**Appendix 1 – Neuroimaging Systematic Search Flow Diagram**

**Search Protocol Developed**

Methodology, Terms & Conditions, Computerized Databases, Inclusion Criteria, Extraction Tool

**Records identified through database searching**

(n=1905)

**Exclusion of non-relevant articles**

(n=1210)

**Screening of citation titles & abstracts**

(n=1447)

**Studies from other sources**

(n=84)

**Records after duplicates removed**

(n=1447)

**Full-text articles excluded**

(n = 161)

* Not a sport sample (n = 57)
* Time point outside 6 months post-injury (n = 40)
* Sub-concussive or exposure sample (n = 64)

**Full text articles retrieved, if necessary**

(n=237)

**Studies included in the qualitative synthesis**

(n= 76)

**Data extraction**

**Assessment of Risk of bias**

**Level of Evidence**

**Narrative synthesis of Findings**

**Reporting of results**

**Discussion**

**Conclusions**

**Fluid Biomarker Systematic Search Flow Diagram**

**Search Protocol Developed**

Methodology, Terms & Conditions, Computerized Databases, Inclusion Criteria, Extraction Tool

**Records identified through database searching**

(n=912)

**Exclusion of non-relevant articles**

(n=681)

**Screening of citation titles & abstracts**

(n=729)

**Studies from other sources**

(n=11)

**Records after duplicates removed**

(n=729)

**Full-text articles excluded**

(n = 31)

* Not a sport sample (n = 6)
* Time point outside 6 months post-injury (n = 5)
* Sub-concussive or exposure sample (n = 20)

**Full text articles retrieved, if necessary**

(n=47)

**Studies included in the qualitative synthesis**

(n= 16)

**Data extraction**

**Assessment of Risk of bias**

**Level of Evidence**

**Narrative synthesis of Findings**

**Reporting of results**

**Discussion**

**Conclusions**

**Genetics Systematic Search Flow Diagram**

**Search Protocol Developed**

Methodology, Terms & Conditions, Computerized Databases, Inclusion Criteria, Extraction Tool

**Records identified through database searching**

(n=310)

**Exclusion of non-relevant articles**

(n=214)

**Screening of citation titles & abstracts**

(n=233)

**Studies from other sources**

(n=0)

**Records after duplicates removed**

(n=233)

**Full-text articles excluded**

(n = 13)

* Not a sport sample (n = 1)
* Time point outside 6 months post-injury (n = 8)
* Sub-concussive or exposure sample (n = 4)

**Full text articles retrieved, if necessary**

(n=19)

**Studies included in the qualitative synthesis**

(n= 6)

**Data extraction**

**Assessment of Risk of bias**

**Level of Evidence**

**Narrative synthesis of Findings**

**Reporting of results**

**Discussion**

**Conclusions**

**Appendix 2**

**MODIFIED QUADAS-2**

Adapted for Use by the working group for Question 5 of the

**5th International Consensus Conference on Concussion in Sport:**

*What advanced or novel tests can assist in the*

*assessment of sport-related concussion?*

**STUDY NUMBER: REVIEWER:**

**PRIMARY AUTHOR:**

**YEAR OF PUBLICATION:**

BRIEF INSTRUCTIONS: Each reviewer will complete a modified QUADAS-2 form for each article they are assigned for review. There are four domains to be evaluated (see below). In each domain, risk of bias and concerns about generalizability are assessed. An overall assessment of concern about risk of bias affecting this study and/or issues regarding generalizability of study findings is also rendered by each reviewer for each study. This rating should be entered by the reviewer into the Excel spreadsheet under the risk of bias column. Reviewer teams will then convene to review ratings and reconcile any discrepancies through consensus. Completed QUADAS-2 forms and Excel spreadsheets should be submitted to the lead investigator.

**DOMAIN 1: PATIENT SELECTION**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1. **RISK OF BIAS** | | | | | | |
| Were study participants recruited prior to injury (e.g., “baseline” enrollment)? | **YES** | **NO** | |  | **UNCLEAR** | |
| Were the inclusion/exclusion criteria appropriate for the stated purpose of the study? | **YES** | **NO** | |  | **UNCLEAR** | |
| Was there a control group included consistent with the stated purpose of the study? | **YES** | **NO** | |  | **UNCLEAR** | |
| **Could the selection of patients have introduced bias?** | **LOW** | **MOD** | | **HIGH** |  | |
|  | All 3 Yes | 2 of 3 Yes | | 0 or 1 Yes |  | |
| 1. **B. CONCERNS REGARDING GENERALIZABILITY** | **LEVEL OF CONCERN** | | | | | |
| **Is there concern that the included participants limit the generalizability of findings on the utility of the tested metrics for the assessment of sport-related concussion?** | **LOW**  There is adequate representation across age, gender and sport among the study participants | | **MOD**  There is  limited representation across age, gender and sport among the study participants | | | **HIGH**  There is  minimal or no representation across age, gender and sport among the study participants |
| **COMMENTS:** | | | | | | |

**DOMAIN 2: INDEX TEST**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1. **RISK OF BIAS** |  |  | |  |  | |
| Were investigators blinded to the injury status of participants when analyzing and interpreting results of the index test? | **YES** | **NO** | |  | **UNCLEAR** | |
| Was there a defined set of hypotheses tested in relation to the index text? | **YES** | **NO** | |  | **UNCLEAR** | |
| Were methods of analysis and interpretation consistently applied across study participants (and groups)? | **YES** | **NO** | |  | **UNCLEAR** | |
| **Could the conduct or interpretation of the index test have introduced bias?** | **LOW** | **MOD** | | **HIGH** |  | |
|  | All 3 Yes | 2 of 3 Yes | | 0 or 1 Yes |  | |
| 1. **CONCERNS REGARDING GENERALIZABILITY** | **LEVEL OF CONCERN** | | | | | |
| **Is there concern that the index test, its conduct, or interpretation limit the generalizability of findings on the utility of the tested metrics for the assessment of sport-related concussion?** | **LOW**  There is adequate representation across age, gender and sport among the study participants administered the index test | | **MOD**  There is  limited representation across age, gender and sport among the study participants administered the index test | | | **HIGH**  There is  minimal or no representation across age, gender and sport among the study participants administered the index test |
| **COMMENTS:** | | | | | | |

**DOMAIN 3: REFERENCE STANDARD**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1. **RISK OF BIAS** |  |  | |  |  | |
| Was the reference standard (definition or method of diagnosing concussion) clearly described? | **YES** | **NO** | |  | **UNCLEAR** | |
| Was the same reference standard applied to all concussed participants? | **YES** | **NO** | |  | **UNCLEAR** | |
| Was the reference standard (definition or method of diagnosing concussion) established independent of index test (e.g., imaging, biomarkers, genetic testing) results? | **YES** | **NO** | |  | **UNCLEAR** | |
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | **LOW** | **MOD** | | **HIGH** |  | |
|  | All 3 Yes | 2 of 3 Yes | | 0 or 1 Yes |  | |
| 1. **CONCERNS REGARDING GENERALIZABILITY** | **LEVEL OF CONCERN** | | | | | |
| **Is there concern that the target condition as defined by the reference standard does not match the review question?** | **LOW**  There is adequate representation across age, gender and sport among the study participants to which the reference standard was applied | | **MOD**  There is  limited representation across age, gender and sport among the study participants to which the reference standard was applied | | | **HIGH**  There is  minimal or no representation across age, gender and sport among the study participants to which the reference standard was applied |
| **COMMENTS:** | | | | | | |

**DOMAIN 4: FLOW AND TIMING**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 1. **RISK OF BIAS** |  |  |  |  |
| Were the data collection time points used in the study relevant to the review question? | **YES** | **NO** |  | **UNCLEAR** |
| Were the data collection time points appropriate based on the stated purpose of the study? | **YES** | **NO** |  | **UNCLEAR** |
| Was the method/justification used to exclude any participants from analysis clearly described? | **YES** | **NO** |  | **UNCLEAR** |
| **Could the patient flow have introduced bias?** | **LOW** | **MOD** | **HIGH** |  |
|  | All 3 Yes | 2 of 3 Yes | 0 or 1 Yes |  |
| **COMMENTS:** | | | | |

**OVERALL RATING:** Please provide an overall rating of concerns related to risk of bias and generalizability based on your assessments above in Domains 1-4.

|  |  |  |  |
| --- | --- | --- | --- |
| **Overall concern about risk of bias affecting this study and/or issues regarding generalizability of study findings?** | **LOW** | **MOD** | **HIGH** |