KCE REPORT 161Cs

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SYNTHESIS

THE ROLE OF BIOMARKERS IN RULING OUT INTRACRANIAL INJURIES IN MILD CRANIAL TRAUMA

KCE REPORT 161Cs
HEALTH TECHNOLOGY ASSESSMENT

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THE ROLE OF BIOMARKERS IN RULING OUT INTRACRANIAL INJURIES IN MILD CRANIAL TRAUMA

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FOREWORD

This morning, Johanne was surprised by the first night frost. On her way to work, the front wheel of her bike slipped on the ground frost and she fell. Since she briefly lost consciousness and had a wound on her forehead, witness of the accident called for assistance and Johanne ended up in the emergency department. Despite a reassuring history and physical examination, the question on whether she could have injured her brain remained unanswered. It is at this point of the story when the protein S100B test, subject of this report, comes into play.

If the test is negative, a brain injury can be excluded with reasonable certainty and therefore a scan can be skipped, which is optimal in the case of a young woman of childbearing age. Unfortunately, the opposite is not true: a positive test does not necessarily indicate the presence of a lesion. In other words, the test is highly sensitive but not specific enough.

Therefore, the appropriate use of this test would not be to diagnose brain injury, but 'merely' to exclude such a diagnosis. And there is the rub, because this approach goes against common daily clinical approaches, primarily aimed at giving the most accurate diagnosis. How can such a test be positioned in daily practice considering its use is counter-intuitive? Already during our study, both the clinical experts invited for consultation and those who validated the study - all perfectly mastering the subject - slipped into this conceptual pitfall.

What in theory seemed simple is nevertheless likely to pose problems in the field. Double trouble, in fact. There is first, the risk that this test, originally aimed at symptomatic cranial trauma patients in whom a CT scan would be considered, could immediately be integrated in the routine battery of tests performed in all victims of a cranial trauma. Then, there is the concern for any negative test results to be interpreted as “inconclusive”, rather than serving as reassurance that there is no intracranial lesion. This would push the patient systematically to the next diagnostic test, that is to say ... the scanner. In both cases, the cost-savings that held promise, would vanish.

For the above mentioned reasons, we must ensure that, alongside the analysis on the technical performance of the test, we also rack our brains to find optimal modalities for its introduction into routine practice. Enjoy reading!

Christian LÉONARD
Deputy general director

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ABSTRACT

BACKGROUND

Patients with mild cranial trauma (mCT), commonly referred to in the scientific literature as mild traumatic brain injuries (mTBI), have a small but significant risk of intracranial lesions which require early identification and treatment. Computerised tomography (CT) scanning is recognised as the gold standard in this field because of its high accuracy at detecting lesions linked to cranial trauma. Nevertheless, it is an expensive procedure that exposes patients to the risk of radiation.

Biomarkers, in combination with clinical decision tools, could help to rule out intracranial injuries without CT investigations, saving CT use for those most at risk and thus, minimising unnecessary radiation exposure and resource use.

METHODS

A systematic review was performed to assess the diagnostic accuracy and economic value of biomarkers compared to CT scan, for intracranial injuries (ICI) in adults and children with mCT.

RESULTS

Most of the available evidence focuses on one biomarker: the protein S100B. There is high quality evidence that protein S100B can reliably rule out the presence of ICI after mCT in adults. There is low quality evidence showing that protein S100B could rule out the presence of ICI after a mCT in children.

There is insufficient evidence to assess the diagnostic accuracy of other biomarkers.

The two economic evaluations identified via our review relied on a number of assumptions for which good data are still lacking to this date. Nevertheless, they show that the proportion of the mCT population in which the protein S100B test should be used, would be a crucial factor to consider.

CONCLUSION

Although protein S100B testing can reliably rule out the presence of ICI after mCT in adults, there is limited prospective data on how to best use this test in daily practice. Special attention needs to be placed on appropriate patient selection to ensure it holds its promise of allowing to rule out ICIs and reducing the overall number of CT scans, and as a consequence of radiation, currently performed to mCT patients.

SYNTHESIS

1. RULING OUT INTRACRANIAL LESIONS IN CASES OF MILD CRANIAL TRAUMA

Key message

Cranial trauma represent a serious public health concern.

Mild cranial trauma (mCT) accounts for the majority of cranial trauma cases (71-98%) and presents a small but genuine risk of serious complications.

Computerised tomography (CT) scanning is recognised as the gold standard to diagnose intracranial lesions in patients considered at risk after clinical assessment, but remains expensive and exposes patients to the risk of radiation.

Biomarkers used after clinical assessment, could help sparing unnecessary CT scans.

1.1. Background

Cranial trauma, known in the scientific literature as traumatic brain injuries (TBI) is the result of a forceful motion of the head or impact, which causes a brief change in mental status. Its main causes include falls, motor vehicle accidents, assaults, alcohol consumption and sports injuries. Cranial trauma may lead to a temporary or permanent impairment of cognitive, physical, or psychosocial functions. They represent one of the most critical public health problems around the world with an estimated annual incidence rate in Europe of 262 per 100 000 population.[1]

Populations more at risk of cranial trauma include children below 4 years of age, young adults (aged below 25) and the elderly (aged over 75).[1]

There is a distinction between mild (or light), moderate and severe cranial trauma. Such distinction is most often based on the Glasgow Coma Scale (GCS): a 3 to 15-point scale used to assess patients' level of consciousness and neurologic functioning after a head injury (see **Table 1**).

Mild cranial trauma (mCT) often defined as GCS 13-15 is by far, the most frequent, accounting for as many as 71% to 98% of cases and is the subject of interest of this review.

Although overall the prognosis of mCT is good, these patients present a small but genuine probability of suffering from serious complications, with an estimated prevalence of intracranial injuries (ICI) of 5%.[2, 3] Factors other than the severity of the injury, such as the location of the injury, or the age and general health condition of the individual, are also known to play a role on the overall prognosis of these injuries.

Computerised tomography (CT) scanning is used only in mCT patients whom clinicians assess as being at risk of intracranial lesions either on the basis of clinical decision rules and/or unstructured assessments[a]. CT scan is currently recognised as the gold standard[b] for diagnosis of ICI because of its wide availability and its sensitivity for intracranial lesions linked to cranial trauma. Nevertheless, it is an expensive procedure that exposes patients to the risk of radiation, making it important to carefully assess the need for it in mCT patients, in order to reduce unnecessary radiation, while still avoid missing ICI. In some cases, clinicians prefer to place patients under observation or hospitalise them for a short period of time, in order to monitor their clinical situation.

Following the first clinical assessment, biomarkers tests could accurately identify patients who do not need a CT scan, if they have a very high sensitivity, i.e. a negative test yields high reassurance that there is no lesion.

No biomarkers were excluded a priori from our review, although the evidence found was practically limited to studies on protein S100B.

Table 1 – Glasgow Coma Scale

Glasgow Coma Scale values (GCS)	Value
I. MOTOR RESPONSE	
Obeys commands fully	6
Localizes to noxious stimuli	5
Withdraws from noxious stimuli	4
Abnormal flexion, i.e. decorticate posturing	3
Extensor response, i.e. decerebrate posturing	2
No response	1
II. VERBAL RESPONSE	
Alert and Oriented	5
Confused, yet coherent, speech	4
Inappropriate words and jumbled phrases consisting of words	3
Incomprehensible sounds	2
No sounds	1
III. EYE OPENING	
Spontaneous eye opening	4
Eyes open to speech	3
Eyes open to pain	2
No eye opening	1
OVERALL SCORE	Addition of values for I+II+III

[a] The extent to which Belgian health professionals apply any specific tool remains, to this date, unknown.

[b] Although Magnetic Resonance Imaging (MRI) is not yet considered a gold standard in this field, it could potentially become so in the future. For completeness it was included in our review but no relevant studies using it as a comparator were identified.

Definitions

mCT: the result of the forceful motion of the head or impact causing a brief change in mental status (confusion, disorientation or loss of memory) or loss of consciousness for less than 30 minutes.

Biomarker: a biochemical, genetic, or molecular characteristic or substance that serves as indicator of the presence or severity of a disease state.

S100B: Protein secreted by astrocytes that can spill from injured cells and enter the bloodstream. Serum levels of S100B below a certain level are associated with low risk of lesions such as intracranial haemorrhage or brain swelling in cranial trauma patients. The usual cut-off is 0.105 µg/L.

Sensitivity: the proportion of patients with a lesion who are correctly identified (true positives) (i.e. the percentage of mCT patients who present lesions and showed a positive test result for the biomarker).

Specificity: the proportion of patients without a lesion who are correctly identified (true negatives) (i.e. the percentage of mCT patients who are not presenting lesions and are identified as "healthy" by means of the biomarker test).

Likelihood ratio + (LR+): the probability of a positive test in a person who has the disease (true positive), divided by the probability of a positive test in a "healthy" individual (false positive).

Likelihood ratio – (LR-): the probability of a negative test in a person who has the disease (false negative), divided by the probability of a negative test in a "healthy" individual (true negative).

In case of a negative test, multiplying the pre-test odds of ICI by the LR- yields the post-test odds of ICI. Therefore, to rule out ICI, a good test should present the lowest LR- possible

2. THE AVAILABLE EVIDENCE

Key messages

1. The vast majority of evidence focuses on one biomarker: the protein S100B.
2. Our review of the clinical evidence shows that S100B testing, performed after appropriate clinical assessment, has the potential to effectively rule out ICI in adults with mCT.
3. S100B testing may reduce the use of CT scans and ultimately, of unnecessary radiation and use of resources.

Clinical evidence

A review of the literature was performed to assess the diagnosis accuracy of biomarkers to rule out ICI compared with CT scan.

A hierarchical approach was used, first searching for high quality recent reviews that were then updated with a systematic review of more recent primary studies. International standards for performing systematic reviews were pursued for the update and pooling of the results was undertaken.

More details on our work and full references can be found in the scientific report. Findings from our review were discussed with a panel of external experts. The scientific report was peer-reviewed and validated by 3 additional external experts.

Nineteen studies reporting on the accuracy of S100B in adults were included in our review of the clinical literature, nine of which were already summarized in a systematic review published by Pandor et al. in 2011[4]. Pooling the results yielded an overall sensitivity of 96.6% (95%CI: 92.3%; 98.5%), and a LR- of 0.10 (95%CI: 0.04; 0.23) (Table 2). This means that the probability of ICI, as estimated by the physician prior to performing the S100B test, is divided by a factor of 10 (95%CI: 4; 25) if the test result is negative[c]. In other words, when the test is negative, we can be nearly certain of the absence of ICI (as identified by a CT-scan), for as long as the probability of presenting such lesions before performing the test, is not too high (for an example, see section 3). The specificity of the test on the contrary, was 33.0% (95%CI: 25.6%; 41.4%). Thus, when the test is positive, we are unsure about the diagnosis and a CT-scan may be appropriate to confirm or refute the presence of an ICI.

The quality of the evidence was rated as high[d]. A sensitivity analysis assessing the effect of time between injury and sampling (less than 3 hours versus more than 3 hours), different commercially available S100B tests (Roche versus DiaSorin), and the existence of a risk of selection bias did not result in statistically significant differences.

Table 2 – Meta-analysis: S100B in adults with mCT

	Studies	Participants	Se (%)	Sp (%)	LR+	LR-
2011 PANDOR[4]	9	2442	96.9 (91.4; 98.9)	42.0 (31.9; 52.8)	1.67 (1.40; 2.00)	0.07 (0.03; 0.21)
UPDATE KCE 2015	10	3795	95.9 (88.2; 98.7)	26.1 (18.2; 35.8)	1.30 (1.16; 1.45)	0.16 (0.06;0.43)
ALL	19	6237	96.6 (92.3; 98.5)	33.0 (25.6; 41.4)	1.44 (1.28; 1.62)	0.10 (0.04; 0.23)

Se: Sensitivity; Sp: Specificity; LR+: Positive Likelihood ratio; LR-: Negative Likelihood Ratio

In children, the sensitivity of protein S100B was 99.1% (95%CI: 68.7; 100) and the LR- was 0.02 (95%CI: 0.0; 0.3), but given the limited evidence (5 studies on a total of 469 children), the high risk of bias and the lack of precision around the point estimate, the quality of overall evidence was in this case considered low.

There was insufficient evidence to assess the diagnosis accuracy of any other biomarker.

Economic evidence

Our review of the economic evidence identified two studies only,[5, 6] one of which remains to this date unpublished.[5] Their results appear to be contradictive. On the one hand, Annemans et al.[5] showed that the introduction of protein S100B testing in the emergency department (ED) in Belgium would be cost saving from a health insurance perspective even under the worst case scenario considered in their analysis (i.e. sensitivity=100%, specificity=28%). Ruan et al.[6] on the other hand, concluded that the low specificity of the S100-B protein test would result in a limited ability to reduce the number of CT scans.

[c] In fact, it is the pre-test ratio that is divided by 10. But for low probabilities (<10%), probabilities and odds ratios are numerically very close

[d] There is very low probability of further research completely changing the presented conclusions.

These contradicting results are primarily a consequence of their departing assumptions. On the one hand, the Belgian study,[5] assumed that the biomarker would only be used in those patients who would have undergone CT scanning under current practice. On the other hand, Ruan et al.[6] assumed all patients presenting to the ED after a cranial trauma accident, meeting the definition of mCT would be tested for S100B protein levels.

Given the low specificity of the test, its use in all (or a very high proportion of) patients could result in a relatively high level of "false positives" which would then undergo an expensive CT scan to rule out ICI.

The sensitivity analysis performed by Annemans et al.[5], found that the biomarker test would be cost saving, for as long as it was provided to a maximum of 80% of those patients presenting to the ED after a mild cranial trauma accident. Although such proportion may appear to be very high, it is important to note that an assumption was used in the model under which those patients with a negative S100B test, were discharged home, while a small proportion of those with a negative CT scan were assumed to remain under observation.

It is clear that avoiding some "observations" by using protein S100B, as opposed to CT scans, could bring in additional savings (on top of pure "testing" costs). However, it remains uncertain whether immediate discharge after a negative protein test would be widely accepted by the clinical community.[3]

Regarding the price of the test, assumptions differed in the economic evaluations reviewed, with the US study[6] using $20 as a reflection of reimbursement rates for other similar immunoassay laboratory tests and the Belgian study[5] using €40 and quoting direct communication with the manufacturer as their source.

Overall, the existing economic evaluations, including the Belgian one, which displayed promising results relied on a number of assumptions for which good data is still lacking to this date.

3. DISCUSSION

Key messages

4. The full potential of protein S100B could only be realised if used in combination (as part of) available clinical decision rules/assessments, as opposed to replacing these.
5. The populations included in the studies are not necessarily representative of all mCT cases presenting to the ED, but rather a subset of patients. This should be carefully considered when using the test.
6. Factors such as the proportion of the mCT population in which the test should be performed, its correct identification and the clinical consequences of a negative S100B will have an important weight on the overall economic value of the protein S100B.

The bulk of evidence on biomarkers for ruling out ICI in case of mCT relates to protein S100B. The potential value of S100B depends on its ability to safely reduce unnecessary CT scans and as a consequence:

- Minimise the risk of radiation in populations not likely to benefit from a CT scan.
- Reduce the waste of limited medical resources by cutting down on CT scans and observation periods (with or without hospitalisation).

Its full potential could only be realised if the marker is used in combination (as part of) available clinical decision rules as opposed to replacing these, since the sensitivity of clinical decision rules based primarily on symptoms, such as nausea, vomiting, drowsiness, memory or sensory deficit, etc., and history of trauma is already relatively high and can help to rule out a number of cases, after which the protein could play a secondary role in better defining the target population for CT scans.

There is high quality evidence that protein S100B could be a valid tool to rule out ICI in cases of mCT in adults. Introducing protein S100B in the management of mCT may facilitate a reduction of a substantial over-triage to CT scans (between 80–99.5% of CT scans after mCT would be normal).[3] As a result, clinical guidelines have been modified accordingly in some

countries, such as Sweden[3], where the use of the protein is recommended under certain circumstances.

Nevertheless, despite its potential clinical value, some points of attention must be considered before deciding whether the dosage of protein S100B in the management of mCT is appropriate in a given setting.

The first one is the applicability of the study findings to a consulting population. It is worth mentioning that the study populations were not representative of all mCT cases presenting in the ED, but rather a subset of patients. Use of anticoagulants was an exclusion criterion in all but one of the included studies,[7] because of the higher risk of ICI that patients on these medications face. Subjects with multiple injuries were excluded from most of the studies, as the specificity of protein S100B is even lower in such patients. A further crucial factor of exclusion from studies was a too long delay between occurrence of trauma and time for measuring protein S100B as the half-life of the protein is quite short. Therefore, the use of the protein in these patient populations would be inappropriate and should not be recommended. The proportion of mCT Belgian patients presenting such factors at admission to the ED is unknown.

Second, the sensitivity of protein S100B is not 100%, the proportion of false negative lies between 1.5% and 7.7%, and the LR- between 0.04 and 0.23 Whether this is an acceptable level of uncertainty given the potential severity of the condition must be cautiously examined. One important element to consider in clinical practice is the incidence of ICI in mCT patients, or the pre-test odds of ICI. The exact incidence of ICI in mCT Belgian patients is unknown to this date, but it is likely to approximate 5% as reported in the international literature, which corresponds to the probability of ICI before testing protein S100B. With a LR- of 0.10 (95% CI: 0.04; 0.23) (see results of our systematic review), the probability of ICI in case of a negative test will downsize to 0.5% (95% CI: 0.2%; 1.2%). This seems to be quite a safe margin of certainty for discharging patients with a negative protein S100B, particularly if a rapid return to hospital is possible in case of appearance of alarming clinical signs. It is worth noting that ICI pre-test probability is even lower than 5 % when validated clinical rules are used (e.g. New Orleans Criteria or Canadian CT Head Rule) and all the items are negative[8]. In contrast, if the pre-test probability is clearly higher than 5%, as appraised by the medical doctor on the basis of the anamnesis and clinical examination, the value of testing protein S100B can be questioned given the uncertainty around the absence of ICI.

Third, the benefit of protein S100B in terms of resource utilisation in the studies was also variable, ranging from 11% to 38% of CT scans possibly avoided. Again, the incidence of ICI is an important contributing factor. If the incidence of ICI is low among people identified as suffering from a mCT, the proportion of false positives among all tested will increase, and thus, the proportion of patients getting both protein S100B and confirmatory CT scans will also increase. It should also be noted that CT scanning is considered the gold standard and that clinicians may be reluctant to rely only on a negative S100B test to discharge a patient. This fact is well illustrated in a Swedish study where 31.8% (44/138) of the patients with a negative protein S100B test were still either hospitalised or received a CT scan or both.[3] However, this evaluation was done only a few months after protein S100B had been integrated in the clinical protocol, and as a consequence, these results may also be a reflection of the time lag to adapt to new recommendations.

From an economic perspective, despite the fact that the conclusions drawn by the authors of the only two evaluations identified via our search[5, 6] appear at first sight contradictory, this is primarily due to their departing assumptions. While one assumed testing with S100B in all patients presenting to the ED, the other one assumed targeted used only in patients who would otherwise undergo a CT scan. Despite the differences in "actual" costs and payment systems between the US and Belgium, (countries where the reviewed economic evaluations were performed), the key cost drivers are unlikely to greatly differ: if the protein is to be used on the overall mCT population, the number of "false positives" due to the low specificity of the test will be large. This population would require some kind of follow-up (either via a confirmatory CT scan, or via observation, hospitalisation, etc.). Such approach would be unlikely to offer cost advantages versus a targeted-CT clinical strategy, independently of country-specific costs. Thus, factors such as the proportion of the mCT population in which the test should be used, its correct identification and the clinical consequences of a negative S100B will all have an important weight on the overall economic value of the protein S100B and should be carefully considered if wanting to ensure some savings will be realised with the introduction of the protein in clinical practice.

Appropriate patient targeting and use of biomarker tests has proved to be a challenge in other fields. This was for example the case of troponin, a biomarker used to evaluate patients suspected of suffering from acute coronary syndrome, for which guidelines recommended targeted use. Despite the clear recommendations, the biomarker was misused in cases where troponin elevation could not add any clinical diagnostic value.[9, 10] Nevertheless, monitoring concordance between use and guidelines of biomarker testing has proven effective in reducing unnecessary use and wastage.[9] Thus, monitoring the appropriate use of S100B testing after its introduction in clinical practice should be encouraged. In order to facilitate such monitoring, the potential for available registries such as the UREG (Register in Emergency Department) to capture in the future Protein S100B test data could be explored.

Regarding the generalisability of the findings specifically linked to the Belgian economic evaluation,[5] it is important to highlight that due to the general lack of data on current management of mCT, the authors of the study based their assumptions on that regard on a retrospective review of ED data from two large university hospitals. Whether such data could be representative of the overall Belgian situation is unclear, although the figure quoted appears to be in line with the results mentioned in a recent systematic review on CT scanning rates following the use of different clinical rules.[11]

In addition, there is, to this date, no prospective data on S100B use which could facilitate a selection of the appropriate target population for the test. As part of a monitoring programme in Belgium, prospective use of S100B testing could be captured in these two university hospitals in order to facilitate a comparison of such prospective data with the retrospective data already captured as part of Annemans et al. economic evaluation.[5] Special attention should be placed in capturing patient characteristics, trauma history and presence (or not) of specific trauma-related symptoms/risk factors.

RECOMMENDATIONS

To the emergency department clinicians:

- We recommend using S100B testing, after appropriate clinical assessment in patients with a Glasgow Coma Score (GCS) of 13-15 and symptomatic (or considered at risk of ICI) in which a CT scan would be considered, under current practice.
- We recommend NOT to use S100B testing in:
  - Patients with multiple trauma;
  - Patients in which the test cannot be performed within max. 6 hours after the trauma;
  - Patients on anticoagulants or anti-platelet treatment;
  - Patients aged 65+;
  - Children;
  - Patients presenting signs of skull fracture;
  - Patients showing any signs or symptoms that would make an active follow-up (observation, hospitalisation and/or CT scanning) necessary and clinically appropriate, independently of S100B test results.

To the Minister of Public Health and Social Affairs and the relevant Committees of the RIZIV/INAMI:

- **We recommend to reimburse Protein S100B testing in the population/circumstances previously specified.**
- **Monitoring the appropriate use of the test is recommended.**

Recommendations for further research:

- **Further research on the effectiveness of S100B testing at ruling out ICI in children is required. Setting up an effectiveness study to assess how the protein is used in real life in Belgium would be of value.**

REFERENCES

1. Peeters W, van den Brande R, Polinder S, Brazinova A, Steyerberg EW, Lingsma HF, et al. Epidemiology of traumatic brain injury in Europe. Acta Neurochir (Wien). 2015;157(10):1683-96.
2. Albers CE, von Allmen M, Evangelopoulos DS, Zisakis AK, Zimmermann H, Exadaktylos AK. What is the incidence of intracranial bleeding in patients with mild traumatic brain injury? A retrospective study in 3088 Canadian CT head rule patients. Biomed Res Int. 2013;2013:453978.
3. Calcagnile O, Unden L, Unden J. Clinical validation of S100B use in management of mild head injury. BMC Emergency Medicine. 2012;12((Calcagnile O., olga.calcagnile@regionhalland.se) Dept of Paediatric Medicine, Halmstad Regional Hospital, Halmstad, Sweden).
4. Pandor A, Goodacre S, Harnan S, Holmes M, Pickering A, Fitzgerald P, et al. Diagnostic management strategies for adults and children with minor head injury: A systematic review and an economic evaluation. Health Technology Assessment. 2011;15(27):1-202.
5. Annemans L, Verhaeghe N, Tack P, Hachimi-Idrissi S, Hubloue I, Lauwaert D. Health Economic Evaluation of the use of S-100B as a screening test in the emergency department management of patients with mild traumatic brain injury. Unpublished manuscript; University of Ghent, Belgium 2015.
6. Ruan S, Noyes K, Bazarian JJ. The economic impact of S-100B as a pre-head CT screening test on emergency department management of adult patients with mild traumatic brain injury (Structured abstract). Journal of NeuroTrauma. 2009;26(10):1655-64.
7. Muller B, Evangelopoulos DS, Bias K, Wildisen A, Zimmermann H, Exadaktylos AK. Can S-100B serum protein help to save cranial CT resources in a peripheral trauma centre? A study and consensus paper. Emergency Medicine Journal. 2011;28(11):938-40.
8. Easter JS, Haukoos JS, Meehan WP, Novack V, Edlow JA. Will Neuroimaging Reveal a Severe Intracranial Injury in This Adult With

Minor Head Trauma?: The Rational Clinical Examination Systematic Review. Jama. 2015;314(24):2672-81.

9. Larochelle MR, Knight AM, Pantle H, Riedel S, Trost JC. Reducing excess cardiac biomarker testing at an academic medical center. J Gen Intern Med. 2014;29(11):1468-74.

10. Nallet O, Arbaoui S, Grenier A, Michaud P, Safrano G, Sergent J. 324 Troponin in Emergency Department: an overused test for patient screening without clinical suspicion of acute coronary syndrome? Archives of Cardiovascular Diseases Supplements. 2011;3(1):109.

11. Stein SC, Fabbri A, Servadei F, Glick HA. A critical comparison of clinical decision instruments for computed tomographic scanning in mild closed traumatic brain injury in adolescents and adults. Ann Emerg Med. 2009;53(2):180-8.

COLOPHON

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