Research Report

CHARLES C. ENGEL, RICHARD SILBERGLITT, BRIAN G. CHOW, MOLLY MORGAN JONES, JONATHAN GRANT[1]

Development of a Knowledge Readiness Level Framework for Medical Research

Policymakers responsible for health research investment decisions have no systematic way of measuring the relative maturity of health research knowledge.[2] Given the substantial investments in health research in the United States and globally, a better understanding of health science maturity could have significant influence on the development of research portfolios. To assist the U.S. Army Medical Research and Materiel Command (USAMRMC) in making such investment decisions, RAND researchers developed knowledge readiness levels (KRLs) for use across different lines of health research. KRLs mark a step forward in thinking about how to assess health research, innovation, and knowledge development.

Military research is requirement-driven and programmed with urgency to resolve priority "gaps" in human performance, operational medicine, training, and care of the ill or injured. A large portion of health research addresses knowledge products (KPs). We define *KP* broadly as **knowledge resulting from research with potential to improve individual or public health**. Analogous technology readiness levels (TRLs) have long been used to grade the maturity of materiel products, but analogous levels for KPs have never been tested.

The goal of this research was to develop and test KRLs to assess the maturity of a KP. The KRL denotes maturity, which is a measure of the stage of progress that health research is making toward improved clinical

KEY FINDINGS

- A KP's scientific maturity can be productively measured in terms of three stages: foundational research, application to human subjects, and application in a real-world context.
- Each of these three stages of health research has unique characteristics that allow reliable assignment of a specific KP to just one of them.
- A KP's maturity can be defined using a nine-point Likert-type scale for KRL and a two-step process: (1) Assign the stage and (2) assign the KP's level of maturity within that stage.
- According to the authors' reliability testing with research publications and real-world testing with research proposals, the KRL and Likert-type scales provide a reliable metric of a KP's scientific maturity.

practices or processes and their implementation into real-world contexts. The KRL concept is based on that of the TRL, which indicates scientific maturity of materiel products (e.g., drugs, biologics, devices) and is currently in wide use. We defined nine KRLs in three groups:

- The first three KRLs (1 through 3) provide the scientific foundation for KP development toward practical application. These KPs are the outputs of health research that seeks basic mechanisms rather than applications and tends to be theoretical or conceptual, often consisting of laboratory, descriptive, or exploratory studies.
- The next three KRLs (4 through 6) are for KPs that seek to generate applied knowledge (i.e., knowledge to eventually perform a non–research-related function or to inform understanding of an application or tool). KRL 4–6 research often asks such questions as whether the application can work under ideal research conditions and, if so, how. To achieve a rating of KRL 4, 5, or 6, the KP must be based on valid, replicated KRL 1–3 research.
- KRL 7–9 ratings are given to KPs resulting from research designed to emphasize external validity (generalizability) of knowledge for use in a specific, real-world application. This research often addresses a policy question: How does the KP compare with usual practice? To achieve a rating of KRL 7, 8, or 9, the KP must be based on valid, replicated KRL 4–6 research.

We developed a Likert-type scale based on the above definitions and a two-step rating process for KPs: (1) Decide which of the three groups of KRL described above—foundation (KRLs 1 through 3), applications (KRLs 4 through 6), or real-world context (KRLs 7 through 9)—best describes the maturity of the KP, and (2) assign the KP to one of the three possible KRL levels within the chosen group. We then tested the rating process and scale for reliability by applying it to ratings of publications from a database of U.S. Department of Defense (DoD)–funded projects from 2007 through 2014 related to posttraumatic stress disorder (PTSD), traumatic brain injury (TBI), and suicide. First, we selected 19 articles at random using a random number generator from the subset of TBI articles. Three of us—Charles Engel, Richard Silberglitt, and PhuongGiang Nguyen—read the articles and rated them independently on a scale of KRL 1 through KRL 9. Subsequently, raters presented and defended their ratings, and the groups discussed the ratings. Discussions aimed to achieve consensus regarding the most appropriate rating for each article, identifying reasons for initial disagreement, refining definitions for each KRL, and standardizing the overall rating process.

After this initial round of review and discussion, we chose a second set of 20 TBI articles based on article title and abstract in order to fill gaps in KRL ratings left over from the first 19 articles. As before, the raters (this time, Engel, Silberglitt, Nguyen, and Brian Chow) reviewed the articles, independently rated them, and discussed them as a group, then determined consensus KRL ratings. We calculated interrater reliability of the KRL ratings separately for the first and second groups of article ratings and

Abbreviations

AAM	advanced airway management
ATA	atmosphere absolute
CR	corona radiata
CSF	cerebrospinal fluid
DENV	dengue virus
DoD	U.S. Department of Defense
DTI	diffusion tensor imaging
GM	gray matter
GMP	good manufacturing practice
HBO_2	hyperbaric oxygen
KP	knowledge product
KRF	knowledge readiness framework
KRL	knowledge readiness level
mTBI	mild traumatic brain injury
OC	orthopedic comparison
PTSD	posttraumatic stress disorder
TBI	traumatic brain injury
TRL	technology readiness level
USAMRMC	U.S. Army Medical Research and Materiel Command

found statistically significant levels of reliability for the second group of ratings.

To test the KRL formalism and ranking scales under real-world conditions, we conducted a Delphi exercise with a group of people who might be expected to use the KRLs if the Army adopted them. The exercise, conducted at Fort Detrick, Maryland, included as participants 30 mid- to high-level research program managers from the USAMRMC. After two rounds, with a discussion period in between, the Delphi participants were able to achieve reasonable levels of group consensus on KRLs of the KPs from the two proposals we selected. Their levels were consistent with KRL estimates that we had made independently.

We drew the following conclusions from the reliability testing and Delphi exercise:

- A KP's scientific maturity can be productively measured in terms of three stages: foundational research, application to human subjects, and application in a real-world context.
- Each of these three stages of health research has unique characteristics that allow reliable assignment of a specific KP to just one of them.
- A KP's maturity can be defined using a nine-point Likert-type scale for KRL using a two-step process: (1) Assign the stage (1 through 3 [foundation], 4 through 6 [application], or 7 through 9 [real-world context]), and (2) assign the KP's level of maturity within that stage.
- According to our reliability testing with research publications and real-world testing with research proposals, the KRL and Likert-type scales provide a reliable metric of a KP's scientific maturity.

We recommend that the USAMRMC adopt and use the KRL as an indicator of scientific maturity. We believe, based on our research, that it offers a high degree of conceptual clarity and simplicity, ease of administration, stakeholder satisfaction, and reliable estimates. We recommend that the KRLs be adopted for routine use as indicators of KP scientific maturity. However, we note that, although the KRL is a sound indicator of scientific maturity, it should not be interpreted as an indicator of health impact: Scientific maturity and health impact are mutually important but orthogonal constructs.

The Need for Knowledge Readiness Levels

Health research frequently involves developing medical materiel (e.g., drugs, biologics, devices) that must meet regulatory requirements before being introduced into diverse settings (e.g., clinical, workplace). For drugs and biologics, DoD uses U.S. Department of Health and Human Services TRLs (see the table) and has adopted these TRLs for device development.[3] A central purpose of TRLs has been to assess the technological maturity of a given materiel product at

Technology Readiness Levels for Drugs and Biologics

Number	Description
1	Review of scientific knowledge base
2	Development of hypotheses and experimental designs
3	Target/candidate identification and characterization of preliminary candidate(s)
4	Candidate optimization and [non–good laboratory practice] in vivo demonstration of activity and efficacy
5	Advanced characterization of candidate and initiation of GMP process development
6	GMP pilot lot production, [investigational new drug] submission, and phase 1 clinical trial(s)
7	Scale-up, initiation of GMP process validation, and phase 2 clinical trial(s)
8	Completion of GMP validation and consistency lot manufacturing, pivotal animal efficacy studies or clinical trials, and [U.S. Food and Drug Administration] approval or licensure
9	Post-licensure and post-approval activities

SOURCE: U.S. Department of Health and Human Services, undated.

NOTE: GMP = good manufacturing practice.

Metrics are needed to track, monitor, and assess the importance of KPs and the potential military health advances that they might enable.

various stages of its development. DoD uses TRLs in wider federal regulatory contexts to improve tracking and monitoring of medical materiel development, adapting the TRLs for military use.[4]

However, health research often seeks or results in new knowledge without developing or commercializing materiel per se. The resulting new knowledge output, or KP, might prove effective when applied in specified real-world settings (e.g., battlefield, workplace, primary care clinic, emergency room). We therefore define *KP* as **knowledge output emerging from scientific research with potential to improve individual or public health**.[5] Like materiel products, KPs fall along a spectrum of product maturity, ranging from conceptual or foundational laboratory-style research through research emphasizing generalizability to an intended, applied (real-world) setting or context. KPs can therefore arise from research addressing questions around conception, formulation, applications, or context-specific uses and policies. Examples of KPs include such outputs of research as

- comparisons of treatment models and clinical service delivery strategies
- training simulations used to prepare field units, field medics, and clinical providers for practice in deployed, field, or fixed facility practice
- conceptual and analytical tools and methods (e.g., comparative effectiveness research)
- health indicators or organizational health response metrics (e.g., standardization of clinical indicators, clinical quality metrics, or status of military forces' health measures)
- information or guidance used to improve health and performance (e.g., practice guidelines; training procedures; technical reports, manuals, and summaries).

KPs involve **knowledge emerging from scientific research** (i.e., systematic, internally valid data collection and analysis aimed at drawing broader, externally valid inferences). We exclude from this report consideration of activities that do not constitute research—that is, those that do not involve analyses intended for drawing generalizable inferences. Often, these include routine service delivery, internal administrative quality improvement, monitoring of health system status (process and outcome monitoring), monitoring of health status (e.g., public health surveillance), or ongoing implementation of screening.[6] Although these activities are a common, reasonable, and even key focus of generalizable research (e.g., health service research), the activities themselves are forms of practice rather than research.

KPs can affect population health in at least two ways. First, KPs can indirectly contribute to medical materiel development. For example, a KP might reveal the need to adapt existing materiel for a new use, such as when the need for a new capability within an electronic health record is identified during research into the relative effectiveness of a health service delivery program. Second, KPs can provide scientific evidence that favors an innovative practice and leads to its successful real-world implementation.

Metrics are needed to track, monitor, and assess the importance of KPs and the potential military health advances that they might enable. To that end, we introduce two knowledge metrics that constitute the core of our proposed knowledge readiness framework (KRF): maturity and impact. *Maturity*, denoted by a KRL, is the focus of this report and indicates a KP's stage of development toward implementable improvements in real-world practices or processes. *Impact*, beyond the scope of the current research, is a KP's estimated potential to have an important effect.

As noted, KP and materiel development are similar in that both can fall along a spectrum of

product maturity. Maturity of a KP can range from conceptual or foundational up to adoption and routine use within a specified real-world context. In the next section, we propose, define, and initially assess the interrater reliability of KRLs for rating KP maturity using a domain-specific Likert scale. In a later section, we describe real-world testing of the KRLs in a Delphi exercise with USAMRMC research program managers.

Methods for Determining Knowledge Readiness Levels and for Reliability Testing of the Rating Scale

We modeled our KRF and levels after the framework and levels (i.e., TRLs) used for the classification, tracking, and monitoring of materiel development. In collaboration with the USAMRMC sponsor of this project, we chose TBI as the research area for initial development of the KRF because it (1) overlaps four of six USAMRMC research program emphases; (2) is a relevant and timely military health research priority; and (3) represents a multidisciplinary research, prevention, and clinical problem with both acute and chronic general and mental health consequences. We proposed a straw-man framework and KRL definitions using TRLs as a guide. We drew individual publications from a recently populated literature database on PTSD, TBI, and suicide; RAND investigators had developed the database while performing a proof of concept for a DoD knowledge management tool. This knowledge management tool includes publications from DoD-funded projects undertaken between 2007 and 2014 related to PTSD, TBI, and suicide. First, we selected 19 articles at random using a random number generator from the subset of TBI articles. Engel, Silberglitt, and Nguyen read the articles and rated them independently on a scale of KRL 1 through KRL 9. Subsequently, raters presented and defended their ratings, then discussed them. Discussions aimed to achieve consensus regarding the most appropriate rating for each article, identifying reasons for initial disagreement, refining definitions for each KRL, and standardizing the overall rating process.

After this initial round of review and discussion, we chose a second set of 20 TBI articles from the knowledge management database (supplemented by external searches as necessary) based on article title and abstract, to fill gaps in KRL ratings left over from the first 19 articles. As before, the raters (this time, Engel, Silberglitt, Nguyen, and Brian Chow) reviewed articles, independently rated them, and discussed them as a group, then determined consensus KRL ratings. For this early KRF testing, as a matter of convenience, we chose to rate articles (rather than research grant applications or research product lines) as the unit of analysis. We briefed the USAMRMC sponsor on preliminary findings, presenting example ratings for feedback, then final edits were made to our KRL criteria and rating process.

We used Krippendorff's alpha for ordinal ratings to calculate interrater reliability of the first and second groups of the KRL ratings, separately.[7] Krippendorff's alpha is a sound, general test of reliability that can be used regardless of the number of raters, levels of measurement, sample size, and presence or absence of missing data. An alpha of 1 indicates perfect reliability, 0 indicates absence of reliability, and negative values indicate systematic disagreement that exceeds what would be expected by chance. For practical purposes, an alpha greater than 0.6 is fair and can be considered analogous to a Cohen's kappa of 0.5; above 0.7 is considered excellent and can be thought of as analogous to Cohen's kappa of 0.7.[8]

Krippendorff's alpha of KRL ratings prior to the round 1 consensus discussion was 0.32. The alpha for round 2 ratings prior to consensus discussion was 0.70. Because Krippendorff's alpha does not result in an indicator of statistical significance, we also calculated two other applicable tests of reliability: Kendall's W and an intraclass correlation coefficient. Both of these methods yielded statistically significant relationships in round 2 and slightly higher but overall very comparable levels of reliability (Kendall's W for round 1 was 0.49, $p = 0.1$, and for round 2 was 0.74, $p < 0.001$; the intraclass correlation coefficient for round 1 was 0.30, $p = 0.02$, and for round 2 was 0.72, $p < 0.001$).

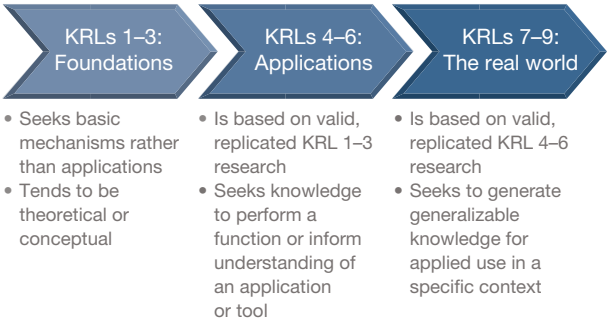
Definition and Reliability of Knowledge Readiness Levels

Figure 1 provides a schematic illustration of the proposed KRF. The framework builds on established translational research models (i.e., models that facilitate the practical application of scientific knowledge toward development and implementation of new ways to prevent, diagnose, or treat illness or injury[9]). Most of these models progress broadly from basic research to clinical research and then from clinical research to community research. We present Figure 1 in a linear fashion strictly for convenience of representation. Indeed, the movement of health research from basic science to application (in medical research, often clinical) and then to emphasis on application use in a specific context rarely follows a straightforward linear progression. KPs commonly move to the left or right of Figure 1 and sometimes skip levels. Also, KPs are frequently widely implemented in real-world contexts without having reached the highest KRL we propose, KRL 9. Because health research typically requires replication and testing under widely ranging conditions and different participant samples before it is accepted for broad implementation, KPs sometimes oscillate across the KRL spectrum as evidence accumulates.

There are parallels and differences between the existing TRLs and our proposed KRLs. Although the two systems do not exactly correspond, they complement one another. Initial research, concept elaboration, hypothesis generation, and hypothesis validation are required for both knowledge and materiel products, so the first group of three KRLs in Figure 1 corresponds closely to the first group of three TRLs. KRLs 4 through 9, although they differ from TRLs 4 through 9, follow a similar logic to that for TRLs 4 through 9, with higher levels reflecting increased confidence in the effectiveness of the materiel (or, for KRLs, KP). Several TRLs in this range, however, relate to production and commercialization of the materiel. KRLs, in contrast, place emphasis on the demonstration of a KP's effectiveness in contexts that are progressively more similar to an eventual real-world context.

FIGURE 1

A Schematic of the Knowledge Readiness Framework



The first three KRLs (1 through 3) provide the scientific foundation for KP development toward practical application. These KPs are the outputs of health research that seeks basic mechanisms rather than applications and tends to be theoretical or conceptual, often consisting of laboratory, descriptive, or exploratory studies. Examples include animal research, nonclinical laboratory research, descriptive epidemiology, and systematic reviews of KRL 1–3 research.

The next three KRLs (4 through 6) are given to KPs that seek to generate applied knowledge (i.e., knowledge to eventually perform a non–research-related function or to inform understanding of an application or tool). KRL 4–6 research often asks such questions as, "can the application work under ideal research conditions?" and "if so, how?" To achieve a rating in the range of KRLs 4 through 6, the KP must be based on valid, replicated KRL 1–3 research. Example applications include KPs that prevent, screen or diagnose, or treat illness and systematic reviews that summarize KRL 4–6 research.

KRL 7–9 ratings are given to KPs resulting from research designed to emphasize external validity (generalizability) of knowledge for use in a specified real-world application. This research often addresses a policy question, such as, "how does it compare with usual practice?" To achieve a rating in the range of KRLs 7 through 9, the KP must be based on valid, replicated KRL 4–6 research. Examples include battlefield interventions, primary care screeners, workplace injury prevention, treatment effectiveness studies and studies of implementation and post-implementation surveillance, systematic reviews of KRL 7–9 research, systematic reviews to inform creation of practice guidelines, and studies of guidelines.

Figure 2 provides more detail about KRLs 1 through 3; their KPs are the outputs of theoretical, conceptual, descriptive, or exploratory research.

KRL 1 research generates initial or very early scientific knowledge without regard to or indication of a specific health use. Its purpose is inferential, with the intention to generalize. Its findings require replication. Examples include descriptive animal studies or those that test, rather than generate, hypotheses.

KRL 2 research expands on or replicates a KRL 1 finding, including systematic review of KRL 1 studies to formulate a theoretical model. Examples include animal studies that test hypotheses or are the first true experiment testing a nascent theory and human studies not based on findings from descriptive or hypothesis-generating animal studies.

KRL 3 research validates hypotheses and hints at future applications (e.g., a tool for prediction, prognosis, screening, diagnosis, treatment, prevention). Its purpose is inferential (i.e., intention to generalize). Examples include research that replicates or systematically reviews well-designed KRL 1–2 studies or theory or descriptive studies, particularly those involving animal research.

Figure 3 provides more detail about KRLs 4 through 6; their KPs are the outputs of research to perform a function or inform the effect of a tool. These KPs answer such research questions as "can it work?" "if so, how?" "how well does it work?" and "for whom?"

KRL 4 research generates initial knowledge regarding a human health–related application or use. KRL 4 findings require subsequent replication. Examples include descriptive human epidemiology or preliminary human studies, human studies that test a clinical hypothesis, pilot tests of interventions or screening or diagnostic tools, and development of instrumentation needed to test intended applications (e.g., outcome measure).

KRL 5 research tests a priori (prespecified) hypotheses using rigorous scientific designs (e.g., randomized-control trials for intervention efficacy) to directly assess whether the tool can work and, if so, how. It expands on or replicates a KRL 4 finding or improves on the design of one or more KRL 4 studies (or both).

FIGURE 2

A Schematic of Knowledge Readiness Levels 1 Through 3: Foundations

- Theoretical, conceptual, descriptive, or exploratory research
- Basic mechanisms rather than applications per se

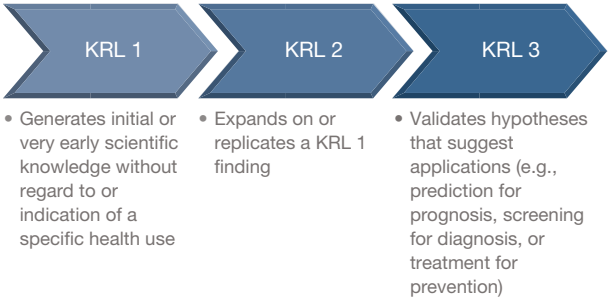
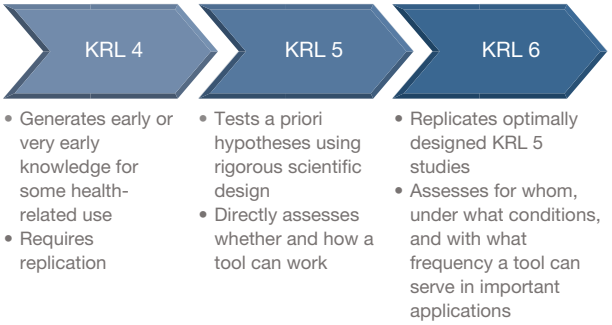


FIGURE 3

A Schematic of Knowledge Readiness Levels 4 Through 6: Applications

- Generates knowledge to perform a function or inform a tool's effect
- Asks such questions as whether a tool can work and, if so, how and for whom



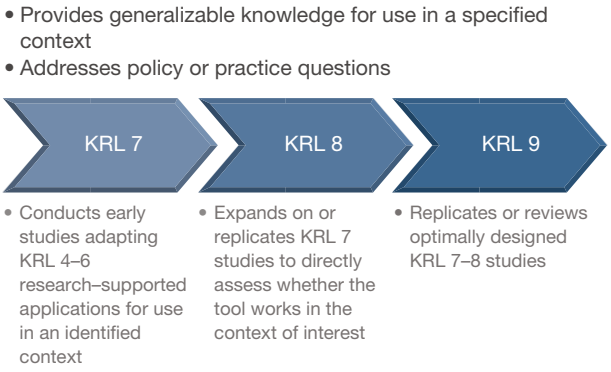
KRL 6 research replicates well-designed KRL 5 studies. It adds nuance to answers from completed studies (e.g., not just whether and how a tool can work but also for whom, under what conditions, or with what frequency). It validates hypotheses that might suggest important application contexts (e.g., battlefield, primary care, emergency room, postdeployment screening). It includes systematic reviews of KRL 4 and KRL 5 studies to address questions of whether and how the tool would work.

Figure 4 provides more detail about KRLs 7 through 9; their KPs are outputs of research to provide generalizable knowledge for use in a specified context or address policy or practice questions.

KRL 7 research consists of early studies adapting applications supported by KRL 4–6 research for

FIGURE 4

A Schematic of Knowledge Readiness Levels 7 Through 9: Real-World Contexts



use in a military health context. Examples include adaptation from a longer screener, feasibility and standardization for postdeployment use of a brief screener, initial multimodal tests of combined KRL 4–6 research–supported interventions to achieve improved outcomes in primary care, adaptation and initial study in military mental health settings of KRL 4–6 research–supported therapy for PTSD, and adaptation and initial study of KRL 4–6 research–supported protective gear for preventing TBI during deployment.

KRL 8 research expands on or replicates KRL 7 studies to directly assess whether the application works in the context of interest. It uses valid designs with emphasis on external validity (generalizability) for an intended context. Example methods include multisite research to obtain average effects, generalizable analyses of real-world (e.g., administrative) data, usual or standard care (not placebo or contact time) controls, and average (not ideal) participants.

KRL 9 research replicates or reviews well-designed KRL 7 and KRL 8 studies. Examples include cost analyses to achieve a desired effect, comparative effectiveness studies to aid context-specific policy development or intervention decisions, systematic reviews to estimate effect size with average participants in a real-world context, and postimplementation surveillance. KRL 9 research assesses whether the application works in a specific context, or it might determine the participants or time period for which the application works within an identified context.

Summary of Knowledge Readiness Level Distinctions

Maturity measures progress toward effective use of a KP under conditions that more and more closely approximate a real-world context (e.g., primary care clinic, battlefield aid station, specialty behavioral health clinic). However, to classify a KP to a specific KRL, one must demonstrate an appropriate **level of evidence** consistently with widely accepted standards of health-related evidence. For KRLs 4 through 6, this is demonstrated safety and efficacy for an applied indication or purpose. These studies often, however, yield results that are not easily generalizable to real-world contexts. They might employ, for example, a single (typically highly managed and controlled) research site based on convenience, with participating patients or subjects being highly selected (ideal) candidates for study and participating practitioners or operators usually being application experts. This often results in exaggerated estimates of effectiveness.

Appropriate levels of evidence for KRLs 7 through 9, by comparison, are designed to demonstrate effectiveness and feasibility in specified real-world contexts. KRL 7–9 research often uses multiple representative sites and practitioners or operators and patients or subjects who are more representative of those found in the context of interest. The result is research results that are more likely to represent the effectiveness that will be observed when and if the application is eventually implemented in the intended real-world context.

We note again, however, that, although we present Figures 1 through 4 conceptually in a linear fashion, strategic health research often skips levels, and KPs move either to the left or the right in the KRL rating spectrum. For example, the results on animal models for vaccines or antidotes for chemical and biological agent exposure are sometimes brought directly into service delivery when such agents are an anticipated battlefield hazard and higher KRL studies are deemed unethical or unfeasible. Also, studies of KPs with higher KRL ratings can raise questions that require additional lower-KRL research. On the other hand, regardless of the number of times that the health research process

goes from higher to lower KRLs, the ultimate goal is to inform and identify practices that will help lead to improved public health.

Example Knowledge Readiness Level Assignments of Selected Knowledge Products

To illustrate and pilot the proposed KRF, we selected five KPs (summarized in individual publications) resulting from research into TBI. For purpose of illustration, in this section, we briefly describe the process of rating several of these publications. We report our KRL estimate for each of these example publications, as well as the rationale behind our KRL estimate.

To maximize the reliability of our KRL assessment procedure, we codified a three-step rating process using the KRL criteria described above. In the initial step, which we label step 0, the rater determined whether the publication described research. We defined *research* as systematic (internally valid) data collection and analysis for drawing broader (externally valid) inferences. We excluded from consideration any publication that described (1) routine clinical quality improvement (no attempt to infer), (2) routine monitoring of health system status (e.g., clinical outcome monitoring), or (3) routine monitoring of health status (e.g., public health surveillance, routine pre- and postdeployment health assessments). In step 1, the rater placed the KP addressed in the publication within one of the three KRL groupings: KRLs 1 through 3, KRLs 4 through 6, or KRLs 7 through 9. In step 2, the rater refined the KRL assessment to an individual level (e.g., a single KRL rather than a group of three KRLs). In the examples that follow, we present only steps 1 and 2, after the raters excluded all nonresearch publications in step 0.

Appendix A provides a complete list of the publications we reviewed to pilot the KRF and rating levels. Appendix B provides the abstract of each publication used in the example KRL ratings.

Examples of Knowledge Products Classified in Knowledge Readiness Levels 1 Through 3

KRL 1–3 KPs are the outputs of exploratory, preapplication research. These cover a wide range of both theoretical and experimental investigations, including animal research, model development and testing, exploration of basic mechanisms, and research that generates hypotheses to be tested in clinical studies. As examples, we have chosen one publication on biomechanical modeling of brain response to blast waves and one on quantitative measurement of iron levels in the brain.

> To classify a KP to a specific KRL, one must demonstrate an appropriate level of evidence consistently with widely accepted standards of health-related evidence.

On Biomechanical Modeling of Brain Response to Blast Waves

Our example publication for this is Linxia Gu, Mehdi S. Chafi, Shailesh Ganpule, and Namas Chandra, "The Influence of Heterogeneous Meninges on the Brain Mechanics Under Primary Blast Loading," *Composites*, Part B: *Engineering*, Vol. 43, No. 8, December 2012, pp. 3160–3166. This research applied a hyperviscoelastic material model to better represent the mechanical response of brain tissue over the large-strain and high-frequency range characteristic of blast scenarios.

- Step 1: Assign the research to a KRL range. The researchers aimed to improve a model of the mechanical response of brain tissue but did not apply the results to human studies. This was foundational research, so we assigned its KP to the KRL 1–3 grouping.
- Step 2: Assign the research to a specific KRL within the range. This research extended prior

KRL 1 work and is relevant to diagnosis and protective-equipment design, so its KP goes beyond KRL 1. However, although it expands the knowledge base on biomechanical modeling, it does not lead to recommended hypotheses to be tested, so it does not meet the criteria for KRL 3. Thus, we assigned it to KRL 2.

Quantitative Measurement of Iron Levels in the Brain

Our example for this is Weili Zheng, Helen Nichol, Saifeng Liu, Yu-Chung N. Cheng, and E. Mark Haacke, "Measuring Iron in the Brain Using Quantitative Susceptibility Mapping and X-Ray Fluorescence Imaging," *NeuroImage*, Vol. 78, September 2013, pp. 68–74. This research compared the use of quantitative mapping of magnetic susceptibility with other existing methods, such as X-ray fluorescence for determining total iron content in the brain.

- Step 1: Assign the research to a KRL range. This was foundational research aimed at developing a tool that could be used in clinical applications. It was preclinical research, so we assigned its KP to the KRL 1–3 grouping.
- Step 2: Assign the research to a specific KRL within the range. Iron has been recognized as a biomarker for neurological disease, and elevated iron is associated with neurological and psychiatric disorders. Measurement of iron content using the quantitative susceptibility mapping method described in this paper thus has potential clinical use for screening and diagnosis. Because this research was based on a large amount of valid KRL 1–3 research and provided a tool for future clinical studies, we assigned its KP to KRL 3.

Examples of Knowledge Products Classified in Knowledge Readiness Levels 4 Through 6

KRL 4–6 KPs are the outputs of human studies that are aimed at proving safety and efficacy in a clinical setting, answering such questions as whether the tool can work and, if so, how. As examples, we have chosen an imaging study of people suffering from mild TBI (mTBI) and an investigation of the effect that hyperbaric oxygen application has on postconcussion symptoms.

Imaging Study of People Suffering from Mild Traumatic Brain Injury

For this example, we used Khader M. Hasan, Elisabeth A. Wilde, Emmy R. Miller, Vipul Kumar Patel, Terrell D. Staewen, Melisa L. Frisby, Hector M. Garza, James J. McCarthy, Jill V. Hunter, Harvey S. Levin, Claudia S. Robertson, and Ponnada A. Narayana, "Serial Atlas-Based Diffusion Tensor Imaging Study of Uncomplicated Mild Traumatic Brain Injury in Adults," *Journal of Neurotrauma*, Vol. 31, No. 5, February 25, 2014, pp. 466–475. This research investigated a specific method of imaging brain tissue in patients with mTBI, with the objective of demonstrating results with potential for clinical use.

- Step 1: Assign the research to a KRL range. This was research on human subjects that sought to generate information on clinical use of a specific imaging method, but it placed no design emphasis on a specific application context. Thus, we assigned its KP to the KRL 4–6 grouping.
- Step 2: Assign the research to a specific KRL within the range. This research was based on replicated KRL 1–3 research and identified potential utility for further study (might identify transient edema in a specific part of the brain). However, its results would require replication, and it does not appear to have tested a clear a priori (prespecified) hypothesis, so its KP does not meet the criteria for KRL 5. Thus, we assigned it to KRL 4.

The Effect That Hyperbaric Oxygen Application Has on Postconcussion Symptoms

Here we used David X. Cifu, Brett B. Hart, Steven L. West, William Walker, and William Carne, "The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms," *Journal of Head Trauma Rehabilitation*, Vol. 29, No. 1, January–February 2014, pp. 11–20. This research investigated the effect that hyperbaric oxygen treatment has on persistent

postconcussion symptoms in military service members with mTBI.

- Step 1: Assign the research to a KRL range. This was human-subject research aimed at assessing the efficacy of a specific treatment within an application context (military service members with persistent postconcussion symptoms). However, although it involved military service members, we assigned its KP to the KRL 4–6 grouping rather than the KRL 7–9 grouping because it was a small, single-site study with sham comparison and was based on what it described as an "unproven theory." Thus, it did not meet the requirement for assignment to the KRL 7–9 grouping of being based on replicated, well-designed KRL 4–6 studies.
- Step 2: Assign the research to a specific KRL within the range. This research did test an a priori (prespecified) hypothesis using a valid design and directly addressed whether the tool could work and, if so, how. Thus, we classified its KP as KRL 5.

Example of Knowledge Products Classified in Knowledge Readiness Levels 7 Through 9

KRL 7–9 KPs are the outputs of studies conducted to demonstrate applicability in real-world contexts. They often address policy and practice questions (e.g., those related to cost and use in a real-world military setting on average, not ideal patients). Because of the uncertainties associated with screening, diagnosis, and treatment of TBI, we found a paucity of research with KPs that meet the criteria for KRLs 7 through 9. Thus, we have just one example: a study of the effect that out-of-hospital advanced airway management has on outcomes of patients suffering from severe TBI or hemorrhagic shock.

Our example was Henry E. Wang, Siobhan P. Brown, Russell D. MacDonald, Shawn K. Dowling, Steve Lin, Daniel Davis, Martin A. Schreiber, Judy Powell, Rardi van Heest, and Mohamud Daya, "Association of Out-of-Hospital Advanced Airway Management with Outcomes After Traumatic Brain Injury and Hemorrhagic Shock in the ROC Hypertonic Saline Trial," *Emergency Medicine Journal*, January 26, 2013 (online first). This research investigated the effect of applying advanced airway management before hospitalization to patients who had suffered severe TBI or hemorrhagic shock.

- Step 1: Assign the research to a KRL range. This was research applied in a real-world military medical context that was based on findings of a large number of previous studies. Thus, we assigned its KP to the KRL 7–9 grouping.
- Step 2: Assign the research to a specific KRL within the range. This was a secondary analysis of data collected in a large, multicenter study with the objective of generalizability within that context. However, we found that its KP did not meet the criteria for assignment to KRL 8 because of potential confounding factors (e.g., hypoxia during the treatment and hyperventilation) and the need for increased understanding of the shock state, for which the outcome of increased mortality was statistically significant (it was not for TBI). Thus, we assigned it to KRL 7.

Real-World Testing of Knowledge Readiness Levels

To test the KRL formalism and ranking scales under real-world conditions, we conducted a Delphi exercise with a group of people who might be expected to use the KRLs if the Army adopted them. The exercise, conducted at Fort Detrick, Maryland, included as participants 30 mid- to high-level research program managers from the USAMRMC. The KRLs were designed to facilitate research policy–related decisions regarding the scientific maturity of health research, especially health research that is not conducted to develop medical materiel (e.g., drug, biologic, device, or information technology).

The objective of the exercise was to determine whether participants would be able to use domain-specific Likert-type rating scales to estimate KRLs and achieve consensus on the scientific maturity of the KPs of the research proposals provided. The exercise achieved this objective in the affirmative.

Background on the Delphi Method

Decades ago, RAND analysts developed the Delphi method that we used as a structured means of generating group consensus.[10] All Delphi group participants answer the same questions based on the same information, and then the participants' answers are anonymously shared with the group in aggregate and discussed. After aggregate data display and participant discussion, participants are given the opportunity to adjust their answers. This process can be repeated over several rounds, with consensus typically improving with each successive round. Consensus failing to improve could reflect (1) problems with the questions used, (2) problems with the criteria participants used to respond to the questions (e.g., differing interpretations of the questions among different participants), or (3) valid differences of perspective between participants (or groups of participants). The Delphi method and its many variants have been used widely in policy analysis.[11] We felt that it was appropriate here because we were seeking USAMRMC consensus views on KRLs of KPs. For this purpose, we used domain-specific Likert-type rating scales.

We felt that the Delphi method was appropriate here because we were seeking USAMRMC consensus views on KRLs of KPs. For this purpose, we used domain-specific Likert-type rating scales.

Conduct of the Delphi Exercise

In preparation for the Delphi exercise, we requested that the USAMRMC provide examples of USAMRMC-funded proposals (with research investigator identification removed) that we could use for the exercise. Five of the USAMRMC's technical components (called Joint Program Committees) provided previously funded research proposals, and we chose two of these proposals for the Delphi exercise. The use of only two proposals was dictated by the limited amount of time (two hours each for two separate groups) available for these busy research administrators to participate in the exercise.[12] We selected the two proposals used to introduce as much breadth and variety as possible under the time limitations. For the exercise, we altered some details of each proposal to respect investigators' privacy and the potential for intellectual property.

In preparation for the Delphi exercise, RAND investigators prepared brief summaries of relevant information from the proposals, highlighting technical information relevant to assigning KRL values. At the Delphi exercise, we provided participants with these brief summaries and a description of the two-step rating process and the Likert-type rating scales for KRL described previously.[13]

Each of the two Delphi sessions began with a briefing in which we explained the overall purpose and plan of the Delphi exercise, as well as the KRL two-step rating process and rating scale. Then, in the initial Delphi round (round 1), we asked each participant to choose the value of the KRL scale that best reflected the scientific maturity of the KP of each proposal before the proposed research was performed. We followed this with a discussion period, during which the results of the first Delphi round for each question were projected and discussed, focusing on the distribution of responses and reasons for outlier responses. The sessions concluded with a final Delphi round (round 2), during which participants reviewed and had the opportunity to revise their own initial responses based on what they had learned during the intervening discussion. In the rest of this section, we reproduce the brief summaries of each proposal.

Proposal 1: Virtual Tissue Modeling for Real-Time Surgical and Interventional Procedure Simulation

This proposal is to develop and evaluate a new virtual tissue modeling methodology for use in military medical training simulators for forward surgical and interventional care of combat injuries. Prior work that will be leveraged includes models of the cardiovascular system and associated combat injury mechanisms developed for skill training of hemorrhage control in extremities, as well as that on organ models for heart and lung, numerical methods for real-time interaction, constitutive tissue modeling, tissue property measurement, and full body anatomic models.

Technical Information Relevant to Assigning a Knowledge Readiness Level

The proposal will extend a number of advances for mathematical modeling of the mechanics of soft tissues that emerged from the [Telemedicine and Advanced Technology Research Center] program from 2001–2006, including a mathematical (finite-element–based) framework that allows model parameter determination in soft tissues with fluid-filled vessels. The models were developed and validated in the context of a motorized indentation tester applied to extra-corporeally–perfused liver tissue. This approach was not able to unambiguously identify the vessel parameters (location and size). The constitutive modeling of the liver that is proposed will extend this approach by accounting, for the first time, for the fluid dynamics of deformable blood-filled vessels and for the model to have a high-resolution (~1 mm3) representation of the underlying anatomy. Model parameters will be determined from a combination of haptic-based *in vivo* testing and medical imaging data. Furthermore, the models will be set up on an open source basis where simulation experts will be provided with both the models as well as the much-needed high performance tools to deform them.

Proposal 2: Predictive Model of Immune Evasion for Dengue Virus Isolates

This proposal is for construction of a dynamic whole-capsid structural model of dengue virus (DENV) and its use to model epitopes of sequenced dengue isolates available at [Walter Reed Army Institute of Research]. Empirical and physics-based methods will be used to identify isolates that contain candidate antigenic escape mutations and to quantify the effect of these mutations on evasion of immunity from tetravalent dengue vaccine (TDV).

Technical Information Relevant to Assigning a Knowledge Readiness Level

The proposal quotes efficacy results of a randomized, controlled phase 2b trial of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren published in the *Lancet* that showed [that] the vaccine was safe but had an overall efficacy of only 30% with substantial variation with respect to each dengue serotype from 90% for DENV-4 to 0% for DENV-2. They propose to use a combination of molecular modeling to construct a whole-envelope model of the dengue virus, and sequence mapping of available dengue isolates to identify candidate antigenic escape mutations, and carry out *in vitro* experimental validation using serum samples from humans vaccinated with a candidate [tetravalent dengue vaccine]. Prior studies have mainly focused on either large-scale sequencing of field isolates, or *in vitro* neutralization studies of a handful of samples. By leveraging bioinformatics and structural biology, they aim to rapidly predict and validate antigenic escape mutations from a large library of available dengue isolates. (Collaborators at [Walter Reed Army Institute of Research] have a database of over 400 sequenced isolates collected over multiple sites in Africa, South America, and Asia.)

Delphi Results and Findings

In this section, we show the distributions of the participant responses to the KRL Delphi question for the two proposals. The figures include all responses from the two Delphi groups, with round 1 responses in blue and round 2 responses in red. As noted, all 30 participants answered the Delphi question for proposal 1, but only 29 answered for proposal 2.

The KRL Delphi question read as follows:

> Using the KRL scale, please choose the KRL of the Knowledge Product of this proposal from the choices below [KRL 1–9 scale provided, together with categories of Foundations (1–3), Applications (4–6), Real-World Contexts (7–9), with only one numerical selection allowed].

Figure 5 shows the distribution of responses for proposal 1 (the virtual tissue model). This distribution narrowed from round 1 to round 2. During the discussion period, we learned that participants in round 1 were uncertain about whether they were estimating the KRL before or after the proposed research was performed. We explained that it was the current level of maturity, or KRL before the proposed research, that we were asking them to estimate. This might have been the reason for the difference between the round 1 and round 2 distributions. The round 2 distribution has a mean of 3.47, with a standard deviation of 1.11.

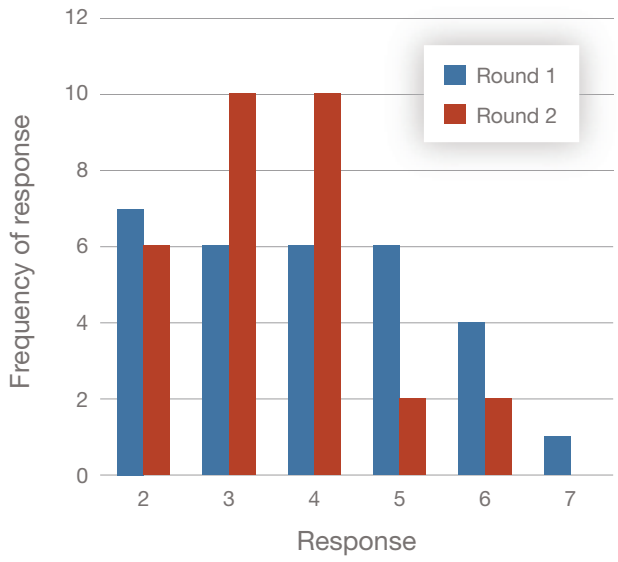
Figure 6 shows the distribution of responses for proposal 2, the dengue virus model. This distribution became more peaked, and the peak moved slightly to higher KRLs from round 1 to round 2. The round 2 answers to this question for this proposal gave a mean of 3.90, with a standard deviation of 1.54.

Summary of Delphi Results

During the two-hour Delphi sessions, all 30 participants were able to use the material presented and the KRL rating scales to rate each of the two proposals. During the discussion period, participants who rated the KRLs at either end of the scale were able to explain the rationales behind their ratings, and the subsequent discussion informed the entire group. Informed by the responses shown above, we conclude that the Delphi procedure (round 1–discussion–round 2) generated reasonable levels of group consensus on KRLs of the KPs of both research proposals.

FIGURE 5

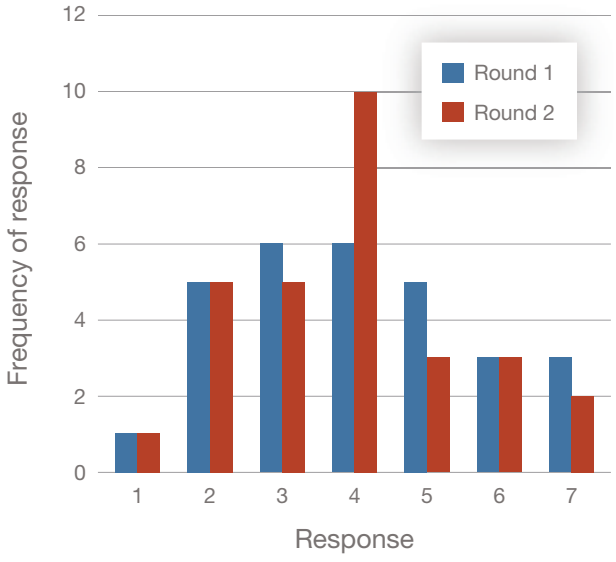
Responses to Delphi Question 1 for Proposal 1, the Virtual Tissue Model



NOTE: $n = 30$.

FIGURE 6

Responses to Delphi Question 1 for Proposal 2, the Dengue Virus Model



NOTE: $n = 29$.

We note, however, based on the discussion of proposal 1, that our initial instructions led to confusion as to whether the KRL rating should be for the KP before or after the proposed research had been conducted. We concluded that the instructions for rating the KRL of a KP from a research proposal should clearly state that it is the KP *before* the research is performed. The consensus values were in agreement with independent RAND investigator estimates, which assigned proposal 1 (the virtual tissue model) to KRL 3 because it was not yet applied to human subjects and proposal 2 (the dengue virus model) to KRL 4 because it was in an early stage of human application.

Conclusions and Recommendations

We have described a preliminary set of KRL criteria for future testing and use and demonstrated KRL ratings for five KPs described in recently published, DoD-funded TBI research. Our proposed KRLs showed evidence of acceptable interrater reliability. Raters were not subject-matter experts, and reliability was assessed prior to second-round criterion adjustments based on discussion of observed misclassification, suggesting that our estimate of reliability is conservative.

KRLs were rated for peer-reviewed research publications, but we believe that the KRF we have outlined can be similarly applied to research proposals (e.g., grant applications) and to specific KP lines (e.g., a health care delivery model). To this end, we tested our KRF and rating scales on research proposals in a Delphi exercise with USAMRMC research program managers who were able to reach consensus on KRL ratings that agreed with independent RAND investigator estimates.

Users of the KRF should be cognizant of key caveats and limitations. First, although our framework occurs along a spectrum, the health knowledge development process, as with that for medical materiel, is generally neither linear nor unidirectional. Second, there is legitimate overlap and consequently modest room for valid disagreement regarding the exact KRL for a given KP. Nevertheless, our preliminary effort to characterize interrater reliability of KRLs suggests acceptable consistency in ratings across our raters. Third (and following from the second), implementation of virtually any KRF and KRL rating system will require careful attention to rating process quality control and recognition of the potential for human factors (e.g., gaming the ratings, developing programs to narrowly "treat the ratings") that could compromise the validity of KRL ratings or create unintended negative effects. Fourth, there are several important possible uses for the application of KRLs to KPs, but ensuring that the KRF we have proposed is maximally appropriate for a given use will require clarification of objectives, ideally before the framework is implemented. Fifth, an effective KRF must be feasible. Just as reliability and validity of the proposed KRF is essential to success, attention to these parameters without ensuring a feasible rating process will obstruct their routine use.

KRLs were rated for peer-reviewed research publications, but we believe that the KRF we have outlined can be similarly applied to research proposals and to specific KP lines.

We draw the following conclusions based on the results described above on the development and testing of the KRF:

- The scientific maturity of KPs can productively be measured in terms of three stages: foundational research, application to human subjects, and application in a real-world context.

- Each of these three stages of health research has unique characteristics that allow reliable assignment of a specific KP to just one of them.
- Maturity of a KP can be defined using a nine-point Likert-type scale for KRL using a two-step process: (1) Assign the stage (1–3 [foundation], 4–6 [application], or 7–9 [real-world context]), and (2) assign the level of maturity within that stage.
- According to our reliability testing with research publications and real-world testing with research proposals, the KRL and Likert-type scales provide a reliable metric for scientific maturity of KPs.

Consequently, we recommend that the USAMRMC adopt and use the KRL as an indicator of scientific maturity. We believe, based on our research, that it offers a high degree of conceptual clarity and simplicity, ease of administration, stakeholder satisfaction, and reliable estimates. We recommend that the KRLs be adopted for routine use as an indicator of KP scientific maturity. However, we note that, although KRL is a sound indicator of scientific maturity, it should not be interpreted as an indicator of health impact because scientific maturity and health impact are mutually important but orthogonal constructs.

Appendix A. Articles Used to Refine the Knowledge Readiness Framework and Knowledge Readiness Level Criteria

Barbey, Aron K., Roberto Colom, and Jordan Grafman, "Distributed Neural System for Emotional Intelligence Revealed by Lesion Mapping," *Social Cognitive and Affective Neuroscience*, Vol. 9, No. 3, March 1, 2014, pp. 265–272. doi: 10.1093/scan/nss124

Brophy, Gretchen M., Stefania Mondello, Linda Papa, Steven A. Robicsek, Andrea Gabrielli, Joseph Tepas III, Andras Buki, Claudia Robertson, Frank C. Tortella, Ronald L. Hayes, and Kevin K. W. Wang, "Biokinetic Analysis of Ubiquitin C-Terminal Hydrolase-L1 (UCH-L1) in Severe Traumatic Brain Injury Patient Biofluids," *Journal of Neurotrauma*, Vol. 28, No. 6, June 2011, pp. 861–870. doi: 10.1089/neu.2010.1564

Brophy, Gretchen M., Jose A. Pineda, Linda Papa, Stephen B. Lewis, Alex B. Valadka, H. Julia Hannay, Shelley C. Heaton, Jason A. Demery, Ming Cheng Liu, Joseph J. Tepas III, Andrea Gabrielli, Steven Robicsek, Kevin K. W. Wang, Claudia S. Robertson, and Ronald L. Hayes, "αII-Spectrin Breakdown Product Cerebrospinal Fluid Exposure Metrics Suggest Differences in Cellular Injury Mechanisms After Severe Traumatic Brain Injury," *Journal of Neurotrauma*, Vol. 26, No. 4, April 2009, pp. 471–479. doi: 10.1089/neu.2008.0657

Brown, Mark C., Alisha H. Creel, Charles C. Engel, Richard K. Herrell, and Charles W. Hoge, "Factors Associated with Interest in Receiving Help for Mental Health Problems in Combat Veterans Returning from Deployment to Iraq," *Journal of Nervous and Mental Disease*, Vol. 199, No. 10, October 2011, pp. 797–801. doi: 10.1097/NMD.0b013e31822fc9bf

Cifu, David X., Brett B. Hart, Steven L. West, William Walker, and William Carne, "The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms," *Journal of Head Trauma Rehabilitation*, Vol. 29, No. 1, January–February 2014, pp. 11–20. doi: 10.1097/HTR.0b013e3182a6aaf0

Drake, Angela I., Kimberly S. Meyer, Lynne M. Cessante, Catherine R. Cheung, Maren A. Cullen, Eric C. McDonald, and Martin C. Holland, "Routine TBI Screening Following Combat Deployments," *Neurorehabilitation*, Vol. 26, No. 3, 2010, pp. 183–189. doi: 10.3233/NRE-2010-0554

Engel, Jerome, Jr., Asla Pitkänen, Jeffrey A. Loeb, F. Edward Dudek, Edward H. Bertram III, Andrew J. Cole, Solomon L. Moshé, Samuel Wiebe, Brandy E. Fureman, Frances E. Jensen, Istvan Mody, Astrid Nehlig, and Annamaria Vezzani, "Epilepsy Biomarkers," *Epilepsia*, Vol. 54, Suppl. 4, August 2013, pp. 61–69. doi: 10.1111/epi.12299

Fowler, Marice, Thomas H. Garza, Terry M. Slater, Christopher V. Maani, and Laura L. McGhee, "The Relationship Between Gabapentin and Pregabalin and Posttraumatic Stress Disorder in Burned Servicemembers," *Journal of Burn Care and Research*, Vol. 33, No. 5, September 1, 2012, pp. 612–618. doi: 10.1097/BCR.0b013e31823dc710

Gu, Linxia, Mehdi S. Chafi, Shailesh Ganpule, and Namas Chandra, "The Influence of Heterogeneous Meninges on the Brain Mechanics Under Primary Blast Loading," *Composites*, Part B: *Engineering*, Vol. 43, No. 8, December 2012, pp. 3160–3166. doi: 10.1016/j.compositesb.2012.04.014

Han, Sohyun C., Frank Castro, Lewina O. Lee, Meredith E. Charney, Brian P. Marx, Kevin Brailey, Susan P. Proctor, and Jennifer J. Vasterling, "Military Unit Support, Postdeployment Social Support, and PTSD Symptoms Among Active Duty and National Guard Soldiers Deployed to Iraq," *Journal of Anxiety Disorders*, Vol. 28, No. 5, June 2014, pp. 446–453. doi: 10.1016/j.janxdis.2014.04.004

Hartings, Jed A., Tomas Watanabe, Ross Bullock, David O. Okonkwo, Martin Fabricius, Johannes Woitzik, Jens P. Dreier, Ava Puccio, Lori A. Shutter, Clemens Pahl, and Anthony J. Strong, "Spreading Depolarizations Have Prolonged Direct Current Shifts and Are Associated with Poor Outcome in Brain Trauma," *Brain*, Vol. 134, No. 5, 2011, pp. 1529–1540. doi: 10.1093/brain/awr048

Hasan, Khader M., Elisabeth A. Wilde, Emmy R. Miller, Vipul Kumar Patel, Terrell D. Staewen, Melisa L. Frisby, Hector M. Garza, James J. McCarthy, Jill V. Hunter, Harvey S. Levin, Claudia S. Robertson, and Ponnada A. Narayana, "Serial Atlas-Based Diffusion Tensor Imaging Study of Uncomplicated Mild Traumatic Brain Injury in Adults," *Journal of Neurotrauma*, Vol. 31, No. 5, March 2014, pp. 466–475. doi: 10.1089/neu.2013.3085

Hetherington, Hoby P., Hamada Hamid, Joseph Kulas, Geoffrey Ling, Faris Bandak, Nihal C. de Lanerolle, and Jullie W. Pan, "MRSI of the Medial Temporal Lobe at 7 T in Explosive Blast Mild Traumatic Brain Injury," *Magnetic Resonance in Medicine*, Vol. 71, No. 4, April 2014, pp. 1358–1367. doi: 10.1002/mrm.24814

Holbrook, Troy Lisa, Michael R. Galarneau, Judy L. Dye, Kimberly Quinn, and Amber L. Dougherty, "Morphine Use After Combat Injury in Iraq and Post-Traumatic Stress Disorder," *New England Journal of Medicine*, Vol. 362, No. 2, January 14, 2010, pp. 110–117. doi: 10.1056/NEJMoa0903326

Howell, David, Louis Osternig, Paul Van Donkelaar, Ulrich Mayr, and Li-Shan Chou, "Effects of Concussion on Attention and Executive Function in Adolescents," *Medicine and Science in Sports and Exercise*, Vol. 45, No. 6, June 2013, pp. 1030–1037. doi: 10.1249/MSS.0b013e3182814595

Juengst, S. B., R. G. Kumar, P. M. Arenth, and A. K. Wagner, "Exploratory Associations with Tumor Necrosis Factor-α, Disinhibition and Suicidal Endorsement After Traumatic Brain Injury," *Brain, Behavior, and Immunity*, Vol. 41, October 2014, pp. 134–143. doi: 10.1016/j.bbi.2014.05.020

Junger, Wolfgang G., Shawn G. Rhind, Sandro B. Rizoli, Joseph Cuschieri, Andrew J. Baker, Pang N. Shek, David B. Hoyt, and Eileen M. Bulger, "Pre-Hospital Hypertonic Saline Resuscitation Attenuates the Activation and Promotes Apoptosis of Neutrophils in Patients with Severe Traumatic Brain Injury," *Shock*, Vol. 40, No. 5, November 2013, pp. 366–374. doi: 10.1097/SHK.0000000000000038

Knutsen, Andrew K., Elizabeth Magrath, Julie E. McEntee, Fangxu Xing, Jerry L. Prince, Philip V. Bayly, John A. Butman, and Dzung L. Pham, "Improved Measurement of Brain Deformation During Mild Head Acceleration Using a Novel Tagged MRI Sequence," *Journal of Biomechanics*, Vol. 47, No. 14, November 7, 2014, pp. 3475–3481. doi: 10.1016/j.jbiomech.2014.09.010

Knutson, Jayme S., Douglas D. Gunzler, Richard D. Wilson, and John Chae, "Contralaterally Controlled Functional Electrical Stimulation Improves Hand Dexterity in Chronic Hemiparesis: A Randomized Trial," *Stroke*, Vol. 47, No. 10, October 2016, pp. 2596–2602. doi: 10.1161/STROKEAHA.116.013791

Koffel, Erin, Melissa A. Polusny, Paul A. Arbisi, and Christopher R. Erbes, "A Preliminary Investigation of the New and Revised Symptoms of Posttraumatic Stress Disorder in DSM-5," *Depression and Anxiety*, Vol. 29, No. 8, August 2012, pp. 731–738. doi: 10.1002/da.21965

Kou, Zhifeng, Ramtilak Gattu, Firas Kobeissy, Robert D. Welch, Brian J. O'Neil, John L. Woodard, Syed Imran Ayaz, Andrew Kulek, Robert Kas-Shamoun, Valerie Mika, Conor Zuk, Francesco Tomasello, and Stefania Mondello, "Combining Biochemical and Imaging Markers to Improve Diagnosis and Characterization of Mild Traumatic Brain Injury in the Acute Setting: Results from a Pilot Study," *PLoS ONE*, Vol. 8, No. 11, November 2013, p. e80296. doi: 10.1371/journal.pone.0080296

Kuceyeski, Amy, Jun Maruta, Sumit N. Niogi, Jamshid Ghajar, and Ashish Raj, "The Generation and Validation of White Matter Connectivity Importance Maps," *NeuroImage*, Vol. 58, No. 1, September 1, 2011, pp. 109–121. doi: 10.1016/j.neuroimage.2011.05.087

Machamer, Joan, Nancy Temkin, and Sureyya Dikmen, "Health-Related Quality of Life in Traumatic Brain Injury: Is a Proxy Report Necessary?" *Journal of Neurotrauma*, Vol. 30, No. 22, November 15, 2013, pp. 1845–1851. doi: 10.1089/neu.2013.2920

Maruta, Jun, Minah Suh, Sumit N. Niogi, Pratik Mukherjee, and Jamshid Ghajar, "Visual Tracking Synchronization as a Metric for Concussion Screening," *Journal of Head Trauma Rehabilitation*, Vol. 25, No. 4, July 2010, pp. 293–305. doi: 10.1097/HTR.0b013e3181e67936

O'Connell, Karen M., Marguerite T. Littleton-Kearney, Elizabeth Bridges, and Sandra C. Bibb, "Evaluating the Joint Theater Trauma Registry as a Data Source to Benchmark Casualty Care," *Military Medicine*, Vol. 177, No. 5, 2012, pp. 546–552.

Panzer, Matthew B., Barry S. Myers, and Cameron R. Bass, "Mesh Considerations for Finite Element Blast Modelling in Biomechanics," *Computer Methods in Biomechanics and Biomedical Engineering*, Vol. 16, No. 6, 2013, pp. 612–621. doi: 10.1080/10255842.2011.629615

Rezaei, A., M. Salimi Jazi, G. Karami, and M. Ziejewski, "A Computational Study on Brain Tissue Under Blast: Primary and Tertiary Blast Injuries," *International Journal for Numerical Methods in Biomedical Engineering*, Vol. 30, No. 8, August 2014, pp. 781–795. doi: 10.1002/cnm.2629

Rincon, Fred, Joon Kang, Matthew Vibbert, Jacqueline Urtecho, M. Kamran Athar, and Jack Jallo, "Significance of Arterial Hyperoxia and Relationship with Case Fatality in Traumatic Brain Injury: A Multicentre Cohort Study," *Journal of Neurology, Neurosurgery and Psychiatry*, Vol. 85, No. 7, 2014, pp. 799–805. doi: 10.1136/jnnp-2013-305505

Roberts, J. C., T. P. Harrigan, E. E. Ward, T. M. Taylor, M. S. Annett, and A. C. Merkle, "Human Head–Neck Computational Model for Assessing Blast Injury," *Journal of Biomechanics*, Vol. 45, No. 16, November 15, 2012, pp. 2899–2906. doi: 10.1016/j.jbiomech.2012.07.027

Russell, Mark, and Steven M. Silver, "Training Needs for the Treatment of Combat-Related Posttraumatic Stress Disorder: A Survey of Department of Defense Clinicians," *Traumatology*, Vol. 13, No. 3, 2007, pp. 4–10.

Stocker, Ryan P. J., Marissa A. Cieply, Benjamin Paul, Hassen Khan, Luke Henry, Anthony P. Kontos, and Anne Germain, "Combat-Related Blast Exposure and Traumatic Brain Injury Influence Brain Glucose Metabolism During REM Sleep in Military Veterans," *NeuroImage*, Vol. 99, October 1, 2014, pp. 207–214. doi: 10.1016/j.neuroimage.2014.05.067

Ustinova, K. I., J. Perkins, W. A. Leonard, and C. J. Hausbeck, "Virtual Reality Game-Based Therapy for Treatment of Postural and Co-Ordination Abnormalities Secondary to TBI: A Pilot Study," *Brain Injury*, Vol. 28, No. 4, 2014, pp. 486–495. doi: 10.3109/02699052.2014.888593

Wang, Henry E., Siobhan P. Brown, Russell D. MacDonald, Shawn K. Dowling, Steve Lin, Daniel Davis, Martin A. Schreiber, Judy Powell, Rardi van Heest, and Mohamud Daya, "Association of Out-of-Hospital Advanced Airway Management with Outcomes After Traumatic Brain Injury and Hemorrhagic Shock in the ROC Hypertonic Saline Trial," *Emergency Medicine Journal*, Vol. 31, No. 3, 2014, pp. 186–191. doi: 10.1136/emermed-2012-202101

Wang, Yalin, Jie Shi, Xiaotian Yin, Xianfeng Gu, Tony F. Chan, Shing-Tung Yau, Arthur W. Toga, and Paul M. Thompson, "Brain Surface Conformal Parameterization with the Ricci Flow," *IEEE Transactions on Medical Imaging*, Vol. 31, No. 2, 2012, pp. 251–264. doi: 10.1109/TMI.2011.2168233

Writer, Brian W., Jason E. Schillerstrom, Heather K. Regwan, and Brent S. Harlan, "Executive Clock Drawing Correlates with Performance-Based Functional Status in People with Combat-Related Mild Traumatic Brain Injury and Comorbid Posttraumatic Stress Disorder," *Journal of Rehabilitation Research and Development*, Vol. 47, No. 9, 2010, pp. 841–850.

Yuh, Esther L., Shelly R. Cooper, Pratik Mukherjee, John K. Yue, Hester F. Lingsma, Wayne A. Gordon, Alex B. Valadka, David O. Okonkwo, David M. Schnyer, Mary J. Vassar, Andrew I. R. Maas, and Geoffrey T. Manley, "Diffusion Tensor Imaging for Outcome Prediction in Mild Traumatic Brain Injury: A TRACK-TBI Study," *Journal of Neurotrauma*, Vol. 31, No. 17, 2014, pp. 1457–1477. doi: 10.1089/neu.2013.3171

Zhang, Yong-Jie, Karen Jansen-West, Ya-Fei Xu, Tania F. Gendron, Kevin F. Bieniek, Wen-Lang Lin, Hiroki Sasaguri, Thomas Caulfield, Jaime Hubbard, Lillian Daughrity, Jeanne Chew, Veronique V. Belzil, Mercedes Prudencio, Jeannette N. Stankowski, Monica Castanedes-Casey, Ena Whitelaw, Peter E. A. Ash, Michael DeTure, Rosa Rademakers, Kevin B. Boylan, Dennis W. Dickson, and Leonard Petrucelli, "Aggregation-Prone c9FTD/ALS poly(GA) RAN-Translated Proteins Cause Neurotoxicity by Inducing ER Stress," *Acta Neuropathologica*, Vol. 128, No. 4, October 2014, pp. 505–524. doi: 10.1007/s00401-014-1336-5

Zheng, Weili, Helen Nichol, Saifeng Liu, Yu-Chung N. Cheng, and E. Mark Haacke, "Measuring Iron in the Brain Using Quantitative Susceptibility Mapping and X-Ray Fluorescence Imaging," *NeuroImage*, Vol. 78, September 2013, pp. 68–74. doi: 10.1016/j.neuroimage.2013.04.022

Zollman, Felise S., Eric B. Larson, Laura K. Wasek-Throm, Cherina M. Cyborski, and Rita K. Bode, "Acupuncture for Treatment of Insomnia in Patients with Traumatic Brain Injury: A Pilot Intervention Study," *Journal of Head Trauma Rehabilitation*, Vol. 27, No. 2, March 2012, pp. 135–142. doi: 10.1097/HTR.0b013e3182051397

Appendix B. Full-Text Articles Used for Knowledge Readiness Level Rating Examples

Example publication 1: Linxia Gu, Mehdi S. Chafi, Shailesh Ganpule, and Namas Chandra, "The Influence of Heterogeneous Meninges on the Brain Mechanics Under Primary Blast Loading," *Composites*, Part B: *Engineering*, Vol. 43, No. 8, December 2012, pp. 3160–3166. doi: 10.1016/j.compositesb.2012.04.014

> In the modeling of brain mechanics subjected to primary blast waves, there is currently no consensus on how many biological components to be used in the brain–meninges–skull complex, and what type of constitutive models to be adopted. The objective of this study is to determine the role of layered meninges in damping the dynamic response of the brain under primary blast loadings. A composite structures composed of eight solid relevant layers (including the pia, cerebrospinal fluid [CSF], dura maters) with different mechanical properties are constructed to mimic the heterogeneous human head. A hyper-viscoelastic material model is developed to better represent the mechanical response of the brain tissue over a large strain/high frequency range applicable for blast scenarios. The effect of meninges on the brain response is examined. Results show that heterogeneous composite structures of the head have a major influence on the intracranial pressure, maximum shear stress, and maximum principal strain in the brain, which is associated with traumatic brain injuries. The meninges serving as protective layers are revealed by mitigating the dynamic response of the brain. In addition, appreciable changes of the pressure and maximum shear stress are observed on the material interfaces between layers of tissues. This may be attributed to the alternation of shock wave speed caused by the impedance mismatch.

Example publication 2: Weili Zheng, Helen Nichol, Saifeng Liu, Yu-Chung N. Cheng, and E. Mark Haacke, "Measuring Iron in the Brain Using Quantitative Susceptibility Mapping and X-Ray Fluorescence Imaging," *NeuroImage*, Vol. 78, September 2013, pp. 68–74. doi: 10.1016/j.neuroimage.2013.04.022

> Measuring iron content in the brain has important implications for a number of neurodegenerative diseases. Quantitative susceptibility mapping (QSM), derived from magnetic resonance images, has been used to measure total iron content in vivo and in post mortem brain. In this paper, we show how magnetic susceptibility from QSM correlates with total iron content measured by X-ray fluorescence (XRF) imaging and by inductively coupled plasma mass spectrometry (ICPMS). The relationship between susceptibility and ferritin iron was estimated at 1.10±0.08 ppb susceptibility per μg iron/g wet tissue, similar to that of iron in fixed (frozen/thawed) cadaveric brain and previously published data from unfixed brains. We conclude that magnetic susceptibility can provide a direct and reliable quantitative measurement of iron content and that it can be used clinically at least in regions with high iron content.

Example publication 3: Khader M. Hasan, Elisabeth A. Wilde, Emmy R. Miller, Vipul Kumar Patel, Terrell D. Staewen, Melisa L. Frisby, Hector M. Garza, James J. McCarthy, Jill V. Hunter, Harvey S. Levin, Claudia S. Robertson, and Ponnada A. Narayana, "Serial Atlas-Based Diffusion Tensor Imaging Study of Uncomplicated Mild Traumatic Brain Injury in Adults," *Journal of Neurotrauma*, Vol. 31, No. 5, March 2014, pp. 466–475. doi: 10.1089/neu.2013.3085

> In this report, we applied diffusion tensor imaging (DTI) methods in 36 patients with uncomplicated mild traumatic brain injury (mTBI) and a comparison group of 37 participants with orthopedic injury. Our aim was to characterize regional and global macro- and microstructural attributes of white matter (WM), gray matter (GM), in addition to volume and diffusivity of cerebrospinal fluid (CSF) to identify and differentiate patterns of acute and short-term recovery. Given that previous DTI reports on mTBI in adults using a region-of-interest approach implicated the corona radiata (CR), corpus callosum, and hippocampus, we analyzed and quantified

DTI metrics of these regions using atlas-based methods. The normalized volume percentages of global CSF, GM, and WM were not different between the mTBI and orthopedic comparison (OC) groups at either the baseline or follow-up time points or between the baseline and follow-up time points within the OC group ($p > 0.17$; uncorrected for multiple comparisons). The DTI metrics did not differ between groups at either occasion. However, an increase was noted on follow-up in the OC group in the global mean diffusivity of GM (uncorrected $p = 0.003$) and WM (uncorrected $p = 0.02$), indicating a decrease in diffusivity at the 3-month postinjury, as compared to the baseline scan. An analysis of the DTI data collected longitudinally in the CR shows insignificant changes in the OC group ($p > 0.08$; $N = 37$). CR radial diffusivity was found to be elevated in the between-group comparison at baseline (mTBI1 vs. OC1), but did not differ in the within-group comparison (mTBI1 vs. mTBI2; $N = 19$), suggesting the possible resolution of edema. Our analysis of the cross-sectional and follow-up data, which is uncorrected for multiple comparisons, demonstrates dissociation between volumetric (macrostructural) and tissue integrity (microstructural) attributes and shows the potential utility of DTI to capture *transient* edema in the CR.

Example publication 4: David X. Cifu, Brett B. Hart, Steven L. West, William Walker, and William Carne, "The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms," *Journal of Head Trauma Rehabilitation*, Vol. 29, No. 1, January–February 2014, pp. 11–20. doi: 10.1097/HTR.0b013e3182a6aaf0

- Background: The high incidence of persistent postconcussion symptoms in service members with combat-related mild traumatic brain injury has prompted research in the use of hyperbaric oxygen (HBO_2) for management.
- Objective: The effects of HBO_2 on persistent postconcussion symptoms in 60 military service members with at least 1 combat-related mild traumatic brain injury were examined in a single-center, double-blind, randomized, sham-controlled, prospective trial at the Naval Medicine Operational Training Center at Naval Air Station Pensacola.
- Methods: Over a 10-week period, subjects received a series of 40, once-daily, hyperbaric chamber compressions at 2.0 atmospheres absolute (ATA). During each session, subjects breathed 1 of 3 preassigned oxygen fractions (10.5%, 75%, or 100%) for 60 minutes, resulting in an oxygen exposure equivalent to breathing surface air, 100% oxygen at 1.5 ATA, or 100% oxygen at 2.0 ATA, respectively. Individual, subscale and total item responses on the Rivermead Postconcussion Symptom Questionnaire and individual and total Posttraumatic Disorder Checklist–Military Version were measured just prior to intervention and immediately postintervention.
- Results: Between-group testing of pre- and postintervention means revealed no significant differences on individual or total scores on the Posttraumatic Disorder Checklist–Military Version or Rivermead Postconcussion Symptom Questionnaire, demonstrating a successful randomization and no significant main effect for HBO_2 at 1.5 or 2.0 ATA equivalent compared with the sham compression. Within-group testing of pre- and postintervention means revealed significant differences on several individual items for each group and difference in the Posttraumatic Disorder Checklist–Military Version total score for the 2.0 ATA HBO_2 group.
- Discussion: The primary analyses of between group differences found no evidence of efficacy for HBO_2. The scattered within group differences are threatened by Type 2 errors and could be explained by nonspecific effects.
- Conclusion: This study demonstrated that HBO_2 at either 1.5 or 2.0 ATA equivalent had no effect on postconcussion symptoms after mild traumatic brain injury when compared with sham compression.

Example publication 5: Henry E. Wang, Siobhan P. Brown, Russell D. MacDonald, Shawn K. Dowling, Steve Lin, Daniel Davis, Martin A. Schreiber, Judy

Powell, Rardi van Heest, and Mohamud Daya, "Association of Out-of-Hospital Advanced Airway Management with Outcomes After Traumatic Brain Injury and Hemorrhagic Shock in the ROC Hypertonic Saline Trial," *Emergency Medicine Journal*, Vol. 31, No. 3, 2014, pp. 186–191. doi: 10.1136/emermed-2012-202101

- Objective: Prior studies suggest adverse associations between out-of-hospital advanced airway management (AAM) and patient outcomes after major trauma. This secondary analysis of data from the Resuscitation Outcomes Consortium Hypertonic Saline Trial evaluated associations between out-of-hospital AAM and outcomes in patients suffering isolated severe traumatic brain injury (TBI) or haemorrhagic shock.
- Methods: This multicentre study included adults with severe TBI ([Glasgow Coma Scale] ≤ 8) or haemorrhagic shock ([systolic blood pressure] ≤ 70 [millimeters of mercury], or ([systolic blood pressure] 71–90 [millimeters of mercury] and heart rate ≥ 108 [beats per minute]). We compared patients receiving out-of-hospital AAM with those receiving emergency department AAM. We evaluated the associations between airway strategy and patient outcomes (28-day mortality, and 6-month poor neurologic or functional outcome) and airway strategy, adjusting for confounders. Analysis was stratified by (1) patients with isolated severe TBI and (2) patients with haemorrhagic shock with or without severe TBI.
- Results: Of 2135 patients, we studied 1116 TBI and 528 shock; excluding 491 who died in the field, did not receive AAM or had missing data. In the shock cohort, out-of-hospital AAM was associated with increased 28-day mortality (adjusted [odds ratio] 5.14; 95% [confidence interval] 2.42 to 10.90). In TBI, out-of-hospital AAM showed a tendency towards increased 28-day mortality (adjusted [odds ratio] 1.57; 95% [confidence interval] 0.93 to 2.64) and 6-month poor functional outcome (1.63; 1.00 to 2.68), but these differences were not statistically significant. Out-of-hospital AAM was associated with poorer 6-month TBI neurologic outcome (1.80; 1.09 to 2.96).
- Conclusions: Out-of-hospital AAM was associated with increased mortality after haemorrhagic shock. The adverse association between out-of-hospital AAM and injury outcome is most pronounced in patients with haemorrhagic shock.

Notes

[1] Jonathan Grant is director of the Policy Institute at King's College London.

[2] We use *health* rather than *medical* except where describing matters relating to medicine per se. Many health strategies are nonmedical (e.g., workplace injury prevention); we prefer the broader term.

[3] U.S. Department of Health and Human Services, "Technology Readiness Levels (TRLs)," undated; Lou Wheatcraft, "Technology Readiness Levels Applied to Medical Device Development," *Requirements Experts* blog, November 30, 2015; Director, Research Directorate, Office of the Director, Defense Research and Engineering, *Department of Defense Technology Readiness Assessment (TRA) Deskbook*, July 2009.

[4] Science Applications International Corporation, *Biomedical Technology Readiness Levels (TRLs)*, prepared for the Commanding General, USAMRMC, June 3, 2003.

[5] Note that the definition is not intended to exclude pure basic research, which can produce discoveries with the potential (even if remote or risky) to eventually improve public health, no matter the motivation for completing the research. Note also that this definition can be interpreted to encompass medical materiel, such that KPs can be materiel or nonmateriel. For purpose of this report, however, we exclude from our KP definition any research contributing solely to the development of medical materiel.

[6] Note, however, that a KP can be applied in or used to improve these activities. For example, health research can show the reliability and validity of a particular measure or administrative data element for routine use in these activities, or it might suggest the effectiveness of a setting-specific care delivery model.

[7] Klaus Krippendorff, *Content Analysis: An Introduction to Its Methodology*, 2nd ed., Thousand Oaks, Calif.: Sage, 2004, Chapter 11 ("Reliability").

[8] Joel Taylor and David Watkinson, "Indexing Reliability for Condition Survey Data," *Conservator*, Vol. 30, No. 1, 2007.

[9] See, for example, Steven H. Woolf, "The Meaning of Translational Research and Why It Matters," *JAMA*, Vol. 299, No. 2, 2008.

[10] Norman Crolee Dalkey, Bernice B. Brown, and S. W. Cochran, *The Delphi Method, III: Use of Self-Ratings to Improve Group Estimates*, Santa Monica, Calif.: RAND Corporation, RM-6115-PR, 1969.

[11] Theodore J. Gordon, "Delphi," in Jerome C. Glenn and Theodore J. Gordon, eds., *Futures Research Methodology*, Version 3.0, Washington, D.C.: Millennium Project, 2009a; Theodore J. Gordon, "Real-Time Delphi," in Jerome C. Glenn and Theodore J. Gordon, eds., *Futures Research Methodology*, Version 3.0, Washington, D.C.: Millennium Project, 2009b.

[12] The Delphi exercise, in addition to the KRL question described here, also had questions concerning a more general KRF that included estimates of the potential impact of KPs. This report describes only the portion of the Delphi exercise devoted to KRLs.

[13] There were 30 Delphi participants, divided into two groups of approximately equal size. The size of the groups was determined by the sizes of available rooms and the number of USAMRMC research managers who signed up to participate.

References

Cifu, David X., Brett B. Hart, Steven L. West, William Walker, and William Carne, "The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms," *Journal of Head Trauma Rehabilitation*, Vol. 29, No. 1, January–February 2014, pp. 11–20.

Dalkey, Norman Crolee, Bernice B. Brown, and S. W. Cochran, *The Delphi Method, III: Use of Self-Ratings to Improve Group Estimates*, Santa Monica, Calif.: RAND Corporation, RM-6115-PR, 1969. As of December 31, 2018: https://www.rand.org/pubs/research_memoranda/RM6115.html

Director, Research Directorate, Office of the Director, Defense Research and Engineering, *Department of Defense Technology Readiness Assessment (TRA) Deskbook*, July 2009. As of December 31, 2018: https://apps.dtic.mil/docs/citations/ADA524200

Gordon, Theodore J., "Delphi," in Jerome C. Glenn and Theodore J. Gordon, eds., *Futures Research Methodology*, Version 3.0, Washington, D.C.: Millennium Project, 2009a.

———, "Real-Time Delphi," in Jerome C. Glenn and Theodore J. Gordon, eds., *Futures Research Methodology*, Version 3.0, Washington, D.C.: Millennium Project, 2009b.

Gu, Linxia, Mehdi S. Chafi, Shailesh Ganpule, and Namas Chandra, "The Influence of Heterogeneous Meninges on the Brain Mechanics Under Primary Blast Loading," *Composites*, Part B: *Engineering*, Vol. 43, No. 8, December 2012, pp. 3160–3166. doi: 10.1016/j.compositesb.2012.04.014

Hasan, Khader M., Elisabeth A. Wilde, Emmy R. Miller, Vipul Kumar Patel, Terrell D. Staewen, Melisa L. Frisby, Hector M. Garza, James J. McCarthy, Jill V. Hunter, Harvey S. Levin, Claudia S. Robertson, and Ponnada A. Narayana, "Serial Atlas-Based Diffusion Tensor Imaging Study of Uncomplicated Mild Traumatic Brain Injury in Adults," *Journal of Neurotrauma*, Vol. 31, No. 5, February 25, 2014, pp. 466–475.

Krippendorff, Klaus, *Content Analysis: An Introduction to Its Methodology*, 2nd ed., Thousand Oaks, Calif.: Sage, 2004.

Science Applications International Corporation, *Biomedical Technology Readiness Levels (TRLs)*, prepared for the Commanding General, U.S. Army Medical Research and Materiel Command, June 3, 2003.

Taylor, Joel, and David Watkinson, "Indexing Reliability for Condition Survey Data," *Conservator*, Vol. 30, No. 1, 2007, pp. 49–62.

U.S. Department of Health and Human Services, "Technology Readiness Levels (TRLs)," undated. As of August 3, 2016: https://www.medicalcountermeasures.gov/federal-initiatives/guidance/integrated-trls.aspx

Wang, Henry E., Siobhan P. Brown, Russell D. MacDonald, Shawn K. Dowling, Steve Lin, Daniel Davis, Martin A. Schreiber, Judy Powell, Rardi van Heest, and Mohamud Daya, "Association of Out-of-Hospital Advanced Airway Management with Outcomes After Traumatic Brain Injury and Hemorrhagic Shock in the ROC Hypertonic Saline Trial," *Emergency Medicine Journal*, January 26, 2013 (online first).

Wheatcraft, Lou, "Technology Readiness Levels Applied to Medical Device Development," *Requirements Experts* blog, November 30, 2015. As of December 31, 2018: https://reqexperts.com/2015/11/30/technology-readiness-levels-applied-to-medical-device-development

Woolf, Steven H., "The Meaning of Translational Research and Why It Matters," *JAMA*, Vol. 299, No. 2, 2008, pp. 211–213.

Zheng, Weili, Helen Nichol, Saifeng Liu, Yu-Chung N. Cheng, and E. Mark Haacke, "Measuring Iron in the Brain Using Quantitative Susceptibility Mapping and X-Ray Fluorescence Imaging," *NeuroImage*, Vol. 78, September 2013, pp. 68–74.

About This Report

In the research reported here, RAND Corporation researchers developed knowledge readiness levels (KRLs). KRLs are used to estimate the scientific maturity of knowledge products emerging from health research. The authors completed the KRLs in consultation with the U.S. Army Medical Research and Materiel Command (USAMRMC) and built on the previous efforts of a USAMRMC working group. The KRLs are intended to provide a consistent and reliable means of measuring and comparing the scientific maturity of diverse knowledge products aimed at advancing scientific methods or capabilities for maximizing human health and related performance.

This research was sponsored by the USAMRMC with the support of the Defense Health Agency and conducted within the Forces and Resources Policy Center and the Acquisition and Technology Policy Center of the RAND National Defense Research Institute, a federally funded research and development center sponsored by the Office of the Secretary of Defense, the Joint Staff, the Unified Combatant Commands, the Navy, the Marine Corps, the defense agencies, and the defense Intelligence Community.

For more information on the RAND Forces and Resources Policy Center, see www.rand.org/nsrd/ndri/centers/frp. For more information on the RAND Acquisition and Technology Policy Center, see www.rand.org/nsrd/ndri/centers/atp. For either center, you can also contact the director (contact information is provided on each center's webpage).

Acknowledgments

We gratefully acknowledge the assistance and support of USAMRMC's and the U.S. Department of Defense's Joint Program Committee-6/Combat Casualty Care Research Program, particularly Col Todd E. Rasmussen and Therese A. West, who were instrumental to the completion of this work, and Col Michael Davis, the current director of the Combat Casualty Care Research Program. We are also greatly appreciative of the excellent support we received from Youngbok Ryu, PhuongGiang Nguyen, and Kristin Sereyko. Ryu helped us to develop and administer Delphi exercise questions and to analyze the results. Nguyen participated in the rating of knowledge products during the development of the KRL rating scale and assisted with KRL reliability testing data analysis. Sereyko provided support for report editing and preparation. Finally, we wish to thank our reviewers, Marjory S. Blumenthal and Melinda Moore, for their thoughtful comments, which challenged our thinking and led to important revisions to this research report that improved its clarity, quality, and usefulness.

For more information on this publication, visit www.rand.org/t/RR2127.

www.rand.org

RR-2127-OSD