Evaluation proposal for the Danish Health Technology Council regarding <technology> for <treatment/use/diagnosis of/in patient population<

Instructions for the applicant

This template is used for submitting evaluation proposals to the Danish Health Technology Council in connection with the request of an assessment of new or existing health technology. Evaluation proposals are completed by the applicant and aim to provide the Danish Health Technology Council with a background for launching evaluations. Applicants are recommended to engage in a dialogue with the Danish Health Technology Council's secretariat to receive guidance for proper completion.

The template covers the following main topics:

- Information about the applicant
- Information about the health technology
- Information about the evidence base for the health technology

The Danish Health Technology Council defines health technologies broadly as any use of medical devices, procedures, or processes applied in the treatment or diagnosis of patients. Evaluations of health technologies by the Danish Health Technology Council are always conducted with the consideration of four perspectives: Clinical Effectiveness and Safety, the Patient Perspective, Organizational Implications, and Health Economics.

Evaluation proposals that are considered by the Danish Health Technology Council will be published on the Danish Health Technology Council's website. If there is confidential information in the evaluation proposal, it must be clearly marked using yellow text highlighting ("example").

The evaluation proposal should be kept as concise as possible and be in either Danish or English. At the end of the document, there is an example of a completed evaluation proposal that applicants can use for inspiration.

If questions arise during the preparation of the evaluation proposal, applicants may contact the Danish Health Technology Council's secretariat for elaboration or clarifications.

In addition to the evaluation proposal, companies, regions, and hospital administrations can complete and include a cost outline that provides an overview of the total costs associated with the use of the health technology. The Danish Health Technology Council's secretariat provides a cost outline template that can be accessed on the Danish Health Technology Council's website.

The completed evaluation proposal is the applicant's product.

Information about the applicant

Name of the applicant (company name or the name of the hospital/region)*:

C2N Diagnostics, LLC

* If you are a public applicant, the Danish Health Technology Council refers to the requirement that the evaluation proposal in its entirety must be approved by the hospital or regional management.

Contact person (name, position):

Daniel Connell, Head of Strategic Alliances

Date of submission of the evaluation proposal:

17-Jun-2024

Information about the health technology

Briefly describe the health technology to be evaluated:

The PrecivityAD® test is for individuals 55 and older undergoing evaluation for a cognitive complaint by a healthcare provider (HCP). The test is intended to be interpreted by an HCP in the context of additional clinical information, ie *not* for general population screening. The PrecivityAD® blood test identifies whether a patient is likely to have the presence or absence of amyloid plaques in the brain, a pathological hallmark of Alzheimer's disease. The PrecivityAD® blood test relies on precise and robust quantitation of Amyloid Beta 42/40 ratio (Aβ 42/40) and detection of Apolipoprotein E proteotype (equivalent to ApoE genotype) in blood samples using C_2N's proprietary mass spectrometry platform, and is performed at a central CAP/CLIA laboratory in St. Louis, MO, USA. Link to PrecivityAD website including links to HCP & patient education

Provide a rationale for why it is relevant to conduct an evaluation of the health technology:

The burden of Alzheimer's Disease is vast and growing given an ageing population, while evidence shows that early diagnosis and lifestyle changes can mitigate Alzheimer's disease progression, thus helping to reduce long-term healthcare costs. Studies show that ~50k Danes remain undiagnosed (link to AlzheimersEurope.org), and part of the problem is the invasiveness of lumbar punctures (LPs) to extract cerebral spinal fluid (CSF) along with a lack of capacity of PET scanners, not to mention a shortage of Neurology Specialists and skilled labor able to conduct LPs. [redacted] The relevance of evaluating the PrecivityAD blood test is to offer a CE-mark regulatory approved blood test to Danish healthcare ecosystem to enable broad access to a simple, convenient and accurate blood

test that can both rule-out and rule-in amyloid pathology, and thus aid in the diagnosis of Alzheimer's Disease (AD).

Recent CEOi international consensus recommendations cite the need to incorporate blood biomarkers (BBMs) into both Primary Care and Memory Care to address growing diagnostic bottlenecks, and also cites minimum performance characteristics for BBM use in both Primary Care & Memory Care.

Acceptable performance of blood biomarker tests of amyloid pathology — recommendations from the Global CEO Initiative on Alzheimer's Disease | Nature Reviews Neurology

Notably, PrecivityAD meets both requirements, whether using the existing cutoffs to yield ~15% Intermediate zone and 86% NPV/PPV, or expanding to ~20% grey zone and achieving ~90% NPV/PPV (from supplemental Appendix of clinical validation study, cited in list below).

Unfortunately clinical examination with tools such as MMSE and MoCA do not have high predictive values for amyloid pathology especially in the early stages of disease, and HCPs using such tools cite limited confidence in diagnosing a patient with only a clinical evaluation (~55% diagnostic confidence cited in primary care). The likely impact is that more patients are being referred from primary care to Memory Centers in cases of borderline cognitive results, which could alleviated if/when pairing a borderline cognitive evaluation with a Low APS PrecivityAD blood test result.

At the other extreme, some patients may be getting a negative cognitive exam result, even though the patient's family was the one who recommended the physician visit having noticed signs and symptoms of dementia, and thus that patient is not being referred to a Memory Center; the inclusion of PrecivityAD could capture those patients who are in the earliest phases of disease transition, where pathological changers are detectable, patient's families are detecting subtle changes, and yet the patient achieves a normal cognitive evaluation with a brief cognitive assessment.

The Knowledge and Attitudes of Primary Care and the Barriers to Early Detection and Diagnosis of Alzheimer's Disease - PMC (nih.gov)

The PrecivityAD blood test could help the Danish healthcare system better diagnose patients when coupling with cognitive evaluations, generating a 2x2 matrix to clarify when and why to incorporate scarce downstream resources. For example when and why to prioritize MRI and/or in-depth NeuroPsychological evaluations for specific subgroups of the 2x2 matrix (ie, APS Low and Cog eval positive; APS high and cog eval negative, etc).

Thus including the PrecivityAD blood test into the Danish AD diagnostic paradigm can improve not only diagnostic confidence but also clarify the diagnostic decision-tree for downstream resource utilization for tools such as MRI, in-depth Neuro-Psychological evaluation, CSF biomarker analysis and/or amyloid PET, disease modifying therapies, etc.

Clinical diagnostic tools that have shown high correlation to detecting amyloid pathology (CSF and amyloid PET) are either invasive, costly or inaccessible to rural communities. Additionally, lumbar punctures (LPs) must be performed by skilled labor, often in acute care settings as opposed to a Primary Care, and numerous publications cite patient reluctance and/or anxiety to undergo an LP (cited below).

Additionally disease modifying therapies (DMTs) that have shown an ability to address the underlying causes of Alzheimer's Disease are being evaluated by the European Medicines Agency that could add an

additional tool in the therapeutic care pathway, thus the urgency of early and accurate diagnosis of AD through the convenience of a blood test that can help to optimize downstream resource utilization.

Finally, intermediate APS and high APS results coupled with system-wide disease education could encourage population focus on modifiable risk factors known to contribute to Alzheimer's pathology, and thus delay progression from Mild Cognitive Impairment to Alzheimer's Disease, which has the potential to reduce long-term Danish healthcare costs such as acute care nursing facilities and hospice care while also increasing labor productivity as caregivers would not need to take as much time off of work to support family suffering from the effects of AD.

[redacted]

Sharing below additional publications on the impact of BBMs:

Optimising Alzheimer's Disease Diagnosis and Treatment: Assessing Cost-Utility of Integrating Blood Biomarkers in Clinical Practice for Disease-Modifying Treatment | The Journal of Prevention of Alzheimer's Disease (springer.com)

Impact of blood biomarkers on cost and wait time in diagnosing treatment-eligible patients for Alzheimer's disease: A simulation study (wiley.com)

Soaring dementia care costs reach £42 billion in UK – and families bear the brunt | Alzheimer's Society (alzheimers.org.uk)

What is the classification of the health technology?

☐Medical device, which is CE marked*

- ☐ Class I
- ☐ Class IIA
- ☐ Class IIB
- ☐ Class III

☒Diagnostic technology, which is CE marked**

- ☐ Class A
- ☒ Class B
- ☐ Class C
- ☐ Class D

☐Procedure (workflow related to diagnostics, treatment, rehabilitation, and/or with a preventive purpose)

If the procedure involves the use of one dominant health technology, describe it, and provide its CE marking and classification

* The Danish Health Technology Council only evaluates medical devices that are CE marked or otherwise meets the legal requirements for medical devices.

** Diagnostic technology utilizing medical equipment for *in vitro* diagnostics.

☒ the applicant hereby declares under penalty of perjury that the above information is accurate and complies with the relevant legislation concerning CE marking.

Briefly describe the current status of the use of the health technology in Denmark and abroad.

PrecivityAD obtained CE-mark in late 2020, and while not currently used in Denmark since PrecivityAD has not yet been commercialized in Europe, PrecivityAD is being used in Eisai's AHEAD 3-45 study (among others not cited in the public domain) which is being conducted in Sweden, UK, Netherlands & Spain, US, Australia & Japan. The PrecivityAD blood test is offered as a CAP/CLIA laboratory developed test and has been used clinically in the US since 2020 by various healthcare institutions, and is also being used in additional European clinical trials given CE-mark. A clinical utility study published the relevance of PrecivityAD to increase confidence of a clinical diagnosis while also leading to statistically significant changes in patient care, changes that were unimpacted by patient sex nor age. Monane MM, Johnson KG, Snider, BJ, et al. **A blood biomarker test for brain amyloid impacts clinical decision making among memory specialists in the evaluation of cognitive impairment.** *Ann Clin Transl Neurol* 2023. http://doi.org/10.1002/acn3.51863 [redacted]

Proposed PICO specification (Population, Intervention, Comparator, Outcome) for framing the evaluation question:

Population – The patient group in/for which the health technology is utilized and which the evaluation focuses on, including the annual number of patients in Denmark:	Individuals and patients 55 years and older who are presenting to a physician with a cognitive complaint. To be used in conjunction with additional clinical information and *not* to be used as a screen for the general population, only for those seeking medical attention for a cognitive complaint. It is estimated that there are ~50k Danes who would benefit from the PrecivityAD blood test.
Intervention – The specific health technology to be evaluated:	PrecivityAD® blood test identifies whether a patient is likely to have the presence or absence of amyloid plaques in the brain, a pathological hallmark of Alzheimer's disease. The PrecivityAD blood test is intended to be used as a substitute for amyloid PET or CSF when evaluating patients for amyloid pathology, eliminating the need for 80-85% of lumbar punctures/CSF nationwide, and

	supplanting the need to build additional capacity for amyloid PET.
Comparator – The health technology or treatment that is natural to compare with and currently used as the best and most widely adopted alternative to the intervention in Denmark (I):	Amyloid PET is the gold standard for assessing amyloid Pathology, however is viewed as costly, exposes patients to radioactivity and is viewed as inconvenient to patients given the need to remain still in a confined space for extended periods of time. Additionally there is a subjective nature to amyloid PET visual interpretation, alleviated in clinical trials via 5 readers for every scan, which is impractical in the real world. Cerebral Spinal Fluid (CSF) testing is widely adopted in Denmark at Memory Specialty clinics to evaluate amyloid pathology. NPV & PPV of CSF vs amyloid PET is in the 80-90% range, respectively. CSF test performance vs amyloid PET is similar to that of PrecivityAD, including the use of a tertiary scoring system of low probability, intermediate probability or high probability of Alzheimer's pathology. Clinical validation of PrecivityAD was conducted versus amyloid PET in a population of patients of whom 85% had Mild Cognitive Impairment.
Outcome – The clinical effectiveness measures that would be relevant to assess the health technology compared to the comparator are:	NPV & PPV vs amyloid PET, Percent falling into an intermediate/gray zone. Performance across race, ethnicity, sex/gender.

* PICO is a tool utilized by the Danish Health Technology Council to formulate precise issues and is crucial in the planning and execution of an evaluation by the Danish Health Technology Council. PICO is further detailed in the Danish Health Technology Council's methods guide, available on the Danish Health Technology Council's website.

Provide a brief description of the proposed comparator and whether the suggested health technology (intervention) is suggested to replace or to be an add on to the current alternative:

Amyloid PET is considered the gold standard to diagnose amyloid pathology, however is costly and not abundantly available, thus CSF is most often being used in Denmark to aid in the diagnosis of Alzheimer's Disease.

At the GP level, most commonly simple cognitive tools are being used and biomarkers are rarely used given the lack of specialty staff to conduct lumbar punctures.

[redacted]

The output of PrecivityAD is the Amyloid Probability Score (APS).

PrecivityAD offers a 3-tier cutoff of Low APS (0-35), Intermediate APS (36-57) and High APS (58-100).

15% of patients typically fall in the Intermediate APS range, thus patients with Intermediate APS results may benefit from adding-on CSF or PET to confirm diagnosis.

[redacted]

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial - The Lancet

Is the health technology mentioned in professional clinical guidelines from institutions like the Danish Health Authority or medical scientific societies? Specify which ones:

No, PrecivityAD is not referenced in Danish guidelines, however PrecivityAD is cited in the 2022 EU/US CTAD Task Force on BBMs.

Angioni D, Delrieu J, Hansson O, et al. ***Blood Biomarkers from Research Use to Clinical Practice: What Must Be Done? A Report from the EU/US CTAD Task Force.*** J Prev Alzheimers Dis. *2022;9(4):569-579. doi:10.14283/jpad.2022.85*

Additionally, C2N's amyloid beta 42/40 assay has shown to be the best performing assay in a head-to-head comparison.

Janelidze et al, ***Head-to-head Comparison of 8 Plasma Amyloid 42/40 Assays in Alzheimer's Disease****; JAMA Neurology, 2021. doi:10.1001/jamaneurol.2021.3180*

Finally, recent CEOi proposed consensus recommendations for BBM performance characteristics, and notably PrecivityAD meets the bar required for use in either Primary Care or Memory Care.

Schindler et al, Nature Reviews Neurology 2024, https://doi.org/10.1038/s41582-024-00977-5).

Has the health technology been evaluated by other HTA institutions (e.g. NICE, Nye Metoder)? Specify which ones:

[redacted]

Provide the names of manufacturers/suppliers of the health technology, if relevant:

C2N Diagnostics, LLC performs all testing in a central CAP/CLIA and ISO 13485 certified lab in St. Louis, MO USA.

[redacted]

Information about the evidence base for the health technology:

Indicate whether the health technology (compared to the current alternative) aims to improve treatment/diagnosis of the patient group as perceived from one or more of the following perspectives (indication of the primary impact of using of the health technology):

☒ Clinical effectiveness and safety	☒ Patient preferences and experiences
☒ Organizational aspects, such as changes to workflows	☒ Costs associated with treatment/diagnostics

*For the evaluation of health technologies, the Danish Health Technology Council employs four perspectives: Clinical Effectiveness and Safety, the Patient Perspective, Organizational Implications, and Health Economics. For further elaboration on these perspectives, refer to the Danish Health Technology Council Council's methods guide for the evaluation of health technologies, available on the Danish Health Technology Council Council's website.

State the expected impact of the health technology within the indicated perspectives above:

Organizational Aspects:

Invasiveness & costs of current alternatives for Alzheimer's disease biomarker testing, and also the lack of Memory Specialists and skilled labor able to perform lumbar punctures, leads to reduced biomarker testing altogether which limits Physician ability to accurately diagnose Alzheimer's Disease. Literature shows that confidence in a diagnosis of Alzheimer's disease is only 55-70% without the use of pathological biomarkers.

Patients on certain medications have contraindications for lumbar punctures, and many patients have a reluctance to get a lumbar puncture altogether to enable CSF testing; costs and capacity constraints associated with PET scanners limit this testing option; radioactive exposure from amyloid PET also a potential patient concern.

Compare all these limitations to the simplicity of a blood test, which from an organizational perspective could be implemented in a General Practitioner's office and/or collected at a primary care physician's office, or possibly even at a patient's home via mobile phlebotomy, for an assay that has shown to have clinical effectiveness of 86% NPV and 86% PPV with only a 15% intermediate zone (or higher NPV/PPV if expanding to a 20% gray zone based on published data).

PrecivityAD can both rule-out and rule-in amyloid pathology at the Low & High APS categories, with increasing NPV/PPV values the further from the tertiary cutoffs and closer to 0 or 100 APS extremes. Intermediate APS results would either serve as impetus to enact lifestyle changes, or encourage a potential reluctant patient to consider an invasive lumbar puncture, if deemed medically necessary.

Health Economics & Costs

The price of PrecivityAD has not yet been established for Denmark however the goal would be to clarify local budget assumptions for CSF & PET, [redacted]

By adopting the PrecivityAD blood test the Danish government would not need to make long-term investments in PET capacity nor need to train more healthcare providers to perform lumbar punctures, rather simply endorse a cost-effective coverage rate that ensures all Danish citizens 55 and older who are seeking medical attention for a cognitive complaint can have access to the PrecivityAD blood test.

Access to accurate blood biomarker testing to aid in the diagnosis of Alzheimer's disease also enables the potential to lower long-term healthcare costs associated with diagnosis via lifestyle changes that have shown to delay progression of disease, and possibly soon DMTs that are under evaluation by EMA, ensuring only the right patient is put on the right drug at the right time.

[redacted]

Patient perspective

From a patient perspective, there are various references to patients' reluctance to undergo a lumbar puncture to assess CSF given the anxiety of the invasive procedure. One such study, Blazel et al J Alz & Dis 2020, https://doi.org/10.3233%2FJAD-200394 cites serial testing as a restricting factor for longitudinally assessing CSF, critically important when considering potential for annual or periodic testing, and different racial & ethnic groups were cited as having less willingness to undergo a lumbar puncture, an important consideration for diagnostic equity and cultural sensitivity throughout the population.

Another study considered qualitative interviews with patients, and anxiety and severe back pain was cited as a patient impact, which is clearly alleviated via simple blood draw: The Patient Experience of Lumbar Puncture at a Teaching Hospital: A Qualitative Descriptive Study (P3.393) | Neurology

Clinical effectiveness

PrecivityAD yielded NPV (86%), PPV (86%) at the low and high cutoff vs amyloid PET, respectively, from two cohorts comprised of 85% having Mild Cognitive Impairment and the remainder early AD, the target intended use patient population.

One cohort was a retrospective analysis of a Phase 3 clinical trial for an anti-amyloid Disease Modifying Therapy (MissionAD) while the other was a prospectively enrolled sub-study of IDEAS, known as PARIS, which was prospectively assessing amyloid PET epidemiology in a US Medicare population.

The output of PrecivityAD is the Amyloid Probability Score, APS, which offers a tertiary outcome of Low APS, Intermediate APS or High APS.

Given the PrecivityAD logistic regression model, NPV & PPV increase as APS values approach the limits, ie 0 and 100 APS, respectively. NPV exceeds 90% at values below 20 APS and PPV exceeds 90% at values above 80 APS (From supplemental appendix of Hu et al, Jama Neurology 2022).

A separate independent validation of PrecivityAD on 200 patients from the Australian AIBL cohort showed PrecivityAD yielded 85% Sensitivity and 96% Specificity vs amyloid PET.

Independent study demonstrates amyloid probability score accurately indicates amyloid pathology (wiley.com)

Additionally a separate prospective clinical utility study showed statistically significant changes in clinician-reported confidence of an AD diagnosis before vs after the PrecivityAD blood test (Monane et al, cited below). Overall, 33% (116/347) of patients had planned changes in their AD drug therapy in this clinical utility study (shared below in references).

Monane MM, Johnson KG, Snider, BJ, et al. ***A blood biomarker test for brain amyloid impacts clinical decision making among memory specialists in the evaluation of cognitive impairment.*** Ann Clin Transl Neurol *2023.* *http://doi.org/10.1002/acn3.51863*

The amyloid beta 42/40 component of PrecivityAD has been studied extensively across race/ethnicity, and in this publication C2N's Mass Spec technology outperformed immunoassays p-tau181 and NeuroFilament Light:

Schindler SE, Karikari TK, Ashton NJ, et al. ***Effect of Race on Prediction of Brain Amyloidosis by Plasma Aβ42/Aβ40, Phosphorylated Tau, and Neurofilament Light.*** Neurology. *2022;99(3):e245-e257. doi:10.1212/WNL.0000000000200358*

Finally PrecivityAD is being used prospectively in the AHEAD 3-45 trial, and recent data shows that while different races and ethnicities indeed have differing levels of circulating plasma protein biomarkers, PrecivityAD showed consistent ability to predict amyloid status regardless of race/ethnicity.

Molina-Henry DP, Raman R, Liu A, et al. ***Racial and ethnic differences in plasma biomarker eligibility for a preclinical Alzheimer's disease trial.*** Alzheimers Dement. *Published online April 17, 2024. doi:10.1002/alz.13803*

Ultimately PrecivityAD has the potential to reduce the need for lumbar punctures and CSF by 85-100%, thus making Alzheimer's Disease biomarker testing more broadly accessible to the Danish population, enabling earlier diagnosis, earlier intervention and earlier lifestyle changes that can serve to dramatically lower long-term Danish healthcare costs – especially once DMTs are available in Denmark.

Provide references* for documentation of the health technology's effects (if possible, include up to 2 key references per perspective):

Clinical effectiveness and safety	1. Hu Y, Kirmess KM, Meyer MR, et al. **Assessment of a plasma amyloid probability score to estimate amyloid positron emission tomography findings among adults with cognitive impairment**. *JAMA Netw Open.* 2022;5:e228392. Published 2022 Apr 1. doi:10.1001/jamanetworkopen.2022.8392 2. Fogelman I, West T, Braunstein JB, et al. **Independent study demonstrates amyloid probability score accurately indicates amyloid pathology.** *Ann Clin Transl Neurol.* 2023; 10(5), 765–778. doi.org/10.1002/acn3.51763
The Patient perspective	1. Monane MM, Johnson KG, Snider, BJ, et al. **A blood biomarker test for brain amyloid impacts clinical decision making among memory specialists in the evaluation of cognitive impairment.** *Ann Clin Transl Neurol* 2023**.** http://doi.org/10.1002/acn3.51863 2. Monane et al, **Patient Age and Sex Do Not Appear to Influence Clinical Decision Making Around a Blood Biomarker Test for the Evaluation of Cognitive Impairment;** *Poster, Canadian Conference on Dementia 2023*
Organizational Implications	1. Mattke et al, **Expected wait times for access to a disease modifying Alzheimer's treatment in England**; Journal of Health Services Research & Policy, 2024 [presumed that Denmark healthcare preparedness is similar to that of England] 2. Jørgensen et al, **Potential for Prevention of Dementia in Denmark**; Alz & Dementia 2023 https://doi.org/10.1002/alz.13030
Health Economics	1. Castenario et al, **Use of a Blood Biomarker Test Improves Economic Utility in the Evaluation of Older Patients Presenting with Cognitive Impairment, *Population Health Management 2024;* DOI:0.1089/pop.2023.03091,** 2. Mattke et al, **Estimated Investment Need to Increase England's Capacity to diagnose Eligibility for an Alzheimer's Treatment to G7 Average Capacity Levels;** J Prev Alz Dis 2024 [presumed Denamrk is similar to England]

* Reference to published, ongoing, or unpublished data.

Indicate whether the health technology is expected to incur additional costs, cost reductions, or be cost-neutral compared to the current alternative. Briefly describe how the costs are expected to be distributed across sectors (hospital, general practice, municipalities, patients, etc.), and what is considered to drive the potential addition or reduction in costs. The Danish Health Technology Council encourages applicants to complete and include the Danish Health Technology Council's cost outline, accessible on the Danish Health Technology Council's website.

☐ Additional costs ☒ Cost reductions ☐ Cost-neutral

In a peer-review published paper, PrecivityAD predicted an 11% reduction in US healthcare costs compared to CSF & PET. Note that the list price of PrecivityAD in the US is equivalent to 8690 DKK, however a price has not yet been established for Denmark.

C2N would seek to customize this model with Danish assumptions upon entrance into the market with a net cost-neutral price [redacted]

Castenario et al, ***Use of a Blood Biomarker Test Improves Economic Utility in the Evaluation of Older Patients Presenting with Cognitive Impairment, Population Health Management 2024; DOI:0.1089/pop.2023.03091,***

[redacted]

ESTIMATED INVESTMENT NEED TO INCREASE ENGLAND'S CAPACITY TO DIAGNOSE ELIGIBILITY FOR AN ALZHEIMER'S TREATMENT TO G7 AVERAGE CAPACITY LEVELS • The Journal of Prevention of Alzheimer's Disease (jpreventionalzheimer.com).

Projected Savings to Canadian Provincial Budgets from Reduced Long-Term Care Home Utilization Due to a Disease-Modifying Alzheimer's Treatment | The Journal of Prevention of Alzheimer's Disease (springer.com)

Free-text field (optional additional information, max 300 words):

Example

Evaluation proposal to the Danish Health Technology Council regarding non-operative treatment of distal radius fractures in patients over 65 years of age.

Information about the applicant

Name of the applicant (company name or the name of the hospital/region)*:

The evaluation proposal has been prepared by the Danish Health Technology Council's secretariat.

* If you are a public applicant, the Danish Health Technology Council refers to the requirement that the evaluation proposal in its entirety must be approved by the hospital or regional management.

Contact person (name, position):

Anders Andersen, Health Science Officer, the Danish Health Technology Council's secretariat

Date of submission of the evaluation proposal:

June 5 2023

Information about the health technology

Briefly describe the health technology to be evaluated:

Non-operative treatment in the form of applying a cast for distal radius fractures. In cases of distal radius fracture, the application of a cast can be utilized to stabilize the fracture and promote proper healing.

Provide a rationale for why it is relevant to conduct an evaluation of the health technology:

New evidence indicates that the clinical effectiveness of surgical treatment and non-invasive treatment with a cast is comparable in terms of outcomes such as physical function and complications (see references for Clinical Effectiveness and Safety). Despite the lack of evidence supporting surgical treatment over casting in this patient group, there is a reported increase in the number of surgeries for distal radius fractures, which could be associated with greater resource consumption than conservative treatment (see references for Health Economics). Therefore, applying a cast for distal radius fractures in patients over 65 years of age might be a cost-effective alternative if the clinical effectiveness is comparable to surgical treatment.

What is the classification of the health technology?

☐Medical device, which is CE marked*

- ☐ Class I
- ☐ Class IIA

☐ Class IIB

☐ Class III

☐Diagnostic technology, which is CE marked**

☐ Class A

☐ Class B

☐ Class C

☐ Class D

☒Procedure (workflow related to diagnostics, treatment, rehabilitation, and/or with a preventive purpose)

If the procedure involves the use of one dominant health technology, describe it, and provide its CE marking and classification

Not relevant

* The Danish Health Technology Council only evaluates medical devices that are CE marked or otherwise meets the legal requirements for medical devices.

** Diagnostic technology utilizing medical equipment for *in vitro* diagnostics.

☒ the applicant hereby declares under penalty of perjury that the above information is accurate and complies with the relevant legislation concerning CE marking.

Briefly describe the current status of the use of the health technology in Denmark and abroad.

Currently, casts are used both in Denmark and abroad. The application of casts is performed across all age groups for various types of fractures.

Proposed PICO specification (Population, Intervention, Comparator, Outcome) for framing the evaluation question:

Population – The patient group in/for which the health technology is utilized and which the evaluation focuses on, including the annual number of patients in Denmark:	The patient population includes individuals over 65 years of age with distal radius fractures. Data from the National Patient Register reveals that in 2022, there were 7,120 patients over 65 years old with fractures at the distal end of the radius (advanced extraction). According to 'Lægehåndbogen', distal radius fractures encompass fractures in the lower part of the radius bone, most commonly Colle's fractures with dorsal displacement.
Intervention – The specific health technology to be evaluated:	The treatment approach under investigation involves non-operative treatment in the form of applying a cast.
Comparator – The health technology or treatment that is natural to compare with and currently used as the best and most widely	The alternative to applying a cast is surgical treatment.

adopted alternative to the intervention in Denmark (I):	
Outcome – The clinical effectiveness measures that would be relevant to assess the health technology compared to the comparator are:	The patients' physical function, complications, mobility, grip strength, and quality of life.

* PICO is a tool utilized by the Danish Health Technology Council to formulate precise issues and is crucial in the planning and execution of an evaluation by the Danish Health Technology Council. PICO is further detailed in the Danish Health Technology Council's methods guide, available on the Danish Health Technology Council's website.

Provide a brief description of the proposed comparator and whether the suggested health technology (intervention) is suggested to replace or to be an add on to the current alternative:

As alternatives to cast treatment for distal radius fractures, several surgical methods are used, including volar locking plate fixation, external fixation, or percutaneous pinning, as indicated by 'Lægehåndbogen'. These three surgical methods involve different health technologies aimed at maintaining fracture stability. According to 'Patienthåndbogen', the choice of surgical method depends on the specific fracture, bone quality, and other patient-specific factors. 'Lægehåndbogen' notes that in certain cases, it might be necessary to combine different surgical methods.
It is expected that cast treatment could replace surgical treatment for distal radius fractures in a portion of the patient population.

Is the health technology mentioned in professional clinical guidelines from institutions like the Danish Health Authority or medical scientific societies? Specify which ones:

The Danish Health Authority published a National Clinical Guideline in 2013, which is no longer in effect:

Sundhedsstyrelsen. National Klinisk retningslinje for behandling af håndledsnære brud (distal radiusfraktur). 2013.
The American Academy of Orthopaedic Surgeons released an evidence-based clinical practice guideline on the management of distal radius fractures in 2020:

American Academy of Orthopaedic Surgeons. Management of Distal Radius Fractures Evidence-Based Clinical Practice Guideline. 2020.

Has the health technology been evaluated by other HTA institutions (e.g. NICE, Nye Metoder)? Specify which ones:

In 2017, SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services) investigated the treatment of arm fractures, including distal radius fractures, in patients over 60 years of age:
Swedish Agency for Health Technology Assessment and Assessment of Social Services. Treatment options of arm fractures in the elderly. 2017.

Provide the names of manufacturers/suppliers of the health technology, if relevant:

There are several manufacturers of medical casts.

Information about the evidence base for the health technology:

Indicate whether the health technology (compared to the current alternative) aims to improve treatment/diagnosis of the patient group as perceived from one or more of the following perspectives (indication of the primary impact of using of the health technology):

☐ Clinical effectiveness and safety	☐ Patient preferences and experiences
☒ Organizational aspects, such as changes to workflows	☒ Costs associated with treatment/diagnostics

*For the evaluation of health technologies, the Danish Health Technology Council employs four perspectives: Clinical Effectiveness and Safety, the Patient Perspective, Organizational Implications, and Health Economics. For further elaboration on these perspectives, refer to the Danish Health Technology Council Council's methods guide for the evaluation of health technologies, available on the Danish Health Technology Council Council's website.

State the expected impact of the health technology within the indicated perspectives above:

Organizational aspects:

- Reducing the number of surgical procedures for distal radius fractures can lead to decreased resource consumption and specialized healthcare personnel (Navarro et al, 2019).
- Fewer surgical procedures can have a positive impact on hospitalization and operation room capacity.
- Reduced surgical procedures may decrease the demand for physiotherapy and home care (Hassellund et al, 2021).

Health economics:

Treatment with casts is cost-effective compared to surgical treatment. This holds true for both short and long-term perspectives.

Provide references* for documentation of the health technology's effects (if possible, include up to 2 key references per perspective):

Clinical effectiveness and safety	1. Li Q, Ke C, Han S, Xu X, Cong Y-X, Shang K, et al. Nonoperative treatment versus volar locking plate fixation for elderly patients with distal radial fracture: a systematic review and meta-analysis. J Orthop Surg Res. juli 2020;15(1):263. 2. Thorninger R, Wæver D, Tjørnild M, Lind M, Rölfing JD. VOLCON: a randomized controlled trial investigating complications and functional outcome of volar plating vs casting of unstable distal radius fractures in patients older than 65 years. Journal of Orthopaedics and Traumatology. 2022;23(1).

The Patient perspective	1. Healy S, Dorflinger E, Michaleff ZA, Marks D. Patient preferences and decision-making when considering surgery for musculoskeletal disorders: A mixed methods systematic review. Musculoskeletal Care. 15. november 2022.
Organizational Implications	1. Navarro CM, Brolund A, Ekholm C, Heintz E, Ekström EH, Josefsson PO, et al. Treatment of radius or ulna fractures in the elderly: A systematic review covering effectiveness, safety, economic aspects and current practice. PLoS One. 2019;14(3):1–28.
Health Economics	1. Navarro CM, Brolund A, Ekholm C, Heintz E, Ekström EH, Josefsson PO, et al. Treatment of radius or ulna fractures in the elderly: A systematic review covering effectiveness, safety, economic aspects and current practice. PLoS One. 2019;14(3):1–28. 2. Hassellund S, Zolic-Karlsson Z, Williksen JH, Husby T, Madsen JE, Frihagen F. Surgical treatment is not cost-effective compared to nonoperative treatment for displaced distal radius fractures in patients 65 years and over. Bone Jt Open. december 2021;2(12):1027–34.

* Reference to published, ongoing, or unpublished data.

Indicate whether the health technology is expected to incur additional costs, cost reductions, or be cost-neutral compared to the current alternative. Briefly describe how the costs are expected to be distributed across sectors (hospital, general practice, municipalities, patients, etc.), and what is considered to drive the potential addition or reduction in costs. The Danish Health Technology Council encourages applicants to complete and include the Danish Health Technology Council's cost outline, accessible on the Danish Health Technology Council's website.

☐ Additional costs ☒ Cost reductions ☐ Cost-neutral

Treatment with casts is cost-effective compared to surgical treatment. This holds true for both short and long-term perspectives.

The cost reduction is primarily driven by the primary treatment costs (Hassellund et al, 2021). The costs associated with the primary treatment incur in the hospital sector, while subsequent treatment-related costs might also be affected the municipal sector and general practice.
The cost components in the identified studies have been validated in the Danish Health Technology Council's cost outline and do not significantly change when using Danish key figures.

Free-text field (optional additional information, max 300 words):