Supplementary material for the article:

Cost–utility analysis of multigene assays to guide treatment decisions for node-negative early breast cancer

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Methods: Detailed parameters

Appendix 1. Costing methods

Chemotherapy and endocrine therapy doses were derived from the NCCN Guidelines for Invasive Breast Cancer (eTable 2).[1] The distribution of patients receiving first-line endocrine therapy was informed by data from Ward et al (eTable 2).[2] The duration of endocrine therapy was assumed to be 5 years from model entry. Short-term adverse events (AE) frequencies and unit costs (eTable 8) were obtained from Wang et al.[3]

Costs of routine monitoring, treatment of disease recurrence, CHF or AML were applied to each cycle spent in the corresponding health state. The cost of the recurrence-free health state was sourced from Kunst et al.[49]

The model did not include the probability of local recurrence in each model cycle. Instead, it was assumed that 10.5% of patients with a previous distant recurrence experience a local recurrence based on de Bock et al.[4] Treatment cost of local recurrence was derived from Wang et al.[3]

The calculation of costs associated with distant recurrence was based on a micro-costing approach, considering the weighted average costs of patients receiving endocrine therapy, chemotherapy, and CDK4/6 inhibitors across the first three lines of treatment in the model (eTable 9-11). The costs for AML and CHF were sourced from Wang et al.[3] For AML, this represents the lifetime cost of treatment and is applied as a one-time cost in the first model cycle following the event. The cost for CHF is initially applied as a one-off expense in the first cycle when the condition is diagnosed, followed by ongoing costs in each subsequent. Costs for terminal care were derived from Kunst et al.[5]

In our analysis, we considered both out-of-pocket (OOP) expenses and costs related to productivity loss, in line with the chosen perspective (eTable 12). The OOP costs for each chemotherapy regimen were sourced from Giordano et al.[6], and it was assumed that these costs are incurred in the first cycle for all patients receiving adjuvant chemotherapy. The cost of lost productivity was calculated based on the number of workdays missed due to chemotherapy administration and development of distant recurrence.[7] This cost was estimated using the median weekly salary figures provided by U.S. Department of Labor.[8]

Table S1. Description of technologies

Technology	Description
21-gene assay (Oncotype DX test)	It measures the expression of 21 genes, including 16 cancer-related genes and 5 reference genes, to calculate the Oncotype DX Breast Recurrence Score result using RT-qPCR. This test evaluates the 9-year risk of distant recurrence and the potential benefit of chemotherapy. Scores range from 0 to 100, estimating the 9-year risk of distant recurrence assuming 5 years of hormonal therapy.[9] This assay categorizes patients into low, intermediate, and high-risk groups.[2] The analysis uses cut-off points and distributions from the TAILORx study for N0, with ranges of 0-10, 11-25, and 26-100 respectively.[9] The recurrence score also suggests the chemotherapy benefit. Results are typically reported within 7 to 10 days after sample receipt.[9] It is the only assay with evidence supporting prediction of chemotherapy benefit, based on findings from the TAILORx phase III randomized controlled trial [10] and the NSABP B-20 study.[11]
70-gene assay (MammaPrint)	70-gene assay (MammaPrint): This test assesses the 10-year risk of distant recurrence and the likelihood of benefiting from chemotherapy. It analyses the expression of 70 cancer-related genes and 465 control genes. Patients are classified as either low or high risk. Results are scored from -1 to +1, indicating the risk of developing distant metastases in the next 10 years without adjuvant therapy. Scores at or below 0 suggest a high risk, while scores above 0 indicate a low risk (10% or less).[9] The cut-off points and distributions were based on the MINDACT study,[12] defining low risk as a Distant Recurrence-Free Survival (DRFS) >88% and high risk as DRFS ≤88%. Results are usually available within 10 days of sample receipt, often in less than 5 days.[9]
12-gene assay (EndoPredict):	12-gene assay (EndoPredict): It predicts the 10-year likelihood of distant recurrence and chemotherapy benefit. The test measures 12 genes to calculate a molecular score (EP score). The EPclin score, combining clinical data and the EP score, is the final result, available 3 to 5 days after sample arrival. This score, which uses RT-qPCR and online software, assesses distant recurrence risk and chemotherapy benefit.[9] The 12-gene assay, initially validated in patients treated with five years of tamoxifen, received further confirmation in the ABCSG-6, ABCSG-8, and ATAC cohorts. This test divides patients into low and high-risk categories, using cut-off points and distributions from the TransATAC study. The thresholds are ≤3.3 for low risk and >3.3 for high risk.
50-gene assay (Prosigna):	This method assesses the expression of 50 genes and classifies the risk of 10-year distant recurrence based on the PAM50 gene signature, subtype, tumor size, nodal status, and proliferation score. Results, usually available within 3 days. The overall recurrence risk score, between 0 and 100, categorizes samples into risk groups based on this score and nodal status.[9] Based on the PAM50 gene signature, to calculate a Risk of Recurrence (ROR) score. The 50-gene assay's validity was established through a combined analysis of data from the ATAC and ABCSG-8 cohorts. Using the TransATAC study for guidance, the N0 risk levels are set as: low (≤40), intermediate (41-60), and high (61-100).

Table S2. Distribution of chemotherapy regimens in early breast cancer in the US

Regimen	% of regimens in N0
AC followed by P	18.9%
AC followed by weekly P	16.7%
TC	56.1%
EC	0.6%
AC followed by T	5.0%
TAC	0.6%
AC	0.6%
CMF	0.6%
Weekly P + carboplatin	0.6%
T + carboplatin	0.6%

Description of the regimens: AC followed by P: doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 × 4 doses, followed by paclitaxel 175 mg/m2 × 4 doses, Neulasta 6mg/0.6ml ×8 doses; AC followed by weekly P: doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 × 4 doses, followed by weekly paclitaxel 80 mg/m2 × 12 doses, Neulasta 6mg/0.6ml × 4 doses; TC: docetaxel 75 mg/m2 and cyclophosphamide 600 mg/m2 ×4 doses, Neulasta 6mg/0.6ml × 4 doses; EC: epirubicin 100 mg/m2 and cyclophosphamide 830 mg/m2 every 3 weeks × 8 doses, Neulasta 6mg/0.6ml × 8 doses; AC followed by T: doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 ×4 doses, followed by docetaxel 100 mg/m2 × 4 doses, Neulasta 6mg/0.6ml × 4 doses; TAC: docetaxel 75 mg/m2 and cyclophosphamide 600 mg/m2 ×6 doses, doxorubicin 50 mg/m2 ×6 doses, Neulasta 6mg/0.6ml × 6 doses; AC: doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 × 4 doses, Neulasta 6mg/0.6ml × 4 doses; CMF: cyclophosphamide 100 mg/m2 days 1-14, methotrexate 40 mg/m2 days 1 & 8, 5-fluorouracil 600 mg/m2 days 1 & 8 ×6 doses; Weekly P + carboplatin paclitaxel 80 mg/m2 × 12 doses, carboplatin AUC 6 × 4 doses, Neulasta 6mg/0.6ml ×4 doses; T + carboplatin: docetaxel 75 mg/m2 × 6 doses, carboplatin AUC 6 × 6 doses, Neulasta 6mg/0.6ml ×6 doses.

Table S3. Acquisition costs

Drug	Dosage	Payment Limit	Source
Doxorubicin hcl injection	10 mg	$2.17	CMS[13]
Cyclophosphamide 100 mg inj	100 mg	$29.15	CMS[13]
Cyclophosphamide 25mg oral	25 mg	$0.81	CMS[13]
Paclitaxel injection	1 mg	$0.13	CMS[13]
Docetaxel injection	1 mg	$0.48	CMS[13]
Methotrexate sodium inj	5 mg	$0.22	CMS[13]
Methotrexate sodium inj	50 mg	$2.16	CMS[13]
Fluorouracil injection	500 mg	$1.70	CMS[13]
Fulvestrant injection	25 mg	$15.98	CMS[13]
Bevacizumab injection	10 mg	$70.41	CMS[13]
Tamoxifen	20 mg	$0.42	EmedNY[14]
Anastrozole	1 mg	$0.18	EmedNY[14]
Exemestane	25 mg	$2.29	EmedNY[14]
Oral everolimus	0.25 mg	$5.92	CMS[13]
Leuprolide	1 mg	$18.32	CMS[13]
Goserelin	3.6 mg	$525.21	CMS[13]
Capecitabine, oral, 150 mg	150 mg	$0.59	CMS[13]
Capecitabine, oral, 500 mg	500 mg	$0.92	CMS[13]
Alpelisib	300 mg	$306.47	CMS part D[15]
Abemaciclib	150 mg	$215.28	CMS part D[15]
Letrozole	2.5 mg	$0.20	EmedNY[14]
Palbociclib	125 mg	$836.01	EmedNY[14]
Ribociclib	200 mg	$155.36	EmedNY[14]
Injection, pegfilgrastim 6mg	6 mg	$2,221.63	CMS[13]

Table S4. Cost of adjuvant chemotherapy regimens per model cycle

Regimen	Dose per admin (mg)	No. of doses	Acquisition cost (no vial sharing)
AC followed by P			
Doxorubicin 60 mg/m²	105.00	4	$95.39
Cyclophosphamide 600 mg/m²	1,050.00	4	$1,282.73
Paclitaxel 175 mg/m²	306.25	4	$160.87
Neulasta 6mg/0.6ml	6.00	8	$17,773.01
AC followed by weekly P			
Doxorubicin 60 mg/m²	105.00	4	$95.39
Cyclophosphamide 600 mg/m²	1,050.00	4	$1,282.73
Paclitaxel 80 mg/m²	140.00	12	$220.08
Neulasta 6mg/0.6ml	6.00	4	$8,886.50
TC			
Cyclophosphamide 600mg/m²	1,050.00	4	$1,282.73
Docetaxel 75mg/m²	131.25	4	$252.91
Neulasta 6mg/0.6ml	6.00	4	$8,886.50
AC			
Doxorubicin 60 mg/m²	87.50	4	$78.05
Cyclophosphamide 600 mg/m²	875.00	4	$1,049.51
Neulasta 6mg/0.6ml	6.00	4	$8,886.50
CMF			
Cyclophosphamide oral 100 mg/m2	175.00	56	$473.93
Methotrexate 40 mg/m2	70.00	8	$36.29
5-fluorouracil 600 mg/m2	1,050.00	8	$61.34
Capecitabine (per month)			
Capecitabine 1250 mg/m2 PO	2187.50	21	$102.19
P (per month)			
Paclitaxel 175 mg/m2	306.25	2	$80.43
T (Docetaxel)			
Capecitabine 1250 mg/m2 PO	175.00	4	$335.30
Bevacizumab + paclitaxel (per month)			
Bevacizumab 10mg/kg	660.00	2	$9,294.38
Paclitaxel 90 mg/m2	157.00	3	$62.09
Alpelisib + fulvestrant (per month)			
Alpelisib 300mg PO	300.00	28	$8,581.26
Fulvestrant 500mg	500.00	1	$319.58

Table S5. Administration costs

Administration	Cost	HCPCS/CPT code or source
Pharmacy cost oral drug (1st in 30-day period)	$24.00	HCPCS Q0511
Pharmacy cost oral drug (2nd+ in 30-day period)	$16.00	HCPCS Q0512
Pharmacy cost IV drug	$50.00	HCPCS Q0510
First admin IV	$490.94	CPT 96365 and CPT 96366
Subsequent admin IV	$181.38	CPT 96417
Admin IM	$60.46	CPT 96372
Admin oral	$0.00	Assumption
Outpatient visit	$105.02	Wang et al.
Laboratory tests	$36.91	Levy et al.

Table S6. Administration and monitoring costs of adjuvant chemotherapy per model cycle or per month

Regimen	No. of administrations per model cycle	Administration cost	Pharmacy cost	Follow-up visits	Monitoring	Total admin and monitoring
AC+P (dose-dense)	8	$1,700.14	$200.00	$840.16	$295.29	$3,035.59
AC+weekly P	16	$4,360.38	$250.00	$1,680.32	$590.59	$6,881.29
TC	4	$1,458.30	$150.00	$420.08	$147.65	$2,176.03
AC (dose-sense)	4	$1,458.30	$100.00	$420.08	$147.65	$2,126.03
CMF	12	$3,151.18	$444.00	$1,260.24	$442.94	$5,298.36
Capecitabine (per month)	21	$0.00	$24.00	$105.02	$36.91	$165.93
P (per month)	2	$732.78	$50.00	$210.04	$73.82	$1,066.64
T (Docetaxel)	4	$1,216.46	$100.00	$420.08	$0.00	$1,736.54
Bevacizumab + paclitaxel (per month)	3	$974.62	$50.00	$315.06	$110.74	$1,450.42
Alpelisib + fulvestrant (per month)	28	$60.46	$24.00	$105.02	$36.91	$226.39

Table S7. Cost of endocrine therapy (early breast cancer)

Endocrine therapy	% of patients	Dose per day	Cost per model cycle
Aromatase inhibitor monotherapy	40%	1mg	$33.16
Tamoxifen monotherapy	40%	20mg	$75.83
Exemestane monotherapy	20%	25mg	$416.01

Table S8. Costs of adverse events

Adverse event	Unit cost
Febrile neutropenia	$7,765
Arthralgia	$4,949
Fatigue	$105
Neutrophil count decrease	$7,765
White blood cell decreased	$7,765
Weighted average	$1,230

Table S9: Distribution of treatments in advanced breast cancer

	First line	Second line	Third line
Endocrine only	25%	47%	60%
Chemotherapy	0%	20%	40%
CDK4/6 inhibitors + Endocrine	75%	33%	0%

Note: Distribution of treatments in advanced breast cancer was derived through interview with clinical experts.

Table S10: Duration of treatment by line in advance breast cancer (months)

Treatment	Line	Length (months)	Reference
Endocrine	1st line	15.0	Kurosky et al.[16]
Endocrine	2nd line	9.5	Kurosky et al.[16]
Endocrine	3rd line	12.0	TA563 manufacturer submission[17]
Chemotherapy	1st line	6.2	Kurosky et al.[16]
Chemotherapy	2nd line	6.0	Kurosky et al.[16]
Chemotherapy	3rd line	12.0	TA563 manufacturer submission[17]
CDK4/6 inhibitors	1st line	17.7	Johnston et al.[18]
CDK4/6 inhibitors	2nd line	17.7	Johnston et al.[18]
CDK4/6 inhibitors	3rd line	0.0	Assumption

Table S11: Summary of regimens in advanced breast cancer

Line/drug	1st line	2nd line	3rd line	Acquisition cost per month	Administration cost per month	Total cost per month
Chemotherapy						
Capecitabine	0%	0%	83%	$102.19	$165.93	$268.12
Paclitaxel	0%	0%	8%	$80.43	$1,066.64	$1,147.08
Alpelisib + fulvestrant	0%	100%	8%	$8,900.84	$226.39	$9,127.23
CDK4/6 inhibitors + Endocrine therapy						
CDK 4/6 inhibitor + aromatase inhibitor	96%	0%	0%	$13,138.61	$0.00	$13,138.61
CDK 4/6 inhibitor + fulvestrant	4%	100%	0%	$13,452.73	$0.00	$13,452.73
CDK 4/6 inhibitor + aromatase inhibitor	96%	0%	0%	$13,138.61	$0.00	$13,138.61
Endocrine therapy						
Aromatase inhibitor monotherapy	40%	14%	0%	$33.16	$0.00	$33.16
Tamoxifen monotherapy	27%	0%	6%	$75.83	$0.00	$75.83
Fulvestrant monotherapy	7%	43%	19%	$2,237.06	$423.22	$2,660.28
Exemestane monotherapy	0%	0%	19%	$416.01	$0.00	$416.01
Ovarian suppression with endocrine therapy	27%	0%	0%	$1,781.78	$362.76	$2,144.54
Everolimus + tamoxifen	0%	9%	28%	$1,153.82	$0.00	$1,153.82
Everolimus + exemestane	0%	34%	28%	$1,493.99	$0.00	$1,493.99

Table S12. Societal cost in the model

Cost category	Values	
OOP cost	**Mean cost (USD)**	
AC followed by P	$3,650.00	
AC followed by weekly P	$3,792.00	
TC	$3,285.00	
EC	$2,753.00	
AC followed by T	$3,763.00	
TAC	$4,153.00	
AC	$3,081.00	
CMF	$2,753.00	
Weekly P + carboplatin	$3,314.00	
T + carboplatin	$3,314.00	
Weighted average	$3,460.44	
Lost productivity cost	**Mean no. of days lost**	**Mean lost productivity cost (USD)**
Adjuvant chemotherapy	36.5	$7,373.00
Distant recurrence	84.4	$17,048.80

Table S13. Utility values in the model

Health state/event	Source	Value (95% CI/SD/SE)
Alternative values		
Recurrence-free	Farkkila et al. (subsequent years of remission)[34]	0.843 (SD 0.189)
Distant recurrence	Farkkila et al.[34]	0.746 (SD 0.251)
	Ibarrondo et al.[33]	0.750 (0.467, 0.701)
	Yousefi et al.[35]	0.552 (SD 0.227)
Local recurrence	Lidgren et al. (decrement)[31]	-0.045 (-0.037, -0.053)
Chemotherapy administration	Ibarrondo et al. (decrement)[33]	-0.047 (-0.038, -0.056)

Table S14. Additional parameters considered for the one-way sensitivity analysis

Parameter	Base case	Sensitivity analysis	Source
% of distant recurrence with prior local recurrence	10.5	8.4-12.6	De Bock et al.[4] +/- 20%
% assigned chemotherapy with Oncotype DX			Range in KOL survey responses
Age≤50 low clin risk RS 0-10 (N0)	2.1	0.0-10.0	
Age≤50 low clin risk RS 11-25 (N0)	26.4	0.0-100.0	
Age≤50 low clin risk RS 26-100 (N0)	91.1	85.0-100.0	
Age≤50 high clin risk RS 0-10 (N0)	12.9	0.0-50.0	
Age≤50 high clin risk RS 11-25 (N0)	48.6	0.0-50.0	
Age≤50 high clin risk RS 26-100 (N0)	96.8	90.0-100.0	
Age>50 low clin risk RS 0-10 (N0)	1.4	0.0-10.0	
Age>50 low clin risk RS 11-25 (N0)	11.4	0.0-40.0	
Age>50 low clin risk RS 26-100 (N0)	83.6	60.0-100.0	
Age>50 high clin risk RS 0-10 (N0)	10.0	0.0-30.0	
Age>50 high clin risk RS 11-25 (N0)	28.6	0.0-100.0	
Age>50 high clin risk RS 26-100 (N0)	92.9	85.0-100.0	
% assigned chemotherapy with MammaPrint			DG34[19]+/- 20%
LN0 low clinical risk, low genomic risk (UKBCG)	1.0	0.8-1.2	
LN0 low clinical risk, high genomic risk (UKBCG)	71.0	56.8-85.2	
LN0 high clinical risk, low genomic risk (UKBCG)	15.0	12.0-18.0	
LN0 high clinical risk, high genomic risk (UKBCG)	92.0	73.6-100.0	
% assigned chemotherapy with EPClin			Bloomfield et al.[20] +/- 20%
LN0, low risk (Bloomfield et al.)	6.7	1.0-12.4	
LN0, high risk (Bloomfield et al.)	77.0	67.3-86.7	
% assigned chemotherapy with Prosigna			Wuerstlein et al.[21] +/- 20%
LN0, low risk	5.9	0.8-11.0	
LN0, intermediate risk	24.3	14.1-34.5	
LN0, high risk	93.0	85.3-100.0	
Related to Distant Recurrence Prob – Oncotype DX			Based on SE reported in TAILORx[22]
9-year DRFI with ET for age≤50 RS 0-10	0.982	0.964-1.000	
9-year DRFI with ET for age≤50 RS 11-25	0.953	0.933-0.973	
9-year DRFI with CET for age≤50 RS 26-100	0.938	0.888-0.988	
9-year DRFI with ET for age≤50 RS 11-25	0.877	0.829-0.925	
9-year DRFI with CET for age≤50 RS 26-100,	0.848	0.782-0.914	
9-year DRFI with ET for age>50 RS 0-10	0.974	0.958-0.990	
9-year DRFI with ET for age>50 RS 11-25	0.965	0.953-0.977	
9-year DRFI with CET for age>50 RS 26-100	0.930	0.882-0.978	
9-year DRFI with ET for age>50 RS 0-10	0.926	0.858-0.994	
9-year DRFI with ET for age>50 RS 11-25	0.907	0.869-0.945	
9-year DRFI with CET for age>50 RS 26-100	0.802	0.724-0.880	
9-year DRFI with ET for age≤50 RS 0-10	0.982	0.964-1.000	
9-year DRFI with ET for age≤50 RS 11-25	0.953	0.933-0.973	
9-year DRFI with CET for age≤50 RS 26-100	0.938	0.888-0.988	
9-year DRFI with ET for age≤50 RS 11-25	0.877	0.829-0.925	
Hazard ratio for CET vs. ET - RS 11-25	0.910	0.710-1.180	TAILORx[10]
Hazard ratio for CET vs. ET - RS 26-100	0.270	0.120-0.620	NSABP B-20[11]

Parameter	Base case	Sensitivity analysis	Source
Related to Distant Recurrence Prob – MammaPrint			Based on SE from MINDACT[23]
DRFS 8-year ET LN0 low clinical risk, low genomic risk	0.947	0.938-0.956	
DRFS 8-year ET LN0 low clinical risk, high genomic risk	0.911	0.884-0.933	
DMFI 8-year ET LN0 high clinical risk, low genomic risk	0.907	0.882-0.927	
DRFS 8-year ET LN0 high clinical risk, high genomic risk	0.821	0.801-0.841	
DRFS 8-year CT LN0 low clinical risk, low genomic risk	0.947	0.938-0.956	
DRFS 8-year CT LN0 low clinical risk, high genomic risk	0.911	0.884-0.933	
DMFI 8-year CT LN0 high clinical risk, low genomic risk	0.931	0.909-0.948	
DRFS 8-year CT LN0 high clinical risk, high genomic risk	0.859	0.842-0.875	
Related to Distant Recurrence Prob – EPClin			Buus et al.[24]
DR LN0 low risk (Buus et al.)	0.941	0.914-0.960	
DR LN0 high risk (Buus et al.)	0.800	0.730-0.854	
Related to Distant Recurrence Prob – Prosigna			Confidence interval reported in DG34[19]
DR LN0 NPI≤3.4 low risk	0.986	0.730-0.854	
DR LN0 NPI≤3.4 intermediate risk	0.933	0.940-0.971	
DR LN0 NPI≤3.4 high risk	0.636	0.826-0.917	
DR LN0 NPI>3.4 low risk	0.923	0.811-0.988	
DR LN0 NPI>3.4 intermediate risk	0.796	0.555-0.698	
DR LN0 NPI>3.4 high risk	0.699	0.962-0.995	
Hazard ratio for CET vs. ET applied for patients assigned to CET after testing with 12-gene and 50-gene tests	0.76	0.532-0.988	DG34[19] with +/- 30% variation
Probability of local recurrence	0.105	0.088-0.123	Assumption
Probability of AML	0.003	0.002-0.003	Petrelli et al.[25]
Annual probability of CHF	0.002	0.001-0.003	Wang et al.[3]
Mortality			
Mortality after distant recurrence – Median OS (months)	46.70	37.36-56.04	Sledge et al.[26] with +/- 20%
Probability of death AML	0.353	0.282-0.423	NICE TA552[27] with +/- 20%
Probability of death CHF	0.135	0.105-0.165	Wang et al.[28] with +/- 20%

Abbreviations: CET: Chemo-endocrine therapy; ET: Endocrine therapy; SE: Standard error

Results

Table S15. Breakdown of cost

Costs	21-gene assay	70-gene assay	12-gene assay	50-gene signature
Test	$3,873	$3,873	$3,873	$2,510
Chemotherapy & endocrine therapy	$4,386	$4,168	$4,035	$3,996
Short-term AEs	$345	$323	$308	$305
Recurrence-free	$8,520	$8,353	$8,425	$8,341
Local recurrence	$263	$334	$305	$337
Distant recurrence	$43,003	$54,553	$49,909	$55,103
AML	$57	$52	$49	$47
CHF	$684	$624	$592	$564
Terminal care	$1,346	$1,728	$1,568	$1,779
Patient OOP*	$972	$908	$868	$857
Lost productivity*	$18,207	$22,406	$20,577	$22,503

Table S16. Base case results (detailed)

Variable	Comparison 1		Comparison 2		Comparison 3		Comparison 4	
	21-gene assay	Current	70-gene assay	Current	12-gene assay	Current	50-gene signature	Current
Total expected cost ($)	81,656	93,485	97,321	96,242	90,509	90,117	96,341	98,751
Incremental cost ($)	-12,189	---	1,079	---	392	---	-2,410	
Total expected QALYs	13.95	13.72	13.75	13.71	13.83	13.78	13.73	13.65
Incremental QALYs	0.23	---	0.04	---	0.05	---	0.07	---
ICER	Dominant	---	27,760	---	7,942	---	Dominant	---
Net monetary benefit (NMB, $)	35,226	---	2,808	---	4,544	---	9,768	---
Incremental life-years	0.27	---	0.05	---	0.06	---	0.09	---
Incremental recurrence free years	0.40	---	0.07	---	0.09	---	0.13	---
Incremental years in distant recurrence	-0.13	---	-0.02	---	-0.02	---	-0.03	---
Absolute change in chemotherapy assignment (%)	1.54	---	-0.30	---	-1.47	---	-1.78	---

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjust life-year

Table S17. Scenario analysis results

Scenario	Δ Costs	Δ QALYs	ICER
21-gene assay vs clinicopathologic risk alone			
Base-case	-$12,189	0.23	Dominant
RS distribution: TransATAC (RS 0-17,18-30,31-100)	-$9,389	0.19	Dominant
RS distribution: Stemmer et al. (RS 0-10,11-25,26-100)	-$18,057	0.31	Dominant
RS distribution: SEER (Choi 2020) (RS 0-10,11-25,26-100)	-$13,292	0.25	Dominant
Probability of chemotherapy 21-gene assay: SEER (Choi et al.)	-$7,384	0.16	Dominant
Probability of chemotherapy clinicopathologic risk alone N0: 5%	-$13,338	0.25	Dominant
Probability of chemotherapy clinicopathologic risk alone N0: 70%	-$9,871	0.20	Dominant
Chemotherapy benefit N0 RS>25: HR=0.12	-$25,736	0.46	Dominant
Chemotherapy benefit N0 RS>25: HR=0.62	-$384	0.06	Dominant
Vial sharing in the calculation of acquisition costs	-$12,186	0.23	Dominant
Distant recurrence probability: TAILORx 9-year DRFS	-$13,395	0.25	Dominant
No reduction in distant recurrence rate after 10 years	-$13,726	0.25	Dominant
Probability of AML set to zero	-$12,149	0.23	Dominant
Probability of CHF set to zero	-$12,060	0.23	Dominant
Set test price discounts to 10%	-$12,576	0.23	Dominant
Set test price increase by 10%	-$11,802	0.23	Dominant
Cost of chemotherapy from Waintraub et al.	-$11,977	0.23	Dominant
Healthcare payer perspective (Medicare)	-$12,242	0.23	Dominant
70-gene assay vs clinicopathologic risk alone			
Base-case	$1,079	0.04	$27,760
Probability of chemotherapy clinicopathologic risk alone N0: 5%	$3,383	0.00	$683,196
Probability of chemotherapy clinicopathologic risk alone N0: 70%	-$3,569	0.11	Dominant
Vial sharing in the calculation of acquisition costs	$1,080	0.04	$27,784
Distant recurrence probability: MINDACT 5-year DRFS	$440	0.05	$9,411
No reduction in distant recurrence rate after 10 years	$618	0.04	$14,200
Probability of AML set to zero	$1,142	0.04	$30,477
Probability of CHF set to zero	$1,323	0.04	$37,776
Set all test price discounts to 10%	$692	0.04	$17,797
Set all test price increase by 10%	$1,466	0.04	$37,724
Cost of chemotherapy from Waintraub et al.	$1,048	0.04	$26,948
Healthcare payer perspective (Medicare)	$1,089	0.04	$28,025
12-gene assay vs clinicopathologic risk alone			
Base-case	$392	0.05	$7,942
Probability of chemotherapy clinicopathologic risk alone N0: 5%	$1,977	0.03	$78,609
Probability of chemotherapy clinicopathologic risk alone N0: 70%	-$2,806	0.10	Dominant
Vial sharing in the calculation of acquisition costs	$394	0.05	$7,982
Distant recurrence probability: Filipits et al.	$1,458	0.03	$43,958
Chemotherapy benefit set to HR=0.53	-$2,412	0.09	Dominant
Chemotherapy benefit set to HR=0.99	$2,884	0.01	$203,474
No reduction in distant recurrence rate after 10 years	$9	0.05	$171
Probability of AML set to zero	$481	0.05	$10,354
Probability of CHF set to zero	$752	0.04	$18,030
Set all test price discounts to 10%	$5	0.05	£96
Set all test price increase by 10%	$779	0.05	£15,788
Cost of chemotherapy from Waintraub et al.	$205	0.05	$4,159
Healthcare payer perspective (Medicare)	$443	0.05	$8,972
50-gene signature vs clinicopathologic risk alone			
Base-case	-$2,410	0.07	Dominant
Probability of chemotherapy clinicopathologic risk alone N0: 5%	-$1,069	0.05	Dominant
Probability of chemotherapy clinicopathologic risk alone N0: 70%	-$5,115	0.11	Dominant

Scenario	Δ Costs	Δ QALYs	ICER
Vial sharing in the calculation of acquisition costs	-$2,407	0.07	Dominant
Distant recurrence probability: Gnant et al.	-$142	0.04	Dominant
Chemotherapy benefit set to HR=0.53	-$6,666	0.13	Dominant
Chemotherapy benefit set to HR=0.99	$1,140	0.02	$55,643
No reduction in distant recurrence rate after 10 years	-$2,507	0.08	Dominant
Probability of AML set to zero	-$2,271	0.07	Dominant
Probability of CHF set to zero	-$1,854	0.06	Dominant
Set all test price discounts to 10%	-$2,661	0.07	Dominant
Set all test price increase by 10%	-$2,159	0.07	Dominant
Cost of chemotherapy from Waintraub et al.	-$2,637	0.07	Dominant
Healthcare payer perspective (Medicare)	-$2,348	0.07	Dominant

PSA methodology

For the probabilistic analysis, gamma distributions were used for cost calculations, beta distributions for probabilities and utilities, and log-normal distributions for hazard ratios associated with distant recurrence post-chemotherapy. Parameters were randomly sampled from these distributions across 5,000 simulations. The results were summarized using the cost-effectiveness plane and cost-effectiveness acceptability curves (CEAC). Univariate and probabilistic analyses were run with a willingness-to-pay per QALY threshold of $100,000 as per Institute for Clinical and Economic Review Health Technology Assessment Guidance.[29]

PSA results

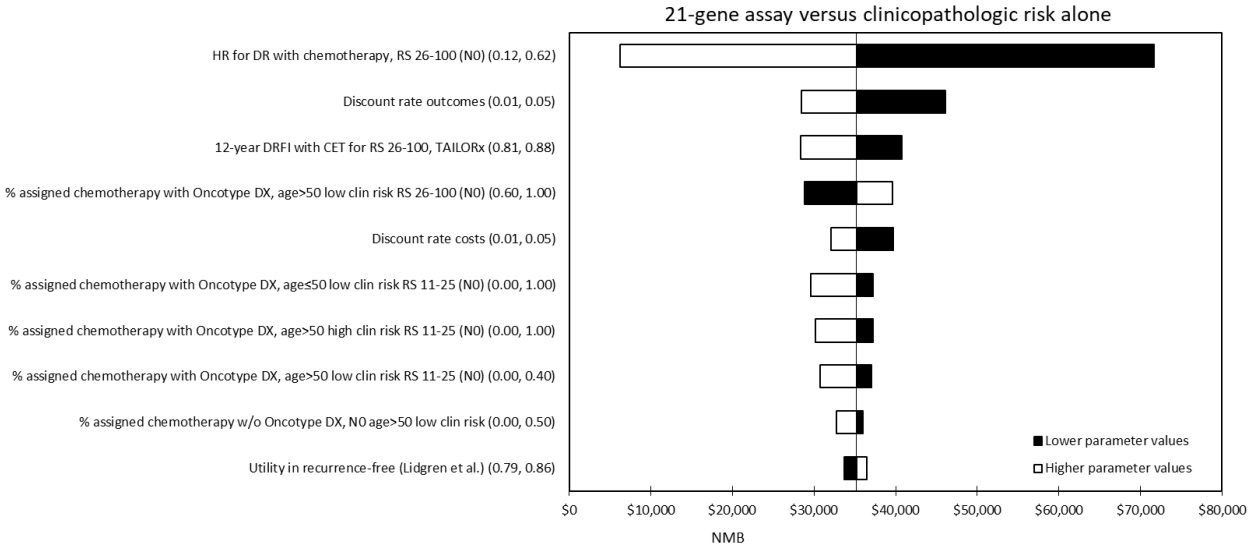
Detailed PSA results are reported in eTable 18. The 21-gene assay had a probability of cost-effectiveness vs. clinicopathologic risk alone of 98.8% at a willingness-to-pay of $100,000 per QALY, with 97.0% of simulations falling in the southeast quadrant, indicating that the strategy was less costly and more effective. The 50-gene assay proved to be cost-effective in 99.4% of simulations, with the majority (91.5%) falling in the southeast quadrant, indicating dominance in most scenarios. The 70-gene assay was cost-effective in 72.3% of simulations, with 44.1% in the northeast quadrant, denoting higher effectiveness but at a greater cost. Similarly, the 12-gene assay was cost-effective in 72.3% of simulations, with a notable 63.5% in the northeast quadrant, also reflecting higher effectiveness accompanied by increased costs.

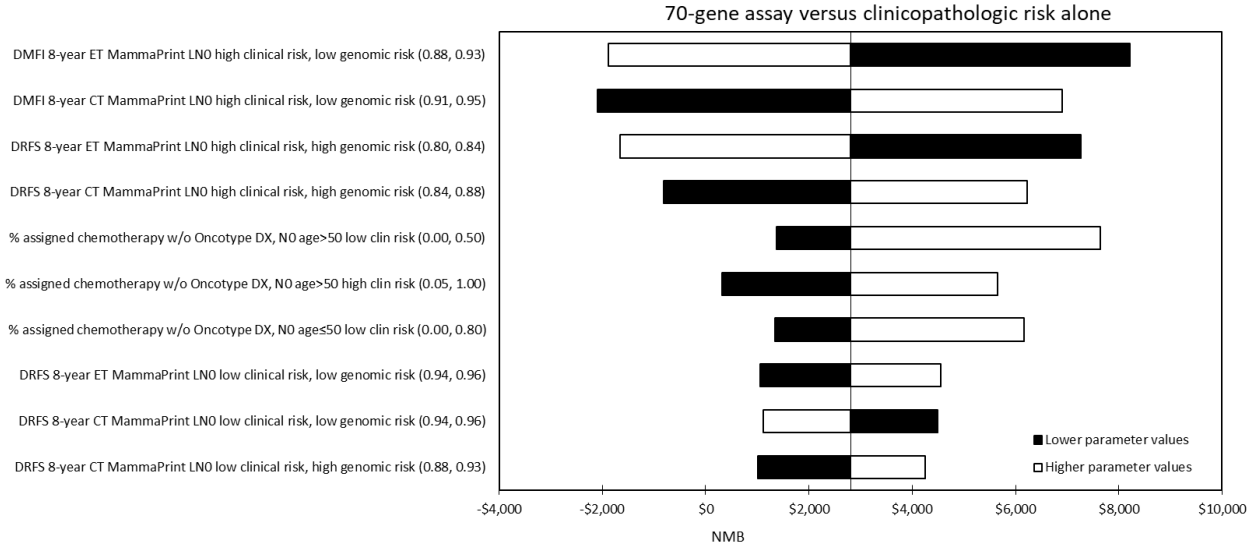
Table S18. Detailed PSA results

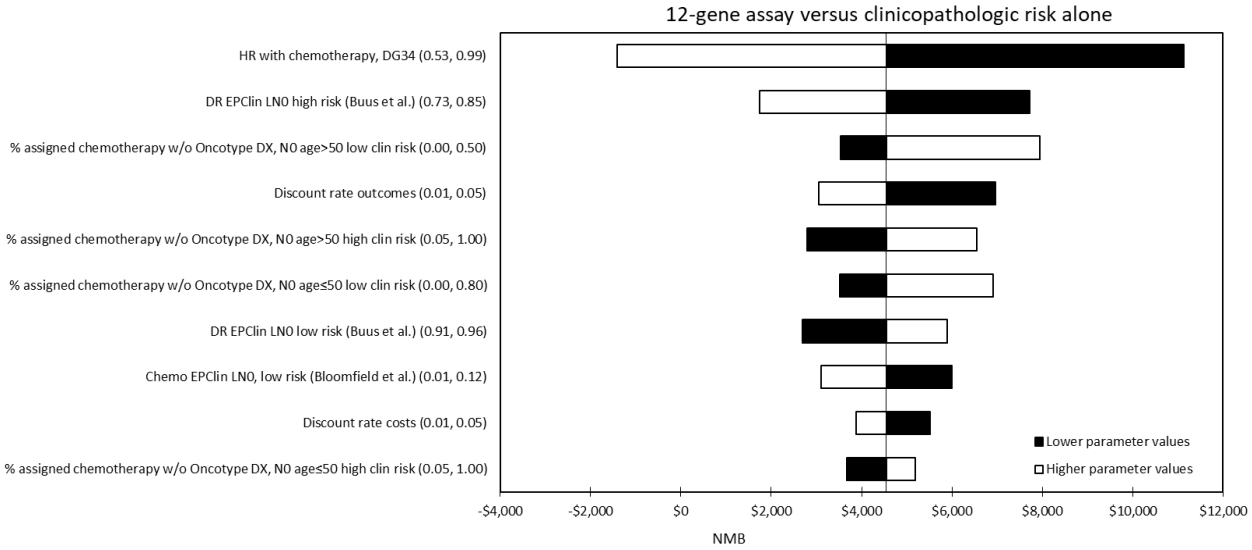
	21-gene assay	70-gene assay	12-gene assay	50-gene assay
Incr. cost	-$12,725	$1,077	$419	-$2,346
Incr. QALYs	0.242	0.039	0.049	0.073
ICER per QALY	Dominant	$27,700	$8,594	Dominant
NMB	$36,884	$2,812	$4,460	$9,659
ICER (deterministic)	Dominant	$27,760	$7,942	Dominant
NMB (deterministic)	$35,226	$2,808	$4,544	$9,768
% cost-effective[†]	99.0%	70.9%	84.9%	93.8%
% dominant	97.4%	34.6%	43.3%	83.3%

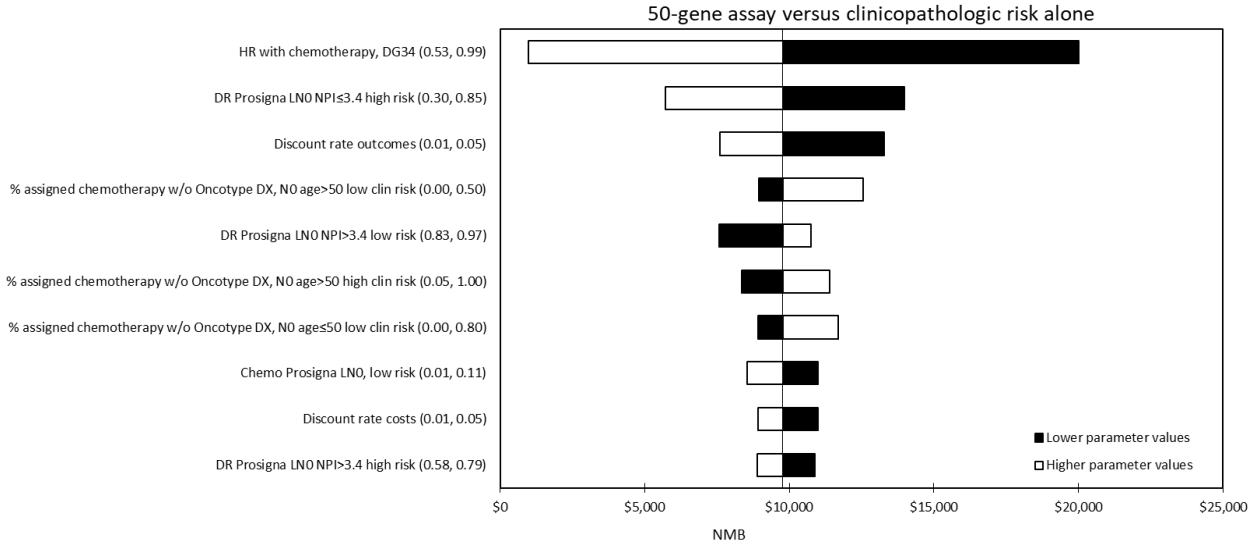
[†] Based on willingness-to-pay threshold of $100,000 per QALY

Figure S1. Tornado diagrams representing the 10 parameters which had the largest impact on the model results for the combined N0 population.









The endpoint of interest for the one-way sensitivity analyses was net monetary benefit (NMB), assuming the ICER willingness-to-pay of $100,000 per QALY: NMB=$100,000 × incremental QALYs – incremental cost. NMB is a more appropriate endpoint to measure uncertainty in the presence of negative ICERs, which are difficult to interpret as they can represent both a dominant (higher incremental QALYs and lower incremental cost) and dominated (lower incremental QALYs and higher incremental cost) result.

Figure S2. PSA scatter diagrams

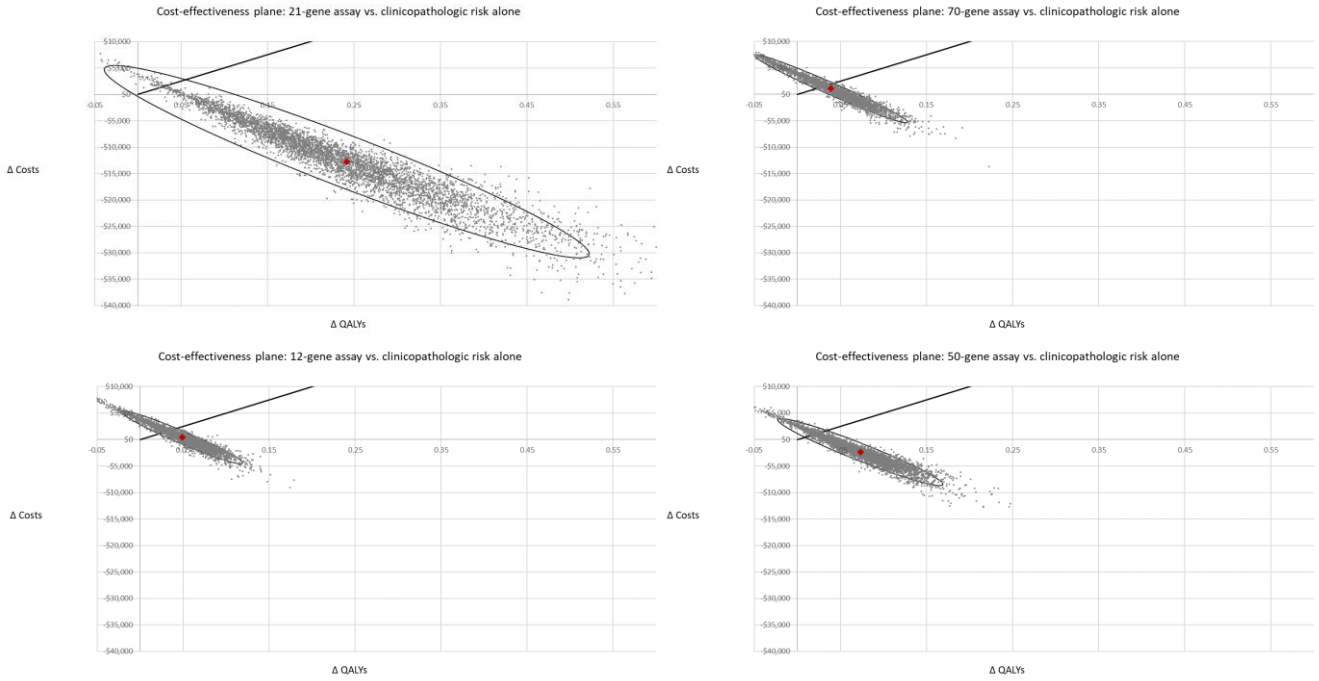


Figure S3. Cost-effectiveness acceptability curves

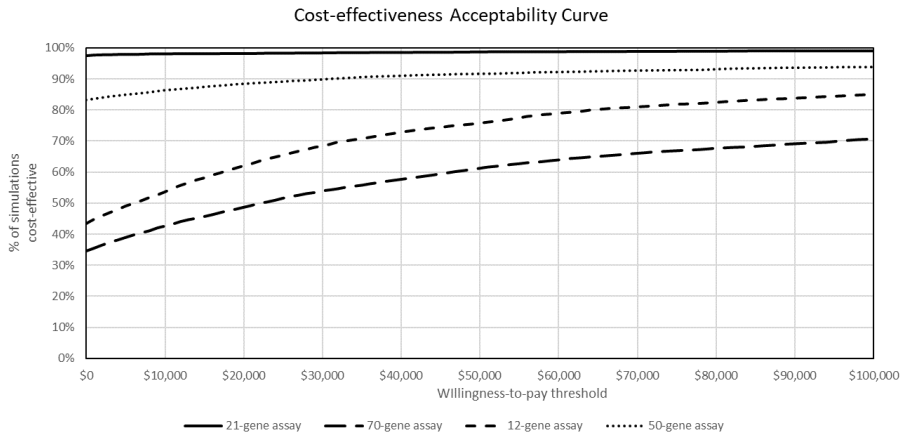
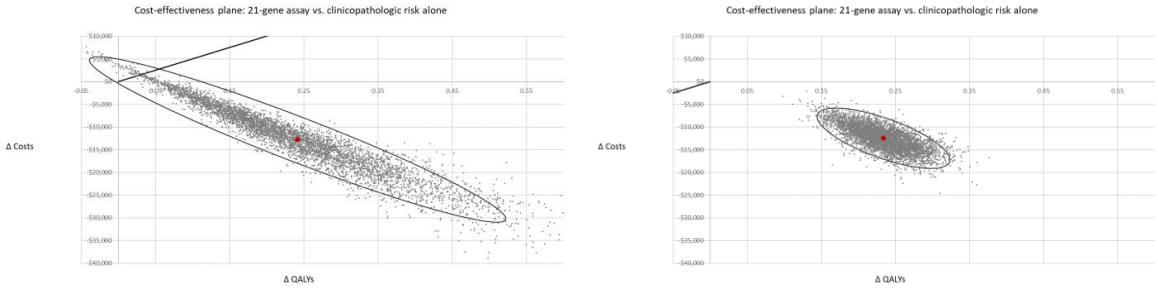


Figure S4. Scatter diagrams for 21-gene test with and without uncertainty from NSABP B-20



The left panels shows the base results of the probabilistic sensitivity analysis, which includes the uncertainty in the chemotherapy benefit for patients with RS>25 based on the expected value and confidence interval for the hazard ratio reported in Geyer et al.[11] On the right is the scatter diagram representing the PSA without varying this parameter.

Alternative PSA

The scatterplot for the 21-gene assay demonstrated higher overall uncertainty compared with the other 3 assays when plotted on the same scale in eFigure 2. This high uncertainty in the HR for chemotherapy benefit for patients with RS results of 26 to 100, as reported in NSABP B-20 (HR: 0.27; 95% confidence interval [CI]: 0.12-0.62), is attributed to the reduced sample size in the subgroup analysis (n=122) and retrospective nature of the analysis. This wide CI resulted in a substantial variation in the sampled HRs from the assigned distribution, leading to large fluctuations in the results, as depicted in the 95% CI ellipse for the ICER. An alternative PSA excluding this parameter was presented in eFigure 4, which demonstrates the contribution of this parameter to overall uncertainty for the 21-gene assay analysis.

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