Proposal for assessment of new health technologies

Important information – read this first!

- Submitted proposals for national health technologies (HTAs) will be published in full. If the proposer thinks there is information necessary for filling out the form, that should not be made public, please contact the secretariat (Nye Metoder) before submission.

  The proposer is aware that the form will be published in its entirety (tick): ☒

- Proposer has filled out point 19 below «Interests and, if any, conflicts of interest» (tick): ☒
- This form serves the purpose to submit proposals for health technology assessment (HTA) at the national level in Nye Metoder - the national system for managed introduction of new health technologies within the specialist health service in Norway. The form does not apply to proposals for research projects. A health technology assessment is a type of evidence review, and for this to be possible, documentation is required, e.g. from completed clinical trials. Lack of documentation may be one of the reasons why the Commissioning Forum (Bestillerforum RHF) does not assign a health technology assessment.
- If the proposal concerns a medical device, the proposer is familiar with the document «Guidance criteria for management of medical devices in the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway» (link) (tick): ☒

Contact information:

Name of the proposer (organization / institution / company / manufacturer)**:**

ViroGates A/S, Denmark

Name of proposal contact:

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Date and locality:

03-01-2019, Copenhagen

1. Proposer's title on the proposal: *
   *This may be changed during the course of the process"

TurbiLatex suPARnostic® test for quantification of biomarker suPAR (soluble urokinase plasminogen activator receptor) in human plasma.

2. Brief description of the health technology proposed to be considered:

This proposal concerns the TurbiLatex suPARnostic® test, a turbidimetric CE/IVD test validated for the measurement of suPAR on turbidimetric platforms such as the Roche Cobas platform. suPAR is a biomarker of disease presence, disease severity and progression. It is in routine clinical use in Denmark (1). The high negative predictive value is of use in the clinical decision of discharge or admission of the acute medical patient.

Other possible methods for quantification of suPAR in blood or plasma includes the suPAR lateral flow technology (suPARnostic® Quick Triage POC test) or ELISA (suPARnostic® ELISA).

All products are produced by the Danish medtech company ViroGates A/S (Listed at NASDAQ Copenhagen as VIRO.CO).

3. Brief description of current standard of care (SOC) (Which health technology (ies) are currently used. What is the status of the technology (ies)? Whether it provides curative treatment, life extension, etc.)
Will the proposed technology replace or be a supplement to today's SOC?

The current standard of care in measuring inflammation and, to some degree, prognosis of the acute medical patient is to measure the level of C-reactive protein (CRP). Similar to CRP, suPAR is an inflammatory marker, but more related to chronic inflammation compared to CRP, which is more related to acute inflammation.

By measuring suPAR, the hospital staff gains insight into the overall health status of the patient. suPAR is an unspecific biomarker elevated by disease in general, and a high suPAR informs the staff that a patient is severely ill and in high risk of 30-day mortality but does not inform on why. It may be cancer, kidney failure, liver failure etc. On the other hand, a low suPAR level is associated with a very good prognosis and can aid in the decision to discharge the patient.

In a large RCT carried out in DK, there was a significantly higher number of patients discharged within 24 hours in those who had suPAR measurement compared to those without suPAR measurement, without affecting mortality or readmission (6). Overall, the length of stay was 6,5 hours shorter in the those with suPAR measurement, resulting in economical savings larger than the cost of the test.

4. This proposal concerns:	Yes	No
A brand new and innovative health technology	☒	☐
Anew application, or a new indication for an established method	☐	☒
A comparison between several methods	☐	☒
A technology that is already in use	☒	☐
If yes – technology used in clinical practice	☒	☐

If yes – technology used in research/clinical trials	☒	☐
A re-evaluation of technology used in clinical practice	☐	☒
The technology is relevant for disinvestment	☐	☒

5. This health technology involves (Multiple ticks are possible)

Pharmaceutical	☐
Medical device/IVD medical device that is CE-marked*	☒

All suPARnostic products carry the CE/IVD mark

Medical device/IVD medical device that is not CE-marked	☐
Procedure	☐
Screening	☒
Highly specialized services / national offers	☒
Organization of the health services	☒
Other (describe)	☐

“If relevant, please include who should be responsible for developing the technology.”

6. Application of the technology:

Prevention	☒
Assessment and diagnostics	☒
Treatment	☒
Rehabilitation	☐
Specialist health care	☒
Primary health care	☐

The technology is relevant when the clinician is in doubt of whether the patient is severely ill or not – and is currently in clinical use in the acute care departments, but may also be relevant specialized departments.

7. Responsibility for funding

	Yes	No
Is the specialized health service responsible for financing the technology today?	☒	☐
May the specialized health service become responsible for funding the health technology?	☐	☐

The test is produced by the Danish company ViroGates A/S and sold to hospitals, mainly in Europe. The test has also been used in the USA (see publications in New England Journal of Medicine, Nature Medicine and Science) but is not yet FDA approved.

8. Is the technology mentioned in the national guidelines or action programs prepared by the Norwegian Directorate of Health?

Yes	No
☐	☒

"Give more details about the relevant national guidelines or action programs."

9. Does the technology involve the use of radiation (ionizing/ non- ionizing)?

Yes	No
☐	☒

"Give a short description of type of radiation source, device and degree of radiation exposure"

10. Which discipline(s) does the health technology apply to, and which patients are affected? (Could the health technology also affect other groups (e.g. health personnel or relatives)?)

suPAR is used for assessing overall disease status in acute medical patients in the Emergency Department – but studies are ongoing to determine the potential use of suPAR in pre-hospital sector (ambulances, GP's etc)(e.g. PRIUS (Prehospital Recognition and Identification of Unspecific Symptoms) study (Clinicaltrials.gov ID NCT03089359), Karolinska Inst, Sweden).

11. Which aspects are relevant to the assessment? (Multiple ticks are possible)

Clinical efficacy	☒
Safety/adverse effects	☒
Costs/resource use	☒
Cost-effectiveness	☒
Organizational consequences	☒
Ethical	☒
Legal	☐

12. Please suggest the main scope/objective for the health technology assessment, as well as secondary scopes/objectives (in compliance with question 10). For those familiar with "PICO" (Patient, Intervention, Comparator, Outcome) – please include tentative suggestions for PICO.

Patient: suPAR is in routine use in acute medical patients. Several studies on children have also been published, showing suPAR is a disease severity biomarker. suPAR has been shown to be a marker of disease progression and outcome independent of race and sex.

Intervention: suPAR is particularly useful in identifying low-risk patients and thereby aid in discharge decisions. An RCT carried out in Denmark showed that patients who had suPAR measured were more often discharged – without increasing readmission or mortality (6).

Comparator: suPAR is often compared to other markers of inflammation, such as white blood cell count, CRP or procalcitonin. However, suPAR is superior to other markers in regard to predicting the outcome of the patient (e.g. readmission or mortality (1, 9, 10).

Outcome: By including suPAR, we hope to reduce crowding, and to improve risk stratification. Crowding can be reduced by discharging more patients base on low suPAR/low risk of severe disease.

But also both with regard to identifying patients with unsuspected underlying severe disease (high suPAR, e.g. cancer) allowing for early intervention – an example is shown in this video from Copenhagen University Hospital Hvidovre (http://biologictube.dk).

13. Please give a brief explanation of why it is important that the health technology assessment proposed should be conducted.

The technology enables improved clinical decision making. suPAR is the strongest prognostic biomarker and outperforms current biomarkers such as CRP, PCT or albumin. As it is unspecific and elevated by disease in general, a low suPAR level (below 3 ng/ml, In Denmark, around 53% of the acute medical patients) is a strong indicator for discharging the patient. On the other hand, an elevated suPAR (above 6 ng/ml) is associated with high risk of resubmission and 30-day mortality, and these patients (In Denmark, 1/8 patients), should undergo additional clinical investigation to identify the disease underlying the bad prognosis) (1,9).

14. Please comment on the technology that is proposed to be assessed with regard to the following points:

The severity of the disease/condition the health technology targets

The technology provides significant independent information on severity of disease and prognosis.

Expected effect

More patients safely discharged leading to economical savings.

Safety

None

Total number of patients in Norway the health technology is applicable to

Acute medical patients where the health staff is in doubt of whether the patient should be discharged or admitted.

Consequences for resource use in the public health service

As part of randomised control trial carried out in Denmark, the company Incentive carried out an economical assessment of the savings of introducing suPAR in Denmark.

This economic assessment showed a mean cost saving potential of 648.305.021 DKK per year in Denmark. This cost saving potential is based on the premise that the suPARnostic® test is applied on all acute medical admitted patients (i.e. systematic use). If the suPARnostic® test is only applied on a selected patient group, the cost saving potential will be lower.

The estimated mean net saving of a systematic use of suPARnostic® ® in acute medical admitted patients in Denmark is 590.036.321 DKK per year. Thus, when taking the price of the suPARnostic® test into account, the saved costs due to a shorter length of hospitalisation outweighs the cost of the suPARnostic® test.

This health economic assessment does not consider any clinical benefits from obtaining suPAR values nor indirect saved costs, e.g. possible lower rate of hospital acquired infections, shorter sick leave, saved patient time at the hospital etc. It merely considers direct saved costs due to a shorter average length of hospitalisation.

Need for revision of existing national guidelines or preparation of new guidelines

suPAR is a biomarker and part of the panel of biomarkers to access the prognosis of the acute medical patient and thereby fit into current guidelines that include biomarkers in risk assessment.

15. Please provide references to documentation of the health technology's effect and safety (i.e. previous technology assessments). (Up to 10 key references can be provided, please do not send attachments in this step of the process):

1: Rasmussen LJH, et al. Combining National Early Warning Score With Soluble Urokinase Plasminogen Activator Receptor (suPAR) Improves Risk Prediction in Acute Medical Patients: A Registry-Based Cohort Study. **Crit Care Med**. 2018 Dec;46(12):1961-1968.

2: Hoenigl M, et al. Soluble Urokinase Plasminogen Activator Receptor (suPAR) is predictive of Non-AIDS Events during Antiretroviral Therapy-mediated Viral Suppression. **Clin Infect Dis**. 2018 Nov 12.

3: Godtfredsen NS, et al. Soluble urokinase plasminogen activator receptor predicts mortality in exacerbated COPD. **Respir Res**. 2018 May 21;19(1):97.

4: Hayek SS, et al. Predicting Mortality in African Americans With Type 2 Diabetes Mellitus: Soluble Urokinase Plasminogen Activator Receptor, Coronary Artery Calcium, and High-Sensitivity C-Reactive Protein. **J Am Heart Assoc**. 2018 May 1;7(9

5: Meyer J, et al. suPAR is associated with risk of future acute surgery and post-operative mortality in acutely admitted medical patients. **Scand J Trauma Resusc Emerg Med**. 2018 Feb 1;26(1):11.

6: Schultz, M et al. Early discharge from the emergency department based on soluble urokinase plasminogen activator receptor levels: a substudy of the triage iii trial. **EuSEM oral presentation,** abstract 18578-FP008 and submitted.

7: Hayek SS, et al: tripartite complex of suPAR, APOL1 risk variants and α(v)β(3) integrin on podocytes mediates chronic kidney disease. **Nat Med**. 2017 Aug;23(8):945-953

8: Rasmussen LJH, et al. Inflammatory biomarkers and cancer: CRP and suPAR as markers of incident cancer in patients with serious nonspecific symptoms and signs of cancer. **Int J Cancer**. 2017 Jul 1;141(1):191-199.

9: Rasmussen LJ, et al. Soluble urokinase plasminogen activator receptor (suPAR) in acute care: a strong marker of disease presence and severity, readmission and mortality. A retrospective cohort study. **Emerg Med J**. 2016 Nov;33(11):769-775.

10: Hayek SS, et al. Soluble Urokinase Receptor and Chronic Kidney Disease. **N Engl J Med**. 2015 Nov 12;373(20):1916-25.

16. Please provide the name of the marketing authorization holder/manufacturer/supplier of the health technology (if applicable/available):

ViroGates A/S, Denmark

17. Marketing Authorization Status (MA) or CE-marking: When is MA or CE- marking expected? If possible, provide the time of planned marketing:

CE/IVD marking has been obtained on lateral flow test (suPARnostic Quick Triage) and on COBAS turbidimetric methods as well as on the less clinical relevant method ELISA.

18. Additional relevant information (up to 300 words.)

Originally, uPAR (urokinase plasminogen activator receptor) was proven a receptor for urokinase (uPA) which splits plasminogen into active plasmin. Moreover, uPAR interacts with other proteins and plays a role cell processes like migration, adhesion, angiogenesis, proliferation, and chemotaxis.

In recent years, soluble uPAR (suPAR) has been associated with several chronic diseases (including cardiovascular, hepatic, renal, and pulmonary diseases), and suPAR is a predictor of a negative outcome of various infectious diseases and in critically ill patients. A feature article in Science in 2018 on suPAR had the headline “Omen in the blood” which in short gives a good idea of what suPAR is.

Across diseases, the suPAR level discriminates non-survivors from survivors. suPAR reflects the level of chronic inflammation, and an elevated level predicts development of chronic diseases and cancer in the general population and prognosis in acute medical patients.

Plasma suPAR is stable with no diurnal variation and no changes following fasting. The level increases and decreases with progression and improvement of a disease, respectively, and show more stable kinetics compared to C-reactive protein (CRP).

A randomized controlled study included 26,653 acute admissions of 16,801 unique patients (6, and submitted). The suPAR level was available at the index admission in 7,905 patients (suPAR group), and no value was available in 8,896 (control group).
The proportion of patients who were discharged within 24 hours of admittance was higher in suPAR group compared to control group: 50.2% (3,966 patients) vs. 48.6% (4,317 patients), P=0.04).
Furthermore, the mean length of hospital stay in the suPAR group was shorter compared to the control group (4.3 days (SD 7.4) vs. 4.6 days (SD 9.4), P=0.04). There was no difference in mortality (1.3% vs. 1.8%, P=0.09) or readmission rate (8.5% vs. 7.7%, P=0.18) in patients discharged within 24 hours, for the suPAR group and control group respectively.

The normal suPAR plasma level is 2-3 ng/mL in healthy individuals, about 3-4 ng/mL in acute medical patients and 9-10 ng/mL in critically ill patients.

19. Interests and potential conflicts of interests

Please describe the proposer’s relationships or activities that may affect, be influenced by, or be perceived by others to be important for further management of the health technology that is proposed assessed. (E.g. proposer has financial interests in the matter. Proposer has or has had assignments in connection with the technology or to other actors with interest in the technology)

The author of this application, Jesper Eugen-Olsen, is CSO at ViroGates A/S, the company that holds the IP and produce the suPARnostic assay range.