The American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury

Running head: MILD TRAUMATIC BRAIN INJURY CRITERIA

The American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury

Noah D. Silverberg, Ph.D.*
Department of Psychology, University of British Columbia; Vancouver Coastal Health Research Institute; Djavad Mowafaghian Centre for Brain Health, Vancouver, British Columbia, Canada; 2136 West Mall, Vancouver, British Columbia, Canada, V6T 1Z4. Phone: 604-822-2755, Email: noah.silverberg@ubc.ca

Grant L. Iverson, Ph.D.**
Department of Physical Medicine and Rehabilitation, Harvard Medical School; Spaulding Rehabilitation Hospital and the Schoen Adams Research Institute at Spaulding Rehabilitation; MassGeneral Hospital for Children Sports Concussion Program; & Home Base, A Red Sox Foundation and Massachusetts General Hospital Program, Boston, Massachusetts, USA; 79/96 Thirteenth Street, Charlestown Navy Yard, Charlestown, MA, 02129. Phone: 617-643-8983, Email: giverson@mgh.harvard.edu

on behalf of the
ACRM Brain Injury Special Interest Group Mild TBI Task Force
and the
ACRM Mild TBI Definition Expert Consensus Group

ACRM Brain Injury Special Interest Group Mild TBI Task Force members (in alphabetical order)

Alison Cogan, Ph.D., OTR/L
Center for the Study of Healthcare Innovation, Implementation & Policy; VA Greater Los Angeles Healthcare System; 11301 Wilshire Blvd, Los Angeles, CA 90073. Email: alisonc79@gmail.com

Kristen Dams-O'Connor, Ph.D.
Department of Rehabilitation and Human Performance & Department of Neurology, Brain Injury Research Center of Mount Sinai, Box 1163, Icahn School of Medicine at Mount Sinai, New York, NY, USA 10029. Email: kristen.dams-o'connor@mountsinai.org

Richard Delmonico, Ph.D.
Kaiser Foundation Rehabilitation Center, The Permanente Medical Group, Kaiser Permanente, Northern California, 975 Sereno Drive, Vallejo, CA, USA 94589. Email: richard.l.delmonico@kp.org

Min Jeong P. Graf, M.D.
Department of Physical Medicine and Rehabilitation, Hennepin Healthcare; Department of Rehabilitation Medicine, University of Minnesota, 701 Park Ave, Minneapolis, MN, USA 55415. Email: minjeong.graf@hcmed.org

Mary Alexis Iaccarino, M.D.
Department of Physical Medicine and Rehabilitation, Massachusetts General Hospital
Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital
Harvard Medical School, 300 1st Ave, Charlestown, MA, USA 02129. Email:
miaccarino@mgh.havard.edu

Maria Kajankova, Ph.D.
Department of Rehabilitation and Human Performance, Brain Injury Research Center of Mount Sinai, Box 1163, Icahn School of Medicine at Mount Sinai, New York, NY, USA 10029. Email:
maria.kajankova@mountsinai.org

Joshua Kamins, M.D.
UCLA Steve Tisch BrainSPORT Program, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA, 300 Medical Plaza Ste B-200 Los Angeles, CA, USA 90095. Email:
jkamins@mednet.ucla.edu

Karen L. McCulloch. PT, Ph.D.
Division of Physical Therapy, Department of Health Sciences, School of Medicine, University of North Carolina at Chapel Hill, 3030 Bondurant Hall, CB# 7135, Chapel Hill, NC, USA 27599-7135. Email:
kmac@med.unc.edu

Gary McKinney, DHSc
Traumatic Brain Injury Center of Excellence, Defense Health Agency, 1335 East West Highway, Silver Spring, MD, USA 20910. Email: gary.l.mckinney.civ@health.mil

Drew Nagele, Psy.D.
School of Professional and Applied Psychology, Philadelphia College of Osteopathic Medicine, 4170 City Ave, Philadelphia, PA, USA 19131. Email: drew.nagele.psyd@gmail.com

William J. Panenka, M.D.
British Columbia Neuropsychiatry Program; Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, UBC, Vancouver, BC, Canada, V6T2A1. Email:
will.panenka@ubc.ca

Amanda R. Rabinowitz, Ph.D.
Moss Rehabilitation Research Institute, 50 Township Line Rd., Elkins Park, PA, USA, 19027.
Email: rabinowa@einstein.edu

Nick Reed, Ph.D.
Department of Occupational Science & Occupational Therapy, University of Toronto, 160-500 University Ave, Toronto, ON, Canada, M5G1V7. Email: nick.reed@utoronto.ca

Jennifer V. Wethe, Ph.D.
Mayo Clinic School of Medicine, 13400 E Shea Blvd, Scottsdale, AZ, USA 85259. Email:
Wethe.Jennifer@mayo.edu

Victoria Whitehair, M.D.
MetroHealth Rehabilitation Institute and Case Western Reserve University; 2500 MetroHealth Drive, Cleveland, OH, USA 44109. Email: vwhitehair@metrohealth.org

ACRM Mild TBI Diagnostic Criteria Expert Consensus Group
(members listed in alphabetical order)

Vicki Anderson, Ph.D.
Murdoch Children's Research Institute; The Royal Children's Hospital, 50 Flemington Road Parkville, Victoria 3052 Australia. Email: vicki.anderson@rch.org.au

David B. Arciniegas, M.D.
University of New Mexico School of Medicine; University of Colorado School of Medicine; 1635 Aurora Ct, Aurora, CO, USA 80045. Email: david.arciniegas@cuanschutz.edu

Mark T. Bayley, M.D.
Toronto Rehabilitation Institute, University Health Network; University of Toronto; Room 3-102-12, 550 University Avenue, Toronto, Ontario, Canada, M5G2A2. Email: mark.bayley@uhn.ca

Jeffrey J. Bazarian, M.D., M.P.H.
University of Rochester School of Medicine and Dentistry; 265 Crittenden Blvd Box 655c, Rochester, NY, USA 14642. Email: jeff_bazarian@urmc.rochester.edu

Kathleen R. Bell, M.D.
University of Texas Southwestern Medical Center; 5323 Harry Hines Blvd, Dallas, TX, USA, 75390. Email: Kathleen.Bell@UTSouthwestern.edu

Steven P. Broglio, Ph.D.
University of Michigan, Michigan Concussion Center; 830 N University Ave., Ann Arbor, MI, USA 48109. Email: broglio@umich.edu

David Cifu, M.D.
Department of Physical Medicine and Rehabilitation, Virginia Commonwealth University School of Medicine; U.S. Department of Veterans Affairs; 1223 East Marshall Street, Richmond, VA, USA 23298. Email: dcifu@vcu.edu

Gavin A. Davis, M.B.B.S., F.R.A.C.S
Cabrini Health; Suite 53 – Neurosurgery, Cabrini Malvern, Victoria, 3144, Australia. Email: gavin.davis@me.com

Jiri Dvorak, M.D., Ph.D.
Schulthess Clinic, Department of Neurology, Swiss Concussion Center; Lengghalde 2, CH-8008, Switzerland. Email: jiri@dvorakmedical.com

Ruben J. Echemendia, Ph.D.
University Orthopedics Center, Concussion Care Clinic; ;
University of Missouri-Kansas City, Kansas City, Missouri, USA.
107 Picadilly Rd., Port Matilda, PA, USA 16870

Email: rechemendia@comcast.net

Gerard A. Gioia, Ph.D.
Division of Neuropsychology/ SCORE Concussion Program, Children's National Hospital, George Washington University School of Medicine; 15245 Shady Grove Road #350, Rockville, MD, USA 20850. Email: ggioia@childrensnational.org

Christopher C. Giza, M.D.
University of California at Los Angeles, Departments of Neurosurgery and Pediatrics, Steve Tisch BrainSPORT Program; Room 557 Wasserman, Department of Neurosurgery, 300 Stein Plaza, UCLA, Los Angeles, CA, USA 90095. Email: cgiza@mednet.ucla.edu

Sidney R. Hinds II, M.D.
Uniformed Services University, Department of Neurology and Radiology, 4301 Jones Bridge Rd, Bethesda, MD 20814. Email: sidney.r.hinds@gmail.com

Douglas I. Katz, M.D.
Department of Neurology, Boston University School of Medicine; 72 E. Concord St. Robinson (B3), Boston University School of Medicine, Boston, MA, USA 02118. Email: dkatz@bu.edu

Brad G. Kurowski, M.D., M.S.
Division of Pediatric Rehabilitation Medicine, Cincinnati Children's Hospital Medical Center, Departments of Pediatrics, Neurology, and Rehabilitation Medicine, University of Cincinnati College of Medicine; 3333 Burnet Avenue, MLC 4009, Cincinnati, OH, USA 45229. Email: brad.kurowski@cchmc.org

John J. Leddy, M.D.
UBMD Department of Orthopaedics and Sports Medicine; SUNY Buffalo Jacobs School of Medicine and Biomedical Sciences; 160 Farber Hall, Buffalo, NY, USA 14214. Email: leddy@buffalo.edu

Natalie Le Sage, M.D., Ph.D.
Population Health and Optimal Health Practices Axis, CHU de Québec-Université Laval Research Centre; VITAM-Centre de recherche en santé durable; 1401, 18e rue, Québec, Canada, G1J 1Z4. Email: natalie.lesage@fmed.ulaval.ca

Angela Lumba-Brown, M.D.
Department of Emergency Medicine, Stanford University; 900 Welch Road, Stanford, CA, USA 94303. Email: alumba@stanford.edu

Andrew I.R. Maas, M.D.
Antwerp University Hospital, Edegem, and University of Antwerp; Drie Eikenstraat 655, 2650 Edegem, Belgium. Email: andrew.maas@uza.be

Geoffrey T. Manley, M.D., Ph.D.
Department of Neurosurgery, University of California, San Francisco; 1001 Potrero Ave, San Francisco, CA, USA 94110. Email: manleyg@ucsf.edu

Michael McCrea, Ph.D.
Medical College of Wisconsin; 8701 Watertown Plank Road, Milwaukee, WI, USA 53226.
Email: mmccrea@mcw.edu

David K. Menon, M.D., Ph.D.
University of Cambridge; Box 93, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK. Email: dkm13@cam.ac.uk

Jennie Ponsford, Ph.D.
Monash University; 18 Innovation Walk, Clayton campus, VIC 3800, Australia. Email: jennie.ponsford@monash.edu

Margot Putukian, M.D.
Consultant, Major League Soccer; Princeton, NJ, USA 08540. Email: mputukian@gmail.com

Stacy J. Suskauer, M.D.
Kennedy Krieger Institute and Department of Physical Medicine & Rehabilitation, Johns Hopkins University School of Medicine; 707 North Broadway, Baltimore, MD, USA 21205.
Email: suskauer@kennedykrieger.org

Joukje van der Naalt, M.D., Ph.D.
Department of Neurology, University of Groningen, University Medical Center Groningen; Netherlands. Email: j.van.der.naalt@umcg.nl

William C. Walker, M.D.
Virginia Commonwealth University; 1223 East Marshall Street, 4th Fl., Box 980677, Richmond, VA, USA 23298-0677. Email: William.walker@vcuhealth.org

Keith Owen Yeates, Ph.D.
Department of Psychology, Alberta Children's Hospital Research Institute, and Hotchkiss Brain Institute, University of Calgary; 2500 University Dr NW, Calgary, AB T2N 1N4, Canada.
Email: kyeates@ucalgary.ca

Ross Zafonte, D.O.
Department of Physical Medicine and Rehabilitation
Spaulding Rehabilitation Hospital/Massachusetts General Hospital/Brigham and Women's Hospital/Harvard Medical School; 300 First Avenue, Boston, MA, USA 02129. Email: rzafonte@mgh.harvard.edu

Nathan D. Zasler, M.D.
Concussion Care Centre of Virginia, Ltd.; 3721 Westerre Parkway, Suite B, Henrico, VA, USA 23233. Email: nzasler@cccv-ltd.com

Roger Zemek, M.D.
Departments of Pediatrics and Emergency Medicine, University of Ottawa;
Children's Hospital of Eastern Ontario; 401 Smyth Road, Ottawa, ON, Canada, K1H 8L1.
Email: rzemek@cheo.on.ca

* Corresponding author

**Member of both the ACRM Mild TBI Definition Expert Consensus Group and the ACRM Brain Injury Special Interest Group Mild TBI Task Force

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clinical and consulting practice in forensic neuropsychology, including expert testimony, involving individuals who have sustained mild TBIs. He has received past research support or funding from several test publishing companies, including ImPACT Applications, Inc., CNS Vital Signs, and Psychological Assessment Resources (PAR, Inc.). He has received research funding as a principal investigator from the National Football League, and subcontract grant funding as a collaborator from the Harvard Integrated Program to Protect and Improve the Health of National Football League Players Association Members. He has received research funding from the Wounded Warrior Project™. He acknowledges unrestricted philanthropic support from ImPACT Applications, Inc., the Mooney-Reed Charitable Foundation, the National Rugby League, Boston Bolts, and the Schoen Adams Research Institute at Spaulding Rehabilitation. Dr. Leddy reports that he is on the Scientific Advisory Boards of Neuronasal, Quadrant Biosciences, and Highmark Innovations, is a minority shareholder in Highmark Innovations and in 360 Concussion Care, an interdisciplinary concussion clinic, and receives expert testimony fees. Dr. Le Sage reports grants as a principal investigator from Canadian Institutes of Health Research (CIHR) and from Fonds de recherche du Québec en Santé (FRQ-S). She is a consultant for the Institut National d'Excellence en santé et en services sociaux (INESSS) and for the Quebec Ministry of Health and Social Services (MSSS). Dr. Manley reports research funding from the Department of Defense, NIH, National Footbal League (NFL), Abbott Laboratories, and grateful patients. Dr. Mass declares grant funding from the Framework 7 program of the European Union (Grant 602150), and consulting fees from PresSura Neuro, Integra Life Sciences, and NeuroTrauma Sciences. Dr. Menon reports grants, personal fees, and non-financial support from GlaxoSmithKline; personal fees from Neurotrauma Sciences, Lantmaanen AB, Pressura, and Pfizer, outside of the submitted work. Dr. McCrea reports research grants from the NIH, Department of Defense, Center for Disease Control and Prevention (CDC), Department of Veterans Affairs, Abbott Laboratories, National Football League (NFL), and National Collegiate Athletic Association (NCAA), and consultancy with the Green Bay Packers and Neurotrauma Sciences, Inc. Dr Ponsford reports grants from the Victorian Transport Accident Commission and National Health and Medical Research Council and provides expert testimony for cases involving mild TBI. Dr. Putukian is a paid consultant for Major League Soccer, and serves on several committees including the NFL Head, Neck & Spine Committee, the Football Association (FA) Research Task Force, the US Soccer Medical Advisory Committee and the NOCSAE Scientific Advisory Committee. She has assisted with the United Kingdom Concussion Foundation Forum, received funding for research from the NCAA-CARE-DoD 2.0 (ended 2020), and has received honoraria and reimbursement for travel for speaking and conferences attended, received royalties for the Netter's Sports Medicine textbook, and received compensation for work as an expert for cases involving concussion, team physician and other sports medicine topics. Dr. Reed reports grants from the Canadian Institutes of Health Research and Special Olympics Canada, and holds a Canada Research Chair (Tier 2) in Pediatric Concussion. He is a co-investigator in a multicentre study funded by the National Football League (NFL) Scientific Advisory Board but does not receive financial support. He is an Executive Board Member for the International Paediatric Brain Injury Society. He is a minority shareholder in 360 Concussion Care, an interdisciplinary concussion clinic. Dr. Silverberg reports grants from the Canadian Institutes of Health Research, Canadian Foundation for Innovation, VGH+UBC Hospital Foundation, and WorkSafeBC, and clinical consulting fees from the National Hockey League and Major League Soccer, and expert testimony fees. Dr. Wethe reports a financial relationship with King-Devick technologies and a financial interest in Mayo Clinic Concussion Check. Dr. Yeates is the recipient of the Ronald and Irene Ward Chair in Pediatric Brain Injury, funded by the Alberta Children's Hospital Foundation. He receives an editorial stipend from the American Psychological Association and book royalties from Guilford

Press and Cambridge University Press. He is the Chair of the Canadian Concussion Network, which is funded by a grant from the Canadian Institutes of Health Research. He is a co-investigator in a multicentre study funded by the National Football League (NFL) Scientific Advisory Board but does not receive financial support. He is a member of the Scientific Advisory Committee for Brain Injury Canada and of the National Research Advisory Council for the National Pediatric Rehabilitation Resource Center. Dr. Zafonte receives royalties from Springer/Demos publishing for serving as co- editor of the text Brain Injury Medicine. Dr. Zafonte serves on the Scientific Advisory Board of Kisbee Nanodiagnostics, and Myomo. He also evaluates patients in the MGH Brain and Body-TRUST Program which is funded by the NFL Players Association. Dr Zafonte also serves on the Mackey White health committee. Dr. Zafonte serves as PI for the Football Players Health Study at Harvard. Dr. Zasler is the sole shareholder in Concussion Care Center of Virginia, LTD. He has a clinical and forensic consulting practice in brain injury medicine. Dr. Zemek reports being a co-investigator in a multicentre study competitively funded by the National Football League (NFL) Scientific Advisory Board; he is a minority shareholder in 360 Concussion Care, an interdisciplinary concussion clinic.

Abstract

Objective: To develop new diagnostic criteria for mild traumatic brain injury (TBI) that are appropriate for use across the lifespan and in sports, civilian trauma, and military settings.

Design: Rapid evidence reviews on 12 clinical questions and Delphi method for expert consensus.

Participants: The Mild Traumatic Brain Injury Task Force of the American Congress of Rehabilitation Medicine Brain Injury Special Interest Group convened a Working Group of 17 members and an external interdisciplinary expert panel of 32 clinician-scientists. Public stakeholder feedback was analyzed from 68 individuals and 23 organizations.

Results: The first two Delphi votes asked the expert panel to rate their agreement with both the diagnostic criteria for mild TBI and the supporting evidence statements. In the first round, 10 of 12 evidence statements reached consensus agreement. Revised evidence statements underwent a second round of expert panel voting, where consensus was achieved for all. For the diagnostic criteria, the final agreement rate, after the third vote, was 90.7%. Public stakeholder feedback was incorporated into the diagnostic criteria revision prior to the third expert panel vote. A terminology question was added to the third round of Delphi voting, where 30 of 32 (93.8%) expert panel members agreed that 'the diagnostic label 'concussion' may be used interchangeably with 'mild TBI' when neuroimaging is normal or not clinically indicated.'

Conclusions: New diagnostic criteria for mild TBI were developed through an evidence review and expert consensus process. Having unified diagnostic criteria for mild TBI can improve the quality and consistency of mild TBI research and clinical care.

Key words: Craniocerebral Trauma, Concussion, Brain Injury, Diagnostic, Consensus

Abbreviations:
ACRM = American Congress of Rehabilitation Medicine
GCS = Glasgow Coma Scale
TBI = Traumatic brain injury

Introduction

In 1993, the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM) published a definition of mild traumatic brain injury (TBI)[1] that has been widely used since. An update of this definition was needed for several reasons. First, scientific research over the past 30 years has considerably improved our understanding of mild TBI and how to assess its acute sequelae. Second, use of the 1993 ACRM definition has exposed important limitations that definitions published since have not remedied, such as not clearly differentiating signs from symptoms. Finally, other definitions of mild TBI have been developed using weak or unclear methodologies.

Alternative mild TBI definitions that differ substantively from each other have proliferated[2-4]. One study applied 17 definitions of mild TBI to a prospectively collected dataset of 11,907 children (aged 3-16) who were evaluated in emergency departments[5]. The proportion of the sample meeting criteria for mild TBI ranged from 7% to 99%, depending on the definition applied. Consequences of diagnostic variability include uneven access to clinical care, ambiguity about who clinical practice guidelines are for, and difficulties comparing or synthesizing research findings, especially between civilian trauma, sports, and military settings[6]. Efforts to develop common data elements for the uniform collection and coding of demographic and clinical data[7], as well as to harmonize outcome measures[8] for "big data" analytics, are being undermined by uncertainty and variability regarding who is enrolled in TBI studies.

This article presents new diagnostic criteria for mild TBI (i.e., a case definition that operationalizes clinical features and specifies which are necessary or sufficient for diagnosis[9,10]) and the methodology used to develop them. Recognizing that expert consensus is needed to develop diagnostic criteria for conditions with heterogenous clinical presentations and no definitive laboratory confirmation[7-10], we undertook a rigorous and transparent Delphi consensus process, supported by rapid evidence reviews. In an effort to create diagnostic criteria that are appropriate for use across the lifespan and in sports, civilian trauma, and military settings, we composed an expert consensus panel with broad, interdisciplinary clinical and research expertise across these subpopulations[3]. Unified diagnostic criteria for mild TBI could improve the quality and consistency of mild TBI research and clinical care.

Methodology for Developing the New Diagnostic Criteria

The Mild TBI Task Force of the ACRM Brain Injury Special Interest Group convened a Working Group in late 2018, consisting of 17 individuals from the Task Force membership. The Working Group, co-led by NDS and GLI, took several steps prior to commencing the Delphi process. First, the Working Group assembled an expert panel and surveyed their views on the diagnostic importance of various signs, symptoms, examination findings, and contextual factors. These processes and results were published online first in the summer of 2020[3]. These survey results were intended to characterize expert opinion on the diagnostic importance of specific elements of the future diagnostic criteria, in anticipation that published empirical evidence for diagnostic accuracy would be insufficient for at least some elements. Second, the Working Group conducted rapid evidence reviews[11] to identify and synthesize research relevant to adding, removing, or modifying elements of 1993 ACRM definition[1] (see *Evidence Statements* below). Finally, the Working Group combined this evidence with expert opinion from the initial survey[3] to generate Version 1.0 of the updated ACRM diagnostic criteria for mild TBI. An overview of these preliminary steps and the Delphi expert consensus process is shown in Figure 1.

Evidence Statements

Based on the initial survey of the expert panel[3], the Working Group identified 12 topics that required evidence-checking, with each topic associated with major revisions under consideration (online supplementary material). Using rapid review methodology[11], members of the Working Group searched MEDLINE between October 2019 and January 2020, using a fixed term set for mild TBI ([exp 'Craniocerebral Trauma' MeSH term] or [*concuss*] or [(mild or minor) and (head or brain) and (injur* or trauma*)]) in combination with key words and variations specific to each topic that was approved by the project lead (NDS). Searches were limited to articles published in English from 1993-present. The Working Group member leading each topic screened abstracts and extracted data for their topic. Studies related to diagnostic accuracy were graded as Class I (low risk of bias) to Class IV (high risk of bias) by a single rater based on the American Academy of Neurology Clinical Practice Guideline Process Manual[12]. Data extraction and risk of bias ratings were verified by a second Working Group member and discrepancies were resolved by the project lead (NDS). The 12 brief evidence statements were presented to the expert panel along with evidence summaries (descriptions of relevant studies with risk of bias ratings and supporting citations) (see the online supplementary material). In addition to rating their agreement with each statement, expert panel members were invited to explain their reasons for disagreement and suggest revisions, as well as to identify additional important articles that were not included by the Working Group's systematic evidence search.

Delphi Process

The Delphi method is a widely used semi-standardized process for pursuing expert consensus[13,14]. The identification, invitation, and characteristics of the expert panel members were described in the previously published article[3]. In brief, all have expertise in mild TBI, from a variety of disciplines (e.g., physiatry, neurology, neuropsychology, neurosurgery, emergency medicine, and sports medicine). Since the initial convening of the expert panel, two new members were added to increase the international representation and gender diversity of the panel (prior to the first Delphi round) and one member resigned for reasons unrelated to this study (after the second Delphi round). The Delphi process was conducted entirely online. In each round, expert panel members were invited to complete an online survey (hosted by Qualtrics) in

which they were presented with diagnostic criteria and asked to rate their agreement on a 4-point scale (agree without reservations, agree with minor reservations, agree with major reservations, or disagree) and enter comments to explain any reasons for reservations or disagreement. Following each round, the expert panel received quantitative (agreement rating frequencies) and qualitative (de-identified aggregated comments) feedback from the previous round. Individual responses remained confidential.

Prior to commencing the Delphi process, the Working Group defined 'consensus' as at least 80% of the expert panel indicating agreement without reservations or with minor reservations. Three rounds of Delphi voting were conducted (see online supplementary material). Prior to the third round of Delphi voting, the expert panel received a summary of the results of the stakeholder survey (described below) and corresponding reasons for further revisions to diagnostic criteria Versions 2.0 and 2.1 (see the online supplementary material). In the third round of Delphi voting, expert panel members were not only asked to rate their agreement with the revised diagnostic criteria (Version 2.2), but also their agreement with the statement 'The diagnostic label 'concussion' may be used interchangeably with 'mild TBI' when neuroimaging is normal or not clinically indicated' with a yes or no response. Expert panel members who responded 'no' were prompted to share their (alternative) opinion about the relationship between the terms 'concussion' and 'mild TBI.'

Stakeholder Feedback

Following the second round of Delphi voting, the Working Group addressed qualitative feedback from the expert panel on Version 2.0 of the ACRM diagnostic criteria, resulting in Version 2.1, and created a stakeholder feedback survey that contained two items. Version 2.1 of the ACRM diagnostic criteria for mild TBI was made available for download and respondents were prompted to provide narrative comments. To solicit their opinion on terminology, respondents were then presented with "'Concussion' may be used interchangeably with 'mild TBI'…" and given five response options (see online supplementary material). The survey (hosted by SurveyMonkey) was disseminated in two ways, (i) through ACRM's email distribution lists and social media channels, and (ii) by direct email invitation to organizations identified by the Working Group as having a mandate relevant to TBI (see online supplementary material). The survey launched on December 18, 2021 and remained open to individuals until January 18, 2022 and to stakeholder organizations until March 15, 2022.

The number and source of submissions from members of the public and stakeholder organizations are summarized in the online supplementary material. We analyzed responses from 68 individuals and 23 stakeholder organizations. The Working Group extracted themes from the narrative comments (see online supplementary material) and attempted to address them in a minor revision of the diagnostic criteria (from Version 2.1 to 2.2).

Results from the Delphi Voting

The first two rounds of Delphi voting included votes relating to both the evidence statements and the diagnostic criteria for mild TBI. In the first round of expert panel voting (October-December of 2020), 10 of 12 evidence statements reached consensus agreement and others exceeded this threshold but were modestly revised to address expert panel member concerns. In total, 9 of 12 evidence statements were revised. The revised evidence statements underwent a second round of expert panel voting (June-July of 2021), where consensus was achieved for all. The final

evidence statements and their agreement ratings are presented in the online supplementary material.

The results through three rounds of Delphi voting on the diagnostic criteria for mild TBI are presented in the online supplementary material. The response rate amongst the expert panel was 100% in all three rounds of voting. The first round of voting yielded an agreement rate of 75.8%. Both the second and third rounds of voting exceeded the agreement necessary for consensus (80%). The final consensus criteria (Version 2.2) had a 90.7% agreement rate (without reservations or with minor reservations). Specific reservations with the final diagnostic criteria in the third round of Delphi voting, paraphrased to preserve anonymity, are reported in the online supplementary material. For the terminology question in the third round of Delphi voting, 30 of 32 (93.8%) expert panel members agreed that "the diagnostic label 'concussion' may be used interchangeably with 'mild TBI' when neuroimaging is normal or not clinically indicated."

ACRM Diagnostic Criteria for Mild Traumatic Brain Injury

The new ACRM diagnostic criteria for mild TBI are presented in Box 1. Definitions and explanatory notes for the diagnostic criteria are presented in Box 2. The diagnostic criteria are illustrated visually in Figure 2. Examples of applying the criteria to patients with various patterns of signs, symptoms, and/or examination findings are illustrated in the online supplementary material.

Box 1. American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury.

Mild traumatic brain injury (TBI) is diagnosed when, following a biomechanically plausible mechanism of injury (Criterion 1) *one or more* of the criteria (i-iii) listed below are met.

i. One or more clinical signs (Criterion 2) attributable to brain injury.

ii. At least two acute symptoms (Criterion 3) and at least one clinical or laboratory finding (Criterion 4) attributable to brain injury.

iii. Neuroimaging evidence of TBI, such as unambiguous trauma-related intracranial abnormalities on computed tomography or structural magnetic resonance imaging (Criterion 5).

Confounding factors do not fully account for the clinical signs (Criterion 2), acute symptoms (Criterion 3), and clinical examination and laboratory findings (Criterion 4) that are necessary for the diagnosis (Criterion 6).

Mild Qualifier: The 'mild' qualifier is not used if any of the injury severity indicators listed below are present. Instead, traumatic brain injury (TBI) is diagnosed (without the 'mild' qualifier).
i. Loss of consciousness duration greater than 30 minutes.
ii. After 30 minutes, a Glasgow Coma Scale (GCS) of less than 13.
iii. Post-traumatic amnesia greater than 24 hours.

Neuroimaging Qualifier: If neuroimaging is abnormal (Criterion 5), the qualifier mild TBI 'with neuroimaging evidence of structural intracranial injury' may be used. When neuroimaging is completed and found to be normal, the qualifier mild TBI 'without neuroimaging evidence of structural intracranial injury' may be used. If neuroimaging is not completed, no qualifier is used.

Concussion: The diagnostic label 'concussion' may be used interchangeably with 'mild TBI' when neuroimaging is normal or not clinically indicated.

Suspected Mild TBI: A mild TBI is suspected when, following a biomechanically plausible mechanism of injury (Criterion 1), one or more of the three criteria listed below are met.
i. At least two acute symptoms (Criterion 3) and the person does not meet other criteria sufficient for diagnosing mild TBI.
ii. At least two clinical examination or laboratory findings (Criterion 4) but the person does not meet other criteria for diagnosing mild TBI.
iii. It is unclear whether signs (Criterion 2), acute symptoms (Criterion 3), and available clinical or laboratory findings (Criterion 4) are accounted for by confounding factors (i.e., it is unclear if Criterion 6 is met).

See Box 2 for definitions and explanatory notes.

Box 2. Definitions, Explanatory Notes, and Qualifiers for the American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury.

Criterion 1: Mechanism of Injury

Traumatic brain injury (TBI) results from a transfer of mechanical energy to the brain from external forces resulting from the (i) head being struck with an object, (ii) head striking a hard object or surface, (iii) brain undergoing an acceleration/deceleration movement without direct contact between the head and an object or surface, and/or (iv) forces generated from a blast or explosion.

Notes: Criterion 1 can be met by direct observation (in person or video review) or collateral (witness) report of the injury event, review of acute care records, or the person's recount of the injury event during an interview.

Criterion 2: Clinical Signs

The injury event causes an acute physiological disruption of brain function, as manifested by *one or more* of the clinical signs listed below.

i. Loss of consciousness immediately following injury (e.g., no protective action taken on falling after impact or lying motionless and unresponsive).

ii. Alteration of mental status immediately following the injury (or upon regaining consciousness), evidenced by reduced responsiveness or inappropriate responses to external stimuli; slowness to respond to questions or instructions; agitated behavior; inability to follow two-part commands; or disorientation to time, place, or situation.

iii. Complete or partial amnesia for events immediately following the injury (or after regaining consciousness). If post-traumatic amnesia cannot be reliably assessed (e.g., due to polytrauma or sedating analgesics), retrograde amnesia (i.e., a gap in memory for events immediately preceding the injury) can be used as a replacement for this criterion.

iv. Other acute neurological sign(s) (e.g., observed motor incoordination upon standing, seizure, or tonic posturing immediately following injury).

Notes: Criterion 2 can be met by direct observation (in person or video review), collateral (witness) report, review of acute care records, or when none of these are available, the person's recount of the injury event.

Criterion 3: Acute Symptoms

The physiological disruption of brain function is manifested by *two or more* new or worsened symptoms from the list below.

i. Acute subjective alteration in mental status: feeling confused, feeling disoriented, and/or feeling dazed.

ii. Physical symptoms: headache, nausea, dizziness, balance problems, vision problems, sensitivity to light, and/or sensitivity to noise.

iii. Cognitive symptoms: feeling slowed down, "mental fog," difficulty concentrating, and/or memory problems.

iv. Emotional symptoms: uncharacteristic emotional lability and/or irritability.

The symptoms may be from one or more categories (i.e., experiencing two symptoms within a single category is sufficient). Other symptoms may be present, but they should not be counted towards Criterion 3. The onset of acute subjective alteration in mental status occurs immediately following the impact or after regaining consciousness. The onset of other symptoms (physical, cognitive, and emotional) may be

delayed by a few hours, but they nearly always appear less than 72 hours from injury.

Notes: Criterion 3 can be met by (i) review of acute care documentation of the injured person's acute symptoms, (ii) interviewing the injured person about the first few days following injury; (iii) having the injured person complete a self-report rating scale documenting symptoms during the first few days following injury; or (iv) collateral observation for an individual who cannot accurately report symptoms due to developmental stage (e.g., children under 5 years old) or pre-injury disability.

Criterion 4: Clinical Examination and Laboratory Findings

The assessment findings listed below can also provide supportive evidence of brain injury.

i. Cognitive impairment on acute clinical examination.

ii. Balance impairment on acute clinical examination.

iii. Oculomotor impairment or symptom provocation in response to vestibular-oculomotor challenge on acute clinical examination.

iv. Elevated blood biomarker(s) indicative of intracranial injury.

Notes: Clinical and laboratory tests that meet standards of reliability and diagnostic accuracy should be considered for Criterion 4. Impairment in Criterion 4i-iii is defined as a clinically meaningful discrepancy between post-injury test performance and age-appropriate normative reference data, or where available, pre-injury test performance. The diagnostic sensitivity of most clinical and laboratory tests decreases over the first 72 hours following injury and the rate of sensitivity decline differs between specific tests.

Criterion 5: Neuroimaging

Trauma-related intracranial abnormalities on computed tomography or structural magnetic resonance imaging.

Notes: Neuroimaging is not necessary to diagnose mild TBI. Its primary clinical role is to rule out head and brain injuries that might require neurosurgical or other medical intervention in an acute care setting. When obtained, neuroimaging may reveal intracranial abnormalities indicative of TBI such as contusion(s) or intracranial hemorrhage.

Criterion 6: Not better accounted for by confounding factors

Confounding factors, including pre-existing and co-occurring health conditions, have been considered and determined to not fully account for the clinical signs, acute symptoms, and clinical examination and laboratory findings that are necessary for the diagnosis.

Notes: A clinical sign only qualifies for Criterion 2 when it is not better accounted for by acute musculoskeletal pain, psychological trauma, alcohol or substance intoxication, pulmonary or circulatory disruption, syncope prior to fall, or other confounding factors. Symptoms should only be counted towards Criterion 3 when they are not better accounted for by drug, alcohol, or medication use; co-occurring physical injuries (e.g., musculoskeletal injury involving the neck or peripheral vestibular dysfunction) or psychological conditions (e.g., an acute stress reaction to trauma); pre-existing health conditions; or symptom exaggeration. Criterion 4 findings must not be better accounted for by drug, alcohol, or medication use; co-occurring physical injuries or psychological conditions; pre-existing health conditions; or factors influencing the validity of the symptom reporting or test results.

General Notes: Consideration should be given to cultural and linguistic differences in symptom reporting and test performance. Caution is warranted when applying the diagnostic criteria for mild TBI to young children and individuals with pre-injury cognitive and/or communication impairments. Due to developmental stage (e.g., children under 5 years old) or pre-injury disability, an individual may not be able to accurately report symptoms in Criterion 3; thus, this criterion could be met based on proxy report or observation of related behaviors (e.g., changes in appetite or behaving out of character). An injured person's behavior should also be interpreted in the context of their developmental stage and pre-injury functioning. Clinical and laboratory test interpretation requires age-appropriate scales and/or cut-off scores.

Figure 2. Visual Representation of the American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury.

Figure Note: See Box 1 for the diagnostic criteria and Box 2 for the definitions and explanatory notes. The qualifier mild TBI 'with neuroimaging evidence of structural intracranial injury' may be used when computed tomography or magnetic resonance imaging reveals a trauma-related intracranial abnormality. A suspected mild TBI is represented by the dashed lines.

Discussion

The Working Group of the ACRM Mild TBI Task Force developed new diagnostic criteria for mild TBI that are appropriate for use across the lifespan and in sports, civilian trauma, and military settings. The diagnostic criteria elements are explained below, highlighting similarities and differences with prior definitions of mild TBI.

Mechanism of Injury (Criterion 1)

A plausible mechanism of injury resulting in an external force inducing a physiological disruption of brain function is necessary for diagnosis, as in prior definitions[1,15-17]. The ACRM diagnostic criteria broaden the possible mechanisms of injury listed in the 1993 ACRM definition to include 'forces generated from a blast or explosion' (see the evidence summary for Evidence Statement #1, online supplementary material), in alignment with more recent definitions of mild TBI[16,18]. Criterion 1 may be met by the patient's own description of the injury event (if they remember it adequately), witness observations, or by inference (e.g., a person is extracted from a high-speed motor vehicle crash with facial lacerations). Criterion 1 avoids referring to the injury event as an 'accident,' considering that intentional assault, including intimate partner violence, is a recognized cause of TBI. The Working Group considered more precisely defining the parameters of impact, as some prior definitions have done[19], but found insufficient expert panel support for the diagnostic importance of variables such as whether the head made direct contact with a surface or the material of the surface[3]. Penetrating brain injury or 'other force yet to be defined'[16] fall outside of the scope of the ACRM diagnostic criteria for mild TBI. Not all head trauma events result in TBI. A diagnosis of mild TBI requires a plausible mechanism (Criterion 1) and clinical evidence of an acute physiological disruption of brain function.

Clinical Signs (Criterion 2)

One or more clinical signs (Criterion 2) attributed to a plausible mechanism of injury (Criterion 1) is sufficient for diagnosing mild TBI. The specific clinical signs listed in the ACRM diagnostic criteria (loss of consciousness, alteration in mental status, amnesia, other acute neurological signs) are similar to those in prior definitions[1,15-17] but, importantly, are given detailed operational definitions and are distinguished from symptoms. Data from video review studies of sport-related concussion (Evidence Statement #5, online supplementary material) helped to identify specific observable behaviors indicative of mild TBI. For example, 'no protective action taken on falling after impact' is included in the definition of loss of consciousness (Criterion 2i).

Clinical signs can be observed (e.g., patients repeatedly asking 'what happened' to cause their injury) or elicited (e.g., assessing orientation in a mental status examination). In contrast, symptoms (Criterion 3) are subjective feelings of a change in health. The distinction between signs and symptoms is perhaps clearest with altered mental status (Criterion 2ii). Prior definitions of mild TBI include some version of altered mental status as a manifestation of disrupted brain function. Characterizations of altered mental status across prior definitions range from relatively narrow ('confusion or disorientation')[20] to broader, including for example 'feeling dazed'[1] or 'difficulty thinking clearly'[18] or 'slowed thinking'[16]. Prior definitions do not clearly differentiate symptoms (e.g., 'feeling confused') from signs (e.g., difficulty answering orientation questions). The ACRM diagnostic criteria attempt to reconcile these variations and

provide a clear operational definition of observable behaviors indicative of altered mental status (Criterion 2ii). Subjectively experienced symptoms of altered mental status appear in Criterion 3. The distinction between signs and symptoms can be less clear when the first medical evaluation occurs after the acute stage and the clinician asks the patient about altered mental status (Criterion 2ii) and post-traumatic amnesia (Criterion 2iii) immediately following the injury, i.e., retrospectively. If the patient did not interact with others immediately following the injury (therefore acute clinical signs were not *observed*), the clinician may need to pose a hypothetical scenario to determine if the signs were *observable* (e.g., would you have been able to answer questions about where you were and what happened immediately following the injury?). In this circumstance, observable behaviors elicited through self-report can be counted as signs.

In most prior definitions of mild TBI, 'a loss of memory for events immediately before or after' the injury is sufficient for diagnosis[1,16,18]. In exception, the World Health Organization Neurotrauma Task Force definition includes post-traumatic amnesia only[20]. Based on evidence that retrograde amnesia rarely occurs without post-traumatic amnesia (see the evidence summary for Evidence Statement #2, online supplementary material) and isolated retrograde amnesia may be more in keeping with a non-TBI mechanism (e.g., syncope or psychological trauma), the ACRM diagnostic criteria recommend considering retrograde amnesia only when assessment of post-traumatic amnesia is precluded (Criterion 2iii).

In the 1993 ACRM definition, 'focal neurological deficit(s)' could rule in TBI. They were not clearly defined. The World Health Organization Neurotrauma Task Force definition[20] provided further clarification: 'transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery' (pg. 140). The Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health definition[16] provided a non-exhaustive list of neurological deficits that included seizure, sensory loss, and weakness/paralysis. Our Working Group considered that *focal* neurological deficits have not been well defined. The ACRM diagnostic criteria include 'other acute neurological sign(s)' (note removal of the word 'focal') as a clinical sign of TBI (Criterion 2iv) and lists examples as observed motor incoordination upon standing, seizure, or tonic posturing immediately following injury, in part motivated by the emerging literature on video analysis of sport-related concussions (see the evidence summary for Evidence Statement #5, online supplementary material).

The World Health Organization Neurotrauma Task Force definition[20] introduced the requirement that clinical signs must not be attributable to confounding factors such as acute pain, psychological trauma, and alcohol intoxication. Subsequent definitions[16,17] and the ACRM diagnostic criteria have similar requirements (Criterion 6).

Acute Symptoms (Criterion 3)

The new ACRM diagnostic criteria allow for diagnosis of mild TBI when there is not clear evidence of a clinical sign. Specifically, having *two or more* symptoms (Criterion 3) *and* one or more abnormal clinical examination or laboratory findings (Criterion 4) attributable to brain injury, is sufficient for diagnosis. It is also possible to have a 'suspected' mild TBI when the only evidence suggestive of brain injury is self-reported symptoms (Criterion 3), including symptoms that become evident only upon attempted exertion[21]. These changes should improve sensitivity over the 1993 ACRM definition. Specificity should be preserved by not counting symptoms with known poor specificity such as fatigue and nervousness towards Criterion 3 (see the evidence

summary for Evidence Statements #4a-c, online supplementary material) and the requirement that new or worsened symptoms must have an acute onset (<72 hours) and not be better accounted for by confounding factors (Criterion 6). Note that the 72 hour time period for headache to be counted towards a diagnosis of mild TBI is shorter than the 7-day time period allowed for the classification of post-traumatic headache diagnosis[22].

Whether 'post-concussion' symptoms, in the absence of clinical signs, can[17,23] or cannot[1,20] rule in mild TBI has been a major source of discrepancy between prior definitions. Available research evidence does not provide a clear answer as to which approach is correct (see the evidence summary for Evidence Statements #3 and #4a-c, online supplementary material). Our expert panel rated symptoms has having variable and generally lower diagnostic importance than observable clinical signs[3].

Our expert panel reached consensus but not unanimity that our approach to incorporating acute symptoms in the ACRM diagnostic criteria would balance over- and under-diagnosis. Similarly, feedback during the stakeholder engagement phase suggested that some respondents viewed the diagnostic criteria as too lenient and others as too stringent. Although imperfect and in need of empirical validation, the handling of the sensitivity/specificity balance in the ACRM diagnostic criteria may be an improvement over prior definitions of mild TBI. The 1993 ACRM definition ambiguously recommended that when evidence of clinical signs is not available, 'it is appropriate to consider symptomatology' to 'suggest the existence' of mild TBI (pg. 86)[1]. The Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health recommend to 'consider TBI as a potential cause' on the basis of symptoms following TBI when clear evidence is not available to establish a diagnosis of TBI[16]. The Concussion in Sport Group's definition[17,24] has been criticized as having an unacceptably high false positive rate because the presence of any symptom (e.g., headache) may be interpreted as sufficient for diagnosis[25].

Clinical Examination and Laboratory Findings (Criterion 4)

The ACRM diagnostic criteria incorporate clinical examination and laboratory findings for the first time, based on expert ratings of their diagnostic importance[3] and the Working Group's rapid evidence reviews (see the evidence summary for Evidence Statements #6, 7, 8, and 9, online supplementary material). These examination findings include objectively measured cognitive impairment, balance impairment, oculomotor impairment, or symptom provocation in response to vestibular-oculomotor challenge on acute clinical examination. Elevated blood biomarkers indicative of intracranial injury are included based on emerging evidence that they not only may help triage for head computed tomography use, but might also help identify individuals with mild TBI regardless of whether computed tomography is performed.

The ACRM diagnostic criteria do not name specific tests, neuroimaging sequences, or blood-based biomarkers to avoid the criteria becoming obsolete with emerging research evidence or advances in technology. This approach has been used in diagnostic criteria for other health conditions[e.g.,26]. We found some limited evidence for the blood-based biomarker glial fibrillary acidic protein (see Evidence Statement #9, online supplementary material), but optimal cut-off scores and timing of blood collection have not yet been established.

Available clinical examination and laboratory findings have imperfect sensitivity and specificity. So, in the ACRM diagnostic criteria, they cannot definitively rule in mild TBI but can raise diagnostic certainty for mild TBI in the context of a plausible mechanism of injury (Criterion 1) and acute symptoms (Criterion 3). Algorithms that combine symptoms with laboratory and clinical examination findings may optimize diagnostic accuracy[27]. In patients who do not report acute symptoms, the presence of two or more clinical examination/laboratory findings (Criterion 4) should raise suspicion for mild TBI (see Figure 2).

Neuroimaging (Criterion 5)

Neuroimaging is not required to diagnose mild TBI using the ACRM diagnostic criteria. However, when computed tomography or structural magnetic resonance imaging is completed and reveals a trauma-related intracranial abnormality, it is sufficient to diagnose TBI. This aligns with some prior definitions[16,20]. Most people with mild TBI will have negative neuroimaging[28,29]. Magnetic resonance imaging is more sensitive than computed tomography in mild TBI[30]. The ACRM diagnostic criteria suggest using the qualifier 'with neuroimaging evidence of structural intracranial injury' when computed tomography or structural magnetic resonance imaging is performed and is positive. Historically, mild TBI 'with neuroimaging evidence of structural intracranial injury" has been referred to as 'complicated' mild TBI[31,32].

Upper Threshold for 'Mild' TBI

Traditional clinical indicators of severity such as the duration of loss of consciousness to differentiate between mild and moderate-severe TBI were retained from prior definitions of mild TBI[1,15-17]. Although this upper threshold for 'mild' TBI was identified as problematic, it was not targeted for revision because efforts to replace it with a more granular severity grading system based on multidimensional biomarkers are currently underway[33,34] but not yet available. We hope and expect that these efforts will eventually produce a replacement for the traditional mild-moderate-severe TBI severity classification scheme, and the ACRM diagnostic criteria can endure as diagnostic criteria for the lower threshold of TBI, without the 'mild' qualifier. Some diagnostic criteria, such as the Veterans Administration/Department of Defense criteria[18], reclassify an otherwise 'mild' TBI as moderate or severe TBI when there are positive findings on conventional neuroimaging. In contrast, the ACRM diagnostic criteria recommend adding a qualifier (see previous section) but retaining the mild TBI classification. This approach recognizes heterogeneity within the mild TBI diagnostic group[35], is in keeping with the largest mild TBI cohort studies over the past five years[36,37], and will enable consistent diagnostic classification as technological advancements continue to enhance the sensitivity of magnetic resonance imaging.

'Concussion' versus 'Mild TBI' Terminology

The ACRM diagnostic criteria consider a concussion to be a mild TBI. There has been longstanding debate over the appropriate terminology for injuries at the milder end of the TBI spectrum[4,38-40]. This debate has largely centered on whether concussion is a subset of mild TBI or whether concussion and mild TBI are synonyms for the same entity. Contemporary definitions of concussion have specifically excluded macrostructural lesions visible on computed topography[17,41].

For the terminology question in the third round of Delphi voting, 30 of 32 (93.8%) expert panel members agreed that "the diagnostic label 'concussion' may be used interchangeably with 'mild TBI' when neuroimaging is normal or not clinically indicated." Individuals and organizations completing the stakeholder survey also favored this statement (see online supplementary material). This is in keeping with the historical use of the term 'concussion' to refer to a physiological disruption of brain function (*commotio cerebri*) with the possibility of microstructural brain injury[40].

Suspected Mild TBI and Implications for Research and Clinical Practice

The ACRM diagnostic criteria operationalize criteria for 'suspected' mild TBI when brain injury is considered a possible or probable explanation for signs and/or symptoms following a plausible mechanism of TBI, but diagnostic certainty is lowered by the subtlety of the clinical presentation, missing information, or prominent confounding factors. The diagnosis of mild TBI often rests on subtle and transient clinical signs and symptoms in the presence of potentially confounding factors (e.g., acute traumatic stress or cervical injury) and without the opportunity for acute medical evaluation. In other cases, in-hospital evaluation for mild TBI with polytrauma may be complicated by sedation for pain or mechanical ventilation. Diagnostic uncertainty, in some cases, is simply a reality of clinical practice. When a patient meets criteria for suspected mild TBI, determination of whether mild TBI is possible versus probable requires clinical judgement and consideration of all the available evidence. The expert panel endorsed this probabilistic framework to address the continuum of diagnostic certainty for mild TBI[3,42-44], such as diagnostic criteria for other health conditions where laboratory confirmation is not possible or feasible[e.g.,45].

A suspected mild TBI identified in the first few days following injury, according to the ACRM diagnostic criteria, means that mild TBI can be considered to have occurred, and so should be clinically managed as such. In other words, a person with suspected mild TBI usually should be treated as if they had a mild TBI[42]. For example, an athlete or military service member with suspected mild TBI should be immediately removed from play or training and required to complete a progressive return to activity protocol[17,46]. This approach mitigates potential consequences of a false negative diagnosis (e.g., experiencing another mild TBI during the period of clinical recovery). In this way, the new ACRM diagnostic criteria are consistent with the 'when in doubt, sit them out' mantra.

Following an initial suspected mild TBI, additional information or examination findings (e.g., impaired cognitive testing in a clinic visit the day after injury; Criterion 4) could increase the certainty of a mild TBI diagnosis but would not necessarily change the clinical management plan (because the person would already be in the process of being managed as having sustained a mild TBI). Alternatively, new evidence (e.g., an athlete's symptom onset and resolution better coincide with their hydration status[42,47] or a cervical strain) may suggest that mild TBI is less likely and clinical management for this condition unnecessary.

Researchers can maximize generalizability by including participants with suspected mild TBI. Natural history or epidemiological surveillance studies, for example, would be well suited to this inclusive approach. On the other hand, certain research endeavors, such as biomarker discovery, may prioritize internal validity by excluding participants with suspected mild TBI or examining them separately from a group with definite mild TBI, to avoid underestimating biomarker

548 performance because of false positives in the mild TBI group. In this way, the ACRM diagnostic
549 criteria could strengthen scientific rigor in mild TBI research.
550
551 **Diagnostic Evaluations Conducted After the Acute Stage**
552
553 Applying the ACRM diagnostic criteria will be most straightforward in an acute medical
554 evaluation. Commonly, however, the clinician or researcher is conducting a post-acute
555 evaluation without details about the injury event and without acute signs and symptoms
556 documented in acute care medical records. Criteria 1, 2, and 3 can be established retrospectively,
557 such as through a detailed history taking of the remote injury event, considering possible recall
558 bias[48,49], response bias[50,51], and confounding factors[2] (Criterion 6). Because most currently
559 available cognitive, balance, oculomotor tests, and blood-based biomarkers lose their diagnostic
560 accuracy by 72 hours following injury, Criterion 4 usually cannot be established in a post-acute
561 assessment. Moreover, most patients with mild TBI presenting for post-acute clinical care will
562 not require structural neuroimaging (Criterion 5)—and if performed it will likely be normal[29] and
563 therefore be diagnostically unhelpful. Therefore, diagnosing mild TBI in a post-acute evaluation
564 relies heavily on the accuracy of a person's retrospective recollection about the injury event and
565 their experience of acute signs and symptoms. As such, there is a risk for both false positive and
566 false negative diagnoses depending upon how accurately the diagnostic criteria can be applied.
567
568 **Diagnosis vs. Clinical Outcome**
569
570 These criteria are intended for diagnosis in clinical practice and case identification in research.
571 The criteria do not address clinical outcome. A person who sustains a mild TBI might recover,
572 from a clinical perspective, on the day of injury, within days or weeks, or have symptoms that
573 persist for a prolonged period of time. Delays in seeking medical attention and receiving a
574 diagnosis of mild TBI might be associated with prolonged recovery[52].
575
576 **Future Directions**
577
578 Poor agreement between assessors on the diagnosis of mild TBI[53,54] is probably due not only to
579 assessors using different case definitions (if any) but also to variability in how they apply the
580 same definition. A structured interview with scripted questions and standardized response coding
581 for the ACRM diagnostic criteria could optimize inter-rater reliability. Structured interviews for
582 diagnosing mild TBI have been successfully developed[55-57] and may only require minor
583 modifications to align with the new ACRM diagnostic criteria before validation studies. Study of
584 the inter-rater reliability of the ACRM diagnostic criteria to identify mild TBI cases from
585 medical records (i.e., no direct interaction with the patient) also will be important. Additional
586 recommendations about how to optimize the definition for case ascertainment from medical
587 records may be beneficial[15,44]. Finally, research is needed to assess the validity of the distinction
588 between diagnosed versus suspected mild TBIs.
589
590 Ongoing communication with professional organizations involved in mild TBI clinical practice
591 guideline and care pathway development can support widespread uptake of the ACRM
592 diagnostic criteria. Our collaboration with the Concussion in Sport Group[58] has been one such
593 example. Additional targeted knowledge translation efforts will likely also be necessary.
594 Processes and activities used to facilitate uptake will be guided by knowledge translation goals,
595 identification of the audience, and leveraging strategies, expertise, and resources described
596 below[59]. The goals of knowledge translation are to promote awareness of the new ACRM

diagnostic criteria, promote changes in clinical practice, inform changes in policy and health system practices (e.g., referral criteria, admission criteria, funding and insurance criteria, etc.), and improve future research. The target audience for this work are healthcare professionals who diagnose mild TBI, healthcare administrators who make decisions on how mild TBI care is delivered and to whom, and researchers in the field of TBI.

We will pursue our knowledge translation goals through a combination of diffusion, dissemination, and application strategies[60]. Diffusion strategies will include peer-reviewed publications, presentations at scientific conferences, and professional magazines targeting healthcare professionals[61]. Dissemination strategies will include the development of tailored written education materials and targeted social media posts. Finally, application strategies will focus on monitoring of knowledge use amongst healthcare professionals (e.g., with surveys) and researchers (e.g., new studies using the ACRM diagnostic criteria as an inclusion criterion). Both the Mild TBI Task Force of the ACRM Brain Injury Special Interest Group and the international, interdisciplinary expert panel engaged in the present initiative will contribute expertise to this knowledge translation plan. Resources for planned knowledge translation activities will be sought from the ACRM and external funding agencies, charitable organizations, and professional associations.

Limitations

The new ACRM diagnostic criteria are evidence-based in that they incorporate the best available research evidence. However, high quality evidence to guide certain Working Group decisions was limited. For example, most studies examining the diagnostic validity of individual symptoms and examination procedures compared people with mild TBI to uninjured controls rather than people being evaluated for possible mild TBI, which is required of Class I studies[12]. The Delphi method addressed such uncertainties with expert consensus. Another limitation of the evidence base related to diagnosis of mild TBI is that much of it was conducted at level 1 trauma centers. These emergency departments likely see higher rates of more severe injuries and polytrauma. Extrapolation to other clinical settings (e.g., primary care) may be misleading. When generating evidence summaries for the expert panel to consider, we followed best practices for rapid reviews[11] with one exception – abstracts were screened by a single rater. To reduce the risk of missing important studies, we invited expert panel members to identify additional relevant studies. The focus on this initiative to update the 1993 ACRM definition was on the lower threshold for diagnosis, because 90% of all TBIs are ‘mild’ and there is usually little diagnostic ambiguity in moderate-severe TBI[62]. Multidimensional biomarkers are poised to redefine TBI severity across a continuum[33]. The expert panel members had less than optimal diversity. Several medical and clinical specialties were represented (physical medicine and rehabilitation, neurology, neurosurgery, neuropsychology, emergency medicine, sports medicine, etc.), but not primary care providers, who are a common point of healthcare system entry for people with mild TBI[63]. The majority of the Working Group members self-identified as women but only one in four expert panel members self-identified as women and one-third of expert panel members were from outside of the United States.

Updating the ACRM diagnostic criteria was intended to improve both their sensitivity and specificity. With no independent method for establishing mild TBI, the true risk for misdiagnosis cannot be determined. Clinicians are encouraged to use all information available to them and their clinical judgement to identify and medically manage a case that does not clearly fit the criteria. For example, a witnessed hard blow to the head creates a high ‘pre-test’ odds for TBI

which in a Bayesian-informed clinical decision making framework[64] should lower the strength of evidence necessary to overcome the threshold of suspected TBI. Alternatively, the presence of atypical clinical features may lower diagnostic certainty even if criteria are technically met. Finally, we recognize that applying all aspects of the ACRM diagnostic criteria will not be feasible in all clinical settings. For example, administering a formal cognitive test such as the Standardized Assessment of Concussion may be impractical in a primary care visit, blood-based biomarker tests are not yet accessible in most emergency departments, and video review evidence of not taking protective action on falling after impact will not be available outside of elite sport settings. Having data on all components of the ACRM diagnostic criteria is not necessary to diagnose mild TBI.

Conclusions

Through an iterative Delphi process, new diagnostic criteria for mild TBI achieved consensus from an international, interdisciplinary expert panel. These diagnostic criteria are designed for use across the lifespan and in civilian trauma, sports, and military settings. As such, they could standardize detection of mild TBI in any context, improving equitable access to clinical care and harmonizing research. As science continues to improve our understanding of mild TBI pathophysiology, clinical presentation, and diagnostic test performance, the diagnostic criteria will need to undergo review and updating.

Disclaimer

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Figure Legends

Figure 1: Gantt Chart of Major Activities and Timelines.

Figure Note: ACRM = American Congress of Rehabilitation Medicine

Figure 2: Visual Representation of the American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury.

Figure Note: See Box 1 for the diagnostic criteria and Box 2 for the definitions and explanatory notes. The qualifier mild TBI 'with neuroimaging evidence of structural intracranial injury' may be used when computed tomography or magnetic resonance imaging reveals a trauma-related intracranial abnormality. A suspected mild TBI is represented by the dashed lines.

Criterion 1:
Mechanism of Injury
(plausible)

Criterion 2:
Clinical Signs
(1 or more)

Criterion 3:
Acute Symptoms
(2 or more)

+

Criterion 4:
Clinical Examination
& Laboratory Findings
(1 or more)

Criterion 5:
Neuroimaging
Abnormality
(if completed)

Does not meet other criteria sufficient for diagnosing TBI, but has:

2 or more acute symptoms
or
2 or more clinical
or laboratory findings

Unclear

Criterion 6:
Not better accounted for
by confounding factors

Suspected

Mild TBI

The 'Mild' qualifier is not used if any of the injury severity indicators listed below are present.

- Loss of consciousness duration greater than 30 minutes.
- After 30 minutes, a Glasgow Coma Scale (GCS) score of less than 13.
- Post traumatic amnesia greater than 24 hours.

Online Supplementary Material

The American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury

Table of Contents

Comparing the 1993 ACRM Definition with the New ACRM Diagnostic Criteria

American Congress of Rehabilitation Medicine (1993) Definition of Mild Traumatic Brain Injury.

A traumatically induced physiological disruption of brain function, as manifested by at least one of the following:

1. any loss of consciousness;
2. any loss of memory for events immediately before or after the accident;
3. any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and
4. focal neurological deficit(s) that may or may not be transient;

but where the severity of the injury does not exceed the following:

- loss of consciousness of approximately 30 minutes or less;
- after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13-15; and
- posttraumatic amnesia (PTA) not greater than 24 hours.

Reprinted from: Kay T, Harrington DE, Adams R, Anderson T, Berrol S, Cicerone K, Dahlberg C, Gerber D, Goka R, Harley P, Hilt J, Horn L, Lehmkuhl D, Malec J. Definition of mild traumatic brain injury. Journal of Head Trauma Rehabilitation. 1993;8(3):86–87.

American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury

Box 1. American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury.

Mild traumatic brain injury (TBI) is diagnosed when, following a biomechanically plausible mechanism of injury (Criterion 1) *one or more* of the criteria (i-iii) listed below are met. i. One or more clinical signs (Criterion 2) attributable to brain injury. ii. At least two acute symptoms (Criterion 3) and at least one clinical or laboratory finding (Criterion 4) attributable to brain injury. iii. Neuroimaging evidence of TBI, such as unambiguous trauma-related intracranial abnormalities on computed tomography or structural magnetic resonance imaging (Criterion 5). Confounding factors do not fully account for the clinical signs (Criterion 2), acute symptoms (Criterion 3), and clinical examination and laboratory findings (Criterion 4) that are necessary for the diagnosis (Criterion 6).
Mild Qualifier: The 'mild' qualifier is not used if any of the injury severity indicators listed below are present. Instead, traumatic brain injury (TBI) is diagnosed (without the 'mild' qualifier). i. Loss of consciousness duration greater than 30 minutes. ii. After 30 minutes, a Glasgow Coma Scale (GCS) of less than 13. iii. Post-traumatic amnesia greater than 24 hours.
Neuroimaging Qualifier: If neuroimaging is abnormal (Criterion 5), the qualifier mild TBI 'with neuroimaging evidence of structural intracranial injury' may be used. When neuroimaging is completed and found to be normal, the qualifier mild TBI 'without neuroimaging evidence of structural intracranial injury' may be used. If neuroimaging is not completed, no qualifier is used.
Concussion: The diagnostic label 'concussion' may be used interchangeably with 'mild TBI' when neuroimaging is normal or not clinically indicated.
Suspected Mild TBI: A mild TBI is suspected when, following a biomechanically plausible mechanism of injury (Criterion 1), one or more of the three criteria listed below are met. i. At least two acute symptoms (Criterion 3) and the person does not meet other criteria sufficient for diagnosing mild TBI. ii. At least two clinical examination or laboratory findings (Criterion 4) but the person does not meet other criteria for diagnosing mild TBI. iii. It is unclear whether signs (Criterion 2), acute symptoms (Criterion 3), and available clinical or laboratory findings (Criterion 4) are accounted for by confounding factors (i.e., it is unclear if Criterion 6 is met).
See Box 2 for definitions and explanatory notes.

Box 2. Definitions, Explanatory Notes, and Qualifiers for the American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury.

Criterion 1: Mechanism of Injury
Traumatic brain injury (TBI) results from a transfer of mechanical energy to the brain from external forces resulting from the (i) head being struck with an object, (ii) head striking a hard object or surface, (iii) brain undergoing an acceleration/deceleration movement without direct contact between the head and an object or surface, and/or (iv) forces generated from a blast or explosion.

Notes: Criterion 1 can be met by direct observation (in person or video review) or collateral (witness) report of the injury event, review of acute care records, or the person's recount of the injury event during an interview.

Criterion 2: Clinical Signs
The injury event causes an acute physiological disruption of brain function, as manifested by *one or more* of the clinical signs listed below.

i. Loss of consciousness immediately following injury (e.g., no protective action taken on falling after impact or lying motionless and unresponsive).

ii. Alteration of mental status immediately following the injury (or upon regaining consciousness), evidenced by reduced responsiveness or inappropriate responses to external stimuli; slowness to respond to questions or instructions; agitated behavior; inability to follow two-part commands; or disorientation to time, place, or situation.

iii. Complete or partial amnesia for events immediately following the injury (or after regaining consciousness). If post-traumatic amnesia cannot be reliably assessed (e.g., due to polytrauma or sedating analgesics), retrograde amnesia (i.e., a gap in memory for events immediately preceding the injury) can be used as a replacement for this criterion.

iv. Other acute neurological sign(s) (e.g., observed motor incoordination upon standing, seizure, or tonic posturing immediately following injury).

Notes: Criterion 2 can be met by direct observation (in person or video review), collateral (witness) report, review of acute care records, or when none of these are available, the person's recount of the injury event.

Criterion 3: Acute Symptoms
The physiological disruption of brain function is manifested by *two or more* new or worsened symptoms from the list below.

i. Acute subjective alteration in mental status: feeling confused, feeling disoriented, and/or feeling dazed.

ii. Physical symptoms: headache, nausea, dizziness, balance problems, vision problems, sensitivity to light, and/or sensitivity to noise.

iii. Cognitive symptoms: feeling slowed down, "mental fog," difficulty concentrating, and/or memory problems.

iv. Emotional symptoms: uncharacteristic emotional lability and/or irritability.

The symptoms may be from one or more categories (i.e., experiencing two symptoms within a single category is sufficient). Other symptoms may be present, but they should not be counted towards Criterion 3. The onset of acute subjective alteration in mental status occurs immediately following the impact or after regaining consciousness. The onset of other symptoms (physical, cognitive, and emotional) may be delayed by a few hours, but they nearly always appear less than 72 hours from injury.

Notes: Criterion 3 can be met by (i) review of acute care documentation of the injured person's acute symptoms, (ii) interviewing the injured person about the first few days following injury; (iii) having the injured person complete a self-report rating scale documenting symptoms during the first few days following injury; or (iv) collateral observation for an individual who cannot accurately report symptoms due to developmental stage (e.g., children under 5 years old) or pre-injury disability.

Criterion 4: Clinical Examination and Laboratory Findings

The assessment findings listed below can also provide supportive evidence of brain injury.

i. Cognitive impairment on acute clinical examination.

ii. Balance impairment on acute clinical examination.

iii. Oculomotor impairment or symptom provocation in response to vestibular-oculomotor challenge on acute clinical examination.

iv. Elevated blood biomarker(s) indicative of intracranial injury.

Notes: Clinical and laboratory tests that meet standards of reliability and diagnostic accuracy should be considered for Criterion 4. Impairment in Criterion 4i-iii is defined as a clinically meaningful discrepancy between post-injury test performance and age-appropriate normative reference data, or where available, pre-injury test performance. The diagnostic sensitivity of most clinical and laboratory tests decreases over the first 72 hours following injury and the rate of sensitivity decline differs between specific tests.

Criterion 5: Neuroimaging

Trauma-related intracranial abnormalities on computed tomography or structural magnetic resonance imaging.

Notes: Neuroimaging is not necessary to diagnose mild TBI. Its primary clinical role is to rule out head and brain injuries that might require neurosurgical or other medical intervention in an acute care setting. When obtained, neuroimaging may reveal intracranial abnormalities indicative of TBI such as contusion(s) or intracranial hemorrhage.

Criterion 6: Not better accounted for by confounding factors

Confounding factors, including pre-existing and co-occurring health conditions, have been considered and determined to not fully account for the clinical signs, acute symptoms, and clinical examination and laboratory findings that are necessary for the diagnosis.

Notes: A clinical sign only qualifies for Criterion 2 when it is not better accounted for by acute musculoskeletal pain, psychological trauma, alcohol or substance intoxication, pulmonary or circulatory disruption, syncope prior to fall, or other confounding factors. Symptoms should only be counted towards Criterion 3 when they are not better accounted for by drug, alcohol, or medication use; co-occurring physical injuries (e.g., musculoskeletal injury involving the neck or peripheral vestibular dysfunction) or psychological conditions (e.g., an acute stress reaction to trauma); pre-existing health conditions; or symptom exaggeration. Criterion 4 findings must not be better accounted for by drug, alcohol, or medication use; co-occurring physical injuries or psychological conditions; pre-existing health conditions; or factors influencing the validity of the symptom reporting or test results.

General Notes: Consideration should be given to cultural and linguistic differences in symptom reporting and test performance. Caution is warranted when applying the diagnostic criteria for mild TBI to young children and individuals with pre-injury cognitive and/or communication impairments. Due to developmental stage (e.g., children under 5 years old) or pre-injury disability, an individual may not be able to accurately report symptoms in Criterion 3; thus, this criterion could be met based on proxy report or observation of related behaviors (e.g., changes in appetite or behaving out of character). An injured person's behavior should also be interpreted in the context of their developmental stage and pre-injury functioning. Clinical and laboratory test interpretation requires age-appropriate scales and/or cut-off scores.

Figure 2. Visual Representation of the American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury.

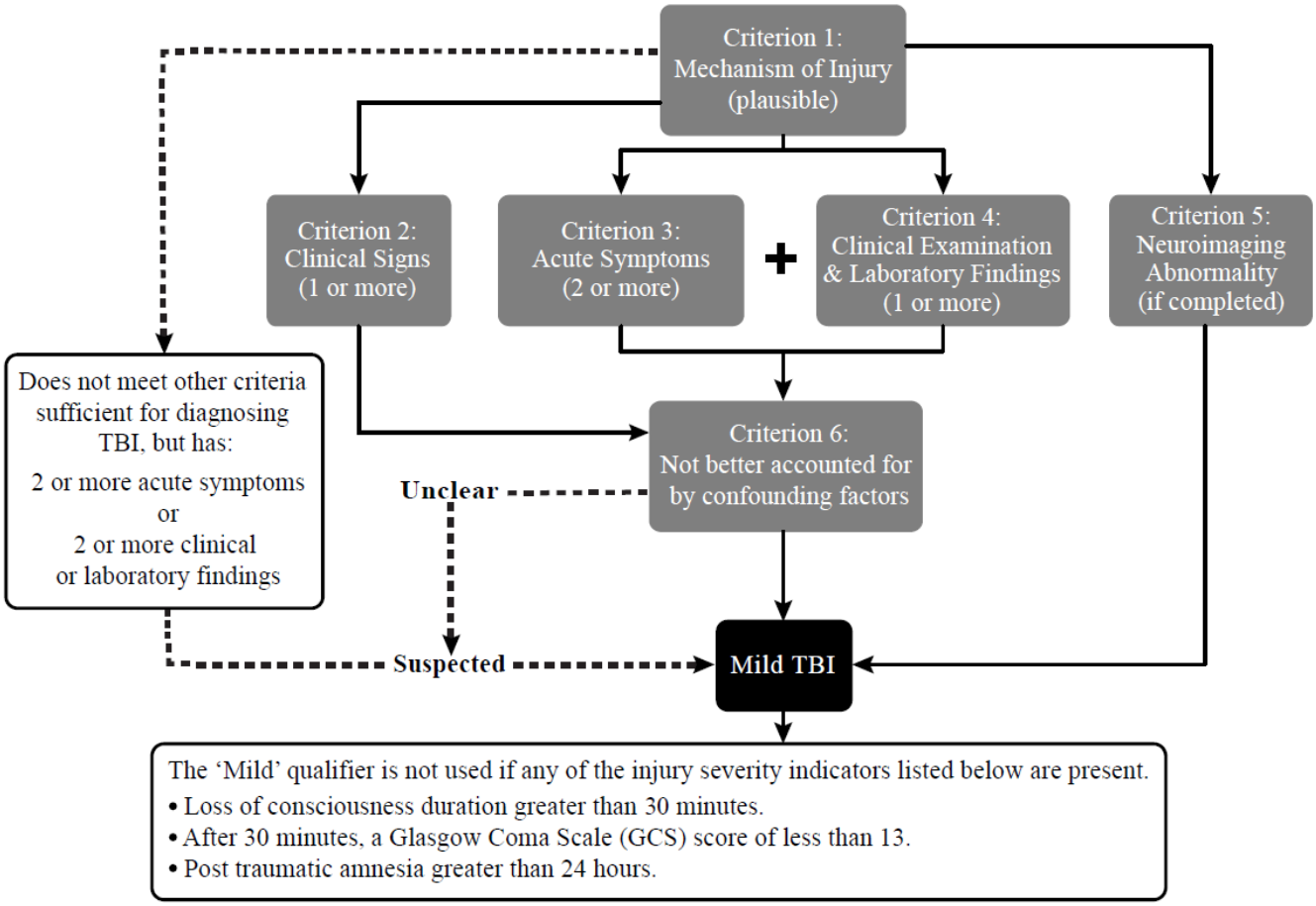

Figure Note: See Box 1 for the diagnostic criteria and Box 2 for the definitions and explanatory notes. The qualifier mild TBI 'with neuroimaging evidence of structural intracranial injury' may be used when computed tomography or magnetic resonance imaging reveals a trauma-related intracranial abnormality. A suspected mild TBI is represented by the dashed lines.

Overview of the Methodology for Developing the New Diagnostic Criteria

An overview of the preliminary steps and the Delphi expert consensus process is shown in Figure 1.

Figure 1. Gantt Chart of Major Activities and Timelines.

Activities	**2019**		**2020**		**2021**		**2022**	
Expert panel members rated the diagnostic importance of signs, symptoms, and examination findings[3].								
Working Group members conducted rapid evidence reviews to create evidence statements and associated evidence summaries.								
The Working Group drafted Version 1.0 of diagnostic criteria based on the diagnostic importance survey[3] and rapid evidence reviews.								
Delphi Round 1: Expert panel members voted on the evidence statements and Version 1.0 of the diagnostic criteria.								
The Working Group revised the diagnostic criteria (Version 1.0) to incorporate qualitative feedback from expert panel members.								
Delphi Round 2: Expert panel members voted on revised evidence statements and Version 2.0 of the diagnostic criteria.								
The Working Group revised the diagnostic criteria (Version 2.0) to incorporate qualitative feedback from expert panel members.								
ACRM elicited stakeholder feedback on the diagnostic criteria (Version 2.1) and terminology.								
The Working Group incorporated qualitative feedback from the stakeholder survey in a minor revision of the diagnostic criteria.								
Delphi Round 3: Expert panel members voted on Version 2.2 of the diagnostic criteria and the terminology question.								

ACRM = American Congress of Rehabilitation Medicine

Results from the Delphi Process of Three Rounds of Voting on the Diagnostic Criteria for Mild TBI.

Delphi round	Dates	Version of the Diagnostic Criteria	Response rate	Agreement ratings
1	October-December 2020	1.0	100%	Agree without reservations = 18 (54.6%) Agree with minor reservations = 7 (21.2%) Agree with major reservations = 5 (15.2%) Disagree = 3 (9.1%)
2	June-July 2021	2.0	100%	Agree without reservations = 16 (48.5%) Agree with minor reservations = 16 (48.5%) Agree with major reservations = 1 (3.0%) Disagree = 0 (0.0%)
3	July-August 2022	2.2	100%	Agree without reservations = 18 (56.3%) Agree with minor reservations = 11 (34.4%) Agree with major reservations = 1 (3.1%) Disagree = 2 (6.3%)

Evidence Statements Considered by the Expert Panel.

Evidence statement	Agreement ratings	Implication for revision
1. Mild TBI due to blast-related force may have a similar acute clinical presentation (<72 hours) as mild TBI due to other mechanisms (e.g., a direct blow to the head).	Agree without reservations = 25 (73.5%) Agree with minor reservations = 4 (11.8%) Agree with major reservations = 0 (0.0%) Disagree = 0 (0.0%) I do not have sufficient expertise to evaluate this statement = 5 (14.7%)	Add blast force as a possible mechanism of injury for mild TBI.
2. Retrograde amnesia may rarely occur in the absence of post-traumatic amnesia.	Agree without reservations = 30 (88.2%) Agree with minor reservations = 1 (2.9%) Agree with major reservations = 1 (2.9%) Disagree = 2 (5.9%) I do not have sufficient expertise to evaluate this statement = 0 (0.0%)	Remove retrograde amnesia as a sufficient criterion for diagnosis.
3. Acute symptoms (e.g., dizziness or cognitive problems) following head trauma can reflect the presence of acute physiological disruption of brain function, even in patients who did not have a loss of consciousness or post-traumatic amnesia.	Agree without reservations = 30 (88.2%) Agree with minor reservations = 2 (5.9%) Agree with major reservations = 2 (5.9%) Disagree = 0 (0.0%) I do not have sufficient expertise to evaluate this statement = 0 (0.0%)	Add a pathway to diagnosis for when clinical signs of brain injury are absent.
4. Acute headache is very common after mild TBI but is also common in patients who sustain an injury to the head or neck but do not experience a TBI.	Agree without reservations = 34 (100%) Agree with minor reservations = 0 (0.0%) Agree with major reservations = 0 (0.0%) Disagree = 0 (0.0%) I do not have sufficient expertise to evaluate this statement = 0 (0.0%)	Consider omitting headache from the diagnostic criteria.
5. Acute post-injury anxiety is non-specific, occurring in patients with mild TBI and in those with traumatic bodily injuries. Acute anxiety can also reflect traumatic stress and/or pre-injury mental health difficulties.	Agree without reservations = 32 (94.1%) Agree with minor reservations = 1 (2.9%) Agree with major reservations = 1 (2.9%) Disagree = 0 (0.0%) I do not have sufficient expertise to evaluate this statement = 0 (0.0%)	Consider omitting anxiety from the diagnostic criteria.

Evidence statement	Agreement ratings	Implication for revision
6. There is insufficient evidence regarding the sensitivity and specificity of other acute symptoms for differentiating patients with mild TBI and those with traumatic bodily injuries.	Agree without reservations = 26 (76.5%) Agree with minor reservations = 6 (17.7%) Agree with major reservations = 1 (2.9%) Disagree = 1 (2.9%) I do not have sufficient expertise to evaluate this statement = 0 (0.0%)	Symptoms alone should not be sufficient for diagnosis.
7. Based on evidence from video review studies in sports, the following observable signs may be associated with a clinical diagnosis of mild TBI: no protective action taken on falling, impact seizure (including tonic posturing), lying motionless/unresponsive, motor incoordination, and a blank/vacant stare.	Agree without reservations = 28 (82.4%) Agree with minor reservations = 6 (17.7%) Agree with major reservations = 0 (0.0%) Disagree = 0 (0.0%) I do not have sufficient expertise to evaluate this statement = 0 (0.0%)	Incorporate 'no protective action taken on falling' and 'lying motionless and unresponsive' to the operational definition of loss of consciousness. Incorporate impact seizure and motor incoordination as clinical signs. Incorporate blank/vacant stare into the operational definition of altered mental status.
8. Impairment on standardized balance testing within the first 24 hours post injury is associated with a clinical diagnosis of mild TBI. However, pre-existing and comorbid conditions can also affect balance performance.	Agree without reservations = 32 (94.1%) Agree with minor reservations = 2 (5.9%) Agree with major reservations = 0 (0.0%) Disagree = 0 (0.0%) I do not have sufficient expertise to evaluate this statement = 0 (0.0%)	Add acute balance impairment as a diagnostic criterion that is neither necessary nor sufficient.
9. Impairment on standardized cognitive testing within the first 72 hours post injury is associated with a clinical diagnosis of mild TBI. However, pre-existing and comorbid conditions can also affect cognitive performance.	Agree without reservations = 31 (91.2%) Agree with minor reservations = 3 (8.8%) Agree with major reservations = 0 (0.0%) Disagree = 0 (0.0%) I do not have sufficient expertise to evaluate this statement = 0 (0.0%)	Add acute cognitive impairment as a diagnostic criterion that is neither necessary nor sufficient.

Evidence statement	Agreement ratings	Implication for revision
10. Impairment on oculomotor testing and symptom provocation during vestibular-oculomotor challenge within the first 24 hours post injury may be associated with a clinical diagnosis of mild TBI. However, pre-existing conditions and other factors can also account for these test findings.	Agree without reservations = 32 (94.1%) Agree with minor reservations = 2 (5.9%) Agree with major reservations = 0 (0.0%) Disagree = 0 (0.0%) I do not have sufficient expertise to evaluate this statement = 0 (0.0%)	Add acute oculomotor impairment as a diagnostic criterion that is neither necessary nor sufficient.
11. For adults, elevated glial fibrillary acidic protein (GFAP) in the blood on the day of injury is associated with intracranial abnormalities on neuroimaging after mild TBI and may also be more likely after a mild TBI without intracranial abnormalities visible on computed tomography compared to a traumatic bodily injury. There is currently insufficient evidence to suggest that other blood biomarkers can differentiate between mild TBI (without intracranial abnormalities visible on computed tomography) compared to a traumatic bodily injury.	Agree without reservations = 22 (64.7%) Agree with minor reservations = 7 (21.2%) Agree with major reservations = 2 (6.9%) Disagree = 1 (2.9%) I do not have sufficient expertise to evaluate this statement = 1 (2.9%) Missing = 1 (2.9%)	Add elevated blood biomarker(s) as a diagnostic criterion that is neither necessary nor sufficient.
12. Persistent symptom reporting in the weeks to months after mild TBI is strongly influenced by premorbid and comorbid factors.	Agree without reservations = 28 (82.4%) Agree with minor reservations = 3 (8.8%) Agree with major reservations = 2 (5.9%) Disagree = 0 (0.0%) I do not have sufficient expertise to evaluate this statement = 0 (0.0%) Missing = 1 (2.9%)	Specify time frame of symptom onset and assessment.

Note: 'Associated with,' in this context, refers to a statistically significant relationship. When present, the variable may increase diagnostic certainty, but it should not be considered a pathognomonic diagnostic sign.

Expert Panel Members' Reservations and Reasons for Disagreement with Version 2.2 of the Updated Diagnostic Criteria.

Type	Paraphrased comments (Agreement Rating)
Formatting	Replace "at least one" with "one or more" to align with "two or more" phrasing elsewhere (Minor Reservations)
	Replace roman numerals with letters (Minor Reservations)
	Move the neuroimaging qualifier after the mild qualifier (Minor Reservations)
	Move the "mild qualifier" earlier (Major Reservations)
	The specific clinical signs should be written out in the diagnostic criteria (Minor Reservations)
	The diagnostic criteria should not be separated from the operational definitions of those criteria (Disagree)
Wording	Replace "unambiguous" with "radiologically confirmed" trauma-related abnormalities on neuroimaging (Minor Reservations)
	Unclear if "suspected" means probable, as in greater than 50% likelihood (Minor Reservations)
	"Mild" may imply that persistent symptoms, impairments, and disability are rare (Minor Reservations)
	Loss of consciousness of greater than 30 minutes is redundant with GCS of less than 13 after 30 minutes (Minor Reservations)
Criterion 1 (Mechanism of injury)	Penetrating brain injury should be incorporated or explicitly excluded as a mechanism of injury (Minor Reservations)
Criterion 2 (Clinical signs)	Omit slowness to respond and require two or more clinical signs to increase the specificity of this criterion (Minor Reservations)
Criterion 3 (Acute symptoms)	Require two or more symptoms from different categories (Minor Reservations)
	Confusion/disorientation should always be required (Minor Reservations)
	One or more symptoms of altered mental status should always be required (Disagree)
Criterion 4 (Associated findings)	There may be insufficient research evidence for vestibulo-oculomotor abnormalities, in combination with a plausible mechanism of injury (but no signs or symptoms), to rule in a diagnosis (Minor Reservations)
	Exercise intolerance should be added a clinical and laboratory finding (Minor Reservations)
	There is insufficient research evidence for the positive predictive value of any specific blood-based biomarker (Minor Reservations)
Criterion 5 (Neuroimaging)	Add an upper threshold for the types of neuroimaging findings (e.g., midline shift or herniation should not be considered "mild") (Major Reservations)
Miscellaneous	Unclear classification of "complicated" mild TBI (Minor Reservations)
	Onset of loss of consciousness may occur after initial lucid period (Minor Reservations)

Examples of Meeting Criteria for Mild Traumatic Brain Injury.

Criterion 2: Clinical Sign(s)	Criterion 3: Acute Symptoms (2 or more)	Criterion 4: Clinical or Laboratory Finding	Criterion 5: Positive Neuroimaging	Not Better Accounted for by Confounding Factor(s)	Diagnosed Mild TBI
Yes	Yes	Yes	Yes	Yes	Yes
Yes	Yes	Yes	No/ND	Yes	Yes
Yes	Yes	No/ND	No/ND	Yes	Yes
Yes	No/ND	Yes	No/ND	Yes	Yes
Yes	No/ND	No/ND	No/ND	Yes	Yes
No/ND	Yes	Yes	Yes	Yes	Yes
No/ND	Yes	Yes	No/ND	Yes	Yes
No/ND	Yes	No/ND	Yes	Yes	Yes
No/ND	No/ND	Yes	Yes	Yes	Yes
No/ND	No/ND	No/ND	Yes	Yes	Yes
No/ND	Yes	No/ND	No/ND	Yes	Suspected
No/ND	No/ND	Yes (2 findings)	No/ND	Yes	Suspected
No/ND	Yes	No/ND	No/ND	Unclear	Suspected
Yes	Yes	Yes	No/ND	Unclear	Suspected
Yes	Yes	No/ND	No/ND	Unclear	Suspected
Yes	No/ND	Yes	No/ND	Unclear	Suspected
Yes	No/ND	No/ND	No/ND	Unclear	Suspected
No/ND	Yes	Yes	No/ND	Unclear	Suspected

Note: Criterion 1, a plausible mechanism, is assumed to be present. ND=not documented. An injury is not considered ‘mild’ if loss of consciousness duration is greater than 30 minutes, after 30 minutes, there is a Glasgow Coma Scale (GCS) of less than 13, or post-traumatic amnesia is greater than 24 hours. If it is unclear whether signs (Criterion 2), acute symptoms (Criterion 3), and clinical or laboratory findings (Criterion 4) that are present are accounted for by confounding factors, including pre-existing and co-occurring health conditions, then the injury is ‘suspected.

Delphi Survey of Expert Consensus Group: Round 1

Expert Consensus Group survey on the updated ACRM mild TBI case definition

Thank you for serving on our expert panel. We have expanded the panel to include a few new members. You will recall that you completed a survey in the past, and we analyzed the results of that survey, prepared a manuscript, submitted it, and it has now been accepted for publication. We are now ready for the next phase of this project.

This next phase will require more of your time than the first survey. For this survey, we think you should plan on spending between 30 minutes and 2 hours. You might realize when reviewing evidence statements that you want to track down some articles for us to include, and thus spending some time looking for literature might take you beyond 2 hours of time commitment. Qualtrics will automatically save your responses as you work. If you wish to partially complete the survey and complete it later, the "Save and Continue" will work as long as you return to the survey on the same computer and on the same web browser, and have not cleared your browser cookies.

Similar to the first survey, we intend to prepare the results of this project for publication and to include those who complete the survey, if they wish, as coauthors.

Please complete this survey by November 13, 2020.

Instructions for Part 1: Evidence Statements

In this first section, you will be asked to rate your agreement with 10 evidence statements. The evidence topics address differences between the 1993 ACRM mild TBI case definition and case definitions subsequently published by other groups (WHO, NINDS CDE, VA/DoD, Concussion in Sport Group, etc.). A Working Group from the ACRM Mild TBI Task Force conducted rapid literature reviews to scan for evidence on each topic (see https://training.cochrane.org/resource/introduction-rapid-reviews for a background on this approach). They assessed risk of bias for diagnostic accuracy studies, grading each as Class I (low risk of bias) to Class IV (high risk of bias) according to the American Academy of Neurology (2017) Clinical Practice Guideline Process Manual. The evidence was then summarized in a statement. We provide a description of the evidence, its implications for the updated ACRM case definition, and key citations for your reference, but ask that you only rate your agreement with the evidence statement. If you do "***agree with reservations"*** or "***disagree"*** with a statement, you will be prompted to explain how you would like to see the statement revised.

In addition, to supplement our rapid literature reviews, please suggest any additional citations relevant to an evidence statement that you think we should review.

Evidence Statement #1 of 10: Blast Injury
Mild TBI due to blast force has a similar acute clinical presentation (≤72 hours) as mild TBI due to other mechanisms (e.g., a direct blow to the head).

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

Impact on ACRM case definition: Add blast force as a possible mechanism of injury for mild TBI.

Summary of supporting evidence: Three prospective cohort studies aimed to determine whether people with mild TBI due to blast force have a different acute clinical presentation than people with mild TBI due to blunt trauma. One Class II study1 (N=82) found that blast mechanism was associated with greater likelihood and duration of loss of consciousness (LOC). Although this Class II study[1] found that headaches (83% vs. 52%), balance problems (45% vs 25%), nausea (54% vs 20%), and vomiting (26% vs 8%) were more common after non-blast mild TBI, two other Class II studies[2,3] found no differences in acute symptom presentation (N=80 in Kontos et al.; N=71 in Dretsch et al.). Differences in acute cognitive performance following blast vs. non-blast mTBI were minimal across three Class II studies.[1,2]

Key Citations
1. Luethcke CA, Bryan CJ, Morrow CE, Isler WC. Comparison of concussive symptoms, cognitive performance, and psychological symptoms between acute blast-versus nonblast-induced mild traumatic brain injury. *J Int Neuropsychol Soc.* 2011;17(1):36-45.
2. Kontos AP, Elbin RJ, Kotwal RS, Lutz RH, Kane S, Benson PJ, et al. The effects of combat-related mild traumatic brain injury (mTBI): Does blast mTBI history matter? *J Trauma Acute Care Surg*. 2015;79(4 Suppl 2):S146-151.
3. Dretsch MN, Kelly MP, Coldren RL, Parish RV, Russell ML. No significant acute and subacute differences between blast and blunt concussions across multiple neurocognitive measures and symptoms in deployed soldiers. *J Neurotrauma*. 2015;32(16):1217-1222.

If you wish, provide citations for any additional relevant scientific studies that should be considered for this evidence statement.

_____

Evidence Statement #2 of 10: Retrograde Amnesia
Retrograde amnesia may rarely occur in the absence of post-traumatic amnesia.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

Impact on ACRM case definition: Retrograde amnesia might not be needed as a core diagnostic criterion for TBI. Retrograde amnesia, in the absence of LOC and PTA, is probably uncommon. Retrograde amnesia in the absence of LOC or PTA might reflect syncope or dissociative amnesia. Retrograde amnesia could be used, under certain circumstances, as a substitute for post-traumatic amnesia if post-traumatic amnesia could not be reliably assessed (e.g., in the context of polytrauma and general anesthesia).

Summary of supporting evidence: There is limited evidence on the co-occurrence of retrograde and anterograde amnesia. Two studies are summarized here. Two prospective cohort studies recruited consecutive patients from Emergency Departments (ED) and routinely screened for retrograde amnesia (RTA) with standardized questions. In one Canadian study[4] 48% had RTA but 0% (0 of 119) reported RTA without any post-traumatic amnesia (PTA). This study was downgraded from Class I to Class IV because the same assessor who queried for RTA also made the mild TBI diagnosis, and RTA alone could have qualified a patient for a mild TBI diagnosis. In a Class I study conducted in Finland[5] 24% had RTA but 1.3% (1 of 75) reported RTA without any PTA.

Key Citations
4. Paniak C, MacDonald J, Toller-Lobe G, Durand A, Nagy J. A preliminary normative profile of mild traumatic brain injury diagnostic criteria. *J Clin Exp Neuropsychol*. 1998;20(6):852-855.
5. Luoto TM, Iverson GL, Losoi H, Wäljas M, Tenovuo O, Kataka A, et al. Clinical correlates of retrograde amnesia in mild traumatic brain injury. *Brain Inj*. 2015;29(5):565-572.

If you wish, provide citations for any additional relevant scientific studies that should be considered for this evidence statement.

_____

Evidence Statement #3 of 10: Acute Symptoms Can Reflect Injury
Acute symptoms following head trauma can reflect the presence of acute physiological disruption of brain function, even in patients who did not initially have a loss of consciousness or post-traumatic amnesia.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

Impact on ACRM case definition: Acute post-concussion symptoms should, in some circumstances, raise the probability of a mild TBI diagnosis.

Summary of supporting evidence: None of the studies reviewed below excluded participants/patients on the basis of having LOC or PTA. Moreover, they did not stratify their findings based on the presence or absence of LOC or PTA. The studies reviewed below examined associations between acute symptom reporting and objective measures of brain function in patient samples where the minority of patients had loss of consciousness or post-traumatic amnesia (when such data were reported).

Multiple small neuroimaging studies (mild TBI sample size=12-30) reported correlations between early self-reported symptoms and neurometabolic changes,[6] cerebral hemodynamic disruption,[7] reduced white matter integrity,[8] and altered task-related brain activation, irrespective of LOC or PTA duration.[9,10] These finding suggest an association between subjective symptoms and objective markers of injury severity.

Patients with mild TBI who underwent computerized cognitive testing within one week of injury and were still symptomatic performed worse than patients who reported symptom resolution.[11,12] Other studies show significant associations between self-reported cognitive symptoms in particular and performance on neuropsychological tests. For example, one study of recently concussed athletes (n=110) found that those reporting persistent fogginess had significantly slower reaction times, reduced memory performance, and slower processing speed.[13] Another study of collegiate athletes evaluated within 48 hours of injury found significant associations between self-reported cognitive symptoms and performance on computer-based cognitive tests.[14]

There is also evidence for an association between self-reported symptoms and objective balance deficits. One study of 108 individuals with mTBI showed an association between self-reported headache and balance deficits.[15] Another found significant correlations between objective assessments of postural control and self-report of “dizziness” and “balance problems” in 32 college athletes within 48 hours of mTBI.[14]

Key Citations

6. Henry LC, Tremblay S, Boulanger Y, Ellemberg D, Lassonde M. Neurometabolic changes in the acute phase after sports concussions correlate with symptom severity. *J Neurotrauma*. 2010;27(1):65-76. doi:10.1089/neu.2009.0962
7. Chen J-K, Johnston KM, Collie A, McCrory P, Ptito A. A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. *J Neurol Neurosurg Psychiatry*. 2007;78(11):1231-1238.
8. Mustafi SM, Harezlak J, Koch KM, et al. Acute white-matter abnormalities in sports-related concussion: A diffusion tensor imaging study from the NCAA-DoD CARE consortium. *J Neurotrauma*. 2018;35(22):2653-2664.
9. Chen JK, Johnston KM, Frey S, Petrides M, Worsley K, Ptito A. Functional abnormalities in symptomatic concussed athletes: An fMRI study. *Neuroimage*. 2004;22(1):68-82.
10. Wylie GR, Freeman K, Thomas A, Shpaner M, Okeefe M, Watts R, et al. Cognitive improvement after mild traumatic brain injury measured with functional neuroimaging during the acute period. *PLoS One*. 2015;11(10):e0126110.
11. Collie A, Makdissi M, Maruff P, Bennell K, McCrory P. Cognition in the days following concussion: Comparison of symptomatic versus asymptomatic athletes. *J Neurol Neurosurg Psychiatry*. 2006;77(2):241-245.
12. Fazio VC, Lovell MR, Pardini JE, Collins MW. The relation between post concussion symptoms and neurocognitive performance in concussed athletes. *NeuroRehabilitation*. 2007;22(3):207-216.
13. Iverson GL, Gaetz M, Lovell MR, Collins MW. Relation between subjective fogginess and neuropsychological testing following concussion. *J Int Neuropsychol Soc*. 2004;10(6):904-906.
14. Broglio SP, Sosnoff JJ, Ferrara MS. The relationship of athlete-reported concussion symptoms and objective measures of neurocognitive function and postural control. *Clin J Sport Med*. 2009;19(5):377-382.
15. Register-Mihalik JK, Mihalik JP, Guskiewicz KM. Balance deficits after sports-related concussion in individuals reporting posttraumatic headache. *Neurosurgery*. 2008;63(1):76-80.

If you wish, provide citations for any additional relevant scientific studies that should be considered for this evidence statement.

Evidence Statement #4a of 10: Headache
Acute headache is very common after mild TBI but is also common in patients who sustain an injury to the head or neck but do not experience a TBI.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

Evidence Statement #4b of 10: Anxiety
Anxiety within the first 72 hours of injury is non-specific, occurring at similar rates in patients with mild TBI and those with traumatic injuries below the clavicles. Acute anxiety can also reflect traumatic stress.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

Evidence Statement #4c of 10: Other Acute Symptoms
The sensitivity and specificity of acute post-concussion symptoms, other than headache and anxiety, is not clear.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

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Impact on ACRM case definition: Because no particular symptom or cluster of symptoms has been found to have sufficient diagnostic accuracy, the presence of post-concussion symptoms alone (i.e., without any supporting signs or test findings) should not be used to rule-in a diagnosis of mild TBI.

Summary of supporting evidence: Four studies examined the diagnostic accuracy of symptoms in acute clinical diagnosis of mild TBI. All were conducted in ED settings. A challenge with these studies is that acute symptoms may have been considered in assigning participants to diagnostic groups.

In a Class III study,[16] parents of children (aged 2-12) with acute mild TBI (n=38) or traumatic orthopedic injury (n=46) rated the severity of various symptoms within 72 hours of injury. Severity ratings were dichotomized. Several symptoms were more common in the mild TBI group (e.g., 90% vs. 15% for headache), whereas other symptoms had similar rates in both groups (e.g., 29% vs 22% for anxiety). A similarly designed study[17] with older children (aged 11-18) who sustained a mild TBI (n=39) or orthopedic injury (n=46) also found that higher endorsement rates in the mild TBI group for some symptoms (e.g., 95% vs 11% for headache) and not others (e.g., 26% vs 30% for nervousness), but did not perform statistical testing.

In a Class II study,[18] 108 adult trauma patients were grouped into mild TBI (n= 39), head trauma without mild TBI (n= 16), and orthopedic injury control groups (n= 53). Acute headache was much more likely in the mild TBI (95% CI for odds ratio = 5.1-267.3) and head trauma groups (95% CI for odds ratio = 6.4-1047.1) compared to the orthopedic injury group, but no more common in the mild TBI vs. head injury groups (95% CI for odds ratio = 0.15-32.0). This same pattern was found for self-reported concentration difficulty. Anxiety was no higher in the mild TBI vs. other groups.

A Class III study[19] examined 118 patients with mild TBI (severe enough to order a head CT) vs 46 orthopedic injury controls vs 98 healthy controls. Participants with mild TBI were more likely to report headache (81.8-85.7%) or pressure in the head (62.1-83.3%) than both control groups (22.2-24.3% for orthopedic injury controls and 16.0-16.7% for healthy controls). Rates of feeling “slowed down” and

"fatigue/low energy" did not differ between patients with mild TBI vs. orthopedic injury.

In a Class III study,[20] 348 children aged 6-18 years (183 orthopedic injury controls, 66 head trauma cases without altered mental status (AMS) and 99 head trauma cases with AMS) completed a post-concussion symptom checklist in the ED. Headache (95% CI for odds ratio = 6.0-36.3%) and nausea (95% CI for odds ratio = 3.3-40.3) best differentiated patients with AMS from orthopedic injury controls. Headache, dizziness, nausea, phonophobia, photophobia, fatigue, blurry or double vision, and tinnitus were all statistically more common in cases with head trauma involving AMS compared to cases with head trauma without AMS, but the difference in symptom rates between these two groups was modest (11-27%). In contrast, complaints of poor concentration, poor balance, vomiting, irritability, and sadness did not significantly differ between head trauma cases with vs. without AMS.

Key Citations

16. Bernard C, McKinlay A, Krieser D, Testa R, Ponsford J. Acute post-concussive symptoms in young children. *Brain Inj*. 2017.;31(11):1414-1421.
17. Nance ML, Callahan JM, Tharakan SJ, Malamet P, Houseknecht EM, Moahoney KR, et al. Utility of neurocognitive testing of mild traumatic brain injury in children treated and released from the emergency department. *Brain Inj*. 2016;30(2):184-190.
18. Pacella M, Prabhu A, Morley J, Huang S, Suffoletto B. Postconcussive Symptoms over the First 14 Days after Mild Traumatic Brain Injury: An Experience Sampling Study. *J Head Trauma Rehabil*. 2018;33(3):E31-E39.
19. Bin Zahid A, Hubbard ME, Dammavalam VM, Basler DY, Pierre G, Kim A, et al. Assessment of acute head injury in an emergency department population using sport concussion assessment tool–3rd edition. *Appl Neuropsychol*. 2018;25(2):110-119.
20. Grubenhoff JA, Kirkwood MW, Deakyne S, Wathen J. Detailed concussion symptom analysis in a paediatric ED population. *Brain Inj*. 2011;25(10):943-949.

If you wish, provide citations for any additional relevant scientific studies that should be considered for this evidence statement.

Evidence Statement #5 of 10: Video review
Based on evidence from video review studies in sports, the following observable signs are associated with a clinical diagnosis of mild TBI: no protective action taken on falling, impact seizure, lying motionless/unresponsive, motor incoordination, and blank/vacant stare.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

Proposed change to ACRM criteria: Certain observable signs at the time of injury can increase diagnostic certainty. However, inter-rater reliability is low to moderate for certain signs, even with high-quality video review of the injury event.

Summary of supporting evidence: Two Class I studies[21,22] and a Class II study[23] provided diagnostic efficiency statistics for various observable signs on video review of sporting events. Motor incoordination (positive likelihood ratio of >2 in 2 out of 3 studies), lying motionless/unresponsive (positive likelihood ratio of >2 in 2 out of 3 studies*), no protective action taken on falling (positive likelihood ratio >2 in 2 out of 3 studies), and impact seizure (positive likelihood ratio >2 in 1 out of 2 studies) were associated with a mild TBI diagnosis. Estimates of inter-rater reliability for these signs when viewed on high quality video were variable (inter-rater reliability coefficient = 0.4 to 0.8). Blank/vacant look was difficult to reliably identify on video (inter-rater reliability coefficient = 0.2 to 0.4), but was consistently associated with a mild TBI diagnosis (positive likelihood ratio >4 in 3 out of 3 studies).

The signs of being slow to get up, clutching head, and facial injury may be cause for further evaluation if associated with head impact, but they were inconsistently associated with concussion diagnosis.

*Note: No protective action on falling was included in the definition and analysis of lying motionless or unresponsive in 2 studies.[22,23]

Key Citations
21. Makdissi M, Davis G. The reliability and validity of video analysis for the assessment of the clinical signs of concussion in Australian football. J Sci Med Sport. 2016;19(10):859-863.
22. Echemendia RJ, Bruce JM, Meeuwisse W, Hutchison MG, Comper P, Aubry M. Can visible signs predict concussion diagnosis in the National Hockey League? Br J Sports Med. 2018;52(17):1149-1154.
23. Gardner AJ, Howell DR, Levi CR, Iverson GL. Evidence of concussion signs in National Rugby League match play: A video review and validation study. Sport Med - Open. 2017;3(1):29.

If you wish, provide citations for any additional relevant scientific studies that should be considered for this evidence statement.

_____

Evidence Statement #6 of 10: Balance
Balance impairment on acute clinical assessment (within the first 24 hours post injury) is associated with a clinical diagnosis of mTBI.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

Proposed change to ACRM criteria: Abnormal findings on acute balance assessment can increase diagnostic certainty.

Summary of supporting evidence: Fourteen studies assessed the diagnostic value of acute (within 72 hours of injury) balance/postural stability evaluation. Most involved exclusively sport-related mild TBI and found group-level differences in postural stability (using athletes' pre-injury performance or an external control group of uninjured athletes as the comparator) within 24 hours of injury, followed by rapid resolution. Some examined balance within minutes or hours of injury.

Seven studies, including one Class II,[24] one Class III,[25] and five Class IV,[26–30] evaluated the Balance Error Scoring System (BESS) or the modified BESS (mBESS) within 72 hours following mild TBI. Four studies found statistically significant differences between mild TBI and control groups when comparing BESS scores <24h after injury; diagnostic accuracy statistics were not reported in most studies.[25,27–29] Normalization of BESS scores varied across these studies from 3-15 days post injury. These findings align with the conclusions of a systematic review of the BESS and mBESS in sport-related concussion.[31] In contrast, Barr et al[26] found no group difference on the BESS between 59 American football players with acute concussion and 31 non-injured football controls. The Class II study[24] employed the mBESS with a commercially available inertial sensor and found significant between-group differences on key objective metrics of postural instability.

A Class IV study[30] assessed patients acutely in the ED with the mBESS and found a mean of 11.28 balance errors in the mTBI group (n=100) compared with a mean of 5.40 balance errors in healthy controls (n=100) (p<.001). Diagnostic accuracy statistics were not reported.

Four studies, one class II,[32] two Class III,[33,34] and one Class IV[35] examined the diagnostic value of the Sensory Organization Test (SOT) with the NeuroCOM Balance Master. All five reported group differences with impaired postural stability the day after injury. A Class III study[33] documented normalization of the SOT by post-injury day 3. Diagnostic accuracy statistics were generally not reported.

One Class IV study[36] examined subjects with both the BESS and the SOT. The authors found significant postural differences between mTBI subjects and controls on both the SOT and BESS on day 1. By day 3, the SOT had normalized and significant differences only remained with foam but not firm surface BESS stances.

Several additional studies conducted preliminary evaluations of novel assessment tools, such as the Chattecx balance system,[37] inertial sensors to measure the peak velocity of head turns,[38] dual-task gait balance control task,[39] force plates to measures postural sway,[40] and generally reported worse balance in athletes with acute sport-related concussion (<72 hours post-injury) compared to healthy uninjured controls, with group differences disappearing over the week following injury.

Key Citations

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If you wish, provide citations for any additional relevant scientific studies that should be considered for this evidence statement.

Evidence Statement #7 of 10: Cognition
Cognitive impairment on acute clinical assessment (within the first 72 hours post-injury) is associated with a clinical diagnosis of mild TBI.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

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Proposed change to ACRM criteria: Abnormal findings on acute clinical assessment of cognition can increase diagnostic certainty.

Summary of supporting evidence: Multiple meta-analyses have documented cognitive impairment within the first 72 hours following a sport-related mild TBI.[41–43] Most studies used the Standardized Assessment of Concussion (SAC), a computerized assessment tool such as the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT®), or a brief battery of traditional pencil-and-paper neuropsychological tests.

A relatively small number of studies have examined cognitive impairment acutely following mild TBI in civilian trauma patients and active duty military service members. A Class II study[44] administered the SAC in an ED setting and found the SAC differentiated 26 individuals with mild TBI and 33 orthopedic injury controls (AUC = 0.76). Another Class II ED study[19] found the SAC discriminated between patients with mild TBI (n=118) and orthopedic injury controls (n=46; AUC=0.66) and healthy uninjured controls (n=98; AUC=0.77). In a Class II study of children aged 6-18 who presented to the ED (165 patients with mild TBI and 183 with orthopedic injury), mean SAC scores were not statistically different between groups.[45] Finally, a Class III study[46] administered the SAC to adult trauma patients who underwent a head CT for suspected mild TBI. Patients with LOC or PTA were classified as mild TBI cases (n=84), patients without LOC and PTA were classified as controls (n=30), and patients with positive CT findings were excluded. The mild TBI group performed significantly worse than the control group on the SAC, but discriminability was weak (AUC=0.65).

Of two adult studies that administered the ImPACT® in ED settings, one (Class II)[47] found that patients with mild TBI (n=23) performed worse than orthopedic injury controls (n=31) on the visual motor speed composite, and the other (Class II)[48] found no significant differences on ImPACT® between patients with mild TBI (n=90) and orthopedic injury controls (n=80). Two studies administered the ImPACT® to children in the ED. A Class II study[17] reported worse performance on visual motor and reaction time composite scores in children (aged 11-19) who sustained a mild TBI (n=39) vs. an orthopedic injury (n=46). Another Class II study[49] found differences only on the visual memory composite between children (aged 8-17) with mild TBI (n=39) vs. orthopedic injury (n=30). ED studies (both Class II)

employing other computerized assessment tools, the CNS Vital Signs[50] and the Cambridge Neuropsychological Test Automated Battery (iPad version),51 found group differences between patients with mild TBI vs. orthopedic injury controls, though neither reported diagnostic accuracy statistics.

Few studies have assessed military service members within 72 hours of a mild TBI. A Class II study[52] evaluated 66 soldiers with acute mild TBI and 146 controls who presented for medical care with an acute injury not involving the head or exposure to a blast. The mild TBI group performed worse on all subtests of the Automatic Neuropsychological Assessment Metrics (ANAM). A combination of ANAM subtests achieved optimal AUC of 0.73. A Class III study[53] reported on day-of-injury SAC performance in deployed service members (n=179). They performed worse than uninjured controls (d=0.90), with an AUC of 0.71.

There is substantial evidence that cognitive tests lose their sensitivity and diagnostic accuracy rapidly over the days following mild TBI.[31,54–56]

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If you wish, provide citations for any additional relevant scientific studies that should be considered for this evidence statement.

Evidence Statement #8 of 10: Oculomotor Functioning
Oculomotor impairments on clinical assessment (within the first 24 hours post injury) are associated with a clinical diagnosis of mild TBI.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

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Proposed change to ACRM criteria: Oculomotor impairment immediately post-injury can increase diagnostic certainty.

Summary of supporting evidence: The Vestibular Oculomotor Screening (VOMS) measures subjectively-experienced symptom provocation associated with visual-vestibular challenge. A Class IV[57] study observed that VOMS scores were significantly elevated following sport-related mild TBI compared to athletes' pre-injury scores, but patient-level classification accuracy statistics were not reported. In another Class IV study,[58] the VOMS was administered at an average of 5.5 days post injury, and the test was able to differentiate athletes with sport-related mild TBI (n=64) from healthy controls (n=78) with an AUC of 0.89. Two additional Class IV studies[59,60] found that VOMS scores differed between patients with mTBI (at 7 days post injury) and healthy controls, but neither reported diagnostic accuracy statistics for the VOMS alone. A history of attention deficit hyperactivity disorder 61 or motion sickness susceptibility[62,63] may be associated with higher VOMS false positive rate.[62–64] No studies compared VOMS performance acutely following mild TBI to orthopedic injury controls.

The King-Devick Test has been evaluated in numerous studies. The extent to which this test measures "oculomotor impairment" and/or other functions is not clear. A systematic review with meta-analysis supported the value of the King-Devick test for sideline assessment of acute sport-related mild TBI, when a pre-injury baseline is available.[65] The pooled AUC value across 15 studies (primarily of contact sport athletes) was 0.90. In additional studies published since this meta-analysis, one class II study[66] of 22 Australian football players compared King Devick performance immediately after suspected concussion with players' baseline test score. They reported overall diagnostic sensitivity and specificity of 0.98 and 0.96. An additional Class II study of individuals in 129 military combat training suggested weak discrimination of the King-Devick test (AUC=0.60) between those who sustained a mild TBI in live sparring (n=31) compared to those who completed training without a suspected mild TBI (n=98), relative to their pre-participating baseline scores.[67]

A Class III study of the King-Devick test in a civilian ED population reported weak discrimination

between mild TBI and orthopedic injury controls (Cohen's d=0.4).[44] Relative to the above-reviewed sport-related concussion studies, patients in this study were assessed later (up to 72 hours post-injury rather than within minutes) and no pre-injury King-Devick scores were available for within-subject comparisons. The King-Devick test was evaluated in another Class III study that used an external (uninjured) control group, where it achieved an AUC of 0.77.[68] In a Class IV study,[60] children recruited from the ED and tested at one week post-injury (n=146) did not differ from healthy controls (n=103) on the King-Devick test.

A systematic review focused on near point convergence (NPC)[69] found 11 eligible studies. NPC values for those with mild TBI ranged from 5.37 to 13.98 (>5 cm considered abnormal). Nine of the 11 studies reported significant differences in NPC for those with mild TBI compared to controls, with mean differences from 1.96 to 7.05 cm in studies where 95% confidence intervals could be calculated (all confidence intervals excluded zero, favoring controls). The authors rated the quality of evidence as moderate, supporting a relationship between mild TBI and receded NPC.

One Class III study of 200 military service members administered oculomotor tests within 72 hours of mild TBI.[68] Patients were compared to age-matched healthy controls. Those with mild TBI demonstrated significantly slower pupil dilation velocity (AUC=0.82) and longer near point conversion (AUC=0.74), and had higher self-reported convergence insufficiency (AUC=0.86). A regression model combining these variables had an AUC of 0.90. The preliminary findings require further validation.

A systematic review of 22 studies on the measurement of eye movement following mild TBI suggests that there are impairments in saccades, smooth pursuits, fixations and nystagmus as compared with healthy controls.[70] There was considerable variability in the devices, positions (e.g., sitting vs. walking), and metrics used across studies, limiting recommendations for clinical practice. A systematic review on eye-tracking technology in 21 studies of sports-related mild TBI also had difficulty drawing conclusions because of inconsistencies in metrics and methodologies. A meta-analysis of 9 studies demonstrated poorer performance in patients with mild TBI (<30 days post injury) on number of self-paced saccades, errors in the antisaccade task, phase lag of smooth pursuits and selected variables for the memory-guided saccades task.

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If you wish, provide citations for any additional relevant scientific studies that should be considered for this evidence statement.

Evidence Statement #9 of 10: Blood Biomarkers
Elevated Glial Fibrillary Acidic Protein (GFAP) in the blood is associated with a clinical diagnosis of mild TBI (vs. orthopedic injury) and with intracranial abnormalities on neuroimaging after mild TBI.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

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Proposed change to ACRM criteria: Elevated blood biomarkers such as GFAP can increase diagnostic certainty. Each blood biomarker has a unique temporal profile (rise, peak, and fall); the timing of their collection strongly influences their diagnostic utility.

Summary of supporting evidence: Most serum biomarkers studies recruited patients in Emergency Departments and examined whether GFAF, UCH-L1, and/or S100B could accurately identify patients with vs. without neuroimaging abnormalities, but some examined presence/absence of a TBI clinical diagnosis as the comparison of interest. Many studies included patients with mild *to moderate* TBI, which could overestimate diagnostic accuracy in mTBI. Available systematic reviews concluded that there was insufficient evidence to consider serum biomarkers as adjunctive diagnostic tools for mild TBI.e.g.,[71–73] However, several studies with a low risk of bias have been published in the last 2 years; these inform the current evidence statement.

GFAP: A meta-analysis of 16 studies involving 2,040 patients that compared those with negative vs. positive CT after mild TBI reported an average AUC value of 0.83.[74] In a more recent Class I study[75] of patients who presented to an ED with mild TBI and clinical indication for CT (n=649), GFAP was most elevated in those with positive CT followed by patients with negative CT/positive MRI, and then patients with negative CT and negative MRI. All three of these mild TBI subgroups had higher GFAP levels than orthopedic injury controls. The area under the curve for negative CT/positive MRI vs. negative CT/negative MRI was 0.78 (95% CI=0.73-0.83). Another Class I study[76] enrolled patients with mild to moderate TBI, but reported findings for a subgroup of patients with Glasgow Coma Scale = 14-15 (n=1,920). The combination of GFAP (cut-off of 22 pg/mL) and UCH-L1 assay had a sensitivity=0.97 and specificity=0.37, with negative predictive power=0.995 (AUC not reported). The classification accuracy of the GFAP-only model was not significantly lower than the combined model (exact values not reported). A Class I study[77] reported that GFAP discriminated between patients with mild TBI and healthy controls (AUC=0.93), as well between patients with mild TBI stratified by CT findings (AUC=0.77), MRI findings (AUC=0.80), and MRI findings among those with a negative CT (AUC=0.74). In another Class I study[78] that enrolled patients aged 0-83, GFAP discriminated between

children (AUC=0.80, 95% CI=0.73-0.87) and adults (AUC=0.76, 95% CI=0.71-0.80) with mild TBI (all Glasgow Coma Scale=15) vs. orthopedic injury controls. GFAP levels were highest among those with mild TBI, followed by those with head trauma without mild TBI, and levels were lowest among orthopedic injury controls. Serial blood draws revealed that GFAP was detectable within 1 hour of mild TBI, reached a peak 20 hours following injury, and retained its diagnostic accuracy beyond 72 hours post-injury.[78] Of note, GFAP may be less strongly associated with head CT findings in older vs. younger and middle-aged adults.[79]

GFAP has also been studied in athletes with sport-related mild TBI. A Class II study compared GFAP levels in athletes with acute sport-related mild TBI to contact sport controls and found an AUC=0.68 (95% CI=0.61-0.75).[80] This study also reported that GFAP increased within-subjects from preseason baseline to the acute post-injury period, and normalized with symptom recovery.[80] Athletes with LOC or PTA following sport-related mild TBI showed higher GFAP levels than acutely injured athletes without these clinical signs.[80] GFAP predicted group membership (sport-related mild TBI vs. control) over and above post-concussion symptom severity.80 A Class III study[81] similarly found that GFAP was highly elevated immediately following sport-related mild TBI compared to preseason baseline (Cohen's d=1.7) and discriminated well between athletes with acute mild TBI and uninjured athlete controls (AUC=0.96, 95% CI=0.93-0.99).

UCH-L1: In a meta-analysis,[74] the pooled AUC for differentiating mild TBI with vs. without CT findings across 5 studies representing 3,108 patients was 0.70. In a Class I study,[76] adding UCH-L1 to GFAP did not significantly improve classification accuracy for CT positive vs. CT negative patients with mild TBI (Glasgow Coma Scale = 14-15) compared to GFAP alone, but adding GFAP did improve classification over UCH-L1 alone. Another Class I study[78] found modest discrimination between children (AUC=0.62, 95% CI=0.53-0.72) and adults (AUC=0.69, 95% CI=0.64-0.74) with mild TBI vs. orthopedic injury controls, and reported that UCH-LI serum concentrations decline rapidly within 48 hours of injury, peaking at 8 hours post injury.

Two studies reported on the diagnostic accuracy of UCH-L1 in sport-related concussion. A Class II study[80] reported that UCH-L1 achieved an AUC of 0.66 (95% CI=0.59-0.74). This study also demonstrated that UCH-L1 increased acutely post injury relative to subjects' preseason baseline, and levels normalized with symptom recovery. This within-subjects finding was not replicated in a similarly designed single-site Class III study.[81] In that study, UCH-L1 also did not discriminate between athletes with acute mild TBI and uninjured controls (AUC=0.56).81

S100B: In a meta-analysis,[74] the pooled AUC for differentiating mild TBI with vs. without CT findings across 30 studies representing 8,464 patients was 0.72. Another meta-analysis[82] of 22 pediatric and adult studies produced a pooled sensitivity of 98.65 (95% CI=95.53-101.77) and specificity of 50.69 (95% CI=40.69-60.69) for identifying CT abnormalities using a cut-off cut-point range 0.16–0.20 mg L-1. A meta-analysis[83] focusing on children with mild TBI pooling 8 studies found an overall sensitivity and specificity of 100% (95% CI = 98%-100%) and 34% (95% CI = 30-38%) for abnormal head CT. A relatively small number of studies have examined the potential of S100B as a stand-alone biomarker to differentiate between people with vs. without acute mild TBI. A recent meta-analysis[74] found only 2 such studies. The pooled AUC was 0.68. In summary, a low S100B value suggests an absence of neuroimaging abnormalities after mild TBI, but there is insufficient evidence that S100B can contribute to a clinical diagnosis of mild TBI.

Other serum biomarkers: Findings for other biomarkers (e.g., neurofilament light) were more limited and mixed.[74,77,80,81,84]

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If you wish, provide citations for any additional relevant scientific studies that should be considered for this evidence statement.

Evidence Statement #10 of 10: Non-Specificity of Post-Acute Symptoms
Current symptom reporting in the weeks to months after mild TBI is often associated with premorbid and comorbid factors.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

Impact on ACRM case definition: Post-acute symptoms, alone, should not be used to diagnose a mild TBI.

Summary of supporting evidence: There is strong evidence that post-acute symptoms following mild TBI are not specific indicators of brain injury, i.e., are associated with non-injury factors. Patients without mild TBI frequently report post-concussion-like symptoms.[85,86] Psychological distress, female gender, and developmental disorders are associated with higher post-concussion-like symptom reporting in uninjured samples.[85–87] Post-concussion symptom reporting after mild TBI is correlated with non-injury factors, such as depression, posttraumatic stress disorder, pre-injury migraine, pre-injury psychiatric diagnoses, and family history of psychiatric diagnoses.[88–103] With longer time since mild TBI, the association between injury characteristics and post-concussion symptom reporting weakens, whereas associations between non-injury factors and post-concussion symptom reporting strengthen.[89,91,96]

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If you wish, provide citations for any additional relevant scientific studies that should be considered for this evidence statement.

Instructions for Part 2: Case Definition of Mild TBI

In this second section of the survey, we present a draft version (1.0) of the updated ACRM definition of mild TBI. It was created by a Working Group from the ACRM Mild TBI Task Force. It incorporates changes to align with the evidence statements (shown in section one of this survey) and the results of our preliminary expert survey on areas of controversy and diagnostic importance of signs, symptoms, acute test findings, and contextual factors (Silverberg et al. Arch Phys Med Rehab). The definition is intended to be used for adults and children in a clinical assessment. A caveat is provided for young children.

We will explain our reasoning for each element of the definition in a detailed position paper that we will invite you to co-author. In the interim, if you have pressing questions about why we included, omitted, or phrased certain elements as we did in draft version 1.0, feel free to write to noah.silverberg@ubc.ca and giverson@mgh.harvard.edu.

We are seeking consensus through a Delphi process. This may require changes to the preliminary draft definition and multiple rounds of voting. After each round, we will compile ratings and comments from the expert consensus panel, share that information with you in an anonymized format, and send a revised case definition back to the panel for voting.

Definition for Mild Traumatic Brain Injury (Draft Version 1.0)

Criteria for Defining a Mild Traumatic Brain Injury

Criterion 1: Mechanism of injury
Traumatic brain injury (TBI) results from a transfer of mechanical energy to the brain from external forces resulting from the (i) head being struck with an object, (ii) head striking a hard object or surface, (iii) brain undergoing an acceleration/deceleration movement without direct contact between the head and an object or surface, and/or (iv) forces generated from a blast or explosion.

Criterion 1 can be met by direct observation (in person or video review) or collateral (witness) report of the injury event, review of acute care records, or the patient's recount of the injury event during a clinical interview.

Criterion 2: Clinical signs
The injury event (Criterion 1) causes an acute physiological disruption of brain function, as manifested by *one or more* of the clinical signs listed below.
i. Loss of consciousness immediately following injury.
ii. Alteration of mental status immediately following the injury (or upon regaining consciousness), evidenced by reduced responsiveness or inappropriate responses to external stimuli; slowness to respond to questions or instructions; indifferent or agitated behavior; inability to follow two-part commands; or disorientation to place or situation.
iii. Complete or partial amnesia for events immediately following the injury (or after regaining consciousness). If post-traumatic amnesia cannot be reliably assessed (e.g., due to polytrauma or sedating analgesics), retrograde amnesia (gap in memory for events immediately preceding the injury) can be used as a replacement for this criterion.
iv. Focal neurological sign(s) (e.g., observed motor incoordination upon standing or ataxia, cranial nerve palsy, hemiparesis).
v. Seizure immediately following injury.

Criterion 2 can be met by direct observation (in person or video review), collateral (witness) report, review of acute care records, or the patient's recount of the injury event during a clinical interview. A clinical sign only qualifies for Criterion 2 when it is not entirely attributable to acute musculoskeletal pain, psychological trauma, alcohol or substance intoxication, pulmonary or circulatory disruption, syncope prior to fall, or other confounding factors.

Criterion 3: Symptoms
The physiological disruption of brain function is manifested by *two or more* of the self-reported symptoms listed below. The symptoms may be from one or more categories (i.e., two symptoms within a single category is sufficient). The onset of acute subjective alteration in mental status occurs immediately following the impact or after regaining consciousness. The onset of other symptoms may be delayed by a few hours, but nearly always appear in less than 72 hours from injury.
i. Acute subjective alteration in mental status: feeling confused, feeling disoriented, and/or feeling dazed.
ii. Physical symptoms: headache, nausea, dizziness, balance problems, vision problems, sensitivity to light, and/or sensitivity to noise.
iii. Cognitive symptoms: feeling slowed down, "mental fog," difficulty concentrating, and/or memory problems.
iv. Emotional symptoms: uncharacteristic emotional lability or irritability.

Criterion 3 can be met by (i) interviewing the patient; (ii) having the person complete a self-report rating scale documenting their symptoms during the first few days following injury; (iii) collateral report of the patient's acutely reported symptoms; or (iv) review of acute care records of the patient's acutely reported symptoms. Symptoms should only be counted towards Criterion 3 when they are not entirely attributable to drug, alcohol, or medication use; co-occurring physical injuries (e.g., orthopedic injury, cervical strain, peripheral vestibular dysfunction, etc.) or psychological conditions (e.g., an acute stress reaction to trauma); pre-existing health conditions; or exaggeration.

Criterion 4: Associated clinical, laboratory, and imaging findings
The assessment findings listed below can also provide evidence of brain injury.
i. Cognitive impairment on acute clinical exam.
ii. Balance impairment on acute clinical exam.
iii. Oculomotor impairment on acute clinical exam.
iv. Elevated blood biomarker(s) indicative of intracranial injury.
v. Trauma-related intracranial abnormalities on computed tomography or structural magnetic resonance imaging.

Clinical and laboratory tests that meet standards of reliability and diagnostic accuracy should be considered for Criterion 4. The accompanying position paper [forthcoming] reviews the best currently available evidence for specific measures of cognition, balance, and oculomotor function as well as specific blood biomarkers. Criterion 4i-iv findings must not be entirely attributable to drug, alcohol, or medication use; co-occurring physical injuries (e.g., orthopedic injury, cervical strain, peripheral vestibular dysfunction, etc.) or psychological conditions (e.g., an acute stress reaction to trauma); pre-existing health conditions; or exaggeration. The diagnostic sensitivity of clinical and laboratory tests (Criterion 4i-iv) generally decreases over the first 72 hours following injury and the rate of sensitivity decline differs between specific tests.

Diagnosing a Mild Traumatic Brain Injury

Mild TBI is *diagnosed* when, following a biomechanically plausible mechanism of injury (Criterion 1) any one of the four operational definitions listed below are met.
i. One or more clinical signs attributable to brain injury (Criterion 2).
ii. At least two symptoms (Criterion 3) and at least one associated clinical or laboratory finding (Criterion 4i-iv).
iii. At least two associated clinical or laboratory findings (Criterion 4i-iv).
iv. Neuroimaging evidence of TBI, such as unambiguous trauma-related intracranial abnormalities on computed tomography or structural magnetic resonance imaging (Criterion 4v). Neuroimaging is not necessary, however, to diagnose mild TBI.

In addition, none of the injury severity criterion listed below are present
i. Loss of consciousness duration greater than 30 minutes.
ii. After 30 minutes, a Glasgow Coma Scale (GCS) of less than 13.
iii. Post-traumatic amnesia greater than 24 hours.
If any of these injury severity criteria are present, TBI is diagnosed (without the "mild" qualifier). The qualifier mild TBI "with neuroimaging evidence of structural intracranial injury" may be used when Criterion 4v is present. The qualifier mild TBI "without neuroimaging evidence of structural intracranial injury" may be used when Criterion 4v is absent.

A mild TBI is *suspected* when, following a biomechanically plausible mechanism of injury (Criterion 1),

a person reports at least two symptoms (Criterion 3). For a suspected mild TBI, no clinical signs (Criterion 2) or associated clinical, laboratory, or imaging findings (Criterion 4) are documented.

Caveat: Caution is warranted when applying the operational definition of mild TBI to young children. For developmental reasons, a child may not be able to accurately report symptoms in Criterion 3; thus, this criterion could be met based on proxy report or observation of related behaviors (e.g., refusing to eat might suggest nausea). An injured person's emotional and behavioral reactions should also be interpreted in a developmental context.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree

Please explain any general concerns you have with this definition and recommend how it should be revised. Feedback on specific elements of the definition can be entered in following section.

_____

_____

Please check any subsection for which you have specific feedback and enter your feedback in the text box(es) that appear.

- ☐ Criterion 1: Mechanism of injury
- ☐ Criterion 2: Clinical signs
- ☐ Criterion 3: Symptoms
- ☐ Criterion 4: Associated clinical, laboratory, and imaging findings
- ☐ Criteria for diagnosing a mild TBI
- ☐ Criteria for suspecting a mild TBI
- ☐ Threshold for differentiating mild from moderate-severe TBI
- ☐ Qualifiers for indicating presence/absence of neuroimaging evidence of structural intracranial injury (previously referred to as complicated/uncomplicated mild TBI)

☐ Caveat for young children

Please provide your specific feedback for Criterion 1: Mechanism of Injury.

Please provide your specific feedback for Criterion 2: Clinical signs.

Please provide your specific feedback for Criterion 3: Symptoms.

Please provide your specific feedback for Criterion 4: Associated clinical, laboratory, and imaging findings.

Please provide your specific feedback on the criteria for diagnosing a mild TBI.

Please provide your specific feedback on the criteria for suspecting a mild TBI.

Please provide your specific feedback for the threshold for differentiating mild from moderate-severe TBI.

Please provide your specific feedback for the qualifiers for indicating presence/absence of neuroimaging evidence of structural intracranial injury.

Please provide your specific feedback for the caveat for young children.

Delphi Survey of Expert Consensus Group: Round 2

Introduction

Thank you for participating in the first round of Delphi voting for our mild TBI case definition initiative. We were thrilled to achieve a 100% response rate and hope to keep it up. **In this survey, we will share quantitative and qualitative results of voting from round one, and then present you with a revised set of evidence statements and a revised mild TBI case definition to vote on.**

We have revised the evidence statements and the definition of mild TBI based on your feedback.

As you know, it is our intention to publish this work with you as a coauthor. Our first expert panel survey has been published (see https://pubmed.ncbi.nlm.nih.gov/33035515/).

We wish to preface this second round of voting with some general comments. **Please read these carefully before proceeding with Delphi voting.**

You will first be presented with a series of evidence statements that have been revised based on feedback from the expert panel. Our goal is to have at least 80% of expert panel members agree (with no reservations or minor reservations) with every evidence statement and the mild TBI case definition. We were not far from this target in the first round. Some statements exceeded this agreement threshold, but where we saw opportunities to improve them further based on your feedback, we revised them too.

We plan to publish the evidence statements and the mild TBI case definition as part of a position paper that you will have the opportunity to co-author. We recognize that there is nuance and context not captured in the brief evidence statements and wording of the case definition. The position paper can provide that nuance and context.

We were encouraged by the degree of agreement in this expert panel on the proposed mild TBI case definition. To achieve higher agreement, it may help to highlight a few areas where panel members expressed differing views and our approach to addressing those differing views.

1. Some members expressed that the case definition was too lenient (e.g., an observable alteration in mental status should be considered necessary to diagnose mild TBI) whereas others expressed that the case definition was too stringent (e.g., subjective symptoms alone should qualify for a mild TBI diagnosis). Some also pointed out that it can be difficult to document the clinical signs that are required for a diagnosis. We attempted to reconcile these views by creating a "suspected" mild TBI category. The suspected mild TBI designation can be used when a person has a biomechanically plausible mechanism of injury (Criterion 1) and reports at least two symptoms (Criterion 3) or has at least two associated clinical or laboratory findings (Criterion 4). Examples of associated findings include (i) cognitive impairment, (ii) balance impairment, and (iii) oculomotor impairment or symptom provocation in response to vestibular-oculomotor challenge on acute clinical exam).

2. Related to point #1, most members seemed to hold the view that trauma-related intracranial abnormalities on neuroimaging could be included in the definition of mild TBI. In contrast, some members expressed that if a trauma-related intracranial abnormality is detected on neuroimaging, a moderate-severe TBI should be diagnosed rather than a mild TBI. We attempted to reconcile these views by offering a modifier for the diagnostic label, mild TBI "with or without neuroimaging evidence of structural intracranial injury."

3. Many members supported the approach to having a “suspected” mild TBI category whereas some were concerned about the implications. We agree that the implications of diagnostic terms with differing certainty warrant careful consideration, which we will have the opportunity to address in the position paper. Our view is that having clear criteria for a “suspected” mild TBI best reflects the clinical reality and can be applied pragmatically. For example, an athlete with “suspected” mild TBI could be placed on the same care and return to sport pathway as an athlete who clearly meets diagnostic criteria for mild TBI. Having this suspected category might also be good for mild TBI research. For example, studies that prioritize internal validity (e.g., early stage biomarker validation) could exclude cases with suspected mild TBI, whereas studies that prioritize external validity could include them. We are encouraged that probabilistic diagnostic criteria, like we are proposing here, have been used for other health conditions (e.g., Alzheimer’s disease) and have advanced clinical care and research in those fields.

4. Some members were enthusiastic about incorporating clinical and laboratory findings in the case definition, whereas others raised concern that these test findings were too heavily weighted, given the current state of the evidence. In the revised definition, clinical and laboratory findings can increase diagnostic certainty (e.g., move a patient into the suspected mild TBI category) but cannot, on their own, rule-in a mild TBI diagnosis.

5. Related to point #4, several members raised concern about whether there is sufficient evidence to support recommending specific tests and cut-off scores. This is consistent with our rapid evidence reviews. In the revised definition, no specific tests or biomarkers are named. In the position paper, we can emphasize the importance of selecting reliable and valid tests and appropriate normative (or pre-injury) reference data, and convey our hope that future iterations of this case definition will be able to specify evidence-based cut-offs. This approach will allow the case definition to remain useful as the evidence for specific clinical and laboratory tests and cut-offs evolves.

6. Regarding the evidence statements about clinical and laboratory findings, some members were concerned that the phrase “associated with” could be misinterpreted as “diagnostic of.” They suggested alternative phrasings, such as “supportive of” and “have potential to improve diagnostic certainty." We agree with the sentiment of these phrases but believe that the evidence statements should summarize what is known about a topic rather than provide clinical recommendations. We added a footnoted definition of “associated with” to prevent misinterpretation. It should be clear in the case definition that a single clinical or laboratory finding cannot be the basis for a mild TBI diagnosis.

7. You will now be presented with each evidence statement. You will see the percentages of expert panel members who agreed with the statement and how the statement has been revised based on feedback.

Evidence Statement #1: Blast Injury

Revised Statement: Mild TBI due to blast-related force may have a similar acute clinical presentation (≤72 hours) as mild TBI due to other mechanisms (e.g., a direct blow to the head).

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

_____

Agreement with original statement: 93% of those who voted (including 43% who agreed with minor reservations; 15% stated that they did not have sufficient expertise to rate this evidence statement)

Note to Panel: Changes to the statement, noted below, are marked with a strikethrough for deletions and italics for additions. Italics are not used for emphasis.

Original statement: Mild TBI due to blast force has a similar acute clinical presentation (≤72 hours) as mild TBI due to other mechanisms (e.g., a direct blow to the head).

Revision to original statement: Mild TBI due to blast-related force has *may have* a similar acute clinical presentation (≤72 hours) as mild TBI due to other mechanisms (e.g., a direct blow to the head).

Rationale for revision: Several expert panel members commented that the evidence to support this statement is limited. They also noted that blast-related injuries in combat might be accompanied by polytrauma, acoustic trauma, and acute traumatic stress. They also noted that there might be differences in underlying neurobiology, but as indicated in the evidence statement the acute clinical presentation is often similar.

Evidence Statement #2: Retrograde Amnesia

Retrograde amnesia may rarely occur in the absence of post-traumatic amnesia.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

_____

Agreement with original statement: 91% (including 15% who agreed with minor reservations)

Revision to original statement: None

Rationale for no revision: There was a high level of agreement with the original evidence Statement. Some panel members raised concerns with how retrograde amnesia would be incorporated into the mild TBI case definition, but they did not raise concerns with the evidence statement above relating to retrograde amnesia.

Evidence Statement #3: Acute Symptoms Can Reflect Injury

Revised Statement: Acute symptoms (e.g., dizziness or cognitive problems) following head trauma can reflect the presence of acute physiological disruption of brain function, even in patients who did not have a loss of consciousness or post-traumatic amnesia.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

_____

Agreement with original statement: 94% (including 15% who agreed with minor reservations)

Note to Panel: Changes to the statement below are marked with a strikethrough for deletions and italics for additions. Italics are not used for emphasis.

Original statement: Acute symptoms following head trauma can reflect the presence of acute physiological disruption of brain function, even in patients who did not initially have a loss of consciousness or post-traumatic amnesia.

Revision to original statement: Acute symptoms *(e.g., dizziness or cognitive problems)* following head trauma can reflect the presence of acute physiological disruption of brain function, even in patients who did not initially have a loss of consciousness or post-traumatic amnesia.

Rationale for revision: Several expert panel members commented that "acute symptoms" is too vague, and including examples would be helpful. It was also noted that acute symptoms might not always reflect neurotrauma, and might be caused by injuries to the head, neck, peripheral sensory systems, and other factors (including psychological factors). The statement, as written, indicates that acute symptoms "can reflect" acute physiological disruption in brain function. These points relating to nonspecificity will be clearly made in the paper describing the evidence statements.

Evidence Statement #4a: Headache

Acute headache is very common after mild TBI but is also common in patients who sustain an injury to the head or neck but do not experience a TBI.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

_____

Agreement with original statement: 93% (including 12% who agreed with minor reservations)

Revision to original statement: None.

Rationale for no revision: There was a high level of agreement with the original evidence statement, as written. Expert panel members made a number of useful comments and suggestions that can be included in the accompanying position paper, such as how neck injuries might result in a different type of headache and that people with injuries to the neck and head are more likely to have headaches than people with orthopedic injuries to the body. They also mentioned that headaches might emerge and peak in intensity 24-72 hours following injury.

Evidence Statement #4b: Anxiety

Revised statement: Acute post-injury anxiety is non-specific, occurring in patients with mild TBI and in those with traumatic bodily injuries. Acute anxiety can also reflect traumatic stress and/or pre-injury mental health difficulties.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

_____

Agreement with original statement: 91% (including 12% who agreed with minor reservations)

Note to Panel: Changes to the statement below are marked with a strikethrough for deletions and italics for additions. Italics are not used for emphasis.

Original statement: Anxiety within the first 72 hours of injury is non-specific, occurring at similar rates in patients with mild TBI and those with traumatic injuries below the clavicles. Acute anxiety can also reflect traumatic stress.

Revision to original statement: *Acute post-injury* anxiety within the first 72 hours of injury is non-specific, occurring at similar rates in patients with mild TBI and in those with traumatic *bodily* injuries. Acute anxiety can also reflect traumatic stress *and/or pre-injury mental health difficulties*.

Rationale for revision: Some expert panel members (reasonably) questioned the 72-hour time period. They thought that level of specificity, in the time period, was not necessary. Others suggested acknowledging pre-injury factors. Others felt that referring to the clavicles was not necessary or potentially confusing. It was also noted that it might not be necessary to state that the rates are similar.

Evidence Statement #4c: Other Acute Symptoms

Revised statement: There is insufficient evidence regarding the sensitivity and specificity of other acute symptoms for differentiating patients with mild TBI and those with traumatic bodily injuries. Note that headache is addressed separately in evidence statement #4a and anxiety is addressed separately in evidence statement #4b.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

_____

Agreement with original statement: 82% (including 36% who agreed with minor reservations)

Note to Panel: Changes to the statement below are marked with a strikethrough for deletions and italics for additions. Italics are not used for emphasis.

Original statement: The sensitivity and specificity of acute post-concussion symptoms, other than headache and anxiety, is not clear.

Revision to original statement: *There is insufficient evidence regarding* the sensitivity and specificity of other acute post-concussion symptoms *for differentiating patients with mild TBI and those with traumatic bodily injuries*, is not clear. *Note that headache is addressed separately in evidence statement #4a and anxiety is addressed separately in evidence statement #4b.*

Rationale for revision: There were many comments on this topic. In general, those comments were mostly in agreement with the original statement, but added important nuances. Most of those points can be addressed in the accompanying position paper and did not run counter to the statement itself. Some expert panel members expressed that certain symptoms (e.g., nausea) are probably more sensitive/specific to mild TBI. Our rapid evidence reviews suggested that headache and anxiety were both non-specific, but we found little consistent evidence regarding the sensitivity or specificity of other symptoms.

Evidence Statement #5: Video review

Revised statement: Based on evidence from video review studies in sports, the following observable signs may be associated with a clinical diagnosis of mild TBI: no protective action taken on falling, impact seizure (including tonic posturing), lying motionless/unresponsive, motor incoordination, and a blank/vacant stare.

Note: "Associated with," in the above statement, refers to a statistically significant relationship. When present, the variable may increase diagnostic certainty, but it should not be considered a pathognomonic diagnostic sign.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

_____

Agreement with original statement: 85% (including 18% who agreed with minor reservations)

Note to Panel: Changes to the statement below are marked with a strikethrough for deletions and italics for additions. Italics are not used for emphasis.

Original statement: Based on evidence from video review studies in sports, the following observable signs are associated with a clinical diagnosis of mild TBI: no protective action taken on falling, impact seizure, lying motionless/unresponsive, motor incoordination, and blank/vacant stare.

Revision to original statement: Based on evidence from video review studies in sports, the following observable signs are *may be* associated with a clinical diagnosis of mild TBI: no protective action taken on falling, impact seizure *(including tonic posturing),* lying motionless/unresponsive, motor incoordination, and *a* blank/vacant stare.

Rationale for revision: There was mostly agreement with the statement, but concerns were expressed relating to nuances in the wording and the reliability and accuracy of video reviews for this purpose. In addition, tonic posturing was been conflated with impact seizures in multiple studies that served as the basis for this statement. We have now separated them. We attempted to clarify the meaning of "associated

with" with a footnoted definition. Other minor concerns expressed by expert panel members can be noted and expounded upon in the accompanying position paper.

Evidence Statement #6: Balance

Revised statement: Impairment on standardized balance testing within the first 24 hours post injury is associated with a clinical diagnosis of mild TBI. However, pre-existing and comorbid conditions can also affect balance performance.

Note: "Associated with," in this context, refers to a statistically significant relationship. When present, the variable may increase diagnostic certainty, but it should not be considered a pathognomonic diagnostic sign.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

_____

Agreement with original statement: 97% (including 30% who agreed with minor reservations)

Note to Panel: Changes to the statement below are marked with a strikethrough for deletions and italics for additions. Italics are not used for emphasis.

Original statement: Balance impairment on acute clinical assessment (within the first 24 hours post injury) is associated with a clinical diagnosis of mTBI.

Revision to original statement: Balance impairment *on standardized balance testing* within the first 24 hours post injury is *statistically* associated with a clinical diagnosis of mild TBI. *However, pre-existing and comorbid conditions can also affect balance performance.*

Rationale for revision: There was a very high level of agreement with the original statement. Several expert panel members recommended including an explicit caveat that factors other than TBI might account for poor balance performance. Some expert panel members suggested a shorter (e.g., 6 hours) or longer (e.g., 72 hours) timeframe. We attempted to clarify the meaning of "associated with" with a footnoted definition. This is reflected in the case definition, where balance impairment can increase diagnostic certainty but cannot serve as the basis for a diagnosis.

Evidence Statement #7: Cognition

Impairment on standardized cognitive testing within the first 72 hours post injury is associated with a clinical diagnosis of mild TBI. However, pre-existing and comorbid conditions can also affect cognitive performance.

Note: "Associated with," in this context, refers to a statistically significant relationship. When present, the variable may increase diagnostic certainty, but it should not be considered a pathognomonic diagnostic sign.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____
_____

Agreement with original statement: 85% (including 24% who agreed with minor reservations)

Note to Panel: Changes to the statement below are marked with a strikethrough for deletions and italics for additions. Italics are not used for emphasis.

Original statement: Cognitive impairment on acute clinical assessment (within the first 72 hours post-injury) is associated with a clinical diagnosis of mild TBI.

Revision to original statement: Cognitive impairment *Impairment on standardized cognitive testing* within the first 72 hours post injury is associated with a clinical diagnosis of mild TBI. *However, pre-existing and comorbid conditions can also affect cognitive performance.*

Rationale for revision: Some expert panel members suggested clarifying that we are referring to an objective, standardized assessment cognitive functioning in this statement. Several expert panel members recommended including an explicit caveat that factors other than TBI might account for poor cognitive performance. Other panel members wanted more clarity on what "associated with" means—for example, associated with does not mean "diagnostic of". We attempted to clarify the meaning of "associated with" with a footnoted definition. This is reflected in the case definition, where cognitive impairment can increase diagnostic certainty but cannot serve as the basis for a diagnosis.

Evidence Statement #8: Oculomotor Functioning

Revised statement: Impairment on oculomotor testing and symptom provocation during vestibular-oculomotor challenge within the first 24 hours post injury may be associated with a clinical diagnosis of mild TBI. However, pre-existing conditions and other factors can also account for these test findings.

Note: "Associated with," in this context, refers to a statistically significant relationship. When present, the variable may increase diagnostic certainty, but it should not be considered a pathognomonic diagnostic sign.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____
_____

Agreement with original statement: 79% (including 30% who agreed with minor reservations)

Note to Panel: Changes to the statement below are marked with a strikethrough for deletions and italics for additions. Italics are not used for emphasis.

Original Statement: Oculomotor impairments on clinical assessment (within the first 24 hours post injury) are associated with a clinical diagnosis of mild TBI.

Revision to original statement: Oculomotor impairments on acute clinical assessment *Impairment on oculomotor testing and symptom provocation during vestibular-oculomotor challenge* within the first 24 hours post injury is *may be statistically* associated with a clinical diagnosis of mild TBI. *However, pre-existing and other factors could also account for these test findings.*

Rationale for revision: Some expert panel members expressed concern about the reliability and accuracy of these tests. Some noted that the vestibular system is involved in tests such as the Vestibular-Oculomotor Screening (VOMS) which we previously referred to as "oculomotor." Several expert panel members recommended including an explicit caveat that factors other than TBI might account for poor oculomotor test performance. We tempered the strength of statement because the evidence base is less mature compared to that for balance and cognitive testing. We attempted to clarify the meaning of "associated with" with a footnoted definition. This is reflected in the case definition, where oculomotor impairment can increase diagnostic certainty but cannot serve as the basis for a diagnosis. Other minor

concerns expressed by expert panel members can be noted and expounded upon in the accompanying position paper.

Evidence Statement #9: Blood Biomarkers

Revised statement: For adults, elevated Glial Fibrillary Acidic Protein (GFAP) in the blood on the day of injury is associated with intracranial abnormalities on neuroimaging after mild TBI and may also be more likely after a mild TBI without intracranial abnormalities visible on computed tomography compared to a traumatic bodily injury. There is currently insufficient evidence to suggest that other blood biomarkers can differentiate between mild TBI (without intracranial abnormalities visible on computed tomography) compared to a traumatic bodily injury.

Note: "Associated with," in this context, refers to a statistically significant relationship. When present, the variable may increase diagnostic certainty, but it should not be considered a pathognomonic diagnostic sign.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____
_____

Agreement with original statement: 73% (including 36% who agreed with minor reservations)

Note to Panel: Changes to the statement below are marked with a strikethrough for deletions and italics for additions. Italics are not used for emphasis.

Original Statement: Elevated Glial Fibrillary Acidic Protein (GFAP) in the blood is associated with a clinical diagnosis of mild TBI (vs. orthopedic injury) and with intracranial abnormalities on neuroimaging after mild TBI.

Revision to original statement: *For adults,* elevated Glial Fibrillary Acidic Protein (GFAP) in the blood *on the day of injury* is associated with a clinical diagnosis of mild TBI (vs. orthopedic injury) and with intracranial abnormalities on neuroimaging after mild TBI *associated with intracranial abnormalities on neuroimaging after mild TBI and may also be more likely after a mild TBI without intracranial abnormalities visible on computed tomography compared to a traumatic bodily injury. There is currently insufficient evidence to suggest that other blood biomarkers can differentiate between mild TBI (without intracranial abnormalities visible on computed tomography) compared to a traumatic bodily injury.*

Rationale for revision: This extensive revision attempts to address a variety of minor to serious concerns with the original evidence statement. There is a greater emphasis in the revised statement on the evidence relating to GFAP and traumatic intracranial abnormalities visible on head CT. The statement describing the association between GFAP and mild TBI diagnosis is tempered with "may be" to more accurately reflect the relative strength of this evidence and the inherent limitations with using clinical diagnosis as the gold standard reference for evaluating the diagnostic accuracy of blood biomarkers. Note that because of these and other concerns raised in response to this evidence statement, we do not recommend any specific blood biomarker or cut-off score in the case definition for mild TBI. We will describe the limitations of using blood biomarkers, clinically, in the accompanying review paper.

Evidence Statement #10: Non-Specificity of Post-Acute Symptoms

Revised statement: Persistent symptom reporting in the weeks to months after mild TBI is strongly influenced by premorbid and comorbid factors.

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation
- ○ Disagree
- ○ I do not have sufficient expertise to evaluate this statement.

Please explain your reservations and recommend how the evidence statement should be revised to address them.

_____

_____

Agreement with original statement: 97% (including 15% who agreed with minor reservations)

Note to Panel: Changes to the statement below are marked with a strikethrough for deletions and italics for additions. Italics are not used for emphasis.

Original Statement: Current symptom reporting in the weeks to months after mild TBI is often associated with premorbid and comorbid factors.

Revision to original statement: Current *Persistent* symptom reporting in the weeks to months after mild TBI *is* often associated with *strongly influenced by* premorbid and comorbid factors.

Rationale for revision: There was very high agreement with this statement. Several expert panel members recommended minor wording changes that could improve clarity.

Definition for Mild Traumatic Brain Injury

Agreement with original definition: 76% (including 21% who agreed with minor reservations)

Before presenting the revised definition, we explain our reasoning for substantive changes.

Rationale for changes to Criterion 2 (Clinical signs)

- We conceptualized no protective action taken on falling and lying motionless/unresponsive as evidence of loss of consciousness. We have made this more explicit by including them as examples of how loss of consciousness can manifest.
- Some members commented that cranial nerve palsy and hemiparesis are rare in the context of mild TBI and may signal a more severe brain injury. Therefore, they were deleted as examples. When listing ways that Criterion 2a (clinical signs) can be established, we added the phrase "*when none of these are available*" to indicate other methods for establishing Criterion 2a (e.g., review of acute care records) are preferable to a clinical interview.
- Some members expressed a preference for the phrase "not accounted for by" instead of "not entirely attributable to."

Rationale for changes to Criterion 3 (Symptoms)

- Some members requested that the list of possible symptoms be expanded. In the absence of empirical evidence regarding which acute symptoms are sensitive and specific to mild TBI (see Evidence Statements 4a, 4b, and 4c), we only included symptoms rated as diagnostically useful or important by our expert consensus panel (see https://pubmed.ncbi.nlm.nih.gov/33035515/)

Rationale for changes to Criterion 4 (Clinical, laboratory, and imaging findings)

- Some members pointed out that "impairment" should be explicitly defined.
- Some members suggested that specific clinical and laboratory tests (with associated cut-off scores) be named in Criterion 4. We would have liked to do this, but we did not for three main reasons. First, recommendations for using specific clinical and laboratory tests would need be tailored to the clinical setting, timing of assessment, and patient characteristics, which is difficult to incorporate into a mild TBI case definition. Second, some tests have relatively strong diagnostic accuracy, but do not yet have externally cross-validated cut-off scores. Third, we want to prevent the diagnostic criteria proposed here from becoming obsolete quickly as new evidence emerges. These issues can be discussed in the accompanying paper.
- In line with recommendations from multiple panel members, we removed neuroimaging from Criterion 4 and created a new Criterion 5 for neuroimaging.

Rationale for changes to Diagnosing a Mild Traumatic Brain Injury

- Some members expressed that clinical and laboratory findings were weighted too heavily. In the revised definition, clinical and laboratory findings can increase diagnostic certainty but cannot be the sole basis for a mild TBI diagnosis.
- Some members questioned the validity of the traditional threshold for differentiating mild from moderate-severe TBI (i.e., LOC>30 min, GCS<13, PTA>24 hours) and highlighted that it artificially divides a continuum of TBI severity. We plan to discuss these important points in the position paper. We retained the clinical cut-offs for moderate-severe TBI in keeping with our aim to update the 1993 ACRM definition of "mild" TBI and to focus on the lowest (minimum) threshold for diagnosing TBI. In the position paper, we will explicitly state that the new criteria can be used for diagnosing TBI of any severity.

- Some members suggested using the label “possible mild TBI” instead of “suspected mild TBI.” The term “suspected” is used because it conveys a diagnostic probability of greater than 50% and an expectation that the person should be treated as if they sustained a mild TBI (e.g., removed from play and required to get medical clearance prior to return to sport).
- Some members suggested reformatting this section into a diagnostic algorithm (e.g., diagram with boxes and arrows). We plan to prepare one for the draft position paper.

Note to Panel: Changes to the diagnostic criteria are marked with a strikethrough for deletions and italics for additions. Italics are not used for emphasis.

REVISED Definition of Mild TBI (version 2.0)

Criterion 1: Mechanism of injury
Traumatic brain injury (TBI) results from a transfer of mechanical energy to the brain from external forces resulting from the (i) head being struck with an object, (ii) head striking a hard object or surface, (iii) brain undergoing an acceleration/deceleration movement without direct contact between the head and an object or surface, and/or (iv) forces generated from a blast or explosion.

Criterion 1 can be met by direct observation (in person or video review) or collateral (witness) report of the injury event, review of acute care records, or the *person's* recount of the injury event during an interview.

Criterion 2: Clinical signs
The injury event (Criterion 1) causes an acute physiological disruption of brain function, as manifested by one or more of the clinical signs listed below.

i. Loss of consciousness immediately following injury *(e.g., no protective action taken on falling after impact or lying motionless and unresponsive)*.
ii. Alteration of mental status immediately following the injury (or upon regaining consciousness), evidenced by reduced responsiveness or inappropriate responses to external stimuli; slowness to respond to questions or instructions; indifferent or agitated behavior; inability to follow two-part commands; or disorientation to place or situation.
iii. Complete or partial amnesia for events immediately following the injury (or after regaining consciousness). If post-traumatic amnesia cannot be reliably assessed (e.g., due to polytrauma or sedating analgesics), retrograde amnesia (*i.e., a* gap in memory for events immediately preceding the injury) can be used as a replacement for this criterion.
iv. Focal neurological sign(s) (e.g., observed motor incoordination upon standing or ataxia, cranial nerve palsy, hemiparesis).
v. Seizure *(including tonic posturing)* immediately following injury.

Criterion 2 can be met by direct observation (in person or video review), collateral (witness) report, review of acute care records, or *when none of these are available,* the *person's* recount of the injury event during a clinical interview. A clinical sign only qualifies for Criterion 2 when it is not entirely attributable to *accounted for by* acute musculoskeletal pain, psychological trauma, alcohol or substance intoxication, pulmonary or circulatory disruption, syncope prior to fall, or other confounding factors.

Criterion 3: Symptoms
The physiological disruption of brain function is manifested by two or more *new or worsened* self-reported symptoms *from the* list below.

i. Acute subjective alteration in mental status: feeling confused, feeling disoriented, *and/or* feeling dazed.
ii. Physical symptoms: headache, nausea, dizziness, balance problems, vision problems, sensitivity to light, and/or sensitivity to noise.
iii. Cognitive symptoms: feeling slowed down, "mental fog," difficulty concentrating, *and/or* memory problems.
iv. Emotional symptoms: uncharacteristic emotional lability *and/*or irritability.
The symptoms may be from one or more categories (i.e., two symptoms within a single category is sufficient). *Other symptoms may be present, but are less diagnostically useful, and so should not be counted towards Criterion 3.* The onset of acute subjective alteration in mental status occurs immediately

following the impact or after regaining consciousness. The onset of other symptoms *(physical, cognitive, and emotional)* may be delayed by a few hours, but they nearly always appear in less than 72 hours from injury.

Criterion 3 can be met by (i) interviewing the *injured person*; (ii) having the *injured* person complete a self-report rating scale documenting their symptoms during the first few days following injury; (iii) collateral report of the *injured person's* acute symptoms; or (iv) review of acute care *documentation of the injured person's acute symptoms*. Symptoms should only be counted towards Criterion 3 when they are not entirely attributable to *accounted for by* drug, alcohol, or medication use; co-occurring physical injuries (e.g., orthopedic injury, cervical strain, peripheral vestibular dysfunction, etc.) or psychological conditions (e.g., an acute stress reaction to trauma); pre-existing health conditions; or exaggeration.

Criterion 4: Associated clinical and laboratory findings
The assessment findings listed below can also provide *supportive* evidence of brain injury.

i. Cognitive impairment on acute clinical exam.
ii. Balance impairment on acute clinical exam.
iii. Oculomotor impairment *or symptom provocation in response to vestibular-oculomotor challenge* on acute clinical exam.
iv. Elevated blood biomarker(s) indicative of intracranial injury.

Clinical and laboratory tests that meet standards of reliability and diagnostic accuracy should be considered for Criterion 4. *Impairment in Criterion 4i-iii is defined as a clinically meaningful discrepancy between post-injury test performance and age-appropriate normative reference data, or where available, pre-injury test performance.* The accompanying position paper [forthcoming] reviews the best currently available evidence for specific measures of cognition, balance, and oculomotor function as well as specific blood biomarkers. Criterion 4 findings must not entirely attributable to *be accounted for by* drug, alcohol, or medication use; co-occurring physical injuries (e.g., orthopedic injury, cervical strain, peripheral vestibular dysfunction, etc.) or psychological conditions (e.g., an acute stress reaction to trauma); pre-existing health conditions; or exaggeration. The diagnostic sensitivity of clinical and laboratory tests generally decreases over the first 72 hours following injury and the rate of sensitivity decline differs between specific tests.

Criterion 5: Neuroimaging
Trauma-related intracranial abnormalities on computed tomography or structural magnetic resonance imaging.

Neuroimaging is not necessary to diagnose mild TBI. Its primary role is to rule out head and brain injuries that might require neurosurgical or other medical intervention in an acute care setting. However, when obtained, neuroimaging may reveal intracranial abnormalities indicative of TBI such as contusion(s) or a subdural hematoma.

Diagnosing a Mild Traumatic Brain Injury

Mild TBI is *diagnosed* when, following a biomechanically plausible mechanism of injury (Criterion 1) any one of the three operational definitions listed below are met.
i. One or more clinical signs attributable to brain injury (Criterion 2).
ii. At least two symptoms (Criterion 3) and at least one associated clinical or laboratory finding (Criterion 4).
iii. At least two associated clinical or laboratory findings (Criterion 4i-iv).
iii. Neuroimaging evidence of TBI, such as unambiguous trauma-related intracranial abnormalities on computed tomography or structural magnetic resonance imaging (*Criterion 5*).

If neuroimaging is abnormal (Criterion 5), the qualifier mild TBI "with neuroimaging evidence of structural intracranial injury" may be used when Criterion 4v is present. When neuroimaging is completed and found to be normal, the qualifier mild TBI "without neuroimaging evidence of structural intracranial injury" may be used and Criterion 4v is absent.

The "mild" qualifier is not used if any of the injury severity criteria listed below are present. *Instead,* traumatic brain injury (TBI) is diagnosed (without the "mild" qualifier). In addition, none of the injury severity criterion listed below are present
i. Loss of consciousness duration greater than 30 minutes.
ii. After 30 minutes, a Glasgow Coma Scale (GCS) of less than 13.
iii. Post-traumatic amnesia greater than 24 hours.

A mild TBI is <u>suspected</u> when, following a biomechanically plausible mechanism of injury (Criterion 1) *any one of the three operational definitions listed below are met*.
i. At least two symptoms (Criterion 3) *but the person does not meet other criteria sufficient for diagnosing mild TBI*.
ii. *At least two associated clinical or laboratory findings (Criterion 4) but the person does not meet other criteria sufficient for diagnosing mild TBI*.
iii. It is unclear whether signs (Criterion 2), symptoms (Criterion 3), and clinical or laboratory findings (Criterion 4) are accounted for by confounding factors, including pre-existing and co-occurring health conditions.

Caveat: Caution is warranted when applying the operational definition of mild TBI to young children and *individuals with developmental delays or disabilities*. For developmental reasons, *an individual* child may not be able to accurately report symptoms in Criterion 3; thus, this criterion could be met based on proxy report or observation of related behaviors (e.g., refusing to eat might suggest nausea). An injured person's emotional and behavioral reactions should also be interpreted *in the context of their developmental stage and pre-injury functioning*. *Clinical and laboratory test interpretation requires age-appropriate scales and/or cut-off scores.*

- ○ Agree without reservations
- ○ Agree with minor reservation
- ○ Agree with major reservation

○ Disagree

Please explain any general concerns you have with this definition and recommend how it should be revised. Feedback on specific elements of the definition can be entered in following section.

_____

_____

Please check any subsection for which you have specific feedback and enter your feedback in the text box(es) that appear.

☐ Criterion 1: Mechanism of injury

☐ Criterion 2: Clinical signs

☐ Criterion 3: Symptoms

☐ Criterion 4: Associated clinical and laboratory findings

☐ Criterion 5: Neuroimaging

☐ Criteria for diagnosing a mild TBI

☐ Criteria for suspecting a mild TBI

☐ Threshold for differentiating mild from moderate-severe TBI

☐ Qualifiers for indicating presence/absence of neuroimaging evidence of structural intracranial injury (previously referred to as complicated/uncomplicated mild TBI)

☐ Caveat for young children and individuals with developmental delays or disabilities

Please provide your specific feedback for Criterion 1: Mechanism of Injury.

_____

_____

Please provide your specific feedback for Criterion 2: Clinical signs.

_____

_____

Please provide your specific feedback for Criterion 3: Symptoms.

_____

Please provide your specific feedback for Criterion 4: Associated clinical and laboratory findings.

Please provide your specific feedback for Criterion 5: Neuroimaging.

Please provide your specific feedback on the criteria for diagnosing a mild TBI.

Please provide your specific feedback on the criteria for suspecting a mild TBI.

Please provide your specific feedback for the threshold for differentiating mild from moderate-severe TBI.

Please provide your specific feedback for the qualifiers for indicating presence/absence of neuroimaging evidence of structural intracranial injury.

Please provide your specific feedback for the caveat for young children and individuals with developmental delays or disabilities.

Delphi Survey of Expert Consensus Group: Round 3

Third Round of Delphi Voting on the Updated Definition of Mild TBI

Thank you for your ongoing participation on the expert panel for the American Congress of Rehabilitation Medicine (ACRM) Mild TBI Task Force's initiative to update the 1993 definition of mild TBI. Before proceeding with this survey, please read our introductory letter [hyperlink removed], which summarizes the results of the public survey and the basis for revisions to version 2.0, which you previously reviewed and rated your agreement with in June-July 2021.

Whereas more than 80% of the expert panel agreed with diagnostic criteria version 2.0 (with and without minor reservations), we hope that agreement with version 2.2 will be even higher, and a greater proportion of panel members will agree without reservations.

Click here [hyperlink removed] to view a clean version of diagnostic criteria version 2.2 and here [hyperlink removed] to view a marked-up version that shows changes from version 2.0 to 2.1 to 2.2. Again, there were major formatting changes but only minor content changes from version 2.0 to 2.2.

If you would like to learn more about why a change was or was not made before you vote, feel free to ask noah.silverberg@ubc.ca.

Please rate your agreement with diagnostic criteria version 2.2 by selecting one of the options below.

- ○ Agree without reservations
- ○ Agree with minor reservations
- ○ Agree with major reservations
- ○ Disagree

If you indicated that you have reservations with diagnostic criteria version 2.2, please elaborate on them here:

_____

_____

In the public and stakeholder survey, many respondents requested clarification about the relationships between the terms “concussion” and “mild TBI.” Based on our initial expert panel survey and the results of our public survey (see Table 1 in the introductory letter [hyperlink removed]), we expect that the following statement will be the most widely accepted: “The diagnostic label ‘concussion’ may be used interchangeably with ‘mild TBI’ when neuroimaging is normal or not clinically indicated.” Do you agree with this statement?

- ○ Yes
- ○ No

Please choose one of the following to indicate your opinion about the relationship between the terms “concussion” and “mild TBI.”

- ○ The diagnostic label ‘concussion’ may be used interchangeably with ‘mild TBI’ regardless of neuroimaging studies (i.e., when neuroimaging is normal, abnormal, or not performed).
- ○ The diagnostic label ‘concussion’ may be used interchangeably with ‘mild TBI’ only when neuroimaging is performed and found to be normal.
- ○ The diagnostic label ‘concussion’ should never be used interchangeably with ‘mild TBI’.
- ○ I am unsure when the diagnostic label ‘concussion’ should be used interchangeably with ‘mild TBI’.
- ○ Other: _____

Letter to the Expert Panel Summarizing the Stakeholder Survey Results

Introductory Message to the Expert Panel
July 5, 2022

Thank you again for participating in the second round of expert panel Delphi voting, between June 8 and July 8, 2021.

You may recall that we last emailed you on September 28, 2021 to share the update that the draft diagnostic criteria version 2.0 achieved more than 80% agreement (without reservations or with minor reservations) from the expert panel, which was our prespecified threshold for consensus. At that time, we explained our plan to:

1. Incorporate qualitative feedback from the second round of Delphi voting to address several expert panel members' minor reservations with clarifications or alternative wordings, creating version 2.1, in hope that we could increase the proportion of expert panel members voting in agreement without reservations.
2. Invite the public to comment on version 2.1 and consider making additional minor revisions based on public feedback.

We have now completed the public survey. The survey launched on December 18, 2021 and remained open to individuals until January 18, 2022 and to stakeholder organizations until March 15, 2022. The number and source of survey submissions are summarized in **Figure 1**. Stakeholder organizations submitting detailed comments included the American Academy of Pediatrics, Association of Academic Physiatrists, American Academy of Physical Medicine & Rehabilitation, Brain Injury Association of America, Brain Injury Australia, Connectivity Traumatic Brain Injury Australia, National Academy of Neuropsychology, National Athletic Trainers' Association, and PINK Concussions.

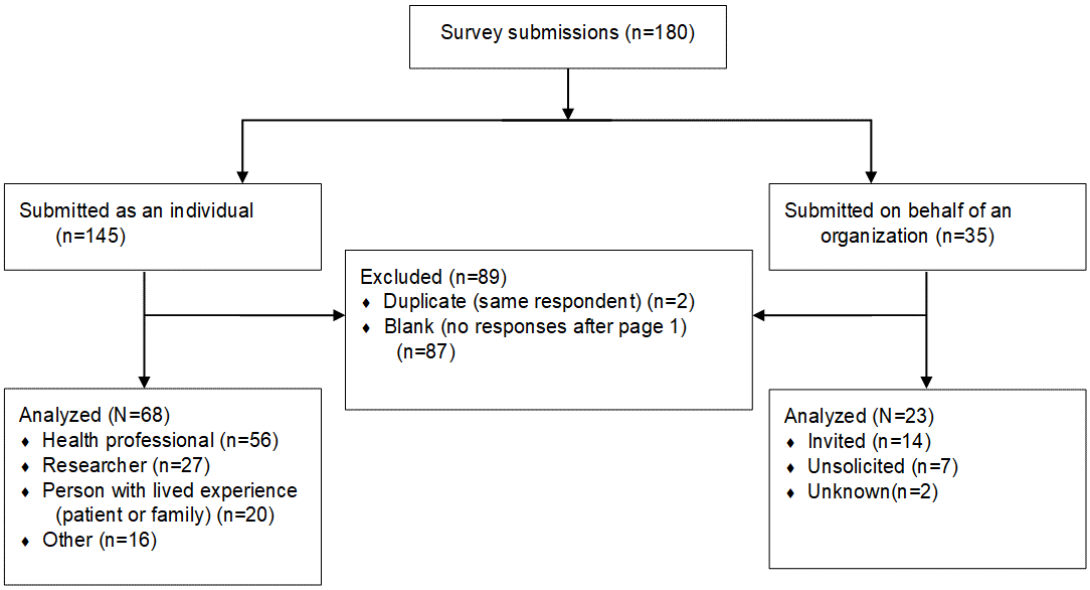

Figure 1. Flow diagram of the public survey.

The majority of the qualitative comments were favorable, indicating overall agreement and/or that the diagnostic criteria were an improvement compared to previously published definitions. The most common concerns or suggestions for improvement, and our proposed response to each are listed below.

1. "The definition is lengthy, complex, and difficult to follow." Proposed revision to the diagnostic criteria: Move text that elaborates on how to apply each diagnostic criterion to footnotes and commentary (i.e., text that is not directly relevant to determining whether a mild TBI occurred) to the position paper. We also propose to reverse the order of the two major sections, placing the diagnostic criteria first, followed by operational definitions of the signs, symptoms, and examination findings. These changes substantially reduce the word count and improve the flow. They altered the "look" of the diagnostic criteria but >95% of the content is identical to the version that most expert panel members supported in the previous round of Delphi voting. We also plan to include a visualization (e.g., decision tree) in the position paper to facilitate application of the diagnostic criteria.

2. "The definition is too lenient" or "…too stringent." A number of respondents expressed concern about false positive diagnoses. A smaller number expressed concern about false negative diagnoses. Proposed revision to the diagnostic criteria: None. These issues will be discussed in the position paper.

3. "Most patients will not have timely access to clinical and laboratory testing." Proposed revision to the diagnostic criteria: None. We recognize that most patients who meet diagnostic criteria for mild TBI will do so without clinical and laboratory testing. In the future, testing might be more available. An aim of the position paper can be to raise awareness regarding the value of early multimodal assessment.

4. "The traditional classification of mild versus moderate-severe TBI based on Glasgow Coma Scale and loss of consciousness and post-traumatic amnesia duration is crude." Proposed revision to the diagnostic criteria: None. We agree with this concern. We will make clear that the innovation of the new diagnostic criteria is in refined operational definitions of the lower threshold for diagnosis and we will advocate in the position paper for further research efforts towards an improved system for stratifying TBI severity, consistent with the NASEM 2022 report (https://www.nationalacademies.org/our-work/accelerating-progress-in-traumatic-brain-injury-research-and-care).

5. "The definition should clarify appropriate use of concussion versus mild TBI terminology." Proposed revision to the diagnostic criteria: Add a note about terminology to the qualifiers section, based on the outcome of the third round of Delphi voting (see below). Because we anticipated questions about terminology, the public survey included an item asking respondents to choose one option to complete the stem "The diagnostic label 'concussion' may be used interchangeably with 'mild TBI'...". Their responses are shown in **Table 1**.

Table 1. "Concussion" may be used interchangeably with "mild TBI" ..., n (%).

	Total sample (N=91)	Individuals (N=68)	Organizations (N=23)
When neuroimaging is normal or abnormal	21 (23.1%)	17 (25.0%)	4 (17.4%)
When neuroimaging is normal or not clinically indicated	24 (26.4%)	19 (27.9%)	5 (21.7%)
Only when neuroimaging is performed and found to be normal	4 (4.4%)	3 (4.4%)	1 (4.4%)
Never	11 (12.1%)	9 (13.2%)	2 (8.7%)
I am unsure	24 (26.4%)	15 (22.1%)	9 (39.1%)
Missing	7 (7.6%)	5 (7.4%)	2 (8.7%)

Note: One organization submitted two responses with different answers. Answers from the most recent submission were used for analysis.

We are proposing other minor revisions to diagnostic criteria version 2.1 based on specific points of feedback from the public survey. These are highlighted in green in version 2.2.

We expect that this will be the final round of Delphi voting. We look forward to co-authoring the position paper with you over the coming months, which will give us an opportunity to disseminate the new diagnostic criteria in a document that provides explanation and elaboration.

Sincerely,

Noah Silverberg, PhD, ACRM Mild TBI Task Force Chair & Project Co-Lead
Grant Iverson, PhD, Project Co-Lead

Working Group Co-Leaders

Noah D. Silverberg, Ph.D.*
Department of Psychology, University of British Columbia; Vancouver Coastal Health Research Institute; Djavad Mowafaghian Centre for Brain Health, Vancouver, British Columbia, Canada; 2136 West Mall, Vancouver, British Columbia, Canada, V6T 1Z4. Phone: 604-822-2755, Email: noah.silverberg@ubc.ca

Grant L. Iverson, Ph.D.**
Department of Physical Medicine and Rehabilitation, Harvard Medical School; Spaulding Rehabilitation Hospital and the Schoen Adams Research Institute at Spaulding Rehabilitation; MassGeneral Hospital for Children Sports Concussion Program; & Home Base, A Red Sox Foundation and Massachusetts General Hospital Program, Boston, Massachusetts, USA; 79/96 Thirteenth Street, Charlestown Navy Yard, Charlestown, MA, 02129. Email: giverson@mgh.harvard.edu

on behalf of the
ACRM Brain Injury Special Interest Group Mild TBI Task Force
and the
ACRM Mild TBI Definition Expert Consensus Group

ACRM Brain Injury Special Interest Group Mild TBI Task Force members
(in alphabetical order)

Jessica Brown, Ph.D., CCC-SLP
Department of Speech, Language, Hearing Sciences, University of Arizona, 1131 E 2nd St, Tucson, AZ, USA 85731.

Alison Cogan, Ph.D., OTR/L
Center for the Study of Healthcare Innovation, Implementation & Policy; VA Greater Los Angeles Healthcare System; 11301 Wilshire Blvd, Los Angeles, CA 90073.

Kristen Dams-O'Connor, Ph.D.
Department of Rehabilitation and Human Performance & Department of Neurology, Brain Injury Research Center of Mount Sinai, Box 1163, Icahn School of Medicine at Mount Sinai, New York, NY, USA 10029.

Richard Delmonico, Ph.D.
Kaiser Foundation Rehabilitation Center, 975 Sereno Drive, Vallejo, CA, USA 94589.

Min Jeong P. Graf, M.D.
Department of Physical Medicine and Rehabilitation, Hennepin Healthcare; Department of Rehabilitation Medicine, University of Minnesota, 701 Park Ave, Minneapolis, MN, USA 55415.

Mary Alexis Iaccarino, M.D.
Department of Physical Medicine and Rehabilitation, Massachusetts General Hospital
Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital
Harvard Medical School, 300 1st Ave, Charlestown, MA, USA 02129.

Maria Kajankova, Ph.D.
Department of Rehabilitation and Human Performance, Brain Injury Research Center of Mount Sinai, Box 1163, Icahn School of Medicine at Mount Sinai, New York, NY, USA 10029.

Joshua Kamins, M.D.
UCLA Steve Tisch BrainSPORT Program, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA, 300 Medical Plaza Ste B-200 Los Angeles, CA, USA 90095.

Karen L. McCulloch. PT, Ph.D.
Division of Physical Therapy, Department of Health Sciences, School of Medicine, University of North Carolina at Chapel Hill, 3030 Bondurant Hall, CB# 7135, Chapel Hill, NC, USA 27599-7135.

Gary McKinney, DHSc
Traumatic Brain Injury Center of Excellence, Defense Health Agency, 1335 East West Highway, Silver Spring, MD, USA 20910.

Drew Nagele, Psy.D.
School of Professional and Applied Psychology, Philadelphia College of Osteopathic Medicine, 4170 City Ave, Philadelphia, PA, USA 19131.

William J. Panenka, M.D.
British Columbia Neuropsychiatry Program; Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, UBC, Vancouver, BC, Canada, V6T2A1.

Amanda R. Rabinowitz, Ph.D.
Moss Rehabilitation Research Institute, 50 Township Line Rd., Elkins Park, PA, USA, 19027.

Nick Reed, Ph.D.
Department of Occupational Science & Occupational Therapy, University of Toronto, 160-500 University Ave, Toronto, ON, Canada, M5G1V7.

Jennifer V. Wethe, Ph.D.
Mayo Clinic School of Medicine, 13400 E Shea Blvd, Scottsdale, AZ, USA 85259.

Victoria Whitehair, M.D.
MetroHealth Rehabilitation Institute and Case Western Reserve University; 2500 MetroHealth Drive, Cleveland, OH, USA 44109.

ACRM Mild TBI Diagnostic Criteria Expert Consensus Group

(members listed in alphabetical order)

Vicki Anderson, Ph.D.
Murdoch Children's Research Institute; The Royal Children's Hospital, 50 Flemington Road
Parkville, Victoria 3052 Australia.

David B. Arciniegas, M.D.
University of New Mexico School of Medicine; University of Colorado School of Medicine; 1635 Aurora Ct, Aurora, CO, USA 80045.

Mark T. Bayley, M.D.
Toronto Rehabilitation Institute, University Health Network; University of Toronto; Room 3-102-12, 550 University Avenue, Toronto, Ontario, Canada, M5G2A2.

Jeffrey J. Bazarian, M.D., M.P.H.
University of Rochester School of Medicine and Dentistry; 265 Crittenden Blvd Box 655c, Rochester, NY, USA 14642.

Kathleen R. Bell, M.D.
University of Texas Southwestern Medical Center; 5323 Harry Hines Blvd, Dallas, TX, USA, 75390.

Steven P. Broglio, Ph.D.
University of Michigan, Michigan Concussion Center; 830 N University Ave., Ann Arbor, MI, USA 48109.

David Cifu, M.D.
Department of Physical Medicine and Rehabilitation, Virginia Commonwealth University School of Medicine; U.S. Department of Veterans Affairs; 1223 East Marshall Street, Richmond, VA, USA 23298.

Gavin A. Davis, M.B.B.S., F.R.A.C.S
Cabrini Health; Suite 53 – Neurosurgery, Cabrini Malvern, Victoria, 3144, Australia.

Jiri Dvorak, M.D., Ph.D.

Schulthess Clinic, Department of Neurology, Swiss Concussion Center; Lengghalde 2, CH-8008, Switzerland.

Ruben J. Echemendia, Ph.D.
University Orthopedics Center, Concussion Care Clinic; ;
University of Missouri-Kansas City, Kansas City, Missouri, USA.
107 Picadilly Rd., Port Matilda, PA, USA 16870

Gerard A. Gioia, Ph.D.
Division of Neuropsychology/ SCORE Concussion Program, Children's National Hospital, George Washington University School of Medicine; 15245 Shady Grove Road #350, Rockville, MD, USA 20850.

Christopher C. Giza, M.D.
University of California at Los Angeles, Departments of Neurosurgery and Pediatrics, Steve Tisch BrainSPORT Program; Room 531 Wasserman, Department of Neurosurgery, 300 Stein Plaza, UCLA, Los Angeles, CA, USA 90095.

Sidney R. Hinds II, M.D.
Uniformed Services University, Department of Neurology and Radiology, 4301 Jones Bridge Rd, Bethesda, MD 20814.

Douglas I. Katz, M.D.
Department of Neurology, Boston University School of Medicine; 72 E. Concord St. Robinson (B3), Boston University School of Medicine, Boston, MA, USA 02118.

Brad G. Kurowski, M.D., M.S.
Division of Pediatric Rehabilitation Medicine, Cincinnati Children's Hospital Medical Center, Departments of Pediatrics, Neurology, and Rehabilitation Medicine, University of Cincinnati College of Medicine; 3333 Burnet Avenue, MLC 4009, Cincinnati, OH, USA 45229.

John J. Leddy, M.D.
UBMD Department of Orthopaedics and Sports Medicine; SUNY Buffalo Jacobs School of Medicine and Biomedical Sciences; 160 Farber Hall, Buffalo, NY, USA 14214.

Natalie Le Sage, M.D., Ph.D.
Population Health and Optimal Health Practices Axis, CHU de Québec-Université Laval Research Centre; VITAM-Centre de recherche en santé durable; 1401, 18e rue, Québec, Canada, G1J 1Z4.

Angela Lumba-Brown, M.D.
Department of Emergency Medicine, Stanford University; 900 Welch Road, Stanford, CA, USA 94303.

Andrew I.R. Maas, M.D.
Antwerp University Hospital, Edegem, and University of Antwerp; Drie Eikenstraat 655, 2650 Edegem, Belgium.

Geoffrey T. Manley, M.D., Ph.D.
Department of Neurosurgery, University of California, San Francisco; 1001 Potrero Ave, San Francisco, CA, USA 94110.

Michael McCrea, Ph.D.
Medical College of Wisconsin; 8701 Watertown Plank Road, Milwaukee, WI, USA 53226.

David K. Menon, M.D., Ph.D.
University of Cambridge; Box 93, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK.

Jennie Ponsford, Ph.D.
Monash University; 18 Innovation Walk, Clayton campus, VIC 3800, Australia.

Margot Putukian, M.D.
Consultant, Major League Soccer; Princeton, NJ, USA 08540.

Stacy J. Suskauer, M.D.

Kennedy Krieger Institute and Department of Physical Medicine & Rehabilitation, Johns Hopkins University School of Medicine; 707 North Broadway, Baltimore, MD, USA 21205.

Joukje van der Naalt, M.D., Ph.D.
Department of Neurology, University of Groningen, University Medical Center Groningen; Netherlands.

William C. Walker, M.D.
Virginia Commonwealth University; 1223 East Marshall Street, 4th Fl., Box 980677, Richmond, VA, USA 23298-0677.

Keith Owen Yeates, Ph.D.
Department of Psychology, Alberta Children's Hospital Research Institute, and Hotchkiss Brain Institute, University of Calgary; 2500 University Dr NW, Calgary, AB T2N 1N4, Canada.

Ross Zafonte, D.O.
Department of Physical Medicine and Rehabilitation
Spaulding Rehabilitation Hospital/Massachusetts General Hospital/Brigham and Women's Hospital/Harvard Medical School; 300 First Avenue, Boston, MA, USA 02129.

Nathan Zasler, M.D.
Tree of Life Services and Concussion Care Centre of Virginia; 3721 Westerre Parkway, Suite B, Henrico, VA, USA 23233.

Roger Zemek, M.D.
Departments of Pediatrics and Emergency Medicine, University of Ottawa;
Children's Hospital of Eastern Ontario; 401 Smyth Road, Ottawa, ON, Canada, K1H 8L1.

* Corresponding author
**Member of both the ACRM Mild TBI Definition Expert Consensus Group and the ACRM Brain Injury Special Interest Group Mild TBI Task Force