EESTI HAIGEKASSA TERVISHOIUTEENUSTE LOETELU MUUTMISE TAOTLUS KOOS TÄITMISJUHISTEGA

Juhime tähelepanu, et haigekassa avalikustab taotlused kodulehel. Konfidentsiaalne informatsioon, mis avalikustamisele ei kuulu, palume tähistada taotluse tekstis märkega „konfidentsiaalne“.

1. Taotluse algataja	
1.1 Organisatsiooni nimi (taotleja) *Tervishoiuteenuste loetelu muutmise ettepaneku (edaspidi taotlus) esitava organisatsiooni (edaspidi taotleja) nimi[1]. Kui taotlus esitatakse mitme erialaühenduse poolt, märgitakse taotluse punktis 1.1 taotluse algatanud erialaühenduse nimi ning seejärel kaasatud erialaühenduse ehk kaastaotleja nimi punktis 1.6.*	Eesti Onkoteraapia Ühing
1.2 Taotleja postiaadress	Puusepa 8, Tartu 50406
1.3 Taotleja telefoninumber	7319800
1.4 Taotleja e-posti aadress	peeter.padrik@kliinikum.ee
1.5 Kaastaotleja	
1.6 Kaastaotleja e-posti aadress	
1.7 Kontaktisiku ees- ja perekonnanimi	Peeter Padrik
1.8 Kontaktisiku telefoninumber	7319800
1.9 Kontaktisiku e-posti aadress	peeter.padrik@kliinikum.ee

2. Taotletav tervishoiuteenus	
2.1. Tervishoiuteenuse kood tervishoiuteenuste loetelus olemasoleva tervishoiuteenuse korral *Kui muudatus ei ole seotud loetelus kehtestatud konkreetse teenusega või on tegemist uue teenuse lisamise ettepanekuga, siis teenuse koodi ei esitata.*	Uus teenus
2.2 Tervishoiuteenuse nimetus	Rinnavähi koe geeniekspressioonanalüüs adjuvantse keemiaravi raviotsuseks
2.3. Taotluse eesmärk *Märkida rist <u>ühe,</u> kõige kohasema taotluse eesmärgi juurde. Risti lisamiseks vajutada sobilikul ruudul parempoolsele hiireklahvile ning avanenud menüüst valida „Properties“ – „Default value“ – „Checked“*	
☒ Uue tervishoiuteenuse lisamine loetellu ☐ Uue ravimiteenuse lisamine loetellu ☐ Uue ravimikomponendi lisamine olemasolevasse ravimiteenusesse ☐ Uue tehnoloogia lisamine loetelus olemasolevasse teenusesse ☐ Olemasolevas tervishoiuteenuses sihtgrupi muutmine (sh. laiendamine või piiramine) ☐ Eriala kaasajastamine (terve ühe eriala teenuste ülevaatamine)	

[1] Vastavalt Ravikindlustuse seaduse § 31 lõikele 5 võib taotluse esitada tervishoiuteenuste osutajate ühendus, erialaühendus või haigekassa.

☐ Loetelus olemasoleva tervishoiuteenuse piirhinna muutmine, mis ei tulene uue ravimikomponendi või tehnoloogia lisamisest olemasolevasse teenusesse (nt. teenuses olemasoleva kulukomponendi muutmine)[2]

☐ Loetelus olemasoleva tervishoiuteenuse kohaldamise tingimuste muutmine, mis ei tulene uue ravimikomponendi või uue tehnoloogia lisamisest olemasolevasse teenusesse ega teenuse sihtgrupi muutmisest (nt. teenuse osutajate ringi laiendamine, teenuse kirjelduse muutmine)[3]

☐ Loetelus olemasoleva tervishoiuteenuse kindlustatud isiku omaosaluse määra, haigekassa poolt kindlustatud isikult ülevõetava tasu maksmise kohustuse piirmäära muutmine[4]

☐ Loetelus olemasoleva tervishoiuteenuse nimetuse muutmine[5]

☐ Tervishoiuteenuse väljaarvamine loetelust[6]

☐ Üldkulude ühikuhindade muutmine vastavalt määruse „Kindlustatud isikult tasu maksmise kohustuse Eesti Haigekassa poolt ülevõtmise kord ja tervishoiuteenuse osutajatele makstava tasu arvutamise metoodika“ § 36 lõikele 2[7]

2.4 Taotluse eesmärgi kokkvõtlik selgitus

Esitada lühidalt taotluse eesmärgi kokkuvõtlik selgitus, mida taotletakse ja millistel põhjustel.

[2] Vajalik on täita taotluse punktid 1-2 ja 6

[3] Vajalik on täita taotluse punktid 1, 2 ja 12 ning kui on kohaldatav, siis ka 7 ja 8

[4] Vajalik on täita taotluse punktid 1, 2, 5.1, 11.4 ja 12.

[5] Vajalik on täita taotluse punktid 1-2

[6] Vajalik on täita taotluse punktid 1-2 ja 5.1

[7] Vajalik on täita taotluse punktid 1 ja 2 ning seejärel esitada kuluandmed metoodika määruse lisades 12 ja 13 toodud vormidel: „Tervishoiuteenuse osutaja kulud ressursside kaupa“ ja „Tervishoiuteenuse osutaja osutatud teenuste hulgad“

Rinnavähi ravis on vajalik otsustada, kas patsient vajab lisaks lokaalsele ravile (operatsioon ja kiiritusravi) ka täiendavat keemiaravi. Rinnavähk jaguneb positiivsete hormonaalsete retseptorite korral (hormoonpositiivne rinnavähk) bioloogiliselt kaugemetastaaside tekke osas madala riskiga ja kõrge riskiga juhtudeks. Madala riski korral piisab täiendavast hormoonravist, kõrge riski korral on vajalik lisaks hormoonravile ka keemiaravi.

Rinnavähi geeniekspressiooni test võimaldab eristada madala ja kõrge riski ravijuhud, aidates vältida asjatut keemiaravi madala riskiga juhtudel.

Eesmärk on vältida mittevajalikku adjuvantset keemiaravi, elimineerides sellega kaasnevad toksilisused, töövõimekao, nendega seotud finantskulud.

Taotlus on esitatud MammaPrint testi (tootjafirma Agendia) andmete põhjal, kuid võib olla rakendatav hiljem ka teiste analoogsete testide kasutamisel.

Tootjafirma Agendia poolne info:

MammaPrint is a prognostic and predictive genomic signature that determines the risk of recurrence of early breast cancer patients and is designed to complement clinical-pathological risk assessment in order to better identify patients who have a high probability of developing metastasis and who will benefit from adjuvant chemotherapy. In addition, the test identifies women with a low probability of recurrence, for whom endocrine therapy has proven to be the optimal treatment and chemotherapy has no clinically relevant benefit. The clarity that MammaPrint delivers helps patients and physicians make informed and confident treatment management decisions.

MammaPrint uses sophisticated microarray technology to measure the expression of 70 genes that have been shown to correlate with the likelihood of distant recurrence in early breast cancer patients, providing prognostic and predictive information. These 70 genes are involved in all 7 genomic pathways of the metastatic cascade. MammaPrint has been extensively researched and is able to guide physicians and patients with their chemotherapy treatment planning, where genomic high risk patients would derive a clinical meaningful benefit from chemotherapy and genomic low risk patients would not. De-escalation of chemotherapy for genomic low risk patients has been research in the randomized prospective trial MINDACT.

3. Tervishoiuteenuse meditsiiniline näidustus	
3.1 Tervishoiuteenuse meditsiiniline näidustus (ehk sõnaline sihtgrupi kirjeldus) *Esitada üksnes teenuse need näidustused, mille korral soovitakse teenust loetellu lisada, ravimikomponendi osas ravimiteenust täiendada, tehnoloogia osas tervishoiuteenust täiendada või teenuse sihtgruppi laiendada.* ***NB!** Kui erinevate näidustuste aluseks on erinev kliiniline tõendusmaterjal, palume iga näidustuse osas eraldi taotlus esitada, välja arvatud juhul, kui teenust osutatakse küll erinevatel näidustustel, kuid ravitulemus ja võrdlusravi erinevate näidustuste lõikes on sama ning teenuse osutamises ei ole olulisi erisusi.*	Patsiendid hormoonpositiivse ja HER2 negatiivse invasiivse rinnakartsinoomiga algkolde levikuulatusega pT1-T2 või opereeritava pT3, 0-3 aksillaarse lümfisõlme metastaasiga, M0 kaugmetastaaside staatusega operatsioonijärgse adjuvantse keemiaravi ravivajaduse otsustamiseks.
3.2 Tervishoiuteenuse meditsiiniline näidustus RHK-10 diagnoosikoodi alusel (kui on kohane)	***C50 Rinnanäärme kartsinoom***
3.3 Näidustuse aluseks oleva haiguse või terviseseisundi iseloomustus	

Kirjeldada haiguse või terviseseisundi levimust, elulemust, sümptomaatikat jm asjasse puutuvat taustainfot.
Rinnavähk on sagedasim pahaloomuline kasvaja naistel, Eestis haigestub rinnavähki üle 800 patsiendi aastas. Varase rinnavähiga naised saavad metastaseerumise riski vähendamiseks sageli adjuvantset hormoonravi, keemiaravi, HER-2 vastase bioloogilise ravi või nende kombinatsioone. Ravi vajadus määratletakse kasvaja suuruse, lümfisõlmede metastaaside, hormoon- ja HER2-retseptorstaatuse, diferentseerumisastme, patsiendi vanuse ja üldstaatuse järgi. Kuid olemasolevad metastaseerumise riski hindavad näitajad ei ole piisavalt täpsed, mistõttu oluline osa patsiente saab adjuvantset keemiaravi üleravina ilma reaalse kliinilise kasuta, kuid samas ravist tuleneva toksilisusega ja täiendava töövõime kaoga. Kasvajakoe geeni-ekspressiooni analüüsid eristavad erinevaid rinnakartsinoomi molekulaarseid tüüpe, aidates iseloomustada erinevate kasvajate prognoosi. Välja on arendatud mitmed testid, mis annavad kasvaja prognoosi määratledes täiendava info, kas adjuvantne keemiaravi on vajalik või mitte. Käesolev taotlus baseerub 70-geeni signatuuril (MammaPrint), mille kohta on olemas prospektiivse III faasi uuringu tulemused. Hinnataotluse eesmärk on rakendada rinnakartsinoomi koe geenieksрressiooni analüüs Eestis eesmärgiga vältida ilma kliinilise kasuta adjuvantset keemiaravi ja säästes sellega rinnavähiga naispatsiente keemiaraviga seotud toksilisusest ja töövõimetusest.

4. Tervishoiuteenuse tõenduspõhisus	
4.1 Teaduskirjanduse otsingu kirjeldus	
Erialasest kirjandusest on tuvastatud prospektiivsed III faasi randomiseeritud uuringud rinnavähi kasvajakoe geenieksрressiooni analüüside kasutamise kohta adjuvantse keemiaravi määramiseks.	
4.2 Tervishoiuteenuse tõenduspõhisuse andmed ravi tulemuslikkuse kohta kliiniliste uuringute ja metaanalüüside alusel	
4.2.1 Uuringu sihtgrupp ja uuritavate arv uuringugruppide lõikes *Märkida uuringusse kaasatud isikute arv uuringugrupi lõikes ning nende lühiiseloomustus, nt. vanus, sugu, eelnev ravi jm.*	**MINDACT uuring** 6693 naist vanuses 18 kuni 70 eluaastat histoloogiliselt tõestatud primaarse invasiivse rinnakartsinoomiga staadiumis T1 või T2 või opereeritav T3. Algses protokollis kaasati patsiendid ilma aksillaarsete metastaasideta, kuid 2009-st aastast muudeti protokolli, kaasates ka patsiente kuni 3 aksillaarse metastaasiga. Patsiendid jagati kas madala või kõrge riski gruppi, kasutades nii kliinilist (C-risk) kui ka genoomset (G-risk) riskihinnangut. Sellel põhinevalt küsiti, kas on ohutu jätta ära keemiaravi madala genoomse riski korral, isegi kui kliiniline risk on kõrge.

Patsiendid C-risk kõrge G-risk madal randomiseeriti keemiaravi ja mittekeemiaravi gruppidesse.

Patsiendid jagati 4 gruppi:

- Madal kliiniline risk ja madal genoome risk
- Madal kliiniline risk ja kõrge genoome risk
- Kõrge kliiniline risk ja madal genoome risk
- Kõrge kliiniline risk ja kõrge genoome risk

Testi tootjafirma Agendia poolne informatsioon:

MINDACT Trial

The Phase III '**M**icroarray **I**n **N**ode-negative and 1 to 3 positive lymph node **D**isease may **A**void **C**hemo**T**herapy' (MINDACT) trial was designed to provide prospective, randomized evidence that MammaPrint Low Risk (genomic Low risk) patients can safely forego chemotherapy (CT).[i] The primary analysis of the MINDACT trial showed that withholding CT from Clinically-high risk/Genomic-low risk (C-high/G-low) patients does not significantly impair outcome. The secondary analysis, that was performed based on a second data cut-off (February 26, 2020), underscored previous findings for 5-years with 90% follow-up compared to 60% follow-up in 2016, and presented 8-year follow-up.[ii]

Patient Population

MINDACT was conducted from 2007 - 2011 at 112 institutions in 9 European countries. Eligible patients were women age 18-70, with histologically proven primary non-metastatic (M0) invasive breast cancer (clinical T1, T2, or operable T3), and 0 or 1-3 positive lymph nodes. The overall patient and tumor characteristics of the eligible patients were median age of 55 (range 23 – 71 years), 79% of patients were LN0 and 21% had 1-3 positive nodes (pN1 micro were considered as LN+ and isolated tumor cells as LN0). The majority of patients (88%) was Estrogen Receptor positive (ER+) and/or Progesterone Receptor positive (PgR+).

Study design

Most physicians agree that an added absolute benefit of 3% survival is necessary to justify recommending chemotherapy.[iii] Although individual patient opinions may differ, most guideline panels would not accept the risk of toxic side effects below this threshold. Therefore, if a treatment benefit of less than 3% survival is to be expected, one should consider de-escalating chemotherapy.

	In MINDACT, all patients were categorized as either low or high risk using both clinical risk (C-risk) and genomic risk (G-risk) assessment. A modified version of Adjuvant! Online 8.0[iv] (A!O) including HER2 was used to standardize the C-risk assessment (see Appendix 1). Based on both risk assessments, MINDACT addressed the true clinical question of safely avoiding chemotherapy in specific patient populations based on tumor genomic profile. If chemotherapy is considered for a patient today (even if patient is presented with clinically high-risk factors such as lymph node positive, grade II/III and tumors >2cm), can a MammaPrint Low Risk result give the patient the option to safely forgo chemotherapy? To answer this question, patients who fell into the discordant risk group C-high/G-low were randomized to CT or no CT using a minimization technique which equally distributes patients with similar characteristics to each arm.
4.2.2 Uuringu aluseks oleva ravi/ teenuse kirjeldus	70-geeni signatuuri analüüs kasvajakoest määratlemaks haiguse genoomset riski kaugmetastaaside tekkeks
4.2.3 Uuringus võrdlusena käsitletud ravi/teenuse kirjeldus	Adjuvantne keemiaravi *versus* mitte-keemiaravi.
4.2.4 Uuringu pikkus	8-aasta jälgimistulemused
4.2.5 Esmane tulemusnäitaja *Uuritava teenuse esmane mõõdetav tulemus /väljund*	Üldine elulemus
4.2.6 Esmase tulemusnäitaja tulemus	Tulemused näitasid, et erinevused keemiaravi ja mittekeemiaravi gruppide vahel olid minimaalsed. Vt. Table 1.

Table 1: Effectiveness of chemotherapy versus no chemotherapy in patients with early breast cancer, C-High/G-low (MINDACT)

OS	Chemotherapy % at x years (95% CI)	No chemotherapy % at x years (95% CI)	Absolute difference in OS
ITT population	**N = 749**	**N = 748**	
After 8 years	95.7 (93.9-97.0)	94.3 (92.2-95.8)	1.4
LN0 (ER+/HER2-)	**N = 349**	**N = 350**	
After 8 years	95.5 (92.5-97.3)	93.9 (90.6-96.1)	1.6
LN+ (ER+/HER2-)	**N = 441**	**N = 453**	
After 8 years	95.5 (92.4-97.4)	94.9 (91.7-96.9)	0.6

OS = Overall Survival, CI = Confidence Interval, ITT = Intention To Treat
Follow-up: ±70% at 8 years

Results

The most relevant outcome measure with long-term follow-up of 8-years is Overall Survival (OS). ***Error! Reference source not found.*** shows the 8-year OS of the chemotherapy and no chemotherapy arm in three

groups. The first being the Intention To Treat (ITT) population, following the inclusion criteria as written in Chapter **Error! Reference source not found.**, and the other two being a lymph node negative and lymph node positive stratification within the luminal (ER+/HER2-) population of MINDACT.

These results show that differences in OS between the chemotherapy and no chemotherapy group were minimal and below the absolute benefit of 3% survival that is necessary to justify recommending chemotherapy.[iii] The absolute difference in OS after 8 years was 1.4% in the ITT population.[ii] Similarly, in the lymph node negative (LN0) and lymph node positive (LN+) subgroup, the absolute difference is below the 3% threshold, with an absolute difference of 1.6% and 0.6%, respectively. The results of both LN0 and LN+ indicate that there is minimal benefit of adjuvant chemotherapy in both groups, and that physicians and patients may consider de-escalation of chemotherapy.[ii]

De-escalation percentage

These results show that physicians may use MammaPrint to determine which patients are at genomic low risk and could therefore forgo chemotherapy. Following the results of MINDACT, it is evident that MammaPrint can realize a net decrease in chemotherapy usage. The MINDACT study included ER- and HER2+ patients as well, however, in clinical practice MammaPrint is being used in ER+/HER2- patients. Therefore, the de-escalation percentage should be derived from this subgroup only to determine the potential impact. Within the ER+/HER2- subgroup that were clinically high risk, 61.1% of patients were classified as low risk by MammaPrint.[8] Given that this group of patients is generally considered as candidate for chemotherapy, the use of the MammaPrint test could significantly decrease the amount of chemotherapy administered. With this, MammaPrint is contributing to personalized medicine, by preventing unnecessary toxicity and costs by reducing overtreatment with chemotherapy, and at the same time ensuring that the patients who will benefit from chemotherapy, are treated accordingly.

Negative Predictive Value (NPV)

Arguably the most important outcome measure for physicians when using MammaPrint is the Negative Predictive value (NPV) of MammaPrint. Here, the NPV of MammaPrint is defined as MammaPrint correctly predicting that a patient will not benefit from chemotherapy. The absolute difference in OS as shown in ***Error! Reference source not found.*** is 1.4%, 1.6% and 0.6% for the ITT, LN0 and LN+ group respectively. As a result, the NPV of MammaPrint in these populations is 98.6%, 98.4% and 99.4%, respectively. This implies one must treat 100 women with chemotherapy, to prevent one event. While for all other women, chemotherapy will only unnecessarily deteriorate the patients' health due to side effects from treatment such as neuropathy, acute myeloid leukemia, and congestive heart failure. In fact, over-treating leads to worse overall health for the patient than if no treatment is given. Hence, it is important for a physician to assess the NPV in order to make an informed treatment decision together with the patient.

4.2.7 Teised tulemusnäitajad *Uuritava teenuse olulised teised tulemused, mida uuringus hinnati*	Keemiaravi lühiajalised ja pikaajalised kõrvalnähud, patsientide töövõime taastumine
4.2.8 Teiste tulemusnäitajate tulemused	Keemiaraviga kaasnevad lühiajalised ja pikaajalised kõrvalnähud on toodud tabelites 2 ja 3, mida saaks ilma keemiaravita vältida. Joonisel 2 on toodud võrdlusandmed patsientide tööle tagasimineku osas erinevate ravivariantide korral.

[8] Piccart 2021, *supplementary appendix* Table S2 (707+696) / (707+696+894) * 100 = 61.1%

Table 2. Frequency of adverse events in MINDACT and in literature during first 6 months

Adverse Event	% of patients with AE in MINDACT (n = 635, treated with anthracycline-based therapy)[5]	% of patients with AE in MINDACT (n = 628, treated with DC)[5]	% of patients with AE, according to literature (treated with anthracycline-based therapy)
Grade 1 – 2			
Nausea	69.0	42.7	35.9[6,7]
Fatigue	69.0	67.4	79.2[7]
Alopecia	61.4	56.4	83.0[8]
Stomatitis	45.8	47.8	18.9[7]
Constipation	28.3	23.2	24.6[7]
Vomiting	29.6	14.0	42.0[9]
Grade 3 – 4			
Neutropenia	39.2	28.6	54.2[10]
Leukopenia	21.9	14.3	88.8[7]
Febrile neutropenia	10.3	7.0	28.3[7]
Severe infections	6.1	5.3	8.0[9]

AE = adverse event, DC = docetaxel-capecitabine

Table 3. Long-term chemotherapy-associated adverse events

Adverse event	% in literature
Cardiotoxicity[13,14,15]	2%
Second (hematological) tumor (e.g., acute myeloid leukemia)[16,32]	0.5-0.6%
Neuropathy[18]	11 – 80%
Cognitive decline[19,20]	61%
Fatigue[27,28]	40 – 56.7%
Problems with body weight[30]	40%
Hot flashes[23]	46%
Amenorrhea[24]	15%

Adverse Events of Chemotherapy

The disadvantages of chemotherapy are numerous, resulting in patients experiencing one or more Adverse Events (AEs) induced by chemotherapy during and after therapy. This Chapter aims to elucidate both the short-and long-term prevalence of chemotherapy induced AEs, and to provide key literature references on these AEs.

Short-term adverse events

In the MINDACT phase III trial, the frequency of AEs was reported within the patient population that was assigned to chemotherapy.[v] The AEs were monitored in patients receiving a standard anthracycline-based regimen and in patients receiving docetaxel-capecitabine regimen. The frequency of the AEs observed in the MINDACT trial were then compared with the frequency of AEs reported in literature. **Error! Reference source not found.** presents an overview of the frequency and types of AEs reported in MINDACT and in literature. In clinical practice, standard anthracycline-based regimens, with or without taxane, are most often used in early-stage breast cancer patients. Therefore, the prevalence of AEs in patients treated with anthracycline-based therapy in MINDACT will most likely be most representable for current clinical practice. Accordingly, the forthcoming comparison between MINDACT AE prevalence and AE prevalence according to literature will focus on AEs caused by anthracycline-based therapy.

As shown in **Error! Reference source not found.**, in MINDACT the most frequently occurring AEs in patients receiving anthracycline-based treatment were nausea (69%), fatigue (69%), alopecia (61%) and stomatitis (46%). Alopecia is often seen as lower grade AE (only grade 1-2). However, it includes not only hair loss on the women's scalp, but all over the body. When eyelashes or eyebrows fall out, there is no wig or treatment that can provide a solution. It is known to be one of the most shocking aspects for breast cancer patients and underestimated by physicians.[vi] Neutropenia and leukopenia are severe AEs (grade 3-4) and occurred in up to

40% of all patients. Neutropenia and leukopenia are hematologic toxicities associated with risk of life-threatening infections, as they suppress the production of respectively neutrophils and leukocytes.[vii]

Frequencies of AEs observed in the MINDACT trial are similar to known AE frequencies of chemotherapy presented in literature (**Error! Reference source not found.**). The AEs reported in the literature are chemotherapy-specific, as the patients either received only chemotherapy, or they received endocrine therapy following chemotherapy, but the AEs were only considered if they occurred during the chemotherapy treatment. Some AEs were reported at a higher rate in the literature than measured in the MINDACT trial, like alopecia, vomiting, neutropenia, and leukopenia. Other AEs were found more frequently in the MINDACT trial, like nausea and stomatitis. Overall, the chemotherapy-specific AEs found in literature correspond to those found in the MINDACT trial. Therefore, the AEs found in the MINDACT trial are likely to be attributable to chemotherapy and underscore the significance of these AEs when making a treatment decision.

Long-term adverse events

Adverse events that occur during treatment or shortly after treatment ends, are considered short-term AEs. Long-term AEs are symptoms that appear weeks, months, or years after treatment ends. The long-term AEs with the most substantial impact on the well-being of patients are the life-threatening events. Both cardiotoxicity[viii,ix,x] and chance of a second (hematological) tumor (such as acute myeloid leukemia)[xi] can appear early or late after the end of treatment and occur in 2-3% of all breast cancer patients.**Error! Bookmark not defined.**[xii] These severe AEs can lead to a decrease in QoL and even mortality.

Neuropathy is the term for pain and discomfort caused by damage to nerves. Neuropathy occurs in up to 80% of patients at one to three years following chemotherapy treatment.[xiii] Another often occurring toxicity following treatment is cancer-related cognitive decline, which on the long term is reported for 61% of patients.[xiv] This effect can persist for at least up to 2 years after diagnosis.[xv] Deterioration in cognitive function results in difficulty with concentration, memory and attention, but also verbal fluency and processing speed. It therefore has a substantial impact on the daily activities of women with breast cancer.[xiv,xv,xvi,xvii]

Reproductive system issues have been reported 18 months after end of treatment, for example problems with hot flashes (46%)[xviii], amenorrhea (15%)[xix], and fatigue (>40%).[xx] Fatigue is often an underestimated side-effect that impacts the patient on the long term where the overall severity of the fatigue can even worsen over time.[xxi] Literature illustrates that 56.7% of patients may experience severe fatigue up to two years after the end of treatment[xxii], and that 40% of patients report significant fatigue for up to 6 years post-treatment. [xxiii] Moreover, fatigue is associated with higher level of disabilities, such as depression.[xxiv] Another long-term side effect are problems with body weight, specifically weight gain, which occurs in 40% of cases.[xxv] Chemotherapy induced weight gain has also been researched in the WHEL study, which showed that chemotherapy was associated with a clinically meaningful weight gain.[xxvi] Additionally, it was unlikely for patients to return to initial weight (baseline) following weight gain for the six years of follow-up.[xxvi]

Even though long-term AEs were not measure in the MINDACT trail, the 'in literature' frequency of long-term AEs is likely to be representative for the MINDACT population as well. The comparison for short term AEs has shown to be similar between the observed frequencies from MINDACT and 'in literature'. Therefore, it is plausible that the same frequency of the long-term AEs in the range found in literature will occur in women treated with chemotherapy in the MINDACT trial, and that these would not occur in women who forego chemotherapy.

Figure 2. Months to (partial) return to work[33]

Type of treatment	N	Partial Return to Work (months)	Full Return to Work (months)
1. No adjuvant therapy	11	5.9	7.2
2. Locoregional radiotherapy	18	7.3	9.0
3. Systemic chemotherapy	9	10.6	12.3
4. Multimodel treatment	32	11.1	13.6
Difference between #1 and #3		4.7	5.1
5. No chemotherapy (#1 & #2)	29	6.8	8.3
6. Chemotherapy (#3 & #4)	41	11.0	13.3
Difference between #5 and #6		4.2	5.0

4.3 Tervishoiuteenuse tõenduspõhisuse andmed ravi ohutuse kohta	
4.3.1. Kõrvaltoimete ja tüsistuste iseloomustus	
Kõrvaltoime/ tüsistuse esinemissagedus	Kõrvaltoime/ tüsistuse nimetus
Väga sage (≥1/10)	Pole kohane
Sage (≥1/100 kuni <1/10)	Pole kohane
Rasked kõrvaltoimed	Pole kohane
Võimalikud tüsistused	Pole kohane
4.3.2 Kõrvaltoimete ja tüsistuste ravi *Kirjeldada, milliseid teenuseid ja ravimeid on vajalik patsiendile osutada ning millises mahus, et ravida tekkinud kõrvaltoimeid ning tüsistusi.* *Nt: Perifeersete dopamiinergiliste toimete põhjustatud kõrvaltoimeid (iiveldus, oksendamine ja ortostaatiline hüpotensioon) saab kontrolli all hoida domperidooni manustamisega kuni tolerantsuse tekkimiseni 3-6 nädala jooksul pärast subkutaanse apomorfiinravi alustamist, mille järel võib domperidooni manustamise lõpetada.*	
Kasvajakoe geneetilisel testimisel ei ole kõrvaltoimeid.	
4.4. Tervishoiuteenuse osutamise kogemus maailmapraktikas *Kirjeldada publitseeritud ravi tulemusi maailmapraktikas, kui puuduvad tervishoiuteenuse tõenduspõhisuse andmed ravi tulemuslikkuse ja ohutuse kohta avaldatud kliiniliste uuringute ja metaanalüüside alusel.*	
Olemas on publitseeritud kliiniliste uuringute andmed.	

5. Tõenduspõhisus võrreldes alternatiivsete tõenduspõhiste raviviisidega
5.1 Ravikindlustuse poolt rahastatav alternatiivne tõenduspõhine raviviis tervishoiuteenuste, soodusravimite või meditsiiniseadmete loetelu kaudu *Maksimaalselt palume kirjeldada 3 alternatiivi.*

Alternatiivi liik *Märkida, millise loetelu (tervishoiuteenused, soodusravimid, meditsiiniseadmed) kaudu on kohane alternatiiv patsiendile kättesaadav*	Alternatiiv *Märkida alternatiivse raviviisi teenuse kood, ravimi toimeaine nimetus või meditsiiniseadme rühma nimetus.*	Lisaselgitus / märkused *Vajadusel lisada siia tulpa täpsustav info*
1. Haigekassa tervishoiuteenuste loetelu	228R Rinnakasvaja HER2-blokaadi mittesisaldav kemoteraapia, kolmenädalane ravikuur	Tavaliselt 6 kuuri. Taotletav teenus geenitestimise abil võimaldaks madala genoomse riskiga patsientidel keemiaravi vältida.
2. Haigekassa tervishoiuteenuste loetelu	Keemiaravi tüsistuste raviga seotud hinnakirja koodid.	Võivad varieeruda laial skaalal.

5.2 Taotletava teenuse ja alternatiivse raviviisi sisaldumine Euroopa riikides aktsepteeritud ravijuhistes

Kui teenus ei kajastu ravijuhistes või antud valdkonnas rahvusvahelised ravijuhised puuduvad, lisada vastav selgitus lahtrisse 5.2.3. Maksimaalselt palume kirjeldada 5 ravijuhist.

Ravijuhise nimi	Ravijuhise ilmumise aasta	Soovitused ravijuhises *Soovitused taotletava teenuse osas* *Soovitused alternatiivse raviviisi osas*	Soovituse tugevus ja soovituse aluseks oleva tõenduspõhisuse tase
MammaPrint testi käsitlus rahvusvahelistes ravijuhistes on toodud ära alljärgnevas loetelus.			

European Society of Medical Oncology (ESMO)

Issued: 2019 (Cardoso et al., 2019)[xxvii]

- *Clinical Practice Guidelines recommended MammaPrint for staging and risk assessment and to inform adjuvant chemotherapy treatment*
- MammaPrint may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict response to adjuvant chemotherapy
- In case of uncertainty regarding indications for adjuvant chemotherapy, MammaPrint may be used to determine the individual recurrence risk and predict the benefit from chemotherapy

Patient group	Recommendation
ER-positive, HER2-negative, Breast cancer with 0-3 lymph nodes involved	• (Neo)Adjuvant ChT is indicated if high risk or high score • ER, PgR and HER2 status should guide all systemic treatment decisions • MammaPrint may be used in conjunction with all clinicopathological factors to guide systemic treatment decisions in patients where these decisions are challenging, such as luminal B-like/HER2-negative and node-negative/nodes 1–3- positive breast cancer • **Level 1A evidence** • Level A strength of recommendation

St. Gallen International Breast Cancer Consensus

Issued: June 2017 (Curigliano et al., 2017)[xxviii]

- The 2017 update expanded the consensus on MammaPrint as a prognostic tool to make treatment decisions for adjuvant chemotherapy in patients with lymph-node positive breast cancer
- MammaPrint testing is already recommended for lymph-node negative patients
- Tumor molecular subtype can be more appropriately determined by a multigene test. e.g., BluePrint and MammaPrint combined.
- In concordance with the 2017 publication, the 2019 panel discussion concluded that genomic signature testing, when accessible, is still used in the consideration of adjuvant chemotherapy.[xxix] The 2021 panel discussion took place in March 2021. At the time of writing the official publication, but the panel discussion brief summary is not available. Generally, the panel was again in concordance with the previous edition. Additionally, the vast majority of physicians (73%) voted in favor of performing genomic assays on core needle biopsies to acquire genomic information for neoadjuvant therapy decision making.[xxx]

Patient group	Recommendation
ER-positive, HER2-negative, **Lymph node-positive** breast cancer	Only MammaPrint and Oncotype DX are recommended. Other gene expression signatures were not uniformly endorsed for making treatment decisions regarding adjuvant chemotherapy in node-positive cases. Patients with genomic low risk tumor scores and a limited degree of nodal involvement appear to have a good prognosis with or without chemotherapy
ER-positive, HER2-negative, **Lymph node-negative** breast cancer	MammaPrint endorsed as a prognostic marker for adjuvant endocrine therapy in node-negative breast cancers. Recommended for guiding the decision on adjuvant chemotherapy, identifying patients at genomic low risk of recurrence, with an excellent prognosis, that would not warrant chemotherapy

Adapted from De-escalating and Escalating Treatments for Early Stage Breast Cancer: The St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017.

European Group on Tumor Markers (EGTM)

Issued: March 2017 (Duffy et al., 2017)[xxxi]

- MammaPrint is the first and only multi-gene test to receive level 1A status, based on findings of the MINDACT trial

- This update is based on evaluation of the most recent evidence available for all multigene tests

Patient group	Recommendation
ER-positive, HER2-negative, Breast cancer with 0-3 lymph nodes involved	• MammaPrint is recommended for determining prognosis and aiding decision-making for administration of adjuvant chemotherapy • Patients at high risk based on clinical and pathological criteria but at low risk based on MammaPrint may be candidates for avoiding having to receive adjuvant chemotherapy • **Level 1A evidence** • Level A strength of recommendation

Adapted from Clinical use of biomarkers in breast cancer: Updated guidelines from the European Group on Tumor Markers (EGTM)

American Society of Clinical Oncology(ASCO)

Issued: July 2017 (Krop et al., 2017)[xxxii]

- Focused update dedicated exclusively to MammaPrint and triggered by the practice-changing results of the MINDACT trial
  - ASCO recommends MammaPrint: For clinical high risk, hormone receptor-positive, HER2-negative breast cancer, to inform decisions on withholding chemotherapy
  - According to ASCO, MammaPrint is currently the only genomic test to guide treatment decisions for 1-3 lymph node-positive early-stage breast cancer
  - In a 2019 focused update by the ASCO panel, no changes were made with regards to the recommendations of MammaPrint. Evidence of testing in high clinical risk patients remains **'high'**, as is also presented in the table below.[xxxiii]

Patient group	Recommendation
ER/PgR-positive, HER2-negative, **Lymph node-negative** breast cancer	• MammaPrint may be used in patients with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit • Evidence quality: **High** • Strength of recommendation: **Strong**
ER/PgR-positive, HER2-negative, **Lymph node-positive** breast cancer,	• MammaPrint may be used in patients with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit • Evidence quality: **High** • Strength of recommendation: **Moderate**

Adapted from Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women with Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology

Issued: March 2021[xxxiv]

Version 8.2021

- The NCCN recommends the MammaPrint with the highest level of evidence, Level 1, for prognostic use in early-stage breast cancer patients with ER+, LN- and LN+ (1-3 positive lymph-nodes) breast cancer
- The MammaPrint is the only assay with Level 1 NCCN status of evidence and consensus for both LN- and LN+ breast cancer regardless of menopausal status, and thus the only level 1 evidence test for all LN+ patients per the NCCN guidelines

Patient group	Recommendation
ER-positive, **Lymph node-positive** breast cancer (1-3 positive lymph-nodes)	MammaPrint received a NCCN Level 1 Evidence and Consensus recommendation. Oncotype DX received Level 1 evidence for postmenopausal patients and level 2A for premenopausal patients. All other multigene assays for node-positive breast cancer were given level 2A recommendation.
ER-positive, **Lymph node-negative** breast cancer	Of the multigene assays considered for lymph node negative breast cancers, only MammaPrint and Oncotype Dx were given Level 1 endorsement.

Adapted from NCCN Guidelines Version 8.2021

German Gynecological Oncology Group (AGO)

Issued: March 2020[xxxv]

- In 2017 the "Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer" gave MammaPrint a level 1A recommendation to justify withholding potentially unnecessary chemotherapy.[xxxvi] Premise still holds in the 2021 update for the "Diagnosis and Treatment of Patients with Early Breast Cancer".[xxxv]

Patient group	Recommendation
HR-positive, HER2-negative, Early Breast cancer with 0-3 lymph nodes involved	• Gene expression assays, including MammaPrint, can be used when clinico-pathological criteria are not sufficient to make a clear treatment decision • Level 1* LOE2009 (Level of Evidence) • Level A* CTS (Category of tumor marker study) • AGO recommendation "+" (for use on selected patients when all other criteria do not allow a therapy decision).

* Simon et al, J Natl Cancer Inst 101: 1446-1452, 2009
Adapted from Diagnosis and Treatment of Patients with Early Breast Cancer, AGO 2021.

National BorstKanker Overleg Nederland (NABON): Dutch breast cancer guidelines

Last authorized: February 2020[xxxvii]

- Gene expression profiles, such as MammaPrint, have prognostic significance in addition to the well-known classical clinical and pathological factors. They should not be a replacement for known classical clinical and pathological factors.
- MammaPrint is recommended to be used in the patient group ER-positive, HER2-negative breast cancer with 0-3 lymph nodes involved

SEOM clinical guidelines in early-stage breast cancer

Issued: online November 2018[xxxviii]

Patient group	Recommendation
ER-positive, HER2-negative, Breast cancer	• MammaPrint risk score may be used for prediction of the risk of distant recurrence at 5 years in patients with hormone receptor (HR)-positive and HER2-negative breast cancer treated with adjuvant endocrine therapy-only • **Level 1A evidence** • Level A strength of recommendation

Adapted from SEOM clinical guidelines in early stage breast cancer (2018)

Sociedad Espanola de Senologia y Ptaologia Mamaira

Issued: online November 2020[xxxix]

Patient group	Recommendation
ER-positive, HER2-negative, Breast cancer with 0-3 lymph nodes involved	• To adapt the complementary treatment in certain situations, there are gene platforms for predicting the risk of recurrence. Of those platforms, MammaPrint is the first and only multi-gene test to receive level 1A status, based on findings of the MINDACT trial. MammaPrint is recommended to be used as a platform to predict the risk of recurrence for decision-making for administration of adjuvant chemotherapy in patients with ER-positive, HER2-negative breast cancer, N0-3. • **Level 1A evidence** • Level A strength of recommendation

Adapted from Sociedad Espanola de Senologia y Ptaologia Mamaria (2020)

5.3 Kokkuvõte tõenduspõhisusest võrreldes alternatiivsete tõenduspõhiste raviviisidega

Esitada kokkuvõtvalt teenuse oodatavad lühi- ja pikaajalised tulemused tervisele. nt. surmajuhtumite vähenemine, haigestumisjuhtude vähenemine, elukvaliteedi paranemine, kõrvaltoimete sageduse vähenemine, tüsistuste sageduse vähenemine.
Lisaks selgitada, kas uus teenus on samaväärne alternatiivse raviviisiga. Väites uue teenuse paremust, tuleb välja tuua, milliste tulemuste osas omab taotletav teenus eeliseid.

It is now known that traditional clinicopathological risk assessment (as well as previous consensus guidelines), for defining risk of recurrence, tends to allocate too many patients to receive chemotherapy. In addition, past guidelines contained subjective components that added variability to risk estimates. As a result, a large proportion of patients were over-treated and were unnecessarily subjected to the high toxicity of chemotherapy without any significant benefit in survival.

Use of MammaPrint, as recommended by current international guidelines, now allows for more reliable and accurate identification of patients at either low or high-risk of recurrence to be used in combination with traditional risk classifiers.

Advances in the understanding of the biology of breast cancer now are guiding the development of individualized treatment plans, aiming to provide each patient with the best chance for curative treatment while optimizing their quality of life. In a large proportion of patients, the ideal approach can in fact mean less treatment.

6. Tervishoiuteenuse osutamiseks vajalike tegevuste kirjeldus

6.1 Teenuse osutamise kirjeldus

Kirjeldada tervishoiuteenuse osutamiseks vajalikud tegevused (sh. ettevalmistavad tegevused), nende esinemise järjekorras, kaasatud personal ja nende rollid, teenuse osutamise koht (palat, protseduuride tuba, operatsioonituba) ning kasutatavad seadmed ja tarvikud. Võimalusel lisada ka tegevuste sooritamise keskmised ajad. Ravimiteenuste korral kirjeldada raviskeem: ravi pikkus, patsiendil kasutatavate annuste suurus.

Teenuse teostamiseks annab patsient kirjaliku teadva nõusoleku, mille järgselt tellib patsiendi raviarst MammaPrint testi teostamise.
Patsiendi opereeritud kasvajakoega parafiinblokk saadetakse kulleriga Agendia laborisse, kus teostatakse geenieksprессiooni analüüs.
Vastus saadetakse patsiendi raviarstile, kes teeb testi vastuse alusel edasised raviotsused.

7. Tingimused ja teenuseosutaja valmisolek kvaliteetse tervishoiuteenuse osutamiseks

7.1 Tervishoiuteenuse osutaja	Onkoloogia tegevusloaga piirkondlik haigla, valikupartner, keskhaigla.

Nimetada kohased teenuse osutajad (nt. piirkondlik haigla, keskhaigla, üldhaigla, kohalik haigla, valikupartner, perearst)	
7.2 Kas tervishoiuteenust osutatakse ambulatoorselt, statsionaarselt, ja/või päevaravis/päevakirurgias? *Loetleda sobivad variandid.*	Ambulatoorselt
7.3 Raviarve eriala *Nimetada, milliste erialade raviarvete peal antud teenus sisaldub lähtudes ravi rahastamise lepingust.*	Onkoloogia
7.4 Minimaalne tervishoiuteenuse osutamise kordade arv kvaliteetse teenuse osutamise tagamiseks *Esitada teenuse minimaalne osutamise kordade arv, mille puhul oleks tagatud teenuse osutamise kvaliteedi säilimine. Lisada selgitused/põhjendused, mille alusel on teenuse minimaalne maht hinnatud.*	Üks.
7.5 Personali (täiendava) väljaõppe vajadus *Kirjeldada, millise kvalifikatsiooniga spetsialist (arst vajadusel eriala täpsusega, õde, füsioteraput vm) teenust osutab ning kas personal vajab teenuse osutamiseks väljaõpet (sh. täiendavat koolitust teatud intervalli tagant). Väljaõppe vajadusel selgitada, kes koolitab, kus väljaõppe läbiviimine toimuks ning kes tasuks koolituskulud (kas koolituse garanteerib seadme müüja või teenuse osutaja ja kulu on arvestatud teenuste hindadesse jm).*	
Teenust osutavad vastava pädevusega onkoloogid.	
7.6 Teenuseosutaja valmisolek *Kirjeldada, milline peaks olema tervishoiuteenuse osutaja töökorraldus, vajalikud meditsiiniseadmed, täiendavate osakondade/teenistuste olemasolu ning kas on põhjendatud ööpäevaringne valmisolek, et oleks tagatud soovitud tulemus. Anda hinnang, kas teenuseosutaja on valmis koheselt teenust osutama või on vajalikud täiendavad investeeringud, koolitused, ruumide loomine vms.*	
Valmisolek on olemas.	

8. Teenuse osutamise kogemus Eestis	
8.1 Kas teenust on varasemalt Eestis osutatud?	On küll, patsientide omafinantseeringuna.
8.2 Aasta, millest alates teenust Eestis osutatakse	2018.
8.3 Eestis teenust saanud isikute arv ja teenuse osutamise kordade arv aastate lõikes	5 patsienti aastas, 15 kokku ehk ligikaudu.
8.4 Eestis teenust osutanud raviasutused	Piirkondlikud haiglad.
8.5. Tervishoiuteenuste loetelu koodid, millega tervishoiuteenuse osutamist on raviarvel kodeeritud	Ei ole kodeeritud.
8.6 Ravi tulemused Eestis	Vastavalt testi näidustustele on nii patsiente, kes on keemiaravi vajanud, kui ka neid, kes testi

	tulemuse põhjal – madal metastaseerumise risk – pole keemiaravi vajanud.

9. Eestis tervishoiuteenust vajavate isikute ja tervishoiuteenuse osutamise kordade arvu prognoos järgneva nelja aasta kohta aastate lõikes			
9.1 Keskmine teenuse osutamise kordade arv ravijuhu (ühele raviarvele kodeerimise) kohta	1		
9.2 Tervishoiuteenust vajavate isikute arv ja tervishoiuteenuse osutamise kordade arvu prognoos järgneva nelja aasta kohta aastate lõikes			
9.2.1 Aasta	9.2.2 Isikute arv *arvestades nii lisanduvaid isikuid kui ravi järgmisel aastal jätkavaid isikuid*	9.2.3 Ravijuhtude arv 1 isiku kohta aastas *arvestades asjaolu, et kõik patsiendid ei pruugi lisanduda teenusele aasta algusest*	9.2.4 Teenuse osutamise kordade arv aastas kokku
1. aasta	257	1	257
2. aasta	257	1	257
3. aasta	257	1	257
4. aasta257	257	1	257

9.3 Prognoosi aluse selgitus

Esitatakse selgitused, mille põhjal on teenust vajavate patsientide arvu hinnatud ning selgitused patsientide arvu muutumise kohta aastate lõikes.

Testi tootjafirma Agendia poolne kalkulatsioon:

For the budget impact calculation, an invasive breast cancer incidence of 835 women in Estonia is assumed based on Globocan statistics.[xl] Within this group, an Estonian registry study has shown that the breast cancer staging distribution is 31% stage I, 40,4% stage II and 19,6% stage III breast cancer.[xli] Given that MammaPrint can also be used in stage IIIa breast cancer, the assumption is made that 33% of the stage III patients are stage IIIa. Considering these percentages, in total 77,9% of the patients meet the first inclusion criteria. For the second inclusion criteria, the target population reduced from 650 to 470, as a result of 72,2% of women having an ER+/HER2- breast cancer tumor (also called luminal). Lastly, as an approximation of the percentage of the third inclusion criteria, the estimated percentage of patients with a luminal tumor that are candidate form chemotherapy is based on the Estonian registry study by Farahani and colleagues. With the percentage of 54,7%[xli], the eligible number of patients for MammaPrint testing comes down to roughly 257 patients.
Within MINDACT, it has been shown that 61,1% of patients with a luminal tumor that are candidate for chemotherapy have a MammaPrint low risk score.[ii] This means that of the 257 eligible patients for testing, 157 may safely forgo chemotherapy based on the information received by MammaPrint.

See tähendab, et kui aastas testitakse keskmiselt 257 patsienti, siis neist senistel andmetel 61,1% on madala riskiga ehk ei vaja täiendavat keemiaravi.

9.4 Tervishoiuteenuse mahtude jagunemine raviasutuste vahel

Tabel on vajalik täita juhul, kui tervishoiuteenuse ravijuhud tuleb planeerida konkreetsetesse raviasutustesse, st. tegu on spetsiifilise tervishoiuteenusega, mida hakkaksid osutama vähesed raviasutused.

9.4.1Raviasutuse nimi	9.4.2 Raviarve eriala raviasutuste lõikes	9.4.3 Teenuse osutamise kordade arv raviarve erialade lõikes
	Onkoloogia	*130*

Sihtasutus Põhja-Eesti Regionaalhaigla		
Sihtasutus Tartu Ülikooli Kliinikum	*Onkoloogia*	*87*
Ida-Tallinna Keskhaigla	*Onkoloogia*	*40*

10. Tervishoiuteenuse seos kehtiva loeteluga, ravimite loeteluga või meditsiiniseadmete loeteluga ning mõju töövõimetusele	
10.1 Tervishoiuteenused, mis lisanduvad taotletava teenuse kasutamisel ravijuhule *Loetleda samal raviarvel kajastuvate tervishoiuteenuste koodid ja teenuse osutamise kordade arv sellel raviarvel.*	Ei lisandu, vaid jääb ära 228R Rinnakasvaja HER2-blokaadi mittesisaldav kemoteraapia, kolmenädalane ravikuur
10.2 Tervishoiuteenused, mis lisanduvad alternatiivse teenuse kasutamisel ravijuhule *Loetleda alternatiivse tervishoiuteenuse samal raviarvel kajastuvate tervishoiuteenuste koodid ning teenuse osutamise kordade arv sellel raviarvel.*	Ravivalik teenuse 228R Rinnakasvaja HER2-blokaadi mittesisaldav kemoteraapia, kolmenädalane ravikuur, teostamiseks tehakse vaid kliiniliste kriteeriumite alusel.
10.3 Kas uus teenus asendab mõnda olemasolevat tervishoiuteenust osaliselt või täielikult? *Kui jah, siis loetleda nende teenuste koodid ning selgitada, kui suures osakaalus asendab uus teenus hetkel loetelus olevaid teenuseid (tuua välja asendamine teenuse osutamise kordades).*	Ei asenda.
10.4 Kui suures osas taotletava teenuse puhul on tegu uute ravijuhtudega? *Kas teenuse kasutusse võtmine tähendab uute ravijuhtude lisandumist või mitte? Kui jah, siis mitu ravijuhtu lisandub?*	Tähendab keemiaravi kuuridega seonduvate ravijuhtude ärajäämist.
10.5 Taotletava tervishoiuteenusega kaasnevad samaaegselt, eelnevalt või järgnevalt vajalikud tervishoiuteenused (mida ei märgita taotletava teenuse raviarvele), soodusravimid, ja meditsiiniseadmed isiku kohta ühel aastal. *Kirjeldatakse täiendavad teenused, ravimid ja/või meditsiiniseadmed, mis on vajalikud kas teenuse määramisel, teostamisel, edasisel jälgimisel: kuidas kasutatakse (ravimite puhul annustamisskeem), ravi kestus/kuuride arv, ravi alustamise ja lõpetamise kriteeriumid.* *Diagnostilise protseduuri puhul esitatakse andmed juhul, kui protseduuri teostamise järel muutub isiku edasises ravis ja/või jälgimisel kasutatavate tervishoiuteenuste ja ravimite kasutus. Juhul kui muutust ei toimu, esitada sellekohane selgitus.*	Ei kaasne.

10.6 Alternatiivse raviviisiga kaasnevad (samaaegselt, eelnevalt või järgnevalt) vajalikud tervishoiuteenused (mida ei märgita taotletava teenuse raviarvele), soodusravimid, ja meditsiiniseadmed isiku kohta ühel aastal. *Vastamisel lähtuda punktis 10.5 toodud selgitustest.*	Ei kaasne.
10.7 Kas uus tervishoiuteenus omab teaduslikult tõendatult erinevat mõju töövõimetuse kestvusele võrreldes alternatiivse raviviisiga? *Kas töövõimetuse kestuse osas on publitseeritud andmeid teaduskirjandusest ning kas raviviiside vahel saab väita erinevust?*	Jah, vähendab töövõimetuse kestvust. Tootjafirma Agendia andmetel: In case of the service of MammaPrint, the information used in chemotherapy decision-making helps to identify patients that may forego chemotherapy. Given that one is unlikely to be able to work during the treatment period of chemotherapy (about 6 months), de-escalation of chemotherapy is likely to positively impact the patient's ability to work. Also, avoiding chemotherapy prevents the onset of toxicity and often times debilitating side effects related to the therapy. Side effects that impair cognitive functioning or cause long-term fatigue, are likely to negatively influence productivity and might force women to reduce their working hours.
10.8 Kui jah, siis mitu päeva viibib isik töövõimetuslehel taotletava teenuse korral ning mitu päeva viibib isik töövõimetuslehel alternatiivse raviviisi korral?	The study of Balak and Colleagues made use of one of the Dutch registers of the occupational health department.[xlii] The registry was a sickness absence registry that recorded about 50,000 employees. The patient cohort was stratified in four groups, based on the known type of adjuvant therapy received: 1. No adjuvant therapy (N=11) 2. Locoregional radiotherapy (N=18) 3. Systemic chemotherapy (N=9) 4. Multimodal treatment (chemotherapy and radiotherapy) (N=32) For those four groups, the period of absence from work is calculated in months. Both between the first day of sick-leave and partial return to work (part of contracted hours per week) and between the first day of sick-leave and full return to work (normal contracted hours per week). Results: look the Figure below:

Type of treatment	N	Partial Return to Work (months)	Full Return to Work (months)
1. No adjuvant therapy	11	5.9	7.2
2. Locoregional radiotherapy	18	7.3	9.0
3. Systemic chemotherapy	9	10.6	12.3
4. Multimodel treatment	32	11.1	13.6
Difference between #1 and #3		4.7	5.1
5. No chemotherapy (#1 & #2)	29	6.8	8.3
6. Chemotherapy (#3 & #4)	41	11.0	13.3
Difference between #5 and #6		4.2	5.0

Looking at the data, in the Figure, it is evident that both patients that are treated with chemotherapy require more months before those women can partially return to work, as well as months required for a full return to work. Complete absence from work as a result of sickness/disease is referred to as 'absenteeism' in health economic terms. The difference of absenteeism between those not treated with chemotherapy and those who are is at least 4.2 months.

The results break down as follows:

- Time to partial return to work without chemotherapy is 5.9 month and 10.6 months with chemotherapy. This means that adding chemotherapy would result in 4.7 productive months lost (Difference between #1 and #3)
- Time to partial return to work without chemotherapy is 6.8 month and 11.0 months with chemotherapy This means adding chemotherapy would result in 4.2 productive months lost (Difference between #5 and #6)

This study shows that unnecessary chemotherapy imposes a large societal burden from both absenteeism, as well as productivity losses arising from being "ill" at work (which is called presenteeism). Patient report outcome measures from the Netherlands have shown that 43% of women that were treated with chemotherapy still experience cognitive problems at work which impairs their productivity.[xliii]

Other research that focused on work absence after breast cancer diagnosis, presented similar findings on prolonged absence from work cause by chemotherapy. A Canadian study of Drolet and colleagues showed that receiving chemotherapy prolongs the work absence duration by 4.1 months.[xliv] A Swedish study, with different methodology, found that the risk of having long-term sickness absence was significantly higher for those treated with radiotherapy/hormonal therapy (Adjusted Odds Ratio = 2.05), radiotherapy combined with chemotherapy and/or hormonal therapy (AOR = 3.88) and chemotherapy with/without hormonal therapy (AOR = 5.71), all when compared to those not receiving any oncological treatment.[xlv] Lastly, a French study, Optisoins01, showed in multivariate analysis that chemotherapy was the only independent factor associated with longer sick-leave (OR: 3.5).[xlvi] The observed trend of the percentage of patients in sick leave between the patients on chemotherapy, versus those who are not, is also clearly displayed in Figure 3

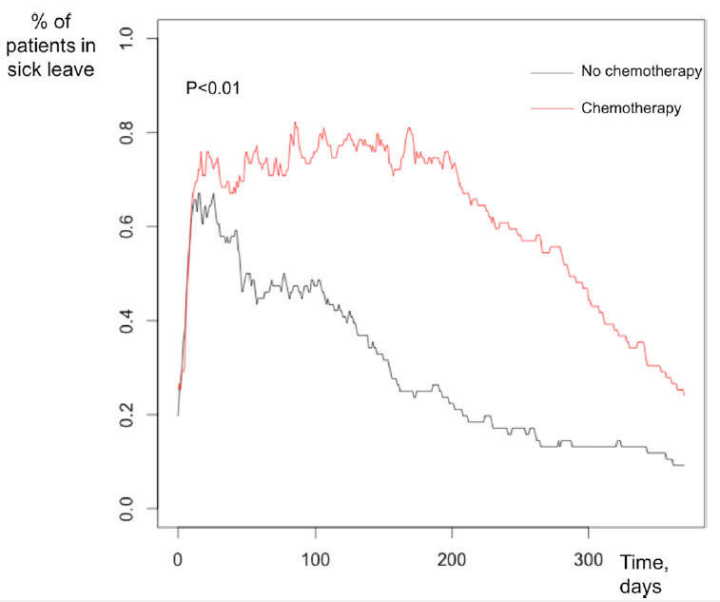

Figure 1. Percentage of patients on sick leave at 1-year follow-up depending on the presence or absence of *chemotherapy.*[xlvi]

(extracted from the paper).

The findings of Balak and colleagues combined with the Canadian, Swedish and French study show the increased disability to work for early-stage breast cancer patients that are treated with chemotherapy as compared early-stage breast cancer patients that are not. In conclusion, the ability to stratify patients at a genomic low risk of recurrence by MammaPrint, allows oncologists in medical decision-making to de-escalate chemotherapy, which in turn results in an increased ability to work both on an individual as well as on a population level.

11. Kulud ja kulutõhusus

11.1 Taotletava tehnoloogia või ravimi maksumus

Esitada taotletavatehnoloogia maksumus. Ravimi maksumuse info palume edastada juhul, kui ravimil puudub Eestis müügiluba ja/või müügiloahoidja esindaja. Sellisel juhul palume esitada ravimi maksumuse koos täpsustusega, millise hinnaga on tegu (ravimi maaletoomishind, hulgimüügi väljamüügihind, lõplik hind haiglaapteegile koos käibemaksuga).
Väli on kohustuslik kui taotluse eesmärgiks on „Uue tehnoloogia lisamine loetelus olemasolevasse teenusesse“

Ühe testi hind on [redacted] + käibemaks (in vitro meditsiiniseade) = [redacted]

11.2. Tervishoiuökonoomilise analüüsi kokkuvõte

Tootjafirma Agendia poolne analüüs:

The budget impact of MammaPrint in Estonia presented here is based on three inclusion criteria:

1. Stadium I, II or IIIa breast cancer
2. ER+ and HER2- tumor (Luminal)
3. Chemotherapy is considered as a treatment option

For the budget impact calculation, an invasive breast cancer incidence of 835 women in Estonia is assumed based on Globocan statistics.[xlvii] Within this group, an Estonian registry study has shown that the breast cancer staging distribution is 31% stage I, 40,4% stage II and 19,6% stage III breast cancer.[xlviii] Given that MammaPrint can also be used in stage IIIa breast cancer, the assumption is made that 33% of the stage III patients are stage IIIa. Considering these percentages, in total 77,9% of the patients meet the first inclusion criteria. For the second inclusion criteria, the target population reduced from 650 to 470, as a result of 72,2% of women having an ER+/HER2- breast cancer tumor (also called luminal). Lastly, as an approximation of the percentage of the third inclusion criteria, the estimated percentage of patients with a luminal tumor that are candidate form chemotherapy is based on the Estonian registry study by Farahani and colleagues. With the percentage of 54,7%[xli], the eligible number of patients for MammaPrint testing comes down to roughly 257 patients.

Within MINDACT, it has been shown that 61,1% of patients with a luminal tumor that are candidate for chemotherapy have a MammaPrint low risk score.[ii] This means that of the 257 eligible patients for testing, 157 may safely forgo chemotherapy based on the information received by MammaPrint.

The direct cost of MammaPrint will be expressed as the difference in cost of the test and the savings on chemotherapy. Here the cost impact of MammaPrint will be based on the chemotherapy costs, the treatment costs of congestive heart failure and acute myeloid leukemia, and the costs of prolonged work absence due to chemotherapy. The MammaPrint costs are [redacted] euro (excluding VAT), the costs of chemotherapy are €1,630.50 and the daily rate the insurance pays for sick leave is €24.10 euro. With 126 additional days on sick leave, this amounts to €3,036.60.[xlii] The per patient costs of treating chemotherapy induced Congestive heart failure (CHF) and Acute myeloid leukemia (AML) are calculated by using the frequency of the adverse events, which is 2% and 0.5% respectively.[xlix,l] This amounts to €221,63 per patient. Given that there are more adverse events than the treatment costs of CHF and AML, the cost item of adverse event treatment is likely to be underestimated in this budget impact analysis.

The costs of testing 257 patients are estimated to be [redacted] (257 * [redacted]) per year. Of these patients, 157 are expected to be genomic low risk, and may therefore safely forgo chemotherapy. The estimated savings as a result of de-escalating chemotherapy amount to €767,126 (157 * €1,630.50 + 157 * €3,036.60 + 157 * €221,63) per year.[9]

When looking at the direct costs of MammaPrint and the savings on chemotherapy and reduced sickness leave, reimbursing MammaPrint leads to a potential savings of [redacted] (€767,530.61 - [redacted]) per year. This represents an average cost savings of [redacted] per patient. Given that the costs of treatment of most adverse events are not accounted for in this budget impact analysis. Therefore, the amount of savings in the Estonian healthcare setting may be underestimated.

[9] Calculations may vary because the Excel file doesn't round up in it's calculations.

11.3 Rahvusvahelised kulutõhususe hinnangud taotletava teenuse (v.a ravimid) näidustuse lõikes *Maksimaalselt palume kajastada 6 hinnangut.*		
11.3.1 Kulutõhususe hinnangu koostanud asutuse nimi	11.3.2 Hinnangu avaldamise aasta	11.3.3 Lühikokkuvõte kulutõhususest *Kas raviviis on hinnatud kulutõhusaks? Palume välja tuua, milline on taotletavast teenusest saadav lisakasu. Näiteks mitu täiendavat eluaastat (life year gained, LYG) või kvaliteedile kohandatud eluaastat (quality adjusted life year, QALY) võidetakse taotletava teenusega või kui palju tüsistusi või meditsiinilise probleemi taasteket võimaldab uus teenus ära hoida. Milline on täiendkulu tõhususe määr (ICER) võidetud tervisetulemi kohta?*

Kulutõhusus:

The cost-effectiveness of MammaPrint depends on the country in which the test is applied. The differences in clinical practice between countries in chemotherapy regimen used and in-country prices of care affect the cost-effectiveness (CE) analysis.

MammaPrint has been evaluated in various cost-effectiveness analyses (Appendix 2), of which none are in an Estonian healthcare setting. However, the two most recent cost-effectiveness analyses (Ontario Health[li] & Retel et al.[lii]) showed cost-effectiveness of MammaPrint in seven countries. Therefore, one could assume that an Estonian CE-study would yield similar results.

Ontario Health's review involved a Canadian evaluation for reimbursement of MammaPrint. The study found that GEP testing, including MammaPrint, is generally cost-effective compared to usual care. The ICER of MammaPrint compared with usual care was $19.793.[li] Research of Retel and colleagues showed the expected cost-effectiveness of the use of MammaPrint in six European countries based on MINDACT 2016 data. Treatment strategies guided by MammaPrint resulted in in more QALYs in all countries and costs were lower in five out of six countries. This led to dominance in Belgium, France, Germany, Netherlands, and US. Annual cost savings were €4.2M, €24.7M, €45.1M, €12.7M and $244M respectively. In the UK it led to cost-effective situation ICER £22,910/QALY, with a budget increase of £8.4M.[lii]

Lastly, it is important to note that the cost-effectiveness assessment of MammaPrint should be ascertained in the context of ER+/HER2- (Luminal) breast cancer. In clinical practice, GEP-tests to assist in chemotherapy decision-making are only used in luminal only. Therefore, the cost-effectiveness analysis of NICE is less relevant in this context, as this assessment included the whole MINDACT-population (Luminal, HER2-positive and Triple Negative breast cancer).

KOKKUVÕTE:

The budget impact analysis showed that in Estonia there are approximately 257 breast cancer patients eligible for MammaPrint annually. By using MammaPrint in treatment decision-making for these patients, it is possible to de-escalate chemotherapy in 61,1% of cases, resulting in potential annual cost savings of [redacted] or [redacted] per patient. These savings may be underestimated because limited adverse event treatment costs were included in the budget impact model. MammaPrint also is shown to be cost-effective in a multitude of studies.

11.4 Hinnang isiku omaosaluse põhjendatusele ja isikute valmisolekule tasuda ise teenuse eest osaliselt või täielikult *Esitatakse isiku omaosaluse vajalikkus ja maksmise võimalused. Omaosaluse vajadusel lisatakse omaosaluse %.* *Omaosaluse valmisoleku esitamisel arvestada Ravikindlustuse seaduse § 31 lõikes 3 sätestatut ning selgitada:* *1) kas teenuse osutamisega taotletav eesmärk on saavutatav teiste, odavamate meetoditega, mis ei ole seotud oluliselt suuremate riskidega ega halvenda muul viisil oluliselt kindlustatud isiku olukorda;* *2) kas teenus on suunatud pigem elukvaliteedi parandamisele kui haiguse ravimisele või kergendamisele;* *3) kas kindlustatud isikud on üldjuhul valmis ise teenuse eest tasuma ning millest nende otsus sõltub.*
Tegemist on töövõime kaotanud vähihaigetega, kelle korral omaosalus ei ole põhjendatud.

12. Tervishoiuteenuse väär- ja liigkasutamise tõenäosus ning kohaldamise tingimused	
12.1 Tervishoiuteenuse väärkasutamise tõenäosus *Esitatakse andmed teenuse võimaliku väärkasutamise kohta (kas on võimalik, mil moel). Nt. risk, et tervishoiuteenust kasutatakse valel patsiendil, mitte piisavat erialast kompetentsi omava tervishoiutöötaja või tugispetsialisti poolt.*	Selgelt sõnastatud testi näidustuse korral on väärkasutuse tõenäosus madal.
12.2 Tervishoiuteenuse liigkasutamise tõenäosus *Esitatakse andmed teenuse võimaliku liigkasutamise kohta (kas on võimalik, mil moel). Nt. ravi ei lõpetata progressiooni ilmnemisel, ravi alustatakse varem, kui eelnevad ravimeetodid on ära proovitud.*	Vältida tuleks testi tegemist selleks näidustust mitteomavatele patsientidele.
12.3 Patsiendi isikupära ja eluviisi võimalik mõju ravi tulemustele *Kas patsiendi sugu, vanus, eluviis vms omab mõju ravi tulemustele? Kui jah, tuua välja faktor ja tema mõju.*	Näidustus tuleneb eeskätt kasvaja bioloogiast.
12.4 Kas tervishoiuteenuse ohutu ja optimaalse kasutamise tagamiseks on vajalik kohaldamise tingimuste sätestamine	Vajalik on sätestada testi teostamise patsientide sihtgrupp.
12.5 Tervishoiuteenuse kohaldamise tingimused *Kui 12.4 on vastatud jaatavalt, palume sõnastada teenusega seotud rakendustingimused, mis aitaksid tagada tervishoiuteenuse ohutut ja optimaalset kasutust.*	
Rinnavähi geenisekspressiooni analüüsi test on näidustatud patsientidele hormoonpositiivse ja HER2 negatiivse invasiivse rinnakartsinoomiga algkolde levikuulatusega pT1-T2 või opereeritava pT3, 0-3 aksillaarse lümfisõlme metastaasiga, M0 kaugmetastaaside staatusega, operatsioonijärgse adjuvantse keemiaravi ravivajaduse otsustamiseks.	

13. Kasutatud kirjandus

Vt alltoodud loetelu.

Taotlusele lisatud failid:

- *Final Value dossier Estonia*
- *Estonia Budget impact*

Taotluse esitamise kuupäev	30.11.2021
Taotleja esindusõigust omava isiku nimi ja allkiri *Elektroonsel esitamisel allkirjastatakse dokument digitaalselt ning nime alla lisatakse järgmine tekst "(allkirjastatud digitaalselt)".*	*Dr Peeter Padrik* *Eesti Onkoteraapia Ühingu juhatuse liige* *Allkirjastatud digitaalselt.*
Kaastaotleja esindusõigust omava isiku nimi ja allkiri *Kui taotlus esitatakse mitme erialaühenduse poolt, tuleb taotlus allkirjastada ka kaastaotleja poolt. Elektroonsel esitamisel allkirjastatakse dokument digitaalselt ning nime alla lisatakse järgmine tekst "(allkirjastatud digitaalselt)".*	-

Kasutatud kirjandus

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