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| Question |
| **Should measuring blood neurobiomarker vs. none be used for predicting good neurological outcomes in children after cardiac arrest?** |
| **Population:** | Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause. |
| **Intervention:** | blood neurobiomarker |
| **Comparison:** | none |
| **Main outcomes:** | Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2. |
| **Study DESIGN** | Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols\*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.  |
| **TIMEFRAME** | All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th 2022. |

# Assessment

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| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Prediction of favourable or unfavorable neurodevelopmental outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.  |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small● Moderate○ Large○ Varies○ Don't know | Only one study reported NSE, S100b and MBP values among 43 children [Fink 2014 664]. Cut off values were calculated and reported to classify either high sensitivity or low FPR for good neurological outcome. At 24 hours s100b level of 0.128 ng/ml predicted a good neurodevelopmental outcome with a sensitivity of 100% although an associated moderately high FPR of 62%. High (100%) sensitivity for predicting good outcome using NSE at 24hrs was identified at a cut off level of 53.1 ng/ml and 76.7 ng/ml at 48 hours (with a corresponding FPR 81 and 77% respectively). MBP level of 5.83 ng/ml at 24 hours and 5.43 ng/ml at 48 hours also had a high predictive sensitivity of 100% but high FPR of 96 and 88% respectively. Lower cut off values of s100B (0.001 ng/ml at 24 hours), NSE (0.48 ng/ml at 48 hours), or MBP (0.05 ng/ml at 48 hours) reported a predicted sensitivity of 6 to 29% with corresponding very low FPR of <6% for good neurological outcome. |  |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large○ Moderate● Small○ Trivial○ Varies○ Don't know | A false positive prediction of a good outcome and continued treatment based on blood neurobiomarkers may lead to inappropriate treatment in a patient with a poor neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity.  |  |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ● Very low○ Low○ Moderate○ High○ No included studies | The certainty of evidence from blood neurobiomarkers is low because of the risk of bias.  |  |
| ValuesIs there important uncertainty about or variability in how much people value the main outcomes? |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability● Possibly important uncertainty or variability○ Probably no important uncertainty or variability○ No important uncertainty or variability | Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a falsely optimistic prediction (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological outcome. |  |
| Balance of effectsDoes the balance between desirable and undesirable effects favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison● Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies○ Don't know | Considering only one study evaluated neurobiomarkers, although at specific cut points the FPR was very low, the balance of effects neither favours for or against the use of the tests for predicting good neurological outcome.  |  |
| Resources requiredHow large are the resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs● Moderate costs○ Negligible costs and savings○ Moderate savings○ Large savings○ Varies○ Don't know | Costs for the assessment of blood neurobiomarkers is variable. However, no study assessing savings from prognostication based on blood neurobiomarkers has been included in our review.  |  |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies | We did not identify any studies assessing cost of blood neurobiomarkers.  |  |
| Cost effectivenessDoes the cost-effectiveness of the intervention favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies● No included studies | We did not identify any studies addressing cost-effectiveness.  |  |
| EquityWhat would be the impact on health equity? |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced● Probably reduced○ Probably no impact○ Probably increased○ Increased○ Varies○ Don't know | Considering the variable cost of blood neurobiomarkers and their limited use in current clinical practice, it is likely that there would be inequity in access to this test. |  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | We have not identified any study assessing acceptability, but acceptability is likely as it is simple to obtain blood and there is no patient harm in obtaining the blood.  |  |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of blood neurobiomarkers requires specialized laboratory equipment to perform- which is becoming more widely available. |  |

# Summary of judgements

|  | **Judgement** |
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| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | **Small** | Trivial |  | Varies | Don't know |
| **Certainty of evidence** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | **Possibly important uncertainty or variability** | Probably no important uncertainty or variability | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | **Probably reduced** | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Type of recommendation

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| Strong recommendation against the intervention | Conditional recommendation against the intervention | **Conditional recommendation for either the intervention or the comparison** | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○  | ○  | **●**  | ○  | ○  |

# Conclusions

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| Recommendation |
| **We cannot make a recommendation for or against the use of blood neurobiomarkers after ROC for predicting good neurological outcome in children after cardiac arrest (weak recommendation, very-low-certainty evidence).**  |
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| Justification |
| Only one study (Fink, 2014) has identified cut-offs for 2 blood neurobiomarkers (S100b and NSE) that are associated with favourable neurological survival with a low FPR, although sensitivity if also low. Furthermore, these tests require specialized laboratory equipment and are not widely available, even though they only require the patient's blood. |

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| Subgroup considerations |
| No specific subgroup considerations. |

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| Implementation considerations |
| Until neurobiomarkers become more widely used (i.e., more indications with higher certainty of evidence), this test will likely be used for research purposes primarily. The field is growing quickly and equipment is becoming more accessible so that the clinician may adopt this test in the future.  |

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| Monitoring and evaluation |
| None |

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| Research priorities |
| This is a relatively new field of research and holds a lot of promise. There are other potential candidate biomarkers that should be explored and subgroups may exist where FPR is much lower. Higher number of participants need to be included in future studies. |

# References Summary