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)**:**

Lyfstone AS

Name of proposal contact:

Stein Lian (contact point) or Frans van Andel (technical questions)

Telephone number:

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Date and locality:

5/12/2021, Tromsø, Norway

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

A Synovial Calprotectin Rule out Diagnostic Test for the Detection of Periprosthetic Joint Infection (PJI) following a total knee or total hip arthroplasty (TKA or THA)

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

The Lyfstone calprotectin test kit is a Lateral Flow Device (LFD) test, providing "Point of Care" (POC) results within minutes following biopsy collection. The speed and ease of use of the test platform allow "near patient" or "bedside" testing to aid diagnostics.

In a prosthetic joint, the first priority is to reliably rule out infection. The Lyfstone test is a CE-IVD labeled POC test, which measures the amount of calprotectin in Synovial Fluid. Calprotectin is abundantly present in neutrophils. Presence of neutrophils is a hallmark of PJI and a massive release of calprotectin occurs upon encounter with pathogens.

Elevated levels of calprotectin are proven indicators of both acute and chronic PJI and this is what the test is measuring. The high accuracy of the Lyfstone calprotectin test was confirmed in a clinical study published in a peer review journal (see elsewhere in this application).

Using the test starts with the extraction of a small amount of synovial fluid subtracted from a patients' joint. The fluid can be analyzed and the results will be available within 15 minutes.

The most important instruction for "used as intended" according to the manufacturer's instructions, is that a 1:101 dilution needs to be made by adding 20 µL synovial fluid to a sample diluent tube supplied by the manufacturer.

The test results are categorized into three groups:

- LOW risk of PJI infection - Calprotectin <14 mg/L
- MODERATE risk of PJI infection – Calprotectin levels 14<50 mg/L
- HIGH risk of PJI infection - Calprotectin levels ≥50 mg/L

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?

Diagnosis of PJI after THA or TKA is challenging, often requiring multiple diagnostic methods. Nevertheless, due to the insufficiency of standardized clinical and evidence-based guidelines, the diagnosis of PJI remains difficult despite the variety of tests available (1).

The lack of a gold standard, impacts the ability to compare results across studies and collect data enough to augment the understanding of a PJI.

A combination of laboratory, imaging studies, histopathology, and microbiology is usually necessary for the most accurate diagnosis of PJI (2).

An algorithm for deciding that a PJI infection is indeed present, has been developed by the Musculoskeletal Infection Society (MSIS) and is depicted in the following table:

	Score	Decision
Major criteria (at least one of the following):		
• Two positive cultures of the same organism		
• Sinus tract with evidence of communication to the joint or visualization of the prosthesis		Infected
Minor criteria (preoperative)		
• Elevated CRP or D-dimer (serum)	2	≥6 Infected
• Elevated ESR (serum)	1	
• Elevated synovial WBC count or LE (synovial)	3	2-5 Possibly infected
• Positive alpha-defensin (synovial)	3	
• Elevated synovial PMN (%) (synovial)	2	0-1 Not infected
• Elevated synovial CRP (synovial)	1	
• Intraoperative diagnosis		
Preoperative score	-	≥6 Infected
• Positive histology	3	
• Positive purulence	3	4-5 Inconclusive
• Single positive culture	2	
		≤3 Not infected

The presented algorithm is usually referred to as the MSIS 2013 diagnostic test panel and is standardly used in many hospitals in Europe and Norway.

It does not need much imagination to understand that applying the test panel is time consuming and involves laboratory assessments which take a varying amount of time to collect, on average 12- 15 days, during which the patient will not be discharged from the hospital, as there is a suspicion of PJI for which frequently prophylactic antibiotic treatment will be initiated as a standard procedure. If it is then confirmed later that the PJI is not present, it means that patients have stayed in the hospital unnecessarily and taken antibiotics for no reason.

References

(1) Parvizi J, Zmistowski B, Berbari EF, Bauer TW, Springer BD, Della Valle CJ, Garvin KL, Mont MA, Wongworawat MD, Zalavras CG. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. *Clin Orthop Relat Res.* 2011 Nov; 469(11):2992-4.

(2) Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR. Executive summary: diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2013 Jan; 56(1):1-10.

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	☐	☒

As current testing regimens for confirming the diagnosis of PJI following TKA and THA are cumbersome and time consuming, there is a need to introduce new testing techniques, which can be used to rule out an early diagnosis of PJI. The Lyfstone synovial calprotectin POC test is such a test and first clinical evaluations have shown the high accuracy of this test. The advantages of ruling out an early diagnosis of PJI are obvious as clinical teams in hospitals and orthopedic departments no longer have to wait for the confirmation of a PJI diagnosis and can take clinical action immediately. Early clinical action translates mostly to discharging a patient early and taking more targeted decisions about medication.

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

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

The Lyfstone Calprotectin for Synovial Fluid Test complies with all applicable Essential Requirements as set out in Annex I in Council Directive 98/79/EC. Technical documentation is established according to the requirements in Annex lll of the Council Directive 98/79/EC.

Lyfstone Calprotectin Test is grouped as a general in vitro diagnostic medical device and intervention by a Notified Body is not required.

INTENDED USE: The Lyfstone Calprotectin for Synovial Fluid test is a method for risk stratification of infection in suspected periprosthetic joint infection (PJI) patients by determination of the calprotectin (CLP) level in human synovial fluid samples in combination with the dedicated Lyfstone smartphone application. The test is intended as a diagnostic aid for screening of suspected PJI patients in a patient near setting or a laboratory. The test is for professional use only.

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." NA

6. Application of the technology:

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

Recently, a CUA analysis was carried out based on the clinical outcome data from the Lyfstone test published in peer reviewed journals and health resource data from the Netherlands (1).

Modelling the outcomes, the analysis showed base case dominant Incremental Cost-Effectiveness Ratio (ICER) values for the Lyfstone synovial calprotectin test with cost savings around EUR 1,827 for THA and EUR 1,855 for TKA per patient versus Standard of Care (SOC) (MIMS2013).

A sensitivity analysis included diagnostic accuracy of both the synovial calprotectin and SOC testing regimen, the cost of testing, the utility function, variations in number of bed days saved, the cost of empiric antibiotics and alternative management approaches. However, the Lyfstone synovial calprotectin test continued to have dominant ICER values versus SOC with varying levels of cost savings in the range of EUR 768 to EUR 2,887 (TKA) and EUR 763 to EUR 2,845 (THA).

The CUA confirmed that the high accuracy and early outcomes of the Lyfstone test compared to SOC, means that patients can be discharged early (i.e. they do not have to wait for the test results form the lab as inpatients), while prophylactic antibiotic regimens are no longer needed.

Thus, the advantages of the Lyfstone test as a rule out test of PJI in orthopedic practice were confirmed by the CUA analysis: early diagnosis of PJI is crucial as clinical teams at orthopedic departments no longer must wait for the confirmation in a laboratory setting of a PJI diagnosis (takes 12-15 days on average) and can take clinical action immediately. Early clinical action means that patients with a confirmed diagnosis with the Lyfstone test, can be immediately discharged from the hospital and do not need prophylactic antibiotic treatment

Reference:

(1) F van Andel, A. Klika, J Mikalsen, M.F. Janssen. Cost Utility Analysis of a Synovial Calprotectin Rule out Diagnostic Test for the Detection of Periprosthetic Joint Infection of the Hip and Knee. Manuscript submitted to the International Journal of Health Technology Assessment

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 Lyfstone test is to be used in the Orthopedic Department of a hospital and will result in improved patient values in combination with cost savings especially as regards bed days and the cost of prophylactic antibiotic treatment.

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

Yes	No
☐	☒

NA – As an emerging technology the Lyfstone test is not yet incorporated in national guidelines prepared by the Norwegian Directorate of Health

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

Yes	No
☐	☒

NA

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)?

Patients are affected because the use of the Lyfstone test will mean that they are diagnosed with high accuracy in a bedside environment, meaning that if the diagnosis of PJI is confirmed at an early stage, appropriate medical intervention action can be taken as follows: (1) in case of confirmation of "no PJI", discharge from the hospital, and (2) in case of confirmation of "PJI", appropriate medical follow-up such as revision surgery.

Orthopedic surgeons are affected because with the Lyfstone test they get an effective tool to rule out PJI at an early stage of the disease. This means they can take appropriate action much earlier in the disease process, which is beneficial for the patient and will save resources such as bed days and prophylactic antibiotic treatment.

The payer will also be affected because – as the above discussed CUA has clarified – the use of the Lyfstone test will result in net savings to the healthcare system. Savings will be generated under any sensitivity analysis scenario of model parameters varied such as the cost of bed days, the number of bed days, the cost of antibiotic treatment and the cost of the Lyfstone test.

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.

For the Lyfstone calprotectin test, the following PICOT cadre is suggested:

- Patient = the relevant patient population - in this case patients suspected of developing a PJI after a TKA or THA;
- Intervention = the intervention to be assessed - the Lyfstone calprotectin POC test;
- Comparison = the intervention to be compared (control intervention) - in this case the test regimen based on the MSIS 2013 criteria (= SOC or "Standard of Care");
- Outcome = the relevant outcomes/outcome measures - in this case relevant outcome measures are the establishment of an accurate diagnosis of PJI as well as the cost-effectiveness and utility patient values of the test;
- Time = minimum required follow-up period - in this case the short turnaround time to produce results from a test.

Please note that an HTA was already carried out on the Lyfstone test based on the clinical data on the test as collected in a pivotal clinical trial and health outcome data from the Netherlands. The HTA was based on state-of-the-art modeling techniques and a decision tree model was developed to compare the outcomes of the Lyfstone test to a MSIS2013 test regimen. The perspective taken in this HTA was a payer perspective and benefits of the Lyfstone test were expressed on the basis of ICER values and the cost per QALY.

Main scope of the HTA could be a replication of the work already carried – a model was developed in Excel and this can be made available to "Nye Metoder". The model could be adapted to Norwegian medical practice of testing for PJI and be populated with Norwegian health resource data.

Primary objective of this work would be to see if the cost savings which were generated with the Lyfstone test in the Netherlands would also accumulate in Norway.

A secondary objective would be to analyze the amount of benefits accrued by the use of the test and which party in Norway would benefit most of this (i.e. patient, orthopedic surgeon or payer).

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

Although an HTA has been carried out based on a dataset from the Netherlands, we are interested to learn if the Lyfstone test will result in similar cost efficiencies and utility functions in Norway.

Based on the decision tree model developed for the Netherlands, we expect similar results in Norway, showing that the Lyfstone test results in significant patient benefits and net savings for the healthcare system and would thus facilitate the adoption of the Lyfstone test in the Norwegian state benefit package.

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

The severity of the disease/condition the health technology targets

PJI is an uncommon, but serious complication of hip and knee replacement surgery, affecting approximately 1% of hip arthroplasties and 1% to 2% of knee arthroplasties. The most common symptom of PJI is pain. In patients presenting with nonspecific pain, diagnostic tests are used to differentiate between septic and aseptic causes, and this guides subsequent treatment. Surgical treatment consists of DAIR (Debridement, Antibiotics, and Implant Retention), one or two-stage revision exchange, either or combined with prophylactic antibiotic treatment.

PJI can be a catastrophic complication for patients, with a reported 5-year survival rate that is lower than that of breast, colon, and testicular cancers.

An accurate and timely diagnosis of PJI facilitates treatment. An incorrect diagnosis of a PJI in a healthy patient (a false positive result) can lead to more complex surgical management than is required. Conversely, a false negative result can lead to less optimal treatment allocations, delayed intervention, and more complex re-operation later. It is important to establish a diagnosis at an early stage, as this can prevent invasive follow-up treatment.

Expected effect

The clinical outcomes of the test were assessed in a recent pivotal clinical trial by Warren et al (1), in which the accuracy of the Lyfstone test was compared to a test regimen of MSIS2013. In the study, which was conducted at the Cleveland Clinic in the USA, synovial fluid samples were prospectively collected from 124 patients that underwent 17 revision TKAs (rTKA) from October 2018 to January 2020.

Patients were defined as aseptic or septic according to the 2013 MSIS criteria by two independent adjudicators blinded to laboratory results of calprotectin assays. This adjudication resulted in 53 rTKA that were defined as MSIS criteria positive (i.e. septic), while 70 were defined as negative (i.e. aseptic).

All synovial fluid collected for the Lyfstone calprotectin POC test analysis was obtained intraoperatively, either before arthrotomy via direct needle aspiration or after arthrotomy in cases where inadequate fluid was obtained prior to arthrotomy.

According to MSIS criteria, 53 rTKAs were septic while 70 rTKA were aseptic. In the (1) >50 mg/mL threshold scenario, the calprotectin POC performance showed a sensitivity, specificity, PPV, NPV, and AUC, respectively, of 98.1%, 95.7%, 94.5%, 98.5%, and 0.969. In the (2) >14 mg/mL threshold scenario, the sensitivity, specificity, PPV, NPV and AUC were 98.1%, 31 87.1%, 85.2%, 98.4%, and 0.926, respectively.

The authors of the study concluded the following:

“The Lyfstone calprotectin lateral flow POC test and ELISA, at a threshold of >50 mg/L and >14 mg/L, demonstrated high sensitivity and specificity for diagnosing PJI in rTKA with the >50 mg/L threshold performing better. Notably the POC performs better than the ELISA at a >14 mg/L threshold. The calprotectin POC test has excellent PJI diagnostic characteristics including high sensitivity and specificity in rTKA patients. This test could be effectively implemented as a rule out test”.

The Warren study confirmed outcomes of earlier work in the UK by Trotter (2). The researchers of the UK study concluded that, “the lateral flow test has a high negative predictive value (NPV) compared to International Consensus Meeting (ICM) criteria, useful for ruling out infection and the test is highly accurate for diagnosing PJI when compared to a clinical review-based gold standard (ICM-CR)”.

References:

(1) Jared Warren, DO, ATC, CSCS, Hiba K. Anis, MD, Kathleen Bowers, BS, Tejbir Pannu, MD, Jesus Villa, MD, Alison K. Klika, MS, Jessica Colon-Franco, PhD, Nicolas S. Piuzzi, MD, and Carlos, A. Higuera, MD. Diagnostic Utility of a Novel Point-of-Care Test of Calprotectin for Periprosthetic Joint Infection After Total Knee Arthroplasty - A Prospective Cohort Study. J Bone Joint Surg Am. 2021;00:1-7 d http://dx.doi.org/10.2106/JBJS.20.01089

(2) Alexander J. Trotter et al. Preliminary evaluation of a rapid lateral flow calprotectin test for the diagnosis of prosthetic joint infection. *Bone Joint Res.* 2020 May; 9(5): 202–210. Published online 2020 Jun 8. doi: 10.1302/2046-3758.95.BJR-2019-0213.R1 PMCID: PMC7284294. PMID: 32566141

Safety

From the clinical studies discussed in the previous section, no untoward effects have been reported when applying the Lyfstone calprotectin test.

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

The incidence of PJI varies with the joint involved . Reported incidences following TKA, THA and total shoulder arthroplasty have been reported to be 0.25% to 2% (0,875 point incidence THA), 0.5% to 1% (0,75 point incidence TKA) and less than 1% respectively (1,2).

Between 23–25% of revision TKA procedures and 12–15% revision THA procedures are performed for PJI (3) . In concordance with these commonly cited figures, the UK National Joint Registry (England, Wales, Northern Ireland and the Isle of Man) reported that in 2018 PJI was the cause of 22.5% of TKA failures and 13.1% of THA failures (4).

While the incidence of PJI remains low the number of patients are likely to increase over time however as the number of arthroplasty procedures performed annually increases.

It should be noted that the incidence of PJI varies throughout the literature. As a result, existing data needs to be interpreted with caution. Wang et al. (5) reported a reduction in the incidence of PJI from 1.9% to 0.76% between 2006 and 2014. Likewise, Runner and colleagues (6) reported a reduction in the incidence of PJI from 1.4% to 0.6% between 2008 and 2016.

This data is at variance with reports from the United States National Inpatient Sample suggesting that between 2001 and 2009 the incidence of PJI in patients having THA increased from 1.99% to 2.18% and 2.05% to 2.18% for patients having TKA (7).

Data from the Nordic Arthroplasty Registry has reported an increase in the rate of revision procedures performed for infected THA from 0.46% to 0.71% between 1999 and 2009 (8).

According to the 2020 report of this registry (9), the total number of THAs recorded in Norway from 1987 to 2019 was 244 555 (7,642 per year) and the revision rate continued to decline from 12.2% in 2019 compared to 14-15% about ten years ago. As regards TKAs, in the period 1994-2019, 104 857 (4,194 per year) knee replacements, were recorded and the registry notes there was an increase of 3.8% in primary knee replacements since 2018.

If for all THAs performed in Norway per year (total 7,642 patients) the Lyfstone test would standardly be used as a rule out test, the total net cost saving would be EUR 13,96 million (EUR 1.827 per patient) and for TKA (4,194 patients per year) EUR 7.78 million (EUR 1,855 per patient), in total EUR 21,74 million.

Please note that these total savings are based on the Dutch CUA presented above and this data needs to be verified by Norwegian data. Please also note that net savings are reported are discounted for the cost of the Lyfstone test!

References:

(1) Namba RS, Inacio MC, Paxton EW. Risk factors associated with deep surgical site infections after primary total knee arthroplasty: an analysis of 56,216 knees. J Bone Joint Surg Am 2013;95:775-82.

(2) Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. Am J Infect Control 2009;37:783-805.

(3) Bozic KJ, Kurtz SM, Lau E, et al. The epidemiology of revision total knee arthroplasty in the United States. Clin Orthop Relat Res 2010;468:45-51

(4) National Joint Registry (NJR). 15th Annual Report 2018: National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. 2018. 13. Parvizi J, Tan TL, Goswami K, Higuera

(5) Wang FD, Wang YP, Chen CF, et al. The incidence rate, trend and microbiological aetiology of prosthetic joint infection after total knee arthroplasty: A 13 years' experience from a tertiary medical center in Taiwan. J Microbiol Immunol Infect 2018;51:717-22

(6) Runner RP, Mener A, Roberson JR, et al. Prosthetic Joint Infection Trends at a Dedicated Orthopaedics Specialty Hospital. Adv Orthop 2019;2019:4629503.

(7) Kurtz SM, Lau E, Watson H, et al. Economic burden of periprosthetic joint infection in the United States. J Arthroplasty 2012;27:61-5.e1.

(8) Dale H, Fenstad AM, Hallan G, et al. Increasing risk of prosthetic joint infection after total hip arthroplasty. Acta Orthop 2012;83:449-58.

(9) REPORT June 2020 Norwegian National Advisory Unit on Arthroplasty and Hip Fractures

Consequences for resource use in the public health service

Consequences for the public health service in Norway are that the present test batch for PJI following THA and TKA should be replaced by the Lyfstone POC test. If this is structurally done for all patients who undergo a THA or TKA in Norway (in total about 11.836 patients per year), there will be net savings of around NOK 217,4 million per year (EUR 21,74 million per year) (mainly in terms of bed capacity and prophylactic use of antibiotics).

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

The present national guidelines of testing patients for PJI after a THA or a TKA should be revised to determine the Lyfstone test as a standard POC rule out test.

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):

F van Andel, A. Klika, J Mikalsen, M.F. Janssen. Cost Utility Analysis of a Synovial Calprotectin Rule out Diagnostic Test for the Detection of Periprosthetic Joint Infection of the Hip and Knee. Manuscript submitted to the International Journal of Health Technology Assessment

Bozic KJ, Kurtz SM, Lau E, et al. The epidemiology of revision total knee arthroplasty in the United States. Clin Orthop Relat Res 2010;468:45-51

Dale H, Fenstad AM, Hallan G, et al. Increasing risk of prosthetic joint infection after total hip arthroplasty. Acta Orthop 2012;83:449-58

Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. Am J Infect Control 2009;37:783-805.

Kurtz SM, Lau E, Watson H, et al. Economic burden of periprosthetic joint infection in the United States. J Arthroplasty 2012;27:61-5.e1.

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Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR. Executive summary: diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2013 Jan; 56(1):1-10.

Parvizi J, Zmistowski B, Berbari EF, Bauer TW, Springer BD, Della Valle CJ, Garvin KL, Mont MA, Wongworawat MD, Zalavras CG. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. *Clin Orthop Relat Res.* 2011 Nov; 469(11):2992-4

REPORT June 2020 Norwegian National Advisory Unit on Arthroplasty and Hip Fractures

Runner RP, Mener A, Roberson JR, et al. Prosthetic Joint Infection Trends at a Dedicated Orthopaedics Specialty Hospital. Adv Orthop 2019;2019:4629503.

Alexander J. Trotter et al. Preliminary evaluation of a rapid lateral flow calprotectin test for the diagnosis of prosthetic joint infection. *Bone Joint Res.* 2020 May; 9(5): 202–210. Published online 2020 Jun 8. doi: 10.1302/2046-3758.95.BJR-2019-0213.R1 PMCID: PMC7284294. PMID: 32566141

Wang FD, Wang YP, Chen CF, et al. The incidence rate, trend and microbiological aetiology of prosthetic joint infection after total knee arthroplasty: A 13 years' experience from a tertiary medical center in Taiwan. J Microbiol Immunol Infect 2018;51:717-22

Jared Warren, DO, ATC, CSCS, Hiba K. Anis, MD, Kathleen Bowers, BS, Tejbir Pannu, MD, Jesus Villa, MD, Alison K. Klika, MS, Jessica Colon-Franco, PhD, Nicolas S. Piuzzi, MD, and Carlos, A. Higuera, MD. Diagnostic Utility of a Novel Point-of-Care Test of Calprotectin for Periprosthetic Joint Infection After Total Knee Arthroplasty - A Prospective Cohort Study. J Bone Joint Surg Am. 2021;00:1-7 d http://dx.doi.org/10.2106/JBJS.20.01089

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

Legal Manufacturer is: Calpro AS Arnstein Arnebergsvei 30 1366 Lysaker Norway

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

The product is already fully authorized for market access. • Compliant with all applicable Essential Requirements as set out in Annex I in Council Directive 98/79/EC and thus CE-marked. • Certificate of Free Sales from the Norwegian Medicines agency no. NO-18/17004, dated 16.11.2018 to the legal manufacturer Calpro AS.

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

Lyfstone AS offers its test in all EU markets and ordering the test via the Lyfstone website is an option. Lyfstone is in the process of arranging reimbursement in the EU and Norway.

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 proposer to "Nye Metoder" is Lyfstone AS, the owner, developer, and sales responsible party of the calprotectin test for PJI following THA and TKA. The initial collection of samples and clinical data in the development of the test was performed at UNN in Tromsø during 2012 – 2014. Subsequent development and validation/verification has been performed internationally.