you have the resources; if not, then you try and utilize the expertise as close to the area as possible. That is why we have local TRICARE networks, and each MTF sort of keeps track of those local providers by specialty who are involved in the TRICARE network.

Senator BURR. Dr. Beck, in late 2007, we passed the Wounded Warrior Act, and in that legislation we created a pilot program that provided residential living options.

Now, in your testimony, you say that we currently have "four veterans with moderate to severe TBI that have been placed in private facilities that specialize in providing rehabilitation services for TBI (residing in Virginia, Wisconsin, Kentucky, and Texas.) Up to 26 veterans are projected to be enrolled in the program in 2010 and 14 more in 2011."

Let me just ask you, why are so few being served under this pilot?

Ms. BECK. We have the capacity to serve more under the model. So far——

Senator BURR. Let me just point out, this is 2010. We passed this in 2007. To date, we have four veterans—and I appreciate your projections of 26 in 2010 and 14 in 2011. But based upon the 3-year ramp-up to get four in, I am somewhat skeptical about the ability to meet those. What has been the problem?

Ms. BECK. We have done extensive outreach, and many of our veterans prefer to get their care in their homes with their families.

Second, I also referred in my testimony to our Transitional Rehabilitation Centers. We have those at our four regional centers, and we frequently use those centers for community reintegration, which is a type of care, community-based reintegration, that we would use before we would go to assisted living.

We are doing extensive outreach to make this program known, and we have identified 267 private sector facilities who can provide assisted living for TBI, and we are——

Senator BURR. Have you identified how many servicemembers this might be appropriate for?

Ms. BECK. We have reached out to our veterans through our OEF/OIF case management programs. We initially identified—they reported to us a possible universe of 168 veterans who were interested and might at some point consider assisted living.

What we are finding is that this is going to be an option we think further out in the recovery period as we look at the stressors that may occur for patients, for our veterans and families when they are at home or in the community.

Senator BURR. Thank you. My time has expired, and I thank the Chairman for his indulgence.

Chairman AKAKA. Thank you very much, Senator Burr.

Senator Murray?

STATEMENT OF HON. PATTY MURRAY,
U.S. SENATOR FROM WASHINGTON

Senator MURRAY. Thank you very much, Mr. Chairman and Senator Burr, for holding this really important hearing. Clearly, we all know that we have to get this approach to treating patients with TBI right. I continue to be concerned as we have a number of veterans returning from Iraq and Afghanistan, and we know that IED explosives continue to be a problem on the ground. At the same time, the VA is having trouble still hiring enough mental and health care professionals to meet the needs that we have not only today but for tomorrow.

So, I am concerned about our long-term plan and making sure we continue to do what we need to do from our end to ensure we have the resources to meet it. I am very concerned that the VA is underestimating the number of patients who are going to seek VA health care as a result of the wars in Iraq and Afghanistan. Like I said, clearly the VA has to be able to hire enough professionals, including mental health care professionals, if it is to maintain the quality of care that we expect.

I wanted to ask today if the DOD and VA casualty prediction models are accurate, in your opinion. Dr. Beck or Colonel Jaffee, either one.

Ms. BECK. I would like to take that for the record. I cannot comment on that at this time.

Dr. Guice is our Federal recovery coordinator and works with our severely injured. I——

Senator MURRAY. So we do not know if they are accurate?

Ms. BECK. I cannot comment on it at this time. Colonel Jaffee?

Colonel JAFFEE. What we are most confident in is the number of servicemembers who, after having received a screen, got a clinical evaluation and got diagnosed as having had symptoms thought to be due to a Traumatic Brain Injury. So they get the appropriate clinical evaluation and use an ICD code. There is a very positive initiative over the past 2 years between the VA, DOD, and the Centers for Disease Control to come to a consensus and a revision of the ICD–9 codes that are being used by clinicians to evaluate these

patients. So we have a—I think we are confident in clarifying the number of patients who get diagnosed and coded.

One of the things that I alluded to in my earlier statement is we are also trying to very much encourage our servicemembers who may be suffering but not coming forward who we may not know about. That is why we are transitioning from the system where it is a voluntary symptom-based approach, requiring them to raise their hand, to this mandatory evaluation which we hope and believe will capture more individuals who may be having symptoms and suffering yet may not be raising their hand. This will allow us to get a more accurate prediction and planning for these servicemembers.

Senator MURRAY. OK. Well, I would like you then to answer for the record because we need to look long term for our budget. And we know that it is not just care the day they get home or even 3 months later, but far into the future. The kinds of facilities or treatment that we will need 5, 10, 15, 20 years from now are important, so I would like to have you respond to that.

[The information requested during the hearing follows:]

RESPONSE TO REQUEST ARISING DURING THE HEARING BY HON. PATTY MURRAY TO LUCILLE BECK, PH.D., CHIEF CONSULTANT, REHABILITATION SERVICES, U.S. DEPARTMENT OF VETERANS AFFAIRS

Response: There is no modeling activity by VA regarding this issue. Casualty Projection modeling is a DOD issue.

Senator MURRAY. Let me turn to another question then. In 2008, the GAO raised concerns about the screening tool that was used by the VA to assess TBI. Now, I understand that the VA is currently examining its TBI screening tools because of that, and I am interested to know where that research stands right now because it is unacceptable for veterans with TBI, whether it is blatant or unreported, to go undiagnosed because of lack of training of someone or medical equipment at the VA.

So can someone describe to me where we are with the screening tool assessment?

Ms. BECK. Yes, Senator Murray, we have three research projects now which are evaluating the screening tool and assessing its reliability and validity. We expect the first of those studies to be completed in fiscal year 2011.

Senator MURRAY. Sometime next year.

Ms. BECK. Sometime next year. And I would like to provide for the record the details as to the status of the other studies.

[The information requested during the hearing follows:]

RESPONSE TO REQUEST ARISING DURING THE HEARING BY HON. PATTY MURRAY TO LUCILLE BECK, PH.D., CHIEF CONSULTANT, REHABILITATION SERVICES, U.S. DEPARTMENT OF VETERANS AFFAIRS

Response. Currently, VA has three studies that are evaluating the TBI Screening and Evaluation Tool (below). Two are underway, and a third study is beginning. Results from these are expected beginning in 2011.

1. SDR 08–377: Evaluation of VA's TBI Clinical Reminder and Secondary Level Evaluation

Judi L Babcock-Parziale PhD
Southern Arizona VA Health Care System, Tucson, AZ
Funding Period: May 2009–April 2011

http://www.hsrd.research.va.gov/research/abstracts.cfm?Project_ID=2141699528

Current Status: Active; recruiting subjects.

Background: Traumatic Brain Injury (TBI) is a leading injury among military personnel serving in the Operation Enduring Freedom/ Operation Iraqi Freedom (OEF/ OIF) combat theaters due largely to improvised explosive devices. While TBI severities range from mild to severe, mTBI is particularly difficult to identify, diagnose and treat. The VA modified a version of the Defense and Veterans Brain Injury Center (DVBIC) tool, which is used to screen returning OEF/OIF servicemembers. The VA's modified screen, the TBI Clinical Reminder, is used to screen a slightly different population. Therefore, results of the validity study for the DVBIC tool are not directly applicable. As a result, the General Accounting Office (GAO) recommended the VA expeditiously evaluate the clinical validity and reliability of its TBI screening tool. The VA's Second Level Evaluation will also be evaluated to determine the sensitivity and specificity of the diagnostic criteria.

Objective(s):

(1) Develop expert-derived mTBI Diagnostic Standards (i.e., proxy gold standards).

(2) Evaluate and compare the performance characteristics of the TBI Clinical Reminder and the Second Level Evaluation using the expert-derived Diagnostic Standards.

These objectives will be realized via: (a) An examination the performance characteristics (diagnostic validity) of the TBI Clinical Reminder and the Second Level Evaluation relative to the expert-derived Diagnostic Standards to determine sensitivity and specificity, (b) Determining whether false positives and/or false negatives are related to Post Traumatic Stress Disorder (PTSD) and how the performance characteristics of the tests differ for PTSD, (c) Ascertaining the concordance among measures of functional impairment, the TBI Clinical Reminder and the Second Level Evaluation, (d) Establishing the concurrent validity between the diagnosis of presence or absence of post-concussion syndrome due to mTBI and measures of functional impairment, (e) Verifying the test/retest reliability for the TBI Clinical Reminder and the Second Level Evaluation and (f) Identifying whether clusters of symptoms or subjects reporting similar patterns of symptoms correspond with any of the eight clinical sub-groups (e.g., mTBI with PTSD, PTSD alone).

Methodology:

The project includes a mixed methods approach with a total sample of 720 OEF/ OIF veterans recruited over 12-months at three VA Polytrauma Network Sites. The subjects will have either symptoms consistent with post-concussion syndrome thereby due to mTBI (True Positive) or symptoms not consistent with post-concussion syndrome thereby not due to mTBI (True Negative). All subjects will be assessed by research clinicians using the TBI Clinical Reminder and the Second Level Evaluation, the Diagnostic Standards, and two measures of functional impairment to determine a true diagnosis of mTBI and/or PTSD.

Diagnostic Standards will be derived from experts using an online Delphi process and will be used to compute sensitivity and specificity for the TBI Clinical Reminder and the Secondary Level Evaluation. Test re-test reliability of the TBI Clinical Reminder and cluster analyses of the Secondary Level Evaluation will be conducted. Cluster analyses will be conducted to further our understanding of how the clinical presentation of patients with mTBI might be classified.

Results:

There are no findings, as the project began May 2009.

Impact:

Anticipated Impact: Determining the clinical validity of the VA's TBI Clinical Reminder and Second Level Evaluation is critical because valid screening and evaluation of mild Traumatic Brain Injury (mTBI) leads to accurate diagnosis and timely treatment. Accurate screening improves clinical efficiency and ensures that resources are provided to those who need them most. The project findings are expected to advance the science of screening and diagnosis by clarifying whether symptoms are consistent with post-concussion syndrome thereby due to mTBI. The anticipated findings will also improve the field's ability to measure mTBI outcomes.

2. C7055-I: Objective Diagnosis of Mild Blast-Induced TBI

Joseph F. Rizzo

Funding Period: 1/1/2010–12/31/2012

Objective(s): This proposal presents a novel plan to develop a diagnostic tool to diagnose TBI.

Research: This proposal seeks to develop a new tool to diagnose mild TBI.

Methodology: We propose to modify existing laboratory-based methods to record eye movements to create a new portable device with similar capabilities. This new

test will be developed and validated in the first year of this proposal. Thereafter, this test will be administered to a small number of veterans with blast-induced Traumatic Brain Injury to judge the feasibility of giving this test to blast victims. The blast-victims will be selected by Neurocognitive scientists at the Boston VA.

Current Status: Active; anticipate data collection beginning August 2010, and preliminary data before the end of fiscal year 2011.

3. SDR 08–411: TBI Screening Instruments and Processes for Clinical Follow-Up

Rodney D. Vanderploeg Ph.D.

James A. Haley Veterans Hospital, Tampa, FL

Funding Period: October 2009–September 2011

Objective(s): The goal is to evaluate the reliability and validity of the existing Traumatic Brain Injury (TBI) Clinical Reminder Screen for OEF/OIF Veterans. There are four objectives:

1. Operationalize a gold standard semi-structured interview for TBI identification using a national panel of experts.
2. Identify VHA system factors and patient characteristics predicting delay in or failure to complete the TBI Clinical Reminder screen (e.g., patient characteristics and VA System levels of Polytrauma care).
3. Using the gold standard semi-structured interview, evaluate the validity (sensitivity and specificity) and reliability of the current TBI Clinical Reminder Screen.
4. Identify approaches to improve the TBI Clinical Reminder screening protocol, including modifications of the screening instrument and process.

Research Design: This is both a retrospective analysis of existing VA patient care data (TBI Clinical Reminder and TBI Comprehensive Evaluation) and a prospective study completing "gold standard" interviews of both positive and negative TBI Screens.

Methodology:

1. Using a panel of national experts develop a "gold standard" semi-structured interview to identify and confirm TBI history.
2. Statistically analyze the TBI Clinical Reminder database from Patient Care Services to identify provider, patient, and system characteristics associated with delays in or failure to successfully complete the TBI screening process.
3. Use the "gold standard" semi-structured interview to complete a prospective study on a sample of veterans at 8 VA sites (2 PRC, 3 PNS, 3 PSCT) to assess the psychometric characteristics of the TBI screen (reliability, sensitivity, and specificity).
4. Improve the current TBI Clinical reminder through examination of each of the questions and response options within the TBI screen to determine which are most related to gold standard identification versus false positive responses.

Current Status: Local Tampa IRB approval, National data requested (not yet received), Expert panel meeting convened, Working on finalizing the "gold standard" semi-structured interview, Recruiting local PIs for the other 7 VA sites to assist with local IRB approval and subject recruitment.

Senator MURRAY. Are we doing anything in the interim to address the concerns about the screening tool that is currently being used? Or are we just waiting for a study?

Ms. BECK. No, Senator Murray, what we are doing is we are recognizing that the screen is a screen, that it probably overrefers, and we are conducting a full and complete evaluation of everyone who screens positive, and providing care and treatment for the symptoms and the disorders that we evaluate during the assessment.

Senator MURRAY. I am out of time, but I do have additional questions, so I will wait until the next round.

Chairman AKAKA. Thank you very much, Senator Murray.

Senator Isakson?

STATEMENT OF HON. JOHNNY ISAKSON, U.S. SENATOR FROM GEORGIA

Senator ISAKSON. Thank you, Mr. Chairman.

Dr. Guice, Laurie Ott at Uptown VA—you are probably already ready for this; I can tell by that smile—sings the praises of your Recovery Coordinator Program and says that it is most particularly beneficial for those that suffer from Traumatic Brain Injury. I understand there are three recovery coordinators at the Uptown VA in Augusta, but I understand there are less than 30 nationwide. What are your plans to expand that program?

Dr. GUICE. Thank you, sir. Laurie is a great supporter of the program, and we appreciate her interest and time in helping us do what we need to do.

We currently have three FRCs at Eisenhower Army Medical Center. We currently have 20 nationwide and are in the process of hiring an additional 5. What we do is we constantly project based on the number of referrals we are getting to the program and the number of individuals who enroll in the program as to the need. So we sort of do a just-in-time staffing. Of course, just-in-time does not mean we can hire them tomorrow. It means we have to have a little bit of lead time. So, I am constantly doing projections to see when those points of hiring need to happen, and we are currently in the process of hiring five additional FRCs.

Senator ISAKSON. When did you originally implement the program?

Dr. GUICE. The program was implemented in—it first started taking clients, which is the best time point, in February 2008.

Senator ISAKSON. And they coordinate the transition from DOD to VA Health Care, too, do they not? Aren't they more like a caseworker that follows in that transition?

Dr. GUICE. It is a very unique program in that we coordinate the care and benefits that these individuals need across the transition. So if you think about any time we have some individual moving from hospital to hospital or hospital to another facility and finally moving from active duty to veteran status, those are all transitions. Sometimes we have difficulty managing transitions.

What the FRCs do is once they have a client assigned to them, they stay with that client throughout all of the transitions, which is relatively unique given the way we have our system structured where most case managers are facility based. So they really do stay with that individual and with that family and really try to mitigate any problems almost before they happen, and coordinate the benefits and care that they need using all the case managers and all the providers that we have.

Senator ISAKSON. Well, I apologize for missing Dr. Beck's testimony, but I note that she is the chief consultant to the VA. So I would just say this: In my experience with veterans returning from Afghanistan and Iraq, particularly those with Traumatic Brain Injury, the single biggest problem we had, which is now lessening, was they fell between the cracks between DOD and VA. These recovery coordinators are a bridge in that transition, which for TBI, probably more than any other injury, is tremendously important. They are doing wonderful work down there—I am prejudiced because I am a hometown guy—at Augusta VA. They have returned some soldiers who have come home from Iraq or Afghanistan with TBI, have rehabilitated them, and some have actually volunteered

to go back, which is an amazing testimony to what Eisenhower has done and what the Uptown VA has done.

Thank you very much, Dr. Guice.

Chairman AKAKA. Thank you very much, Senator Isakson.

Senator Tester?

Senator TESTER. Yes, thank you, Mr. Chairman.

I have a couple different ways to go here. I think I am going to put forward a couple of examples, and then I have got a question for you, Dr. Beck, in relation to these.

One, there is a *New York Times* article that described a scenario of a wife of a soldier who happened to be recovering from TBI at Fort Carson's warrior transition unit. She was reprimanded when she sought additional therapy for her husband, told by an NCO that he does not deserve his uniform, he should give it to her.

Two, about 3 years ago, I visited with a young lieutenant from Shelby, MT, who was at Walter Reed dealing with a very serious leg injury. He and his wife were very frank with me. They told me they had an impossible time handling the bureaucracy, getting appointments scheduled, and trying to get through the discharge process.

I recall thinking at that point in time you have got a bright, young officer whose wife is in law school. These folks are having a tough time getting through the process. How does anybody ever get anything done here if they do not have an advocate?

The question I have is: Have things improved in the last 3 years? How have they improved in the last 3 years? And do you see this as a problem? I am talking about making sure the needs of the soldier are met without having to have a mother, a father, a wife, a sibling quit their job to advocate for them?

Ms. BECK. Thank you, Senator Tester. We have placed VA military liaisons, social workers, at the military treatment facilities. We currently have 33 of those VA military liaisons at 18 of our military treatment facilities. We are in discussions with the Army currently to expand those numbers.

We have found that the liaison capability of VA social workers working with the military care coordinators and social workers has improved the transition.

Senator TESTER. OK. And just so I get your numbers right, you have got 33 transition workers at 18 facilities?

Ms. BECK. That is correct, sir, social work liaisons.

Senator TESTER. So a little less than two per facility, is that fair to say?

Ms. BECK. They are distributed——

Senator TESTER. OK, based on numbers? And what is that ratio? What are those numbers? I mean, how many soldiers does it take to say we need another one?

Ms. BECK. Well, I think we do it based on size and scope of medical services at the military treatment facilities, and we work collaboratively with the commanders at those facilities to determine——

Senator TESTER. OK. So give me—what I am looking for is an idea of how many people these folks could be responsible for, helping them through the maze. And I do not mean that in a bad way, but it kind of represents it. Are we talking one worker per five sol-

diers, 10 soldiers, 20 soldiers, 100 soldiers? And you can answer, Colonel, if you would like. However you want to do it. I am just trying to get an idea if we are even close to meeting the demand that is out there. Are we? I mean, I think they are probably effective. I mean, I do not doubt that a bit.

Ms. BECK. They are—Senator——

Senator TESTER. But if we are understaffed, that is another issue that this Committee probably will want to address.

Ms. BECK. The positions and the roles are effective. We recognize that we can always do more, and that is the reason that we are continually working with the military service and the commanders to identify opportunities.

For example, because so many of the seriously injured and the wounded are returning to Walter Reed and Bethesda, we have a higher number of social workers there than we do——

Senator TESTER. That makes sense. Could you get back to us with some numbers so we can get some sort of scope?

Ms. BECK. Yes.

Senator TESTER. And I am sure it is going to vary from soup to nuts, but if you could give us the number of social workers at each of those 18 facilities and how many soldiers—that is really the key.

Ms. BECK. Yes.

Senator TESTER. How many soldiers they are working with——

Ms. BECK. Yes, sir.

Senator TESTER. That would be great.

Ms. BECK. We have those numbers, and we have the number of referrals, and I would——

Senator TESTER. That would be great.

Ms. BECK [continuing]. Provide it for the record.

Senator TESTER. Thank you very much.

[The information requested during the hearing follows:]

RESPONSE TO REQUEST ARISING DURING THE HEARING BY HON. JON TESTER TO LUCILLE BECK, PH.D., CHIEF CONSULTANT, REHABILITATION SERVICES, U.S. DEPARTMENT OF VETERANS AFFAIRS

Response. The Department of Veterans Affairs (VA) has a robust system in place to transition severely ill and injured Servicemembers from the Department of Defense (DOD) to VA's system of care, as well as transitions to their home or the most appropriate facility capable of providing the specialized services their medical condition requires. The VA Liaisons for Health Care represent a key component for this process. The VA Liaisons for Health Care, either social workers or nurses, are placed strategically in Military Treatment Facilities (MTF) with concentrations of recovering Servicemembers returning from Operation Enduring Freedom or Operation Iraqi Freedom (OEF/OIF). This program has grown in size from a single Liaison supporting both Walter Reed Army Medical Center and the National Naval Medical Center at Bethesda to now supporting 33 VA Liaisons for Health Care at 18 MTFs.

VA Liaisons are co-located with DOD Case Managers at MTFs where possible and provide onsite consultation and collaboration regarding VA resources and treatment options. The Liaisons work closely with the military case managers who are providing case management for these Servicemembers, as well as the receiving VA case managers who will be providing ongoing case management through the transition and once they arrive at the VA medical center. VA Liaisons educate Servicemembers and their families about the VA system of care, coordinate the Servicemember's initial registration with VA, and secure outpatient appointments or inpatient transfer to a VA health care facility as appropriate. VA Liaisons make early connections with Servicemembers and families to begin building a positive relationship with VA. VA Liaisons coordinated 4,567 referrals for health care and provided over 24,000 professional consultations in fiscal year 2009. In the first two quarters of fiscal year 2010,

VA Liaisons have coordinated 3,201 referrals for health care and provided over 14,191 professional consultations.

Locations	Number of VA Liaisons
• Walter Reed Army Medical Center, Washington, DC	5
• National Naval Medical Center, Bethesda, Maryland	1
• Brooke Army Medical Center, Ft. Sam Houston, Texas	4
• Eisenhower Army Medical Center, Ft. Gordon, Georgia	2
• Madigan Army Medical Center, Ft. Lewis, Washington	3
• Darnall Army Medical Center, Ft. Hood, Texas	2
• Evans Army Community Hospital, Ft. Carson, Colorado	2
• Womack Army Medical Center, Ft. Bragg, North Carolina	2
• Naval Hospital Camp Pendleton, Camp Pendleton, California	2
• Naval Medical Center San Diego, California (Balboa)	2
• Martin Army Community Hospital, Fort Benning, Georgia	1
• Winn Army Community Hospital, Fort Stewart, Georgia	1
• William Beaumont Army Medical Center, Fort Bliss, Texas	1
• Irwin Army Community Hospital, Fort Riley, Kansas	1
• Medical Activity, Fort Drum, New York	1
• McDonald Army Health Center, Fort Eustis, Virginia	1
• Ireland Army Medical Center, Fort Knox, Tennessee	1
• Blanchfield Army Community Hospital, Fort Campbell, Kentucky	1

Senator TESTER. With the exception of my friend Senator Begich here to my left, we have got the highest per capita percentage of veterans in the United States. Alaska beats us out. But we have got a bunch. The polytrauma network rehabilitation within—I mean, our nearest center—let me get right to it—is in Seattle or Denver. Senator Baucus and I introduced legislation that would task the VA with a study to establish a new polytrauma center in the area that Montana is in. I think it is a good idea. My question is: Would you commit to doing that study?

Ms. BECK. We are aware of the introduction of that legislation to do that study, and we are preparing views and costs. The Department is preparing views now.

Senator TESTER. It would be good. I mean, I think the issue is—and I am going to give up the microphone here because I am out of time. But I think the issue is when you are dealing with—and I know you talked about distance, condition, and specialty care—but when you are dealing with a 12-hour drive—and, actually, that is not the longest. That is from where I live to a place like Seattle or Denver. I live in the center part of the State of Montana. It becomes a real issue even if it is a minor injury to make that kind of travel.

So thank you very much. I appreciate the panel for being here. Thank you very much. A panel of five docs. That is pretty impressive. Thanks.

[Laughter.]

Chairman AKAKA. Thank you very much, Senator Tester.

Senator Begich?

STATEMENT OF HON. MARK BEGICH, U.S. SENATOR FROM ALASKA

Senator BEGICH. Thank you very much, Mr. Chairman.

If I can just tag on to one of the questions that Senator Tester had, Dr. Beck, you have—and I will use my phrases—33 social workers that are distributed around. When you decided to imple-

ment that program, I am assuming you did some analysis of the need and, therefore, you had to have some understanding of how many you would need to do the job which you estimated before you started that program. Am I assuming that right?

Ms. BECK. Yes, sir.

Senator BEGICH. So there is nothing wrong with saying we do not have enough, and I want you to kind of be okay with that.

Ms. BECK. Yes.

Senator BEGICH. If we need more, we need to know that. So I know you had to do an analysis. A program—anything with the VA or the military does not get implemented unless there is a huge analysis behind it. So my assumption is you did an analysis based on what you saw the growth would be in this area with the folks coming back, as well as people who are here that needed services of social workers from the VA connected with the DOD. So in doing that, you must have had some ratio, some analysis of where you needed to be to be at optimum delivery level.

Can you share that with us at some point? I know you do not have it now. That will tell me what your thinking was rather than what you think you need right now, because that was the basis for moving forward on this, which I think is a great idea to have those social workers there. My staff to this Committee is a social worker, so she is probably very excited about it. I cannot see her facial expression.

Ms. BECK. She is.

Senator BEGICH [continuing]. But I am sure she is.

Ms. BECK. She is, sir.

Senator BEGICH. So that analysis to me is a document that makes a difference.

Ms. BECK. Absolutely.

Senator BEGICH. So I can only assume you have that, so I will leave it at that. I do not want to speak for Senator Tester, but I think we want to help you in this area because we think the social workers are an important component.

[The information requested during the hearing follows:]

RESPONSE TO REQUEST ARISING DURING THE HEARING BY HON. MARK BEGICH TO LUCILLE BECK, PH.D., CHIEF CONSULTANT, REHABILITATION SERVICES, U.S. DEPARTMENT OF VETERANS AFFAIRS

Response. The VA Liaison Program was established in October 2003. VA recognized the need to establish a seamless transition process to ensure all Servicemembers transitioning from DOD to VA receive world-class service and transition assistance. The first VA Liaison served at both Walter Reed Army Medical Center and National Naval Medical Center in Bethesda to transition severely ill and injured Servicemembers transitioning from MTFs to VA. Since that time, the program has continued to grow, and VA has placed additional VA Liaisons at MTFs with concentrations of recovering Servicemembers returning from Iraq and Afghanistan. DOD requests assistance for VA Liaisons and recommends locations based on the following criteria.

- Numbers of wounded, ill and injured Servicemembers at a given MTF
- Severity of conditions at a given MTF
- Likelihood that wounded, ill and injured will need to access VA health care
- Number of population that will return to duty

Senator BEGICH. Along with that, in the health care piece of legislation we passed, there was a provision there called the Alaska Federal Interagency Task Force to look at improved services

throughout Alaska on health care. It actually started with us looking at VA, as well as certain services to our active military, but now it is a little broader.

One, are you aware of it? If not, we want to make sure you are engaged in this, because the idea is to look at the delivery of services in a very rural State. As Senator Tester said, we both have a very high percentage per capita of veterans that are not necessarily in urban areas, and we need to look at how we integrate TBI services in remote areas.

So, one, are you aware of that? If not, we will get you information on it. We want to engage you to make sure we are not disconnected from this. I do not know if anyone can answer that, but I will just start with you.

Ms. BECK. We are aware of that initiative related to providing services in Alaska, and we will make sure that our rehab services group, our Federal Recovery Coordinator Program, and our Social Work Case Management Program is engaged in that initiative.

Senator BEGICH. Fantastic.

The other is, again, in rural areas, telemedicine is—you know, a lot of pioneering has been done in Alaska. I know the VA has done some especially around physical therapy and speech therapy.

Ms. BECK. Yes.

Senator BEGICH. How do you see TBI, if at all, used in telemedicine? And are you using it now? And what is your kind of analysis of that? Whoever wants to answer that.

Ms. BECK. I will start and others can add. We are very committed to and looking carefully at the technologies in telehealth and how they can help us. Currently, we have two projects under way with Traumatic Brain Injury.

One was referred to earlier, and that is the screening, conducting our screening and our evaluations. Denver actually pioneered that TBI screening and evaluation tool, and we have three other sites that are currently using it. We are evaluating the accuracy, the consistency, and the effectiveness of using that tool.

The second initiative that we are evaluating is a case management tool, and it allows us to use what we call a telebuddy system, which looks a lot like a personal assistant or a telephone or an iPhone, and we are establishing capability to dialog. So every morning the patient can say good morning, work with the case manager: "Have you done this today? Have you done that today?" And then the dialog exists so that we can call the case manager.

There has been some very good work done in Seattle in the rural environments, which may have involved Alaska as well, by a rehab group there that has shown that it is an effective mechanism. Actually Dr. Bell, Kathy Bell, who is the chief of physical medicine and rehab at the University of Washington, was a consultant and worked with us on the development of the dialog.

Senator BEGICH. Very good.

Ms. BECK. So we are working to implement that this year and see that as a way to do good remote case management in telehealth.

Senator BEGICH. Very good. Thank you for that.

I will just end on this last question. Should the mental health professionals—you know, lots of times it is the VA kind of going

this way with DOD, but DOD has a lot of additional mental health professionals working on the ground in the field all the way through the process. As a member of the Armed Services Committee, we hear a lot about it.

Is there enough of activity from the DOD mental health professional who is following, say, an individual soldier who is starting to show signs of issues that that carries forward into the VA? In other words, that DOD mental health professional starts their service and then VA picks it up on it next? Is there enough transition, and do they do enough coming in your direction? VA does a lot going this direction. I know that. You have a much smaller budget. DOD has a huge budget. But do they do enough coming this way? And if you do not want to counter that—I do not want you to have DOD calling you in a few minutes and saying, "Why did you say that?" But I want you to, if you could, just quickly respond, and then my time is up.

Ms. BECK. I have Dr. Batten at the table with us today, and she is VA's representative and is the Deputy Director of the Defense Center of Excellence. We have had an ongoing project and integrated work through the Defense Center of Excellence, and Dr. Batten, I think, can comment on that.

Ms. BATTEN. Thank you, sir. It is a great question and one that both Departments have identified as an important area of emphasis. In fact, a new program was implemented about 6 months ago, maybe closer to 9 months ago, called the In Transition Program that is focused on exactly the need you are identifying, where coaches are assigned to individuals who are in mental health treatment and are transitioning from one care setting to another. That actually works both for individuals who may be transferring from one MTF to another as well as from an MTF to a VA, to make sure that that transition is kept up. So it is a great point, and it is one that we are addressing.

Senator BEGICH. Thank you very much.

Thank you, Mr. Chairman.

Chairman AKAKA. Thank you very much, Senator Begich.

Let me ask two fast questions here of Dr. Beck and Dr. Jaffee. We have talked about screening and about coordination, but proper diagnosis is one of the major challenges in treating TBI. The question is: What state-of-the-art imaging techniques, if any, are being used and how? Dr. Beck?

Ms. BECK. Next to me is Colonel Jaffee who has a great amount of expertise in this area. I am going to ask him to respond.

Chairman AKAKA. Colonel Jaffee.

Colonel JAFFEE. In our research, Investment Resources has been very committed to exploring the latest advances in neurodiagnostics to include neuroimaging and other forms of biomarkers. To summarize a couple of the neuroimaging initiatives, we have done a lot of work with the technology known as diffusion tensor imaging. It allows us to look at some of the subcortical white matter tracks in the brain. We actually were able to complete the first study comparing the patterns on DTI in patients who had blasts as a component of their injury compared to more traditional forms of injury. This research was actually recognized by the American Academy of Neurology as one of the six most important late-break-

ing research findings of the year and was featured at their annual meeting last year.

We have had DVBIC researchers coordinate with those at the University of California at San Diego evaluating the use of MEG, magnetoencephalography, an advanced imaging technique looking at some of the gray matter in the brain.

We have had investigators and surgeons at the National Naval Medical Center use near-infrared spectroscopy to help in their angiography, getting better pictures and better understanding of the vasculature and the vascular damage that may occur in significant injuries.

There has been a bit of work done on PET scans; specifically, Walter Reed has done a great deal of work on that. The SPECT scans, another form of functional imaging that has been utilized with soldiers at Fort Carson, and there is a protocol about to further evaluate that in San Antonio.

The CDMRP process, the Congressionally Directed Medical Research Process funded some initiatives looking at functional MRI. We have been working with industry as industry is working to modify some of their imaging equipment to make CT and MRI scanners smaller, more portable, utilizing head-only. These would possibly lead to being able to place such devices farther forward in the field to be closer to the points of injury. We have been looking at other technologies in addition to imaging such as: quantitative EEG in neurophysiology; electrical signals from the skull known as piezoelectricity; and looking at ultrasound technologies.

One of the things that I am proud of is that at end of this month, May 24 through 27, USU, the Uniformed Services University, is hosting the 7th Annual World Congress of the International Brain Mapping and Intraoperative Surgical Planning Society. This conference features academic presentations featuring the latest technologies in neuroimaging and other translational technologies. DOD, DVBIC, and the NIH are sponsors. Last year's keynote speaker included our Chairman of the Joint Chiefs, Admiral Mullen, and currently slated this year as our keynote speaker is President Obama.

Chairman AKAKA. Thank you very much.

Dr. Beck, please update us on the status of the TBI registry that was mandated in 2008, NDAA. How are DOD and VA working together to keep the registry up to date?

Ms. BECK. The TBI Veterans Health Registry is functional, and it is currently providing reports on a monthly basis. We are in a data validation mode now—identifying the data sources, assuring that all of the data feeds that we need are available and assuring that the data coming from the registry is valid.

We received a roster from DOD of veterans who have separated and become—or of active-duty servicemembers who have been deployed in support of OEF/OIF and have become veterans. We also are receiving pre-deployment health assessments and post-deployment health risk assessments. We have those available for integration into the record.

We are also receiving and have added—all of the veterans who have any service connection for Traumatic Brain Injury are in the record. That is approximately 24,000 veterans to date.

Chairman AKAKA. Thank you.

Senator Burr?

[No response.]

Chairman AKAKA. Senator Murray?

Senator MURRAY. Thank you. I just had one quick question. I wanted to know, maybe Colonel Jaffee or Dr. Batten, how the DOD is working to distinguish between TBI and PTSD.

Colonel JAFFEE. That is an excellent question which has been a major focus of emphasis for both of us in the DOD and VA over the past several years. There has been an ongoing amount of research dedicated to that process, to that end. DVBIC cosponsored with the Congressional Brain Injury Task Force an international symposium on behavioral health and Traumatic Brain Injury, bringing together a lot of the best researchers in the country throughout the VA and DOD systems and around the world to evaluate the state of the science and develop appropriate ways to manage this.

There have been consensus conferences hosted by the VA, including the DOD, looking at ways to handle what we call these dual diagnoses or comorbidities. Our current guidelines, as we have them, is that if you are identified with symptoms that have either one of them, then you need to undergo screening and evaluation, because our whole philosophy in our current treatment plan and guidelines is that we want to make sure that we are aware of all the conditions an individual may have and incorporate that into their management plan.

We have found from experience that if we focus only on one and not the other, the ultimate outcomes are not as favorable as if we can integrated both together. So, what we have found is when we—looking at a lot of data and research, which is actually from our VA colleagues who have been very excellent in quantifying this—we have found that not everyone who has a TBI has PTSD; not everyone who has PTSD has a TBI; but there is a robust overlap, and that overlap tends to cluster at approximately 45 percent, which makes that holistic evaluation and incorporation into the treatment plan a very important aspect of that process.

So through these combined efforts, I think we have been able to, through our educational efforts, get people away from the paradigm of a few years ago, which was looking at this as an either/or phenomenon and looking at this as a comorbidity that requires a comprehensive management plan.

Senator MURRAY. OK. I appreciate that. I assume the treatment is different depending on whether you have TBI or PTSD or both.

Colonel JAFFEE. There are considerations that need to be taken into account if one has both. As one example, if someone has residual cognitive deficits from their Traumatic Brain Injury, they may not be as capable of participating in the types of psychotherapies that one might choose in certain cases of Post Traumatic Stress Disorder. So being able to quantify and identify these aspects allows us to target the most appropriate treatments for all the symptoms that the individual may have.

Senator MURRAY. OK. I appreciate that.

Thank you, Mr. Chairman.

Chairman AKAKA. Thank you very much, Senator Murray.

Senator Isakson, any questions?

Senator ISAKSON. No.

Chairman AKAKA. Senator Tester?

Senator TESTER. Yes, very quickly. Thank you, Mr. Chairman.

Dr. Beck, are you familiar with VA's Office of Rural Health?

Ms. BECK. I am sorry. Can you repeat the question?

Senator TESTER. Are you familiar with the VA's Office of Rural Health?

Ms. BECK. Oh, yes, sir. I am sorry. I did not——

Senator TESTER. How closely do you work with them?

Ms. BECK. We work closely with the office. We have participated with the ORH in the development of requests for proposals and reviews of the projects that Rural Health is undertaking.

Senator TESTER. And what kind of projects—are you using—let me just cut right to it. I mean, do you use them for devising plans for outreach to veterans in rural America and treatment efforts? Is that something that is within their purview and that you would utilize them for?

Ms. BECK. I would like to take that for the record, sir, because the scope of services that our Office of Rural Health is providing right now, I think we would like to give you a full listing of those.

Senator TESTER. That is fine. I was just wondering how you are utilizing them, if they are effective, if there is something that we can do to make them more effective.

[The information requested during the hearing follows:]

RESPONSE TO REQUEST ARISING DURING THE HEARING BY HON. JON TESTER TO LUCILLE BECK, PH.D., CHIEF CONSULTANT, REHABILITATION SERVICES, U.S. DEPARTMENT OF VETERANS AFFAIRS

Response: VA has no specific outreach efforts or initiatives directly related to Veterans with Traumatic Brain Injury (TBI) residing in rural areas. However, VHA Rural Health has two TBI telehealth initiatives that will be useful in rural settings. They are the TBI telehealth screening and the TBI case management home buddy dialog. Both were mentioned at the hearing.

Senator TESTER. My last question is—Senator Begich asked a little bit about this. How effective is telemed in dealing with TBI or PTSD?

Ms. BECK. We are in the early stages of evaluating telemedicine and telehealth technologies for TBI, and——

Senator TESTER. How long is this evaluation going to take? The reason I ask is because we are dealing with something that is pretty time sensitive here. I mean, there are all sorts of issues. Senator Begich has told me about a soldier who came back——

Ms. BECK. Yes, we are fast-tracked to look at these technologies.

Senator TESTER. So what kind of timeframe are we looking at?

Ms. BECK. I expect that we will have our TBI screening up and running this year and be able to give you some feedback on the way the implementation of that program is working.

Senator TESTER. As far as the effectiveness of the telemed.

Ms. BECK. Effectiveness and usefulness of that program.

Senator TESTER. OK. Thank you very much.

Thank you, Mr. Chairman.

[The information requested during the hearing follows:]

RESPONSE TO REQUEST ARISING DURING THE HEARING BY HON. JON TESTER TO LUCILLE BECK, PH.D., CHIEF CONSULTANT, REHABILITATION SERVICES, U.S. DEPARTMENT OF VETERANS AFFAIRS

Response: See our response to Sen. Murray about the status of TBI screening. Findings of these programs are not yet available, and are expected in fiscal year 2011.

Ms. BATTEN. There are actually several PTSD studies that have been completed. They are with smaller groups because they were pilot studies, but they have shown that telemedicine for PTSD is—at this point, it looks like it is approximately as effective as treatment in person. So those are pilot studies. They are smaller. We cannot draw large generalizations. But so far the pilot data are good.

Senator TESTER. Well, I think that is a good sign. The margin for error here is we want to make it as close to zero as possible, and that is why I think it is critically important in rural areas because it is one of the ways that are being utilized to reach out to veterans. I think it makes sense if it is effective. If it is not effective, we should not be wasting our time on it.

Chairman AKAKA. Thank you very much, Senator Tester.

Senator Begich?

Senator BEGICH. I do not have anything further right now.

Chairman AKAKA. Thank you. Thank you very much.

Let me thank this panel for your statements. It is valuable for what we are trying to do together. And I want to stress that word "together" between DOD and VA as well as the Congress. We would certainly like to do all we can to give the best service possible to the servicemembers and veterans of our country.

Thank you very much.

Ms. BECK. Thank you.

Chairman AKAKA. Now I would like to welcome the witnesses on our second panel.

They are: Mrs. Karen Bohlinger, the Second Lady of Montana; Mr. Jonathan Barrs, an Operation Iraqi Freedom Veteran; Dr. Bruce Gans, who is the Executive Vice President and Chief Medical Officer at the Kessler Institute for Rehabilitation; Mr. Michael Dabbs, President of the Brain Injury Association of Michigan; and joining him today is the veterans program manager, Retired Air Force Major Richard Briggs, Jr., who is seated in the front row.

Senator Isakson would like to welcome our next panelist.

Senator ISAKSON. Thank you, first of all, Mr. Chairman, for allowing Dr. LaPlaca to testify today. I am very proud as a Georgian, even though I graduated from the University of Georgia, to introduce a distinguished professor at the Georgia Institute of Technology in Atlanta, and Emory University in biomedical engineering. Dr. LaPlaca received her doctorate degree from the University of Pennsylvania, is trained in neurosurgery, and is funded by both the National Institute of Health and the National Science Foundation in her research on brain injury, spinal cord injury, and cognitive disabilities from both injury as well as aging. We are delighted to welcome her today to testify.

Thank you, Mr. Chairman.

Chairman AKAKA. Thank you very much.

I thank all of you for being here. Your full testimony will appear in the record.

Ms. Bohlinger, would you please proceed with your statement?

STATEMENT OF KAREN L. BOHLINGER, SECOND LADY, STATE OF MONTANA

Ms. BOHLINGER. Thank you, Mr. Chairman and Members of the Committee. I appreciate the opportunity to speak with you today about TBI from a very personal view. My son, a former Special Forces officer with nearly 12 years of experience, has one severe and one moderate head injury. He is now classified as 100 percent disabled.

We are over 4 years into active and ongoing treatment with moderate results. However, this is primarily due to my personal commitment of time and money invested in my son's care, as opposed to the services he has received through the Veteran Administration Health Care System, and he had the unfortunate experience of being one of the early TBIs, so I just need to make that clear, because there have been some incredible improvements since the early years.

I continue to fly to Seattle every 10 days and stay as long as necessary to monitor and assist in his care. I think it was 2008 when I was home 22 days out of 365. He is determined to live independently and has surpassed all predictions for functional independence. I cannot bring him home to Montana as Montana does not have appropriate follow-up care for him, and, again, that rural issue is huge. These are individuals whose culture is rural. They are not used to being in a city environment, and as we all know, additional stress is not good for a TBI.

Since 2007, I have tried to be an advocate for other veterans and their families, with the hope of their receiving more timely, effective, and state-of-the-art care. I have personally visited several VA medical centers throughout the United States to observe and learn. And I will tell you this very forthrightly, that the guided tour as the Second Lady of Montana and my going in just as an individual are two entirely different experiences.

Our Montana congressional delegation, especially our Senator Tester, and Secretary Shinseki of the Veteran's Administration have been very accessible and responsive. I feel they have shown extraordinary leadership for our veterans and their families.

Changes in the delivery of care since 2008 are unprecedented from my perspective as an organizational psychologist in an institutional setting. Inclusion of family members in case management, caregiver status for reimbursement, care coordination, and outreach efforts are absolutely necessary components of treatment, and while they are mandated by what you all have passed into law, they are not being implemented across all the VA centers at all. And while we are grateful for the many devoted and competent VA employees—and I would say Dr. Jay Umamoto at the Seattle VA is an extraordinary asset to the VA—what we know is that consistent standards of care should be available to all veterans.

I cannot stress enough the importance of family involvement, as TBI self-assessment is often very different from the family mem-

ber's assessment. These guys do not want anything wrong with them. It takes a long time to break through that denial.

The VA Medical System in Baltimore, MD, for TBI/PTSD is one shining example of what your legislation did, and so I would just like to let you know that they have a model that preserves the dignity and respect for the veteran. They include the family members. They bring them into a room, and from the very first point, it is total family, open involvement that builds trust rather than separate groups that undermine trust. They really have worked at how to best transition the new life together.

I have met and worked with, on a volunteer basis, literally hundreds of soldiers, veterans, and family members. There is not a day that goes by that I do not have a phone call or an interaction, especially with young wives, who have not the life experience to deal with what is now going on in their family.

I have learned some important insights to pass on to you. Number 1 is this: neuroimaging is a critical component in a TBI assessment, treatment planning, and, most importantly, the disability rating. There have been so many cases where the opinion said this soldier is 10 percent disabled, yet their life disintegrates. Then, after they get a scan, it is set at 100 percent. Scans are available in the private sector. Our soldiers deserve no less.

Technology is available that demonstrates brain function. We have already heard about that today. My message is this is not a guessing game. These are people's lives. My son was given many medications which ultimately caused more damage than his original injury. We have been through hell literally, which was not necessary.

I private-paid for a brain scan to determine what course of care was scientifically needed. Latest and best technology must be available to all. News correspondent Bob Woodruff—and you all know him—was given the best medical treatment money could buy. His family was with him every step of the way. They were not separated into separate groups. He had a spirit that would not quit, and his recovery has been remarkable, and he is still advocating for veterans, most recently on suicide prevention and including family members. Our wounded warriors have the spirit, no doubt about it, but lack the same level of medical care.

When neuroimaging is integrated with neuropsychological and neurocognitive evaluations, biometrics and social functioning, you can get an effective treatment plan and really make a difference in the soldier's recovery.

Number 2, Pre/Post Assessments for cognitive and neural functioning. Current technology allows for biomarker testing. I do not know what the components are of the screening that the gentleman referred to before, but I would be interested to know if that is included. What I do know is that this is a scientific baseline. It is a statement that cannot be changed. A lot of us know that the self- and counselor assessments are not always accurate. People tell us that they lie on them, period. So that much we know.

We also know that we do not need more money for this. It is already covered under TRICARE. It is a $450 test. We already give a blood test to all the soldiers.

Number 3, follow-up treatment. Functional independence is a realistic goal for many. Relearning their own abilities and developing strategies to make up for injury-related deficiencies and losses—it works. We just know that it works.

Treatment must be personal, bring about patient engagement, positive response, and include performance-based outcomes.

I was employed one time as a caseworker early in my career at a hospital, and if we did not have measurable outcomes, we did not have a job. That is not the current state of situation that you have going on right now.

Services should be veteran driven and not for the staff's convenience. Scheduling a TBI group during peak traffic hours is a disincentive for participation because it creates more stress than benefits. As Mrs. Murray knows, eight lanes of traffic in Seattle getting to the hospital on Columbia Way between 3 and 5 o'clock——

Senator MURRAY. It is stressful for me.

[Laughter.]

Ms. BOHLINGER. Me, too, as the mom driving. It is not good for them, and so this last group was canceled. So when you all get the paperwork, it is going to say, "Gee, there were not enough soldiers who wanted to participate." That is not the case. They just cannot do it at that time of day.

Also, their TBI group was canceled a couple of days before Thanksgiving until the end of January. When do these people need care the most? When do they need a contact? Because they have lost their wives. My son lost his high school sweetheart wife. That is when they need the care. So when I say it should not be staff convenience, I mean it should be veteran-centered.

And this one I feel very passionate about.

There are many active-duty soldiers and marines who would ask for help if they could without consequences to their career. Last fall, I was part of a meeting on a military base with over 400 soldiers in attendance, and family members in addition to that. Many had served at least three tours in Iraq. When asked through a confidential questionnaire how many felt they had symptoms of either TBI or PTSD, over 40 percent responded yes and that they would ask for help if there were not negative consequences attached.

One example I would like to give you is a soldier with 19 years—19 years—in the Army. He has been to Iraq four times. And he was ordered to go again. He told his commanding officer, "Sir, I cannot do that. I am not OK." He has a wife and four children. His commanding officer said, "Well, sir, then you are going to get a dishonorable discharge." So the wife called me, and I got a doctor to donate a scan for him, and he is a mess. He has a severe TBI along with PTSD, and now he is on a medical stay. So those are the things that we are talking about. Their family did not have the money for a scan.

Additional treatment is not always about more money, however. Effective use of current dollars, with measurable outcomes that would include feedback from veterans and family members—I listened to all of what is going on in this testimony, and I find it really interesting because my personal experience has been so different with no mechanism by which for me to give feedback—good, objec-

tive, accurate feedback. I think that that is a critical component in any care, especially of this magnitude.

Also, create incentives that benefit the veteran. Are they in healthy social networks? You know, what are they involved in? Instead, we have created a system where the community mental health providers for the VA are reimbursed for the number of DSM-IV diagnoses. So they may come in with TBI and PTSD, and now they are diagnosed with depression, sleep disorder, "Oh, you might be bipolar," and, "You know, I think you have a borderline personality as well."

I was in a training session with over 250 VA providers. I overheard them discussing how to "tag" the veteran with multiple diagnoses so they could make more money. Clearly, that does not benefit the veteran, and it does not benefit the taxpayer.

Chairman AKAKA. Ms. Bohlinger, will you please summarize your statement?

Ms. BOHLINGER. Yes, OK. I just admire that you continue to do this. They fought for us, protected our freedom. We need to protect them.

I would just say to you: What does my son miss most? Just working. He is a Montanan. He wants to work.

Thanks.

[The prepared statement of Ms. Bohlinger follows:]

PREPARED STATEMENT OF KAREN L. BOHLINGER, SECOND LADY, STATE OF MONTANA

Dear Mr. Chairman and Members of the Committee: I appreciate the opportunity to speak with you today about TBI from a very personal view. My son, a former Special Forces officer with nearly 12 years of service, has one severe and one moderate head injury. He is classified as 100% disabled.

We are 4½ years into active and ongoing treatment with moderate results. However, this is primarily due to my personal commitment of time and money invested in my son's care, as opposed to the services he has received through the Veteran Administration Healthcare System.

I continue to fly to Seattle every 10 days and stay as long as necessary to assist in and monitor his care. He is determined to live independently and has surpassed all predictions for functional independence. I cannot bring him home as Montana does not provide the follow up TBI care he needs.

Since 2007, I have tried to be an advocate for other veterans and their families, with the hope of their receiving more timely, effective and state-of-the-art care. I have personally visited several VA medical centers throughout the United States to observe and learn.

Our Montana Congressional Delegation and Secretary Shinseki, of the Veteran's Administration, have been accessible and responsive. They have shown extraordinary leadership for our veterans and their families.

Changes in the delivery of care since 2008 are unprecedented in an institutional setting. Inclusion of family members in case management, caregiver status for reimbursement, care coordination and outreach efforts are necessary components of treatment, and while mandated are not implemented in all VA Centers. While we are grateful for the many devoted and competent VA employees, consistent standards of care should be available to all veterans.

I cannot stress enough the importance of family involvement, as TBI self assessment can often be very different than the family member assessment. It requires a team effort for best outcomes.

The VA Medical System in Baltimore, Maryland for TBI/PTSD is a model that preserves the dignity, and respect for the veteran, while including and training family members in how to best transition to their new life together.

I have met and worked with, on a volunteer basis, hundreds of soldiers, veterans and their family members, especially young wives, who have not the life experience or training to understand their new reality.

I feel I have learned some important insights to pass on to you:

1. *Neuroimaging is a critical component in TBI assessment, treatment planning and disability rating.*

Technology is available which demonstrates brain function and activity. It is not a guessing game. My son was given many medications, which ultimately caused more damage than his original injuries. We have been through hell, unnecessarily.

I had to private pay for a brain scan to determine what course of care was scientifically needed. Latest and best technology must be made available for all TBI veterans. News correspondent Bob Woodruff was given the best medical treatment money can buy. His family was with him every step of the way and he had a spirit that would not quit, and look at his remarkable recovery. Our wounded warriors also have the spirit, but lack the same level of medical care.

When neuroimagaging is integrated with neuropsychological and neurocognitive evaluations, biometrics and social functioning, a more effective treatment plan can be developed.

2. *Pre/Post Assessments for cognitive and neural functioning*. Current technology allows for bio-marker testing. This would provide a scientific baseline. This is a statement that cannot be changed. It ensures accuracy. Self and counselor assessments are not always accurate.

3. *Follow-up treatment:*

A. Functional independence is a realistic goal for many. Re-learning their own abilities and developing strategies to make up for injury related deficiencies/losses works.

B. Treatment must be personal, bring about patient engagement, positive response and include performance based outcome measures.

C. Services should be veteran driven not for the staff's convenience. Scheduling a TBI group during peak traffic hours is a disincentive for participation, because it creates more stress than benefits.

4. There are many active duty soldiers and Marines who would ask for help if they could do so, without consequences to their career. Last fall, I was part of a meeting on a military base with over 400 soldiers in attendance; many had served over 3 tours of duty in Iraq. When asked through a confidential questionnaire how many felt they had symptoms of either TBI or PTSD, over 40% responded yes and would like help, but did not feel they could ask for it, without negative consequences.

Additional treatment is not always about more money. Effective use of current dollars, with measurable outcomes that includes feedback from the veterans and family members, would provide accurate information about what is working and what is not.

Create incentives that benefit the veteran. For example, current community mental health providers for the VA are reimbursed per the number of DSM III diagnosis. In a training session of over 250 VA providers, I overheard providers discussing how to "tag" the veteran with multiple diagnoses so they could make more money. Clearly this does not benefit the veteran, or the tax paying public.

I admire the continuing commitment and the bi-partisan effort to make the necessary changes that will provide the best possible services for our veterans. They have fought for and protected our freedom; it is our duty to protect them. They deserve respect, dignity and self worth.

What does my son miss most? Working! He is after all a Montanan and we work! He loves his country and would go active military if he could. Thank you for listening!

Senator MURRAY [presiding]. Thank you very much for that testimony. It is extremely helpful. We will accommodate you in Seattle any time, although I know the heart of Montana wants to be back home.

Mr. Barrs?

STATEMENT OF JONATHAN W. BARRS, OPERATION IRAQI FREEDOM VETERAN

Mr. BARRS. Well, good morning, Mr. Chairman, Ranking Member Burr, and other Members of the Committee. As you know, my name is Jonathan Barrs, and I live in Cameron, NC. I just want to thank you for inviting me to testify today before this Committee.

I am 24 years old, and I served in the Marine Corps in Iraq in 2005–06 and also in 2007–08. During my first deployment in 2005–2006, I was a turret gunner in a Humvee. During combat operations, I experienced two improvised explosive device (IED) blasts in a period of a week. The first IED detonated approximately 30 to 50 feet from my vehicle. When it exploded, the concussion from the blast slammed me into the turret. Glass from the vehicle became embedded in my head, but I did not think much of it at the time and I did not seek medical care. The second IED blast occurred about the same distance away as the first. After the second blast, the corpsman checked me out. It was never really documented. He just shined a light in my eyes to see if I could stay with him, and he asked me what day of the week it was. Of course, I never knew what day of the week it was, but shortly afterwards, I was kept off of mission due to stomach problems. I was eventually taken to another Forward Operating Base, also known as a FOB, because of excessive weight loss and was given steroids to fix the problem.

I was screened by the DOD for TBI, and was diagnosed with it in November 2008. At that time, I never looked to see exactly how it would impact me in the future. Basically, all I knew was I still wanted to be in the Marine Corps, and I did not know exactly what was going on.

I was medically retired in May 2009. The hand-off from DOD to the VA was very slow. I have been out of the Marine Corps for almost a year now, and I am just now getting care for the TBI. I have also been screened by VA for PTSD, and I have been diagnosed with PTSD and depression.

So far, the VA care has been good, but this whole time of waiting was very hard. I had to keep asking my primary care doctor for a consult, which took a very long time. I have a case manager at VA in Fayetteville. Her name is Robin. She is a great woman. She really does do everything she can in her power to help me, mostly by just checking up on me. I get random phone calls from her asking me how I am doing, and she reschedules my appointments when I miss them. She is currently helping me change my primary care doctor. The reason behind that is because the doctor seems like he is not really concerned about me, just more concerned about what the books tell him to do.

The honest truth is dealing with TBI is like a living horror film over and over again. Daily things you are supposed to do, you forget. I have missed at least five important VA appointments, also others not so important. I missed a job interview because I forgot about it. When you forget, the PTSD side of you rolls around because you knew you were never like this before, and it makes it very hard for people to deal with you. For example, the relationship I have with my girlfriend. It has been over a year now, and things are not really right due to the injuries, just mostly because I forget things and I get to the point where I just kind of snap. So dealing with all that is pretty hard.

I went to junior college and tried to get through the course work to get a degree, but I was trying and still failing tests. The teachers found out I was in a special populations group and felt sorry for me, and they started giving me all this leeway and saying they will

do whatever it takes for me to get a passing grade. I knew that getting passing grades I had not earned would not be the way I wanted to do things. I was only trying to better myself, and they were making it hard to do that because they were willing to make excuses for me.

In conclusion, of all these things that have been addressed, life for me as of now is hard because I look for jobs and the documentation of my Marine Corps—excuse me. I am sorry. I look for jobs, and when the documentation of my Marine Corps career is shown to the interviewer, just the look on their face will say it all; basically, judging off of what my DD–214 is telling them, and when all is said and done, I am denied a job just because they see the words "temporarily disabled."

For the time being I am focused on getting my VA and Social Security squared away and still looking for another career path.

Thank you, ladies and gentlemen, for your time and efforts to help me and also hopefully other veterans down the road. I will be happy to answer any questions that you have for me.

[The prepared statement of Mr. Barrs follows:]

PREPARED STATEMENT OF JONATHAN W. BARRS, OPERATION IRAQI FREEDOM

Good morning Chairman Akaka and Ranking Member Burr. My name is Jonathan Barrs and I live in Cameron, North Carolina. Thank you for inviting me to testify today before this Committee.

I am twenty-four and served as a Marine in Iraq in 2005–2006 and 2007–2008. During my first deployment in 2005–2006, I was in a turret gunner in a Humvee. During combat operations, I experienced two Improvised Explosive Device (IED) blasts in a period of a week. The first IED detonated approximately thirty to fifty feet from my vehicle. When it exploded, the concussion from the blast slammed me into the turret. Glass from the vehicle became embedded in my head, but I did not think much of it at the time and did not seek any medical care. The second IED blast occurred about the same distance away as the first. After the second blast, the corpsman checked me out. He shined a light in my eyes and asked me what day it was just to see if I was able to stay with him.

Documentation was never given for the IED explosions, but shortly afterwards I was kept off of mission due to stomach problems and eventually taken to another Forward Operating Base because of excessive weight loss and was given steroids to fix the problem.

I was screened by the DOD for TBI and it was diagnosed in November 2008. At the time, I never looked to see exactly how this would impact me in the future.

I was medically retired in May 2009. The hand-off from DOD to VA was very slow. I have been out of the Marine Corps for almost a year now and I am just now getting care for the TBI. I have also been screened by VA for PTSD and I have been diagnosed with PTSD and depression.

So far, the VA care has been good, but this whole time of waiting was very hard and I had to keep asking my primary care doctor for a consult, which took a very long time. I have a case manager at VA in Fayetteville. Her name is Robin she is a great woman who does everything in her power to help me help myself by checking up on me and rescheduling my appointments when missed and currently helping me change my primary care doctor, because the doctor seems like he isn't really concerned about me, just more concerned about what the book tells him to do.

The honest truth is dealing with TBI is like a living horror film over and over again. Daily things that you know you're supposed to do, you forget. I have missed at least five important VA appointments also others not so important and I missed a job interview because I forgot about it. When you forget, the PTSD side of you rolls around because you knew you were never like this and it makes it very hard for people to deal with you. For example, the relationship I have with my girlfriend. It's been over a year now, but things aren't really right due to injuries that occurred while I was in the Marine Corps and I am still dealing with now I am out of the Marine Corps.

I went to junior college and tried to get through the coursework to get a degree, but I tried so hard and I was still failing tests. The teachers found out because I

was in a special populations group and felt sorry for me and they started giving me all this leeway and saying they will do whatever it took to get me a passing grade. I knew that getting passing grades I hadn't earned wouldn't be the way I wanted to do things. I was only trying to better myself and they were making it hard to do that because they were willing to make excuses for me.

In conclusion, of all things that have been addressed, life for me as of now is very hard because I look for jobs and when the documentation of my Marine Corps career is shown to the interviewer, just the look on there face says it all, basically judging off of what my DD–214 is telling them and when all is said and done I am denied a job just because they see the words "temporarily disabled" on my DD–214. For the time being I am focusing on getting my VA and Social Security squared away and still looking for another career path.

Thank you, ladies and gentlemen, for your time and efforts to help me and also other veterans. I will be happy to answer any questions that you have for me.

Senator MURRAY. Mr. Barrs, thank you so much for your courage in coming forward and telling your story to help us understand others. I appreciate your being here.

Mr. BARRS. You are welcome, ma'am.

Senator MURRAY. Dr. Gans?

STATEMENT OF BRUCE M. GANS, M.D., EXECUTIVE VICE PRESIDENT AND CHIEF MEDICAL OFFICER, KESSLER INSTITUTE FOR REHABILITATION

Dr. GANS. Thank you very much, Ranking Member Burr and Members of the Committee. I am Dr. Bruce Gans. I had the pleasure to be here in 2007 and to provide some input, and I am very pleased to be able to be back here and try to give you some sense of, at least from my view, what has changed, where the advances are, and where we still have opportunities for improvement.

In 2007 I made a few recommendations, and I would just like to give you a sense of what those were and my view of what happened since then.

The big theme was trying to find coordination between the private sector and the VA and DOD, to find a way for the organizations to work together, not just on a day-to-day operational basis but strategically, to plan together, to create seamless systems of care that could take advantage of all the collective resources that would be available. We suggested the creation of a Coordinating Council as a mechanism to do that. I am not aware of that type of enterprise having been conducted, and I am not aware of an organized strategic plan between the field, the private providers as a community, and VA and DOD as systems of care to try to make a seamless system of care available to veterans and active servicemembers.

We also talked about the case management and care coordination services and how they needed to be improved. There has been very significant improvement, as we have heard today. There are still some deficiencies that I will tell you about when I tell you some stories of family members that I have interviewed recently in anticipation of coming here before you.

In 2007 I also talked about research that was ongoing and urged that there be some collaboration and cooperation between the existing network of Traumatic Brain Injury research systems, the model systems, and the VA and DOD. I am happy to tell you that there has been some increasing collaboration. There are some data collection efforts with the model systems and the VA Polytrauma Rehab

Centers. We heard about a number of research projects that are also being funded, but I will also tell you there are still opportunities in that regard as well.

In terms of the current state of treatment of individuals with especially severe, the most severe Traumatic Brain Injuries, there are diagnostic tools that Dr. Jaffee, Col. Jaffee mentioned to you. I will mention a few others. In addition to the functional magnetic resonance imaging and the magnetoencephalography, there is magnetic resonance spectroscopy, there is quantitative electroencephalography, and near infrared spectroscopy. These are tools that are existing but, frankly, not commonly used and not readily available. And more than just diagnostic tools, we are now starting to see that they can even be used as tools to guide treatment, to suggest interventions, to monitor the effect of medications, to determine what is going on, and to guide changes in treatment management.

On the treatment front, there really have been some dramatic new technologies made available for patients. Many of them are not yet proven scientifically. We have growing clinical experience. We have anecdotes. We do have some examples of specific studies. I want to mention just a couple of them.

In the use of medications to treat brain injuries, conventional medicine would have you use one drug at a time and be careful in its administration to figure out what it does. Now the notion is going to be using many drugs all at the same time by expert clinicians who understand the interaction of these drugs and the fact that in combination they may work differently than individual effect. These so-called drug cocktails, which are actually quite a common strategy in cancer care, have not traditionally been part of the care of patients in rehabilitation from serious brain injuries.

Adding nutraceuticals—these are materials that are available that are not classified as drugs but are drug-like in their effect. They have many interesting properties. Some come from Eastern medicine. There are centers experimenting with and trying to use these additional stimulating drugs in ways that influence the brain neurochemistry.

And there are a whole host of very intriguing interventional strategies available: peripheral nerve stimulation to help arouse the most severely unconscious individuals; and direct brain stimulation using either direct current or magnetic stimulation. These are available technologies. They are non-invasive, they are not harmful. They have very low risks, and they have very, very rapidly expanding scope of potential impact. But they are not being widely used in the world of brain injury rehabilitation, partly because they are so new that the full body of research is not totally available.

The strategies in our clinical experiences at Kessler and a few other centers really suggest that the combination of using neuroimaging technologies and multi-drug and multi-physical modality interventions, along with the traditional rehabilitation strategies that we use, seem to have the best potential for making very significant differences in the lives of the most severely involved individuals.

We have had these kinds of experiences at Kessler with patients. We recently submitted an article that has been approved for publi-

cation describing our clinical experiences and are about to launch a very significant research project trying to understand these multi-modality approaches and what beneficial effect they really have to offer.

Another problem that you need to be aware of—it was actually mentioned—is there is a very significant shortage of professionals who know how to take care of people with brain injuries. Whether it is physicians, therapists, psychologists, or neuropsychologists, there just are not a lot of people who are highly skilled and dedicated to this population. These patients are extremely difficult to take care of; they are stressful for providers to take care of. And there is not that great a capacity to train people in this country. I am going to make a recommendation or two specifically in that regard as well.

In terms of the coordination opportunities, there have been significant advances in the VA system, and I would like to recognize and applaud the work that has gone on. I personally had the opportunity to visit the Richmond VA Polytrauma Center and I have had a chance to visit the Center for the Intrepid in San Antonio, just as a couple of examples of where the DOD and the private sector and the VA have really made significant improvements in capacity in general to provide for care.

But to find out what it seems to be like in the real world that I live in, I interviewed about two dozen providers of rehabilitation—executives, physicians, people in research, people who run large companies of rehab, people that provide or are part of advocacy organizations—to just ask them 3 years later, how is it going, what is your view, what are you seeing in the real world about how the private community is able to work with veterans, active military? What is going on? And that is, sadly, where I have to tell you that from the views of those that I talked to, there just does not seem to be a lot that is different. There definitely are some centers that have had a slow trickle of individuals. Most places have become capable of working with TRICARE to provide services under that financing mechanism. Yet, the single most common word I heard from the people I talked to is "frustrating." These are folks who have the capacity to provide high-quality brain injury care and services, want to do it, want to be able to work within the system, but just have not consistently had a flow of individuals.

In late 2008, some folks experienced a slight increase in referrals. Many of those seemed to disappear with time. It seemed to be coordinated with when the VA became—was able to staff up and build capacity. That may be just fine, but it is an observation that we made.

I would like to just contrast that experience with what is going on with the VA and the DOD in another area, and that is with amputations. We see a number of patients who have traumatic amputations and injuries, and in that case we have seen dramatic advances in the technology of prosthetics by collaboration between the DOD, VA, and private providers. There are new exciting limbs being developed by DARPA for upper extremity amputees. We have seen significant improvement in the capacity to care for the amputees and their prosthetic needs. I would point out that it was said to me that about 97 percent of the amputee care that is provided

by the VA is done through private contractors. So in that particular case, the VA does use a network of community-based prosthetists to actually deliver the care and services, and it is high quality and has all the characteristics I think people would want to see.

Another comment that I would like to share with you is the significant improvement in case management services. But what is interesting is that—what I was told is that—well, they are managing the people, but they are still not able to help them get access to the care, because although they are case managing and coordinating, there are still very significant limitations of who is available to be seen, to be referred to, to provide expert services. So the coordination is good, but the consequence of that coordination, the actual impact by having services delivered seems to still be deficient per the experience of the folks whom I talked to and to some degree the experience——

Chairman AKAKA [presiding]. Dr. Gans, please summarize your statement.

Dr. GANS. I will.

The last thing I would just like to say is I did talk with three active-duty servicemembers and their families Monday afternoon who are currently at Kessler, and they wanted me to share just a few of their experiences with you. They found that they would like to see easier ways of working with the system, the bureaucracy and the difficulty of having their choice to be expressed, to want to move to another provider outside of the VA Polytrauma System. One wife told me it took her a year from the time she started requesting until she was finally able to get a referral to—it happened to be Kessler in this case, and that was a lot of work and energy. That led to a sense of guilt. If they had only been able to start sooner, might things have been different? They felt that it just all took too long, and they also felt that there was a significant problem with access to services if they were to move into or accept medical discharge. They felt their resource access would be substantially reduced in terms of their flexibility to actually receive care and services.

I guess I would like to close by thanking you for giving me the time to speak to you again, appreciating all the work the VA has done, but saying there are still things left unfinished.

[The prepared statement of Dr. Gans follows:]

PREPARED STATEMENT OF BRUCE M. GANS, M.D., EXECUTIVE VICE PRESIDENT AND CHIEF MEDICAL OFFICER, KESSLER INSTITUTE FOR REHABILITATION

Good morning, Senator Akaka and Members of the Committee. Thank you for inviting me back to testify before this Committee regarding progress that has been made in the diagnosis and treatment of Traumatic Brain Injuries (TBI) and our experiences working with the VA to provide treatment and rehabilitation to servicemembers and veterans.

I am Dr. Bruce Gans, a physician specializing in Physical Medicine and Rehabilitation (PM&R). I hold the positions of Executive Vice President and Chief Medical Officer for the Kessler Institute for Rehabilitation in New Jersey. I am a past-president of the Association of Academic Physiatrists (the society that serves medical school faculty members and departments), and the American Academy of PM&R, which represents approximately 8,000 physicians who specialize in PM&R. Currently, I serve as Chair of the Board of the American Medical Rehabilitation Providers Association (AMRPA), the national association that represents our Nation's rehabilitation hospitals and units. At the UMDNJ-New Jersey Medical School I am a Professor of Physical Medicine and Rehabilitation. In the past, I have practiced

in academic medical centers as a faculty member at the University of Washington in Seattle, Tufts University in Boston, Massachusetts, Wayne State University in Detroit, Michigan, and the Albert Einstein College of Medicine in New York. In Detroit I also served as President and CEO of the Rehabilitation Institute of Michigan for 10 years.

Kessler Institute for Rehabilitation is the largest medical rehabilitation hospital in the Nation. We operate specialized Centers of Excellence to treat adults with Traumatic Brain Injuries, spinal cord injuries, amputations, strokes and many other neurological and musculoskeletal diseases and injuries. We also operate more than 70 sites for outpatient rehabilitation services in New Jersey that provide medical care, physical therapy, prosthetic fabrication and fitting, cognitive rehabilitation treatment, high technology wheelchairs and electronic assistive device fittings, and many other services.

We are also a major medical rehabilitation education and research facility. In cooperation with the Kessler Foundation and the UMDNJ-New Jersey Medical School, we train physicians, therapists, psychologists, and many other disciplines to provide rehabilitation services and run rehabilitation programs. We also conduct many research programs and projects to advance the knowledge and science of medical rehabilitation. Much of this research is funded under Federal grants from the National Institutes of Health (NIH), the National Institute for Disability and Rehabilitation Research (NIDRR), other Federal and state organizations and private foundations.

PREVIOUS TESTIMONY

When I testified before this Committee in 2007, I expressed concern that the civilian rehabilitation providers in this country were capable, available and interested in providing high quality rehabilitation care and treatment to servicemembers and veterans but they were not being utilized. In particular, providers wanted to make themselves available to patients from their own communities so that long stays in far distant care centers could be prevented. I noted that there was little evidence of cooperative planning among the DOD, VA, and civilian sectors to make the best services available in a timely way in home communities.

At that time I recommended the creation of a Coordinating Council on which leaders from all three stakeholders would participate in order to work together to strike a balance between building up care delivery capacity in Military Treatment Facilities (MTF) or VA health centers, and utilizing private partnerships when they were more cost effective and more appropriate for the needs of servicemembers and veterans. I also urged targeting case management and care coordination services so that individual patients and families could be helped to navigate among the military, VA, and private sectors to help make their care seamless and effective with a view to long-term needs once they returned to their home communities.

In addition, I recommended that there be close collaboration and cooperation among the DOD, VA and the private TBI research community (especially the TBI Model Systems programs of NIDRR) to study the effectiveness of current treatment approaches, and to develop new breakthroughs in how to care for all levels of TBI, from mild, to moderate or severe. The allocation of research funds that could be used to sponsor research partnerships among the DOD, VA and private research community was also proposed.

THE CURRENT STATE OF TBI REHABILITATION

Happily there have been some advances in the state-of-the-art for treating individuals with serious brain injuries. Many of the most advanced and innovative approaches have not yet found their ways into common practice. The newest innovations have not been fully researched to prove their efficacy, but clinical experience and some retrospective studies are showing much promise.

Diagnosis

New diagnostic tools such as Functional Magnetic Resonance Imaging (FMRI), Magnetoencephalography (MEG), Magnetic Resonance Spectroscopy (MRS), quantitative Electroencephalographic brain mapping (QEEG) and Near Infrared Spectroscopy (NIRS) are all non-invasive methods of observing brain activity and responses to treatments. These evaluative tools are allowing clinicians to be aware of patient responses when behaviors cannot be observed, and serving as guides to how treatments should be modified.

Treatment

Innovative treatments are also being utilized. Pharmaceuticals are being much more aggressively used to help patients be aroused from coma, better organize their thinking, and control difficult behaviors. Multiple drug “cocktails” used by expert

clinicians appear to have beneficial effects. Supplemental uses of nutraceuticals are also being pursued, and intriguing clinical experience being accumulated. Physical modalities are being applied with much more intensity to attempt to help patients. They include peripheral nerve stimulation, brain stimulation by direct or magnetically induced currents, and neurofeedback.

More interestingly, the use of these diagnostic and therapeutic modalities together, with multi-modal interventions, may be more effective than the conventional "one at a time" approach used previously. Clinical experience gained at Kessler Institute and other centers in this regard has prompted the development of significant research projects to test these findings. A large study of this type is expected to begin shortly at Kessler Institute in partnership with the International Brain Research Foundation and the Kessler Foundation.

Workforce Shortages

There is a shortage of trained and experienced clinicians with experience in the treatment of TBI patients. Physicians in PM&R or Neurology, neuropsychologists, physical therapists and other rehabilitation disciplines are all highly sought after because of the demands of treating these patients and the shortage of available talent. For this reason, in part, patients have waited for prolonged periods to access treatment centers, and been shunted to regional or national centers of excellence, both the VA Polytrauma Rehabilitation Centers, and occasionally at institutions like Kessler.

CARE DELIVERY AND COORDINATION AMONG THE DOD, VA, AND CIVILIAN PROVIDERS

The proposed Coordinating Council was never pursued and, at least to my knowledge, the VA did not develop any organized method of identifying high quality providers in communities to supplement or obviate the need for them to hire scarce staff to treat patients internally.

It is not my place to detail the changes in care delivery capacity of the VA or their relationship with the military. It is clear that the VA has strengthened the care delivered through its Polytrauma Rehabilitation Centers and Polytrauma Network, and their coordination with the MTFs. I have personally had the opportunity to visit the Polytrauma Rehabilitation Center in Richmond, Virginia, and the Center for the Intrepid in San Antonio, Texas, and was impressed by both of these facilities.

In an effort to gauge the current status of the relationship between private providers and the VA and DOD and to share with this Committee, I communicated with more than 16 medical and administrative leaders in the field. These individuals ranged from rural providers to large national companies, and included community hospitals and large academic health systems. I asked these leaders to share with me their views on how care is being provided to patients in their communities, and what their facility experiences have been in working with the VA or the DOD.

It appears that little has changed since 2007 regarding the use of local care providers for TBI care. Some private sector rehabilitation hospitals experienced a transient increase in referrals for evaluative services. Most if not all, had established relationships with TRICARE so that they could see patients and get reimbursed for the care they hoped to provide. The most common word used to describe the situation was "frustrating". Repeatedly, I heard comments such as, "we have high quality services available, but patients and their families are being uprooted to distant care settings for long periods of time. When they finally come back to their home community, there is little available to them for their long term needs."

One interviewee contrasted the TBI situation to that of Amputees. He pointed out the significant research partnerships among the DOD (DARPA in particular), VA, private centers and commercial interests to develop new advanced prostheses. He also pointed out that the vast majority of prosthetic care delivered by the VA is done through private contractors.

Another individual commented that there has been a substantial increase in the availability of case management services. While individuals who work with specific patients are now more available, families have expressed great frustration that they don't have contact with physicians and direct care providers; so the availability of case managers is not sufficiently helpful since they haven't got access to the care itself.

I can speak most readily about the experience of my own hospital, Kessler Institute for Rehabilitation. Since March 2007, Kessler Institute has cared for 10 servicemembers. Two patients currently are receiving inpatient care at our hospital. All were Active Duty at the time of admission. All 10 had serious TBI. Three also had Spinal Cord Injuries. One had multiple amputations as well as the TBI. Six of these patients were injured in theater, five from IEDs. The other four patients were injured in motor vehicle accidents. VA funds supported two of the patients while

TRICARE sponsored 9 (one patient transitioned from VA to TRICARE while at Kessler).

Ironically, one of the first patients in this group was the son of Denise Mettie, the parent who testified to this Committee just before I did in 2007. Our chance meeting on that day led to her pressing for Evan to be referred to Kessler for ongoing care. Her experience of needing to be a strong and uncompromising advocate for her loved one has been a common thread for many of the families of the patients we have seen. Only with sustained pressure were many of these patients allowed to be referred to us. This observation is similar to the experience described by other leaders in the field whom I interviewed.

TBI RESEARCH COOPERATION

There have been some advances in the collaboration among the DOD, VA and private sector in rehabilitation research. The Polytrauma Rehabilitation Centers have initiated work with the TBI Model Systems for data contribution and other purposes. Also, research centers around the country have been applying for funding from DOD solicitations in this area, and a number of active projects are underway at centers such as our own, Spaulding Rehabilitation Hospital and Harvard University, and Rehabilitation Institute of Chicago. The research being conducted ranges from retrospective reviews of secondary data to assess outcomes and long-term effects, to clinical trials of innovative treatment approaches in the hope of finding breakthroughs in care.

OVERALL ASSESSMENT OF THE RELATIONSHIP BETWEEN THE VA AND CIVILIAN PROVIDERS

The VA has clearly improved its capacity to care for patients with TBI. It has not done so with an eye to the long term needs of patients who return to more remote communities, however, and has, instead, chosen to strengthen its internal capacity.

While I may have a limited sample, it appears that family members are dissatisfied with their inability to access providers of choice outside of the VA system, and that the case management system is not consistently resulting in better access to care. These observations may not be generally applicable, but seem to be on target for the most severely injured patients and their families.

The research collaborations are encouraging, but not pushing the envelope far enough or fast enough. The truly innovative neurodiagnostic and therapeutic work appears to be being conducted outside of the VA, not within it. In fact, the conventional research establishment is showing some resistance to the most innovative approaches (multi-modal treatment protocols, for example).

RECOMMENDATIONS

It is important to commend the VA and the DOD for their hard work and the progress they have made in the acute and early-phase care of patients with TBI. My concerns remain for the breadth and depth of that capacity and the anticipated life-long needs of a new generation of brain injured veterans.

I still contend that collaboration with the private sector and enhanced efforts in this regard are the right thing to do. As large as the TBI problem in the military sector is, it is dwarfed by the magnitude of the problem in the civilian population. Over a million brain injuries occur in the US every year. Admittedly, not many are blast injuries, but when it comes to rehabilitation care, that is not a major distinguishing feature. Hence, the capacity in the civilian sector will not only be great, it will be available for the long term. The VA and DOD should work for strategic alliances with civilian providers so that a sustainable infrastructure of care delivery capacity for servicemembers and civilians is available now and for the foreseeable future. This could be accomplished beginning with creating the Coordinating Council I recommended previously.

Congress could create incentives for the VA and DOD to improve collaboration by establishing a budget item for each to support this activity, and structuring the budgets so that rather than being penalized at the local level, a VA facility could access special supplemental funds if it found a way to utilize local resources to create a sustainable care delivery capacity.

In particular, the VA and DOD should develop a method of early identification of individuals who are clearly going to be destined for medical discharge because of their injury. This “pre-discharge” determination should be a guiding condition that triggers care planning based not on regionalized care delivery within the VA, but prioritizes accessing closer to home providers that will be life-long resources to the patients and their families.

Congress could prioritize the research budgets for both the VA and DOD to promote searching for breakthrough research to dramatically advance the state of treatment and rehabilitation of TBI. Whether it supports stem-cell techniques to develop brain grafting possibilities, multi-modal rehabilitation interventions, or telerehabilitation, it should place a premium on dramatically improving our care capacity, not just incrementally advancing it.

Further emphasis on funding training for TBI-related health professionals in more innovative ways is also an important possibility. For example, while the VA does currently support medical residency training and some fellowship training, there are administrative barriers for some of these positions to utilize advanced training settings outside of the VA. Rules should be changed as needed to allow trainees to learn in the most appropriate settings, regardless of whether they are within a VA or a civilian facility.

The VA should explore how the innovative health care delivery ideas contained in the recently passed Health Care Reform legislation may be relevant to this population. In particular, demonstrations of an Accountable Care Organization focused on the TBI population could be implemented. Being charged with managing the best outcomes for the best value, regardless of provider setting, might stimulate new levels of collaboration. Similarly, establishing a demonstration Medical Home for TBI patients could show another way in which the care coordination resources and medical management obligations could be integrated to the benefit of patients and their families.

CONCLUSIONS

In closing, I would like to express my gratitude to the men and women of our armed services and the agencies themselves for their dedication and sacrifices to defend and protect our country. I hope that these observations and suggestions can help to provide more and better care for those who have given so much for our Nation.

RESPONSE TO POST-HEARING QUESTIONS SUBMITTED BY HON. DANIEL K. AKAKA TO BRUCE M. GANS, M.D., EXECUTIVE VICE PRESIDENT AND CHIEF MEDICAL OFFICER, KESSLER INSTITUTE FOR REHABILITATION

Question 1. In her testimony, Mrs. Bohlinger discussed the importance of brain imaging to improve the accuracy of TBI screening. From your perspectives, what new imaging technologies are being developed or can be made available to VA?

Response. There are many emerging imaging techniques that can both improve the diagnostic accuracy of identifying brain injury, and help to guide therapeutic interventions. One receiving the most attention right now is Functional Magnetic Resonance Imaging (fMRI) because it is capable of showing areas of metabolic activity in relationship to brain functions, such as motor, sensory, and even thought processes. Diffusion Tensor Imaging (DTI) can be very helpful in detecting subtle brain injuries. Magnetic Resonance Spectroscopy (MRS) is becoming useful for observing metabolic activity within the brain and using that information for diagnostic purposes.

Electrical "imaging" of the brain through studies of the wave patterns and analysis with quantitative electroencephalography (qEEG) allows useful diagnostic information to be accumulated. In addition, magnetic electroencephalography (MEG) detects the magnetic fields generated by the electrical activity of the brain, and is potentially useful as a diagnostic tool.

Near Infrared Spectroscopy (NIRS) is a non-invasive method of studying the metabolic activity of the brain by observing blood flow patterns. It may serve to partially substitute for fMRI studies but is limited to allowing observation of only the activity at the surface levels of the brain (fMRI allows observation of deeper structures).

Each of these methods has its strengths and limitations for contributing to the diagnosis and treatment of TBI. Their use depends on what information is needed or what treatment goals are being pursued. Many of these techniques are still being studied to better understand their value and ultimate role in the care of patients with TBI. As the research and clinical experience mature, it will become clearer as to which should become routinely available, which should be used just for research purposes, and which should be discarded because they do not contribute to helping in the care of patients.

Today, the imaging methods that should be readily available to patients are fMRI (especially for patients with severe brain injury) and DTI (to help diagnose patients who have experienced a mild TBI).

Question 2. Cooperation with the private sector is important to expand access to care. However, veterans are a unique population. What steps has your organization, or other private entities with which you may be familiar, taken to become more "culturally literate" with respect to servicemembers and veterans?

Response. Familiarity with the VA (more so than the military) health system is quite pervasive for physicians, since most of us have had at least part of our medical training in VA hospitals. As an organization, Kessler Institute has taken many steps to enhance its understanding and ability to work with both VA and military medicine. We have visited a number of military and VA health care facilities, interacted extensively with professionals from both settings, and encouraged close interactions between our case managers and other clinicians with military or VA care givers, coordinators, and administrators around the planning and delivery of care to patients, both active military and veterans.

In addition, many senior officers have visited Kessler Institute to observe the care we have been providing to the servicemembers whom we have been allowed to treat. We have also received visitations by a number of VA professionals.

Nationally, the field has reached out to both military and VA professionals to conduct training sessions, provide lectures, encouraged them to interact with their civilian colleagues, and promoted their participation in meetings of the American Academy of Physical Medicine and Rehabilitation (AAPM&R), the professional society of physicians who practice physiatry, and the American Medical Rehabilitation Providers Association (AMRPA), the national organization that represents rehabilitation hospitals and units. Both the AMRPA and the AAPM&R have reached out to the VA to attempt to systematically build mutual understanding and establish a relationship.

It is common for civilian health care facilities to treat a diverse patient population, and at Kessler Institute, we train our staff formally in the concepts of cultural diversity. Our experience with the military and VA is not that different from other patients who identify with a specific culture, and I believe we have demonstrated sensitivity to each individual's background, needs and concerns. The military and VA have done a great job of staying actively involved with the patients we have cared for, and helped us on a day-to-day basis to deal with the unique issues associated with their culture and systems. Family members also help to provide us with important insight and guidance on a regular basis.

Question 3. Does your organization, or ones you are familiar with, use telehealth technologies to provide care and services to individuals with TBI?

Response. Kessler Institute has limited experience with telemedicine. We do use remote radiology services to review all imaging studies; the images are transmitted digitally to offsite radiologists who read the films and transmit their reports electronically. There are institutions that do have experience in a variety of tele-rehabilitation activities. For example, the University of Pittsburgh operates a Rehabilitation Engineering Research Center (RERC) dedicated to tele-rehabilitation. It is funded by the National Institute on Disability and Rehabilitation Research (NIDRR) within the Department of Education.

Question 4. Your testimony discussed that Kessler Institute will begin a study regarding the effectiveness of combining diagnostic and therapeutic modalities for treating TBI. Do you anticipate this new form of treatment would have a significant impact on cost?

Response. If our research demonstrates the clinical effectiveness and value of these interventions, it is likely that they would become the standard of care. There are certainly short-term incremental costs associated with the use of these drugs, nutraceuticals, imaging studies, and electrical stimulation modalities. But, if these therapies help a patient to become more conscious ("wake up") and able to walk, communicate, function, and return home instead of being a permanent resident of an institution, then the ultimate total costs of care will be substantially reduced and the cost benefit will be enormous.

Question 5. Is there a benefit to continuing rehabilitation therapy, with the goal of maintaining a current level of functioning, for those with severe TBI for whom no further gains in functioning are expected?

Response. The question of maintenance therapy is frequently addressed in medical rehabilitation. In many cases, formal therapy can be replaced with self-care programs performed by patients on their own or with family caregiver assistance. There are situations, however, where patients and families cannot sustain these activities on their own. The need for continuing formal therapy then depends on what the risks of deterioration are. Each case is unique, of course, so generalizations are difficult. The risks of disengaging from even seemingly simple therapies such as range of motion exercises can be profound. I have seen patients develop severe con-

tractures, serious skin ulcers, and even die from the lack of what was described as "only maintenance" therapy. So, in the end, there needs to be reasoned clinical judgment applied to the individual patient.

The other question is whether more improvement can be achieved with additional therapies or if the patient has "plateaued" and will not benefit any further. Recovery from serious brain injury can be likened to athletic training. For an athlete to obtain peak performance, sustained, intensive and consistent training is required. For a seriously impaired patient with a brain injury, it may take similar sustained, intensive and consistent therapy to make any improvements. For certain patients, even modest incremental gains can be very meaningful. How much further improvement is "enough" will depend on the individual, their goals and needs. In the case of our wounded warriors, I would give them the benefit of the doubt, and support longer term access to therapies, even if only "modest" benefits were expected. Once again, it is a matter of individual situations and expert clinical judgment.

Chairman AKAKA. Thank you very much, Dr. Gans.

Mr. Dabbs?

STATEMENT OF MICHAEL F. DABBS, PRESIDENT, BRAIN INJURY ASSOCIATION OF MICHIGAN

Mr. DABBS. Good morning, and thank you, Senator Akaka, Senator Brown, and members of the staff of the Senate Committee on Veterans' Affairs, for the opportunity to address you about how effective State, local, and private entities have been engaged by the Veterans Administration to provide the best access to care and services for veterans with TBI.

The Brain Injury Association of Michigan was incorporated in 1981 as a 501(c)(3) nonprofit organization and is one of 44 chartered State affiliates of the Brain Injury Association of America. We are one of the leading State affiliates due to Michigan having more brain injury rehabilitation providers than any other State in the country. This extensive provider network has been developed over the past 37 years as a result of Michigan's auto no-fault insurance system. It provides a lifetime continuum of care with a singular focus: to assist the injured victim recover to their fullest potential. My written testimony provides a comprehensive overview of our association: its veterans program under the guidance of Major Richard Briggs, Jr., U.S. Air Force (Retired), who is with me today; and the collaboration with the Michigan Department of Military and Veterans Affairs, the members of the Joint Veterans Council, the Veterans Service Organizations, the Michigan Association of County Veterans Counselors, and the Veterans Integrated Service Network 11 director and staff. As a result of this collaboration, I will share my observations, possible approaches, and potential solutions in response to the Committee's inquiry. My comments only reflect my experiences within the Michigan region of VISN–11, which is the lower peninsula of Michigan.

In Secretary Shinseki's report, he indicated a number of "landmark programs and initiatives that VA has implemented to provide world-class rehabilitation services for veterans and active-duty servicemembers with TBI." These are important developments, but let me express a few concerns.

One, Enclosure A of his report, page 2, states that "VA directed medical facilities are to identify public and private entities within their catchment area that have expertise in neurobehavioral rehabilitation and recovery programs for TBI." To date, in Michigan there have been only three such referrals according to the VISN–

11 Cooperative TBI Agreements Patient Tracking fiscal year 2009 report. One of these was due to a mother's insistence that such care be provided to her son.

This is a critical part of my testimony. I have provided a chart based on the information shown on the Commission on Accreditation of Rehabilitation Facilities, better known as CARF, Web site that indicates all accredited brain injury providers in the United States. This report indicates that in military commission alone, there are nine brain injury residential rehabilitation providers with 78 facilities; that is 24 percent of the U.S. total. Eight brain injury home and community-based rehabilitation providers with 16 facilities; that is 33 percent. There are similar percentages for outpatient rehabilitation providers and vocational rehabilitation services.

There are even more non-CARF-accredited providers in Michigan, but, unfortunately, none of these providers or the CARF-accredited providers are being utilized to the extent they should be by the VA. I am going to provide the Committee with this book, which is our Directory of Facilities and Services in Michigan as a future reference.

[The aforementioned Directory was received and is being held in Committee files.]

Point 2, Enclosure A, page 2, of Secretary Shinseki's report, the second paragraph states the numbers and cost of veterans with TBI receiving inpatient and outpatient hospital care through public and private entities for fiscal year 2009. The average cost indicated is approximately $5,800 per veteran. Let me give you a comparison.

As part of the Michigan Department of Community Health's TBI Grant from HRSA, Michigan's Medicaid data during the past 4 years indicates an annual average cost of $28,500 just for services with a TBI diagnosis; and an annual average cost of $41,200 for services with TBI and non-TBI diagnosis. I believe these numbers may be further indication of less than optimal use of outside contractors or, at the very least, not fully using these contractors and should be reviewed in greater depth.

Point 3, Enclosure A, page 4, number 4 discusses "Programs to maximize Veterans' independence, quality-of-life, and community integration, and establish an assisted living pilot." I would recommend to the VA that they immediately explore and/or expand such a pilot using the Michigan CARF-accredited providers. In fact, the solider whose mother was insistent on the care outside of the VA system might be one to include in such a pilot.

There are other concerns of equal importance that have been stated to us by the Michigan Department of Military and Veterans Affairs. I urge the Committee to review these as part of my report to you in terms of your future actions.

Again, let me thank the Committee for allowing me to testify. Brain injury is an unique injury that has by some been called a "life sentence" to veterans and to their families who do not receive timely—and I want to emphasize that word, "timely"—comprehensive, and sufficient cognitive rehabilitative care.

In wrapping up, let me personally testify to this fact. My father, who served with the U.S. Marines during the assault on Guadalcanal, sustained a brain injury that we learned about near the end

of his life. His undiagnosed brain injury was diagnosed in the late 1970s, early 1980s as PTSD. The VA's treatment at that time was to overprescribe (my opinion) medication. It was not until there was a determination that there was a brain injury and the medication protocol was greatly changed did he ever have the quality-of-life he should have had while raising his family.

On behalf of today's veterans, let me plead that we collectively do everything in our wisdom and power to prevent their lives having the same fate. Thank you.

[The prepared statement of Mr. Dabbs follows:]

PREPARED STATEMENT OF MICHAEL F. DABBS, PRESIDENT,
BRAIN INJURY ASSOCIATION OF MICHIGAN

Let me begin by expressing my sincere appreciation to Senator Akaka and all senators of the U.S. Senate Committee on Veteran Affairs for the opportunity to address you on the issue of our Association's experience in working with the VA to provide brain injury treatment and rehabilitation to veterans. As part of my testimony I will address how effectively state, local and private entities have been engaged by the VA to provide the best access to care and services for veterans with TBI.

Before discussing this matter, allow me to provide you with some basic information about the Brain Injury Association of Michigan and in particular, its Veterans Program. The Brain Injury Association of Michigan was incorporated in 1981 as a 501(c)(3) nonprofit organization by individuals with a brain injury, their families and professionals in the field of brain injury to provide support and education to one another, as well as to advocate on behalf of persons with a brain injury and their families. Additionally, research and prevention programs were primary goals. Our Association is one of 44 chartered state affiliates of the Brain Injury Association of America.

In 2007, with funding provided by the Health Resources Services Administration to the State of Michigan Department of Community Health (MDCH) as part of the Federal Government Traumatic Brain Injury State Grant program, a portion of these funds were sub-contracted to our Association to serve the needs of Michigan veterans. Through the guidance of the MDCH's TBI Grant Services and Prevention Council the following goals were established:

- Goal 1—Create a comprehensive and coordinated state-wide Traumatic Brain Injury (TBI) awareness and resource program for veterans, their families and friends/co-workers through implementation of a Veteran TBI Awareness Campaign.
- Goal 2—Create a working relationship with the Michigan based VA VISN 11, VA medical centers and subordinate VA health care providers.
- Goal 3—Survey all TBI health care providers to ascertain their interest in and capabilities of providing care for military personnel.

In order to accomplish these goals, Major Richard Briggs, Jr., USAF (Retired) was hired to manage this program and accompanies me today. Though I would be pleased to share a more comprehensive report about our Veterans Program accomplishments, I will limit my comments to addressing our activities as it relates to Goal 2 and its relevancy to the stated purpose of this hearing.

Major Briggs developed a working relationship with the Michigan Department of Military Affairs and with their assistance was able to create partnerships with the Veterans Service Organizations' Council and the VA County Counselors. Also, because of this relationship with the Department of Military Affairs, he and I were invited to meet with the Veterans Integrated Service Network (VISN) 11 director and staff. As a result of these meetings, Major Briggs was able to meet with the four VA Medical Center Directors in Michigan, as well as their respective OEF/OIF Coordinators. These meetings afforded Major Briggs the opportunity to share with them the unique capabilities for brain injury rehabilitation available in Michigan. These capabilities will be explained at further length below as it pertains to the Committee's inquiry.

Finally, let me share with the Committee that the Brain Injury Association of Michigan's Veterans Program was just recently ranked 21st out of 128 nonprofits providing support and service to our veterans in a recently-conducted 2010 Veterans Choice Campaign special survey done by Great Nonprofits.

The information above is provided to serve as credible evidence of our ability to address the Committee's meeting purpose and to demonstrate our efforts to reach

out and work with the VA and the main organizations that already exist that work with the VA, or collaborate closely with it.

It is my intention with the comments that follow to suggest to the Committee possible approaches or potential solutions to consider as it attempts to ensure that the intent of the Federal legislation is in-fact carried forward at the local level. Let me be clear that my comments only reflect the experiences of our Association with VISN–11 and in particular, the Michigan region of VISN–11, which is the lower peninsula of Michigan.

In my nearly 18 years as president of the Brain Injury Association of Michigan, I have rarely seen as comprehensive a piece of legislation regarding brain injury and best practices as what was included in Title XVI, Wounded Warriors Matters of the "National Defense Authorization Act for Fiscal Year 2008." In addition, the Veterans Omnibus Health Services Act of 2010 (S. 1963) also is an excellent piece of legislation as it pertains to soldiers who have sustained a Traumatic Brain Injury (TBI). In fact, some of the proposed approaches that I will mention address some of the provisions (sections 506, 507, 509, and 515) of this bill.

In Secretary Shinseki's report to the Committee dated March 23, 2010 indicated a number of "* * * landmark programs and initiatives that VA has implemented to provide world class rehabilitation services for Veterans and active duty Servicemembers with TBI * * *" It is my opinion that these are valuable and important developments; but here are a few concerns I have regarding this.

1. The first point mentions "* * * 108 specialized rehabilitation sites across the VA medical centers that offer treatment by interdisciplinary teams of rehabilitation specialists * * *"—

I agree that the VA medical centers do offer such rehabilitation; however the VA appears to be limited in providing brain injury rehabilitation. Our experience in Michigan however, is that these hospitals are over-burdened and given their patient load simply are unable to provide timely care and frequency of care that is required for a person who has suffered a TBI.

Furthermore, as we have witnessed with one of the four VA medical centers in Michigan that is located in close proximity to a major hospital medical school, this VA medical center only has one doctor who is qualified to administer Neuro-psychological testing. Neuro-psychological testing is critical to the proper and thorough screening of soldiers who have a suspected TBI.

As further evidence of the significance of this problem, let me provide you with one of the recommendations given to me by the State of Michigan Department of Military Affairs in preparation for this testimony:

> "Access problems and long waits continue to be problematic despite the best attempts of the VA."

One additional point to consider regarding this issue of adequacy of resources—it is my understanding that Michigan has over 725,000 Veterans, and only 207,000 are registered with the VA. Yet as stated above, the current VA medical centers are seriously over-whelmed with trying to provide care to those they are servicing. Assuming the Michigan numbers of Veterans and the Veterans who are registered with the VA are reflective of other states, this would dictate that the VA absolutely must aggressively seek outside contractors to assist them with providing care to our Veterans. Simply put, the VA must use its financial resources to contract with public and private partners to provide care and not spend these funds trying to build facilities and staff them. I implore this Committee and the VA to immediately take action on this issue. Veterans who have a TBI need treatment now—not in a few years when a few more facilities might be operational. Does it even seem reasonable to think that there are sufficient funds to build enough facilities in Michigan to meet the long-term care needs of Veterans with TBI, if the numbers above are correct; much less the rest of U.S.?

2. The second point indicates that "TBI screening and evaluation program to ensure that Veterans with TBI are identified and receive appropriate treatment for their conditions"—though this has been implemented, the current assessment that I believe is being referred to—a four question survey—is not adequate. Another one of the State of Michigan Department of Military Affairs recommendations states:

> "TBI continues to be missed when it co-occurs with other disorders. Soldiers who are being diagnosed with disorders such as Bipolar Disorder and PTSD should be universally screened for TBI because of the similarities in their presentation. Likewise all soldier receiving VA disability for hearing loss or Tinnitus (ear ringing) should have mandated TBI screen."

3. Enclosure A, Page 2 notes that "* * * VA directed medical facilities to identify public and private entities within their catchment area that have expertise in

neurobehavioral rehabilitation and recovery programs for TBI, and to ensure that referrals for services are made seamlessly when necessary." A similar point is made in S. 1963, Section 507. To date in Michigan, there have been only three such referrals according to the VISN–11 Cooperative TBI Agreements Patient Tracking FY 2009. One of these was due to a mother's insistence that such care be provided to her son.

This is a critical point of my testimony. For over 37 years, Michigan, due to its unique automobile no-fault insurance system, provides comprehensive lifetime care for those sustaining injuries in an automobile crash in Michigan. The care provided is unique to each person and provides cognitive rehabilitation care. As a result, there are more brain injury rehabilitation providers than any other state in the U.S. I have provided a chart that we created as an attachment to this testimony. This information was taken directly from the Commission on Accreditation of Rehabilitation Facilities (CARF) Web site that indicates all certified brain injury providers in the United States. Let me give you just a couple of the more salient points. There are 9 brain injury residential rehabilitation providers with 78 facilities in Michigan—this is 24% of the total in the U.S. Michigan has 8 brain injury home and community-based rehabilitation providers with 16 facilities in Michigan—this is 33% of the total in the U.S. Brain Injury outpatient rehabilitation providers in Michigan number 12 with 22 facilities, which represent 15% of similar providers in the Nation. And finally, there are six providers with 12 facilities, which is 24% of the total in the U.S.

Again, these are CARF accredited providers and represent only a fraction of similar program providers within Michigan who are not certified. A copy of the Brain Injury Association of Michigan's Directory of Facilities and Services will be provided to the Committee's staff to provide you with an idea of just how extensive these resources are throughout Michigan. All of these providers are spread across Michigan, though the preponderance are located in or near the larger urban areas of the state. Attached is a Michigan map with just the CARF accredited facilities.

4. Enclosure A, page 2, second paragraph also states the numbers of Veterans with TBI receiving inpatient and outpatient hospital care through public and private entities for FY 2009. The average cost per Veteran would be $5,800.

By way of comparison, as part of the MDCH TBI Grant from HRSA, Michigan has done an extensive analysis of its Medicaid Data for the past 10 years. During the past four years, our analysis of a subset of TBI cases who receive Medicaid provide us a the cleanest estimate of cost (that is, Medicaid cases who had no other insurance, were not in Medicaid prior to their TBI hospitalization, had Medicaid eligibility for at least a year after the TBI hospitalization and had Fee For Service cost data) showed the following:

> Annual average cost of $28,539 just for services with a TBI diagnosis.
> Annual average cost of $41,243 for services with TBI and non-TBI diagnosis.

An issue to consider regarding this data is that I believe that Medicaid is more restrictive of services than would be available through the VA.

5. Enclosure A, page 4, #4 discusses "Programs to maximize Veterans' independence, quality of life, and community integration, and establish an assisted living pilot." I believe this program could have been expedited had the VA utilized the resources available in Michigan. I would encourage the Committee to recommend to the VA that they immediately explore and/or expand such a pilot utilizing the CARF accredited providers that I have mentioned above. In fact, the solider mentioned above whose mother was insistent on the care outside of the VA system might be one to include in such a pilot.

RECOMMENDATIONS

The Brain Injury Association of Michigan would readily welcome the opportunity to partner with the Veterans Administration to work expeditiously to implement the policy directives and guidance that Congress and the VA have directed. With the collaboration of the partners that I indicated in the beginning of this testimony, I believe that we can effectively assist with demonstrating how the "new" VA can operate in the 21st Century to meet its congressionally mandated responsibility of providing care to our Nation's Veterans.

1. Create a pilot study in Michigan that utilizes the extensive continuum of care of CARF accredited brain injury rehabilitation providers. The goal of such a pilot would be to validate Secretary Shinseki's desire for a seamless system of care between VA and private or public partners. Additionally, its greatest value would be to ensure the Veteran is receiving the most comprehensive program of brain injury rehabilitation that would give them the greatest opportunity to reintegrate into the community.

2. Review current legislation and possibly creating additional legislation as required creating a program that would address some of the following concerns (this is not comprehensive, simply a starting point):

– Automatically enroll a soldier into the VA upon discharge from active duty;
– Improved TBI screening;
– Comprehensive case-management;
– Increased educational offerings and support regarding their loved-ones who have a TBI pertaining to their challenges and limitations;
– Realization of "seamless transitions" and an interdisciplinary approach between health care providers across disciplines to assure that the Veterans challenges is not navigation through bureaucracy or red tape.

3. The VA should undertake a study of medical specialties that they have shortages of and what opportunities exist in their region to ensure that more timely care is rendered to Veterans who have sustained a TBI.

CONCLUSION

In conclusion, let me again express my sincere thanks to the Committee for allowing me to testify. Brain injury is an unique injury that can be a "life-sentence" as one radio personality once called it. It can be a needless life-sentence to the Veteran who does not receive timely, comprehensive and sufficient rehabilitative care. I would also suggest that it is a life-sentence for their loved ones. It impacts the family and the community. I can personally testify to this fact as my father who served with the U.S. Marines during the assault on Guadalcanal sustained a brain injury that we learned about near the end of his life. His undiagnosed brain injury was diagnosed in the late 1970's, early 1980's as PTSD. The VA's treatment at the time was to over-prescribe (my opinion) medication. It wasn't until there was a determination that there was brain injury and the medication protocol was greatly changed did he ever have the quality of life; he should have had while raising his family. On behalf of today's Veterans let me plead that we collectively do everything in our wisdom and power to prevent their lives having the same fate.

Attachments:
1. CARF Statistics Table for Michigan
2. State of Michigan map identifying CARF accredited providers

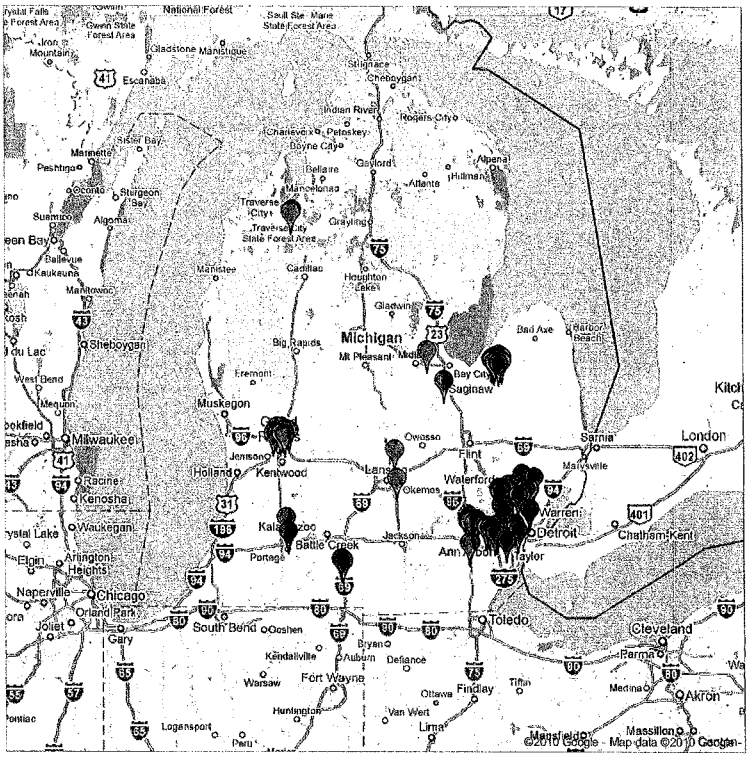
Commission on Accreditation of Rehabilitation Facilities (CARF)
Accredited Brain Injury Providers In Michigan
April 30, 2010

Provider Parent Company	Parent Company	Home & Community Based Rehab	Residential Rehabilitation	Outpatient Rehabilitation	Vocational Services	Inpatient Hospital	Long Term Residental	Skilled Nursing
Ann Arbor Rehabilitation Centers Inc	1	5		1				
Borgess Medical Center	1					1		
Childrens Hospital	1			2				
Coach House Rehabilitation Center	1	2	3	1			3	
Covenant Health Care	1					1		
Eisenhower Center	1		3		3		3	
Irvine Head Injury	1		2	1			2	
Hope Network Rehabilitation Services	1	3	4	3	2		7	
Learning Services Corp	1						1	
Lighthouse Inc	1		13	2	2		13	
Mary Free Bed Rehabilitation	1			1		1		
Munson Medical - Memory & Attention Tng Cntr	1	1		1	1			
Origami Briain Injury Rehabilitation Center	1	1	1	1	1		1	
Rainbow Rehabilitation Center	1	2	34	3	3		34	
Rehab Without Walls	1	1						
Rehabilitation Institute of Michigan	1			1		1		
Spectrum Health Continuing Care	1	1	1				1	1
Special Tree Rehabilitation	1		17	5			17	
TOTAL	**18**	**16**	**78**	**22**	**12**	**4**	**82**	**1**
National Totals		49	330	145	51	115	333	5
Michigan Percentage of National Total		**33%**	**24%**	**15%**	**24%**	**3%**	**25%**	**20%**

N:PermenantDocuments/Resources/CARF/Ricks Michigan CARF List04302010

ATTACHMENT 2—STATE OF MICHIGAN MAPS IDENTIFYING CARF ACCREDITED PROVIDERS

Google maps



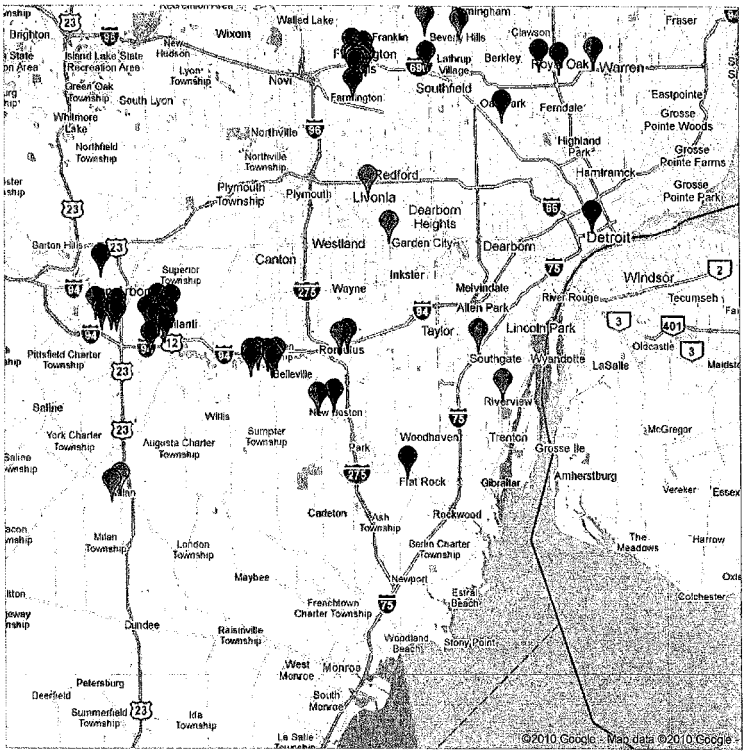
Michigan CARF Brain Injury Rehab Providers
0 views - Public
Created on Apr 30 - Updated < 1 minute ago
By veterans
Rate this map - Write a comment

Borgess Med Center Hospital

4/30/2010 2:21 PM

Google maps

Get Google Maps on your phone
Text the word "GMAPS" to 466453



Michigan CARF Brain Injury Rehab Providers
0 views - Public
Created on Apr 30 - Updated < 1 minute ago
By veterans
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4/30/2010 2:22 PM

RESPONSE TO POST-HEARING QUESTIONS SUBMITTED BY SENATOR DANIEL K. AKAKA TO MICHAEL F. DABBS, PRESIDENT, BRAIN INJURY ASSOCIATION OF MICHIGAN

Question 1. You stated that you have concerns with the current TBI screening tool. Concerns have also been expressed about the clinical validity of this tool. Please specifically identify your reservations in addition to possible ways to improve the tool.

Response. I do not have expert knowledge or training regarding TBI screening tools for me to be able to provide specific concerns or more importantly about how it can be improved. However, let me share these observations regarding the current tool (I am referring to the VA's TBI Pre-screening Tool—four questions evaluation tool). First, it does not require much experience or knowledge to recognize that these limited and broad questions are inadequate at best. These questions would appear to disproportionately identify the number of soldiers, which may lead to unnecessarily overloading the medical systems of the DOD and VA.

Second, though it may not be intended by the military command, we have heard many anecdotal comments from soldiers who believed responding affirmatively to

any of the questions on this tool would jeopardize their career. I have no potential solutions regarding this; however, this may be one of the most difficult and pressing issues requiring attention.

Third, it is puzzling as to why this tool was developed when there has been a great deal of research into various concussion tools. I certainly do not know all of the details in the development of this tool and at this point it is meaningless to discuss; other than to realize that in the future, greater effort should be made to seek out and use the state-of-the-art resources available and expend the effort to improve them.

Fourth, as directed by the 2008 National Defense Authorization Act for pre and post-deployment testing, as well as in the combat theater testing, this directive does not appear to have been applied, or at least not fully to National Guard soldiers—as indicated by experiences in Michigan. This would create problems for soldiers, whose brain injury is not addressed as quickly as possible that could lead to problems with their family, holding a job, substance abuse and others. Additionally, it further exacerbates issues with the soldier that the VA must contend with.

Question 2. Cooperation with the private sector is important to expand access to care. However, veterans are a unique population. What steps has your organization, or other private entities with which you may be familiar, taken to become more "culturally literate" with respect to servicemembers and veterans?

Response. In the first sentence, it is stated that "Cooperation with the private sector is important * * *" with which I totally agree. Unfortunately, as I indicated in my testimony this has not been borne out by execution of this policy. Michigan's wealth of TBI rehabilitation continuum of care services has not been effectively used despite the relationships we have established with VISN–11 and the four VA medical centers. Furthermore, I believe in the testimony that I witnessed at the hearing that indicated that the VA was going to have a pilot of less than 12 veterans using services is an embarrassment. Such a limited number when compared to the thousands requiring services should be seen as unacceptable. In my judgment, if there were 12 sent to Michigan rehab facilities, I would see it as unacceptable. Furthermore, why is it that a pilot is only now being done—nearly 10 years since the start of the conflict?

The poly-trauma system that was created, I believe was an excellent, well-conceived approach to dealing with brain injuries and other trauma. What has not been dealt with effectively is the long-term rehabilitative care necessary. Appointments at a VA Medical Center every couple of months (or even longer) is woefully inadequate to providing cognitive rehabilitation. Again, let me urge that the over 35 year history of brain injury rehabilitation and expansive network of care in Michigan be utilized, to demonstrate what can be done in assisting a soldier recover.

In regards to our Association's being "cultural literate" it is for this very reason why Richard Briggs, Major, USAF (Retired) was hired. As a former U.S. Army Captain, I was keenly aware of the need to hire an individual with a military background to work on this issue. It was clear to me that the individual managing the Association's efforts with veterans must understand the chain of command, military terminology, and be able to relate to those in the military.

Unfortunately as mentioned above, there has been nearly no interaction with other private facilities by the VA in the State of Michigan; thus, the military literacy issue has not been an issue to date. However, we completely agree that this will be a key component in the development of any relationships. We pledge our efforts to ensure that any such facility receives training about the military culture to ensure they can provide effective rehabilitation.

Finally, Major Briggs has worked with numerous public and private entities on recreational activities for soldiers. As part of those efforts, Major Briggs has ensured that there is an understanding and respect for the military culture, which has won him many words of praise from participants. Most notable was a comment following a recent fishing event from a Viet Nam era veteran who commented that seeing all of the American and Service flags flying along the pier, as well as people cheering and waving made him feel that for the first time since he returned from Viet Nam, he was finally welcomed home!

Question 3. Does your organization, or others with which you are familiar, use tele-health technologies to provide care and services to individuals with TBI?

Response. Our Association has not utilized nor has there been a need for telehealth technologies. However, because of comments we have received from many of the soldiers who desire support but do not wish that support to be in a typical support group environment, we will be introducing in the third quarter of the calendar year a telephonic support group. This will enable a veteran to remain in their home (without the need to travel) and know that at a prescribed time they can meet with

other veterans via phone (possibly video in the future) to receive support and provide support.

Included with my response, I am including an outline of the TBI Resource Optimization Center's Brain Injury Navigator, which is being piloted at the current time. As shown, the purpose is to assist a soldier or their family with identifying needed services in or near where they live.

CONCLUSION

Once again, I deeply appreciate the opportunity to address the U.S. Senate Committee on Veterans Affairs and to respond to these questions. Senator Akaka asked a very significant question during the Question and Answer period at the Hearing, which I did not feel I responded to in an adequate manner. In essence, the question was, is the VA doing a more effective job treating brain injury today than they were two or three years ago. In considering this question during the past few weeks, I would respond that Congress has enacted cutting edge laws and guidance to address the needs of veterans with a Traumatic Brain Injury. Thus, there has been an effort made to improve care—or, said another way, when there was effectively nothing to begin with, anything is better.

However, the execution of these laws and policies remains less than adequate and therein is the problem that is creating the distrust, mistrust and futility being experienced by many veterans. The VA so jealously guards its Congressional mandated responsibility to care for our veterans; however, the sheer numbers of veterans and the limited number of VA medical facilities simply prohibit the VA from being able to carry out this responsibility properly or fully. I do not believe that adequate funds can be appropriated to the VA to build the needed facilities, staff them and operate them. Furthermore, it is highly unlikely there can ever be sufficient facilities so as to make them convenient to where veterans live. Thus, a new paradigm must be used—namely contracting with private providers and the VA effectively monitoring the delivery of care.

Finally, allow me to reiterate my comment pertaining to TRICARE and its rules, which effectively sets up the VA to not be as effective as it could be in treating a veteran with a brain injury. It is my understanding that TRICARE currently operates using Medicare rules. Medicare rules do not address cognitive rehabilitation or long-term rehabilitative care and yet this is the essence to the continuum of care needs of the veteran. Because cognitive rehabilitation is not provided immediately following the time of injury, once the soldier leaves the active military and must use the VA system, significant time has elapsed. This dramatically decreases the opportunity for the soldier to recover skills both cognitively and emotionally that may have been impaired by their Traumatic Brain Injury.

Changing the Medicare Rules to expand coverage to cognitive rehabilitation could be one of the quickest and most effective changes to providing comprehensive brain injury rehabilitation to soldiers, which would give them a greater opportunity to return to the quality of life they enjoyed prior to their military duty. I believe it would also lessen the demands for brain injury rehabilitation on the VA system.

Enclosure: TBI-ROC Brain Injury Navigator

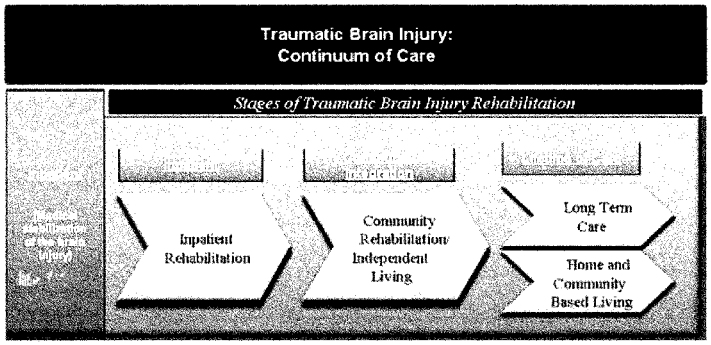
ENCLOSURE—TBI-ROC BRAIN INJURY NAVIGATOR

TBI-ROC

TRAUMATIC BRAIN INJURY RESOURCE OPTIMIZATION CENTER

The Brain Injury Navigator

The Brain Injury Navigator (BIN) is a one-stop, first of its kind web-based resource for persons with traumatic brain injury across the lifespan and their family members, caregivers, and providers. It provides individually tailored geographic service information-based reports based on queries of its clearinghouse, comprehensive database, and use of Internet search engines. It empowers the individual with a TBI and the family by educating them on the impact of a brain injury and the importance of the continuum of rehabilitation services, locating brain injury services according to individual and family need, and facilitating long term rehabilitation planning and the coordination of care.



The need for the BIN arises from the complex health and social repercussions of TBI on the people who suffer from it; their need for sustained, multidimensional treatment and services; and the challenges they face navigating an often-fragmented service system. At least 3.17 million Americans live with TBI, with 1.4 million new cases diagnosed each year[1]. Direct medical costs and indirect costs (e.g., lost productivity) for TBI are estimated at $60 billion per year[2]. Confounding this major public health issue is the common failure of rehabilitation systems across the country in meeting the needs of persons affected by TBI that can lead

[1]Brain Injury Association of America. (2008). About brain injury. Retrieved December 17, 2009, from **http://www.biausa.org/aboutbi.htm**

[2]Finkelstein, E., Corso, P., & Miller T. (2006). The incidence and economic burden of injuries in the United States. New York: Oxford University Press.

to avoidable regression in health and social outcomes. In 2006, the Institute of Medicine reported that, "...many people with TBI experience persistent, lifelong disabilities. For these individuals, and their caregivers, finding needed services is, far too often, an overwhelming logistical, financial, and psychological challenge. Individuals with TBI-related disabilities, their family members, and caregivers report substantial problems in getting basic services, including housing, vocational services, neurobehavioral services, transportation, and respite for caregivers. Yet efforts to address these issues are stymied by inadequate data systems, insufficient resources, and lack of coordination. TBI services are rarely coordinated across programs except in some service sites. Furthermore, in most states, there is no single entry point into TBI systems of care[3]." The BIN is designed specifically to help mitigate these challenges, support successful interactions between individuals affected by TBI and health and human service systems, and lead to enhanced health and social outcomes.

There is no national-based resource tool that identifies brain injury service options according to need/rehabilitation stage, service accreditation/certification, evidence-based/promising practice(s), and supports case/care management to facilitate the individual's service selection process.

Structure of the BIN

The Brain Injury Navigator consists of six components: Service Locator, Education, Evidence-Based/Promising Practices, Payer Sources, e-Helpdesk, and Electronic Care Coordinator (ECC), and e-Helpdesk. A continuous quality improvement (CQI) process including specified performance measures supports the BIN's content and currency.

- The *Service Locator* provides a unique set of functions to provide the individual, family member, caregiver, and provider with a complete list of continuously updated relevant services, along with comprehensive details of each service along the rehabilitation continuum.
- The *Education* component is a set of tools to educate BIN users on understanding the structure and content of the Service Locator including:
  - Continuum of care
  - Service "taxonomy"
  - Evidence-based/promising practices
  - Healthcare benefits and coverage (including mental health and substance abuse)
  - TBI supporting laws and regulations
  - BIN utilization
- The *Evidence-Based/Promising Practices* component provides a comprehensive set of TBI related EBP's according to rehabilitation stage and service type with explanation of how these practices are defined, collected and incorporated into the Service Locator.
- The *Payer Sources* component provides a comprehensive list of public and private payers by payer type. Users can access general information and guides to understand various states' payer policies and coverage. This component provides links to payer resources with specific information.
- The *e-Helpdesk* component provides a supplemental information resource for users who cannot understand or find needed information on the BIN. Users can submit questions and obtain answers via phone, live chat, or email. Phone support is available from 8 a.m. to 6 p.m. EST, Monday through Friday.
- The *Electronic Care Coordinator (ECC)* component provides the BIN user with a personally controlled continuous account of service, education, and evidence-based practice information gathered by the user and automatically updated.

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[3]North America Brain Injury Society (2008). Barriers and Recommendations: Addressing the challenge of brain injury in America. Retrieved December 28, 2009, from **http://www.nabis.org/files/Barriers-Recommendations-2008.pdf**

Continuous Quality Improvement (CQI): Specified improvement performance measures support the evaluation and refinement of each BIN component listed above. Critical features of this CQI evaluation methodology are: Clear client communications protocols and reporting mechanisms for constant coordination and responsive problem solving; flexibility that allows for taking advantage of evolving technologies and user feedback; and addressing the complex labor requirements involved in development, implementation, monitoring, and management of the BIN. The measures generate data that assesses quality of information and appropriate staff expertise for each of the BIN components.

BIN Component Development

Completed activities of each ready to launch BIN component are:

- *Service Locator:* Designed, developed, beta tested, and refined the first version of the Service Locator coupled with a targeted promotion campaign for users (i.e. persons with TBI, their families, and providers) for the states of Michigan, Massachusetts and Maryland.
- *Education:* Designed, developed, and refined generic and stakeholder specific education tools per the above explained Education component.
- *Evidence-Based/Promising Practices:* In partnership with Boston University's Sargent College, we are conducting a literature review to collect accepted evidence-based/ best practices,
- *Service Definitions:* In partnership with George Washington University, we have convened a Subject Matter Expert (SME) group to define service criteria for all services per each component of the rehabilitation continuum.
- *Payer Sources:* Provide, in multiple formats, a consolidated list of public and private payer sources for the states of Michigan, Massachusetts and Maryland, definitions of TBI, information about basic eligibility and coverage, and other pertinent state-based information. A formal review occurs every 4 months to ensure payer data is current.
- *e-Helpdesk:* Staff an information specialist who is knowledgeable and sensitive to user needs. This specialist will ensure currency and overall quality by channeling questions and concerns of users through the BIN CQI process that is the mechanism for updating and improving the BIN. A primary reference for the specialist will be an e-Helpdesk knowledge base that integrates information on TBI and services from the BIN's Education component and other authoritative sources that provide approved language for responding to common inquiries. It will include an inquiry tracking system that records information on types of users, inquiries, and responses provided.
- *Electronic Care Coordinator (ECC):* The ECC is based existing models currently being researched, piloted and refined, and prepared for integration into the BIN.

The BIN's design, implementation and management are under the auspices of JBS International, Inc. through the Traumatic Brain Injury-Resource Optimization Center (TBI-ROC). The TBI-ROC addresses the fragmentation and service gaps in the nation's Brain Injury Rehabilitation Continuum and the BIN's CQI process through its Advisory Group, a permanent body of interdisciplinary experts.

Eileen Elias
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Phone: 301.495.1080 • *Email:* e-TBIROC@jbsinternational.com
www.jbsinternational.com

Chairman AKAKA. Thank you very much, Mr. Dabbs. And now we will receive the statement of Dr. LaPlaca.

STATEMENT OF MICHELLE C. LAPLACA, PH.D., ASSOCIATE PROFESSOR, WALLACE H. COULTER DEPARTMENT OF BIOMEDICAL ENGINEERING, GEORGIA INSTITUTE OF TECHNOLOGY AND EMORY UNIVERSITY, INSTITUTE OF BIOENGINEERING AND BIOSCIENCE, LABORATORY OF NEUROENGINEERING, ATLANTA, GA

Ms. LAPLACA. Good morning, and thank you, Mr. Chairman and the Committee, for the opportunity to share my thoughts and experience from a professor and a researcher's point of view on the current state of Traumatic Brain Injury research, diagnosis, and treatment.

We have heard a lot about transitioning between DOD and Veterans Affiars. What I am going to be discussing is a transition that occurs before then in terms of getting the latest research into the clinic and to our warfighters and our veterans in a timely manner.

My primary research interests, as Senator Isakson pointed out, are in Traumatic Brain Injury. I studied biomechanics as well as acute mechanisms and different treatments.

I first became interested in the brain when I took a research assistant position at Walter Reed Army Institute of Research as a sophomore in college. The complexity of the brain is what intrigued me then and what still drives my enthusiasm today over 20 years later. Since that time, we have passed what NIH termed the "Decade of the Brain," entered a new century and several military conflicts which have exposed new war-related health care issues.

The advent of new protective materials, as has been noted, has improved survivability, and that is a wonderful thing. I commend the biomaterials and the engineer folks who developed those protective mechanisms. But they have left us with more injured warfighters and more disabled veterans than ever before to care for. So I will highlight some of the advances, some of which have already been noted. I will be brief.

Collectively, TBI researchers—and that is in military labs as well as academic labs—have uncovered numerous cell pathways over the past few decades that lead to cell damage. Cells can be compromised in different ways. They can be injured from both what we are calling a traditional brain injury—a contusion—and from a blast. In both cases, the brain tissue itself undergoes deformation, although blasts produce that deformation at a much higher frequency. We need to learn what we can from existing models of brain injury because they do tell us things that blast injury models have yet to uncover.

We have refocused attention on damaged receptors, membranes, and white matter, all of which affect cell communication and lead to ultimate disabled function.

Inflammation, vascular damage, and edema are all events that have multiple components to them and are being revisited by scientists. How exactly these are related to each other and how they can be targeted for therapeutic intervention, however, is still not well understood.

Genomics and proteomics—techniques where large numbers of genes and proteins can be screened—offer an enormous opportunity, also an enormous amount of information that must be analyzed using very sophisticated models. A repository of both experi-

mental and clinical data would provide data sets to researchers to drive validation studies and generate new directions of research and potential treatments.

As of today, we have no FDA-approved treatments for TBI itself. Most clinical interventions will stabilize symptoms, such as reducing intracranial pressure, and then the warfighter, the TBI patient goes on to rehabilitation and post-care. Some of the reasons for that are divided into four broad categories.

One, the heterogeneity. No two Traumatic Brain Injuries are alike. We heard about polytrauma that is now being appreciated. We do not model polytrauma in the lab. This is a huge gap in research.

Variables like age, underlying health, genetic make-up, and environment factors all affect injury outcome. One size does not fit all in terms of treatment or rehabilitation, and personalized care must be sought.

Complexity is the number 2 reason for no treatments. Injury mechanisms are poorly understood and leave the question as when to intervene and how to intervene. Combination therapies are likely.

Diagnosis is different and crude due to the heterogeneity and the complexity I just discussed, as well as the clinical classification systems. New diagnostic tools such as biomarkers and imaging must be worked into this classification system. There are poor clinical translation avenues. Most of the clinical trials are funded by industry; most researchers do not know how to translate their successful results. Clinical trials must be done on sound science, yet many of the successful experimental results are never tested in the pre-clinical setting.

Last, some of the challenges that were faced as a result of this: continued and increased collaboration between academic, medical, and military training facilities in terms of medical care, TBI awareness and treatment strategies; programs that fund pre-clinical experiments; better diagnostic and uniform registries across the country. These need to be developed in parallel with point-of-care technologies and diagnostics.

More coordination is needed between basic and clinical research. One of the most underutilized laboratories is the clinic itself. Systems engineering and informatics approach to handle the vast amounts of data will be needed to implement and decipher all of these complex data sets. And continued dissemination of findings and dialog among educators and the clinic and the VA is required.

Clinical trials must be fast-tracked and have uniform injury management guidelines, as well as deal with HIPAA and IRB compliance. These are major hurdles in the current system.

So, in closing, the fields of neurotrauma and trauma medicine are at a very exciting crossroads, and I thank the Committee for providing me the opportunity to share my thoughts on this.

[The prepared statement of Ms. LaPlaca follows:]

PREPARED STATEMENT OF MICHELLE C. LAPLACA, PH.D., ASSOCIATE PROFESSOR, WALLACE H. COULTER DEPARTMENT OF BIOMEDICAL ENGINEERING, GEORGIA INSTITUTE OF TECHNOLOGY AND EMORY UNIVERSITY, INSTITUTE OF BIOENGINEERING AND BIOSCIENCE, LABORATORY OF NEUROENGINEERING

Mr. Chairman, Mr. Ranking Member, and Members of the Committee: I appreciate the opportunity to appear today to discuss the Department of Veterans' Affairs (VA) efforts to address the progress in Traumatic Brain Injury research, diagnosis, and treatment as it relates to academia-VA collaborations and ultimate clinical implementation.

PROGRESS THAT HAS BEEN MADE IN UNDERSTANDING, DIAGNOSING, AND TREATING TRAUMATIC BRAIN INJURY (TBI)

The annual incidence of TBI in the US is estimated at 1.5 million, and brain injury remains a major cause of long-term disability or death. Additionally, the yearly economic burden exceeds $60 billion, which does not include the social and emotional toll on patients, families, and the community. The understanding of TBI mechanisms has increased tremendously over the past 30 years, although this progress in scientific findings has not paralleled improvements in diagnosing and treatments for brain injured patients. Scientists have better tools to investigate cellular mechanisms of injury (i.e. what happens to the cells of the brain when they are injured) due to general advancements in genetics, molecular biology and biochemistry. Engineers use computers with much more computing power than previous generations. Working at the micro- and nano-levels, while unimaginable 20 years ago, is becoming commonplace at top research universities. Imaging techniques and processing capabilities has advanced quite rapidly, however, most hospitals do not have access to trained personnel, even IF they can afford the imaging equipment. These are just a few examples underlying improvements in TBI research and treatment.

Understanding TBI

The devastating events that surround a TBI are associated not only with the physical deformation of the brain, but also with secondary complications (such as inflammation, altered cellular signaling, and changes in gene expression—all of which affect cell function, organ function, and overall functional ability of the wounded). It is worthy to note that the high incidence of blast-related brain injuries in recent and ongoing US military operations has caused engineers and scientists to reconsider some of the animal models being used to study blast injury versus injury types that commonly occur in the US civilian population. Specifically, blast injuries occur at a much higher frequency than even motor vehicle accidents. The questions remain as to whether we can treat the basic mechanisms, learned over the past several decades, as the same in both populations. In addition, the competition among researchers—academic and military alike—in developing these models has been overwhelming and very unlike the advent of animal models developed in the 1980's and 1990's for concussive and diffuse brain injury.

In both humans and animal models, complications that result from the primary insult (blast, head acceleration, or impact) can lead to cell death and progressive neurodegeneration, accompanied by prolonged or permanent loss of sensory, motor, and/or cognitive function. In order to understand the physical tolerance of neurons to traumatic insults, engineers and neuroscientists have attempted to reproduce the biomechanical environment during a traumatic event using cell, animal, and computer modeling. This approach allows one to begin to unravel the underlying injury mechanisms that lead to cell dysfunction and death as a function of input physics. To date, several cellular events have been identified that contribute to damage, such as cell membrane damage, imbalance of ions, abnormal release and deployment of normally controlled molecules, neurotransmitters, hormones, and enzymes. However, how these events relate to each other and how they can be targeted for therapeutic intervention are not well understood.

Diagnosing TBI

In October, 2007, the National Institute of NeurologicalDisorders and Stroke, with support from the Brain Injury Association of America, the Defense and Veterans Brain Injury Center, and the National Institute of Disability and Rehabilitation Research, convened a workshop to outline the steps needed to develop a reliable, efficient and valid classification system for TBI that could be used to link specific patterns of brain and neurovascular injury with appropriate therapeutic interventions. The primary system is the Glascow coma scale, as well as injury type, injury severity, pathoanatomy, and pathophysiology. It was agreed that compliant data sharing,

uniform diagnostic criteria, and sophisticated modeling (prognostic modeling, informatics-based analyses, and more personalized diagnostics) are reasonable approaches to better stratifying patients. Success of the proposed changes, however, will require large center trials, integration of systems informatics to the neurotrauma field, and cooperation between academic and VA researchers.

On the advent of diagnostic techniques are biomarkers. Biomarkers are substances released in to the blood stream at high levels that may be associated with a particular type of lesion/region affected. The process is analogous to the blood tests given to help diagnosis heart attack severity.

Treating TBI—Current Clinical Therapies

Unfortunately, the current clinical treatments for TBI are very limited. Emergency care primarily addresses the acute physiological responses (e.g., controlling elevations in intracranial pressure and cerebral perfusion pressure) and long-term therapies are largely palliative measures. A large number of pharmacological therapies have gone to clinical trials for TBI; however, such treatments either focus on a single signaling cascade or the target spectrum has collateral detrimental effects systemically and have failed in clinical trials. As there are currently no FDA-approved therapeutic interventions for the treatment of TBI, developing efficacious treatment strategies remains an important research priority. TBI initiates an abundant number of highly complex molecular signaling pathways; thus, a multifaceted therapy is required to attenuate the degenerating injury environment. Other current clinical trials include therapies aimed at hindering the inflammatory response and provide neuroprotective effects, such as acute hypothermia (Adelson et al. 2005; Davies 2005), and early administration of erythropoietin (Grasso et al. 2007), progesterone (Wright et al. 2005), and citicoline (Calatayud Maldonado et al. 1991). Moreover, clinical trials are also evaluating pharmaceutical therapies for post-TBI behavioral issues, such as depression, irritation, and aggression. Sertraline, a selective serotonin reuptake inhibitor, is one example of this treatment that addresses behavioral disorders that persist after a TBI (Fann et al. 2001; Zafonte et al. 2002). Each of these treatment modalities target specific events that occur after injury. Indeed, recent clinical advances using combination therapy, such as Highly Active Antiretroviral Therapy (HAART) to treat AIDS or in metastatic breast cancer, lend credence to this approach. Combination therapies for TBI is a relatively new approach only recently gaining acceptance. Their discovery may significantly shift clinical practice to target the underlying pathology rather than relying on surgical or symptomatic (i.e. intracranial pressure) management.

Given the complex and dynamic injury environment and interactions among secondary injury mechanisms, it is likely, if not required, that multiple agents will be needed to provide neuroprotection after TBI. Neuroprotection refers to the ability to SAVE cells. Repair and regeneration cannot provide their maximal benefit if the environment of the injured brain is not stabilized and receptive to regeneration. However, testing drug combinations is challenging given the combinatorial explosion of formulations. A traditional study may choose to test only two drugs, but such a strategy could easily miss more effective combinations and is essentially a fishing-expedition in a very tiny bucket. As an alternative, we have proposes a highly systematic, rigorous statistical approach to sample from a larger pool of literature-based candidates, whereby providing predictive capability for evaluation in vivo, streamlining the route to pre-clinical and clinical trials. The following categories of secondary damage have been selected, based on a wide literature search: 1) acute damage and excitotoxicity, 2) free radical damage and compromised energetics, and 3) inflammation. This is an example of a research approach that will operate out of the box and will hopefully be an example for others to follow on the path to translational discovery in neurotrauma. For example, novel combinations of FDA-approved drugs may be discovered, which could be fast-tracked into the clinic. These results will require non-biased dissemination, as well as a robust analysis platform.

Summarizing some of the top reasons why we don't have more options to treat TBI highlights the complexity faced and underlines the need for more cooperation and collaboration:

1) Heterogeneity of injuries between patients and within the brain means that one size will not fit all patients in terms of treatment or rehabilitation;

2) Injury mechanisms are poorly understood, due to the complexity of the brain microenvironment;

3) TBI changes over time (primary versus secondary mechanisms; propensity to sudden onset neurodegenerative disease; complication with aging and other health issues), leaving the question as to when to intervene and how often;

4) Polytrauma, or trauma to many bodily systems (physiological and psychological), is commonplace, but not well studied, complicating research findings, diagnosis and treatment

5) The classification system (GCS and experimental) and the diagnosis systems are variable and crude;

6) No effective treatments exist clinically and we (all researchers and clinicians) need better avenues for collaboration and clinical translation;

7) It is unclear what are the right treatment target(s) to focus on? For example, is it neuroprotection versus repair versus regeneration versus replacement?

EXPERIENCE IN COLLABORATING WITH VA ON TBI RESEARCH AND IMPLEMENTATION OF RESEARCH FINDINGS

I have limited experience collaborating with the VA in Atlanta. The Atlanta VAMC Rehabilitation R&D Center of Excellence has recently undergone some restructuring and this will prompt reorganization and/or priorities shifting. The investigator and clinical staff have been extremely supportive and encouraging in navigating the system in order to find the right collaborators and passing along funding opportunities. I plan to submit to the fall cycle and in parallel seek a partial appointment at the VA. In addition to these plans, the Veterans' Innovation Center (VIC) (www.hinri.com) is an excellent example of local enthusiasm and timeliness. I commend Senator Isakson for his support of this initiative.

My impression is that the VA scientists are eager to collaborate with academic institutions and vis versa. There are several issues that hinder this process. The VA has a highly specialized and secured computer network. Virtual, secure data rooms may be a solution to the difficulty in communication and data sharing. There are different types of bureaucracy, but each is poorly understood by the other party.

Federal money for TBI research seems to be in silos, making cross-institutional and cross-agency collaboration difficult. It is my perception that TBI research finding within the Department of Defense is not shared with non-military institutions and vis versa, unless published in the public domain. The notion that upper-level review committees will match qualified grant applicants to appropriate researchers within military research institutions is nice in theory, but the most successful collaborations come from the ground up, not top-down. Conferences and other venues for data sharing need to include both civilian and military research sharing. Without this, the relationships will not develop and the collaboration success will move at a snail's pace.

CHALLENGES OF THE FUTURE

Below are a summary of challenges that face researchers and clinicians, together with suggestions for improvement:

1) Cooperation between academic, medical, and military training facilities in terms of TBI awareness and care;

2) Better diagnostics—biomarkers—imaging—uniform registries across Level 1 Trauma Centers;

3) Platforms for deploying small, inexpensive diagnostic "kits" to smaller hospitals and portable/temporary medical units—i.e. no large equipment, easy steps, stable at a range of environment conditions;

4) Many more and uniformed programs to filter research findings in an unbiased manner. In other words, beyond open access journals, the mere volume of scientific papers published limits investigators. Government databases with secure access that are professional designed to maximize dissemination and interpretation of published work;

5) Programs that encourage and fund pre-clinical experiments with large numbers of interventions (pharmaceuticals, biologics) and in combinations that provide widespread screening, rather that narrow investigations that don't take into consideration the complexity of TBI;

6) Cross-agency collaborative funding mechanisms designed for data sharing, uniform financial and administrative responsibility, and shared resources;

7) Proactive involvement of informatics and information science to consolidate and analyze large and diverse data sets from basic lab studies to pre-clinical studies to clinical trials. The advent of traumanomics—to follow along with the "—omic" nomenclature adopted in the 21st Century—is relatively new, but yet few investigators understand or appreciate the necessity to use unbiased statistical and multilevel modeling. Freely providing data to such "number crunching" efforts goes against the culture of publications;

8) Open dissemination of findings, including unpublished data and protocols;

9) Open dialog among educators, policymakers, clinical leadership, and research directors.

In closing, the fields of neurotrauma and trauma medicine are at a very exciting crossroads. We have learned so much about injury mechanisms and are beginning to appreciate the complexity and wide variety of pathologies associated with TBI. Successful implementation of the findings is possible, providing cooperation is focused on the patient or warfighter/veteran. I thank the Committee for providing me the opportunity to share my experience and recommendations on TBI with respect to veteran's healthcare.

RESPONSE TO POST-HEARING QUESTIONS SUBMITTED BY HON. DANIEL K. AKAKA TO MICHELLE C. LAPLACA, PH.D., ASSOCIATE PROFESSOR, WALLACE H. COULTER DEPARTMENT OF BIOMEDICAL ENGINEERING, GEORGIA INSTITUTE OF TECHNOLOGY

Question 1. Please elaborate on the long-term effects of adopting combination therapies, in terms of improving treatment and management of TBI.

Response. The long-term effects of adopting combination therapies is unknown, however, this is true of many treatment in clinical practice today. The FDA has a responsibility to enforce regulations for any therapy in which the risks are minimal compared to the potential benefits. Furthermore, even if more than one drug is given (the definition of a combination therapy in the context of the hearing discussion), the effects rely on the target(s), the duration of action, and the interaction with other physiological systems. For example, one drug may act on many targets and may be beneficial, while two drugs—each with a narrow function—may affect two specific targets, and not have the "magnitude" of effects that the single drug has. Therefore, the challenge is similar that that of translating a single drug to market, with the additional burden of dosing for each individual drug and the potential drug interactions at each dose that may affect ultimate function (in other words, a more complex pharmacokinetics analysis).

In the best case, the long-term effects of combination therapies are that overall function is improved and therefore, fewer complications arise, such as continued memory loss. The potential danger is that an acute therapy—whether a single agent or combination—may result in side effects that are detrimental, such as saving cells that are dysfunctional. The reality is somewhere in between these extremes. Many of the drugs that are being considered pre-clinically and clinically are aimed at protecting cells and halting the progression of tissue damage. The premise here is that saving cells in the early period will preserve nerve function within the brain and reduce aberrant nervous system control of systems such as motor, sensory, cardiovascular, renal, etc. The benefit of most drugs under consideration for early intervention is that they are "short-acting", meaning that long-term side effects are unlikely. The "window" of delivery is very important, however, since we want to have available interventions that will be effective past the acute period. It is generally thought that the more delayed a neuroprotective agent is given the less effect it will have (presumably since more cells are dead by then and there are less that need to be "rescued"), but this is a subject that deserves further study. A potential benefit of the "combination approach" is that different drugs or drug combinations could be given at different times, depending on variables such as time since injury, age, other health issues, responsiveness to a particular therapy, and other individual factors. In the case of delayed treatment (days, weeks, months post-injury), a neuroprotective approach may be mute, as cell death, although ongoing, has slowed. Here combinations of drugs that augment residual function and/or encourage regeneration are possible, as is the combination of drug therapy with occupational and other rehabilitative interventions.

In summary, combination therapy is an avenue worthy of investigation, given that TBI is a complex disorder, and it is unlikely that there will be a "magic bullet" that corresponds to a single treatment. Given the complexity of TBI and of the pharmacology involved in combining drugs with different (or overlapping) mechanisms of action, it is necessary to approach the study of such approaches with rational studies and analyses.

See attached article summarizing the combination therapy approach for TBI. Marguiles et al. Combination Therapies for Traumatic Brain Injury: Prospective Considerations *Journal of Neurotrauma*; Vol 26: 925–939, June 2009. (Attachment 1)

Question 2. Is there a benefit to continuing rehabilitation therapy, with the goal of maintaining a current level of functioning, for those with severe TBI for whom no further gains in functioning are expected?

Response. Yes, there may be benefit for continued rehabilitation therapy even is no further gains are expected. As an individual ages, loss of function may become

more pronounced, and therefore a cessation of therapy could cause rapid decline. Even if no gains in functioning are expected, the maintenance of function is crucial for day-to-day living, and will reduce caregiver burden and additional long-term health decline. If those with severe TBI are not mobile and cannot carryout routine hygiene care, however, then continued rehabilitation in a VA hospital or nursing home setting may not benefit the individual. The quality of life should be considered for those who are not on life support, but are still bed- or home-bound. In addition to routine care to avoid infections (e.g., weight shifting, turning to avoid bed ulcers, etc.) and blood clots (e.g., passive leg and trunk movement), other types of therapy should be considered. Sensory stimuli such as touch (e.g., massage, grooming), sound and visual therapy, and companionship can have beneficial effects on psychological states as well as physiological wellness. Home therapies that are simplified version of in-patient rehabilitation warrant study, as there is cost savings for the VA system in both short term patient satisfaction and long-term health costs and needs. And, while the chance for recovery of function declines with age and with time from the original injury, it is not impossible. Intensive early therapy (according to clinical guidelines for appropriate delay from time of injury and rest) should be considered for motor, sensory, and cognitive rehabilitation. An effort to treat the entire TBI patient and not just the symptom(s), throughout a person's life, will be the most beneficial approach.

See attached article for opinion about therapies for TBI. There is a section about the use of rehabilitation as a treatment (p. 15, section 7.7). Xiong et al. Emerging treatments for Traumatic Brain Injury. *Expert Opin Emerg Drugs.*; Vol 14 (issue 1): 67–84, March 2009. (Attachment 2)

Question 3. In her testimony, Mrs. Bohlinger discussed the importance of brain imaging to improve the accuracy of TBI screening. From your perspective, what new imaging technologies are being developed or should be adopted by VA?

Response. Brain imaging advances have been made in the past decade that can contribute to TBI screening, diagnosis, and outcome monitoring. Although brain imaging is beyond my area of expertise, I am aware that diffusion tensor imaging (or DTI) is an improvement over other methods in detecting edema as well as some structural defects. I believe that in the current form, DTI (or other imaging techniques) will be best used for diagnosis and outcome monitoring, not screening per se. It is currently too expensive for screening and the availability is limited. Following further evaluation and validation of imaging as an effective diagnostic tool, portable versions should be further developed and deployed in the military and to facilities that do not have the space or money to install large imaging equipment. The rationale is that something is better than nothing, but that the utility of imaging, either alone or with other diagnostic tools, has to be systemically and rigorously tested. It is my understanding that many facilities have expensive imaging equipment, but do not have trained personnel. There is a danger in non-experts interpreting clinical imaging scans. Therefore, a large need exists for more training, as well as standardized protocols before imaging can be routinely used on a widespread basis. There are several centers across the country that have the expertise in TBI imaging (for example, UCLA, Univ. Pennsylvania, among others). Standard of care in Level 1 Trauma Centers should be established, followed by training in other Centers with existing equipment. See the attached article for further comments on the classification of TBI, which include imaging as a potential future tool.

See the attached review article for more about the future of imaging (and other issues) for TBI. Saatman et al., Classification of Traumatic Brain Injury for Targeted Therapies. *Journal of Neurotrauma* Vol 25, p. 719–738, July 2008. (Attachment 3)

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Combination Therapies for Traumatic Brain Injury: Prospective Considerations

Susan Margulies,[1] Ramona Hicks,[2] and The Combination Therapies for Traumatic Brain Injury Workshop Leaders*

Many of life's failures are people who did not realize how close they were to success when they gave up.
—Thomas A. Edison (1847–1931)

Abstract

Traumatic brain injury (TBI) initiates a cascade of numerous pathophysiological events that evolve over time. Despite the complexity of TBI, research aimed at therapy development has almost exclusively focused on single therapies, all of which have failed in multicenter clinical trials. Therefore, in February 2008 the National Institute of Neurological Disorders and Stroke, with support from the National Institute of Child Health and Development, the National Heart, Lung, and Blood Institute, and the Department of Veterans Affairs, convened a workshop to discuss the opportunities and challenges of testing combination therapies for TBI. Workshop participants included clinicians and scientists from a variety of disciplines, institutions, and agencies. The objectives of the workshop were to: (1) identify the most promising combinations of therapies for TBI; (2) identify challenges of testing combination therapies in clinical and pre-clinical studies; and (3) propose research methodologies and study designs to overcome these challenges. Several promising combination therapies were discussed, but no one combination was identified as being the most promising. Rather, the general recommendation was to combine agents with complementary targets and effects (e.g., mechanisms and time-points), rather than focusing on a single target with multiple agents. In addition, it was recommended that clinical management guidelines be carefully considered when designing pre-clinical studies for therapeutic development. To overcome the challenges of testing combination therapies it was recommended that statisticians and the U.S. Food and Drug Administration be included in early discussions of experimental design. Furthermore, it was agreed that an efficient and validated screening platform for candidate therapeutics, sensitive and clinically relevant biomarkers and outcome measures, and standardization and data sharing across centers would greatly facilitate the development of successful combination therapies for TBI. Overall there was great enthusiasm for working collaboratively to act on these recommendations.

Key words: clinical trials; head injury; injury mechanisms; intervention; *in-vitro* and *in-vivo* models

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Introduction

TRAUMATIC BRAIN INJURY (TBI) is a major medical problem (Centers for Disease Control and Prevention, 2000) for which there are management guidelines, but no Class I evidence supporting any standard therapy (McIntosh et al., 1996; Roberts et al., 1998; Cochrane, 2005; Brain Trauma Foundation, 2007). In recognition of the significant public health impact, as well as the complexity of TBI, the National Institute of Neurological Disorders and Stroke (NINDS), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Child Health and Human Development (NICHD), and the Department of Veteran's Affairs sponsored a workshop on *Combination Therapies for Traumatic Brain Injury* on February 27–28, 2008. The purpose of the workshop was to convene scientists across biomedical disciplines to address the challenges and opportunities associated with selecting and testing combination therapies for TBI neuroprotection. Although the organizers acknowledged the importance of therapies aimed at regeneration and repair processes as well as neuroprotection, the scope of the workshop was limited to the first 72 h after TBI. The objectives of the workshop were to: (1) identify the most promising combinations of therapies based on stages and types of human TBI pathophysiology, and also on potential synergistic and antagonistic effects of the therapies; (2) identify the issues and challenges of testing combination therapies in clinical and pre-clinical studies; and (3) propose research methodologies and study designs to overcome these issues. The following is a summary of the workshop proceedings.

Objective 1: Identifying Promising Combinations

Over the past 30 years considerable research effort has been directed at understanding the secondary injury cascade that is a consequence of the primary mechanical trauma to the head. This research formed a basis for programs directed at the discovery of neuroprotective drugs for the acute treatment of TBI. As a result of these early studies, over 20 late phase II or phase III clinical trials for moderate and/or severe TBI patients were undertaken (Maas, 2007; Narayan et al., 2002). All of the clinically tested therapies failed to achieve the primary end-point of an overall benefit across the full cohort of treated patients compared to those who received the placebo treatment. The lack of success of TBI clinical trials has led scientists and clinicians to identify the probable factors for those failures, including (1) inadequate understanding of secondary injury mechanisms (e.g., translation of therapeutic windows and plasma levels between animals and humans); (2) inadequate pre-clinical testing in multiple injury models, species, ages, and genders; (3) lack of thorough investigation of pharmacokinetics; (4) a heterogeneous patient population; and (5) inadequate functional assessment scales and biomarkers for injury progression and recovery (Faden, 2002; Narayan et al., 2002; Doppenberg et al., 2004; Povlishock and Katz, 2005).

In addition to the factors cited above, the complexity of TBI is another major challenge for developing effective treatments. TBI represents a constellation of primary injury processes, which commonly include contusion, diffuse axonal injury, hematomas, and subarachnoid hemorrhage (SAH) (Adams et al., 1982; Adams et al., 1983; Moppett, 2007; Saatman et al., 2008). The initial injury typically evolves into various secondary injuries such as ischemia, edema, inflammation, and brain herniation (Brain Trauma Foundation, 2007). Often multiple primary and secondary injuries coexist in TBI. However, even in cases in whom trauma appears to result in a single type of injury, numerous cellular and molecular events are initiated within minutes, hours, or days, to mediate cell damage (see Table 1 for details) (Raghupathi, 2004; Povlishock and Katz, 2005; Marklund et al., 2006; Schouten, 2007; Werner and Engelhard, 2007). In addition to the heterogeneity of the injury mechanisms, factors such as age, gender, alcohol/drug use, co-morbidities, polytrauma, and genetics can also influence the effects of an intervention following TBI (Maas et al., 2007). Some of the variability may be reduced through an improved classification system enabling the identification of people most likely to respond to the intervention (Saatman et al., 2008). In any case, the complexity of TBI provides a strong rationale for the use of combination therapies.

Another reason for exploring combination therapies for TBI is the success of this approach for other medical conditions, such as HIV/AIDS (Harrington and Carpenter, 2000; Holtgrave, 2005; May et al., 2006). After presentation of the syndrome of AIDS, HIV was rather quickly characterized, and details of the life cycle of the virus allowed rational development of drug therapy. The initial drugs developed, which inhibit the reverse transcriptase of the virus, demonstrated clear efficacy, but were frustratingly transient in their effects. The development of drugs targeted at multiple parts of the life cycle of the virus led to improvements in the prognosis for patients with HIV, and transformed a fatal disease to one that a large majority of patients can live with for decades (Mitsuyasu, 2002; Yeni et al., 2002; Cotelle, 2006; Salzwedel et al., 2007).

Currently, more than 130 single or monotherapies have demonstrated efficacy in animal models of TBI (Marklund et al., 2006). Ways to potentially increase the efficacy of seven promising single therapies by combining them with other treatments were presented at the workshop. In particular, scientific experts were asked to review what is known about the mechanisms of action of a single therapy on acute TBI pathophysiology, and then propose ways to enhance its neuroprotective and or neuroregenerative actions by using it with therapies that have complimentary, synergistic actions. Summaries of the presentations follow.

Citicoline

Citicoline (cytidine 5′-diphosphocholine or CDP-choline) is a naturally occurring endogenous compound (Kennedy et al., 2003) that may exert acute neuroprotective effects (Adibhatla and Hatcher, 2002), as well as potentiate neurorecovery in chronic TBI and stroke (Cohadon et al., 1982; Levin, 1991; Warach et al., 2000; Secades and Lorenzo, 2006). Citicoline has virtually no side effects, excellent tolerance, and well-described pharmacokinetics, toxicity, and bioavailability profiles (Adibhatla and Hatcher, 2005; Secades and Lorenzo, 2006). Animal data suggest that citicoline works via numerous mechanisms to attenuate neuronal injury after TBI, including increased synthesis of phosphatidylcholine, inhibition of oxidative stress and apoptotic pathways, and activation of pro-survival pathways and cholinergic and dopaminergic neurotransmission. The diversity of citicoline's mechanisms of action and pre-clinical efficiacy data make it an attractive

TABLE 1. INITIATION OF ACUTE SECONDARY EVENTS POST-TBI

Within minutes[a]	*Minutes–24 h*[a]	*24–72 h*[a]
Cell/axon stretching, compaction of neurofilaments, impaired axonal transport, axonal swelling, axonal disconnection	Oxidative damage: Increased reactive oxygen and nitrogen species (lipid peroxidation, protein oxidation, peroxynitrite), reduction in endogenous antioxidants (e.g., glutathione)	Non-ischemic metabolic failure
Disruption of the blood–brain barrier	Ischemia	
Excessive neuronal activity: Glutamate release	Edema: Cytotoxic, vasogenic	
Widespread changes in neurotransmitters: Catecholamines, serotonin, histamine, GABA, acetylcholine	Enzymatic activation: kallikrein-kinins, calpains, caspases, endonucleases, metalloproteinases	
Hemorrhage (heme, iron-mediated toxicity)	Decreased ATP: Changes in brain metabolism (altered glucose utilization and switch to alternative fuels), elevated lactate	
Seizures	Cytoskeleton changes in cell somas and axons	
Physiologic disturbances: Decreased cerebral blood flow, hypotension, hypoxemia, increased intracranial pressure, decreased cerebral perfusion pressure	Widespread changes in gene expression: cell cycle, metabolism, inflammation, receptors, channels and transporters, signal transduction, cytoskeleton, membrane proteins, neuropeptides, growth factors, and proteins involved in transcription/translation	
Increased free radical production	Inflammation: Cytokines, chemokines, cell adhesion molecules, influx of leukocytes, activation of resident macrophages	
Disruption of calcium homeostasis		
Mitochondrial disturbances		

Traumatic brain injury rapidly initiates a series of secondary events that collectively contribute to cell injury and/or repair. These secondary events often create long-term neurological consequences, including cognitive dysfunction. Based primarily upon rodent models of TBI, these early events can generally be divided into three periods, beginning with those that arise within minutes after injury, to those that evolve over the first 24 h, and finally to events that may be more delayed in onset, appearing between 24 and 72 h post-injury.

For further details see Clark et al., 1997; Floyd, 1999; Graham et al., 2000; Graham et al., 2002; Lo et al., 2002; Smith et al., 2003; Raghupathi, 2004; Unterberg et al., 2004; Povlishock and Katz, 2005; Sofroniew, 2005; Thompson et al., 2005; Marklund et al., 2006; Yi and Hazell, 2006; Floyd and Lyeth, 2007; Morganti-Kossmann et al., 2007; Pasternak and Lanier, 2007; Schouten, 2007; Werner and Engelhard, 2007.

[a]Each of these periods reflects only an estimation of the onset of these pathogenic events, as details about their temporal profile and interactions are incompletely understood, but most extend for days post-TBI. Variability in onset and frequency, as well as the duration of these events, is governed in part by the type and magnitude of the injury.

candidate for therapeutic development, and a large multicenter trial for TBI is currently underway. Citicoline has already been used for pre-clinical stroke studies in combination with tPA, urokinase, or MK-801(Hickenbottom and Grotta, 1998). For TBI, citicoline should be combined with treatments that complement its actions on neuronal injury, such as drugs that target axonal injury or have anti-inflammatory actions. Promising potential agents to combine with citicoline include hypertonic saline, statins, progesterone, erythropoietin, and cyclosporine A. Detailed investigations regarding route of administration and brain uptake are needed, as well as mechanistic studies to evaluate the effect of a second treatment on citicoline's therapeutic effects.

Erythropoietin

Erythropoietin (Epo) is a hematopoietic growth factor that is produced in the kidney and in fetal liver. Binding to the Epo receptor (EpoR) controls the terminal maturation of red blood cells (RBCs), stimulating production of RBCs. Epo is approved for clinical use in the treatment of chronic anemia associated with kidney disease, cancer, and HIV. There is increasing interest in the use of Epo in critically ill patients to reduce the need for blood transfusion and its related problems (Corwin et al., 1999; Corwin et al., 2002). A recent large clinical trial suggested that Epo may also reduce mortality in trauma patients (Corwin et al., 2007). EpoR is expressed in the brain and Epo is produced in the brain in response to injury (Digicaylioglu et al., 1995; Juul et al., 1999). Epo administration is neuroprotective in a wide variety of CNS injury models, including trauma. Epo is an attractive candidate for treatment of TBI because it is neuroprotective and enhances recovery, has few side effects, and has a practical therapeutic time window of 6 h (Brines et al., 2000; Cherian et al., 2007). When Epo is given early post-injury, the following neuroprotective mechanisms may play a role: Epo inhibits apoptosis, Epo has anti-inflammatory activity, and Epo reduces cerebral vasospasm and improves cerebral blood flow (CBF) (Brines et al., 2000; Grasso, 2001; Springborg et al., 2002; Chong et al., 2003a; Chong et al., 2003b; Kanagy et al., 2003). Even with delayed Epo administration, the following effects may still be beneficial: Epo enhances neurogenesis and angiogenesis (Marti et al., 2000; Springborg et al., 2002; Wang et al., 2004; Lu et al., 2005), and Epo increases the hematocrit, reducing the need for blood transfusion. The only serious side effect of Epo for the TBI patient population is that Epo increases the risk of deep vein thrombosis (DVT) by twofold (Corwin et al., 2007). However, a subgroup analysis of a large clinical trial revealed that prophylactic heparin administration prevents the increased risk of DVT caused by Epo administration in critically ill patients (Corwin et al., 2007). In developing combination treatments, previous studies have examined potential synergistic effects with Epo. Specifically, investigators found that Epo augments the increase in CBF that is induced

by L-arginine in contused brain after cortical impact injury (Cherian et al., 2007). Second, steroid administration after experimental spinal cord injury reduces the anti-inflammatory effect of Epo (Gorio et al., 2005).

Hypothermia

Hypothermia activates cell survival pathways via ERK signaling (Atkins et al., 2007), and attenuates many of the neurological sequelae of TBI, including altered brain metabolism (Vink et al., 1987; Kaibara et al., 1999), tissue loss (Bramlett et al., 1997), axonal damage (Koizumi and Povlishock, 1998), microvascular dysfunction (Smith and Hall, 1996; Suehiro et al., 2003), edema (Mansfield et al., 1996; Sahuquillo and Vilalta, 2007), and behavioral abnormalities (Clifton et al., 1991; Bramlett et al., 1997). These positive effects generated enthusiasm and support for two Phase III trials of hypothermia for TBI, one for adult and one for pediatric populations. However, important questions remain regarding the optimal temperature, treatment period, and therapeutic window for maximizing neuroprotection and minimizing systemic complications (Brain Trauma Foundation, 2007; Peterson et al., 2008). Recent evidence also suggests that hypothermia constitutes a beneficial platform for the subsequent use of additional therapies. For example, post-traumatic hypothermia significantly extended the therapeutic window of oxygen radical scavengers (Baranova et al., 2008), and their combined use also had additive effects on vascular protection. While the mechanisms are unclear, one possibility is that hypothermia provided this enhanced protective effect via its reduction of brain metabolism and drug degradation/clearance (Tortorici et al., 2007), However, while evidence suggests that hypothermia may extend the therapeutic window of other interventions, it may also slow the pharmacokinetic and pharmacodynamic properties of them as well.

Progesterone

Progesterone, while best known for its effects on the female reproductive system, also has abundant receptors in the CNS of males and females (Camacho-Arroyo et al., 1994; Camacho-Arroyo et al., 1996; Genazzani et al., 1996), and has long been known to influence neuronal differentiation during fetal development. Progesterone is a pleiotropic drug that has been shown to (1) protect and reconstitute the blood–brain barrier, (2) reduce cerebral edema through decreasing vasogenic and cytotoxic edema and modulating brain water regulation via aquaporin channels, (3) downregulate the inflammatory cascade and pro-inflammatory cytokines in response to neurotrauma, (4) reduce free radicals and lipid peroxidation, and (5) decrease apoptosis (Camacho-Arroyo et al., 1994; Camacho-Arroyo et al., 1996; Genazzani et al., 1996; Limmroth et al., 1996; Reddy and Kulkarni, 1996; Baulieu and Schumacher, 1997; Wright et al., 2001; Stein et al., 2007). Two Phase II trials have demonstrated its safety and potential benefits (Wright et al., 2007; Xiao et al., 2008), and Phase III trials are now in preparation. To further enhance the pleiotropic effects of progesterone on TBI, it might be advantageous to combine it with agents that (1) protect the intracerebral vasculature, (2) diminish the effects of glutamate release and calcium influx, (3) more directly protect the mitochondria, (4) protect against the toxic effects of heme breakdown products, (5) enhance free radical scavenging, (6) enhance cerebral blood flow, (7) modulate the kallikrein-kinin system, (8) protect the axonal and cytoskeleton infrastructure, and (9) protect against diffuse axonal injury. Additionally, combining progesterone with hypothermia may be beneficial, especially during the rewarming stage of therapy.

Cyclosporine A

Cyclosporine A (CsA) attenuates mitochondrial failure, which is known to be an important injury mechanism in TBI. Mitochondrial failure leads to energy imbalance, ionic imbalance, swelling of mitochondria, pro-apoptotic events, reduced brain ATP levels, and release of cytochrome C (Sullivan et al., 2005). The locus of action for CsA is in stabilizing the mitochondrial transition pore (Sullivan et al., 2000). Several pre-clinical TBI and ischemia studies (mostly in rodents) have demonstrated neuroprotection (Folbergrova et al., 1997; Li et al., 2000; Sullivan et al., 2000; Alessandri et al., 2002; Ferrand-Drake et al., 2003; Fukui et al., 2003; Hansson et al., 2003; Suehiro et al., 2003; Signoretti et al., 2004). The advantages of CsA are that it is FDA-approved and off-patent, and therefore is inexpensively manufactured by several companies, and it has well-described safety and dosing profiles. CsA is also one of the most potent stabilizers of the mitochondrial transition pore. Secondary to the inhibition of mitochondrial transition pore opening, CsA also attenuates mitochondrial free radical oxidative damage to mitochondrial proteins and thus it acts as an indirect antioxidant (Mbye et al., 2009). A disadvantage is that chronic usage adversely impacts the immune system, but acute usage for TBI neuroprotection satisfied a broad range of safety parameters in a Phase I clinical trial. Another disadvantage is that CsA has relatively poor brain penetration; however, improvements in increased cerebral perfusion pressure, improved glucose levels, and reduced brain swelling were noted in the Phase I trial (personal communication, R. Bullock). Efforts to block excretion of CsA from the brain with ketoconazole were not successful. Phase III trials for CsA are now in preparation. Because of its slow entry into the brain (6 h), the mitochondrial benefits of CsA might be enhanced if combined with hypothermia, by both prolonging the treatment window and through their synergistic effects on preservation of brain bioenergetics, but combining CsA with hypothermia has the potential risk of infection because of the immune suppression. Because of this potential risk, one might exclude patients with multiple injuries from combined treatment with CsA and hypothermia. CsA might also be used in combination with NMDA inhibitors to block calcium flux, a precipitator for the mitochondrial damage, thus enhancing mitochondrial protection. One pharmacological caveat is that the neuroprotective dose-response curve for CsA is biphasic, so using it in combination would require a very careful evaluation of the pharmacokinetics and dose response.

Statins

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, which are potent inhibitors of cholesterol biosynthesis. There is growing clinical and preclinical evidence that the statin class of drugs may have additional pleiotropic properties that are potentially neuroprotective, independent of their effect on serum cholesterol (Cucchiara and Kasner, 2001). For example, in the acute phase

of TBI, statins exert anti-inflammatory effects (Weitz-Schmidt et al., 2001; Chen et al., 2007; Wang et al., 2007), which may reduce the later development of cerebral edema and intracranial hypertension. Statins also cause an upregulation of eNOS and stabilize endothelial surfaces (Laufs et al., 1998), which may result in improved cerebral perfusion following trauma (Lu et al., 2005; Wang et al., 2007). In the subacute period and chronic period following cerebral injury, statins may facilitate recovery via their effects on neurogenesis and angiogenesis (Chen et al., 2003; Lu et al., 2004a; Lu et al., 2007). In addition to these multiple mechanisms of action, there are a number of features that make the use of statins attractive in the treatment of acute brain injury. Based on pre-clinical observations in a murine model of SAH (McGirt et al., 2002), statins have been demonstrated to reduce clinical and radiographic vasospasm and improve outcome following aneurysmal SAH (Lynch et al., 2005; Tseng et al., 2005). Pre-clinical evidence also suggests that the use of statins improve outcomes in rodent models of TBI (Lu et al., 2004; Lu et al., 2004a & b) and intracranial hemorrhage (Jung et al., 2004; Lu et al., 2004c; Seyfried et al., 2004). Statins are well tolerated, easy to administer, and have a long, safe clinical track record. Adverse events, primarily myopathy and transaminitis, have been well defined and can be easily monitored. Moreover, clinical experience suggests that statins are well-tolerated in patients with life-threatening neurological disease (Lynch et al., 2005; Tseng et al., 2005). Thus statins may represent a novel adjunct strategy in combination therapy treatments for TBI.

Hypertonic saline

Hypertonic saline is an attractive treatment for TBI because it restores blood pressure, increases organ blood flow, exerts a positive inotropic effect, and is thought to mobilize water across the intact blood–brain barrier by dehydrating endothelial cells and erythrocytes (Tommasino and Picozzi, 2007). It also affects leukocyte adhesion and reduces the inflammatory response to injury (Pascual et al., 2003). The effects of hypertonic saline on TBI include improved hemodynamics through plasma volume expansion, vasoregulation via effects on vascular endothelium, a decrease in cerebral edema, and cellular modulation through both immunologic and excitotoxic effects (Doyle et al., 2001). Hypertonic saline has been used extensively in the pre-hospital arena and in ICUs around the world. There have been several clinical trials evaluating hypertonic saline in TBI. The safety profile is good and improvements in intracranial pressure and survival have been observed, but no improvements have been seen in functional outcomes. Currently a large randomized clinical trial of pre-hospital treatment with hypertonic saline versus normal saline in patients with TBI is in progress. Hypertonic saline should be strongly considered for use in conjunction with other promising therapies that target neuronal and axonal injury mechanisms.

Objective 2: Challenges for Testing Combination Therapies

Pharmacokinetics, pharmacodynamics, regulatory considerations, and experimental design and analysis were identified as important topics for discussion during the workshop. Scientific experts were invited to give presentations to launch the discussions, which are summarized below.

Pharmacokinetics and pharmacodynamics

Pharmacokinetics and pharmacodynamics may be altered, not only when two drugs are combined, but also when a drug is combined with another treatment. Thus it is critically important to study these interactions in parallel with the evaluation of the therapeutic effect. Specifically, a careful dose-response analysis needs to be performed for the combination treatment. Ideally, the combination would not only allow for a greater level of protective efficacy (improved pharmacodynamics), but also allow for lower doses of either drug to be administered, such that the therapeutic index (i.e., safety margin) is also improved over that seen with either drug alone. The combined administration of two or more drugs could also result in altered pharmacokinetic interactions with regard to absorption (in the case of orally administered drugs), distribution (e.g., plasma protein binding and brain penetration), metabolism (mainly hepatic), or renal excretion. Similarly, hypothermia could significantly modify the pharmacokinetics of a drug by modifying cardiac output and organ blood flow or hepatic metabolic rate.

An example of a combination therapy for enhanced neuroprotection that could potentially alter the pharmacokinetics is the co-administration of tirilazad (the 21-aminosteroid lipid peroxidation inhibitor) (Hall et al., 1994), and the mitochondrial protective agent CsA. Both drugs have less-than-ideal brain penetration because they are known to interact with the blood–brain barrier P-glycoprotein that pumps them out of the brain. However, when administered together, a secondary benefit might be that they enhance each other's brain penetration, since they would compete for the P-glycoprotein efflux mechanism. Because there are many such possible interactions, pre-clinical pharmacokinetic studies are needed in order to maximize both efficacy and safety in subsequent clinical trials of combination therapies for TBI.

Regulatory considerations

Regulatory considerations for combination therapies are the responsibility of the FDA. There are three main centers that deal with human clinical research: the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH). Products that fall under the purview of these centers may be classified as a combination product, as explicitly defined in 21 CFR 3.2(e) (U.S. Food and Drug Administration, 2008). Operationally, such a product exists if two or more components are combined into a single entity, two or more components are packaged together, an investigational component is used with an approved product but packaged separately with cross-labeling, or separate investigational components are packaged separately with cross-labeling. Drug-drug combinations are *not* defined as combination products by the FDA and represent a distinct regulatory entity. Such combinations are referred to as fixed-combination drugs and are defined in 21 CFR 300.50 (U.S. Food and Drug Administration, 2008). This regulation states, in part, that two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects. This has implications for study design during clinical development. In a typical situation, it is not sufficient to simply study the combination versus placebo, nor is it sufficient to study the combination versus only one of the

two components. A full factorial design is typically used to demonstrate the benefit of fixed-combination drugs. Aside from the requirement to demonstrate that each component of a fixed-combination drug makes a contribution to the claimed effects, the approval process for fixed-combination drugs is normally similar to that of individual drugs.

Combination products contain components that are subject to the regulatory requirements of more than one center. The Office of Combination Products (OCP) at the FDA has broad responsibilities covering the regulatory life-cycle of combination products. The formal duties of the OCP are found in 21 USC 353(g) (U.S. Food and Drug Administration, 2008). For the purposes of this discussion, one of the more important duties is assigning CDER, CBER, or CDRH primary jurisdiction for review of a combination product., It is important to note that primary regulatory responsibilities for, and oversight of, specific combination products will remain in the assigned center, not the OCP. Assignment of primary jurisdiction is based on a determination of the primary mode of action (PMOA), defined as the single mode of action (MOA) of a combination product that provides its most important therapeutic action. MOA is the means by which a product achieves its intended therapeutic effect or action. If the PMOA is indeterminate, such as when a product has independent MOAs, neither of which is subordinate to the other, an algorithm is used for assignment. This algorithm first examines the new product's consistency with other combination products raising similar safety and effectiveness questions, and assigns the new product to the center that had jurisdiction over these similar products. If no similar products are suitable for comparison, then the new product is assigned to the center with the greatest expertise to evaluate the most significant safety and effectiveness questions raised by the combination product. The center of primary jurisdiction is of significant importance to both the sponsor and the FDA because although all centers are charged with determining safety and effectiveness, the specific regulations governing this determination may differ. Even once a primary center has been identified, however, the additional centers may remain involved in the review process in a consultative or collaborative role.

In summary, combination therapies represent a distinct regulatory entity and a sponsor may face unique challenges in their clinical development. Familiarity with the issues involved in the review of a combination therapy will enhance the opportunity for a successful outcome. Both the various FDA centers and the OCP are appropriate resources for investigators contemplating a combination product submission. Investigators contemplating a submission for a combination product or fixed-combination drugs were encouraged to consult the FDA early in the experimental design process.

Study design and statistical considerations

Study design and statistical considerations are also critical for reaching the ultimate objective of randomized clinical trials for combination therapies, which is to demonstrate a large synergistic effect between treatments A and B. Whereas the objective of single-therapy trials is to prove that treatment A is clinically better than the current standard of therapy, the combination therapy trial needs to show that the combination of treatment A and B is clinically better than treatment A alone, treatment B alone, and better than the current standard therapy. In general, combination therapy studies should use a factorial experimental design with one-fourth of the subjects receiving treatment A, one-fourth receiving treatment B, one-fourth getting neither A nor B, and one-fourth receiving A and B together. A complete analysis of the groups would involve all six possible comparisons of the four groups. However, if the single therapies by themselves are not effective, then the standard analysis could eliminate the comparisons of treatment A to non-treatment A, and treatment B to non-treatment B, and only compare the combination treatment A + B to the other three groups. Alternatively, if the single therapies are effective, then one should conduct a complete factorial analysis.

When combination therapies are administered sequentially, investigators might consider an experimental design in which patients are randomized to the first therapy, and then those patients who survive to the next phase are re-randomized for the second intervention. This design provides the most statistical power, with equal numbers in the treatment arms. However, sequential combination studies also increase the risk for missing data, because not all subjects will make it to the second treatment. This needs to be addressed and the end-points are defined in a way that covers all eventualities. Another suggestion for more efficient testing of sequential combination therapies is to incorporate interim analyses into the study design to determine the efficacy of the first treatment alone. The exclusion criteria required for combination therapies raises another challenge. The exclusion criteria for the study population should include anyone who has contraindications for either treatment A or B. For sequential combination treatments one must consider not only contraindications at baseline, but must anticipate that one of the treatments might lead to adverse effects that appear as a contraindication to the second treatment. As with all randomized controlled trials, one encounters barriers due to safety concerns for treatment A or B, as well as fear of attenuated effects. Another concern is the increased potential for bias related to safety profiles. For example, if one treatment leads to more or less hemorrhaging on CTs and that increases surveillance, then that situation may bias ascertainment of surrogate or clinical outcomes as the trial continues. Therefore, combination therapy trials may end up focusing on a highly specific patient population, which may create challenges for enrolling the required number of patients.

Similar to studies of single therapies, the relevant outcome metrics for monitoring combination therapy efficacy fall into two major categories: surrogate outcomes, and functional outcomes. Surrogate outcomes are useful in pre-clinical and Phase I and II clinical studies to reveal treatment actions and interactions, and to determine the relative advantage of concurrent versus sequential administration on the time course of TBI. Functional outcomes are the best metrics to evaluate efficacy, effectiveness, and safety.

In addition, interim analyses of futility (also referred to as non-inferiority studies) should be considered in both mono- and multi-therapy clinical trials, as they substantially lower sample size and have the potential to reject drugs or treatment designs which are clearly ineffective. A futility experimental design incorporates the view that in the early phases of clinical development of a new therapy, it is in fact riskier to discard a potentially useful treatment than it is to fail to

definitively identify efficacy. In contrast, in traditional studies, it is customary to set alpha at 0.05 (the likelihood of a false-positive result of less than 5%), and beta at 0.2 (the likelihood of a false-negative result—or that a beneficial effect will be missed—is less than 20%). However, in a futility study the null hypothesis is that treatment has promise and will therefore produce results exceeding a meaningful threshold. Thus, an alpha of 0.1 in a futility study means that the chance of beneficial effect being missed is less than 10%. In a futility design, if the efficacy threshold is not met, the null hypothesis is rejected and further study of the treatment is considered futile (Schwid and Cutter, 2006). Futility design trials were pioneered in cancer chemotherapy studies, and have recently been used in Phase II clinical trials of neurological disorders such as Parkinson's disease (Tilley et al., 2006) and stroke (Palesch et al., 2005).

Objective 3: Optimized Strategies for Developing Single and Combination Therapies

As part of the workshop, three parallel breakout sessions discussed the steps required to develop combination therapies for TBI using *in-vitro* and *in-vivo* pre-clinical models, and clinical trial platforms. During the discussions it became apparent that many of the strategies put forward were also relevant to the development of single therapies for TBI.

In-vitro *TBI models*

In-vitro TBI models have higher throughput than *in-vivo* models. They offer lower-cost alternatives for evaluating a wide range of timing and dosing parameters, which increase geometrically when testing combination therapies. *In-vitro* models aim to reproduce the traumatic tissue distortion of TBI to activate some of the same secondary injury mechanisms that occur *in vivo* (animals and humans). However, like all model systems, they have limitations, which need to be considered carefully when developing a screening platform for TBI.

The first consideration is which *in-vitro* model or models to use. *Substrate deformation* models reproduce non-penetrating injuries such as falls, blunt impacts, and inertial loading, and are advantageous because of ease of use and commercial availability. One caveat is that not all systems produce uniform deformations. *Transection* models scratch or cut cultured cells or brain slices, are easy to use, and most closely mimic penetrating head injuries (Tecoma et al., 1989; Mukhin et al., 1997; Toni et al., 1997; Mukhin et al., 1998). *Crush* or *weight drop* models use an indenter to press on cultured tissue slices and reproduce contusion-type injuries (Sieg et al., 1999; Frantseva et al., 2002; Bendel et al., 2004). *Fluid shear* models induce cellular deformation with rotating fluid flow between two plates and are advantageous in that cells can be imaged during application of the fluid shear (LaPlaca and Thibault, 1997; Edwards et al., 2001; Serbest et al., 2005). In *hydrostatic pressure* models, cells or tissues are placed in a chamber which is pressurized, either with a transient pressure pulse (similar to a fluid percussion injury) or a tonic applied load (Panizzon et al., 1998; Etzion and Grossman, 2000; Panickar et al., 2002). *Combined injury* models have also been developed. For example, *substrate deformation* models and *transection* models have been combined with an ischemia/hypoxic or NMDA excitotoxic challenge, and the combination model demonstrated greater necrotic and apoptotic cell death than each injury model alone (Cargill and Thibault, 1996; Allen et al., 1999; Glass et al., 2002; Arundine et al., 2004; Glass et al., 2004; Engel et al., 2005). Rather than developing additional models, the *in-vitro* break-out group recommended that there be greater commercialization and standardization of existing models, and hands-on training programs to learn how to use them.

A second consideration is the choice of a cell or tissue culture system to best represent the *in-vivo* environment. *Cell lines* (e.g., PC12, NT2, SH-SY5Y, and NG-108 cells) are generally easier to use than primary cell culture, and can be differentiated from their mitotic state into a neuronal-like phenotype. These cell lines can also be manipulated at the molecular level to facilitate broad screening for new drug discovery in single and combination therapies for TBI. *Dissociated primary cell cultures* (neurons, astrocytes, oligodendrocytes, microglia, and mixed cultures) from embryonic or neonatal brains are the most widely used culture system, and data suggest that mixed cultures respond differently than homogeneous cultures (Mukhin et al., 1997; Katano et al., 1999; Ahmed et al., 2000; Lea et al., 2002; Lea et al., 2003). The effects of the physical manipulations during harvest and suspension are unknown, but receptor expression profiles likely vary as the cells mature over days and weeks in culture. Caution should be used when comparing across culture conditions and extrapolating results to the adult. Immature organotypic *brain slice cultures* (200–400 μm thick) from cortex (Elkin and Morrison, 2007), hippocampus (Stoppini et al., 1993; Hong and Chang, 1995), and thalamus (Sieg et al., 1999) have been maintained in culture for extended periods of time. A significant advantage of slice cultures is that the *in-vivo* cellular interconnections and heterogeneity are maintained in these cultures. Drawbacks include a lack of vasculature, some remodeling of intrinsic circuitry (Gahwiler, 1984; Zimmer and Gahwiler, 1984; Caeser and Aertsen, 1991; Robain et al., 1994; Kamada et al., 2004), and maturation during culture (Buchs et al., 1993; Bahr et al., 1995; Collin et al., 1997; Hartel and Matus, 1997). An advantage over dissociated cultures, the slice may be able to clear dead cells and severed processes within the first 5 days in culture (De Simoni et al., 2003), fill denuded dendritic fields, and re-establish connections. For all *in-vitro* model systems, standardization of methods across laboratories would improve inter-laboratory consistency in therapeutic development.

A third consideration is what outcomes to measure to capture clinically relevant information. There are many options, including measures of neuronal and astrocytic death, assessment of biochemical or electrophysiological function, alterations in gross and microscopic structures, and released biomarkers that could be used to "synchronize" time-lines between *in-vitro*, *in-vivo*, and human injury responses. Interestingly, swelling and bulbs in axons or the morphological changes seen in the injured cortex and hippocampus *in vivo* (Adams et al., 1982; Adams et al., 1983; Povlishock et al., 1983; Povlishock, 1992; Foda and Marmarou, 1994) are only rarely reported for *in-vitro* models (Gross et al., 1983; Emery et al., 1987; Gross and Higgins, 1987; Lucas et al., 1990; Stoppini et al., 1993; Smith et al., 1999; Morrison et al., 2003).

In summary, further research to establish the validity and fidelity of *in-vitro* models is recommended. Once this is established, it is expected that *in-vitro* models could be used

to test permutations and combinations of therapies more rapidly than the *in-vivo* models. Furthermore *in-vitro* models could be used to scan for new compounds with available small molecule libraries, and provide a valuable new dimension for developing therapies. Given the heterogeneity of human TBI, it is important to select the relevant *in-vitro* model and cell/tissue when testing the effectiveness of therapies.

In-vivo *TBI models*

In-vivo TBI models play a key role in optimizing the design of clinical trials. Criteria for success have been established by both the Stroke Therapy Academic Industry Roundtable (STAIR) working group (STAIR, 1999; STAIR-II, 2001; Feuerstein et al., 2008; Fisher et al., 2009), and by a TBI focus group (Narayan et al., 2002). These criteria are relevant to development of both single and combination therapies for TBI and are summarized in Table 2. However, in addition to meeting these study design criteria, combination therapies should be designed to achieve at least one of the following goals: (1) affect multiple targets; (2) produce synergistic effects on a single target (e.g., by convergent signaling pathways), (3) increase distribution and half-life or decrease toxicity, (4) target sequential stages of injury (e.g., combining acute neuroprotection with agents that promote brain repair), (5) involve different domains (such as drugs, delivery devices, or even activity-based rehabilitative strategies), or (6) focus on either novel therapeutics or previously tested drugs in combinations.

The end-points for combination trials in animal models should include early measures of drug activity to identify potential negative interactions on treatment effect, metabolism, absorption, toxicity, or brain penetration. In addition, because of the importance of co-morbidities and physiological responses in the severely head-injured population, special care should be taken to measure interactive effects on clinically important parameters such as vulnerability to infection, hemodynamic variables, temperature, edema, and electrolyte homeostasis. Pre-clinical toxicology studies of the combined agents may be necessary to ensure safety prior to entering a clinical trial. Untoward interactions are a major concern, even with previously approved drugs whose activity or dose-response may be altered in the presence of another active agent. Retesting of dose-response curves is especially important for agents with a narrow therapeutic index or a biphasic dose-response curve.

Ideally, many combination therapies should undergo pre-clinical testing, with the best combinations chosen for further clinical testing. To prioritize those combinations it is important to develop standardized screening experiments in animal models so that results from different combinations can be compared across laboratories and species. Both positive and negative data from the animal experiments should be made publicly available so that research may focus on the most promising combinations, and unnecessary redundancy is avoided. For an initial proof of principle pre-clinical study, the combination therapy group might be investigated before inclusion of single-therapy groups. The improvements could be in efficacy or in therapeutic safety. Prioritizing treatments that have demonstrated efficacy as a single therapy (e.g., CsA and hypothermia) may be the most efficient strategy for initial screening. Later, direct pre-clinical comparisons of promising combinations could help prioritize them for future clinical testing. A comprehensive pre-clinical study design must also optimize a dosing methodology (dose, route, and timing), evaluate the mechanism of action, and assess the pharmacokinetic properties of the combination treatment. Definitions of failure include demonstrating loss or neutralization of activity of either component of the combination, increased mortality, or failure to improve the effect of either single therapy. The eventual study design should parallel clinical studies in terms of treatment groups, delay to treatment, dosing, and the time course of the evaluation of responses. Finally, standards of care in pre-clinical studies should be designed to include standards of care routinely followed in clinical trials (e.g., blood pressure and management of intracranial pressure).

In summary, pre-clinical studies play an essential role in combination therapy development for TBI. To ensure optimal translation to Phase I and II clinical trials, pre-clinical studies of combination therapies should include testing in multiple animal models, characterization of trauma-response relationships and pharmacokinetics, and utilization of multiple surrogate markers of efficacy and multiple functional outcome measures relevant to the clinical population (Table 2). The creation of a consortium of laboratories for conducting coordinated pre-clinical screening and efficacy studies, with uniform standards of animal care and outcome measures, could contribute to the development of both single and combination therapies for TBI.

Table 2. Study Design Considerations for Pre-Clinical TBI Single and Combination Therapy Development[a]

- Was the candidate therapy evaluated in multiple models and in both rodent and gyrencephalic species?
- Was the dose–response effect evaluated over a clinically relevant time window?
- Did the studies include clinically relevant physiological monitoring?
- Were the studies blinded and randomized?
- Were the pharmacokinetics assessed in the target tissue of the experimental species and under conditions that reflect real-life clinical situations?
- Were surrogate markers evaluated to determine if the therapy attenuates the specific injury mechanisms that are being targeted?
- Were histological and functional outcome measures assessed following a prolonged survival interval to ensure that early treatment effects are not diminished?
- Was the candidate therapy evaluated in both genders, across the life-span, and across the spectrum of injury severities?
- Were the treatment effects replicated in several laboratories and/or observed in a multicenter pre-clinical consortium?

[a]Based on the STAIR Recommendations for Preclinical Stroke Drug Development (STAIR, 1999; STAIR, 2001; Fisher et al., 2009), a workshop on clinical trials in head injury (Narayan et al., 2002), and the current workshop.

Clinical trials

Clinical trials for combination therapies will require efficient *in-vitro* and *in-vivo* pre-clinical efficacy studies as previously discussed to select the best combinations among the

many possibilities. Also, it should be noted that drugs previously tested and shown to be ineffective as a single therapy should not necessarily be excluded as possible candidates for use in combination therapy. This is based in part on the caffeinol study, in which ethanol plus caffeine produced a dramatic reduction in overall infarct volume in a model of ischemic stroke, although neither therapy worked as a single therapy (Strong et al., 2000; Aronowski et al., 2003). Drugs that have multiple and pleiotropic mechanisms of action and target multiple mechanisms may be advantageous for TBI because of its complexity and heterogeneity (Table 1). Also, TBI often occurs along with multiple types of injuries to other organs (polytrauma). Thus, combining two drugs with multiple mechanisms of action may produce the largest effects for such a heterogeneous injury. Alternatively, one could select therapies that exert neuroprotective actions on a single specific target, but this approach may be premature until a new classification system to reduce the heterogeneity of subjects is available (Saatman et al., 2008), and until more TBI therapies have a well-understood mechanism of action.

The temporal evolution of TBI is another important issue, especially when designing effective serial combination therapies. The focus of this NIH workshop was on the first 72 h after injury (Table 1) because early intervention has the potential to prevent secondary injuries, and most of the data on mechanisms of TBI injury are on acute injury. Consequently, it is important to consider agents that act over clinically relevant time periods and can be given via practical routes of administration. For example, during the first 30–60 min post-injury, when the patient is typically cared for by paramedics during transport to the hospital, the problems receiving the most attention are maintenance of adequate ventilation, blood pressure, and pulse. A comprehensive sequential combination treatment for acute TBI might be early administration of chilled hypertonic saline plus L-arginine (Prough et al., 2006) to provide a small-volume resuscitation, followed by Epo at the emergency medical center. Another rapid response treatment that could be applied in the field is hyperoxia.

Combination therapies also increase the need for widely accepted, validated biomarkers (clinical, biochemical, or imaging) to detect and monitor secondary injuries. Ongoing studies using novel MRI methods and proteomic strategies hold much promise, but substantial work remains to be done. Identification of these biomarkers will greatly facilitate development of therapies, and will be of particular use in combination therapies for understanding the interactions. For example, if combining drugs produces negative or synergistic effects, biomarkers will help to determine the reason for these non-additive effects.

Detecting additive or synergistic effects of therapies used in combination, a requirement of the FDA, will require more sensitive and specific outcome measures. The commonly used dichotomized Glasgow Outcome Score (GOS) and Glasgow Outcome Score-Extended (GOS-E) are insensitive to the important but subtle deficits in memory, executive function, and affect that produce significant disability (McCauley et al., 2001). Furthermore, because disability after TBI encompasses multiple domains of dysfunction, a single functional assessment scale may not be able to identify important deficits in all patients. There are several mathematical approaches to compare two groups with respect to more than one outcome. The options available include using Bonferroni or other adjustments for multiple comparisons, reducing the dimensions of the problem by averaging the outcomes, or applying a global test based on multiple correlated binary outcomes (Lefkopoulou and Ryan, 1993; Lu and Tilley, 2001). Of these, the latter approach has been found to be useful in a variety of clinical settings. Incorporating several different measures, which although correlated measure different domains of dysfunction after TBI, significantly lowers the sample size required. The recently completed magnesium sulfate clinical trial for TBI used a composite outcome measure (Temkin et al., 2007). Center-to-center variability becomes even more important when using combination therapies, because this by itself increases the complexity of the study protocol and monitoring. Plus, anything that increases "noise" in the data will have a negative effect on detecting additive effects of the combination therapies that are required for the pilot studies.

In summary, attractive candidates for combination therapies should be based not only on robust pre-clinical efficacy data, but also address the temporal evolution and heterogeneous phenotype of TBI. Thus, using therapies that target multiple mechanisms rather than a single mechanism is recommended. Using composite outcome measures and standardization of patient care protocols across trial centers may be useful for minimizing the required number of subjects and for detecting significant effects.

Summary of Recommendations

The workshop participants (listed below) agreed that the heterogeneity of TBI provides a strong rationale for the hypothesis that combination therapies will improve clinical outcomes compared to current single-agent interventions. Several steps were identified for moving research on combination therapies forward, including the following:

- Select therapies for use in combination that target multiple and complementary mechanisms of action.
- Validate surrogate markers to monitor treatment effects on brain injury and recovery for all stages of therapy development (*in-vitro*, animal, and human).
- Develop *in-vitro*, animal, and clinical platforms for coordinated studies across multiple laboratories.
- Use efficient designs for trials and data analysis.
- Be informed of the FDA regulations.
- Adopt a uniform standard of care for clinical trials, and mimic these standards in pre-clinical studies.
- Establish a shared database of positive and negative clinical and pre-clinical data.

The workshop participants also emphasized the importance of furthering communication, coordination, and collaboration between basic scientists, clinicians, and bioengineers, as well as between academia, industry, and government.

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Author Disclosure Statement

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ATTACHMENT 2

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Emerging treatments for traumatic brain injury

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Abstract

Background—This review summarizes promising approaches for the treatment of traumatic brain injury (TBI), which are either in preclinical or clinical trials.

Objective—The pathophysiology underlying neurological deficits after TBI is described. An overview of select therapies for TBI with neuroprotective and neurorestorative effects is presented.

Methods—A literature review of pre-clinical TBI studies and clinical TBI trials related to neuroprotective and neurorestorative therapeutic approaches is provided.

Results/conclusion—Nearly all phase II/III clinical trials in neuroprotection have failed to show any consistent improvement in outcome for TBI patients. The next decade will witness an increasing number of clinical trials which seek to translate preclinical research discoveries to the clinic. Promising drug- or cell-based therapeutic approaches include erythropoietin and its carbamylated form, statins, bone marrow stromal cells, stem cells singularly or in combination or with biomaterials to reduce brain injury via neuroprotection and promote brain remodeling via angiogenesis, neurogenesis, and synaptogenesis with a final goal to improve functional outcome of TBI patients. In addition, enriched environment and voluntary physical exercise show promise in promoting functional outcome after TBI, and should be evaluated alone or in combination with other treatments as therapeutic approaches for TBI.

Keywords

clinical trials; neurogenesis; neuroprotection; neurorestoration; pharmacological; traumatic brain injury

1. Background

1.1 TBI

Traumatic brain injury (TBI) is the leading cause of death and disability in the most active population (<45 years of age). An estimated 1.4 million people sustain TBI each year in the United States alone, and more than 5 million people are coping with disabilities from TBI and costs $56 billion a year [1] A review of European epidemiological data estimated a TBI incidence (hospitalized and fatal) of 235 per 100,000 per year and a case fatality rate of 11 per 100 with 775,500 new cases occurring each year [2]. In addition, TBI is an epigenetic risk factor for Alzheimer's and Parkinson's diseases [3]. Thus, TBI is a significant health concern and an enormous socioeconomic burden.

The most prevalent and debilitating features in survivors of brain trauma are cognitive deficits and motor dysfunctions. The most common cognitive impairment among severe TBI patients is memory loss, characterized by some loss of specific memories and the partial inability to form or store new ones. Natural recovery after TBI is greatest within the first 6 months after

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the injury and is more gradual after that, but outcome varies with different types of brain injury [4,5]. To date, there is no effective treatment to promote functional recovery except for routine medical intervention and care [4,6–8]. Thus, the development of improved treatment modalities would be of enormous clinical and economic benefit.

1.2. Pathophysiology of TBI

TBI results from direct impact to the head or from acceleration-deceleration injury. TBI results in functional deficits due to both primary and secondary mechanisms. Primary injury is the result of immediate mechanical damage that occurs at the time of injury. TBI is also associated with secondary injury that evolves over a period of hours to days to even months after the primary insult, and is the result of biochemical and physiological events which ultimately lead to neuronal cell death. In the past decades, several biochemical derangements responsible for secondary injury have been demonstrated, including perturbation of cellular calcium homeostasis [9,10], increased free radical generation and lipid peroxidation [11–13], mitochondrial dysfunction [10,14,15], inflammation, apoptosis, and diffuse axonal injury [16]. The period of evolution of secondary injury provides a window of opportunity for therapeutic intervention with the potential to prevent and/or reduce secondary damage and to improve long-term patient outcome. To date, however, promising preclinical results have not been translated into successful clinical trials. There is now strong indication that the pathophysiological heterogeneity of TBI patients, lack of sufficient pharmacokinetic analysis for determination of optimal dose and therapeutic window of the target compounds have led the clinical trials to fail [17].

2. Medical needs

As the primary injury, which represents the direct mechanical damage, cannot be mended, therapeutic targets focus on the secondary damage. The multidimensional cascade of secondary brain injury can result in dramatically impaired sensorimotor and cognitive deficits as well as offer multiple therapeutic options [16]. Since the first Guidelines for Management of TBI were published in 1995, there have been several studies clearly demonstrating that management of TBI in accordance with the Guidelines can achieve substantially better outcomes such as improved functional outcome scores and reduced mortality rate, length of hospital stay, and costs [18]. Although many multi-center clinical trials, aimed to determine the clinical value of a range of approaches to the treatment of TBI patients, have been conducted since 1985, most involved pharmacologic agents; none have demonstrated a convincing benefit in the overall TBI population [6]. Therefore, it is warranted to identify and design novel approaches capable of improving motor, sensory and cognitive outcome in order to enhance the quality of life of the TBI patients.

3. Existing treatments

Many preclinical studies have tested therapeutic efficacy of drugs in animal TBI models by targeting secondary injury mechanisms including calcium channel blockers, corticosteroids, excitatory amino acid inhibitors, N-methyl D-aspartate (NMDA) receptor antagonist, free radical scavengers, magnesium sulfate, and growth factors [6]. Several phase-II clinical trials have shown favorable effects including polyethylene glycol-conjugated superoxide dismutase (PEG-SOD), moderate hypothermia, nimodopine, and triamcinolone [6]. Unfortunately, all the compounds or approaches that have been tested thus far in phase-III trials have failed to clearly show efficacy [19]. The efficacy of existing neuroprotective treatments for TBI remains uncertain. For example, mannitol is sometimes effective in reducing brain swelling after TBI. However, its effectiveness in the ongoing treatment of severe TBI remains unclear. There is evidence that excessive administration of mannitol may be harmful, for mannitol passes from the bloodstream into the brain, increases pressure within the skull, and worsens brain swelling

[20]. A small benefit arises when mannitol treatment is directed by measurement of intracranial pressure (ICP) compared to standard treatment. There is insufficient data on the effectiveness of pre-hospital administration of mannitol [20]. Updated meta-analysis supports previous findings that hypothermic therapy constitutes a beneficial treatment of TBI in specific circumstances. Until more evidence from well-conducted trials becomes available, clinicians should continue to exercise caution when considering administering hypothermia for treatment of TBI [21]. High ICP is still the most frequent cause of death and disability after severe TBI. Elevated ICP is usually defined as an ICP above 15 to 20 mm Hg when measured within any intracranial space (the subdural, intraventricular, extradural, or intraparenchymal compartments). Mortality and morbidity after severe TBI have been strongly related to raised ICP [22]. The cause of high ICP is an increase in brain volume at the expense of one or more intracranial components. Mass lesions and an increase in brain water content (edema) and cerebral blood volume contribute to raised ICP in TBI [23]. However, there is no evidence to support the routine use of decompressive craniotomy (DC) to improve mortality and quality of life in TBI adults with high ICP[23]. The results of non-randomized trials and controlled trials with historical controls involving adults, suggest that DC may be a useful option when maximal medical treatment has failed to control ICP. There is one ongoing randomized controlled trial of DC (DECRA) with severe TBI that may allow further conclusions on the efficacy of this procedure in adults [24].

4. Therapeutic class review

Recent reviews have identified several therapeutic classes showing promise for the treatment of TBI [25]. These includes erythropoietin (EPO), carbamylated form of EPO (CEPO), statins, bone marrow stromal cells (MSC), methylphenidate, progesterone, dexanabinol, and rivastigmine [25]. So far, the preclinical and clinical trials have exclusively focused on neuroprotective strategies with the goal to prevent and/or reduce brain damage induced by secondary injury. However, recent preclinical studies have revealed that TBI induces neurogenesis in the subgranular zone (SGZ) of the dentate gyrus (DG) in rat and mouse and treatments that enhance neurogenesis promote cognitive function after TBI [26,27]. Newly generated neurons in the SGZ are capable of projecting axons to the CA3 region in normal [28] and injured adult rats [29]. Previous studies show that treatment of TBI with EPO [30], S100B [31], MSC [32] or other manipulations such as environmental enrichment (EE) [33] enhance neurogenesis along with functional improvement. In addition to neurogenesis, the brain remodeling after TBI includes angiogenesis, axonal sprouting and synaptogenesis [34, 35]. All the TBI clinical trials so far are related to neuroprotective strategies. The approaches that enhance brain remodeling may represent another promising strategy (neurorestoration) to improve the neurological function [34]. We will present some of these promising strategies in this review.

5. Competitive environment

Publicly disclosed information regarding new compounds, and new approaches of already marketed compounds, undergoing clinical trials in human TBI were searched on Pharmaprojects, Pub Med, and ClinicalTrials.gov in November 2008. At the time of writing, these searches yielded some compounds of interest (Table 1).

6. Neuroprotective approaches

6.1 Calcium channel blockers

Calcium channel blockers (calcium antagonists) have been used in an attempt to prevent cerebral vasospasm after injury, maintain blood flow to the brain, and thereby to prevent further damage [36]. The first report on nimodipine treatment in patients with severe TBI dates from

1984 [37]. The first randomized controlled trials investigating the effect of nimodipine in head injury, the Head Injury Trials (HIT) 1 and 2, were published in the early 1990s [38,39]. Recently, 6 randomized controlled trials involving 1862 participants were reviewed [40]. This review of randomized controlled trials of calcium channel blockers in acute TBI patients shows that considerable uncertainty remains over their effects. Nimodipine administered to a subgroup of brain injury patients with subarachnoid hemorrhage shows a beneficial effect although there was an increase in adverse reactions (suffered by the intervention group which may mean that the drug is harmful for some patients) [40]. However, a recent systematic review including 1074 patients with traumatic subarachnoid hemorrhage [41] did not confirm the beneficial effects of nimodipine shown in a previous review [40] that included 460 patients with this condition. The recent review [41] presents data from all head-injury trials, including previously unpublished results from head injury trial 4 (HIT 4). The occurrence of poor outcome was similar in patients treated with nimodipine (39%) and those treated with placebo (40%). Mortality rates did not differ between nimodipine (26%) and placebo (27%) treated patients. These results do not lend support to the finding of a beneficial effect of nimodipine on outcome in patients with traumatic subarachnoid hemorrhage, as reported in an earlier review by Langham et al [40]. Intracellular calcium overload following TBI has been implicated in the pathogenesis of neuronal injury and death [42,43]. SNX-111, also known as ziconotide, is an N-type calcium channel blocker [44]. An important finding in studies of stroke mechanisms was that this drug was effective if given 24 hr after transient forebrain ischemia [45]. Posttraumatic administration of SNX-111 (15 min to 6 hr) was effective in improving mitochondrial function after TBI in rats [44]. This long "window of opportunity" was one of the attractive features of the drug. One hundred sixty patients were enrolled in a clinical trial before the trial was terminated. The mortality for the SNX arm was almost 25% because the drug caused hypotension, and for the placebo arm it was 15%. More recently, direct injection of SNX-185, another specific N-type Voltage-gated calcium channel blocker, into the CA2-3 region of the hippocampus reduced neuronal injury 24 hr after TBI and increased neuronal survival at 42 days. Behavioral outcome in both the beam walk and Morris water maze was also improved by SNX-185 [43]. Although the results of this direct cerebral injection in rodents subjected to TBI is promising without evidence of side effects found after systemic administration, application to TBI patients is problematic.

6.2 Corticosteroids

After TBI, the brain may swell which can cause a fatal elevation of ICP. Corticosteroids have been used to treat head injuries for more than 3 decades because they are thought to reduce ICP [46]. Some examples of corticosteroids are dexamethasone and methylprednisolone [47]. Edwards et al randomly allocated 10,008 adults with TBI and a Glasgow Coma Scale score of 14 or less, within 8 hr of injury, to a 48-hr infusion of corticosteroid (methylprednisolone) or placebo [48]. Data at 6 months were obtained for 9673 (96.7%) patients. The risk of death was higher in the corticosteroid group than in the placebo group (25.7% vs 22.3%), as was the risk of death or severe disability (38.1% vs 36.3%). There was no evidence that the effect of corticosteroids differed by injury severity or time since injury. These results support the conclusion that corticosteroids should not be used routinely in the treatment of TBI [48]. Twenty trials with 12,303 randomized participants were identified in a recent report [47]. The effect of corticosteroids on the risk of death was reported in 17 included trials. The largest trial, with about 80% of all randomized participants, found a significant increase in the risk ratio of death with steroids and an increased risk of death or severe disability. The increase in mortality with steroids in this trial suggests that steroids should no longer be routinely used in people with TBI [47].

6.3 Mannitol

Mannitol is sometimes effective in reversing acute brain swelling [49], but its effectiveness in the ongoing management of severe TBI remains unclear. Four eligible randomized controlled trials were identified [20]. One trial compared ICP-directed therapy to standard care. One trial compared mannitol to pentobarbital. One trial compared mannitol to hypertonic saline. One trial tested the effectiveness of pre-hospital administration of mannitol against placebo. Mannitol therapy for raised ICP may reduce mortality when compared to pentobarbital treatment, but may have a detrimental effect on mortality when compared to hypertonic saline [20]. ICP-directed treatment shows a small beneficial effect compared to treatment directed by neurological signs and physiological indicators. There are insufficient data on the effectiveness of pre-hospital administration of mannitol to draw any conclusion [20]. Although mannitol proved to significantly decrease the neuroinflammatory response and calpain activity in rats after TBI, it did not affect apoptosis, and its effect was significantly less than that of hypertonic saline [50]. However, a large retrospective study of high-frequency ICP data quantitatively shows that the effect of mannitol on ICP is dose-dependent and that higher doses provide a more durable reduction in ICP [51]. In a study of 34 TBI patients, acute infusion of a sodium lactate-based hyperosmolar solution was effective in treating intracranial hypertension following TBI. This therapeutic response is significantly more pronounced than that of an equivalent osmotic load of mannitol. Additionally, long-term outcome was better in terms of Glasgow Outcome Score (GOS) in those receiving sodium lactate-based hyperosmolar solutions than mannitol. Larger trials are warranted to confirm these findings [52].

6.4 Magnesium

Magnesium is a potential therapeutic tool because of its activity on NMDA-receptors, calcium channels and neuron membranes [53]. Animal studies have indicated a beneficial effect of magnesium on outcome such as cognitive function and sensorimotor function after TBI [54–57]. In addition, magnesium sulfate treatment was found to be the most effective choice due to the absence of side effects and comparable efficacy to corticosteroids [58]. But its efficacy in humans is still unknown. There is currently no evidence to support the use of magnesium salts in patients with acute TBI [59]. In a double-blind trial, 499 patients aged 14 years or older were admitted to a level-1 regional trauma center between August, 1998, and October, 2004, with moderate or severe TBI and were randomly assigned one of two doses of magnesium or placebo within 8 hr of injury and continuing for 5 days. Continuous infusions of magnesium for 5 days given to patients within 8 hr of moderate or severe TBI were not neuroprotective and might even have had a negative effect in the treatment of TBI [60].

6.5 Modest cooling

The benefits of reducing body temperature to between 35 °C and 37.5 °C after TBI has been reviewed [61]. Physical cooling techniques include cooling blankets, use of ice, fans or other devices. Chemical cooling techniques include drugs used to reduce fever, like paracetamol (acetaminophen). This review did not identify any randomized controlled trials or controlled clinical trials. Based on present evidence, no recommendations can be made for the use of interventions that reduce body temperature to between 35 °C and 37.5 °C after TBI because there is no satisfactory research that shows this therapy to be effective and safe [61].

6.6 Hypothermia

When hypothermia (32 °C) was administered immediately or 1 hr after TBI, injured rats showed an improvement in functional outcome and a decrease in edema while delayed hypothermia treatment had no effect on functional outcome or on edema [62]. A recent review of patients treated with hypothermia finds that reductions in risk of mortality were greatest and favorable neurologic outcomes much more common when hypothermia was maintained for more than

48 hr. However, this evidence comes with the suggestion that the potential benefits of hypothermia may likely be offset by a significant increase in risk of pneumonia [21]. This updated meta-analysis supports previous findings that hypothermic therapy constitutes a beneficial treatment of TBI in specific circumstances. Accordingly, the Brain Trauma Foundation/American Association of Neurological Surgeons guidelines task force has issued a Level III recommendation for optional and cautious use of hypothermia for adults with TBI [21]. There remains significant interest in the benefits of hypothermia after TBI and, in particular, traumatic axonal injury (TAI), which is believed to significantly contribute to morbidity and mortality of TBI patients [63]. Hypothermia (32 °C) initiated 1 hr after TBI partially preserves vascular function in rats [64]. However, there is no evidence that interventions aimed at reducing body temperature to between 35 °C and 37.5 °C in the first week after TBI improves patient outcomes [61]. The basic mechanisms through which hypothermia protects the brain are clearly multifactorial and include at least the following: reduction in brain metabolic rate, effects on cerebral blood flow, reduction of the critical threshold for oxygen delivery, calcium antagonism, blockade of excitotoxic mechanisms, preservation of protein synthesis, reduction of brain thermopooling, modulation of the inflammatory response, a decrease in edema formation, neuroprotection of the white matter and modulation of apoptotic cell death [65]. By targeting many of the abnormal neurochemical cascades initiated after TBI, induced hypothermia may modulate neurotoxicity and, consequently, may play a unique role in opening up new therapeutic avenues for treating severe TBI and reducing its devastating effects. Furthermore, greater understanding of the pathophysiology of TBI, new data from both basic and clinical research, the good clinical results obtained in randomized clinical trials in cardiac arrest and better and more reliable cooling methods have given hypothermia a second chance in the treatment of TBI patients. A critical evaluation of hypothermia is therefore mandatory to elucidate the reasons for previous failures. Further multi-center randomized clinical trials are warranted that would definitively confirm or refute the potential of this therapeutic modality in the management of severe TBI [65]. Several methods of conferring preferential neuroprotection via selective hypothermia currently are being tested in the experimental phases, including surface cooling, intranasal selective hypothermia, transarterial or transvenous endovascular cooling, extraluminal vascular cooling, and epidural cerebral cooling [66].

6.7 Decompressive craniotomy

Decompressive craniotomy (DC) is used to treat elevated ICP that is unresponsive to conventional treatment modalities [23]. In addition to infusion of hypertonic solutions, e.g., mannitol, and other medical measures, DC by surgical removal of a portion of the cranium (craniotomy) has been used for many decades as an intuitive strategy for the treatment of post-traumatic ICP increase. Controversial experimental data and lack of evidence-based clinical data, however, resulted in DC to be recommended by most national and international guidelines only as a third tier therapy for the treatment of pathologically elevated ICP [23]. In a trial with a pediatric population DC was associated with increased death and an unfavorable outcome (i.e., death, vegetative status, or severe disability 6 to 12 months after injury) [23]. However, in another study with a small pediatric population, DC reduced the refractory elevated ICP to less than 20 mm Hg [67]. To date, no results are available to confirm or refute the effectiveness of DC in adults. There is no evidence from randomized controlled trials that supports the routine use of secondary DC to reduce unfavorable outcomes in adults with severe TBI and refractory high ICP. The timing of DC may be of utmost importance in order to exploit the full neuroprotective potential of DC following TBI [68]. Early DC prevents secondary brain damage and significantly reduces brain edema formation after experimental TBI [69]. There is one ongoing randomized controlled trial of early DC (DECRA-Phase III) that will allow further conclusions on the efficacy of this procedure in adults after severe TBI [24]. Ongoing clinical trials on the use of DC after TBI may clarify many aspects of the clinical application

of this technique, however, some important pathophysiological issues, e.g. the timing of DC, its effect on brain edema formation, and its role for secondary brain damage, are still widely discussed and can only be addressed in experimental settings [23].

6.8 Excitatory amino acid (EAA) inhibitors

Reduced cerebral blood flow depletes energy stores and causes membrane depolarization. EAAs (mainly glutamate) are released into the synapse in supra-physiological concentrations and overstimulate mainly the NMDA receptor [70]. Ionic imbalance occurs with potassium ion efflux and sodium and calcium ion influx, leading to further depolarization which can overcome the magnesium ion blockade of the NMDA receptor [71]. Glutamate reuptake is diminished due to the ionic imbalance, and the concentration is further elevated. The increase in calcium ion leads to neuronal death, while the efflux of potassium ion leads to swelling in the brain [72]. Neuroprotective therapy is aimed at interrupting the excitotoxic cascade in brain tissues before neuronal toxicity is irreversible [70], leading to a reduction in severity of damage. The dopaminergic agonist amantadine has effects on both dopamine and NMDA channels and has been the subject of considerable interest and clinical use in acute TBI [73]. There was a consistent trend toward a more rapid functional improvement regardless of when a patient with DAI-associated TBI was started on amantadine in the first 3 months after injury [74]. Amantadine enhances presynaptic dopamine release and inhibits dopamine reuptake, resulting in an increased amount of dopamine in the synaptic cleft. Amantadine may also increase the density of postsynaptic dopamine receptors and alter the conformation of these receptors. Amantadine acts as an NMDA receptor antagonist, blocking glutamate, an NMDA channel activator. This effect may be responsible for possible beneficial effect of amantadine soon after TBI [74]. At doses of 200 400 mg/day, amantadine appears to safely improve arousal and cognition in patients with TBI. Additional prospective controlled studies with homogeneous patient populations will better define the role of amantadine for early arousal [75]. Dexanabinol (HU 211, dexanabinone, sinnabidol, PA 50211, PRS 211007), a non-psychotropic cannabinoid NMDA receptor antagonist under development by Pharmos Corp, may prevent some of the bad effects of glutamate on the brain and may protect the brain against uncontrollable swelling and death. Severe TBI patients (861) admitted to 86 specialist centers from 15 countries were included in a multi-centre, placebo-controlled, phase III trial [76]. Patients were randomized to receive a single intravenous 150 mg dose of dexanabinol or placebo within 6 hr of injury. The primary outcome was the extended Glasgow outcome scale assessed at 6 months, with the point of dichotomization into unfavorable versus favorable outcome differentiated by baseline prognostic risk. This clinical trial shows that dexanabinol is safe, but is not efficacious in the treatment of TBI [76].

6.9 Beta 2 receptor

The release of kinins is thought to be an important factor in the development of cerebral vasogenic edema and the detrimental role of beta 2 receptor (B2R) in the development of the inflammatory secondary injury and of the neurological deficits resulting from diffuse TBI [77]. Therefore, blockade of bradykinin B2R might represent a therapeutic approach in the pharmacological treatment of TBI. B2R antagonist, anatibant, administered as single subcutaneous injections of 3.75 mg and 22.5 mg, was well tolerated in severe TBI patients without clinical adverse events or biological abnormalities observed [78]. Three studies were included, involving 178 participants [78]. There is no reliable evidence that B2R antagonists are effective in reducing mortality or disability after TBI. Further well-conducted randomized controlled trials are required [79].

6.10 Barbiturates

ICP is an important complication of severe TBI, and is associated with a high mortality rate. Barbiturates are believed to reduce ICP by suppressing cerebral metabolism, thus reducing cerebral metabolic demands and cerebral blood volume [80]. However, barbiturates also reduce blood pressure and may, therefore, adversely affect cerebral perfusion pressure [80]. One study found pentobarbital was less effective than mannitol for control of raised ICP. There is no evidence that barbiturate therapy in patients with acute severe TBI improves outcome. Barbiturate therapy results in a fall in blood pressure in 25% TBI patients. This hypotensive effect will offset any ICP-lowering effect on cerebral perfusion pressure [80]. Although barbiturate coma is the second tier measure recommended by guidelines to treat post-traumatic refractory ICP and systemic hypotension is its most important side effect, recent evidence suggests that low-dose corticosteroid therapy may be used in a subset of patients with TBI to avoid hypotension [81]. However, TBI patients treated with barbiturate coma are at higher risk of developing adrenal insufficiency [81]. Some TBI patients treated with barbiturates developed adrenal impairment and required higher doses of norepinephrine to maintain cerebral perfusion pressure than patients treated with barbiturates without adrenal impairment [81].

6.11 Progesterone

To date, most of the pharmacological trials for TBI and stroke have failed. One reason may be that many of these drugs targeted a single aspect of the injury cascade. Preclinical studies have indicated that administering relatively large doses of progesterone during the first few hours to days after injury significantly limits brain damage, reduces loss of neural tissue, and improves functional recovery [82]. Although the research published to date has focused primarily on progesterone's effects on blunt traumatic brain injury, there is evidence that the hormone affords protection from several forms of acute central nervous system injury, including penetrating brain trauma, stroke, anoxic brain injury, and spinal cord injury. Progesterone appears to exert its protective effects by protecting or rebuilding the blood-brain barrier, decreasing development of cerebral edema, down-regulating the inflammatory cascade, and limiting cellular necrosis and apoptosis [83]. The single clinical trial investigating progesterone was performed on closed head blunt trauma with moderate to severe damage in 100 male and female patients [84]. Over 70% of the patients sustained severe TBI. These patients received emergency treatment plus progesterone or vehicle. The progesterone group received 3 days of post-injury continuous intravenous treatment. At 30 days post-injury, the severe TBI patients showed a statistically significant reduction in mortality compared to those receiving vehicle (i.e., 13.4% vs. 33.6%). Progesterone-treated moderate TBI patients had significantly better functional outcome (Disability Rating Scale) scores than the placebo group [84]. Recently, Xiao and colleagues performed an in-hospital, double-blind, randomized, controlled clinical trial utilizing progesterone in the treatment of acute TBI patients evaluating safety and long-term clinical outcomes [85]. These data, combined with the results of the previously published ProTECT trial (phase II, randomized, double-blind, placebo-controlled trial) [84], show progesterone to be safe and potentially efficacious in the treatment of TBI. Larger phase-III trials will be necessary to verify results prior to clinical implementation [86]. Progesterone treatment of blunt TBI is ongoing at Emory University [24]. In a recent preclinical trial, a continuous infusion of progesterone after TBI decreased edema and anxiety and increased activity, thus enhancing behavioral recovery [[87]. These results suggest that a continuous mode of pharmacological administration may prove to be more beneficial in translational and clinical testing than bolus injections over the same period of time.

6.12 Monoaminergic agonists

Methylphenidate is a dopamine agonist that blocks the dopamine transporter. Ten clinical trials (1966-June 2004) evaluating the safety and efficacy of methylphenidate in pediatric and adult patients with TBI are reviewed by Siddall [88]. Improvements in different aspects of cognition and behavior were evaluated before, during, and after methylphenidate treatment. The results demonstrated that methylphenidate is likely to improve memory, attention, concentration, and mental processing, but its effects on behavior have not been determined [88]. Animal models suggest that agents enhancing monoaminergic transmission, particularly amphetamines, promote motor recovery from focal brain injury and it is proposed that this might represent a complementary means of therapeutic intervention in the later post-injury phase [89]. However, there is, at present, insufficient evidence to support the routine use of mono-amino acids to promote recovery from TBI [89]. Larger, double-blind, placebo-controlled studies are needed to determine optimal doses, phase of recovery in which to begin treatment, length of treatment, and the long-term effects for patients with mild, moderate, and severe TBI [88].

6.13 Recombinant factor VIIa

Recombinant factor VIIa (rFVIIa, NovoSeven) is a hemostatic agent that has been shown to limit intracerebral hemorrhage (ICH) expansion in patients with spontaneous ICH (sICH) [90]. The similarities of hemorrhage progression in sICH and traumatic ICH (tICH) as well as the possibly related secondary injuries, provide an appropriate rationale for exploring the use of rFVIIa in TBI [91]. tICHs typically form early after TBI and tend to demonstrate maximum expansion in the first hours after injury. Surgical evacuation of tICHs can be of uncertain benefit, especially if the hematoma is deep or in eloquent areas of the brain and, therefore, is usually undertaken for large lesions (>25 ml), most frequently only after secondary deterioration has occurred. Therefore, identifying methods to limit hemorrhagic progression in TBI is desirable. In the heterogeneous diseases like TBI, the use of clinical outcome scales alone as the primary end point can make trials long, expensive, and impractical. The reduction of hematoma expansion as demonstrated by serial CT scans can serve as a useful indicator of pharmacological efficacy and as a surrogate for outcome. This dose-escalation study in patients with tICHs shows the potential for rFVIIa to limit hematoma expansion at doses of 80 μg/kg or greater in a manner very similar to that seen in sICH. However, a possible increase in the rate of deep venous thrombosis (DVT) was observed in the rFVIIa group. In any future study to confirm the clinical benefit of rFVIIa in tICH, DVT risk should be carefully monitored [90]. In a recent report, rFVIIa rapidly and effectively reversed coagulopathy in patients with severe TBI [92]. rFVIIa decreased the time to intervention and decreased the use of blood products without increasing the rate of thromboembolic complications [92].

6.14 Free radical scavengers

Free radicals are highly reactive species generated predominantly during cellular respiration and normal metabolism [93]. Imbalance between cellular production and scavenging of free radicals is referred to as oxidative stress. Oxidative stress has been implicated as a potential contributor to the pathogenesis of acute central nervous system injury [93]. After brain injury, the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) leads to tissue damage via several different cellular molecular pathways. Radicals can cause damage to lipids, proteins, and nucleic acids (e.g., DNA), leading to subsequent cell death [94]. A few agents with antioxidant effects are neuroprotective in experimental TBI including corticosteroids [47,48]. However, their neuroprotective efficacy has not been successfully translated into the clinical setting [6]. Polyethylene glycol (PEG)-conjugated SOD (PEG-SOD or pegorgotein) has been demonstrated to be the only agent showing efficacy in a Phase II trial of TBI patients receiving 10,000 U/kg of PEG-SOD [95]. In a larger multicenter Phase III trial with 463 patients randomized, 162 received placebo; 149 received PEG-SOD 10 000 U/kg;

and 152 received PEG-SOD 20 000 U/kg [96]. Although, at 3 months, there was an absolute difference of 7.9% improvement, and at 6 months, a 6% improvement using the dichotomized GOS (good recovery or moderately disabled vs. severely disabled, vegetative or dead) [96] in this clinical trial with severe head injury, no statistically significant difference in neurologic outcome or mortality was observed between patients treated with PEG-SOD and those receiving placebo. It should be noted that in the Phase II and III trials PEG-SOD was administered approximately 4 or 8 hr after TBI [95,96]. This delayed treatment of TBI with a single dose of PEG-SOD may not provide timely antioxidant effects. After TBI, there is an immediate, posttraumatic burst in hydroxyl radical formation, followed by a progressive increase in lipid peroxidation in injured brain [97]. A recent study with lecithinized superoxide dismutase (PC-SOD) prevented CA3 neuronal loss 3 days after TBI, and increased the number of surviving CA3 neurons 7 days after TBI when administered 1 min and every 24 hr until 2 or 3 days post-TBI in rats [98]. Further investigations on efficacy of free radical scavengers such as PEG-SOD or PC-SOD for treatment of TBI are warranted in terms of therapeutic windows and dosing paradigms.

7. Promising neuroprotective and neurorestorative approaches

7.1 Erythropoietin (EPO)

EPO, a naturally occurring cytokine, is most widely recognized for its role in stimulating the maturation, differentiation and survival of hematopoietic progenitor cells [99,100]. While EPO and its receptor (EPOR) are only weakly expressed in normal adult brain, expression of EPO and the EPORs is greatly increased in neurons, neuronal progenitor cells, glia and cerebrovascular endothelial cells in response to many different types of cell injury [101,102]. Intraperitoneal administration of rhEPO crosses the blood brain barrier to protect against brain injury [103,104]. When EPO binds to its receptors, it causes dimerization of receptor, autophosphorylation of Janus-tyrosine-kinase-2 (JAK-2) and receptor activation. JAK-2 activation leads to phosphorylation of several downstream signaling pathways such as phosphatidylinositol 3-kinase (PI3K) [105]. PI3K then activates v-akt murine thymoma viral oncogene homolog (Akt) [106]. These pathways are crucial for the therapeutic efficacy of EPO, since specific inhibitors of the PI3K pathway largely abolish the EPO-increased neuronal survival in a model of hypoxia [106]. EPO activates PI3K/Akt and extracellular signal-regulated kinase (ERK1/2) and promotes neural progenitor cell migration in cultured mouse brain endothelial cells [107].

A systemic injection of a single dose of rhEPO transiently increases adult hippocampal neurogenesis without long-term effects in normal mice [108]. However, rhEPO administration for 14 days significantly increases the number of BrdU-labeled cells in both the contralateral and ipsilateral DG after TBI and promotes restoration of spatial memory after TBI [26]. rhEPO administration significantly increases the percentage of newly generated cells that differentiate into mature neurons in the granular cell layer of both the contralateral and ipsilateral DG. A significant increase in BDNF expression and improvement in spatial learning are seen in animals treated with rhEPO or CEPO after TBI [109]. Interestingly, after treatment of TBI with rhEPO, male mice exhibit higher neurogenesis in the DG and cortex than the female mice [30]. At present, there are three ongoing clinical trials for treatment of TBI with EPO [23]: EPO effects after TBI (Medical College of Wisconsin, NCT00260052), Effects of EPO on cerebral vascular dysfunction and anemia in TBI (Baylor College of Medicine, NCT00313716), and safety of darbepoetin alfa treatment in patients with severe TBI (Royal Alexandra Hospital, University of Alberta, NCT00375869). CEPO devoid of hematopoietic bioactivity (i.e., does not increase hematocrit) has also been shown to improve functional recovery after stroke and TBI [109,110]. A safety study using CEPO (Lu AA24493) to treat patients with acute ischemic stroke is ongoing (NCT00756249) [24].

More recently, it has been demonstrated that helix B (amino acid residues 58-82) of EPO and an 11-aa peptide composed of adjacent amino acids forming the aqueous face of helix B are both tissue protective, as confirmed by its therapeutic benefit in models of ischemic stroke and renal ischemia-reperfusion [111]. Further, this peptide simulating the aqueous surface of helix B also exhibits EPO's trophic effects by accelerating wound healing and augmenting cognitive function in rats [111]. As anticipated, neither helix B nor the 11-aa peptide is erythropoietic in vitro or in vivo. Thus, the tissue-protective activities of EPO are mimicked by small, nonerythropoietic peptides that simulate a portion of EPO's three-dimensional structure. These peptides have promise for treatment of brain injury because they do not have side effects of increased hematocrit by EPO.

7.2 Statins

Statins, potent inhibitors of cholesterol biosynthesis, also benefit brain injury. Many of the pleiotropic effects of statins are cholesterol independent, such as improvement of endothelial function, increased NO bioavailability, antioxidant properties, inhibition of inflammatory responses, immunomodulatory actions, upregulation of endothelial nitric oxide synthase (eNOS), decrease of platelet activation, regulation of angiogenesis, neurogenesis and synaptogenesis [112].

Atorvastatin administration after brain injury significantly reduces neurological functional deficits, increases neuronal survival and synaptogenesis in the boundary zone of the lesion and in the CA3 regions of the hippocampus, and induces angiogenesis in these regions in rats subjected to TBI [113].

Simvastatin treatment increases phosphorylation of Akt, glycogen synthase kinase-3β (GSK-3β), and cAMP response element-binding proteins (CREB); elevates the expression of brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) in the DG; increases cell proliferation and differentiation in the DG; and enhances the recovery of spatial learning [114]. Pre-administration of lovastatin to rats subjected to TBI improves functional outcomes and reduces the extent of brain damage, with a concomitant decrease in tissue levels of tumor necrosis factor-α (TNF-α) and interleukin-1 β (IL-1β) mRNA and protein [115]. Protective mechanisms for lovastatin may be partly attributed to a dampening of the inflammatory response [108]. Treatment with atorvastatin or simvastatin (20mg/kg sc., daily once for 3 consecutive days starting at 30 min post injury) markedly reduces functional neurological deficits and degenerating hippocampal neurons, suppresses inflammatory cytokine mRNA expression in brain parenchyma after TBI in mice [116]. Furthermore, statin treatment improves cerebral hemodynamics in mice following TBI [116].

Amnesia is a common sequelae following TBI, for which there is no current treatment. Statins promote rapid recovery of spatial memory after TBI in animals [114,117]. A double-blind randomized clinical trial of 21 patients with TBI (16–50 years of age), with Glasgow Coma Scale scores of 9–13, and intracranial lesions as demonstrated by computed tomography scan has been performed [118]. Each patient received the same treatment and was randomly allocated to receive either rosuvastatin (20 mg/day orally) or placebo over a period of 10 days. No difference was detected in disability at 3 months. While statins may reduce amnesia time after TBI, possibly by immunomodulation, further trials are needed in order to confirm this positive association. Given the wide use of statins, their favorable safety profile in patients, the extensive preclinical data showing both neuroprotection and neurorestoration, and provocative positive clinical data in patients, further clinical studies are warranted to determine the neuroprotective and neurorestorative properties of statins after TBI.

When administered in combination with bone marrow stromal cells (MSCs), atorvastatin increases MSC access and/or survival within the injured brain and enhances functional

recovery compared with monotherapy [119]. Statins induce neuroglial differentiation of human MSCs [120]. A combination therapy of MSCs and atorvastatin amplifies endogenous cellular proliferation [119]. These cholesterol-lowering agents might be used in conjunction with MSC transplantation in the future for treating neurological disorders and injuries.

7.3 Nitric oxide (NO)

NO activates soluble guanylyl cyclase, leading to the formation of cyclic GMP (cGMP). As a second messenger, cGMP is involved in diverse cellular processes, including regulation of cellular proliferation. Increases in cGMP levels enhance proliferation of endothelial cells and motor neurons [112]. Thus, increased cGMP production may facilitate neuroprotection and neurorestoration after TBI. cGMP levels in brain may be increased by cGMP production via increases in NO or inhibition of cGMP hydrolysis using phosphodiesterase 5 inhibitors, e.g. Sildenafil [112].

In the CNS, NO is an important messenger involved in the modulation of sensory motor functions, control of cerebral blood flow and neuroprotection and neurotoxicity after cerebral synaptic formation and remodeling, brain development, synaptic plasticity, neuroendocrine secretion, sensory processing, and cerebral blood flow [121]. However, its role in neurogenesis has not been identified until recently. The inhibitory effect of nNOS-derived NO on DG and SVZ neurogenesis has been demonstrated; an opposite effect has been found for eNOS- and iNOS-derived NO [122]. While the proliferative effect of NO on endogenous progenitor cells in adult brain could be mediated through an increase in the tissue levels of cGMP [123], the antiproliferative effect of NO depends on the inhibition of cyclin-dependent kinases and transcription factors by p53 and the Rb protein, respectively [124]. Atorvastatin upregulates the eNOS isoform and thus increases cGMP [125]. NO donors increase cGMP levels via activation of soluble guanylyl cyclase [123]. Moreover, the effect of cGMP on neurogenesis could be related to the activation of cGMP-dependent protein kinase type I, which has been described to enhance sensory neuron precursor proliferation [126]. Clarification of the effects of different NOS isoforms on neuronal plasticity, survival rate and neurological functions after TBI is needed.

NO promotes angiogenesis, and neurogenesis, and increases neuroblast migration after brain injury such as stroke [112,122,125,127–129]. Our previous findings show that TBI increases proliferation of the progenitor cells in the hippocampus, SVZ, and cortex in both the ipsilateral and contralateral hemispheres [130]. TBI alters the migration pathway of SVZ progenitor cells from the rostral migratory stream (RMS) to the striatum and corpus callosum. Treatment with NO donor, DETA/NONOate, enhances these responses. DETA/NONOate increases progenitor cell migration, induces differentiation of the progenitor cells, and enhances the survival of the newly generated cells in the striatum, corpus callosum, and boundary zone of the lesion. DETA/NONOate treatment improves the neurological outcome in rats subjected to TBI [130]. In addition, injection of DETA/NONOate enhances the TBI-induced cell proliferation in the SGZ, hilus, and CA1 3 of the ipsilateral hippocampus after TBI. Use of DETA/NONOate also promotes survival of the newly generated cells in the hippocampus after TBI. Therefore, DETA/NONOate enhances progenitor cell proliferation and survival in the hippocampal formation after TBI in rats, which may contribute to neurological functional improvement. Sildenafil, a phosphodiesterase type-5 inhibitor, increases cGMP level [131]. A clinical trial of Sildenafil for treatment of subacute ischemic stroke is ongoing in Henry Ford Health System (NCT00452582) [24].

7.4 S100B

The S100B protein belongs to a multigenic family of low molecular weight calcium-binding S100 proteins [132]. S100B is primarily produced by glial cells [133]. S100B acts as a

neurotrophic factor and a neuronal survival protein. In contrast, overproduction of S100B by activated glia can lead to exacerbation of neuroinflammation and neuronal dysfunction [134]. S100B is released after brain insults, and serum levels are positively correlated with the degree of injury and negatively correlated with outcome [135,136]. Serum and brain S100B levels are poorly correlated, with serum levels dependent primarily on the integrity of the blood-brain barrier, and not the level of S100B in the brain. Cerebrospinal S100B may be useful as one of the outcome predictors in cases of severe TBI in adults [137], but is not a reliable prognostic index in pediatric TBI [138].

Interestingly, while higher serum levels of S100B seem to reflect the degree of blood brain barrier opening and severity of injury, a beneficial effect of intraventricular S100B administration on long-term functional recovery after TBI has been demonstrated [139]. S100B has been shown to improve memory function [31]. S100B profoundly increases hippocampal neurogenesis 5 weeks after TBI. Spatial learning ability, as assessed by the Morris water maze on day 30–34 post-injury, reveals an improved cognitive performance after S100B infusion. An intraventricular S100B infusion induces neurogenesis within the hippocampus, which can be associated with an enhanced cognitive function following experimental TBI [140]. So far, S-100B has not been used for clinical treatment of TBI. However, in a clinical trial entitled S-100B as Pre-Head CT Scan Screening Test After Mild TBI (NCT00717301) [24], S-100B will be used to determine the ability of a serum to predict traumatic abnormalities on brain CT scan after mild TBI. The secondary objective is to determine the relationship between initial S-100B levels and cognitive outcome at one month. In a recent report with 102 adult patients with severe TBI admitted between June 2001 and November 2003, serum S-100B levels were measured on admission and every 24 hr thereafter for a maximum of 7 days. Initial S-100B levels were significantly related to pupillary status, computed tomography severity 1, and 1-month survival. Initial S-100B was an independent predictor of 1-month survival, in the presence of dilated pupils, and with increased age. Subjects with initial levels above 1 μg/l had a nearly threefold increased probability of death within 1 month. Serum S-100B alteration indicated neurological improvement or deterioration. Finally, surgical treatment reduced S-100B levels. Serum S-100B protein reflects injury severity and improves prediction of outcome after severe TBI. S-100B may also have a role in assessing the efficacy of treatment after severe TBI [141].

7.5 Bone marrow stromal cells (MSCs)

Neuronal tissue has limited capacity to repair after injury. Cellular therapies using neural stem/progenitor cells are promising approaches for the treatment of brain injury. However, the clinical use of embryonic stem cells or fetal tissues is limited by ethical considerations and other scientific problems. Thus, MSCs could represent an alternative source of stem cells for cell replacement therapies. MSCs are mesoderm-derived cells, primarily resident in adult bone marrow. MSCs can give rise to neuronal cells as well as many tissue-specific cell phenotypes [142,143].

MSCs spontaneously express certain neuronal phenotype markers in culture, in the absence of specialized induction reagents [144]. When cultured in neural stem cell (NSC) culture conditions, 8% of MSCs are able to generate neurospheres. These MSC-derived neurospheres express characteristic NSC antigens (nestin and musashi-1) and are capable of self-renewal and multi-lineage differentiation into neurons, astrocytes and oligodendrocytes. When these MSC-derived neurospheres are co-cultured with primary astrocytes, they differentiate into neurons, forming dendrites, axonal processes and synapses as well as firing tetrodotoxin-sensitive action potentials [145]. Nestin-positive MSCs can differentiate in vitro into excitable neuron-like cells. MSC-derived neuron-like cells exhibit several electrophysiological key properties classically devoted to neurons, including firing of action potentials [146].

When grafted into the lateral ventricles of neonatal mouse brain, MSCs migrate extensively and differentiate into olfactory bulb (OB) granule cells and periventricular astrocytes [144]. Intra-arterially infused rat MSCs can migrate into injured rat brain and survive [147]. Most of these cells are distributed in the boundary zone of the lesion and the corpus callosum of the ipsilateral hemisphere. Some implanted cells express the markers for neurons and astrocytes. MSC treatment significantly improves neurological functional recovery after TBI [147–149].

When MSCs are administered 24 hours after TBI, functional outcome is significantly improved after treatment [32,150–153]. This benefit is probably not attributable to the very few MSCs that differentiate into brain cells [147]. Instead, it seems to be that MSCs secrete various growth factors [34,154–156] that promote functional outcome after injury, thus amplifying their endogenous brain levels. MSCs also induce intrinsic parenchymal cells to produce these growth factors [155]. Recent data indicate that growth factors such as fibroblast growth factor-2 (FGF-2), VEGF, and BDNF and promote neurogenesis [156–158]. The improvement in functional outcome observed after MSC treatment of TBI involves more than one mechanism. MSCs produce and induce within parenchymal cells many cytokines and trophic factors that enhance angiogenesis and vascular stabilization in the lesion boundary zone, where the majority of MSCs that survive in the brain are located. In addition, MSCs induce other proteins within injured brain, such as bone morphogenetic proteins BMP2 and BMP4 or connexin 43 expression in astrocytes [159]. In concert with enhancing angiogenesis, neurogenesis, and synaptogenesis, MSCs significantly decrease glial scar formation and promote glial–axonal remodeling [160]. MSCs influence several neural restorative functions such as synaptogenesis [34], angiogenesis [34,153], and neurogenesis [112]. Thus, MSCs act in a pleiotropic way to stimulate brain remodeling. MSCs alone do not reduce the lesion volume after TBI. Our recent study shows that collagen scaffolds populated with MSCs improve spatial learning and sensorimotor function, reduce the lesion volume, and foster the migration of MSCs into the lesion boundary zone after TBI in rats compared to MSCs without scaffolds [161].

The safety and feasibility of autologous MSC treatment of TBI patients have been assessed a single center [162]. TBI patients received autologous cell transplantation of MSCs isolated by bone marrow aspiration and expanded in culture. A primary administration of MSCs was applied directly to the injured area during the cranial operation with a second iv dose of MSCs. There was no immediate or delayed toxicity related to the cell administration within the 6-month follow-up period. Neurologic function was significantly improved at 6 months after MSC therapy [162].

7.6 Inhibitors of complement system

Activation of the innate immune response, including the complement system, plays an important role in the pathogenesis of TBI [163]. Research strategies to prevent the neuroinflammatory pathological sequelae of TBI have largely failed in clinical trials [6], exemplified by the recent failure of the "CRASH" trial (Corticosteroid randomization after significant head injury) [164]. These data imply that the "pan"-inhibition of the immune response by the use of glucocorticoids may represent an approach that is too broad and unspecific for controlling neuroinflammation after TBI. Complement can be activated either through the classical, lectin, or alternative pathways [165]. Thus, research efforts are currently focusing on more specific therapeutic modalities, such as the inhibition of the complement cascade [166]. For instance, by the use of a recombinant Crry molecule (termed Crry-Ig), a potent murine complement inhibitor at the level of C3 convertases, the systemic injection of 1 mg Crry-Ig at 1 and 24 hr after TBI resulted in a significant neurological improvement for up to 7 days [167]. A monoclonal anti-factor B antibody, a specific and potent inhibitor of the alternative complement pathway, led to a substantial attenuation of cerebral tissue damage and neuronal cell death when administered at 1 and 24 hr after TBI [165]. Pharmacological

complement inhibition represents a promising approach for attenuation of neuroinflammation and secondary neurodegeneration after TBI. Although activation of the complement system is known to promote tissue injury, recent evidence has also indicated that this process can have neuroprotective effects [168,169]. Further studies on the therapeutic effects of inhibition of the complement system should be pursued with caution.

7.7 Physical therapy

7.7.1 Environmental enrichment (EE)—New neurons are generated in two areas of the adult brain, the SVZ and the SGZ, throughout life and integrate into the normal functional circuitry. This process is not fixed, but can be highly manipulated, revealing a plastic mechanism by which the performance of brain can be optimized for a given environment [170]. Adult hippocampal neurogenesis in mice living in an enriched environment (EE) is higher than in controls [171]. EE doubles the amount of new hippocampal granule cells. Relatively, the increase in neuronal phenotypes is entirely at the expense of newly generated astrocytes [172]. EE (particularly during the earlier period) improves performance on the Morris water maze and tends to increase immunoreactivity to CREB in the hippocampus [173]. Late application of EE is also sufficient for a continuous restoration of neurological functions after TBI [174].

EE and voluntary exercise (VE) have consistently been shown to increase adult hippocampal neurogenesis and improve spatial learning ability. Evidence exists that EE and VE affect different phases of the neurogenic process in distinct ways. EE increases the likelihood of survival of new cells, whereas VE increases the level of proliferation of progenitor cells [175]. BDNF is required for the enhancement of hippocampal neurogenesis following EE [176]. Increasing hippocampal VEGF increases neurogenesis associated with improved cognition in adult rats. Inhibition of VEGF expression by RNA interference completely blocks the environmental induction of neurogenesis [177]. EE leads to improved long-term recognition memory and increases hippocampal neurogenesis. Elimination of dividing cells with methylazoxymethanol acetate treatment during EE completely prevents both the increase in neurogenesis and enrichment-induced long-term memory improvement [178]. Relatively low doses of irradiation can acutely abolish precursor cell proliferation in the DG by more than 90% [179]. This reduction in precursor proliferation is persistent and led to a significant decline in the granule cell population 9 months later. EE housing enhances the number of newborn neurons and increases residual neurogenesis. EE also significantly increases the total number of immature neurons in the DG. These irradiated animals after EE housing show a significant improvement in spatial learning and memory during the water-maze test and in rotarod motor. These results support that adult-generated neurons participate in modulating memory function.

Among EE, physical exercise and training, training/learning is generally more effective on structural and functional assessments of recovery than physical exercise, and EE is a more potent therapy than either of these two other treatments [180], the combination of enriched experience with other neurosurgical and/or pharmacological treatments may further improve its therapeutic effectiveness.

The beneficial effects of EE on behavioral recovery following fluid percussion injury may be related to increased neurogenesis in the granular cell layer [32]. EE-mediated functional improvement after TBI is contingent on task-specific neurobehavioral experience [181]. EE is a very effective treatment which improves motor function and spatial learning after TBI [182]. Interestingly, intervention with EE after experimental TBI enhances cognitive recovery in male but not female rats [183].

7.7.2 Exercise—Physical activity also causes a robust increase in neurogenesis in the DG of the hippocampus, a brain area important for learning and memory. The positive correlation

between running and neurogenesis has generated the hypothesis that the new hippocampal neurons may contribute to, in part, improved learning associated with exercise [184]. Exercise increases synaptic plasticity by directly affecting synaptic structure and potentiating synaptic strength, and by strengthening the underlying systems that support plasticity including neurogenesis, metabolism and vascular function [185].

Exercise can increase levels of BDNF, stimulate neurogenesis, increase resistance to brain insult and improve learning and mental performance. In addition to increasing levels of BDNF, exercise mobilizes gene expression profiles that would be predicted to benefit brain plasticity processes [186]. Thus, exercise could provide a simple and effective means to maintain brain function and promote brain plasticity. Running doubles the number of surviving newborn cells in amounts similar to EE [187]. Lack of exercise via hindlimb suspension reduces neurogenesis with downregulation of neurotrophic factors [188]. However, the low-, but not the high-, intensity exercise paradigm results in significantly increased expression of BDNF, NMDAR1, and Flk-1 mRNA, which contribute to hippocampal neurogenesis [189].

However, at present there are no standardized recommendations concerning physiotherapy of individuals with TBI resulting in a high variability of methods and intensity [190]. Fourteen studies met the inclusion criteria and were grouped into subgroups: sensory stimulation, therapy intensity, casting/splinting, exercise or aerobic training and functional skill training. While for sensory stimulation evidence could not be proven, strong evidence exists that more intensive rehabilitation programs lead to earlier functional abilities.

8. Expert opinion

The current medical management of TBI patients mainly includes specialized prehospital care, intensive clinical care and long-term rehabilitation, but lacks clinically proven effective management with neuroprotective agents to limit secondary injury or enhance repair [191]. The enormous burden of TBI, however, clearly supports the need for such neuroprotective and/or neurorestorative agents or approaches. However, translating promising preclinical benefit into the clinical setting has proven difficult. The disappointing clinical phase-III trials may be due to heterogeneity of the population of TBI patients and variability in treatment approaches. However, there are many aspects that need to be considered before and during the clinical trials. First, prior to translation of an agent into clinical trial, preclinical evidence should be sufficiently strong, based on multiple experiments, preferably in several models, and include optimal administration routes and doses, single doses versus multiple doses, bolus dose versus continuous infusion, and therapeutic windows. Extensive pharmacokinetic evaluation of the potential neuroprotective agents in the injured brain should also be performed, ensuring adequate tissue penetration once the agent is studied in efficacy trials. Second, although many pathophysiologic cascades inducing secondary injury have been identified, it remains uncertain which of and where these cascades are active in individual TBI patients after injury. Moreover, some pathways may initially be detrimental, but can be protective at later stages. Therefore, effective translation of agents into clinical trials will probably require a more mechanistic approach, i.e., only patients with the proven presence of a certain pathophysiological mechanism are included in trials evaluating a compound that interferes with this particular mechanism. Third, many pathophysiologic cascades may contribute to secondary injury after TBI. Combined treatments may provide better benefits. These potential combinations include agents (e.g., pharmaceuticals or cytokines) or cells (e.g., MSCs, neural stem cells) or other approaches (physical or electric stimulation). Fourth, inadequacy in the design and analysis of clinical trials may affect the outcome. A more sensitive analysis of outcome in new clinical trials is warranted, with an important role for surrogate outcome measures as well as new types of outcome analysis. Further development of evidence-based treatments and implementation

of these suggestions are likely to improve the chance that experimentally effective agents will show positive results in future clinical trials.

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Table 1

Competitive environment

Drugs or approaches	Company group	Development stage (trial name)	Mechanism of action
Nimodipine	Bayer	HIT 4	Calcium channel blocker
SNX-111	Neurox/Parke Davis	I/II (terminated due to high mortality)	N-type calcium channel blocker
Corticosteroids	Pharmacia/Upjohn, Pfizer	CRASH	Anti oxidative effect
Darbepoetin alfa	Amgen	II	Erythropoiesis and neuroprotection
Dexanabinol	Pharmos	III	NMDA receptor antagonist
Recombinant factor VIIa	NovoSeven	I	Haemostatic effect
Methylphenidate (Ritalin)	Novartis	IV	Dopamine antagonist
Amantadine	Banner Pharmacaps	II	Dopaminergic agonist
Anatibant	Solvay	II	Bradykinin B2 antagonist
Progesterone	Emory University Investigational Drug Service	II (ProTECT)	Multiple effects (anti-inflammatory, anti-oxidative, anti- apoptotic)
Rosuvastatin(Crestor)	AstraZeneca	I	β-hydroxy-β-methylglutaryl coenzyme A reductase inhibitor
EPO	Amgen	III	Erythropoiesis and neuroprotection

ATTACHMENT 3

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Classification of Traumatic Brain Injury for Targeted Therapies

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ABSTRACT

The heterogeneity of traumatic brain injury (TBI) is considered one of the most significant barriers to finding effective therapeutic interventions. In October, 2007, the National Institute of Neurological Disorders and Stroke, with support from the Brain Injury Association of America, the Defense and Veterans Brain Injury Center, and the National Institute of Disability and Rehabilitation Research, convened a workshop to outline the steps needed to develop a reliable, efficient and valid classification system for TBI that could be used to link specific patterns of brain and neurovascular injury with appropriate therapeutic interventions. Currently, the Glasgow Coma Scale (GCS) is the primary selection criterion for inclusion in most TBI clinical trials. While the GCS is extremely useful in the clinical management and prognosis of TBI, it does not provide specific information about the pathophysiologic mechanisms which are responsible for neurological deficits and targeted by interventions. On the premise that brain injuries with similar pathoanatomic features are likely to share common pathophysiologic mechanisms, participants proposed that a new, multidimensional classification system should be developed for TBI clinical trials. It was agreed that preclinical mod-

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els were vital in establishing pathophysiologic mechanisms relevant to specific pathoanatomic types of TBI and verifying that a given therapeutic approach improves outcome in these targeted TBI types. In a clinical trial, patients with the targeted pathoanatomic injury type would be selected using an initial diagnostic entry criterion, including their severity of injury. Coexisting brain injury types would be identified and multivariate prognostic modeling used for refinement of inclusion/exclusion criteria and patient stratification. Outcome assessment would utilize endpoints relevant to the targeted injury type. Advantages and disadvantages of currently available diagnostic, monitoring, and assessment tools were discussed. Recommendations were made for enhancing the utility of available or emerging tools in order to facilitate implementation of a pathoanatomic classification approach for clinical trials.

Key words: clinical trial; head injury; intervention; outcome; therapy

INTRODUCTION

TRAUMATIC BRAIN INJURY (TBI) remains a major cause of death and disability. Although much has been learned about the molecular and cellular mechanisms of TBI in the past 20 years, these advances have failed to translate into a successful clinical trial, and thus there has been no significant improvement in treatment. Among the numerous barriers to finding effective interventions to improve outcomes after TBI, the heterogeneity of the injury and identification and classification of patients most likely to benefit from the treatment are considered some of the most significant challenges (Doppenberg et al., 2004; Marshall, 2000; Narayan et al., 2002).

The type of classification one develops depends on the available data and the purpose of the classification system. An *etiological classification* describes the factors to change in order to prevent the condition. A *symptom classification* describes the clinical manifestation of the problem to be solved. A *prognostic classification* describes the factors associated with outcome, and a *pathoanatomic classification* describes the abnormality to be targeted by the treatment. Most diseases were originally classified on the basis of the clinical picture using a symptom-based classification system. Beginning in the 18th century, autopsies became more routine, and an increasing number of disease conditions were classified by their pathoanatomic lesions. With improvement of diagnostic tools, modern disease classification in most fields of medicine uses a mixture of anatomically, physiologically, metabolically, immunologically, and genetically defined parameters.

Currently, the primary selection criterion for inclusion in a TBI clinical trial is the Glasgow Coma Scale (GCS), a clinical scale that assesses the level of consciousness after TBI. Patients are typically divided into the broad categories of mild, moderate, and severe injury. While the GCS has proved to be extremely useful in the clinical management and prognosis of TBI, it does not provide specific information about the pathophysiologic mechanisms responsible for the neurological deficits. This is clearly demonstrated in Figure 1, in which all six patients are classified as having a severe TBI. Given the heterogeneity of the pathoanatomic features depicted in these computed tomography (CT) scans, it is difficult to see how a therapy targeted simply for severe TBI could effectively treat all of these different types of injury. Many tools such as CT scans and magnetic resonance imaging (MRI) already exist to help differentiate the multiple types of brain injury and variety of host factors and other confounders that might influence the yield of clinical trials. In addition, newer advances in neuroimaging, biomarkers, and bioinformatics may increase the effectiveness of clinical trials by helping to classify patients into groups most likely to benefit from specific treatments.

In order to review what is known about the heterogeneity of TBI and to develop strategies to capture and incorporate this information into research studies, the National Institute of Neurological Disorders and Stroke (NINDS) sponsored a workshop on *Classification of TBI for Targeted Therapies* in October, 2007. Co-sponsors included the Brain Injury Association of America, the Defense and Veterans Brain Injury Center, and the National Institute on Disability and Rehabilitation Research.

WORKSHOP FORMAT

The workshop organizing committee was co-chaired by Geoffrey Manley and Ramona Hicks, and members included Ronald Hayes, Linda Phillips, and Hilaire Thompson. Using the "grand challenge" approach for accelerating the advancement of science, three multidisciplinary teams were charged with proposing ways to (1)

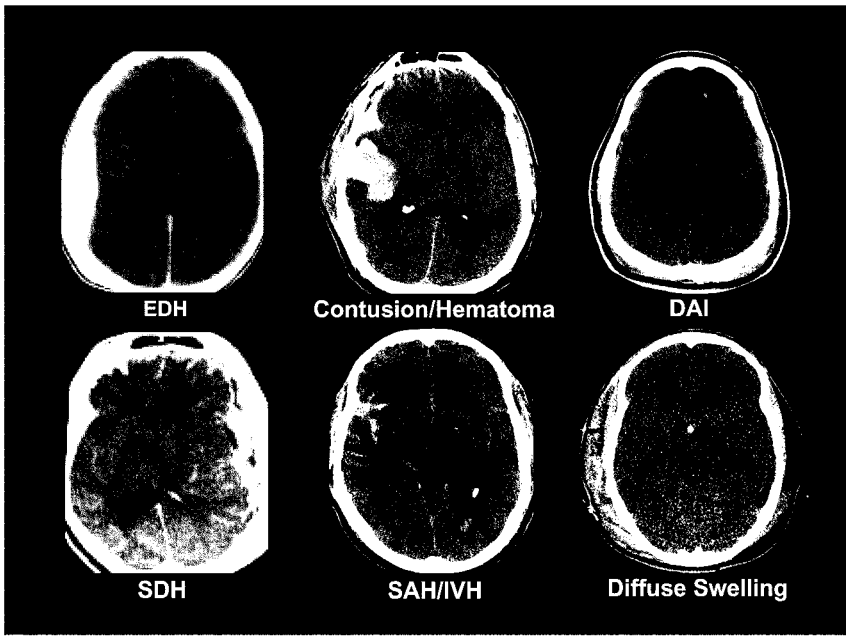

FIG. 1. Heterogeneity of severe traumatic brain injury (TBI). Computed tomography (CT) scans of six different patients with severe TBI, defined as a Glasgow Coma Scale score of <8, highlighting the significant heterogeneity of pathological findings. CT scans represent patients with epidural hematomas (EDH), contusions and parenchymal hematomas (Contusion/Hematoma), diffuse axonal injury (DAI), subdural hematoma (SDH), subarachnoid hemorrhage and intraventricular hemorrhage (SAH/IVH), and diffuse brain swelling (Diffuse Swelling).

use existing and emerging tools to detect the most common types and patterns of injury associated with TBI; and (2) develop a classification scheme that would cluster TBI patients into groups based on these major types of injury (see Appendix for workshop agenda). The teams had wide geographic representation across the USA and Europe, and represented scientists at various stages of their careers.

Prior to the workshop, each team was asked to prepare a position paper to:

- Summarize the current classification systems for TBI;
- List the most common forms of brain and neurovascular injury associated with TBI and their frequency;
- Identify currently available diagnostic tools and describe a protocol for using these tools to clearly delineate these common forms of brain and neurovascular injury and their severity;
- List data elements required for classifying TBI patients into groups based on the nature and severity of their injury;
- Describe the steps needed to develop a reliable, efficient and valid classification system for TBI that will be used to link specific patterns of brain and neurovascular injury with appropriate medical interventions.

The position papers were forwarded to an advisory panel before the workshop to allow them to prepare discussion questions. Information from the position papers

and from the discussions during the workshop provided the basis for this manuscript.

OVERVIEW OF CURRENT CLASSIFICATION SYSTEMS FOR TRAUMATIC BRAIN INJURY

Head injuries most often have been classified by one of three main systems: (1) clinical indices of severity, used most often in clinical research to compare patients among centers; (2) pathoanatomic type, used most often to describe injuries for acute management; and (3) physical mechanism (i.e., causative forces associated with the injury), used most often in the biomechanics and prevention fields. In addition, pathophysiology of injury and evolution of injury cascades have been used to characterize aspects of TBI, particularly in basic science and research. Finally, multiple features can be combined, typically with the help of biostatisticians, to create prognostic classification criteria. Many of these schemes overlap with one another, and workers in different fields may use terminology in different ways, adding to some of the confusion in the head injury field and in clinical trial efforts. In addition, classification schemes will likely continue to evolve as new tools and concepts shed light on the causes and consequences of the disease process.

Classification by Injury Severity

In the head injury field, symptom classification generally has been based on clinical indices of injury severity at presentation. To date, the majority of clinical treatment trials for TBI have classified and entered patients based on neurologic injury severity criteria (Narayan et al., 2002). The 15-point GCS (Teasdale et al., 1974) is the most commonly used neurologic injury severity scale for adults, because of its high inter-observer reliability and generally good prognostic capabilities (Narayan et al., 2002). Patients with severe TBI, defined typically as GCS of 8 or less, have most often been enrolled in clinical trials. This group has the highest mortality and morbidity and was presumed to have the best chance of demonstrating a treatment effect. In addition, hundreds of preclinical trials, mostly using rodent models, have targeted animals with clinically and/or histologically significant injuries.

Other neurological severity scales include the Brussells Coma Grades, Grady Coma Grades, Innsbruck Coma Scale, and the FOUR score scale (Brihaye et al., 1978; Fleischer et al., 1976; Gerstenbrand et al., 1970; Wijdicks et al., 2005). A number of scales are also available to assess extracranial injury and physiologic instability which can influence outcome, including the Abbreviated Injury Scale (AIS) (Medicine AftAoA., 1976; Medicine AftAoA., 1990) and the Injury Severity Score (ISS) (Baker et al., 1974). The AIS is a detailed injury scoring system for each of six body regions; the ISS is designed to quantify the severity of multiple body region injuries. The Trauma Score is a simplified scale which includes the GCS, respiratory rate, respiratory expansion, systolic blood pressure, and capillary refill in order to give an overall score (1–16) to assess injury severity (Champion et al., 1981). It has the advantage of being rapidly applied in the emergency setting.

Several problems arise from utilizing clinical injury severity indices as entry criteria into clinical trials for head injury. Factors such as patient age, extracranial injuries, and physiologic instability influence outcome (Marmarou et al., 2007; Murray et al., 2007). Thus, when trials are analyzed without taking these variables into account, confounding prognostic factors may override potential treatment effects. Furthermore, improvements in prehospital care and routine transfer of patients from community facilities to trauma centers mean that the majority of patients with more significant-appearing injuries now receive intervention prior to arrival at the study center. Intubation, sedation, pharmacologic paralysis, and intoxication complicate and often preclude the accurate assessment of neurologic injury severity on clinical grounds (Balestreri et al., 2004; Gabbe et al., 2003; Stocchetti et al., 2004). Specific populations of patients are difficult to assess with the GCS, including infants, young children and patients with pre-existing neurologic impairment. The GCS is also a poor discriminator for less severe TBI, which account for 80–90% of all cases.

A more fundamental issue surrounding trial entry solely based on clinical indices is whether this is really the most scientifically appropriate way to match specific treatments to specific patients. Clearly, patients who have in common a "severe" injury phenotype may vary widely in other injury classification schemes, such as those based on pathoanatomic or pathophysiological features (Fig. 1), which may be more relevant to the neuroprotectant action of a particular intervention.

Pathoanatomic Classification

A pathoanatomic classification describes the location or anatomical features of the abnormality to be targeted by a treatment, and generally falls into the scheme of "where and what" terminology. The majority of patients with more severe injuries have more than one injury type when classified in this way. Going from the outside of the head and working inwards, injury types include scalp laceration and contusion, skull fracture, epidural hemorrhage, subdural hemorrhage, subarachnoid hemorrhage

(SAH), brain contusion and laceration, intraparenchymal hemorrhage, intraventricular hemorrhage, and focal and diffuse patterns of axonal injury. Each of these entities can be further described by their extent, location, multiplicity, and distribution. Other radiologically and/or pathologically visible entities do not fit a strict "pathoanatomic" classification, but overlap with pathophysiologic classifications (e.g., ischemia, diffuse brain swelling) or mechanistic classifications (e.g., gunshot wounds, blast injuries).

That pathoanatomic type of injury influences outcome has long been recognized, particularly once imaging of patients with neurotrauma became routine (Gennarelli et al., 1982a). A number of classification schemes of these entities have been used for pathoanatomic description in many acute head injury studies, including the Marshall score for CT findings (Marshall et al., 1992) and the Rotterdam score (Maas et al., 2005). When applied to CT scans in early severe and moderate TBI, the Marshall score, an ordinal numbering score with 6 categories, has been shown to be powerful in predicting both the risk of increased intracranial pressure (ICP) and outcome in adults. The Marshall classification is widely used and pragmatic, but has many recognized and accepted limitations, including difficulties in classifying patients with multiple injury types and standardization of certain features of the CT scan. The Rotterdam score is a more recent and standardized CT-based classification system, which uses combinations of findings to predict outcome. This system has not been fully validated, and requires more study, but overcomes some of the limitations of the Marshall score.

Classification by Physical Mechanism

Etiological classification of head injuries by physical mechanism of injury has certain advantages in understanding how specific forces at specific magnitudes result in predictable patterns of injury. Thus, injuries can be classified according to whether the head is struck or strikes an object (contact or "impact" loading) and/or the brain moves within the skull (noncontact or "inertial" loading). The magnitude and direction of each type or combination of loading forces may predict type and severity of injury (Gennarelli et al., 1985). There is considerable, but not perfect, correlation between physical mechanism of injury and pathoanatomic injury type. For instance, most focal injuries, such as skull fracture, brain contusion, and epidural hematoma, result from impact loading, whereas inertial loading generally causes more diffuse injuries such as concussion, subdural hematoma and diffuse axonal injury (DAI). Recently there has been increased interest in blast mechanisms of brain injury, which are at present incompletely understood. Mechanistic classification has great utility in modeling injuries and in prevention. However, in clinical practice most often the loading conditions must be estimated from incomplete details of the traumatic event, and inferred in combination with the pathoanatomic findings and the clinical severity of injury.

Classification by Pathophysiology

Alternatively, pathophysiologic mechanisms may form the basis of an etiologic classification and/or characterization of targets for treatment. In head injury, these can include processes which are set in motion by the injury event and take time to evolve, as well as events which compound or complicate the brain injury such as systemic insults. One widely used scheme in head injury relating to pathophysiologic processes is that which differentiates "primary" versus "secondary" damage (Adams et al., 1994). While authors vary in exactly how these terms are used, in general, primary injury refers to the unavoidable, immediate parenchymal damage occurring at the time of injury, while secondary injury refers to potentially avoidable damage that occurs at variable times after injury. The importance of secondary insults, such as hypoxia, hypertension, hypercarbia, hyponatremia, and seizures, has gained widespread recognition. However, pathophysiologic classification schemes have not been commonly used in treatment trials. This may be due, in part, to challenges associated with capturing a spatiotemporal profile of the patient's injury, limited availability and usage of sophisticated monitoring techniques needed for measurement of physiologic parameters, and difficulties in distinguishing inevitable but progressive cell damage from potentially reversible injury cascades.

Classification by Prognostic Modeling

In early clinical research in head injury, investigators found that it was difficult to establish confident predictions of outcome after TBI on admission or to compare outcomes among centers. Thus, the GCS was designed as an early injury severity assessment tool and proved to have prognostic value (Jennett et al., 1975). However, the GCS provides information only in one knowledge domain (clinical severity) and may be difficult to measure on admission, as discussed earlier. Recent work from the International Mission for Prognosis and Clinical Trial (IMPACT) studies (Murray et al., 2007) has shown that predictions can be made on admission and has resulted in the development of three valid prognostic models of increasing complexity. This work is particularly relevant to mitigating the effects of prognostic variability in Phase III trials rather than specifically identifying subgroups of

patients likely to benefit from a given targeted intervention.

In an ideal world, a TBI classification system would be able to select out patients with the potential to benefit from the intervention under investigation, from pathoanatomic, pathophysiologic, and prognostic perspectives. It is crucial to differentiate between the concepts of prognostic factors and factors which relate to a patient's potential to benefit from an intervention. Whereas certain prognostic factors are also markers of potential benefit (e.g., CT evidence of the nature of the brain injury), other factors such as age and impairment of consciousness are primarily prognostic factors. More direct, diagnostic measures of the underlying pathophysiology (e.g., ICP, lesion volume, microdialysis, blood flow, tissue oxygenation, coagulation status) are likely to have greater potential to identify patients who will benefit from a given intervention. Therefore, the intent and focus of this workshop was on developing an improved classification system for TBI that incorporates both diagnostic and prognostic perspectives with the goal of enhancing the success of future clinical trials.

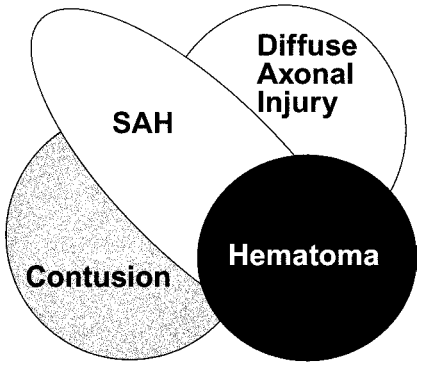

FIG. 2. Common pathoanatomic sequelae of traumatic brain injury (TBI). The Venn diagram represents the four main pathoanatomic sequelae of TBI: hematomas, including epidural, subdural, and parenchymal lesions; diffuse axonal injury; subarachnoid hemorrhage (SAH); and contusions.

COMMON PATHOANATOMICAL AND PATHOPHYSIOLOGICAL SEQUELAE OF TRAUMATIC BRAIN INJURY

Numerous postmortem studies and imaging studies have shown that there are four main pathoanatomical sequelae of TBI: contusions; SAH; hematomas, including epidural, subdural, and intraparenchymal lesions; and DAI (Fig. 2). While there is general consensus regarding the definition for most of these lesions, DAI is defined differently by different specialties, and the definition has evolved over time. Initially, the term was coined to describe the neuropathologic pattern created from pure inertial (noncontact) loading in a large animal model (Gennarelli et al., 1982b) which was developed to explain the clinical and pathologic findings seen in human patients with severe head injuries who died or had poor outcomes without mass lesions (Adams et al., 1977, 1982; Strich, 1956, 1961). Patients with this traditional definition of DAI are in profound coma from the onset of injury and usually have a poor outcome. As MRI techniques and sensitivity have improved, the radiologic pattern associated with DAI is now seen in patients with much milder injuries. Because some animal models and human patients have more restricted patterns of axonal injury than that seen in the classic descriptions, the term "traumatic axonal injury" (TAI) has been used for these more limited injuries. For these reasons, the term "DAI" needs to be carefully defined in clinical studies of TBI.

Ischemic brain injury, cerebral edema and other pathophysiologic sequelae, in some cases, might be included in a "pathoanatomic" classification scheme, but in other instances would be more accurately described as pathophysiologic cascades or secondary insults. Depending on the specific entity and etiology, such processes could be viewed as therapeutic targets—that is, processes set in motion by the initial injury event which might be remediable. Alternatively, these could be viewed as confounding or prognostic variables which occur in some patients with a primary pathoanatomic injury type (for instance, subdural hematoma with an episode of delayed hypotension and ischemia). Many pathophysiologic sequelae have been extensively described in fatal TBI using autopsy specimens (Graham et al., 2005). Insights into the etiology and temporal evolution of these events, which may vary from patient to patient, have been provided by newer diagnostic modalities, such as CT angiography, cerebral blood flow measurement, transcranial Doppler (TCD), and angiography. These tools have also revealed additional pathophysiologic sequelae. For example, TCD data suggest that posttraumatic vasospasm may occur in up to 25% of patients with severe head injury (Oertel et al., 2005), often when severe basal SAH is present. Recent reports on blast injury suggest that vasospasm is especially important in modern military TBI (Armonda et al., 2006). Many of the above sequelae often coexist in patients with severe and fatal injuries as

well as patients with moderate and mild injuries as classified by GCS (Fig. 2).

Although the incidence of isolated, specific types of injury is known for fatal cases of TBI, the incidence, patterns and magnitude of overlapping injuries across a spectrum of injury severity have not been clearly described. To better understand these complex relationships, more information about common patterns of injury across the spectrum of TBI is critical for developing an improved classification system for targeted therapies.

SUMMARY OF KEY WORKSHOP RECOMMENDATIONS

The initial response of the workshop participants to developing a new classification system for TBI ranged from enthusiasm for improving the approach used for clinical trials by exploring the use of existing and new technologies to skepticism about what could realistically be achieved. Others believed that the workshop was "reinventing the wheel" because similar discussions had taken place decades ago. In retrospect, the varying perspectives in terms of enthusiasm for the concept, scientific and medical disciplines, years in the field, and geographic localities all contributed greatly to the workshop discussions and recommendations. In the end, there was widespread agreement that patient selection based on the pathoanatomic features of the individual's brain injury should be the cornerstone for a new TBI classification approach for clinical trials.

A central tenet of this approach is that brain injuries with similar pathoanatomic features are likely to share common pathophysiologic mechanisms of cell and tissue injury. In this manner, patients with the greatest potential to benefit from a given intervention, based on the mechanisms of action of the therapy, would be selected for study. The number of nonresponders should also be reduced, thereby increasing effect size.

The conceptual framework of a multidimensional, pathoanatomic classification approach for clinical trials is as follows:

- Use preclinical models to: (1) Evaluate pathophysiologic mechanisms and identify those pathoanatomic types of TBI for which the mechanisms are relevant. This would establish the "targeted injury type." Although certain brain injury pathologies such as diffuse brain swelling, hypoxia, and ischemia do not fit cleanly into pathoanatomic classification categories, mechanisms underlying these TBI-associated pathologies also represent important targets for study. (2) Establish that an intervention strategy designed to affect one or more of these mechanisms mitigates cellular damage and functional impairment in the relevant targeted injury type(s). (3) Guide selection of patient populations likely to benefit (i.e., those with the targeted injury type).
- Determine which patients have the targeted injury type(s) using an initial diagnostic entry criterion (e.g., based on CT or MRI).
- Measure or grade injury severity, and include or exclude patients according to predetermined selection parameters. The approach for assessment of severity may vary with injury type but would ideally describe distribution (e.g., extent and location of injury measured using a radiologic grading scheme), clinical effects (e.g., GCS and neurologic exam) and possibly physiologic effects (e.g., microdialysis, biomarkers).
- Identify and characterize additional brain injury types that may be present because these may influence outcome.
- Use multivariate prognostic modeling to further refine inclusion/exclusion criteria and to permit stratification. These models can incorporate varying degrees of complexity, as desired, including demographic data (e.g., age, gender, education, cause of injury, ethnicity, genotype), physiological data (e.g., extracranial injuries, hypoxia, hypo/hypertension, temperature, elevated ICP, apnea, acidosis, cerebral blood flow, biomarkers), and data related to clinical status (e.g., GCS, level of alertness, pupillary status, neurologic exam, neuropsychologic exam). The inclusion of GCS and an assessment of extracranial injuries (e.g., ISS/AIS) was felt to be of particular importance.
- Select endpoints for outcome assessment which are relevant to the targeted injury type and utilize tools optimal for detection of the targeted pathophysiology. Outcomes may include radiologic endpoints (e.g., MRI, MR spectroscopy, diffusion tensor imaging (DTI), CT perfusion), physiologic endpoints (e.g., microdialysis, electroencephalogram (EEG), ICP, biomarkers, brain pO_2, cerebral blood flow), or clinical endpoints (e.g., Glasgow Outcome Scale (GOS), health-related quality of life measures, focal neurologic deficits, neuropsychologic exam). The times at which endpoints are measured may vary with scientific question.

The workshop participants acknowledged that there are substantial hurdles to overcome before implementation of a new classification system could take place. However, an atmosphere of optimism persisted, based in large part on the firm belief that many of the tools needed to

implement such a system are already in hand. We have learned a great deal about injury mechanisms and the primary pathologies unique to various subtypes of brain injuries through animal and human studies. Our clinical assessment tools are useful and, in many cases, are widely available and well validated. We have learned important lessons from previous clinical trials (Narayan et al., 2002), and multivariate prognostic models have been developed (Murray et al., 2007). Nonetheless, there were several recommendations regarding the refinement of tools used for the assessment of TBI and for data collection and dissemination:

- Establish a patient database to: (1) Characterize common pathoanatomic patterns of injury across the entire spectrum of injury severities and across the lifespan. (2) Identify correlations between demographics, injury severity, physical mechanisms and pathoanatomic patterns of injury to enable rapid diagnosis and treatment of common patterns of injury. (3) Share clinical data across TBI research centers for the purpose of developing a pathoanatomic classification system.
- Trial inclusion criteria should be broadened to include less severely injured TBI patients. Many expressed concern that patients classified as having mild TBI based solely on GCS are excluded from clinical trials, despite debilitating and persistent symptoms.
- Neuroimaging modalities such as CT are likely to be used as the primary tool to identify the features of a TBI, thereby enabling pathoanatomic classification. Existing CT grading schemes are useful; however, they should be modified to include additional detail, such as information on lesion location, and further validated.
- More widespread use of acute MRI will be important to provide additional detail necessary for accurate pathoanatomic classification, particularly of the TAI/DAI spectrum. Efforts should be coordinated to identify and eliminate barriers to the implementation of acute MRI for TBI clinical trials and to standardize and validate MRI grading schemes.
- Incorporating endpoints related to the specific, targeted pathophysiology will be especially critical for evaluating the success of Phase II trials, and should increase sensitivity of effect detection.
- Additional functional outcome measures that simulate real-life tasks or functions with ecological validity should be developed, validated, and incorporated in a standardized fashion into future clinical trials.
- More complex statistical and bioinformatics techniques (e.g., covariate adjustment, ordinal outcome modeling) are necessary to increase sensitivity of trials and allow classification utilizing multiple vectors.
- Additional education/instruction is needed to improve standardization and reliability in the use of existing tools, such as grading and classification schemes.
- A mutually agreed upon set of common data elements for TBI for all levels of severity should be established, in cooperation with NINDS initiative on common data elements (www.nindscommondataelements.org/CommonForms.aspx).
- Appropriate elements and tools for special populations (e.g., pediatric TBI, geriatric TBI, blast TBI) should be developed.
- Possibilities should be explored for expanding the Traumatic Coma Data Bank or establishing a new databank as a basis for developing a classification system for targeted therapies. In addition, state-of-the-science platforms for data sharing and analysis should be explored.

ROUNDTABLE DISCUSSIONS

Roundtable Discussion: Pathoanatomic Heterogeneity and Laboratory Models

This roundtable group focused on the heterogeneity of TBI pathology and its implications for animal models and preclinical studies. Goals for the discussion were to (1) identify in vivo, in vitro, and computational models that might be useful in the validation of tools that detect and discriminate between the various types of TBI, (2) compare the advantages and disadvantages of these models for this purpose, and (3) recommend ways to address any limitations and gaps in the models.

Preclinical animal models of focal and diffuse insults (Povlishock et al., 1994; Thompson et al., 2005) were discussed. Traditionally, focal insult models have emphasized production of targeted contusion and local ischemia, whereas the most commonly used diffuse injury models aim to create DAI or diffuse ischemia. Contusion can be produced by controlled cortical impact and by the generation of either local hematoma or hemorrhagic lesions. Focal ischemia is commonly produced with controlled vascular occlusion. Models producing inertial acceleration-deceleration or acceleration through a distributed impact are typically used for generating DAI. Manipulations of cerebral perfusion and oxygenation to generate diffuse ischemia may be useful to differentiate neuropathologic profiles of global ischemia from DAI (Povlishock et al., 2005) aiding in the design of targeted therapies. Other variants of head injury, including pene-

trating missile and blast injury, are of increased importance in the military arena (Warden, 2006). The development and evaluation of models for these other forms of TBI are challenged by the paucity of information regarding their pathobiology and the fact that recovery assessment may be seriously confounded by complex posttraumatic stress disorder (Kennedy et al., 2007; Kim et al., 2007).

While in vitro TBI models provide elegant ways to test detailed aspects of trauma pathophysiology, they generally have not been exploited for discriminating between the different types of TBI for the purposes of clinical intervention. Computational models of relationships between applied physical forces and tissue damage have been utilized primarily for injury prevention research rather than for guiding treatment strategies. However, prediction of anatomical location of injury, vulnerable tissue or cell types, or the severity or progression of a lesion could have important applications to a pathoanatomic classification system and may represent an opportunity for the future.

In summary, in vivo modeling will continue to provide critical insights into the pathobiology of specific types of TBI and the efficacy of candidate therapeutics. Although a sound roster of animal models exists for evaluating major brain injury types, the roundtable participants acknowledged certain limitations and made the following recommendations:

- Thorough pharmacokinetic studies of investigational drugs should be done in a standardized, well-controlled fashion.
- Rodent models predominate in the field of TBI, leading to challenges with respect to scale and anatomy when translating to humans. Differences in brain size, organization and maturation may affect, for example, the biomechanical response of the brain, the delivery of a therapeutic, and the functional or physiologic consequences of "comparable" injuries across species. Therefore, a significant change in large areas of the lissencephalic rodent brain may only translate into small effects in the gyrencephalic human, or vice versa (Manley et al., 2006; Povlishock et al., 1995; Statler et al., 2001). The group recommended moving some of the injury paradigms into larger, gyrencephalic species. This was felt to be particularly important for validating imaging modalities through postmortem assessment of brain pathology.
- The majority of preclinical studies have focused on acute interventions and outcomes. In contrast, the success of human trials has been judged using long-term outcome, assessed months after TBI. The chronic posttraumatic interval is characterized by the activation of a secondary adaptive recovery, which is not generally considered in acute or subacute animal assessments. Preclinical model analysis should be extended to include periods of recovery and brain plasticity. In addition to the assessment of motor and sensory recovery, other tests should be developed to dissect complex brain recovery mechanisms (e.g., cognitive integration, emotion) which occur with long-term survival.
- Variability in pre-existing physiological status and in extracranial injuries and complications resulting from traumatic injury in humans is not represented in animal models. Real world patient heterogeneity requires a variety of interventions applied across the phases of injury and recovery. Well-monitored animals subjected to standardized models of TBI have less variability and, therefore, a much lower risk-to-benefit ratio for a given treatment. The group recommended that laboratory modeling of TBI should always consider the 'bedside to bench' strategy, using human brain pathology to identify the specific biological variables most affected by injury. Such variables should exhibit the most significant effects in animal models and better replicate the human condition. In addition, the fact that controls for systemic effects associated with TBI are not in place for humans should be considered when translating the efficacy of interventions from rodent models. Given that we have good rodent models in place, choosing therapeutic manipulations which result in larger, measurable signals may increase the likelihood that experimental treatment effects will be detectable above the expected variability of outcomes in humans.
- Models do not capture the full spectrum of injury severity. This is especially true for milder forms of injury, for which new models should be validated and fully characterized.
- Models of blast injury need further development and validation for studies on both military and civilian populations.
- Animal models of posttraumatic stress should be developed and tested for interaction with TBI. This combination is emerging more frequently, particularly in association with blast injury.

Roundtable Discussion: Acute Clinical Monitoring

The goals of this roundtable discussion were to compare the advantages and disadvantages of acute clinical monitoring tools, to make recommendations for which tools to use and when, and to recommend ways to ad-

dress limitations in the current tools. By tools, here, we refer to indices of patient condition that might be used for management decisions, severity assessment, or surrogate outcome measures in some clinical trials. These tools might include various ways to more fully characterize (a) specific pathoanatomic type or extent of injury, (b) severity of neurologic or neuropsychologic deficits, (c) pathophysiology of injury-initiated cascades or secondary insults, or (d) evolution of injury. In clinical trials, each of these features might be used to standardize entry criteria or to follow a specific target for intervention.

The primary initial evaluation of a patient with a TBI currently includes the GCS, complemented by CT and a detailed neurologic exam to the extent feasible and dictated by patient clinical status. The initial clinical evaluation, however, is frequently unreliable and further clouded by use of sedative and neuromuscular blockade medications in the emergency setting. These difficulties with the early clinical evaluation run counter to the need for rapid assessment, recruitment, and enrollment of patients in clinical trials addressing early therapeutic interventions. Therefore, additional concrete and valid assessments tools are needed in the early phase.

- In the acute phase (0–4 h), there is consensus that despite the limitations noted, the GCS score remains the standard and most well-validated index of overall neurologic injury severity. However, it is most helpful on the more severe end of the injury spectrum. Protocols are clearly needed to better characterize injury type and severity in patients on the less severe end of the spectrum. This may be in the form of early MRI, serum biomarkers, rapid neuropsychologic tests, or innovative techniques such as magnetoencephalography attempting to quantify the extent of neurologic/physiologic disturbance as a result of a more minor or moderate TBI.
- Moving beyond the acute phase evaluation and into the "Intensive Care Unit phase" (approximately 4—12 h postinjury), additional parameters may be incorporated into the early clinical evaluation and characterization of injury. Appropriate tools might serve to better define specific injury type, extent, pathophysiology, and evolution of injury over time. Where appropriate, ICP monitoring, microdialysis sampling, brain tissue pO_2 measurements, and EEG may have a role.
- Age-appropriate measurement techniques are needed to distinguish specific injury types, pathophysiology, and evolution of injury in pediatric patients, the aged, or other populations in which these features may be distinctive.
- More widespread use and validation of existing tools, such as CT perfusion scans, electrophysiology, and DTI, is clearly needed. Additional functional and feasible acute measures (e.g., biomarkers, CT perfusion, early neuropsychologic batteries) must be developed, validated, and related to delayed modalities with known prognostic significance.
- Our current armamentarium is insufficient, and there is a need for better, more sophisticated tools to measure extent of injury and occurrence of specific pathophysiologic mechanisms as summarized in Table 1.
- In order to reduce multicenter variance, clinical monitoring in the acute phase should be performed with uniformity across participating centers and in such a manner that common data elements are populated and sample sizes for clinical studies controlled.

Roundtable Discussion: Neuroimaging

The goals of this roundtable discussion were to compare the advantages and disadvantages of neuroimaging tools, to make recommendations for which tools to use and when, and recommend ways to address limitations and gaps in the current tools. The discussion began by acknowledging the distinction between the use of imaging for acute classification of pathoanatomic injury type and the use of neuroimaging tools to answer specific research questions about pathophysiology, extent of injury, secondary injury, evolution of pathology, and treatment effects.

With respect to use of imaging for acute classification, it is widely accepted that for most injury types, especially at higher levels of injury severity, CT scan is the initial test of choice (Table 2). This arises from its wide availability and its high reliability in identifying the presence of hemorrhages, contusions, and mass effect, which guides acute management and has proven prognostic significance. However, more complex classification schemes, such as the Rotterdam scale and others, are needed to handle heterogeneity in the size, location, and multiplicity of lesions, as well as findings such as swelling, loss of grey-white differentiation, presence or absence of cisterns and sulci, tissue shifts, and herniation effects. Thus, it was felt that within most of the common pathoanatomic categories, data are available from tools already at hand to help stratify patients and predict outcome using current neuroimaging techniques. It was also recognized that development of computer-aided diagnostic tools is needed for more objective and quantitative image analysis and to improve workflow for clinical trials.

For some diagnoses, MRI has higher sensitivity and specificity for detection and classification, particularly

Table 1. Tools for Pathoanatomic and Pathophysiologic Sequelae

Common pathoanatomic and pathophysiologic sequelae	*Acute monitoring and diagnostic tools*	
	Available	*Additional validation needed*
Hematoma, contusion, subarachnoid hemorrhage	Imaging,[a] clinical exam	Biomarkers of coagulopathy, assessment of ischemia/perfusion (Xenon CT, CT perfusion), risk for hemorrhage expansion, risk for malignant intracranial hypertension
Diffuse axonal injury	Imaging,[a] clinical exam	Biomarkers, imaging (susceptibility weighted imaging, diffusion tensor imaging)
Intracranial hypertension	ICP monitoring, clinical exam	Non-invasive ICP monitoring
Cerebral hypoxia/ischemia[b]	PET, clinical exam, Xenon CT	Continuous bedside measurements ($PbtO_2$, $SjvO_2$, near-infrared Spectroscopy, TCD), microdialysis
Cerebral swelling[c]	Imaging,[a] clinical exam	Continuous bedside measurements (CBF, brain compliance, tissue water content)

[a]See Table 2.

[b]Includes post-traumatic vasospasm.

[c]Cerebral swelling due to increased blood volume or edema.

CBF, cerebral blood flow; CT, computed tomography; ICP, intracranial pressure; PET, positron emission tomography; $PbtO_2$, brain tissue oxygen tension; $SjVO_2$, jugular venous oxygen tension; TCD, transcranial Doppler.

Table 2. Imaging Modalities for Pathoanatomic and Pathophysiologic Sequelae

Modality	*Hematoma*	*Contusion*	*SAH*	*DAI*	*Ischemia*	*Vasospasm*
CT	+++	++	+++	+/0	+/0	0
CTA	0	0	+	0	+	+++
CTP	+	+	0	0	++	++
T2 FLAIR	+	+++	+++	+	+	0
1.5T T2* GRE	+	+	+++	+	0	0
3T T2* GRE	+	+	+++	++	0	0
SWI	+++	++	++	+++	0	0
DTI	+	+	0	+++	+++	0
PWI	+	+	0	+	++	++
MRSI	0	0	0	++	+	0
MRA	0	0	+	0	++	+++
fMRI	0	0	0	?	0	0
PET	0	+	0	?	+++	0

Scoring: little/no data, ?; insensitive, 0; minimally sensitive, +/0; mildly sensitive, +; moderately sensitive ++; highly sensitive, +++.

CT, computed tomography; CTA, computed tomography angiography; CTP, computed tomography perfusion; DAI, diffuse axonal injury; DTI, diffusion tensor imaging; fMRI, blood oxygenation level dependent (BOLD) functional magnetic resonance imaging; MRA, 3D time-of-flight MR angiography; MRSI, MR spectroscopic imaging; PET, positron emission tomography; PWI, dynamic susceptibility contrast perfusion-weighted imaging; SAH, subarachnoid hemorrhage; SWI, susceptibility-weighted imaging; T2 FLAIR, T2-weighted fluid attenuated inversion recovery; T2*GRE, T2*-weighted gradient echo.

for DAI and more subtle imaging manifestations found in "concussive" type head injury. Therefore, for purposes of some study questions, MRI would be a preferable initial imaging modality. In the spectrum of diffuse white matter injuries, fluid-attenuated inversion recovery (FLAIR) and T2 sequences are sensitive for non-hemorrhagic white matter lesions, and gradient echo and susceptibility-weighted imaging for blood products. Diffusion-weighted imaging is also very sensitive for DAI but, as is the case with ischemia, its sensitivity is limited to the acute setting. It is not yet clear whether DTI or other emerging techniques will demonstrate even greater sensitivity in recognizing axonal injury or will be able to track or predict functional recovery or response to intervention, though significant progress has been made (Gallagher et al., 2007).

Both MRI and specialized CT techniques provide unique information about some pathophysiologic processes involving ischemia and blood flow abnormalities (Table 2). These techniques include CT and MR perfusion, diffusion-weighted imaging, and CT and MR angiography. With some MR techniques, the presence of blood products creates artifacts which can distort the images, making these applications less robust in the setting of TBI than they have proven to date in nontraumatic ischemic pathologies such as stroke. Currently, perfusion-CT techniques do not offer whole-brain coverage, a drawback that will be eliminated with the advent of large coverage (256- or 320-slice) CT scanners. Isotope or metabolite-based techniques such as xenon CT, single photon emission CT or positron emission tomography (PET) are useful at present for patients with TBI mostly in the research setting, but have given insight into the complex relationship between brain perfusion and metabolism While neuroimaging techniques have the significant disadvantage of reflecting only one point in time, imaging has the major advantage of providing region-specific information. In contrast, the majority of bedside cerebral monitoring techniques concerned with cerebral blood flow, oxygen tension, and other physiologic variables can provide continuous measurements, but they reflect only one geographic point in a very large and often heterogeneous intracranial compartment. For this reason, it was felt that neuroimaging would continue to play an increasing role in research questions involving cerebral hemodynamics and metabolism.

Other neuroimaging techniques may be useful for tracking specific aspects of pathophysiology or recovery. MRI volumetric analyses have been used by several groups to follow head-injured patients over time and to correlate patterns and extent of tissue loss in specific regions with neuropsychologic outcomes. MR spectroscopy has been used in severe injuries to show major loss of metabolic integrity, but at present is less well studied for distinguishing among patients or predicting outcome in those with milder injuries. There has been some hope that specialized MR spectroscopic or PET techniques which can localize and quantify neurotransmitters or other molecules may prove useful in tracking response to treatment with various neuroprotective or psychoactive medications. Although functional MRI has been used to track recovery in some acquired conditions such as surgery for tumors or epilepsy, its use in trauma depends in part on the location of the damage and specific functions impaired. Magnetoencephalography, used largely in studying epilepsy, is still in the early stages of use in head-injured patients, and as yet little is known about what information it may provide in this setting. Most of these advanced imaging techniques currently suffer from the lack of normative databases and protocol standardization.

Overall, the imaging roundtable group concluded that current imaging techniques provide an excellent start on injury classification, especially with schemes which recognize the varying severity and multiplicity of injuries. In addition, the wide variety and continuous refinement of emerging imaging techniques should be watched closely and kept in mind as TBI research moves ahead. These techniques will become increasingly important for improved injury classification, pathophysiology characterization, prognostication, and treatment effects analysis.

Roundtable Discussion: Biomarkers

The goals of this roundtable discussion were to evaluate the status of biomarkers as a tool for TBI classification and to recommend ways to facilitate research in this area. A number of putative serum, cerebrospinal fluid (CSF), or microdialysate biomarkers have been evaluated in animal models and clinical studies of TBI, with S100 and neuron-specific enolase being among the most widely investigated. However, many of these candidate biomarkers have failed to exhibit adequate sensitivity and specificity for central nervous system (CNS) injury or yield significant prognostic value. Therefore, the discussion of a role for biomarkers in clinical trials for TBI was infused with an air of caution. As with any newly developed tool, biomarkers should demonstrate diagnostic or prognostic value above that available with existing tools. In general, biomarkers were felt to be insufficiently characterized to serve as a classification tool, a prognostic factor, or a surrogate outcome marker in clinical trials in the immediate future. However, there was enthusiasm for the continued development and validation of biomarkers.

The development of biomarkers generally progresses from detection and characterization in the brain to measurement and validation in CSF and then in serum. The roundtable group discussed a number of challenges that arise during this process, and the implications for the use of biomarkers in TBI clinical trials. With respect to a potential pathoanatomic classification approach for TBI patients, the most important question is whether current biomarkers are useful for differentiating injury type. That is, do we have biomarkers specific for contusion versus subdural hematoma? Workshop participants agreed that we do not currently have this capability and felt this represented an important, but long-term, goal of biomarker development.

In the initial classification of injury, biomarkers might be used in an alternative fashion, to grade injury severity. Levels of certain biomarkers may correlate with injury severity, as assessed by other clinical indicators such as GCS (Pineda et al., 2007). The use of a biomarker to assess injury severity could avoid problems with unreliable GCS assessments in patients who are intoxicated or intubated. While CSF biomarkers that reflect injury severity might be available for widespread use in the near future, more skepticism was expressed regarding the likelihood that serum biomarkers would possess adequate sensitivity to differentiate injury severity. Additionally, the loss of spatial information in CSF or serum biomarker data raised concerns about the ability of biomarkers to differentiate between a mild injury encompassing a large brain area and a severe injury involving a small region of brain, for example, or between two equivalent-size lesions in different parts of the brain that result in greatly different clinical presentations. Local biomarker levels assessed through microdialysis may provide critical information in these types of cases. Nonetheless, biomarkers likely represent a tool which will supplement, rather than replace, existing approaches such as neuroimaging and GCS in classification of patients for trials.

In addition to aiding in the initial assessment of injury type and severity, biomarkers may serve as a prognostic indicator for TBI. The utility of biomarkers in improving prognostic capabilities lies in the sensitivity and specificity of the biomarker. There was particular enthusiasm for the development of biomarkers that would aid in the prognosis of mild TBI. In a patient with a normal CT scan or MRI, a biomarker that could predict worsening neurological status would have great clinical utility. Similarly, biomarkers that could predict the likelihood of secondary injuries such as ischemia or hypoxia would be valuable.

In summary, the roundtable participants encouraged the continued exploration and validation of biomarkers for TBI. Biomarkers will likely supplement existing tools such as GCS and neuroimaging for the initial classification of brain injury in the near future. The use of biomarkers to identify at-risk patients with mild TBI or to differentiate injury pathology types were felt to be important, but long-range, goals.

Roundtable Discussion: Clinical Outcome Measures

The goal of this roundtable discussion was to describe the role of outcome measurements in developing a pathoanatomic classification system for targeted therapies. To this end it was agreed that the choice of an outcome measure determines the degree to which the efficacy of any clinical trial is, at minimum, documented and, at maximum, comprehensively defined. This is relevant to the issue of classification, because with greater clarity in defining the focus of the intervention, ramifications for outcome measurement may emerge. For example, does greater specificity in defining the type of brain injury or the nature, etiology and type of neuropathology lead to different expectations with respect to outcome and, therefore, different measurement needs?

A clear view of the range of points at which "success" can be measured is needed prior to choosing one or more appropriate measures to describe the impact of an intervention. For example, the impact of an intervention designed to reduce mortality or secondary complications during the acute stages of care may require assessing both short-term and long-term functioning within different International Classification of Functioning domains (World Health Organization, 2001). This intervention will require a different type of outcome assessment than one that is seeking solely to improve functioning in the community. Thus, the GOS (Jennett et al., 1975, 1981) or Disability Rating Scale (Rappaport et al., 1982) might be appropriate for use as global measures of immediate outcome in an acute trial. In contrast, measures that assess in more detail constructs such as participation and health-related quality of life, for example, the Mayo-Portland Adaptability Inventory (Lezak et al., 2003), the Neurobehavioral Rating Scale (Levin et al., 1987), the Participation Objective, Participation Subjective (Brown et al., 2004), or the Satisfaction with Life Scale (Diener et al., 1985), might be useful when examining the more distal impact of residual impairments or disability on the person's functioning within activity and participation domains.

Consideration must be given to the appropriate level of outcome analysis when examining specific questions with regard to the effectiveness of an intervention. For example, while neuropsychological tests are sometimes viewed as useful outcome measures for clinical trials, the utility of test scores in defining outcomes depends on the

purpose of the trial. Thus, if a pharmaceutical is hypothesized to improve memory function, it is appropriate to use a neuropsychological test of memory function to document outcome. However, neuropsychological tests have been criticized for their lack of "ecological validity" (Burgess et al., 2006); that is, performance on a test often bears little relationship to the person's day-to-day function. In response, Alderman et al. (2003) have developed the "Multiple Errands Test" to describe the level of executive deficits of individuals with brain injury in the context of carrying out everyday tasks. This test examines the performance of the individual in standardized situations (e.g., purchase of a greeting card, locating a business in a building) and has been found to be sensitive in discriminating between different types of deficits in executive function. Further research examining the validity of this approach is needed prior to recommending that it be applied as an outcome measure in a clinical trial. Another alternative to neuropsychological tests is the Assessment of Motor and Process Skills (AMPS) (Merritt et al., 2003). This measure must be administered by an AMPS-certified occupational therapist and consists of groups of functional tasks of graded difficulty, for example, cooking and other homemaking activities. It has been found to be moderately correlated with cognitive function (Bouwens et al., 2008) and to be sensitive to the effects of rehabilitation (Waehrens et al., 2007). Thus, while the AMPS has promise as an outcome measure, its widespread application is limited by restrictions placed on its use. Considerable development research is needed before ecologically valid measures are appropriate for consideration as outcome measures in clinical trials.

Roundtable Discussion: Data Collection and Management

The goals of this roundtable discussion group were to identify and discuss available databases and to make recommendations for which, if any, of these resources might be useful for developing a pathoanatomic classification system for TBI. While a well-designed and well-conducted (RCT) remains the gold standard, data analyses of disease registries and cohorts have contributed significantly to the development of current guidelines for the management of severe TBI (Guidelines, 2007) and to the formulation of research hypotheses. Historically, two databases have made major contributions to the current management of TBI. The CNS Trauma Database included all severities of head injury and preceded the Traumatic Coma Data Bank, which was primarily limited to severe brain injuries. Recently, the IMPACT team in Europe created a large database by combining information from 9205 patients collected in eight RCTs and three observational studies (Marmarou et al., 2007). However, the IMPACT database includes data from nearly 20 years ago, which do not necessarily reflect current relationships between classifiers and outcome. In addition, as with many databases, datasets were not collected in a uniform manner, leading to large amounts of missing data for some items (Van Beek et al., 2007).

Thus, current databases are not optimal for achieving the purpose described by this workshop, which is to develop a classification system by which to better separate patients who will respond to a treatment from those who will not. While one of the underlying tenets of a RCT is the presumption of clinical equipoise, the notion of performing a trial amongst those who have a good chance of responding to a particular form of treatment is very generally accepted (Friedman et al., 1998). The problem this sets for classification is that each treatment may require a different classifier; alternatively, the classifier may be able to finely divide the patients into small subgroups which are then collapsed into treatment-specific groups. Regardless, the classifier must be designed to fit a specific purpose.

Considerations and suggestions for data collection and management follow.

- A new database should be created with uniform data collection criteria on a well-defined set of possible classifiers. This dataset could then be used to validate current classifiers and create new classifiers.
- One form of this database may grow from the NINDS effort to define a common set of data elements (www.nindscommondataelements.org/CommonForms.aspx) with additional TBI-specific elements added using a critical evaluation of existing core datasets and the recently established BrainIT group (Chambers et al., 2006; Piper et al., 2003). If these items were to be collected from every future clinical trial in TBI and placed in a common data repository, a contemporaneous equivalent to the IMPACT database could be created. The multisite phase III proTECT trial could serve as a model to begin such data collection.
- Common data elements for inclusion in a TBI database may be arranged into a manageable number of modules: demographic, physiologic, clinical, and imaging. Much of the groundwork in this area has been begun by the IMPACT team and should be included in the design of a new database. Each data element could be further grouped as a classifier based on whether it is experimental or experiential (Table 3).
- Any newly created database would need to be open to the entire TBI research community.

TABLE 3. COMMON DATA ELEMENTS FOR INCLUSION IN A TBI DATABASE

	Status of classifier	
Common data cluster	*Evidence-based*	*Experimental*
Demographic	Age, education, cause of injury (e.g., MVC, fall)	Gender, genotype
Clinical	GCS, systemic injuries, ethanol, serum glucose	Inflammation, oxidative stress
Physiologic	Temperature, ICP, CPP, MAP, CBF, $PbtO_2$, $SjvO_2$, neurophysiologic testing	Biomarkers, microdialysis
Imaging	Extra-axial hematoma, intra-axial hematoma, DAI, fracture	Perfusion MRI, DTI, NMR spectroscopy, PET

CBF, cerebral blood flow; CPP, cerebral perfusion pressure; DAI, diffuse axonal injury; DTI, diffusion tensor imaging; GCS, Glasgow Coma Scale; ICP, intracranial pressure; MAP, mean arterial pressure; MR, magnetic resonance; MRI, magnetic resonance imaging; MVC, motor vehicle crash; NMR, nuclear magnetic resonance; $PbtO_2$, brain tissue oxygen tension; PET, positron emission tomography; $SjVO_2$, jugular venous oxygen tension; TBI, traumatic brain injury.

- Any new database must carefully define the reference population, which will define the inclusion and exclusion criteria and the population to which the information derived is to be generalized. For example, if the database is to include all severities of brain injury, are the data items which apply to a patient with a GCS of 4 likely to be of interest in a patient with a GCS of 15? These definitions will then determine the number and kind of clinical sites from which to collect information. Even if a perfect set of data items is selected at a given time, it is likely that this set will need modification as knowledge grows.
- The manner in which data are collected is also a substantial issue for the utility of such databases. Collecting data without a clear reason is difficult, as witnessed by the amount of missing data in existing databases. Any new database will require using all possible technical means to automate data collection to reduce the burden on the individual sites.

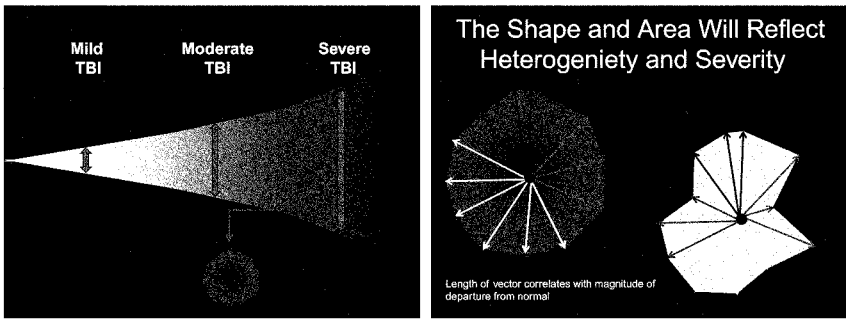

FIG. 3. Multiple vector-based analytical scheme. Tensor representations of the high dimensional data associated with traumatic brain injury (TBI) may enhance classification, as has been demonstrated with other fields such as cancer and image recognition. However, the correct internal consistency or normalization of these vector components will be required to allow appropriate comparison of the patient groupings or classification scheme.

- There is a clear need for multivariable prognostic models which are validated and sensitive to therapeutic interventions. The IMPACT team has created the most recent, and perhaps the most comprehensive, of these models. They have largely limited themselves to models based on logistic regression which are meant to predict a global outcome measure, the GOS. These results provide an excellent basis for choosing classifiers (Maas et al., 2007; Murray et al., 2007). Older multivariable classifiers have included other logistic regression models (Narayan et al., 1981) and a classification tree model (Choi et al., 1988, 1991).
- It may be informative to apply regression models to examine the data for effect modifiers (interactions) and to determine the shape of the relationship of predictor to response. Other classification techniques which have not been tried, such as classification and regression tree, nearest neighbor clustering, or neural networks (Peto et al., 1976), may offer advantages over regression-based methods.
- The long-term solution will require application of techniques from statistics and bioinformatics. The resulting classification scheme can be both qualitative and quantitative. An example of a multiple vector-based analytical scheme is illustrated in Figure 3. Vectors might include clinical exam, imaging studies, demographics, clinical course, genomics, and serum markers.

One additional area of interest raised at the workshop was that of misclassification at randomization due to delay in presentation of information. For example, a trial may be designed to exclude patients with an intraparenchymal hematoma. These hematomas can develop over time, so that a patient may have only a mild contusion at randomization but have a consolidated hematoma three days later. Although it might seem desirable to remove the patient from the study at this time, this is not acceptable for three reasons. First, in good trial design, only data that is collected prior to enrollment in the RCT should be used in the withdrawal decision-making process due to violations of entry criteria (Peto et al., 1976). Second, removing patients from a study following randomization is not acceptable to most regulatory agencies (Guidelines, 1988). Third and most importantly, there is no way to determine whether the treatment had any effect on the development of the hematoma. A better solution would be to develop classification models which predict the development of a delayed hematoma, and use this information at the time of randomization for patient classification. Depending on the strength of the model, this approach will reduce the incidence of misclassification and can be taken for any condition which results in delayed presentation.

In conclusion, the development of tools to classify TBI will likely follow the classic "learn and confirm" paradigm found in most of science. The tools will initially be tried on an existing set of data, modifications will be made until the tool seems satisfactory, and then the tool will be applied to a new set of data and its utility assessed. To fully verify a new tool, advanced statistical methods, contemporary datasets, and well-constructed validation studies need to be available to and used by the TBI community.

CONCLUSION

As we have seen with other diseases such as cancer, improved classification systems have led to a better understanding of the mechanisms of disease and helped to refine treatments and improve outcome. The major conclusion from the workshop was that there is a need for a pathoanatomically based classification system for TBI if we are to successfully translate targeted therapies from the bench to the bedside. This does not diminish the importance of prognostic, etiologic, and symptom-based classification systems, which remain important for prevention, clinical management, and prediction of outcome in patients with TBI. The evaluation of targeted therapies for specific pathoanatomic lesions will likely require inclusion of less severely injured patients with more homogeneous injuries. Although this is a departure from traditional TBI clinical trial design, lessons learned from the study of these less complicated and more easily modeled injuries could then be applied to more severely injured patients.

A new TBI classification system for targeted therapies can be achieved within the next five years, but to do so will take a sustained and coordinated effort. Short-term efforts (12–18 months) that need to be undertaken include establishing several small, multidisciplinary working groups to review the literature and propose protocols for optimizing and standardizing TBI patient assessment. The working groups should be formed around the following topics: acute clinical assessment, neuroradiologic assessment, biomarkers, and functional outcomes assessment. An additional working group should be formed to identify resources and tools available for the development of a large, multidimensional database, including common data elements, data sharing, data mining, and bioinformatics.

Review papers from these working groups would form the basis for the next step, which is to create a TBI data warehouse to facilitate multi-institutional collaboration and knowledge discovery. The database should be prospective, multidimensional, and inclusive of all severities of TBI and all ages. Given the very large numbers of people who sustain a TBI, it should be possible to enroll the necessary number of patients for the purpose of developing a new TBI classification system for targeted therapies within two years. These are not small tasks, and can only be achieved by a concerted, international effort. This workshop served primarily to start the process:

> *"Make no little plans; they have no magic to stir men's blood. . . . Make big plans . . . aim high in hope and work." (Daniel Burnham)*

APPENDIX: TBI CLASSIFICATION WORKSHOP AGENDA AND PARTICIPANT LIST

Day 1—October 16, 2007

Background and Goals of the Workshop: Geoff Manley

Overview of Scientific Team Proposals for an Improved TBI Classification System
Moderator: David Hovda*[32]
Team Leaders: Alex Valadka, Andrew Maas, Ross Bullock

What is known about the heterogeneity of TBI and what are the major gaps in our knowledge?
Moderator: Geoff Ling*[33]
Panelists: Clay Goodman, Ross Bullock, Ewout Steyerberg

Which "tools" are recommended for discriminating between the heterogeneous TBI pathologies? What are the gaps and/or limitations?
Moderator: Douglas Smith*[34]
Panelists: David Wright, Juan Sahuquillo, Ramon Diaz-Arrastia

Round Table Discussions by Topic and Expertise

Pathoanatomical Heterogeneity & Animal Models
Moderator: David Hovda
Discussants: Tony Marmarou, Nikolous Plesnila, Pramod Dash, Linda Phillips, Frank Tortella*[35], Leslie Shupenko*[16], Graham Teasdale, Ed Hall*[1], John Povlishock*[15]

Clinical Monitoring: Acute Phase
Moderator: Walter Koroshetz*[11]
Discussants: David Wright, Daryl Gress*[36], Neeraj Badjatia*[37], Rob Silbergleit, Courtney Robertson, Nino Stocchetti, David Okonkwo, Gregory O'Shanick*[38], Jam Ghajar*[39]

Neuroimaging Tools
Moderator: Debra Babcock*[11]
Discussants: Larry Latour*[9], Dave Brody, Alisa Gean, Geoff Manley, Doug Smith, Tina Duhaime, Juan Sahuquillo

Biomarkers
Moderator: Joe Pancrazio*[11]
Discussants: Ron Hayes, Ramon Diaz-Arrastia, Kathy Saatman, Stephanie Fertig, Andrew Maas, Lawrence Marshall*[40]

Clinical Monitoring: Outcomes
Moderator: Ramona Hicks
Discussants: Lindsay Wilson, Wayne Gordon, Gordon Murray, Sandra Salan*[41], Kathy Helmick*[16], Louis French*[42], Emmeline Edwards*[11], Rebecca Desrocher*[11], Ross Bullock, Alex Valadka, Nancy Temkin, Mark Ashley*[43]

Data Management
Moderator: Peter Gilbert*[11]
Discussants: Linda Papa, David Moore, Jean Langlois, Ewout Steyerberg, Hilaire Thompson, Charlie Contant, Clay Goodman

Round Table Summary & Recommendations
Moderator: Doug Smith
Presentors: Walter Koroshetz, Debra Babcock, Joe Pancrazio, Wayne Gordon, Peter Gilbert, David Hovda

*Additional Participant Affiliations: [32]University of California, Los Angeles, CA, [33]Defense Advanced Research Projects Agency, Arlington, VA, [34]University of Pennsylvania, Philadelphia, PA, [35]Walter Reed Army Institute of Research, Silver Spring, MD, [36]University of Virginia, Charlottesville, VA, [37]Columbia University Medical Center, New York, NY, [38]Brain Injury Association of America, McLean, VA, [39]Brain Trauma Foundation, New York, NY, [40]UCSD Medical Center, San Diego, CA, [41]Social Security Administration, Office of Medical Policy, Washington, DC, [42]Walter Reed Army Medical Center, Washington, DC, [43]Centre for Neuro Skills, Bakersfield, CA.

Day 2—October 17, 2007

What are the critical data elements and how should they be collected and analyzed to develop a TBI classification system for targeted interventions?

Moderator: David Hovda

Panelists: Lindsay Wilson, Linda Papa, Clay Goodman

Advisory Panel Summary and Recommendations

Moderator: Doug Smith

Panelists: Kathy Saatman and Members of Advisory Panel

Action Plan – Geoff Manley and Ron Hayes

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AUTHOR DISCLOSURE STATEMENT

No conflicting financial interests exist.

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Chairman AKAKA. Thank you very much, Dr. LaPlaca.

This question is for all the witnesses. You can answer it in one word or a brief comment. It is my view that VA care for TBI has dramatically improved since the start of the war in Iraq. My simple question to you is: Do you share that view?

[Ms. Bohlinger nodding affirmatively.]

Chairman AKAKA. Ms. Bohlinger says yes.
Mr. Barrs?
Mr. BARRS. Yes, sir.
Chairman AKAKA. Dr. Gans?
Dr. GANS. Yes, it has.
Mr. DABBS. I would tend to agree.
Ms. LAPLACA. I would agree.
Chairman AKAKA. Now, Ms. Bohlinger, you mentioned the importance of family, family involvement in treatment, and I certainly agree with you. As the mother of a veteran with TBI, and as a family caregiver, what services and support have been most important to you in helping to care for your son?
Ms. BOHLINGER. I would say, Mr. Chairman, the most important has been the TBI group on an ongoing basis, because what it does is give him real people to be around. His life is very isolated now, and even the telemedicine, while that is going to be really important, for some of these individuals their worlds have become so small that they do not get much person-to-person contact.
So I would say that group setting has been helpful. They just need to schedule it at a time that is convenient for the veteran.
Chairman AKAKA. What services did you not receive that would have been helpful?
Ms. BOHLINGER. Services that I did not receive would include the scan when that was requested, because I knew the other assessments were not correct. Services for me, you know, it is wearing. I am emotionally, physically, financially exhausted after 5 years. When we talked about integrating family members in our situation, that is not going on yet. They set up separate groups. Then they used information, very candid information that we gave, and then went to our loved one and told him, which undermined trust. So you can imagine then having to create another bridge to get back with your loved one and have him trust you.
Really, it just all needs to be together. It needs to all be together.
Chairman AKAKA. Thank you.
Mr. Dabbs, you mentioned that in VISN–11 only three veterans have been referred to private care by VA. Do you have any sense of why this is the case or how many other veterans could benefit by increasing referrals?
Mr. DABBS. Yes, sir. I think as it pertains to your question and in answer to this one as well, the VA has made significant strides of improving care, but I believe, at least what we are seeing in Michigan, that there is total inadequate resources available within the VA to be able to execute that care for the numbers of people involved. Therein lies the problem. I think it speaks a bit to Dr. Gans' point a moment ago where he indicated that there is a very finite number of people who work in the field of brain injury and brain injury rehabilitation. The VA does not have them. The private sector does not have them. It means that it is more critical than ever that the two work together closely to be able to provide this care that is needed.
Chairman AKAKA. Thank you.
Dr. LaPlaca, while I am a strong supporter of VA research, your testimony about the difficulty you have had in cooperating with VA

is unfortunate. What benefits would you expect to see if you were able to work more closely with VA?

Ms. LAPLACA. Thank you for the question. It is a very important issue. There are many successful research collaborations between academic professors and VA researchers, and there is a lot of encouragement to do so. So although I have had some frustration at the level between myself and other researchers, there is a lot of enthusiasm to share ideas, share research resources.

I think an added benefit for me is to have more exposure to the patient. The VA researchers have a more realistic idea of the needs and how that can trickle down and what needs to drive our research.

I think the main problem is that there is bureaucracy. There are a lot of IT issues. You know, computers cannot come out of the VA, so data sharing has to be done pretty much offsite, which requires approval. There are hurdles like that which are just—that part of it is frustrating, but it is possible. The VA system has made it possible for academic researchers to have appointments within the system and compete for VA merit grants. But it is not widespread, and it can be difficult.

Chairman AKAKA. Thank you very much.

Senator Tester?

Senator TESTER. Thank you, Mr. Chairman.

I think it is important to point out before I get into my questions that the previous panel stuck around—and I want to thank them for that—to listen to the comments of this panel. I very much appreciate that, and I appreciate your commitment.

I want to start with Ms. Bohlinger. You talked about the fact that your son is a rural kid living in Seattle in an urban area, and it is just impossible to get them back to the State. What would the VA have to do to be able to allow you to bring your son back to a State like Montana?

Ms. BOHLINGER. Well, I would like to see a polytrauma center, because he goes in twice a week still for services, and we do not have those services available. His medical team is important.

Senator TESTER. So if a polytrauma center was set up, that would take care of it.

Ms. BOHLINGER. Yes.

Senator TESTER. OK. One of the things that I think is very important is everybody has equal access, and you talked about in your opening remarks that you got different treatment as—I will just say "as a regular person" than as the Second Lady of Montana. Could you tell me what the difference was? Can you give me an example of how it was different? Because it should not have been. It should not have been different for you or me or anybody in the audience. The level of respect and treatment should be the same.

Ms. BOHLINGER. An example would be when I was led through a particular center, I was able to talk with certain veterans only. I went back on my own time to talk to whoever I wanted to, and the other veterans that they steered me away from, they said, "Oh, no, you cannot go in that door; that gentleman is having issues," I went back and talked to people and found out what they were really experiencing.

Senator TESTER. OK. Dr. LaPlaca, you talked about—and I am not a researcher. I am not an M.D. I majored in music, not in science, so this is out of my area. You talked about how you could not duplicate polytrauma in the law. I do not want to put words in your mouth, but that is what I heard you say.

Is that because we have not tried, or is that because it just cannot be done?

Ms. LAPLACA. No, let me rephrase that. Perhaps I misspoke. I said it is not studied in the laboratory.

Senator TESTER. OK.

Ms. LAPLACA. It is not a common—our injuries that we study are very homogeneous, not heterogeneous like the real population.

Senator TESTER. Would it be your advocacy then that we head in that direction?

Ms. LAPLACA. I think it is going to be very important. I think there will be some hesitation to do that because even studying an isolated brain injury alone is so complex that I think it scares most researchers to think, OK, well, let us add, you know, a leg injury or a lung injury to that.

However, I think we have to bite the bullet, and we have to move forward in that direction in order to—I mean, a drug that works on a brain injury may not work or may be adverse to give to a patient who has multiple thoracic injuries.

Senator TESTER. OK. Thank you very much.

I want to thank everybody on the panel today for being here and sharing your time and your stories and your vision with us. Thank you very much.

Thank you, Mr. Chairman.

Chairman AKAKA. Thank you very much, Senator Tester.

Senator Brown?

STATEMENT OF HON. SCOTT P. BROWN,
U.S. SENATOR FROM MASSACHUSETTS

Senator BROWN OF MASSACHUSETTS. Thank you, Mr. Chairman. I appreciate your patience with me running around today. I have a bunch of different hearings, so thank you. And thank you to the panel.

Jonathan, in dealing with your situation—first of all, thank you for your service and your sacrifice. I know you are dealing with trying to get your life back on track. What can you tell me that would help other soldiers who are in similar situations? Because in reading about you and having my team brief me, it seems to me the biggest problem was time and the fact that it moved like molasses. You always felt like you were in quicksand trying to get the answers, trying, you know, to get help, trying to get services. I was hoping you could tell us what would be something that we could do and make recommendations to the appropriate agencies?

Mr. BARRS. Thank you, sir. I would say when I first got out I was still—I guess as you can say, I can meet a new person, it is OK, because, you know, you got new guys coming in the Marine Corps all the time. And like I said in one of my statements, I just started getting treatment for my TBI. That was last month. I think if they were to be faster with it, it would be—I cannot think of the word.

Senator BROWN OF MASSACHUSETTS. Better results? Quicker results?

Mr. BARRS. Along that track, and also you would be able to, I guess, talk to somebody and let them know, because hearing Mrs. Bohlinger talk about her son, I actually know what she is talking about. I am not very good at meeting new people, and I am isolated. I do not just speak for myself. I think it is for everybody else out there that also has this injury.

So I think waiting on, for instance, Winston-Salem to give me a letter, I mean, I can wait all day for that. But when you got a primary care doctor, as I stated, he is more going by the book, what the book is telling him to do. I am asking for certain things. I am not asking it—well, as they say, "I am not asking for my health." Actually, I am.

[Laughter.]

Ms. BOHLINGER. That is OK.

Mr. BARRS. It is just the doctors—it seems like the doctors I have met—I guess that is where the problem starts. It is like they are 9 to 5 people. You know, I am over here struggling wondering how I am going to get the next meal on the table because I have not received my VA rating yet. This guy is making $100,000 a year and he is just basically pushing me off.

Senator BROWN OF MASSACHUSETTS. So let me ask you a question. When you came off of active duty, traditionally you get, you know, the—you get evaluated, you get determined if there is any type of disabilities, any injuries. Did you go through that exit process with your unit?

Mr. BARRS. What happened, see, as you guys said, yes, there is a pre-deployment and post-deployment exam, but I can say—and I do not mean to sound rude—you have to realize that yes, I have seen combat. I know I am going to be different. And I am not going to write on some piece of paper, yes, I have seen this, yes, I have seen this, because, yes, there are consequences. I never wanted to get out. But—I just totally lost my point. I am sorry.

Senator BROWN OF MASSACHUSETTS. No, that is OK, because what I am trying to just figure out is in my experience as a JAG in the military, one of the biggest problems that I recognize, Mr. Chairman and members of the panel, is that as a lawyer I look at, OK, this is the problem, how do we solve it, how do we make it better, how do we streamline and how do we get the services and access better. And not to put Jonathan on the spot, but what I found—and I am hoping that you all can address, whoever is in the room dealing with these things—is when the people are doing their post-deployment process and they are being evaluated, we need to make sure that we have—that every State has—the tools and resources to quickly, effectively, and compassionately evaluate our soldiers, because you are taught in the military to be macho and to be tough and to, you know, bite the bullet, pull up your pants, you know, the whole—it is the same with postpartum depression with women. I am hopeful that each State—and Massachusetts is a little bit different. We have identified it a little bit better. Montana is different, it seems.

So how do we make sure that each soldier that is getting through with their duty is quickly and effectively evaluated? And is there anyone on the panel that can address that? Sir?

Mr. DABBS. Senator, what we have done in Michigan, Major Briggs has developed a great working relationship, and every single unit that comes back Major Briggs briefs regarding brain injury. Also as part of that, he briefs their families. And it is really—as Mrs. Bohlinger indicated earlier, it is often the family that is really the key person, the key group to help identify.

That does not solve the screening issue or any of that, I realize, but I think it is the easiest step that could be executed immediately in almost every State of this country if we were to choose to do so.

Senator BROWN OF MASSACHUSETTS. Well, is there a national plan that is, in fact, being instituted or is it being left up to individual States to do this? Is there a national model where we are saying to the States and/or the individual units, whether Guard, Reserve, active, "Hey, this is what you guys need to do. When somebody gets home, this is going to happen. We are going to brief the families and let them know"—is there a plan like that?

Mr. DABBS. Sir, I am not aware of one. And let me as part of that thought, throw out one other point that I think the Committee needs to recognize. We talk about the VA, or at least what we have seen in Michigan, being overburdened. I got some figures yesterday from the Department of Military and Veterans Affairs of Michigan that indicate that there are over 725,000 veterans in Michigan, and yet only 230,000 are enrolled in the VA. So not everyone is even taking advantage of that system, yet the system is already overburdened. Just overburdened.

Senator BROWN OF MASSACHUSETTS. Right. Mr. Chairman, do I have a chance to continue on for a little bit?

Chairman AKAKA. Surely.

Senator BROWN OF MASSACHUSETTS. Thank you.

And that is one of those reasons because, you know, not everybody stays in the military system. They get better primary care coverages, obviously. And one of the biggest complaints that I have heard in my many, many years of serving and just being alive is that people do not feel that they are getting the best service or the most quality services from the VA as evidenced by what happened a few years ago.

I know we are trying to tackle those very sensitive problems, but, ma'am, if I could direct my question to you. Thank you for your sacrifice, your family's sacrifice, and your son's service. You mentioned briefly the respite care that you have, and you have made the resources a little better for you to travel and go see your son and the like. And being who you are, you get that little extra help, which is—whatever it is, if it was my son, I would not care. I would go through the wall. It does not matter.

What suggestions or improvements can you give to us that we can convey to the appropriate authorities as to how to help people in your situation who are affected by, you know, the change in their kids' lives.

Ms. BOHLINGER. Thank you for that question. I would just refer back quickly to what Jonathan said because I think this is at the

core of it. It is that length of time delay. While I did have resources, I have spent over $180,000 of my retirement funds on his care.

Senator BROWN OF MASSACHUSETTS. Right.

Ms. BOHLINGER. Now, that is going to be difficult at my age to try to make up. Frankly, I will spend it all if I need to. But when he said, "I do not know where the next meal is coming from"—because there are no resources in between. If you do not have a family member who is going to pay your rent, buy your groceries, pay your bills, get everything taken care of for you, a couple of years go by, and that is a lot of money. And it is very stressful, if I may say this, for the individual because these guys are taught to be macho. Failure is not an option. They take the warrior creed. So then, to not only be dependent and know that your life has changed, but now you have to ask someone to, you know, buy your groceries and help you put food on the table because you served your country and in a year or two they cannot get that determination done?

Senator BROWN OF MASSACHUSETTS. Right. You know, Mr. Chairman, one of the things I would hope that with your leadership we could direct and insist that we speed up the process, because when somebody is hurt like this and they need our help and resources, I feel the delay is the biggest obstacle. We should be able to process these soldiers quickly and effectively and give them the funds and care and love and attention that they need right away. To think that somebody is going a couple of years before they even get, you know, screened properly and properly identified in this day and age just blows my mind. I do not know if offline we can talk, the three of us, to kind of come up with a plan and get some guidance; try to push the buttons and put the fire under somebody, because it is unacceptable to me, Mr. Chairman. And I thank you for your allowing me to inquire.

Ms. LAPLACA. Excuse me. May I add to that? I think there is another reason to speed up the time, not just in terms of these very important issues, but also because the injury is getting worse over time.

Senator BROWN OF MASSACHUSETTS. The recovery time.

Ms. LAPLACA. The window for recovery is——

Senator BROWN OF MASSACHUSETTS. It gets smaller and smaller.

Ms. LAPLACA. It is small. Things are ongoing. You can do delayed treatment, but the longer you wait, the less beneficial it is going to be for most veterans.

Senator BROWN OF MASSACHUSETTS. That makes sense with any injury, and since you spoke up, how do you think the VA can better partner with nongovernmental health care providers to help in that effort?

Ms. LAPLACA. I think more of what we are already doing in terms of collaboration, I think multi-agency funding mechanisms that require and encourage basic findings to get to the right level, and——

Senator BROWN OF MASSACHUSETTS. But none of that is in place now, right, really? In reality, none of that——

Ms. LAPLACA. No, the previous panel spoke about many granting programs that are in place, and the 2007 appropriations for Trau-

matic Brain Injury research included both clinical and basic research. But I think, you know, that was a good boost for the community, but it needs to continue. We need more of it. We need more cooperation among the agencies.

Senator BROWN OF MASSACHUSETTS. Thank you.

Mr. Chairman, I have to get back to the other hearing now. Thank you.

Chairman AKAKA. Senator Brown, thank you so much for your questions and the responses that you received. I agree with you. This is why we are holding these hearings, to bring the different parts of our Government, including Congress and the Administration, together so that we can move more quickly. I would tell you also that we are so fortunate we have brought into play advanced funding to deal with this because without resources we cannot do it. So now it is a little easier to do it because we now have the possibility for better resources.

So all of these are coming in quickly, and I expect to see movements faster than there has ever been before. And so with your experience and your recommendations, we can move more quickly in a concerted way.

Mr. Dabbs, do you have a comment to make?

Mr. DABBS. Senator, if I may—and it may go out of the purview of this Committee, but I would like to at least toss out the idea that one of the hindrances that we have seen with TRICARE is that they operate under the Medicare guidelines. The Medicare guidelines do not provide for cognitive rehabilitation for long-term care, and therein lies one of the major stumbling points that is affecting the VA as well as DOD. So I would urge, if there is a way which that could be addressed, I would certainly be willing to share our thoughts with the Committee at a later date.

Chairman AKAKA. Well, with that, I ask any member of the panel if you want to make a closing statement as to what you think about what we can do. Dr. Gans?

Dr. GANS. I would like to just add that the notion that I have heard from family members and those patients who are able to advocate for themselves is very similar to what Ms. Bohlinger and Jonathan Barrs have said: It is timely access and it is choice. Whether it is choice of staying within the VA Polytrauma System, which many people are very happy with and that is their choice, that is great, but if it is choice for using a facility that has certain other resources available in a different location or if it is choice to be closer to home and community—it is timeliness. The stories that I heard from the family members I talked about, waiting a year and fighting for a year to provide services, getting Members of Congress to help advocate on their behalf to get services provided; it is just not the right way to treat these folks.

Chairman AKAKA. Thank you.

Dr. LaPlaca?

Ms. LAPLACA. Chairman, as an engineer and as a scientist, we are constantly looking for innovative solutions to these very problems. However, I do think we need to take a look at home health care and simple solutions. I mean, cognitive rehab over a long period of time can be done in a simple manner, in an inexpensive manner, if it is organized and if it is part of these programs.

So while people are waiting for the doctor—I mean, there are a lot of problems here that need to be addressed. But organizing these case managers and some of these transitional programs, it is worthwhile, in my opinion, to look for simple solutions that can be implemented and taken home, and that I think partially addresses some of the rural area problems as well as some of the cognitive rehabilitation that is so critical.

Chairman AKAKA. Let me ask a final question to Mr. Barrs because I think your answer and what you have been through will help us. I am very concerned about your testimony that you were twice exposed to IED blasts in your first tour, but were not screened for TBI until late 2008. In the interim, you were sent back for a second tour without proper treatment. Were you ever told why it took so long for you to be screened and treated?

Mr. BARRS. Mr. Chairman, when I was in Iraq for my first tour, we were at this train station that we were building up, so we did not really have that much to work with. And I had in my statement that I had to go to another FOB, also known as the Forward Operating Base, because of excessive weight loss. I was puking every day. I could not hold anything down. I lost approximately 40 pounds in 2 weeks. That was my biggest issue then, I guess. And because we had really nobody—I never really noticed that I had glass in my head until I got back to the FOB. I took off my Kevlar, and then when I ran my fingers through my hair, that is when I noticed it. So I did not really say anything before then. I am still walking. You know, the good Lord kept me alive, so I was just, like, OK.

And the second blast, it was noted though it was never put into my medical record. The corpsman just checked me out and I never said anything on my, you know, post-deployment/pre-deployment stuff because I am a U.S. Marine. I am not going to argue. The only thing that really got it started was I had these horrible migraines, and finally it took several BAS appointments just to get looked at for migraines; and as soon as that hit, I really did not have time to think. It was appointment, appointment, OK, you are out of the Marine Corps now.

So it could have been, you know, it could be my fault, too, that it was not done quickly. But like I said, I am a U.S. Marine, and I am not going to argue about what I do.

Chairman AKAKA. Thank you very much, Mr. Barrs. I asked that because we need to deal with some of these delays that have occurred and improve our system.

I believe that together we have made important strides in caring for veterans with TBI. VA has dramatically improved services for these veterans. We are learning more each day about how to screen, diagnose, and treat this signature wound of the current wars. I thank the VA employees and providers throughout the entire VA system for making this possible. However, as long as we have any veterans with undiagnosed TBI, partnerships with community providers left untapped, or research left unused, there is still work to do.

I will conclude by thanking all of our witnesses for your testimony today. Your insights, without question, have been helpful in better understanding the state of TBI care. I especially thank Mr.

Barrs for his service and his sacrifice. Also, Mrs. Bohlinger, I thank you and thank your son for his service, as well.

Finally, I again acknowledge and commend the roughly 280,000 VA employees who choose to work for veterans and their families. As many of you know, this is Public Service Recognition Week, an ideal opportunity to recognize and thank those who serve our former servicemembers with such dedication and commitment. I offer you our gratitude.

Thank you very much, and thank you for this great hearing. This hearing is now adjourned.

[Whereupon, at 12:06 p.m., the Committee was adjourned.]

A P P E N D I X

PREPARED STATEMENT OF SARAH WADE, WOUNDED WARRIOR PROJECT

Chairman Akaka, Ranking Member Burr and Members of the Committee, Thank you for inviting Wounded Warrior Project (WWP) to provide a perspective on the Department of Veterans Affairs (VA) efforts to respond to the rehabilitation needs of veterans with Traumatic Brain Injury.

Through our extensive work both with servicemembers and veterans who have sustained severe Traumatic Brain Injuries, and with their family caregivers, Wounded Warrior Project brings a keen appreciation of VA's critically important role in the care and rehabilitation of these warriors. I've had the opportunity to work with many of these families, and will attempt to include their experiences as well as my own into our testimony.

My husband Ted sustained a severe Traumatic Brain Injury in February 2004 as a result of an IED while serving in Operation Iraqi Freedom. Given the gravity of his injuries, we were told it was doubtful Ted would survive, and were approached with the option to withdraw care. Ted did pull through, but remained in a coma for two more months. Ted is alive today because of the extraordinary neurosurgical care he received. No one ever questioned doing the costly surgeries that saved Ted's life. In fact, because Ted's case was so complicated, the Army arranged for the surgeries to be performed by experts at a German university hospital, and later Walter Reed brought in an outside neurologist to provide care.

We had been told that it was highly unlikely that Ted would ever function at a higher level. In fact, he is living far more independently and functioning at a far higher level than many would have imagined because of the outstanding rehabilitative care he got later. But, in contrast to the Army's "exhaust-all-possibilities" approach, I've had to fight over the years to get VA to authorize many of the rehabilitative services that have truly made a difference, enabling Ted to live in the community and to continue to progress.

VA has certainly made very substantial strides in responding to the treatment and rehabilitative needs of veterans with severe TBI. Among its very important achievements are the build-out of a polytrauma network, the establishment of OEF/OIF coordinators and Federal Recovery Coordinators, and more frequent use of fee-basis and contracting authority. But notwithstanding very real and tangible institutional changes and compassionate care provided by many, many dedicated clinical staff, there remain troubling gaps. We deeply appreciate the Committee's concern with closing those gaps, and ensuring these veterans the opportunity to realize the highest level of independence and functioning they can attain.

GAPS IN VA REHABILITATIVE SERVICES FOR VETERANS WITH TRAUMATIC BRAIN INJURY

As you know, Mr. Chairman, our troops have sustained relatively few casualties in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF), and servicemembers who would likely not have survived in previous conflicts are returning home with unprecedented complex, severe injuries. Some 1,500 have sustained a severe TBI since October 2001.[1] Many of these young men and women will require assistance for life, ranging from total care for the most basic needs, to supports for semi-independent living.

Veteran-centered care: Each case of Traumatic Brain Injury is unique. Depending on the site of the injury and other factors, patients may experience a wide range of medical and related physical effects—from profound neurological deficits, to problems with speaking, vision, eating, incontinence, etc.—as well as dramatic behavioral symptoms and cognitive deficits. As VA clinicians themselves recognize, it is

[1] Defense and Veterans Brain Injury Center, http://www.dvbic.org/TBI-Numbers.aspx

difficult to predict a person's ultimate level of recovery.[2] But to be effective in helping an individual recover from a brain injury and return to a life as independent and productive as possible, rehabilitation must be targeted to the specific needs of the individual patient. In VA parlance, rehabilitation must be "veteran-centered." This simple principle is a critical touchstone by which to gauge VA's progress in TBI care. Is VA providing "veteran-centered TBI care?" We see progress; but the system does not live up to the VA's claim of "world class" service,[3] in our view. Let me highlight some of the critical gaps.

Access to the right services:

Given that every case of TBI is unique and each patient's care and rehabilitative needs differ, it is unrealistic to believe that every VA medical center, or even most, can have the needed range of expertise "in-house" to meet the wide-ranging, often complex needs of all TBI patients. WWP's experience is that even the over 100 VA facilities that have received additional staffing, equipment and training and constitute its TBI/Polytrauma System of Care are not fully equipped to provide the wide range of services TBI patients need.

Even a facility with the most well equipped, well-staffed rehabilitation service may not be the right setting for some TBI patients. A young veteran who needs help with community reintegration and relearning basic life skills cannot be expected to make meaningful gains in a geriatric facility. Too often, VA TBI care for OEF/OIF veterans is not age-appropriate.

Unlike the Army's willingness to bring in outside experts when it was not fully prepared to meet Ted's clinical needs, my own experience and that of other families is that VA facilities have been much less open to acknowledge limitations in expertise or lack of options when they exist and to offer alternatives that might produce better outcomes. We have noted that with greater congressional focus on the issue, VA has demonstrated greater openness to authorizing non-VA sources to provide rehab services that are not available at, or cannot feasibly be provided, through VA facilities. But surely in a veteran-centered system of care a patient's spouse would not have to take the lead on researching how best to meet her husband's rehabilitative needs and have to press to get those services approved. And as the examples cited below reflect, a more veteran-centered system would not so routinely reject such requests.

Individualized Rehabilitation Plans:

VA has advised this Committee that "[a]n individualized rehabilitation and community reintegration plan is developed for every Veteran and active duty Servicemember who requires ongoing rehabilitation care for TBI;" VA has also reported to you that "[t]he patient and family participate in development of the treatment plan and receive a copy of the plan from the care coordinator."[4] Of course, VA is required by law to develop such plans, engage family and veteran in the plan's development, and provide copies of the plan to the veteran and family.[5] But caregivers with whom I've worked closely have never seen a rehabilitation plan, and—while they acknowledge that VA clinicians may develop a plan—they report that they have not been afforded an opportunity to play a role in its development. I have seen a VA document that was described to me as a veteran's TBI rehab plan but was little more than a list of the services VA would be providing or had authorized. In contrast, the law makes it clear that these plans are to include rehabilitative objectives for improving the physical, cognitive, and vocational functioning of the individual with the goal of maximizing the independence and reintegration of such individual into the community.[6] It is critical, in our view, that those rehab objectives are clearly identified, and that the veteran and family are active participants in setting those objectives and in identifying the specific treatments and services to be provided to achieve those objectives. Effective rehabilitation requires that providers, patients and their families work together to achieve the best possible outcomes. That must start with rehabilitation planning. Veteran-centered rehabilitation demands no less.

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[2] Sharon M. Benedict, Ph.D., "Polytrauma Rehabilitation Family Education Manual," Department of Veterans Affairs Polytrauma Rehabilitation Center, McGuire VA Medical Center, Richmond, Virginia; http://saa.dva.state.wi.us/Docs/TBI/Family_Ed_Manual112007.pdf (accessed April 27, 2010).

[3] Eric K. Shinseki, Secretary of Veterans Affairs to the Honorable Daniel Akaka, Chairman, Committee on Veterans' Affairs, U.S. Senate, 23 March 2010.

[4] Id.

[5] 38 U.S.C. sec. 1710C.

[6] 38 U.S.C. sec. 1710C(b)(1).

Effectiveness of case-management and care-coordination:

The Federal Recovery Coordination Program has proven an exceptional initiative in assisting many who were severely injured in Iraq and Afghanistan, and their families, to access needed care, services, and benefits. It has been especially important for veterans with multiple complex needs, such as those with severe TBI. But as the program was not established until 2007, many who were severely wounded earlier in the war and who are still struggling years after their injuries, lack this singular support. In all, only about 460 warriors have Federal Recovery Coordinators (FRC's). There is a clear need to augment the number of FRC's assigned to help wounded warriors, particularly those with the complex needs associated with a severe brain injury.

But as helpful as FRCs have been in removing barriers to services, having an FRC does not solve all problems. Not all case-managers and care-coordinators necessarily have experience with brain injury. And as FRC's are for the most part located at a handful of key DOD acute-care facilities, these individuals are generally not familiar with the resources in the veteran's community. Given deep resistance at many VA facilities to draw on community expertise, the FRC's limited ability to navigate locally is concerning. But an even more fundamental, troubling issue is the deeply engrained culture of "no" that too often confronts veterans and their advocates, whether parents, spouses, or care-coordinators attempting to meet the veteran's needs. Too often, VA facilities do not seem hesitant to say "no" to FRCs.

In short, the individual case-management assistance afforded by an FRC is no substitute for more thorough-going system changes.

Scope and duration of rehabilitative services:

While many VA facilities have dedicated rehabilitation physicians, therapists and other specialists, the scope of services actually provided these veterans is often limited, both in duration and in the range of services VA will provide or authorize. Such barriers needlessly constrain rehabilitative and long-term care options, and as a result, prevent too many veterans with severe TBI from attaining their goal of continued recovery and maximum quality of life.

The literature indicates that some people make a good recovery after suffering a severe TBI. But many have considerable difficulty with community integration even after undergoing rehabilitative care, and may need further services and supports.[7] But it is all too common for families—reliant on VA to help a loved one recover after sustaining a severe Traumatic Brain Injury—to be told that VA can no longer provide a particular service because the veteran is no longer making significant progress. Imagine the frustration and feeling of abandonment when a Department whose mission is to "care for him who has borne the battle" says, "no more therapy!"

It is not clear whether VA's failure to provide veterans who sustained severe TBI with ongoing maintenance rehabilitation is based on a perception that VA's statutory authority is limited to therapy to "regain function," on cost concerns, or on other considerations. But it is clear that ongoing rehabilitation is often needed to maintain function.[8] Whatever the explanation for limiting the duration of a veteran's therapy, there is profound reason for concern that many veterans denied maintenance therapy will regress, losing cognitive, physical and other gains made during earlier rehabilitation.

Significantly, VA facilities are also denying requests to provide TBI patients with what might be deemed "non-medical" supports. Yet supports like community-reintegration therapy, life-skills coaching, or supported employment, for example, afford the veteran the opportunity to gain greater independence and improved quality of life. Given TBI sequellae that cause individuals considerable difficulty re-integrating into the community, VA's rigid adherence to a medical model of rehabilitation—and foreclosing social supports—is a formula for denying a veteran the promise of full recovery.

VETERAN AND FAMILY PROFILES

In attempting to emphasize the importance of making TBI-care truly veteran-centered, let me give you some context by sharing the perspectives of a few of family members with whom I've worked who have a son or spouse who suffered a TBI.

Houston VAMC: After her son sustained a severe TBI and was medically retired in 2006, one mother-turned-caregiver encountered a VA system she has experienced as inflexible and quick to say "no." Despite "spots of brilliance" in the care her son

[7] Nathan D. Cope, M.D., and William E. Reynolds, DDS, MPH; "Systems of Care," in Textbook of Traumatic Brain Injury (4th ed.), American Psychiatric Publishing (2005), 533–568.

[8] Id.

has received, the process of gaining access to needed services has often been "dogged and exhausting." After long acting as her son's full-time at-home caretaker, she encountered repeated VA refusals to provide a few hours/day of home-attendant services on the basis that the services "weren't medically necessary." Ultimately, she pursued congressional help to win the Houston VAMC's agreement to provide assistance she discovered was routinely furnished by other VA facilities. But the medical center would authorize that help only one-hour per day, three times weekly—insufficient to give her the respite she so badly needed. The home attendant assistance also lacked the structure and routine that young TBI patients so desperately need, with attendants coming at varying and unpredictable hours each day. Frustrated with a system that was much more attuned to the needs of geriatric patients rather than young wounded warriors like her son, she canceled the VA-arranged home-attendant care in favor of more age-appropriate help that the family covered out of pocket.

As the veteran has slowly regained cognition, his needs and those of his family have changed. When his mother requested counseling (as provided for by law) for the veteran's two younger siblings to help them cope with the trauma and profound adjustments associated with their brother's injuries, VA rejected the request. The medical center's unwillingness to recognize the direct relationship between the mental health of the caretaking family and the veteran's continuing therapy continues to trouble her. A Federal Recovery Coordinator has made a difference in winning approval of some needed services. But when she recently sought approval to get a mode of therapy to help her son learn to progress toward vocational and other personal goals, her VA social worker questioned "when is enough enough" in terms of further therapy. The subliminal message was clear: "the clock is running out on providing more therapy for your son." I think we can all agree that this is not the message of a "veteran centered" system.

Tampa VAMC: After making dramatic progress in recovering from an open head wound incurred in March 2006, this OIF veteran had a setback while undergoing rehab at VA's Tampa polytrauma center. His mother, a nurse herself, had found the clinical staff agonizingly slow in responding to her plea to compare her slowly-dying son's CT scans with those last taken at Walter Reed. At last discovering a massive buildup of brain fluid, Tampa returned the veteran to Walter Reed for emergency brain surgery. After re-entering therapy from ground zero, the veteran progressed well for about a year. In the first of what became a series of problems, the Tampa VA was unwilling to provide physical therapy to help him restore left-arm movement. In frustration, his mother turned to a Member of Congress; VA did then arrange for the needed therapy to be provided at the University of Alabama-Birmingham. When Tampa later refused her requests for further therapy to prevent reversal in the gains he had made, she turned to Medicare. That apparently prompted Tampa to discharge the veteran altogether, with no follow-up plan whatsoever. He moved into his own apartment, but—without structure and supervision, and with a condition marked by impulsivity and lack of insight—he spun out of control, and has struggled since then with PTSD, depression, and substance-use complicating his TBI problems. In describing just one chapter of the family's long ordeal with his self-destructive behaviors, his mom reports having begged Tampa for help with his complex problems, and being told they didn't feel it was their responsibility as this veteran wasn't asking for help. Despite Tampa's lack of cooperation, she ultimately succeeded in having him admitted to Bethesda Naval Hospital for neuropsychiatric care. While his neuropsychiatrist at Bethesda, after a four-month hospitalization, recommended that he be provided a full-time life-skills coach to furnish constant supervision and structure, Tampa ultimately agreed instead to provide a home health aide and regular VA outpatient treatment. The veteran's mother observed that "while Tampa has stepped up" since the neuropsychiatrist's involvement, they seem to "have only one care plan, and if you don't fit into it, you're out of luck."

Iowa City VAMC: Caregiver; accountant; occupational therapist; physical therapist; driver; mental health counselor; life coach. These are all roles an Iowa wife has taken on since her husband was injured in a mortar attack in 2005 in Iraq. He sustained a penetrating injury to the right side of his brain, leaving him hemiplegic, and without a right eye. After two trips to Walter Reed and a seven month stay at the Minneapolis VA, the veteran returned home, becoming Iowa City VA's first polytrauma patient. But despite its classification as one of the VA's 108 specialized rehabilitation centers, Iowa City VAMC has proven ill-equipped to provide the range of services the veteran needed, particularly, physical, occupational, and cognitive therapy. While the facility arranged for the veteran to receive rehab services from a better-equipped private facility, it discontinued the services after a year based apparently on the view that he wasn't improving quickly enough. It intermittently pro-

vided brief periods of fee-basis physical therapy in response to the wife's concerns that the veteran fell frequently, but discontinued that therapy, citing funding constraints and a policy of limiting patients to no more than 24 such sessions. She was advised that it was time for the family to pay for further physical therapy. The decision left the veteran's wife to become her husband's physical and occupational therapist, using the techniques she videotaped at the independent facility. She later taught a nursing assistant, who VA furnishes twice-weekly through a home-health agency, to administer physical therapy. While she has requested VA to allow the agency to send a physical therapist to their home, the medical center refused. She expressed reluctance to push any harder for the needed therapy for fear of "burning bridges" with the VA—her husband's only source of health care.

CLOSING THE GAPS

VA leaders have taken important steps toward establishing both a TBI system of care and policies aimed at fostering optimal recoveries for veterans and servicemembers with severe TBI. But deep, troubling gaps in that system are compromising realization of too many veterans' potential for full rehabilitation. This must change—and the needed change must be in a single direction—toward truly veteran-centered care.

The principle of veteran-centered care must be more than a slogan. It must be a core value at the heart of VA's TBI program. If rehabilitation and care is to be veteran-centered, VA facilities must develop truly individualized rehabilitation plans built around goals developed in concert with the veteran and his/her family. Those plans must also provide for access to all "appropriate rehabilitative components,"[9] a requirement that encompasses "age-appropriate" services. Providing veteran-centered care also requires a fundamental change aimed at meeting each veteran's rehabilitation needs—whether through services VA provides or procures. If VA TBI care is to be veteran-centered and "world class," it can no longer reflect an approach that says, in effect, "we don't provide that service; you'll have to accept our service or pay for the care you want out of pocket." Successful rehabilitation must build on the strengths and needs of the injured individual; requiring the injured veteran to adapt to arbitrary VA requirements or limitations is a sure path to rehabilitative failure. To put it another way, VA must become a system that looks for ways to say "yes," rather than "no."

But achieving veteran-centered care will also require statutory change. Under current law, the Veterans Health Administration (VHA) is to provide a comprehensive program of long-term care for post-acute Traumatic Brain Injury rehabilitation that includes residential, community, and home-based components using interdisciplinary treatment teams.[10] Rehabilitative services, however, are defined in law to mean "such professional, counseling, and guidance services and treatment programs as are necessary to restore, to the maximum extent possible, the physical, mental, and psychological functioning of an ill or disabled person."[11] Our experience, however, is that while VA furnishes services to restore function, wounded warriors are not necessarily assured under this statutory framework—or under current practice—of continued therapy to sustain function and to prevent loss of the gains achieved. The distinction is critically important to the well-being of a warrior with severe Traumatic Brain Injury. In addition, VA's authority to provide rehabilitative services (as defined above) suggests the provision of services under a medical model. But a traditional medical model may not best meet the range of rehabilitative needs of a profoundly injured young warrior. Rehabilitation after a moderate to severe TBI requires more than just addressing physical deficits; it is also about improving and sustaining to the greatest extent possible that injured individual's quality of life.[12] It is vital that rehabilitative care and services for very severely injured warriors be individualized and holistic in nature, and that these warriors have reasonable access to, and a choice of options geared to their age and injury, whether through government facilities, private, or a combination.

Mr. Chairman, we urge you, accordingly, to take up legislation to clarify VA's authority to provide maintenance-rehabilitation to those with Traumatic Brain Injury as well as to enable VA to provide individualized rehabilitative services (not limited to a restrictive medical model) and patient-centered supports to permit the severely wounded warrior to live as normal a life as possible in whatever setting is most appropriate, to include in-home or in home-like residential options. Such legislation

[9] 38 U.S.C. sec. 1710C(b)(2).
[10] 38 U.S.C. sec. 1710D(a).
[11] 38 U.S.C. sec. 1701(8).
[12] James F. Malec, "Ethical and evidence-based practice in brain injury rehabilitation," *Neuropsychological Rehabilitation* 19, no. 6 (2009), 800.

would be a step toward moving VA to pioneer new approaches to rehabilitation and community living for young veterans learning to live with Traumatic Brain Injury, and to educating and training a new generation of specialists in Traumatic Brain Injury rehabilitation.

We would welcome the opportunity to work with the Committee to shape such legislation.

PREPARED STATEMENT OF THE NATIONAL ASSOCIATION OF STATE HEAD INJURY ADMINISTRATORS

Dear Chairman Akaka and Members of the Senate Veterans' Affairs Committee: The National Association of State Head Injury Administrators (NASHIA) appreciates this opportunity to submit testimony about how the Veterans Administration (VA) can best meet the needs of veterans with Traumatic Brain Injury (TBI). The National Defense Authorization Act for Fiscal Year 2008 directs the VA to collaborate with local, State, and private entities to improve services for veterans with TBI. It is NASHIA's experience that the collaboration to date has largely been as the result of State and local initiatives. Greater efforts on the part of the VA and Department of Defense to coordinate with State resources and services could help fill the gaps in information and referral and service delivery.

NASHIA AND THE ROLE OF STATES IN SERVING PERSONS WITH TBI

NASHIA was established in 1990 as a non-profit organization representing State governmental officials who administer an array of short-term and long-term rehabilitation and community services and supports for individuals with TBI and their families. NASHIA members include State officials administering public TBI programs and services, and associate members who are professionals, provider agencies, state affiliates of the Brain Injury Association of America (BIAA), family members and individuals with brain injury. NASHIA holds annual State-of-the-States conferences throughout the United States and public policy seminars with Federal officials and Congressional staff, serves as a resource to the Congressional Brain Injury Task Force and provides technical assistance and advice to State TBI program managers.

Most long-term care services and supports for persons with TBI are administered by the States, and funded mainly through the shared Federal/State Medicaid Home and Community-based Services Waivers (HCBS), nursing homes, Medicaid State Plan services, such as personal assistance and in-home care; State funds; and designated trust funds, derived primarily through traffic fines. Medicaid HCBS Waivers for Individuals with TBI have grown significantly in recent years, doubling from 5,400 individuals served in 2002 to 11,214 in 2006, at a cost of $155 million in 2002 to $327 million in 2006 (Kaiser Commission on Medicaid and the Uninsured (2007, December); *Medicaid Home and Community-Based Service Programs: Data Update*, The Henry J. Kaiser Family Foundation, Washington DC). Individuals with TBI are also served in other State waiver programs designed for physical disabilities, developmental disabilities, elderly and other populations. Individuals with TBI who are not Medicaid eligible receive similar services through programs funded by State general revenue and trust funds, and may also receive services through other disability programs such as Vocational Rehabilitation. Almost half of the States have enacted TBI trust legislation generating approximately $70 million a year for services and supports.

Individuals with TBI seek State services often as the last resort. Private insurance generally has not provided for extended rehabilitation and long-term care, supports and services. And, in some instances, States have developed HCBS Waiver programs to end costly out of State placements. Families and individuals with TBI seek services in crisis situations, when families are in turmoil due to job loss, out of control behaviors or substance abuse that may result in family violence or dangerous situations to self and others.

Without appropriate services and supports, individuals with TBI often are inappropriately placed in institutional settings or end up in State Correctional facilities due to their cognitive and behavioral disabilities. A recent report issued by the Centers for Disease Control and Prevention (CDC) cited other jail and prison studies indicating that 25–87% of inmates report having experienced a TBI as compared to 8.5% in a general population reporting a history of TBI.

Often States provide the first contact for persons with TBI and their families, and provide referral to appropriate rehabilitative resources or advocacy services such as are provided by BIAA affiliates. Especially in cases where TBI has been undiagnosed, it is often when a person is homeless, the police are involved, that State serv-

ices are called upon and appropriate services are coordinated. A critical service that States provide is service coordination to help coordinate and maximize resources and supports for individuals with TBI and their families.

THE INCIDENCE AND PREVALENCE OF TBI IS ON THE RISE

CDC recently released new data showing that the incidence and prevalence of TBI in the United States is on the rise. CDC reported that "each year, and estimated 1.7 million people sustain a TBI. Of them: 52,000 die; 275,000 are hospitalized; and 1.365 million (nearly 80%) are treated and released from an emergency department. TBI is a contributing factor to a third (30.5%) of all injury-related deaths in the United States. About 75% of TBIs that occur each year are concussions or other forms of mild TBI. The number of people with TBI who are not seen in an emergency department or who receive no care is unknown." (www.cdc.gov/Traumatic BrainInjury/statistics.hml)

The data collected by CDC relies heavily on State data, gathered through State Registries and hospital discharge data.

These numbers do not include the veterans who sustained TBIs in Iraq or Afghanistan and now use private or State funded resources for care, or undiagnosed TBIs.

STATE RESOURCES AND SERVICES

Over the past 25 years, States have developed service delivery systems that generally offer information and referral, service coordination, rehabilitation, in-home support, personal care, counseling, transportation, housing, vocational and other support services for persons with TBI and their families. These services are funded by State appropriations, designated funding (trust funds), Medicaid and Rehabilitation Act programs and administered by programs located in the State public health, vocational rehabilitation, mental health, Medicaid, developmental disabilities or social services agencies.

Approximately half of all States have a dedicated funding mechanism, mainly through traffic related fines, that fund services and about half of all States also administer a Medicaid Home and Community-Based Services Waiver for individuals with brain injury who are Medicaid eligible. Some States have the advantage of both of these funding mechanisms in addition to other State and Federal resources. Most States have identified a lead agency responsible for providing and or coordinating services and most States have an advisory board or council to plan and coordinate public policies to better serve individuals who frequently needs assistance from multiple agencies and funding streams in order to address the complexity of their needs.

Under the TBI Act of 1996, the US Department of Health and Human Services, Health Resources and Services Administration (HRSA) provides grants to States to expand services and resources particularly to underserved populations. Since the program began, almost every State has received TBI Act funding, but there are currently less than 20 States participating in the program due to a lack of sufficient Federal funding.

STATE COLLABORATIVE EFFORTS TO ADDRESS THE NEEDS OF VETERANS

Since servicemembers and veterans first began to return from Iraq and Afghanistan, NASHIA and some individual States have reached out to VA staff to participate in educational forums and national TBI conferences. Some States have reached out to work with the VA, particularly staff from individual Polytrauma Centers, to promote collaboration in order to better understand VA benefits for veterans that may be seeking State services, and for VA to understand what is available in the communities. In addition, some States have added representatives from VA, National Guard and Reserves, State Veterans Affairs, and/or veterans organizations to serve on their State advisory board in order to improve communications and policies across these programs.

Some States have used the HRSA grant funding to address the needs of returning servicemembers and veterans with TBI.

With the knowledge that veterans could fall through the cracks between discharge from the military or veteran care and community reentry, States have responded in a variety of ways. Here are a few examples:

• Alaska convened an informal group of representatives from the State TBI Program, 3rd Medical Group (Elmendorf Air Force base), Alaska VA, Vet Centers, Alaska Federal Health Care Partnership, Alaska Native Tribal Health Consortium, hospital providers, behavioral health providers, workforce development agencies, and disability advocacy organizations. The purpose of this group is to assess the services

and resources available in Alaska and partner in the planning of a comprehensive system of care; emergency medical services, acute/trauma care, post-acute rehabilitation, community re-entry, and long-term supports.

• The Nebraska Veterans Brain Injury Task Force, which includes representatives from the civilian and military sector, and key State and Federal Government agencies, addresses the increasing needs for brain injury awareness and education among returning servicemembers from Iraq and Afghanistan.

• The Vermont TBI program and the State Division of Vocational Rehabilitation share the cost of a neuro-resource facilitation (NRF) Job Developer to educate and coordinate training for the Vermont business community to increase awareness of the issue facing returning veterans with TBI. Similarly, the State TBI Program shares the cost of a NR Facilitator with the Department of Mental Health as a liaison to the mental health court, specifically serving veterans involved with the Department of Corrections.

• Using funds from the American Recovery and Reinvestment Act of 2009, the California Department of Rehabilitation, the lead agency for TBI, awarded a grant ($486,923) to the Central Coast Center for Independent Living to increase independent living service capacity and coordinate existing services and programs for veterans with TBI and other TBI survivors.

• The New York TBI Program and the Brain Injury Association of New York partner to promote awareness, training, outreach and support to Iraq and Afghanistan military with TBI and their families.

• Similarly, the Massachusetts Brain Injury & Statewide Specialized Community Services Department, known as SHIP, is partnering with the Veterans Administration, Veterans Organizations, TBI providers and the Brain Injury Association of Massachusetts to conducting outreach, information and referral services.

RECOMMENDATIONS FOR THE FUTURE

Given State history with providing rehabilitation and community short-term and long-term services and supports for 25 years, NASHIA recommends the following:

1) Linkages to services are critical at the time of hospital or rehabilitation discharge. Some States, such as Missouri and Florida, found that individuals were often 7–9 years post injury before accessing community services and resources. After implementing an early referral program linking families and individuals with service coordination at the time of hospital discharge, Missouri found that individuals had better outcomes than those who were not linked early in the reintegration process.

2) Systems need to be flexible and responsive. State systems strive to provide the right services at the right time. Such services are provided on a short-term, long-term and episodic basis. Individuals with TBI may receive services for a period of time, then later, they may require similar or different services. Therefore, systems need to have policies that do not impose caps or timelines on services, and they must be able to respond to crisis or changes that may occur within the individual's environment, such as a job change or a caretaker change; or changes that may occur as the result of the TBI, such as behavior or personality changes. A good system will have the capability of providing on-going supports to help prevent crisis from occurring.

3) Veterans with TBI need to be empowered to choose services and supports that best suit their needs and enable them to live in their own homes and communities. As a result of the US Supreme Court Olmstead Decision affirming the rights of individuals with disabilities to live in the community, States have expanded community options, and the Federal Government has provided funds over the years to help States balance institutional and community services for individuals with disabilities. While directed at civilians with disabilities, these rights no doubt apply to veterans with disabilities as well.

4) State and Federal systems are complex and difficult to negotiate. Individuals with TBI frequently request services from different systems, such as Vocational Rehabilitation, behavioral health, substance abuse, and TBI programs. They may also need help with housing, utilities, food, day care for their children, transportation to jobs and other financial assistance. Service coordination or case management is critical to facilitating the coordination and maximization of these resources.

5) Workforce that has training and understanding of TBI. Most States that provide an array of services provide opportunities for on-going training and education through web training, conferences or on-site training. A few have developed core competencies for in-home support staff. Not all community providers that offer similar services to individuals with disabilities understand the behavioral and cognitive problems associated with brain injury.

6) In 2008, the VA began collaboration with the Administration on Aging (AoA) to provide an additional opportunity to State Units on Aging (SUAs) and Area Agencies on Aging (AAAs) to serve veterans at risk of nursing home placement. This initiative demonstrates the willingness to coordinate with State and local agencies to support veterans living in the community. However, the AAAs serve primarily seniors within the States, not necessarily young adults with TBI at risk of being referred to nursing home for long-term care and supports. We believe that expanding this initiative to collaborate with NASHIA and State agencies that serve TBI would help families and veterans to locate and receive coordinated community services and supports.

7) The Institute of Medicine's (IOM) Preliminary Assessment on the Readjustment Needs of Veterans, Servicemembers and their families notes that there is a paucity of information on the lifetime needs of persons with TBI in the military and civilian sectors and recommends additional research into protocols to manage the lifetime effects of TBI. NASHIA supports such research efforts and recommends that it be conducted in coordination with State data and resources. States have experience in this area.

8) The IOM notes the critical shortage of health care specialists and that veterans having to wait for appropriate care remains a problem. In the meantime, families and veterans with TBI are calling State TBI programs for assistance. In some cases, when military discharge status is unsettled, veterans turn to State resources first. State TBI programs are often the point of contact for information and referral for families and returning soldiers and veterans seeking local services, especially with regard to the National Guard and Reserves. NASHIA supports greater collaboration with the civilian sector with the recruitment and training of TBI specialists.

9) NASHIA strongly agrees with the IOM's recommendation that DOD and VA improve coordination and communication among the multitude of programs that have been created to meet the needs of returning servicemembers and veterans.

10) The VA Secretary stated in the March 23, 2010, report to your Committee that "collaborations with private sector facilities are regularly used to successfully meet the individualized needs of Veterans and complement VA care." This has been limited to medical care and treatment. The next step is to extend similar policies to community providers that offer home, community and family supports and services.

In closing, NASHIA offers its expertise, experience and assistance to further improve the connection between community services and supports to enable veterans with TBI to live in their communities after receiving acute and post acute care, rehabilitation and other services through the VA. Given these difficult budget times, NASHIA recommends greater coordination among all Federal, State and local resources in order to improve the lives of veterans with TBI and to enable them to live as independently as possible.

We applaud your leadership and efforts to address the needs of our veterans with TBI and their families. The Department of Defense and VA's TBI initiatives for servicemembers and veterans will no doubt help civilians with TBI as well, so that all Americans with TBI, regardless of cause, will benefit from the research, education, care, treatment, rehabilitation and community supports carried out by these departments.

For additional information or assistance, please contact Lorraine Wargo, Executive Director at awarg@madriver.com or Susan Vaughn, Director of Public Policy, at susanvaughn@mchsi.com, phone: 573–636–6946.

PREPARED STATEMENT OF CHARLES M. "MASON" POE, SSGT USMC (RET.)

Mr. Chairman, Ranking Member Senator Burr, and Members of the Committee: My name is Mason Poe, SSGT USMC (ret), and I come from a strong military minded family. I am a medically retired SSGT after serving one week shy of a nine year service in our beloved United States Marine Corps.

First and foremost, I would like to thank the veterans in which have been wounded in our previous wars and/or conflicts. They have set the high standards of care provided by today's Department of Defense and our Veterans Affairs which provided the necessary healthcare that I needed in 2004 and still need today.

On April 20, 2004, after being informed of the safety of a squad of Marines, my Marines and I were returning back to the Forward Operating Base in Haditah, Iraq, where I was severely wounded after our Humvee was directly hit by an Improvised Explosive Device.

After being in a medically induced coma for approximately one month and bedridden for 3½ months, I was wheeled out of the hospital and my recovery started in August 2004. Due to my significant injuries I was told I would never walk again

and the chances of being a father were limited. For the record, no doctor should ever tell a Marine he will never walk again, as I walked into this building to speak to our Nation's elected officials on May 5, 2010. Furthermore, my wife and I are proud parents of a beautiful 10½-month-old daughter. I personally find it hard to understand people who do not believe in a higher power. My faith is stronger now more than ever.

After six years of recovery and 30-plus surgeries, doctors and I have come to the decision that on June 7, 2010, I will undergo yet another surgery at Duke University Medical Center by having a below-the-knee amputation of my right leg.

I have undergone mostly all physical injuries. Please note; I am not a "disabled" Marine whereas I am a Marine with limitations. The doctors and non-profit organizations such as Wounded Warrior Project and Military Missions in Action from North Carolina can help, assist, and offer ideas and solutions to my physical limitations. However, in my particular case there is one limitation in which only the Lord and I can overcome.

When I was wounded, I was thrown 40-plus feet, my flak jacket was separated and Kevlar helmet was displaced, which did not allow protection when I impacted the ground. After a field tracheotomy was performed in order to clear my airway I was resuscitated and was flown to Baghdad to begin my critical care. As I suffered from a skull fracture, a stint was placed in my brain to reduce the swelling. This leads to why I am here.

Traumatic Brain Injury or TBI, is an injury known as the "unseen injury" for many reasons. The average person will never be able to tell without speaking to you for a period of time that you may have problems accomplishing everyday tasks. Please note, Doctors can fix a broken bone but there is no known cure from TBI. I was screened by the DOD for TBI prior to discharge but the issues regarding TBI have been addressed by the VA.

Every day I struggle with this injury. I have trouble remembering things such as: meetings, phone calls, grocery lists, times to pick up my daughter, and remembering people's names.

Fortunately, Marines are taught from day one to adapt and overcome, therefore I have learned ways to accomplish my tasks successfully.

Transitioning to civilian life has been trying because I am no longer physically able to do the things I used to. The reason I am speaking before this congressional committee today and testifying before you is to inform you of my particular case and care that I have received. I am satisfied with how I have been treated at my local Veterans Affairs hospital.

My case manager, Ms. Collette Wallace, keeps me informed by calling and reminding me of my appointments on a regular basis. I also receive letters of verification of my appointments. I have even attended classes at the VA regarding ways to accommodate my memory issues and have successfully completed a college course in Introduction to Business Administration at my local community college. I have considered returning to the school atmosphere, however that one course I took was more time consuming than I expected as I struggled to recall information required in order to pass each test. As the number of veterans needing medical care from Operation Iraqi Freedom and Enduring Freedom increase the number of case managers at our VA facilities needs to as well.

The VA has provided me with a PDA and recorder to assist me in overcoming some of these memory issues. Whereas these devices have assisted me I cannot rely on them 100% of the time. Luckily, I have a wonderful wife to help me remember names as well as help me around the house with any other limitations I may suffer from.

My local VA hospital in Durham, North Carolina has seen to it that my medical treatments have been and continue to be satisfactorily met and a supportive reassurance for me. I know that I am not traveling this road to recovery on my own. However, I have been informed by other veterans throughout the Nation that all veterans do not receive the same satisfactory care such as mine.

Other organizations that have made it possible for me to heal are Wounded Warrior Project and Military Missions in Action. Wounded Warrior Project has called once a month to check in with my health. They are always asking ways to help with my transition and recovery. My case is difficult as I am 100% permanent and total "disabled" and have loss use of my lower right limb and suffer from double vision but have not actually lost my limb. Military Missions in Action realized the physical help I needed and has made it possible to assist my wife more in the care of our daughter. Military Missions in Action from North Carolina has made a huge impact on my quality of life. I would not be able to undergo this upcoming surgery if they had not added a master bedroom downstairs.

In the future I hope to have a successful service contracting business where I can still honorably serve our country. I look forward to actively being involved with my daughter and wife with a prosthetic leg. I hope to have started a cycling team for Military Missions in Action in order to successfully recover and improve the quality of life of other wounded servicemembers.

I would like to thank those elected officials in which are striving to improve the lives of my fellow Marines and servicemen and women that suffer from wounds in our current conflicts abroad. I hope that our current administration will show the priority of healthcare needed to all our veterans which ultimately allows all Americans to live free.

My final thought to the Committee is regardless of the amount of cutbacks this country is facing on a day-to-day basis, can we really afford cutting back the healthcare provided to these veterans. Who is going to take long term care of them after they have taken care of us and given this country its freedoms?

MRS. KRISTIN M. POE
Washington, DC, May 5, 2010.

Hon. DANIEL K. AKAKA,
Chairman,
Hon. RICHARD BURR,
Ranking Member,
Committee on Veterans' Affairs
U.S. Senate, Washington, DC.

DEAR CHAIRMAN AKAKA AND RANKING MEMBER BURR: "I am ten feet tall and bullet proof." This is what Mason said to me as he told me he had been recalled and volunteered to deploy to Iraq. On April 20, 2004, I found out his angels were ten feet tall and bullet proof. This day has changed our lives forever.

Mason and I met here in DC at a Carolina vs. Capitals hockey game. Although warned not to date Marines because they would break your heart, Mason managed to steal mine. If I had to choose one word to describe Mason it would be "active." There was not one moment where he would sit still; we could hardly get through a movie. Mason volunteered at a fire department in Maryland while stationed at Marine Barracks under Presidential security. I always knew to bring homework while spending time with him because consequently there was going to be time where he was either running a fire call or dealing with Marines. Mason got honorably discharged June 2003 and was voluntarily recalled December 2003.

As Mason's best friend insisted upon picking me up and driving to Dunn, NC, just to hang out with a group of friends, I briefly thought Mason had come home early from his deployment. As we drove up to his parent's house, my stomach sank when I saw the amount of cars outside the house. His mother walked up to me and murmured those words no one wants to hear, "Mason has been wounded. He is in critical condition." As the days went by we learned more of his injuries and the list of them just kept growing. Sandstorms kept his aircraft from leaving Baghdad Hospital and it seemed nothing was in our favor.

Finally, Mason arrived at Landstuhl Army Hospital in Germany a few days later. However due to the severity of the case and the only neurosurgeon at the other base hospital in Ramstein, Mason had to be transferred to Homburg, a private German hospital. Things were looking better until we got a call saying Mason had taken a turn for the worse and the military was flying his parents to Germany to say their "Good-Byes." Since we were not married at the time I was not a priority to go. Luckily Mason's brother, Gunner Poe, was able to get it worked out so that, although I had to take a civilian flight, I was able to accompany his parents to Germany.

Mason stayed at Homburg hospital for a month. We were only allowed to visit him for two hours a day. As you can imagine the 22 hours between visits seemed like a lifetime. The Fischer House was an enormous help while we were in Germany. We had an affordable room, free use of the kitchen, drivers to the grocery store and I even finished my finals using their computer.

As Mason began to heal plans were made to get him back to the states and although our prayers were being answered we knew he still had a long way to go. Mason was just coming out of the medically induced coma at the end of the May.

Mason spent the next month in Bethesda Naval Hospital in Maryland surrounded by friends and family. There he made enough progress to be sent to an inpatient rehabilitation facility in North Carolina. Mason still had fixators in both legs and could not move by himself but the doctors felt he was ready to start therapy.

While at Southeastern Medical Center, Mason continued making great improvements. He surpassed all of the doctors' expectations. By the end of the June he was

walking about 100 feet on a walker. From the day he left the hospital until today he has never stopped fighting. He is one of the most determined people I know.

Mason was not medically discharged until May 2008 when most of his healing had come to a standpoint. I firmly believe that one of the main reasons mason had such good care was the military allowed him to stay active duty until he was thoroughly healed. This gave him options to find the best therapy to fit his needs.

Although the transition from the military to civilian life has been tough, Mason continues to find ways to stay active. He is involved with many civic organizations like the Rotary, Scottish Rites, Masonic Lodge, and the Shriners. Mason just recently cofounded a Marine Corps League in Dunn, North Carolina which also helps with fundraisers like Toys for Tots.

As Mason mentioned the organization Military Missions in Action has been a God send for us. They have made it possible for us to adapt our house to fit Mason's needs. This allows him to be able to take care of his daughter, move comfortably around the house, and have a peace of mind for his recovery in June.

Many people may ask me if Mason is the same person as before he left for Iraq. Ironically, the answer lies within the Marine Corps saying. Although he has had to adapt and overcome a lot of physical and emotional limitations Mason still continues to be just as active and determined as he has always been.

Sincerely,

KRISTIN M. POE.

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