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***Title*** Evaluation of the METAglut1™ test in the diagnosis of glucose transporter type 1 deficiency syndrome

***Agency*** HAS (French National Authority for Health - *Haute Autorité de santé*)
5 avenue du Stade de France – F 93218 La Plaine Cedex, France
Tel.: +33 (0)1 55 93 70 00 - Fax: +33 (0)1 55 93 74 35, contact.seap@has-santé.fr, www.has-sante.fr

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**Aim**

Glucose transporter type 1 (Glut1) deficiency syndrome is an encephalopathy characterised, in its typical form, by treatment-resistant infantile-onset epilepsy, slowed head circumference growth resulting in microcephaly, delayed psychomotor development, spasticity, ataxia, dysarthria and other paroxysmal neurological disorders. “Atypical” forms, including a very broad variety of phenotypes, are also described. The prevalence of the condition is between 1/83,000 and 1/24,000.

The diagnosis of Glut1 deficiency syndrome is based on demonstration of hypoglycorrhachia as the reference test. This requires the performance of a lumbar puncture. An additional genetic test (molecular analysis of the SLC2A1 gene) can be used to confirm the diagnosis.

The METAglut1™ test is an in vitro diagnostic medical device (IVDMD). The test is performed on a blood sample to detect a reduction in glucose transporter (Glut1) expression on the surface of circulating erythrocytes and therefore diagnose glucose transporter type 1 deficiency syndrome.

In November 2017, METAFORA Biosystems SAS, the company that markets the METAglut1™ test, received the approval of the HAS to carry out a clinical study as part of the French *“forfait innovation”* innovation funding programme. The clinical study proposed in this context aimed to evaluate the diagnostic performance of the METAglut1™ test in patients with a clinical presentation compatible with glucose transporter type 1 deficiency syndrome, thereby providing the clinical data required for a procedure to be able to claim a sufficient expected clinical benefit.

With the clinical study now completed, the French Directorate General of Healthcare Provision (DGOS) therefore consulted the HAS on 29 April 2022, with a view to assessing whether it would be appropriate for this test to be funded by the French National Health Insurance system.

The objective of this work is to evaluate the diagnostic performance of the METAglut1™ test in comparison with glycorrhachia after lumbar puncture, in terms of sensitivity, specificity, positive predictive value and negative predictive value (NPV), in the diagnosis of glucose transporter type 1 deficiency syndrome, with a view to positioning the METAglut1™ test as a first-line test in place of glycorrhachia.

**Conclusions and results**

The conclusions issued by the HAS are as follows:

– the concordance between the METAglut1™ test and glycorrhachia is considered to be moderate;

– depending on the estimations, the sensitivity of the METAglut1™ test is either equivalent to that of glycorrhachia or 6% lower;

– the specificity of the METAglut1™ test is equivalent to that of glycorrhachia;

– the projections made in the context of this report indicate that the negative predictive value of the METAglut1™ test remains above 90% irrespective of the sensitivity value used;

– the METAglut1™ test is less invasive and easier to perform than a glycorrhachia test, which requires a lumbar puncture;

– the professionals involved in the management of glucose transporter type 1 deficiency syndrome have a high level of confidence in the METAglut1™ test;

– in the presence of clinical suspicion of glucose transporter type 1 deficiency syndrome, the METAglut1™ test may be performed as the first-line test in place of glycorrhachia. In order to significantly reduce the number of lumbar punctures, in the event of a negative METAglut1™ test, an analysis of the SLC2A1 gene or a gene panel/whole-exome analysis may be performed depending on the clinical conviction (for example, for a patient with epilepsy, epilepsy gene panel; for a patient with paroxysmal abnormal movements, abnormal movement gene panel; for a patient with intellectual disability, exome or genome analysis);

– the METAglut1™ test must be prescribed by a physician (paediatric neurologist, neurologist or geneticist); interpretation and validation of the results will be performed by a biologist who has been trained and authorised to carry out the test.

**Recommendations**

There are few data available in the literature, and the estimates resulting from the clinical trial carried out in the context of the *“forfait innovation”* innovation funding programme are not very precise due to the wide range of the confidence intervals. It therefore seems appropriate to set up a database of patients who have undergone the METAglut1™ test to collate information concerning the tests performed in the context of the diagnostic management of glucose transporter type 1 deficiency syndrome. Ultimately, analysis of this database would enable the performance data from the *“forfait innovation”* study to be confirmed.

Furthermore, in the context of the study, an additional analysis sets the optimal positivity threshold of the METAglut1™ test at 76% instead of 80%. At this positivity threshold, the sensitivity of the METAglut1™ test remains unchanged compared to that estimated with a positivity threshold set at 80%, but the specificity of the test was improved, increasing from 97.7%, CI95% [95.2%-100%] to 99.2%, CI95% [97.8%-100%]. The professionals consider that this 76% threshold should be applied in routine practice. Additional data (including real-world data from the database mentioned above) will be needed to confirm whether the 76% positivity threshold is indeed the optimal threshold.

**Methods**

The professional procedure rapid assessment process was selected by the HAS for this request. The assessment was based partly on an analysis of the results from the available literature, and partly on the views of professionals involved in the management of glucose transporter type 1 deficiency syndrome and patient associations.

The analysis of the literature included the clinical trial published by Mochel et al., conducted in the context of the *"forfait innovation"* innovation funding programme, and a proof of concept study on the METAGlut1 test (GRAS et al., 2017).

The coordinating investigator of the clinical trial, French national councils for healthcare professionals (CNPs) in the fields of paediatrics and neurology, the G2M rare diseases networks (hereditary metabolic diseases) and the Glut-1 deficiency syndrome patient association were consulted in the context of this report.

**Written by**

Nassim BRAHMI, HAS (French National Authority for Health - *Haute Autorité de santé*), France.