## Cytostatika vid tidig bröstcancer

Läkartidningen DEBATT

# Patienten bör inte behöva betala för betydelsefulla test

**Sven Tägerud**, professor i farmakologi, Linnéuniversitetet, Kalmar
sven.tagerud@lnu.se

**CITERAS SOM:**
Läkartidningen. 2019;116:FMDY
Läkartidningen 16-17/2019
Lakartidningen.se 2019-04-16

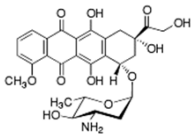
**Nya forskningsrön sprids snabbt i** samhället, och sjukvården måste hitta sätt att bevaka forskning så att vårdpersonal blir informerad om nya metoder och behandlingar minst lika snabbt som patienter. Hälsoekonomiska bedömningar kan krävas, men bör inte få försena införande av betydelsefulla nya metoder. Om målsättningen är lika vård för alla är det tveksamt om patienter ska behöva föreslå och betala för ett test som kan bli helt avgörande för en behandling.

## Cytostatika vid tidig bröstcancer

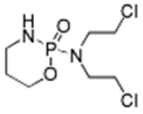
Kvinna 61 år;
invasiv duktal cancer 17x18x16 mm;
histologisk grad 3; tubuli 3; kärnatypier 3;
mitoser 2/10;
ingen kärlinväxt;
östrogenreceptor 99 procent;
progesteronreceptor 50 procent;
HER2-negativ;
Ki67-index 37 procent;
Nottingham prognostic index (NPI): 4,36;
två benigna portvaktskörtlar.

## Cytostatika vid tidig bröstcancer

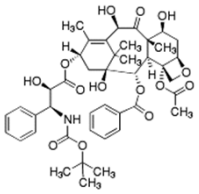
Multidiciplinär konferens rekommenderade cytostatikabehandling, sekventiellt med E90C följt av taxaner.



epirubicin (antracyklin, interkalerare)



cyklofosfamid (alkylerare)



docetaxel, mitoshämmare, stabiliserar mikrotubuli

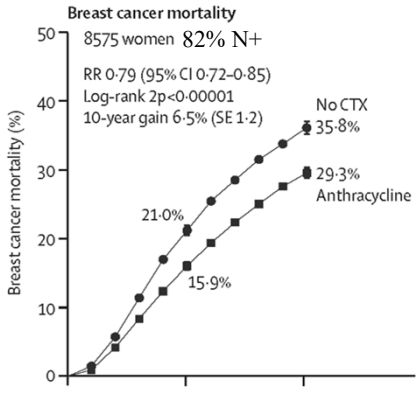
## Cytostatika vid tidig bröstcancer

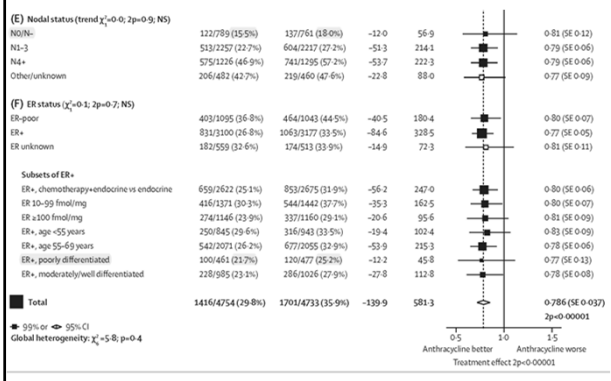
**Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials**

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

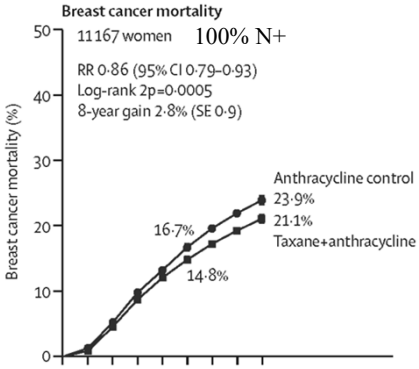
Lancet 2012;379:432-444

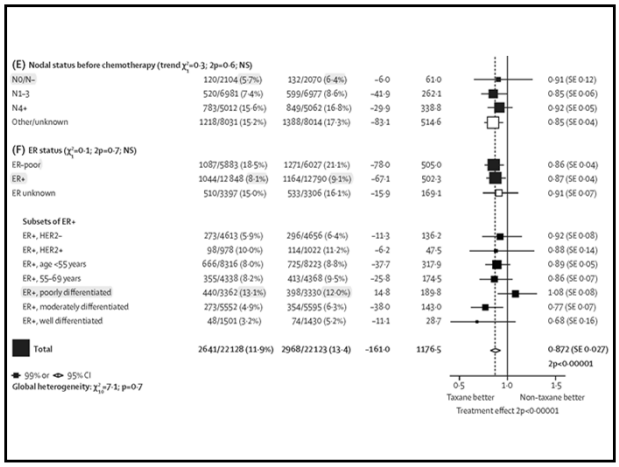
## Cytostatika vid tidig bröstcancer



## Cytostatika vid tidig bröstcancer




## Cytostatika vid tidig bröstcancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

NEJM 2018; 379:111-121

TAILORx-studien: Trial Assigning Individualized Options for Treatment

+ ökad risk
- minskad risk

21-gene expression assay (Oncotype DX):

Testet mäter uttrycket av vissa gener i bröstcancervävnad och ett RS-värde (recurrence score) från 0–100 beräknas.

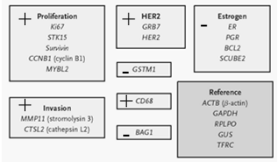



Figure 1. **Panel of 21 Genes and the Recurrence-Score Algorithm.**
The recurrence score on a scale from 0 to 100 is derived from the reference-normalized expression measurements in four steps. First, expression for each gene is normalized relative to the expression of the five reference genes (*ACTB* [the gene encoding β-actin], *GAPDH*, *GUS*, *RPLPO*, and *TFRC*). Reference-normalized expression measurements range from 0 to 15, with a 1 unit increase reflecting approximately a doubling of RNA. Genes are grouped on the basis of function, correlated expression, or both. Second, the *GRB7*, *ER*, proliferation, and invasion group scores are calculated from individual gene-expression measurements, as follows: *GRB7* group score = 0.9 × *GRB7*+0.1 × *HER2* (if the result is less than 8, then the *GRB7* group score is considered 8); *ER* group score = (0.8 × *ER*+1.2 × *PGR*+*BCL2*+*SCUBE2*) ÷ 4; proliferation group score = (*Survivin*+*Ki67*+*MYBL2*+*CCNB1* [the gene encoding cyclin B1]+*STK15*) ÷ 5 (if the result is less than 6.5, then the proliferation group score is considered 6.5); and invasion group score = (*CTSL2* [the gene encoding cathepsin L2] + *MMP11* [the gene encoding stromolysin 3]) ÷ 2. The unscaled recurrence score ($RS_U$) is calculated with the use of coefficients that are predefined on the basis of regression analysis of gene expression and recurrence in the three training studies[24-26]: $RS_U$ = +0.47 × *GRB7* group score − 0.34 × *ER* group score + 1.04 × proliferation group score + 0.10 × invasion group score + 0.05 × *CD68* − 0.08 × *GSTM1* − 0.07 × *BAG1*. A plus sign indicates that increased expression is associated with an increased risk of recurrence, and a minus sign indicates that increased expression is associated with a decreased risk of recurrence. Fourth, the recurrence score (RS) is rescaled from the unscaled recurrence score, as follows: RS = 0 if $RS_U$ < 0; RS = 20 × ($RS_U$ − 6.7) if 0 ≤ $RS_U$ ≤ 100; and RS = 100 if $RS_U$ > 100.

Paik et al. 2004. NEJM 351:2817-2826

## Cytostatika vid tidig bröstcancer

För testet Oncotype DX hade tidigare studier visat att det fanns anledning att tro att vid RS≥25 minskar cytostatikabehandling risken för återfall medan vid RS<11 är risken för återfall liten och nytta med cytostatikabehandling saknas.

Huvudsyftet med TAILORx-studien var att undersöka om det finns nytta med cytostatikabehandling vid RS11-25.

## Cytostatika vid tidig bröstcancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

METHODS

We performed a prospective trial involving 10,273 women with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, axillary node–negative breast cancer. Of the 9719 eligible patients with follow-up information, 6711 (69%) had a midrange recurrence score of 11 to 25 and were randomly assigned to receive either chemoendocrine therapy or endocrine therapy alone. The

NEJM 2018; 379:111-121

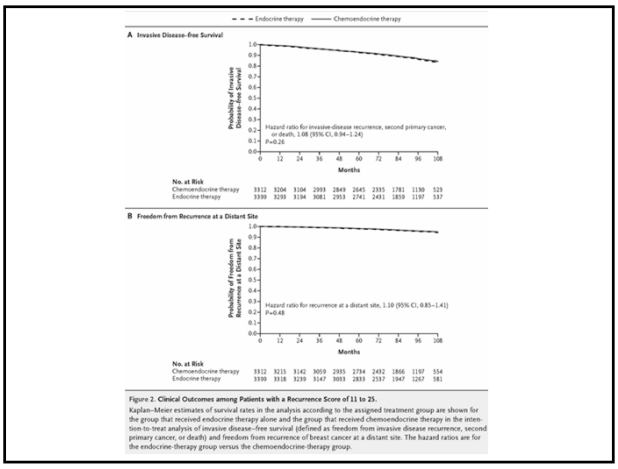



Figure 2. **Clinical Outcomes among Patients with a Recurrence Score of 11 to 25.**
Kaplan–Meier estimates of survival rates in the analysis according to the assigned treatment group are shown for the group that received endocrine therapy alone and the group that received chemoendocrine therapy in the intention-to-treat analysis of invasive disease–free survival (defined as freedom from invasive disease recurrence, second primary cancer, or death) and freedom from recurrence of breast cancer at a distant site. The hazard ratios are for the endocrine-therapy group versus the chemoendocrine-therapy group.

Table 2. **Estimated Survival Rates According to Recurrence Score and Assigned Treatment in the Intention-to-Treat Population.***

| End Point and Treatment Group | Rate at 5 Yr | Rate at 9 Yr |
|---|---|---|
| | *percent* | |
| Invasive disease–free survival† | | |
| Score of ≤10, endocrine therapy | 94.0±0.6 | 84.0±1.3 |
| Score of 11–25, endocrine therapy | 92.8±0.5 | 83.3±0.9 |
| Score of 11–25, chemoendocrine therapy | 93.1±0.5 | 84.3±0.8 |
| Score of ≥26, chemoendocrine therapy | 87.6±1.0 | 75.7±2.2 |
| Freedom from recurrence of breast cancer at a distant site | | |
| Score of ≤10, endocrine therapy | 99.3±0.2 | 96.8±0.7 |
| Score of 11–25, endocrine therapy | 98.0±0.3 | 94.5±0.5 |
| Score of 11–25, chemoendocrine therapy | 98.2±0.2 | 95.0±0.5 |
| Score of ≥26, chemoendocrine therapy | 93.0±0.8 | 86.8±1.7 |
| Freedom from recurrence of breast cancer at a distant or local–regional site | | |
| Score of ≤10, endocrine therapy | 98.8±0.3 | 95.0±0.8 |
| Score of 11–25, endocrine therapy | 96.9±0.3 | 92.2±0.6 |
| Score of 11–25, chemoendocrine therapy | 97.0±0.3 | 92.9±0.6 |
| Score of ≥26, chemoendocrine therapy | 91.0±0.8 | 84.8±1.7 |
| Overall survival | | |
| Score of ≤10, endocrine therapy | 98.0±0.4 | 93.7±0.8 |
| Score of 11–25, endocrine therapy | 98.0±0.2 | 93.9±0.5 |
| Score of 11–25, chemoendocrine therapy | 98.1±0.2 | 93.8±0.5 |
| Score of ≥26, chemoendocrine therapy | 95.9±0.6 | 89.3±1.4 |

* Plus–minus values are Kaplan–Meier estimates ±SE.
† Invasive disease–free survival was defined as freedom from invasive disease recurrence, second primary cancer, or death.

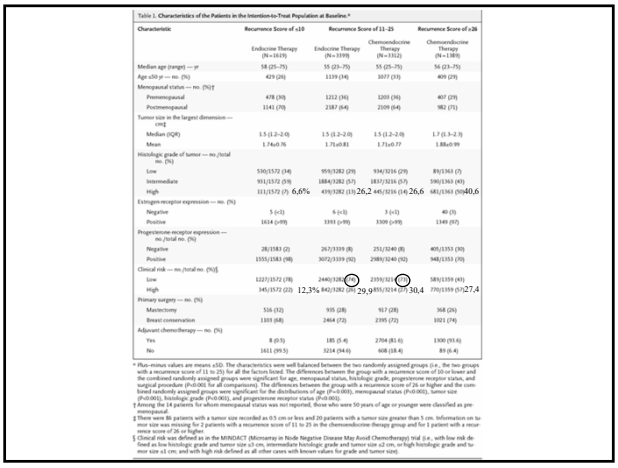


Table 1. **Characteristics of the Patients in the Intention-to-Treat Population at Baseline.***

| Characteristic | Recurrence Score of ≤10 | Recurrence Score of 11–25 | | Recurrence Score of ≥26 | |
|---|---|---|---|---|---|
| | Endocrine Therapy (N=1619) | Endocrine Therapy (N=3339) | Chemoendocrine Therapy (N=3312) | Chemoendocrine Therapy (N=1389) | |
| Median age (range) — yr | 58 (25–75) | 55 (23–75) | 55 (25–75) | 56 (23–75) | |
| Age ≤50 yr — no. (%) | 429 (26) | 1139 (34) | 1077 (33) | 409 (29) | |
| Menopausal status — no. (%)† | | | | | |
| Premenopausal | 478 (30) | 1212 (36) | 1203 (36) | 407 (29) | |
| Postmenopausal | 1141 (70) | 2187 (64) | 2109 (64) | 982 (71) | |
| Tumor size in the largest dimension — cm‡ | | | | | |
| Median (IQR) | 1.5 (1.2–2.0) | 1.5 (1.2–2.0) | 1.5 (1.2–2.0) | 1.7 (1.3–2.3) | |
| Mean | 1.74±0.76 | 1.71±0.81 | 1.71±0.77 | 1.88±0.99 | |
| Histologic grade of tumor — no./total no. (%) | | | | | |
| Low | 530/1572 (34) | 959/3282 (29) | 934/3216 (29) | 89/1363 (7) | |
| Intermediate | 931/1572 (59) | 1884/3282 (57) | 1837/3216 (57) | 590/1363 (43) | |
| High | 111/1572 (7) | 439/3282 (13) | 445/3216 (14) | 681/1363 (50) | |
| Estrogen-receptor expression — no. (%) | | | | | |
| Negative | 5 (<1) | 6 (<1) | 3 (<1) | 40 (3) | |
| Positive | 1614 (>99) | 3333 (>99) | 3309 (>99) | 1349 (97) | |
| Progesterone-receptor expression — no./total no. (%) | | | | | |
| Negative | 28/1583 (2) | 267/3319 (8) | 251/3240 (8) | 405/1353 (30) | |
| Positive | 1555/1583 (98) | 3072/3319 (92) | 2989/3240 (92) | 948/1353 (70) | |
| Clinical risk — no./total no. (%)§ | | | | | |
| Low | 1227/1572 (78) | 2440/3282 (74) | 2359/3216 (73) | 583/1359 (43) | |
| High | 345/1572 (22) | 842/3282 (26) | 855/3214 (27) | 770/1359 (57) | |
| Primary surgery — no. (%) | | | | | |
| Mastectomy | 516 (32) | 935 (28) | 917 (28) | 368 (26) | |
| Breast conservation | 1103 (68) | 2404 (72) | 2395 (72) | 1021 (74) | |
| Adjuvant chemotherapy — no. (%) | | | | | |
| Yes | 8 (0.5) | 185 (5.4) | 2704 (81.6) | 1300 (93.6) | |
| No | 1611 (99.5) | 3214 (94.6) | 608 (18.4) | 89 (6.4) | |

* Plus–minus values are means ±SD. The characteristics were well balanced between the two randomly assigned groups (i.e., the two groups with a recurrence score of 11 to 25) for all the factors listed. The differences between the group with a recurrence score of 10 or lower and the combined randomly assigned groups were significant for age, menopausal status, histologic grade, progesterone receptor status, and surgical procedure ($P<0.001$ for all comparisons). The differences between the group with a recurrence score of 26 or higher and the combined randomly assigned groups were significant for the distributions of age ($P<0.001$), menopausal status ($P=0.002$), tumor size ($P=0.002$), histologic grade ($P=0.002$), and progesterone receptor status ($P=0.003$).
† Among the 14 patients for whom menopausal status was not reported, those who were 50 years of age or younger were classified as premenopausal.
‡ There were 86 patients with a tumor size recorded as 0.5 cm or less and 20 patients with a tumor size greater than 5 cm. Information on tumor size was missing for 2 patients with a recurrence score of 11 to 25 in the chemoendocrine-therapy group and for 1 patient with a recurrence score of 26 or higher.
§ Clinical risk was defined as in the MINDACT (Microarray in Node Negative Disease May Avoid Chemotherapy) trial (i.e., with low risk defined as low histologic grade and tumor size ≤3 cm, intermediate histologic grade and tumor size ≤2 cm, or high histologic grade and tumor size ≤1 cm; and with high risk defined as all other cases with known values for grade and tumor size).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer

J.A. Sparano, R.J. Gray, P.M. Ravdin, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, M.M. Keane, H.L.G. Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

N Engl J Med. 2019;380:2395-2405.

Table 1. **Distant or Locoregional Disease Recurrence, Second Primary Cancer, or Death, and Distant Recurrence at 9 Years, According to Use or Nonuse of Adjuvant Chemotherapy, Stratified According to Age, Recurrence Score, and Clinical Risk (Intention-to-Treat Population).***

| Variable | Clinical Risk | No. of Patients | Estimated Probability of Recurrence, Second Primary Cancer, or Death | Hazard Ratio for Recurrence, Second Primary Cancer, or Death (95% CI)† | Estimated Probability of Distant Recurrence | Hazard Ratio for Distant Recurrence (95% CI)† |
|---|---|---|---|---|---|---|
| | | | *percent* | | *percent* | |
| **Patients >50 yr** | | 6469 | | | | |
| Low recurrence score (0–10) | | | | | | |
| No chemotherapy | High | 281 | 27.2±4.5 | 2.09 (1.47–2.96) | 7.4±3.4 | 2.20 (0.95–5.08) |
| No chemotherapy | Low | 879 | 13.3±1.5 | | 2.6±0.8 | |
| Intermediate recurrence score (11–25) | | | | | | |
| No chemotherapy | High | 577 | 23.2±2.6 | 1.56 (1.21–2.00) | 9.3±1.9 | 2.61 (1.65–4.11) |
| No chemotherapy | Low | 1605 | 13.6±1.1 | | 3.5±0.6 | |
| Chemotherapy | High | 603 | 22.6±2.3 | 1.61 (1.27–2.04) | 8.3±1.5 | 2.49 (1.60–3.87) |
| Chemotherapy | Low | 1568 | 15.7±1.3 | | 4.0±0.7 | |
| High recurrence score (26–100) | | | | | | |
| Chemotherapy | High | 542 | 32.1±4.4 | 1.85 (1.28–2.66) | 19.8±3.9 | 3.35 (1.82–6.14) |
| Chemotherapy | Low | 414 | 19.3±3.8 | | 7.0±2.4 | |

N Engl J Med. 2019;380:2395-2405.

* Plus–minus values are Kaplan–Meier estimates ± SE.

# Cytostatika vid tidig bröstcancer

**Recurrence Score® Result**

**0**

**Oncotype DX® Breast Recurrence Score test** uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score result is calculated from the gene expression results and ranges from 0-100.

**The findings are applicable** to women who have stage I or II node negative (N–), estrogen receptor positive (ER+) breast cancer, and will be treated with 5 years of tamoxifen (tam). It is unknown whether the findings apply to other patients outside these criteria.

**Clinical Experience:** The following results are from a clinical validation study that included 668 patients from the NSABP B-14 study. The study included female patients with stage I or II, N–, ER+ breast cancer treated with 5 years of tam.[1]

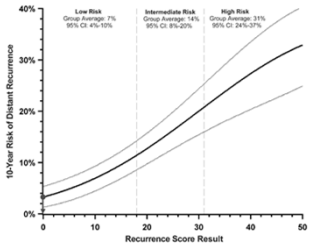
**Prognosis: 10-Year Risk of Distant Recurrence after 5 Years of Tam, Based on the Recurrence Score Result (from NSABP B-14)**

**10-Year Risk of Distant Recurrence**

**Tam Alone**

**3%**

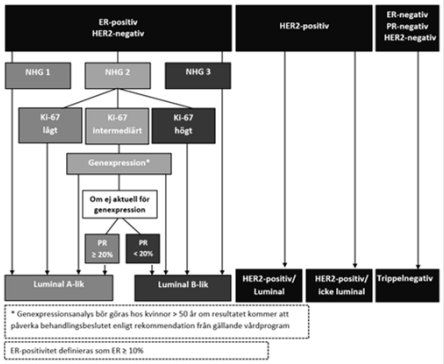
(95% CI: 1%–5%)



## Cytostatika vid tidig bröstcancer

NHG = Nottingham Histologic Grade

Figur 10. Indelning av bröstcancer i molekylära subtyper.




Nationellt vårdprogram bröstcancer 201022

## Cytostatika vid tidig bröstcancer

Hälsoekonomisk bedömning av Oncotype DX vid bröstcancer

TLV har tagit fram en hälsoekonomisk bedömning till regionerna för den medicintekniska produkten Oncotype DX. Oncotype DX är ett test som uppskattar risken för att cancern sprider sig till andra delar av kroppen hos patienter med bröstcancer. Testet ger även information om den förväntade nyttan av cellgiftsbehandling.

På beställning av regionernas medicintekniska produktråd, MTP-rådet, har TLV utfört en hälsoekonomisk bedömning av Oncotype DX. Beställningen från MTP-rådet togs fram i samråd med Nationella arbetsgruppen för cancerläkemedel och Nationellt programområde för medicinsk diagnostik inom det nationella kunskapsstyrningssystemet för hälso- och sjukvård. TLV:s hälsoekonomiska bedömning är en av TLV:s två första leveranser till MTP-rådet och ingår i beslutsunderlaget inför MTP-rådets kommande nationella rekommendation för Oncotype DX.

TLV 12 juli 2021

Medicintekniska produktrådet, MTP-rådet, startade januari 2020.

## Cytostatika vid tidig bröstcancer

I det svenska vårdprogrammet för bröstcancer rekommenderas genexpressionsanalys för en särskild undergrupp av patienter där det är svårt att bedöma risken för att cancern sprider sig och om patienten därmed ska behandlas med cellgifter. Rekommendationen bedöms i vårdprogrammet ha "måttligt starkt vetenskapligt underlag". Oncotype DX är en av de produkter som omnämns i vårdprogrammet. Patientgruppen som ingår i TLV:s huvudanalys är vald för att avspegla rekommendationen i vårdprogrammet så nära som möjligt.

Analysen visar att användning av Oncotype DX i tillägg till klinisk-patologisk bedömning leder till 0,24 vunna kvalitetsjusterade levnadsår i genomsnitt och att behandlingskostnaden minskar med cirka 50 500 kronor i jämförelse med enbart klinisk-patologisk bedömning. Analysen i den hälsoekonomiska bedömningen pekar därmed på att användningen av Oncotype DX ger större nytta än jämförelsealternativet, dessutom till en lägre kostnad.

TLV 12 juli 2021