Behandlingsrådet

DAGSORDEN

Mødetitel	Rådsmøde den 29. august 2024
Sted	Teams-møde
Dato og tid	29-08-2024 10:00 - 12:30

Deltagerkreds	Michael Dall (formand)
	Anna-Marie Bloch Münster
	Dan Brun Petersen
	Nils Falk Bjerregaard
	Søren Pihlkjær Hjortshøj, Afbud
	Jannick Brennum
	Kirsten Møller
	Irene Wessel
	Pia Dreyer
	Klaus Lunding
	Sif Holst
	Jan Sørensen
	Kristian Kidholm
	Maj-Britt Juhl Poulsen, Afbud
	Mikkel Bruun Pedersen
	Malene Møller Nielsen
	Tine Bro
	Trine Kart
	Mette Bejder

INDHOLD

1. Status på igangværende sager

Resume

"Status på igangværende sager" indgår som et fast punkt på dagsorden til rådsmøderne med henblik på at give Rådet en status på Behandlingsrådets sager.

Sagsfremstilling

Som et fast punkt til Rådsmøderne vil Malene Møller ved det enkelte rådsmøde give en status på de igangværende sager i Behandlingsrådet.

Indstilling

Sekretariatet indstiller, at Behandlingsrådet:

1. Tager orienteringen til efterretning.

Referat

Direktør Malene Møller orienterede om status på igangværende evalueringer og analyser.

2. Godkendelse af evalueringsforslag, C2N Diagnostics

Resume

Behandlingsrådet har den 17. juni 2024 modtaget et evalueringsforslag fra C2N Diagnostics vedrørende PrecivityAD, der er en blodtest der identificerer, om en patient sandsynligvis har tilstedeværelsen eller fraværet af amyloidplak i hjernen, der er et patologisk kendetegn ved Alzheimers sygdom. Formålet med PrecivityAD er at kunne tilbyde en bredt anvendelig blodtest, som både kan udelukke og bekræfte tilstedeværelsen af amyloidpatologi, og dermed støtte diagnosticeringen af Alzheimers sygdom.

Sekretariatet indstiller, at Behandlingsrådet igangsætter evalueringen af PrecivityAD til diagnosticering af Alzheimerz.

Sagsfremstilling

Alzheimers sygdom er en progressiv neurodegenerativ lidelse, som primært rammer hukommelsen og andre kognitive funktioner. Sygdommen begynder ofte med milde symptomer, som f.eks. glemsomhed eller forvirring, men udvikler sig over tid til svær demens. Den centrale årsag til Alzheimers sygdom menes at være ophobning eller sammenfiltring af proteiner i hjernen (hhv. amyloid plaques og tau-tangles), som forstyrrer kommunikationen mellem hjerneceller.

Studier viser, at der i Danmark er omkring 50.000, der lever med udiagnosticeret alzheimers. I dag diagnostiseres alzheimers sygdom enten gennem lumbalpunkturer for at udvinde cerebrospinalvæske eller gennem PET-skanning. Årsagen til de mange udiagnosticerede tilfælde skyldes dels, at udvinding af cerebrospinalvæske er et invasivt indgreb, mangel på neurologer til at udføre dem og mangel på PET-skannere. Der

findes ingen behandling mod alzheimers, men der er evidens for, at tidlig diagnose og livsstilsændringer kan medvirke til at afbøde progressionen af Alzheimers sygdom.

PrecivityAD foreslås af ansøger derfor som erstatning for amyloid PET-skanning i alle normale tilfælde (dog med få undtagelser) og foreslås også som erstatning for udvinding af cerebrospinalvæske i tilfælde, hvor patienter ikke ønsker eller er i stand til at få foretaget en lumbalpunktur til cerebrospinalvæske, eller i situationer, hvor det ikke er muligt grundet kapacitetsudfordringer, ventelister og lignende.

Klinisk effekt og sikkerhed

PrecivityAD blodprøven identificerer, om en patient sandsynligvis har tilstedeværelsen eller fraværet af amyloid plaques i hjernen, et patologisk kendetegn ved Alzheimers sygdom. PrecivityAD-blodprøven er beregnet til at blive brugt som en erstatning for amyloid PET-skanning eller udvinding af cerebrospinalvæske, når patienter vurderes for amyloidpatologi, hvilket eliminerer behovet for 80-85% af lumbalpunkturer/cerebrospinalvæske på landsplan og erstatter behovet for at opbygge yderligere kapacitet til amyloid PET-skanning.

Komparater

Det vurderes, at komparator bør være undersøgelse af cerebrospinalvæsken ved lumpalpunktur, da det er den bredest anvendte metode til at diagnosticere Alzheimers i Danmark. Det bemærkes dog, at Amyloid PET-skanning er guldstandarden for vurdering af amyloidpatologi, men at det anses som dyrt, og udsætter patienter for radioaktivitet.

Sundhedsøkonomi

Det vurderes, at tidlig diagnosticering af Alzheimers sygdom kan medvirke til at afbøde progressionen af sygdommen og dermed bidrage

til at reducere langsigtede sundhedsudgifter. PrecivityAD kan anvendes til alle 55 årige, der henvender sig til deres læge med kognitive udfordringer og på den måde medvirke til at sikre tidligere diagnosticering af flere patienter.

Prioriteringsfaktorer

Sekretariatet vurderer, at den pågældende teknologi, PrecivityAD, kan relateres til flere af Behandlingsrådets prioriteringsfaktorer.

PRIORITERINGSFAKTORER:	
Genstandsfelt	Biomarkører til diagnosticering af Alzheimers
Population	55+ årige, der henvender sig til lægen med kognitive udfordringer
Sikkerhed/risikoklasse	Diagnostisk teknologi, klasse B
Øvrige forhold	Sekretariatet vurderer, at der foreligger tilstrækkelig evidens til at gennemføre evalueringen. PrecivityAD anvendes på nuværende tidspunkt ikke i Danmark.
Effekt	PrecivityAD identificerer, om der er amyloid plaques i hjernen, der er et patologisk kendetegn på Alzheimers. Mange kan dermed undgå dyrere og mere invasive alternativer i form af udvinding af cerebrospinalvæske og amyloid PET-skanning. Det er også muligt at teste flere for Alzheimers end der er kapacitet til i dag, og dermed medvirke til, at flere kan foretage livsstilsændringer, der kan hæmme progressionen af Alzheimers.
Alvorlighed	Med den nuværende tilgang får patienter foretaget invasive, kapacitetsudfordrede tests. PrecivityAD havde givet svar på 85 % tilfælde gennem blødprøve og dermed nedsætte behovet for PET-skanning og udvinding af cerebrospinalvæske.
Omkostningsbillede	Precivity er ikke prissat endnu. Det forventes at blive billigere end amyloid PET-skanning og udvinding af cerebrospinalvæske.
Generel relevans	Alzheimers er en meget alvorlig sygdom. Tidligere diagnosticering kan potentielt hæmme udviklingen til stor gavn for den enkelte.

Danske Regioner har i forbindelse med nedlukning af virksomhedssporet i Behandlingsrådet besluttet, at virksomheder ikke kan søge om udsættelse af afleveringsfrist for deres ansøgning. Ansøgningen skal derfor afleveres senest 9 måneder efter virksomhedens har modtaget evalueringsdesign fra Behandlingsrådet.

Indstilling

Sekretariatet indstiller, at Behandlingsrådet:

1. Beslutter, hvorvidt der skal igangsættes en evaluering af PrecivityAD
2. Såfremt Rådet beslutter at igangsætte en evaluering, udpeger det faglige selskab som skal varetage formandsposten, samt hvilke yderligere kompetencer, der skal repræsenteres i et fagudvalg.

Referat

Rådet drøftede forslaget fra virksomheden. Området for demenssygdomme er i stor udvikling i disse år bl.a. inden for det diagnostiske område. Rådet havde i sine drøftelser opmærksomhed på en række områder, herunder på risiko for dobbeltdiagnostik, hvis ikke brugen af testen indbefatter et tilsvarende fald i brugen af CSV og PET-scanning, at den foreslåede indikation for blodprøven bør skærpes af hensyn til at mindske andelen af falsk positive svar, samt at evalueringen bør have et fokus på organiseringen omkring, hvem der kan bestille blodprøven.

Rådet besluttede at igangsætte evalueringen af PrecivityAD.

Rådet besluttede følgende vedr. fagudvalgets sammensætning: Formanden udpeges af LVS gennem Dansk Neurologisk Selskab. Regionerne vil blive bedt om at udpege repræsentanter med lægefaglige

kompetencer inden for neurologi og klinisk biokemi. Der var en opmærksomhed på, at der fra regional side evt. kan udpeges fra Nationalt Videnscenter for Demens. Derudover vil Dansk Selskab for Almen Medicin blive bedt om at udpege et medlem. Danske Handicaporganisationer og Danske Patienter vil blive bedt om at udpege patientrepræsentanter.

Bilag

Navn
evalueringsforslagsskabelon_eng_C2N Diagnostics_PrecivityAD blood test_FINAL_Jun_17_2024_sløret_Bortredigeret

3. Lukket punkt.

4. Godkendelse af evalueringsforslag, Exact Sciences

Resume

Virksomheden Exact Sciences har d. 5. juli 2024 indsendt det vedhæftede evalueringsforslag vedr. sundhedsteknologien Oncotype DX Breast Recurrence Score test (Oncotype DX).
Oncotype DX er en diagnostisk gentest, som på baggrund af test for 21 gener, kan bestemme risikoen for tilbagefald hos en subgruppe af patienter med brystkræft i tidligt stadie samt estimere, i hvilken grad kemoterapi kan være med til at reducere denne risiko. Hermed kan Oncotype DX vejlede i beslutningen vedr. adjuverende kemoterapi ved at identificere, hvilke patienter med den anførte brystkræft type, der har/ikke har effekt af adjuverende kemoterapi som et tillæg til standardbehandling.

Sekretariatet indstiller, at Behandlingsrådet beslutter, hvorvidt der skal igangsættes en evaluering af Oncotype DX.

Sagsfremstilling

Oncotype DX Breast Recurrence Score test (Oncotype DX) er en ikke-invasiv diagnostisk test til at vejlede i kliniske beslutninger vedr. adjuverende kemoterapibehandling til personer med hormonreceptor-positiv (HR+), HER2-negativ (HER2-) invasiv brystkræft i stadium I-IIIa. Testen analyserer ekspressionen af 21 gener i brysttumorvæv og kan bidrage med information om risikoen for tilbagefald af kræftsygdommen samt give en indikation på, hvorvidt kemoterapi vil reducere denne risiko for tilbagefald.

Præ-menopausale patienter modtager i dag både endokrin behandling og kemoterapi. Hos post-menopausale patienter anvendes en prognostisk klinisk score (PSI, prognostic standard mortality score), som inddeler patienterne i 4 grupper (Q1, Q2, Q3, Q4). Scoren beregnes på

baggrund af tumorkarakteristika og beskriver den forventede overdødelighed sammenlignet med baggrundsdødeligheden. Patienter i Q1 modtager udelukkende endokrin behandling, mens Q3-4 behandles med en kombination af endokrin behandling samt kemoterapi. Patienter i Q2 får foretaget genekspression ved anvendelse af testen PAM50, som deler gruppen op i henholdsvis type A patienter, der behandles med endokrin behandling og type B patienter, der behandles med kemoterapi og endokrin behandling.

Ansøger anfører at tilføjelse af adjuverende kemoterapi kun forbedrer resultaterne for få patienter med denne type brystkræft.

Oncotype DX giver information om den grundlæggende risiko for tilbagefald eller dødelighed uden kemoterapi, og kan desuden angive i hvor høj grad tilføjelse af kemoterapi vil reducere risikoen herfor. Teknologien skal derfor anvendes som et supplement til allerede eksisterende risikovurderingsmetode og hjælpe til at målrette adjuverende kemoterapibehandling til de rigtige patienter.

Ifølge ansøge var der i år 2022 5.259 nye tilfælde af brystkræft i Danmark. Ud af disse var ca. 2.700 lymfeknude-negative og postmenopausale lymfeknude-positive patienter og dermed kandidater til Oncotype DX-testen.

Klinisk effekt og sikkerhed

- Oncotype DX kan identificere patienter med tidlig stadie brystkræft af typen HR+, HER2-, som ikke vil have gavn af kemoterapi, hvilket fører til, at flere patienter kan behandles udelukkende med endokrin adjuverende behandling, og undgår derfor at blive udsat for bivirkninger forbundet med kemoterapi.
- Teknologien kan identificere patienter, der med stor sandsynlighed vil have gavn af kemoterapibehandling, men som med nuværende

metoder ikke er kandidater til kemoterapi, hvilket kan resultere i lavere dødelighed.
- Oncotype DX anvender vævsprøver, der rutinemæssigt indsamles for denne patientgruppe og udgør derfor ingen sikkerhedsrisiko.

Valg af komparator

Det vurderes, at Oncotype DX bør sammenlignes med nuværende risikovurderingsprocedure, som baserer sig på en beregnet PSI-score på baggrund af kliniske tumorkarakteristika. Denne komparator ses ligeledes anvendt i flere andre sundhedsteknologivurderinger. Genekspression ved hjælp af PAM50 udføres som tidligere beskrevet til post-menopausale patienter i Q2. PAM50 opdeler yderligere Q2 i type A og type B, hvoraf sidstnævnte ofte behandles med kemoterapi. Det vurderes derfor, at PAM50 også anvendes som komparator til denne undergruppe af patientpopulationen.

Sundhedsøkonomi

Det forventes, at teknologien er omkostningseffektiv sammenlignet med nuværende procedure til beslutningstagen vedr. adjuverende kemobehandling til den angivne patientgruppe i Danmark. Dette er baseret på forventede besparelser ved at reducere forbruget af kemoterapi og nedsætte forekomsten af tilbagefald.

Prioriteringsfaktorer

Sekretariatet vurderer, at den pågældende teknologi, Oncotype DX, kan relateres til flere af Behandlingsrådets prioriteringsfaktorer.

PRIORITERINGSFAKTORER:	
Genstandsfelt	Oncotype DX Breast Recurrence Score test
Patientpopulation/Målpopulation	Patienter med HR positiv, HER2 negativ type brystkræft i tidligt stadie I-IIIa
Sikkerhed/risikoklasse	Diagnostisk teknologi, klasse C

Øvrige forhold	Sekretariatet vurderer, at der foreligger tilstrækkelig evidens til at gennemføre en evaluering, men kan være i tvivl om hvorvidt det afspejler dansk praksis. Selve gentesten udføres i et centrallaboratorium i USA. Testen udføres på en prøve identificeret ved en QR-kode, og testresultatet knyttes først til patienten, når resultatet returneres til klinikeren i Danmark via en online EU-portal.
Effekt	Oncotype DX identificerer patienter med tidlig stadie brystkræft af typen HR+, HER2-, som kan undvære kemoterapi uden øget risiko for tilbagefald. Teknologien kan derfor identificere de patienter, der kan undvære kemoterapi på tværs af risikogrupper og herved spare patienter for unødige risici for bivirkninger forbundet med kemobehandling.
Alvorlighed	Med den nuværende tilgang risikerer patienter at blive udsat for bivirkninger ved kemoterapi uden at opnå en fordel af behandlingen, hvilket kan påvirke livskvaliteten negativt. Desuden kan en mindre andel af patienter, for hvem kemoterapi i øjeblikket udelades baseret på PSI-scoren, opleve et tilbagefald, som kunne have været forhindret med kemoterapi, hvilket kan føre til højere dødelighed.
Omkostningsbillede	Det forventes, at teknologien kan medføre en nettobesparelse for sundhedsvæsenet.
Generel relevans	Oncotype DX testen udføres ikke rutinemæssigt i Danmark, men den udføres rutinemæssigt i mange andre europæiske og andre vestlige lande. Til dato er der udført mere end 1,5 millioner Oncotype DX tests i mere end 90 lande.

Danske Regioner har i forbindelse med nedlukning af virksomhedssporet i Behandlingsrådet besluttet, at virksomheder ikke kan søge om udsættelse af afleveringsfrist for deres ansøgning. Ansøgningen skal derfor afleveres senest 9 måneder efter virksomhedens har modtaget evalueringsdesign fra Behandlingsrådet.

Indstilling

Sekretariatet indstiller, at Behandlingsrådet:

1. Beslutter, hvorvidt der skal igangsættes en evaluering af Oncotype DX.
2. Såfremt Rådet beslutter at igangsætte en evaluering, udpeger det faglige selskab som skal varetage formandsposten, samt hvilke yderligere kompetencer, der skal repræsenteres i et fagudvalg.

Referat

Rådet drøftede virksomhedens forslag. Rådet bemærkede bl.a. at en evaluering bør afspejle dansk praksis, ligesom man drøftede valg af komparator. Rådet er opmærksomme på den hurtige udvikling inden for gentest og anbefaler at Sekretariatet rækker ud til eksperter på området mhp på kort at afdække konteksten for evalueringen forud for udarbejdelsen af evalueringsdesignet.

Rådet besluttede at igangsætte en evaluering af Oncotype DX.

Rådet besluttede følgende vedr. Fagudvalgets sammensætning:
Formanden udpeges af LVS gennem Dansk Onkologisk Selskab.
Regionerne vil blive bedt om at udpege repræsentanter inden for onkologi og eventuelt klinisk genetik.
Danske Handicaporganisationer og Danske Patienter vil blive bedt om at udpege patientrepræsentanter.

Bilag

Navn
Evaluation proposal Oncotype DX

5. Lukket punkt.

6. Orientering om status på lukning af virksomhedssporet

Resume

Danske Regioner har truffet beslutning omkring forløbet for nedlukning af Behandlingsrådets virksomhedsspor. Beslutningen indebærer, at rådsmødet i slutningen af september er sidste mulighed for at igangsætte evalueringer.
Evalueringer, som er igangsat, færdiggøres som planlagt med anbefalinger fra Rådet.

Direktør Malene Møller orienterer nærmere om sagen på rådsmødet.

Det indstilles at Rådet tager orienteringen til efterretning.

Sagsfremstilling

I forbindelse med, at Behandlingsrådet og RKKP fra 2025 sammenlægges og bliver til Sundhedsvæsenets Kvalitetsinstitut, har Danske Regioner besluttet at lukke Behandlingsrådet virksomhedsspor.

Fra 1. august 2024 opstarter Behandlingsrådet derfor ikke nye dialoger med virksomheder. For de virksomheder, som allerede er i dialog med Behandlingsrådet om igangsætning af en evaluering, er rådsmødet den 26. september 2024 sidste mulighed for at få godkendt et evalueringsforslag. For de virksomheder, hvis evaluering bliver igangsat i perioden 1. august til 26. september, er der ikke mulighed for at ansøge om forlængelse af ansøgningsperioden, og virksomhederne har således 9 måneder til at indlevere deres ansøgning.

Evalueringer, som allerede er igangsat eller bliver igangsat frem til 26. september, færdiggøres som planlagt med anbefalinger fra Rådet og efterfølgende implementering i regionerne.

Behandlingsrådets sekretariat har kontaktet de virksomheder, som der allerede er dialog med, for en konkret afklaring af deres videre forløb.

Direktør Malene Møller vil på mødet orientere nærmere om status på virksomhedssporet.

Indstilling

Sekretariatet indstiller, at Behandlingsrådet:

1. Tager orienteringen til efterretning.

Referat

Sekretariatet orienterede om nedlukningen af virksomhedssporet.

7. Orientering om forlængelse af sundhedsøkonomiske rådsmedlemmers repræsentation i Rådet

Resume

Formanden for Behandlingsrådet har med accept fra de sundhedsøkonomiske repræsentanter i Rådet, godkendt en forlængelse af de sundhedsøkonomiske rådsmedlemmers udpegning i Rådet frem til udgangen af 2024, hvor Sundhedsvæsnets Kvalitetsinstitut oprettes.

Det indstilles, at Rådet tager beslutningen til efterretning.

Sagsfremstilling

På rådsmøde i september 2023 blev processen for udskiftning/genudpegninger af rådsmedlemmer i Behandlingsrådet fremlagt. Som det fremgår, er de sundhedsøkonomiske repræsentanter udpeget for en 3-årig periode og denne periode udløber officielt til august.

Da Rådet kun har få måneder tilbage i sin nuværende form, jf. beslutningen om at integrere Behandlingsrådet i det nye Sundhedsvæsnets Kvalitetsinstitut, forlænges udpegningen af de to sundhedsøkonomiske rådsmedlemmer med formandens godkendelse. Begge rådsmedlemmer har tilkendegivet, at de ønsker at fortsætte i Rådet frem til oprettelsen af det nye institut i starten af 2025.

Indstilling

Sekretariatet indstiller, at Behandlingsrådet:

1. Tager orienteringen til efterretning.

Referat

Michael Dall orienterede om, at udpegningsperioden for sundhedsøkonomerne i Rådet, Kristian Kidholm og Jan Sørensen, er blevet forlænget til udgangen af 2024, hvor Behandlingsrådet nedlægges i sin nuværende form og bliver en del af Sundhedsvæsenets Kvalitetsinstitut.

8. Eventuelt

Referat

Intet at bemærke

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):

Behandlingsrådet

Evaluation proposal for the Danish Health Technology Council regarding the Oncotype DX® test for guiding adjuvant chemotherapy treatment decisions in early-stage hormone receptor positive breast cancer

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)*:

Exact Sciences International Gmbh.

The Oncotype DX test is performed by Exact Sciences wholly owned subsidiary Genomic Health Inc.

* 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):

Lars Holger Ehlers. Director of Nordic Institute of Health Economics.

Date of submission of the evaluation proposal:

5th July 2024

Information about the health technology

Briefly describe the health technology to be evaluated:

The Oncotype DX Breast Recurrence Score® test (the Oncotype DX® test) is a non-invasive diagnostic test to guide adjuvant chemotherapy treatment decisions for individuals with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), early-stage (I-IIIa) invasive breast cancer. The test provides two pieces of information: 1. the recurrence risk and 2. the benefit of adding chemotherapy in order to reduce the risk.
The test analyses the expression of 21 genes in breast tumour tissue based on RT-PCR. It does not require additional tumour material beyond the surgically excised tissue.

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

Adjuvant treatment planning in this patient group seeks to reduce the risk of cancer recurrence and mortality. Most patients receive hormone therapy, and a course of chemotherapy is also added beforehand unless its omission is not expected to affect mortality.

Adding chemotherapy only improves outcomes for a small proportion (**4-8%)** of patients in this group (EBCTCG. Lancet. 2012). However, currently a much larger proportion of patients are assigned to chemotherapy based on current treatment guidelines, meaning there may be substantial over-treatment (DBCG). TLV (Sweden) and NIPH (Norway) assessments indicate **38%-63%** of node-negative & positive patients receive chemotherapy without the Oncotype DX test (TLV, Hälsoekonomisk bedömning av Oncotype DX Breast Recurrence Score Test, 2021; NIPH, Single Technology Assessment: Oncotype DX Breast Cancer Recurrence Score Test, 2023).

This is because with the current approach it is not possible to identify the individuals who will benefit, or a smaller subgroup most likely to benefit. Instead, the current approach identifies a subset of patients estimated to have the lowest risk of mortality, based on the presence of lower risk tumor characteristics (such as tumors of smaller size and/or lower grade), for whom chemotherapy is omitted (Ejlertsen et al. 2014;

DBCG). The remaining large proportion of patients classified as 'intermediate risk' or 'high risk' are likely to receive chemotherapy (DBCG).

This means with the current approach many patients may be exposed to short and long-term chemotherapy side-effects without gaining a benefit, negatively impacting quality of life and leading to greater healthcare resource, capacity and budget consumption.

Additionally, a smaller proportion of patients for whom chemotherapy is currently omitted based on lower risk tumour characteristics, may experience a cancer recurrence that could have been prevented with chemotherapy, leading to higher mortality, and higher costs and resource consumption associated with the management of late-stage cancer and end of life care.

Two pieces of information are crucial for precisely targeting chemotherapy treatment to the right patients:

- **the baseline risk of cancer recurrence or mortality without chemotherapy** (available with the current approach)
- **the extent to which adding chemotherapy would reduce the risk** (not available with the current approach)

The Oncotype DX test is designed and validated to both refine the baseline risk estimate, but crucially also to directly determine whether and by how much this risk would be reduced by adding chemotherapy (Paik et al, 2004, Paik et al, 2006; Albain et al, 2010; Sparano et al, 2018; Kalinski et al, 2021). This allows patients to make informed treatment decisions by identifying:

- ~80% of lymph node-negative (N0) and postmenopausal lymph node-positive (N1) patients for whom adding chemotherapy would have no benefit, independent from clinical risk (Sparano et al, 2018; Kalinski et al, 2021).
- ~20% of patients most likely to benefit from chemotherapy (74% and 41% relative risk reduction from chemotherapy among lymph node-negative and node-positive patients with high Recurrence Score results) (Paik et al, 2006; Albain et al, 2010; Sparano et al, 2018; Kalinski et al, 2021)

Use of the Oncotype DX test leads to a large proportion of patients avoiding either over or undertreatment with chemotherapy, and greatly reduces the overall proportion of patients receiving chemotherapy, without negatively impacting recurrence or mortality rates (TLV, Hälsoekonomisk bedömning av Oncotype DX Breast Recurrence Score Test, 2021; NIPH, Single Technology Assessment: Oncotype DX Breast Cancer Recurrence Score Test, 2023; NICE DG34/DG58). A European decision-impact study involving 2,471 patients, reported that use of the Oncotype DX test resulted in a 43% reduction in overall chemotherapy use (Barni et al. 2018).

Therefore, introducing the Oncotype DX test to help guide adjuvant chemotherapy treatment decisions with greater precision for pre- and postmenopausal N0 and postmenopausal N1 patients may be a cost-saving and health gaining alternative to the current chemotherapy decision-making approach in Denmark, as has been reported for other healthcare systems.

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.

The Oncotype DX test is not currently routinely conducted in Denmark, but is routinely conducted for both lymph node-negative (pre and postmenopausal) and lymph nodes-positive (postmenopausal) patients in many other European and other Western countries. To date, more than 1.5 million Oncotype DX tests have been conducted in more than 90 countries.

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 with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), early-stage (I-IIIa) invasive breast cancer. Data from Globocan reveals that in 2022, there were 5,259 new breast cancer cases in Denmark. Approximately 90% are stage I-IIIa, 69% are HR+ & HER2-, 95% are N0 or N1 (excluding N2), 80% are N0 / 20% are N1, 80% of N1 are postmenopausal, and 94% are assumed to be candidates for chemotherapy, meaning approximately **2,700** lymph node-negative and postmenopausal lymph node-positive patients eligible for the Oncotype DX test.

	Two separate patient subgroups are suggested for health economic analysis: • **lymph node-negative (N0) patients (pre- and postmenopausal)** • **postmenopausal lymph node-positive (N1) patients**
Intervention – The specific health technology to be evaluated:	The Oncotype DX Breast Recurrence Score® test (the Oncotype DX® test)
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):	The most widely adopted alternative is chemotherapy treatment decision-making using **traditional risk assessment based on tumour characteristics** (DBCG). The **PAM50/Prosigna** test is also used for a specific subset of post-menopausal patients and so could be a relevant comparator (subject to feasibility based on comparative data availability).
Outcome – The clinical effectiveness measures that would be relevant to assess the health technology compared to the comparator are:	Relevant clinical effectiveness measures: • **Relative risk reduction from chemotherapy by test result category.** • **Impact on chemotherapy treatment decisions.** • **Expected lifetime QALYs** • **Expected life years gained (mortality)** • **Expected recurrence rate** • **Expected chemotherapy treatment rate** Please note: measures of sensitivity and specificity do not apply to multi-gene panel tests as they do for single biomarker tests reporting binary results i.e., the ability to correctly detect the presence (sensitivity) or absence (specificity) of a biomarker. Clinical validity and utility are more relevant for multi-gene panel tests. Clinical validation of a multi-gene panel test designed to predict treatment effect involves demonstrating a correlation between test result and treatment-dependent effect i.e., lack of treatment effect for patients with a 'low' score and

	large effect (risk reduction) for patients with a 'high' score. Clinical utility of a multi-gene panel test focuses on the impact of the test on treatment decisions (so-called decision-impact studies) i.e., treatment changed for patients with a low test result to avoid unnecessary treatment, and changed for patients with a high test result to avoid missing out on effective treatment.

* 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:

Chemotherapy treatment decision-making using the current traditional risk assessment approach (based on clinical tumour characteristics) was selected as the comparator in multiple health technology assessments in several other countries, including the TLV in Sweden, NIPH in Norway and NICE in the UK (TLV, Hälsoekonomisk bedömning av Oncotype DX Breast Recurrence Score Test, 2021; NIPH, Single Technology Assessment: Oncotype DX Breast Cancer Recurrence Score Test, 2023; NICE DG34/DG58).

This is also the most widely adopted approach to chemotherapy treatment decision making in Denmark. Gene expression profiling using PAM50/Prosigna is currently only conducted for a small subset of patients (postmenopausal patients estimated to have intermediate-low risk) (DBCG guidelines).

It is important to note that the Prosigna test is not the same as the Oncotype DX test, and the tests are not interchangeable. The Prosigna test measures a different panel of genes and does not provide the same type of information, as acknowledged in multiple international clinical guidelines and health technology assessments across Europe. The Prosigna test is for prognostic risk assessment only (as per the traditional clinical approach) and is not currently validated to determine chemotherapy benefit (NCCN Guidelines Insights: Breast Cancer, version 4.2022; Andre et al. J Clin Oncol 2022; Burstein et al. Ann Oncol. 2021; Curigliano et al. Ann Oncol. 2023; Cardoso et al. Ann Oncol 2019; Loibl et al. Annals of Oncology 2024; TLV, Hälsoekonomisk bedömning av Oncotype DX Breast Recurrence Score Test, 2021; NIPH, Single Technology Assessment: Oncotype DX Breast Cancer Recurrence Score Test, 2023; NICE DG34/DG58).

We suggest the most appropriate comparator therefore remains current chemotherapy treatment decision-making based on traditional clinical risk assessment.

The Oncotype DX test is intended to be used alongside traditional risk assessment to help target adjuvant chemotherapy treatment with greater precision. However, use of the Oncotype DX test is not intended to be restricted to the narrow 'risk-stratified' patient group in which the PAM50/Prosigna test is used.

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

The Oncotype DX test is not currently included in Danish clinical guidelines.

The Oncotype DX test is included in several international breast cancer clinical guidelines:

National Comprehensive Cancer Network (NCCN), 2022[1]:

- The Oncotype DX test is the only test recognized by NCCN guidelines to predict adjuvant chemotherapy benefit.
- The Oncotype DX test is the only test classified as the "preferred" test in both N0 and post-menopausal N1 patients with HR-positive, HER2-negative breast cancer.
- Specific recommendations regarding the interpretation of the Recurrence Score result for patient subpopulations, based on the TAILORx and RxPONDER studies.

European Society for Medical Oncology (ESMO), 2019[2]:

- The Oncotype DX test may be used to gain additional prognostic and/or predictive information, based on Level 1A evidence to complement pathology assessment.
- The Oncotype DX test may be used to predict the benefit of adjuvant chemotherapy.

St Gallen International Consensus Panel, 2023[3]:

- Test strongly endorsed for vast majority of N0 and N1, HR+, HER2- early-stage breast cancer patients, TAILORx and RxPONDER cutoffs to guide treatment decisions.
- The 2023 St Gallen guidelines update highlighted the need to test premenopausal patients with the Oncotype DX test, as not all of these patients require chemotherapy.

American Society of Clinical Oncology (ASCO), 2022[4]:

- The Oncotype DX test is the only test strongly recommended for all N0 and postmenopausal N1 patients with ER+, HER2- early breast cancer.
- Recommendation is irrespective of clinical risk.
- Recommendation is based on "high" evidence quality.

References:

1. NCCN Guidelines Insights: Breast Cancer, version 4.2022.
2. Loibl et al. Annals of Oncology 2024.
3. Curigliano et al. Ann Oncol. 2023.
4. Andre et al. J Clin Oncol 2022.

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

The Oncotype DX test has been positively evaluated by several HTA institutions.

NICE, UK:

- Diagnostics Guidance 58 (DG58) published 9 May 2024.
    - Updated Diagnostics Guidance 34 (DG34) published 19 December 2018, which made a positive recommendation for certain individuals with lymph node-negative and micro-metastatic breast cancer.

- Recommendation for lymph node-positive early breast cancer: Use EndoPredict, Oncotype DX or Prosigna as options alongside consideration of clinical risk factors to guide adjuvant chemotherapy decisions.
- Recommendation for Lymph node-negative and micrometastatic early breast cancer: EndoPredict, Oncotype DX or Prosigna can be used (under certain conditions) for patients if they have an intermediate risk of distant recurrence using a validated tool such as Predict or the Nottingham Prognostic Index.

Nye Metoder/NIPH, Norway:

- Single technology assessment of the Oncotype DX test, published October 2023.
- Concluded that the Oncotype DX test seems to be more effective and less costly compared to no gene-profiling test.
- Concluded that the Oncotype DX test predicts chemotherapy benefit in patients with ER+ HER- early-stage breast cancer who were node negative (regardless of menopausal status) or postmenopausal and node positive (1-3 lymph nodes).

TLV, Sweden:

- Health economic assessment of Oncotype DX test, published in June 2021.
- Concluded that the Oncotype DX test is expected to be more effective and less costly compared to no gene-profiling test.
- The results were largely driven by the product's ability to predict the expected relative benefit of chemotherapy (predictive ability) and thus reduce both under- and over-treatment.

HIQA, Ireland:

- A rapid health technology assessment of gene expression profiling tests for guiding the use of adjuvant chemotherapy in early-stage invasive breast cancer, published February 2023.
- Oncotype DX® is currently the only Gene Expression Profiling test that is reimbursed by the Health Service Executive in Ireland.
- HIQA concluded that the available evidence supports the continued use of Oncotype DX® among N0 patients and the evidence most strongly supports the continued use of Oncotype DX® in postmenopausal women, based on available five-year follow-up data among N+ patients.

IQWIG, Germany:

- A multi-technology assessment published in 2018.
- IQWIG concluded that with the results of TAILORx, only Oncotype DX® has sufficient evidence to guide adjuvant chemotherapy decisions in patients with early stage, node-negative, invasive breast cancer.

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

The Oncotype DX test is performed by Exact Sciences wholly owned subsidiary Genomic Health Inc.

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:

Clinical effectiveness and safety:

The literature on Oncotype can demonstrate a significant and clinically meaningful reduction in the number of patients assigned to chemotherapy and that patients avoiding chemotherapy based on a low RS result can do so without affecting recurrence or survival outcomes (Holt et al, 2024; NICE DG34/DG58; Paik et al, 2006; Albain et al, 2010; Sparano et al, 2018; Kalinski et al, 2021).

The proposed effect of the intervention is as follows:

- The ability to identify patients who do not benefit from chemotherapy, leading to more patients being able to be safely switched from CET to ET treatment, with RCT evidence proving no negative impact on distant recurrence or mortality.
- The ability to identify patients who are highly likely to benefit from chemotherapy treatment (with a substantially greater than average relative risk reduction from chemotherapy), for whom chemotherapy can be targeted more precisely to reduce the rate of recurrence.

The Oncotype DX test uses tissue samples that are routinely collected for this patient group, and so does not represent a safety concern.

Costs associated with treatment/diagnostics:

The Oncotype DX test does not require additional tumour material beyond the surgically excised tissue and does not require additional resources and expenditure beyond the all-inclusive purchase price for the test, as it is offered as a full testing service including shipping costs.

Use of the Oncotype DX test to reduce over and under-treatment is expected to lead to the following cost-savings:

- **Reduction in adjuvant chemotherapy treatment-related costs**: including drug acquisition costs, costs of administering and monitoring treatment, and costs of managing short and long-term side-effects resulting from chemotherapy treatment.
- **Reduction in advanced/metastatic cancer-related costs**: including high acquisition cost of metastatic treatments e.g., CDK4/6 inhibitors, and end of life care (TLV, Hälsoekonomisk bedömning av

Oncotype DX Breast Recurrence Score Test, 2021; NIPH, Single Technology Assessment: Oncotype DX Breast Cancer Recurrence Score Test, 2023; NICEDG34/DG58).

Health economic evidence can demonstrate cost-effectiveness and costs savings (please see further information below). It is important that a long-term time horizon is applied in health economic analysis to capture the full value of the Oncotype DX test in terms of reduced distant recurrence and mortality rates.

Organizational aspects, such as changes to workflows:

Reducing the number of patients receiving adjuvant chemotherapy can lead to decreased resource consumption and alleviate burden on specialized healthcare personnel (including Oncologists and nurses).

Reduced chemotherapy may decrease the demand for infusion services, including chemotherapy chair time.

Reducing the number of patients progressing to advanced/metastatic cancer can also lead to decreased resource consumption and alleviate burden on specialized healthcare personnel.

The Oncotype DX® test is carried out in a state-of-the-art central laboratory in the US. A dedicated quality control and assurance team, as well as testing of all samples in triplicate, and extensive lab process automation, provides precision & reproducibility of a highly standardised process, with ISO 15189 / CLIA / CAP accreditations.

Exact Sciences offers a secure online portal, fully compliant with the General Data Protection Regulation (GDPR) for test ordering, tracking and reporting. Strict measures are followed to secure data privacy and GDPR compliance will be assured with the implementation of Oncotype DX in Denmark. Personal data are encrypted and pseudonymized and the encryption key remains in Europe so in no case does the laboratory in the US have access to patient personal information when performing the test. The test is performed on a sample identified by a QR code and the test result is associated with patient info only when the result is returned to the ordering clinician via the secure online EU portal. The Encryption process follows a strict principle of minimization of data access based on a privacy by design approach with clear definition of responsibilities and authorizations. Full details of the patient data security measures in place for the Oncotype DX testing service will be shared with the full evaluation submission.

Patient preferences and experiences:

Shared treatment decision-making between a patient and their clinician is of vital importance, especially considering the important consequences of the decision whether to have chemotherapy treatment. Chemotherapy side-effects can be severe, for example potentially leading to infertility for premenopausal women, impacting family planning, or leading to long-term health problems.

With the current approach patients do not have access to information about how having chemotherapy would affect the chances of their cancer coming back. Patients are therefore having to make very difficult treatment decisions based on suboptimal information, which may lead to additional anxiety.

A recent study reported that patients who had access to their Recurrence Score result had increased confidence when making their treatment decision (Holt et al. 2024).

Furthermore, patients undergoing unnecessary chemotherapy treatment may experience debilitating and life-changing short and long-term side-effects, potentially requiring taking time out of paid employment for themselves and/or carers i.e. a reduction in productivity costs.

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. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018;379(2):111-21. 2. Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF, et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. N Engl J Med. 2021;385(25):2336-47. The Oncotype DX test is supported by a wealth of additional data, including RCTs and large real-world datasets.
The Patient perspective	1. Holt, S., Verrill, M., Pettit, L. et al. A UK prospective multicentre decision impact, decision conflict and economic evaluation of the 21-gene assay in women with node+ve, hormone receptor+ve, HER2-ve breast cancer. Br J Cancer 130, 1149–1156 (2024). 2. Parsekar K, Howard Wilsher S, Sweeting A, et al. Societal costs of chemotherapy in the UK: an incidence-based cost-of-illness model for early breast cancer. BMJ Open. 2021 Jan 11;11(1):e039412.
Organizational Implications	1. TLV, Hälsoekonomisk bedömning av Oncotype DX Breast Recurrence Score Test, 2021 2. NIPH, Single Technology Assessment: Oncotype DX Breast Cancer Recurrence Score Test, 2023
Health Economics	1. Berdunov V, Millen S, Paramore A, et al. Cost-effectiveness analysis of the Oncotype DX Breast Recurrence Score test in node-positive early breast cancer. J Med Econ. 2022 Jan-Dec;25(1):591-604. 2. Berdunov V, Millen S, Paramore A, et al. Cost-Effectiveness Analysis of the Oncotype DX Breast Recurrence Score® Test in Node-Negative Early Breast Cancer. Clinicoecon Outcomes Res. 2022 Sep 19;14:619-633.

* 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

Health economic analyses of the Oncotype DX test estimate that use of the test leads to overall savings for the healthcare system (including after considering the cost of testing) due to reduced adjuvant chemotherapy treatment-related costs and reduced distant recurrence and end of life care costs.

A cost-effectiveness analysis of the Oncotype DX test in the node-negative patient subgroup in the UK estimated that testing was more effective (0.17 more quality-adjusted life years) at a lower cost (-£519) over a lifetime compared to clinical risk alone. This result was primarily driven by a reduction in distant recurrence among patients with a treatment change to add chemotherapy based on a high test result identifying significant treatment benefit (Berdunov et al, 2022).

A similar cost-effectiveness analysis in the node-positive patient subgroup in the UK, again estimated that testing was more effective (0.02 more quality-adjusted life years) at a lower cost (-£989) over a lifetime compared to clinical risk alone. Due to much higher pre-test chemotherapy treatment rates among N1 patients, cost savings in the N1 subgroup was primarily driven by a large reduction in chemotherapy treatment among patients with a low test result, identifying that chemotherapy would offer no benefit (Berdunov et al, 2022).

The latter analysis included both pre- and postmenopausal N1 patients. For the recently published NICE DG58 guidance recommending testing only postmenopausal N1 patients, the External Assessment Group published a cost-effectiveness subgroup analysis in their Technology Assessment Report, specifically for the postmenopausal N1 patient subgroup. The conclusion was again that testing is expected to be more effective (0.11 more quality-adjusted life years) at a lower cost (-£4,273).

TLV in Sweden and NIPH also concluded from their health technology assessments of the Oncotype DX test that testing is expected to be cost saving.

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

Additional references

1. Geyer CE, Jr., Tang G, Mamounas EP, Rastogi P, Paik S, Shak S, et al. 21-Gene assay as predictor of chemotherapy benefit in HER2-negative breast cancer. NPJ Breast Cancer. 2018;4:37.
2. Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF, et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. N Engl J Med. 2021;385(25):2336-47.
3. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018;379(2):111-21.
4. Paik S, Shak S, Kim C, Baker J, Cronin M, Baehner R, et al. Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients - NSABP studies B-20 and B-14. 2003. S10-S1 p.
5. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer. New England Journal of Medicine. 2004;351(27):2817-26.

6. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006;24(23):3726-34.
7. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol. 2010;11(1):55-65.
8. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687-717.
9. Early Breast Cancer Trialists' Collaborative Group. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet. 2012;379(9814):432-44.
10. Holt, S., Verrill, M., Pettit, L. et al. A UK prospective multicentre decision impact, decision conflict and economic evaluation of the 21-gene assay in women with node+ve, hormone receptor+ve, HER2-ve breast cancer. Br J Cancer 130, 1149–1156 (2024).
11. Tao JJ, Visvanathan K, Wolff AC. Long term side effects of adjuvant chemotherapy in patients with early breast cancer. Breast. 2015;24 Suppl 2:S149-53.
12. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 2009;101(21):1446-52.
13. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2015;373(21):2005-14.
14. Stemmer SM, Steiner M, Rizel S, Geffen DB, Nisenbaum B, Peretz T, et al. Clinical outcomes in ER+ HER2 -node-positive breast cancer patients who were treated according to the Recurrence Score results: evidence from a large prospectively designed registry. NPJ Breast Cancer. 2017;3:32.
15. Stemmer SM, Steiner M, Rizel S, Ben-Baruch N, Uziely B, Jakubowski DM, et al. Ten-year clinical outcomes in N0 ER+ breast cancer patients with Recurrence Score-guided therapy. npj Breast Cancer. 2019;5(1):41.
16. Nitz U, Gluz O, Christgen M, Kates RE, Clemens M, Malter W, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat. 2017;165(3):573-83.
17. Barni S, Curtit E, Cognetti F, Bourgeois D, Masetti R, Zilberman S, et al, Real-life Utilization of Genomic Testing for Invasive Breast Cancer Patients in Italy and France Reduces Chemotherapy Recommendations. #194P, ESMO, 2018.
18. Berdunov V, Millen S, Paramore A, Griffin J, Reynia S, Fryer N, et al. Cost-Effectiveness Analysis of the Oncotype DX Breast Recurrence Score(®) Test in Node-Negative Early Breast Cancer. Clinicoecon Outcomes Res. 2022;14:619-33.
19. Berdunov V, Millen S, Paramore A, Hall P, Perren T, Brown R, et al. Cost-effectiveness analysis of the Oncotype DX Breast Recurrence Score(R) test in node-positive early breast cancer. J Med Econ. 2022:1-48.
20. McSorley LM, Tharmabala M, Al Rahbi F, Chew S, Evoy D, Geraghty JG, et al. Real-world analysis of clinical and economic impact of 21-gene recurrence score (RS) testing in early-stage breast cancer (ESBC) in Ireland. Journal of Clinical Oncology. 2021;38(15_suppl):540-.