



Breast Cancer in the Elderly Systemic Adjuvant Therapy & Genomic Tools

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Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study

Roberta De Angelis, Milena Sant, Michel P Coleman, Silvia Francisci, Paolo Baili, Daniela Pierannunzio, Annalisa Trama, Otto Visser, Hermann Brenner, Eva Ardanaz, Magdalena Błaska-Lasota, Gerda Engblom, Alice Nenneke, Sabine Siesling, Franco Berrino, Riccardo Capocaccia, and the EUROCARE-5 Working Group*

Summary

Background Cancer survival is a key measure of the effectiveness of health-care systems. EUROCARE—the largest cooperative study of population-based cancer survival in Europe—has shown persistent differences between countries for cancer survival, although in general, cancer survival is improving. Major changes in cancer diagnosis, treatment, and rehabilitation occurred in the early 2000s. EUROCARE-5 assesses their effect on cancer survival in 29 European countries.

Methods In this retrospective observational study, we analysed data from 107 cancer registries for more than 10 million patients with cancer diagnosed up to 2007 and followed up to 2008. Uniform quality control procedures were applied to all datasets. For patients diagnosed 2000–07, we calculated 5-year relative survival for 46 cancers weighted by age and country. We also calculated country-specific and age-specific survival for ten common cancers, together with survival differences between time periods (for 1999–2001, 2002–04, and 2005–07).

Findings 5-year relative survival generally increased steadily over time for all European regions. The largest increases from 1999–2001 to 2005–07 were for prostate cancer (73.4% [95% CI 72.9–73.9] vs 81.7% [81.3–82.1]), non-Hodgkin lymphoma (53.8% [53.3–54.4] vs 60.4% [60.0–60.9]), and rectal cancer (52.1% [51.6–52.6] vs 57.6% [57.1–58.1]). Survival in eastern Europe was generally low and below the European mean, particularly for cancers with good or intermediate prognosis. Survival was highest for northern, central, and southern Europe. Survival in the UK and Ireland was intermediate for rectal cancer, breast cancer, prostate cancer, skin melanoma, and non-Hodgkin lymphoma, but low for kidney, stomach, ovarian, colon, and lung cancers. Survival for lung cancer in the UK and Ireland was much lower than for other regions for all periods, although results for lung cancer in some regions (central and eastern Europe) might be affected by overestimation. Survival usually decreased with age, although to different degrees depending on region and cancer type.

Interpretation The major advances in cancer management that occurred up to 2007 seem to have resulted in improved survival in Europe. Likely explanations of differences in survival between countries include: differences in stage at diagnosis and accessibility to good care, different diagnostic intensity and screening approaches, and differences in cancer biology. Variations in socioeconomic, lifestyle, and general health between populations might also have a role. Further studies are needed to fully interpret these findings and how to remedy disparities.

Funding Italian Ministry of Health, European Commission, Compagnia di San Paolo Foundation, Cariplo Foundation.

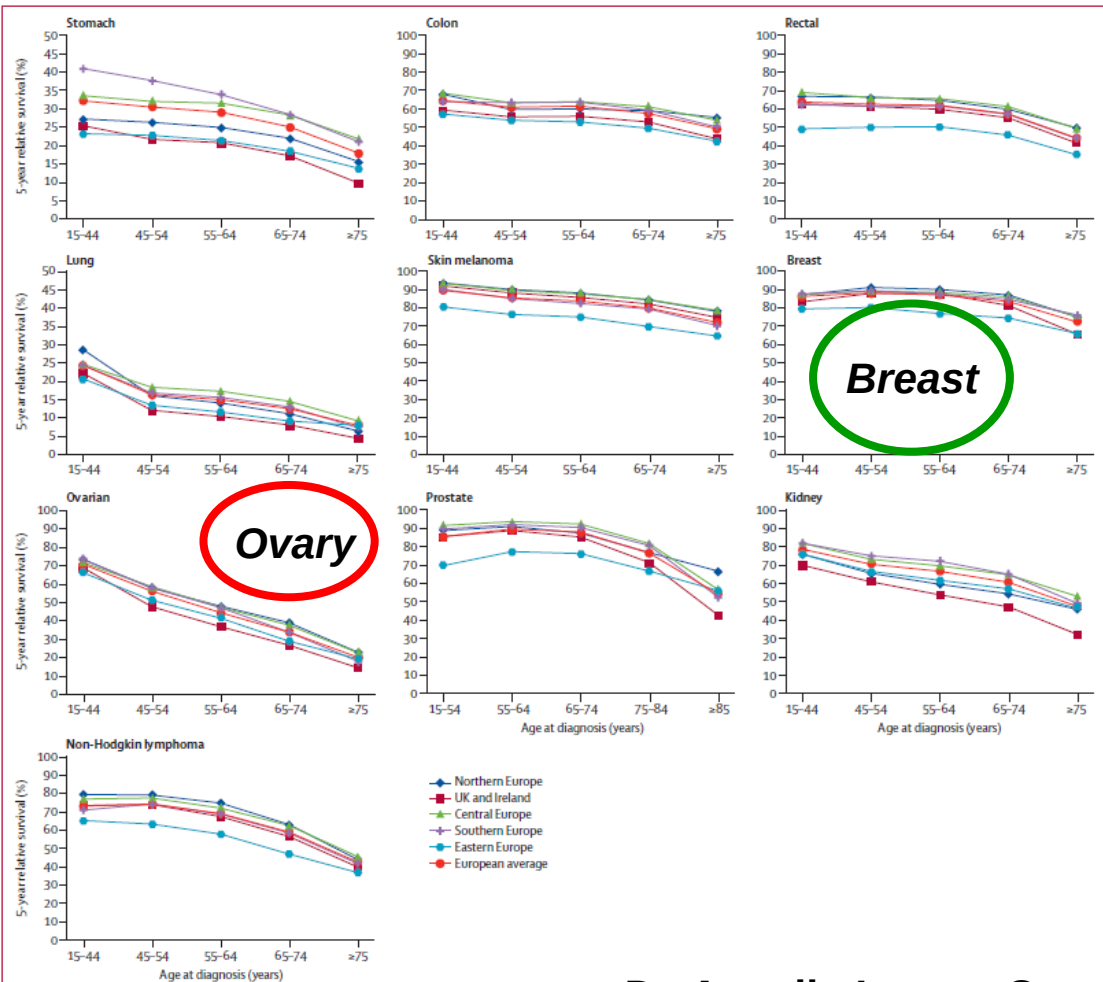


Figure 2: Age-specific 5-year relative survival for adults with cancer diagnosed in 2000–07
The European mean is the (population) weighted mean of country-specific relative survival estimates.

Current dilemma and extreme positions

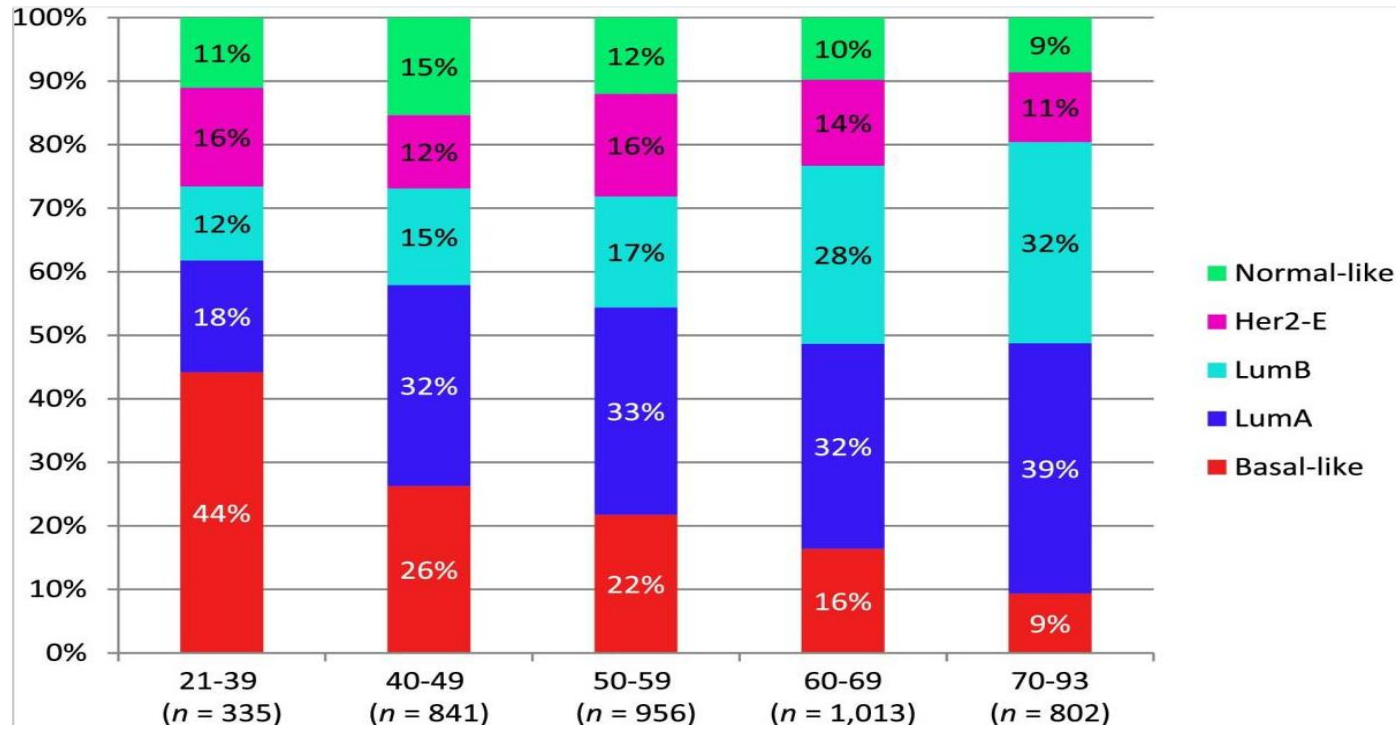
1. Therapeutic **nihilism**
 - Elderly patients **do not receive** any treatment
2. The **intermediate** position?
 - Elderly patients **may** benefit from treatments
3. Blind therapeutic **enthusiasm**
 - Elderly patients **receive futile/non beneficial** treatments

→ Place and role of **geriatrician** and **oncologist**



Pelike from Attica 480–470 BC
Musée du Louvre

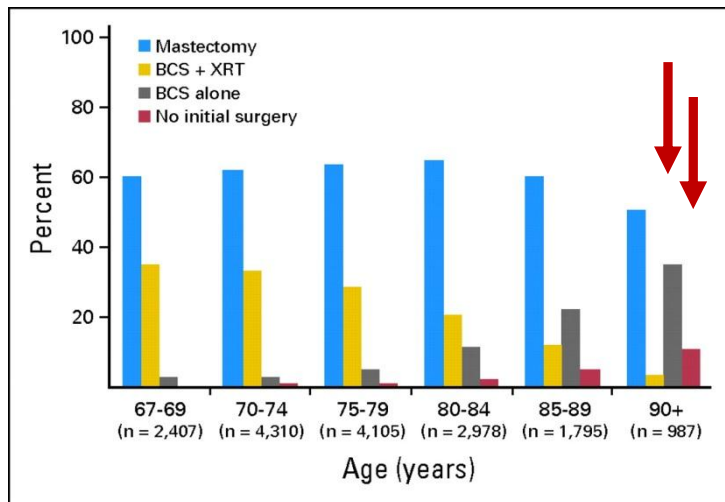
BC biology according to age



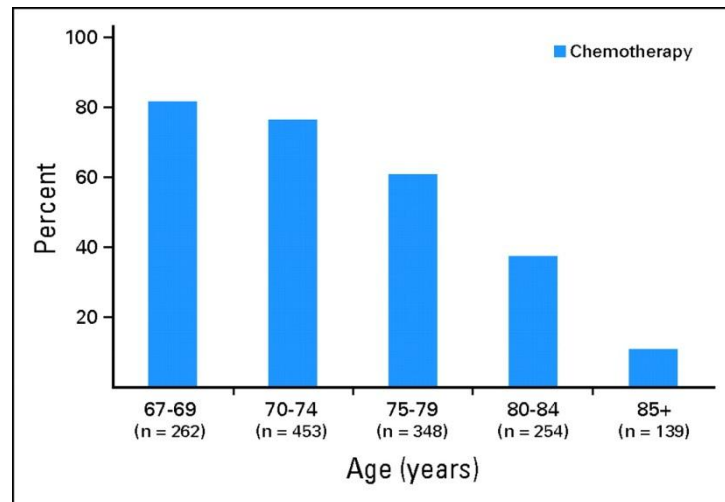
Undertreatment

SEER database ; 49616 women with stage I/II breast cancer ≥ 67 y

Initial treatment for stage II breast cancer by age



Treated with chemotherapy if ER+ N+ stage I/II breast cancer



BCS = breast conserving surgery ; XRT = radiotherapy

Undertreatment

Characteristic	HR of Death Due to Breast Cancer	Range	HR of Death Due to Other Causes	Range
Age group, years				
67-69	Reference		Reference	
70-74	1.0	0.9-1.2	1.3	1.2-1.4
75-79	1.1	0.99-1.3	1.9	1.8-2.2
80-84	1.2	1.1-1.4	3.0	2.7-3.3
85-89	1.5	1.3-1.7	4.1	3.7-4.6
≥ 90	1.8	1.5-2.2	5.9	5.2-6.7

Substudy from TEAM trial (adjuvant exemestane)



Breast cancer mortality

Other cause mortality

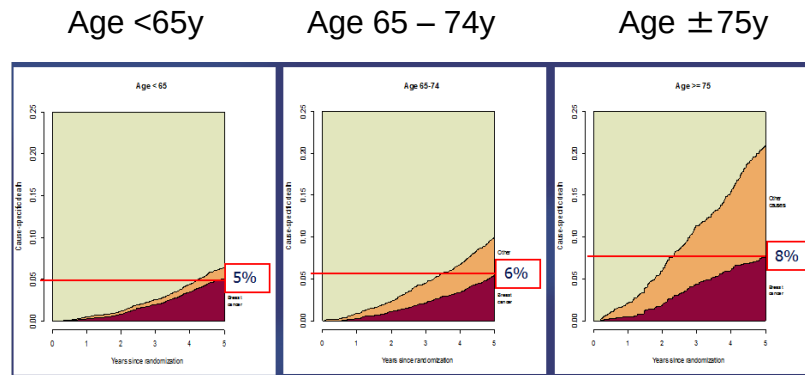
- Univariate HR 1.66

(95% CI 1.34-2.06), $p < 0.001$

- Multivariable HR 1.63

(95% CI 1.23-2.16), $p < 0.001$

Cause specific death



Schonberg JCO 2010, Van de Water JAMA 2012

Overtreatment

- A sizeable proportion of elderly with operable breast cancer **die of NON-CANCER-related causes**

N = 14048 new early breast cancer, ≥ 50 y, FUP 4,7y

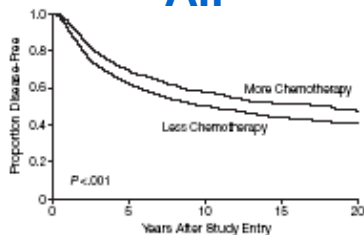
	Total deaths	Deaths from breast cancer	%
50–69	1334	933	70
70–74	514	293	57
75–79	696	329	47
≥ 80	1681	663	39
Total	4225	2218	53

- Absolute **benefit** of treatments is **lower**

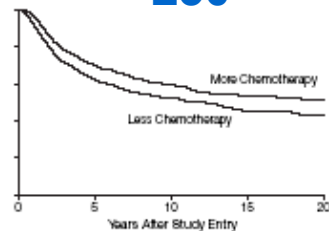
Adjuvant chemo

DFS

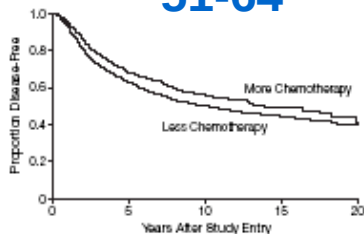
All



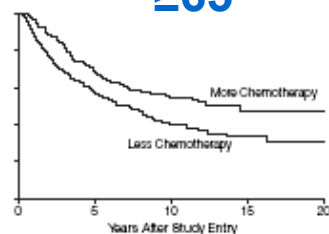
≤50



51-64



≥65



Results

- Benefit
- Toxicity

identical
careful!!

- Toxic deaths 1.5%

- CALGB (1975-1999)
- 4 randomized trials
- 6487 pts

> 65 yo

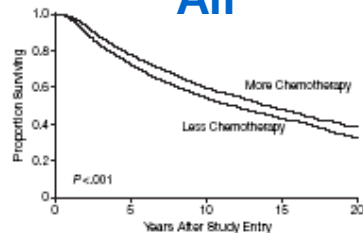
542 (8%)

> 70 yo

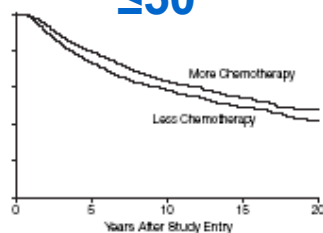
159 (2%)

OS

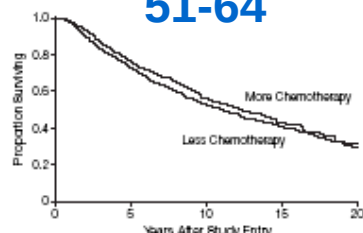
All



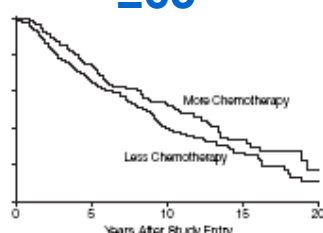
≤50



51-64



≥65



Muss JAMA 2005

Adjuvant chemotherapy and mortality

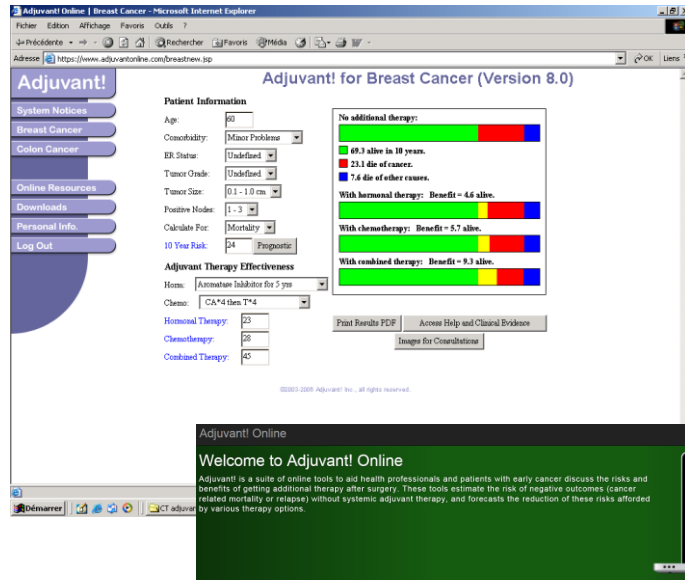
		Giordano*	Elkin
	No. total No. w/CT	I-III, ▽ ER , 65+ 41,390 4,500	I-III, ER- , 66+ 5,081 1,711
pN	ER	HR (95% IC)	HR (95% IC)
pN0	▽	1.05 (0.85-1.31)	NA
pN+	+	1.05 (0.85-1.31)	NA
both	-	NA	0.85 (0.77-0.95)
pN+	-	0.72 (0.54-0.96)	0.76 (0.65-0.88)
pN+ > 70 yo	-	0.74 (0.56-0.97)	

*: BC specific mortality



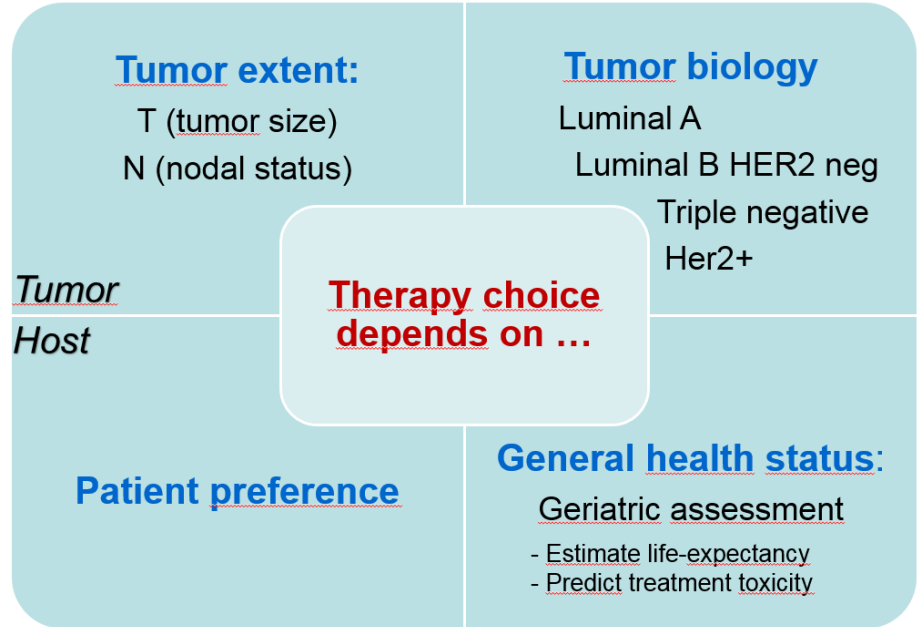
**Adjuvant chemo is useful FIRST
in ER-, pN0 or pN+, even > 70 yo**

Standard decision tools

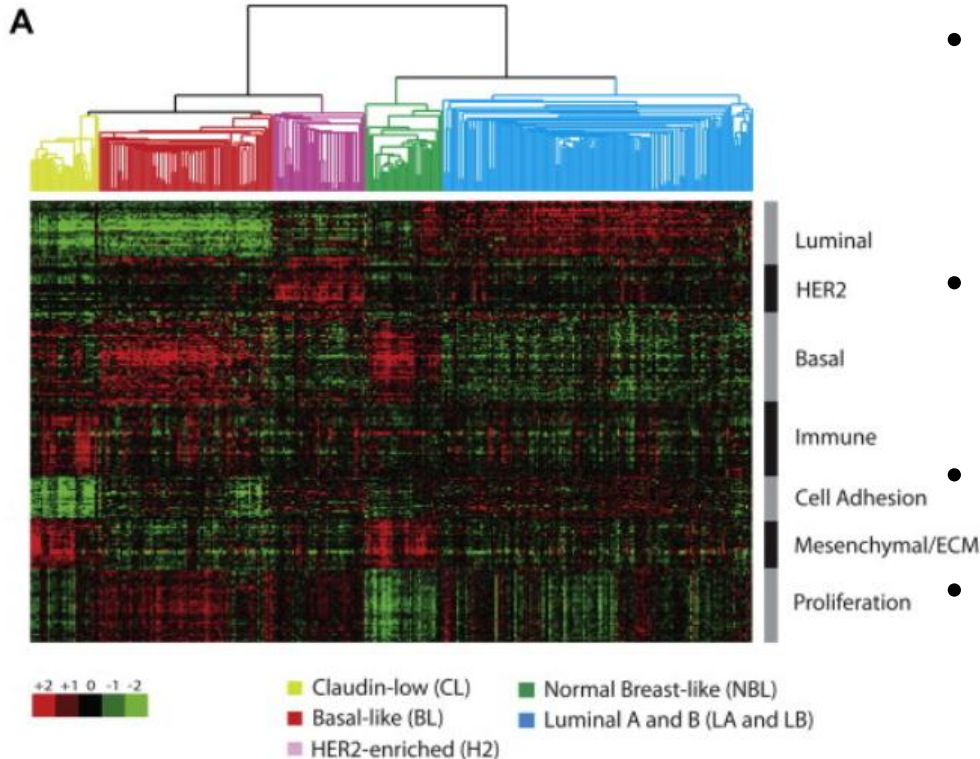


- **Adjuvant! Online**
- **Predict**

not accurate in older patients
quite accurate for OS prediction



Early 2000s: 1st GEP (intrinsic classification)



- Quantification of mRNA or cDNA of genes involved in tumour proliferation
- To identify patients requiring chemo despite good standard prognostic factors
- To avoid chemo in others
- Better individual risk stratification

	MammaPrint	Oncotype DX	Breast Cancer Index	Mapquant DX	PAM 50 ROR	EndoPredict
Provider	Agendia	Genomic Health	Biotheranostics	Ipsogen	NanoString	Sividon
Type of Assay	70-gene assay	21-gene recurrence score	2-gene ratio (H/I) and molecular grade index	Genomic grade	50-gene assay	12-gene assay
Type of Sample	Fresh or frozen or FFPE	FFPE	FFPE	Fresh or frozen or FFPE	FFPE	FFPE
Technique	DNA microarray or qRT-PCR	qRT-PCR	qRT-PCR	DNA microarray or qRT-PCR	qRT-PCR	qRT-PCR
Clinical Application	Prognosis of NO, < 5 cm, stage I/II, age < 61	Prediction of recurrence risk in ER+ and NO treated with TAM	Prognostic in ER+, prediction of response to TAM	Molecular grading for ER+, histologic grade II disease	Originally for intrinsic subtyping, recurrence prediction	Recurrence prediction for ER+ HER2–
Results Presentation	Dichotomous, good or poor prognosis	Continuous variable	Continuous variable	Dichotomous, GGI I or GGI III	Continuous variable	Dichotomous, low or high risk
Level of Evidence	I	I	III	III	I	I
FDA Approval	YES	NO	NO	NO	YES	NO

Abbreviations: ER+, estrogen receptor–positive; FDA, U.S. Food and Drug Administration; FFPE, formalin-fixed, paraffin-embedded; GGI, Genomic Grade Index; qRT-PCR, quantitative reverse transcription polymerase chain reaction; TAM, tamoxifen.

MammaPrint

Summary of Results

PATIENT NAME: Last Name, First Name

DOB: 10-Jan-1961



GENDER: Female
SPECIMEN ID: MRN 123456
PATIENT/MRN: 945839302
CUSTOMER REF: 123456789

ORDERED BY: Dr. Doe, John
ACCOUNT: John Doe Hospital
1234 Main St.
Irvine CA 92618 USA

REQUISITION #: 1234567
SPECIMEN TYPE: FFPE, Core
SPECIMEN SOURCE: Left Breast
COLLECTED DATE: 18-Feb-2014
RECEIVED DATE: 19-Feb-2014
REPORTED DATE: 21-Feb-2014

Summary of Results: **High Risk Luminal-type (B)**

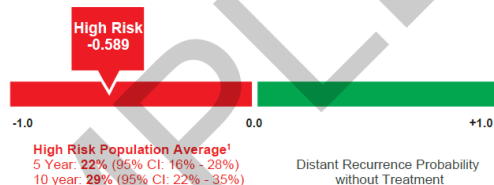
Risk of Recurrence

High Risk

Molecular Subtype

Luminal-type

MammaPrint® FFPE: 70-Gene Breast Cancer Recurrence Assay

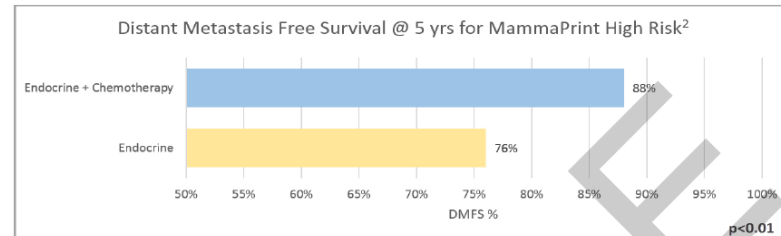


**Risk of distant recurrence risk
@ 5 years
w/ no treatment**

PATIENT NAME: Jane Doe-Jane Doe-Jane

REPORTED DATE: 21-Feb-2014

Adjuvant Response to Therapy



- The MammaPrint result provides independently validated, statistically significant, additive information for physicians to assist them in making treatment decisions for early stage breast cancer patients.
- If the risk assessment by MammaPrint and clinicopathological characteristics is concordant and indicates a High Risk of recurrence, the use of combined endocrine and chemotherapy (ET+CT) seems clinically indicated.
- If the risk assessment by MammaPrint and clinicopathological characteristics is discordant, MammaPrint High Risk and clinically stratified Low Risk patients will likely benefit from chemotherapy. If these patients are highly endocrine-responsive ($\geq 50\%$ ER positivity), endocrine therapy (ET) alone might be the desired option; however, withholding chemotherapy might not be supported due to the observed improvement in DMFS at 5 years for MammaPrint High Risk patients who received ET+CT.
- Other factors, such as age and co-morbidities, may influence the decision-making process for systemic adjuvant therapy shared between the physicians and patients. Distant metastasis-free survival (DMFS) is defined as time from surgery to any distant metastasis.

Estimated benefit in breast cancer specific survival by trastuzumab:

For women with early-stage HER2-positive breast cancer, addition of trastuzumab to paclitaxel after doxorubicin and cyclophosphamide results in a 10-year absolute benefit of 9% in overall survival (OS) and 11% in disease-free survival (DFS).³

General results

<http://www.agendia.com/healthcare-professionals/breast-cancer/test-results/>



MINDACT

Microarray In Node-negative
and 1 to 3 positive lymph node
Disease may Avoid ChemoTherapy
EORTC 10041 / BIG 3-04



The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

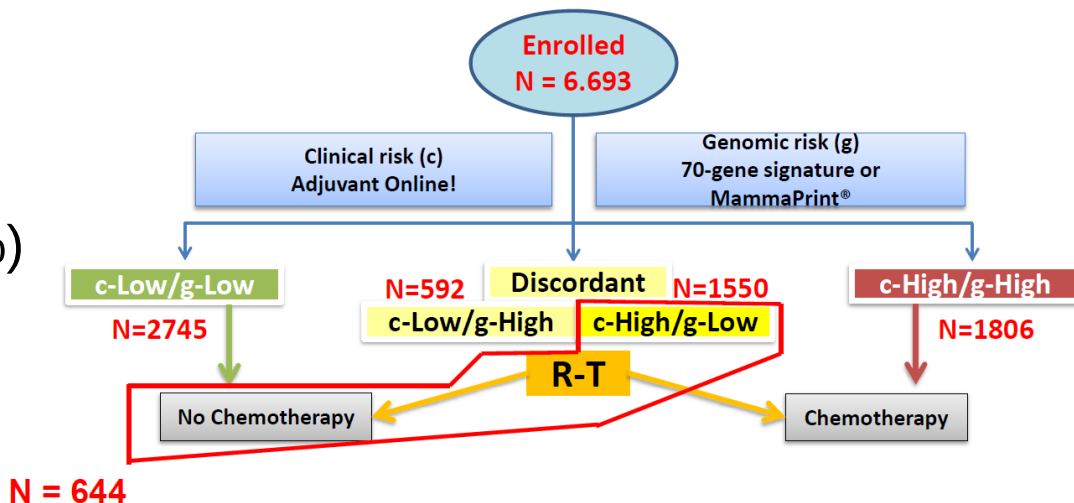
AUGUST 25, 2016

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70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

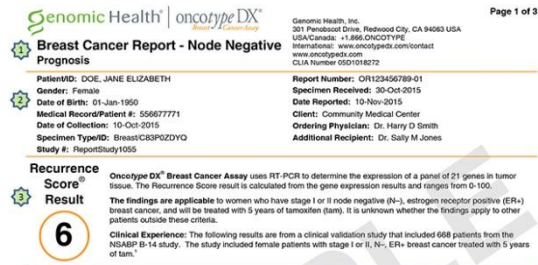
F. Cardoso, L.J. van't Veer, J. Bogaerts, L. Slaets, G. Viale, S. Delaloge, J.-Y. Pierga, E. Brain, S. Causeret, M. DeLorenzi, A.M. Glas, V. Goulinopoulos, T. Goulioti, S. Knox, E. Matos, B. Meulemans, P.A. Neijenhuis, U. Nitz, R. Passalacqua, P. Ravdin, I.T. Rubio, M. Saghatchian, T.J. Smilde, C. Sotiriou, L. Stork, C. Straehle, G. Thomas, A.M. Thompson, J.M. van der Hoeven, P. Vuylsteke, R. Bernards, K. Tryfonidis, E. Rutgers, and M. Piccart, for the MINDACT Investigators*

- 6,600 pts < 70
 - FEB 2007-AUG 2011
 - 11,291 registered pts
 - 6,673 enrolled (59.1%)

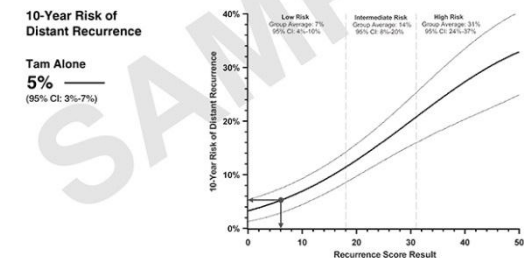


OncotypeDX

pN0



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



¹ Pish et al. N Engl J Med. 2006.

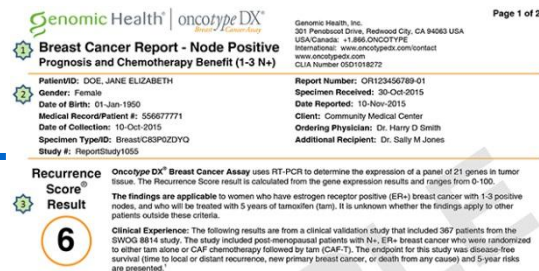
Laboratory Director(s): S. Shak, MD; J. Anderson, MD; F. Baehner, MD & P. Joseph, MD

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

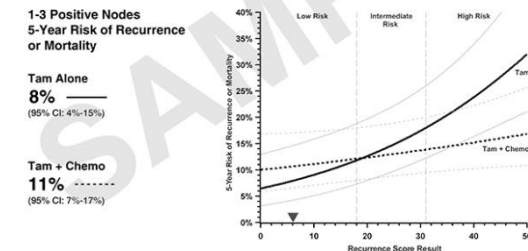
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**Risk of distant recurrence
@ 10 years
w/ TAM 5 years**

pN+



Prognosis and Chemotherapy Benefit: 5-Year Risk of Recurrence or Mortality after 5 Years of Tam, Based on the Recurrence Score Result



¹ Arzoo et al. Breast Cancer. 2005.

Laboratory Director(s): S. Shak, MD; J. Anderson, MD; F. Baehner, MD & P. Joseph, MD

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

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**Risk of distant recurrence
@ 5 years
w/ TAM 5 years**

Personal results

OUTCOME DISPARITIES BY AGE AND 21-GENE RECURRENCE SCORE RESULT IN HORMONE RECEPTOR-POSITIVE (HR+) BREAST CANCER

Shak S,¹ Miller DP,¹ Howlader N,² Gliner N,¹ Howe W,³ Schussler N,³ Cronin K,² Baehner FL,^{1,4} Penberthy L,²
Petkov VI²

1. Genomic Health, Inc., Redwood City, CA, USA

2. National Cancer Institute, Rockville, MD, USA

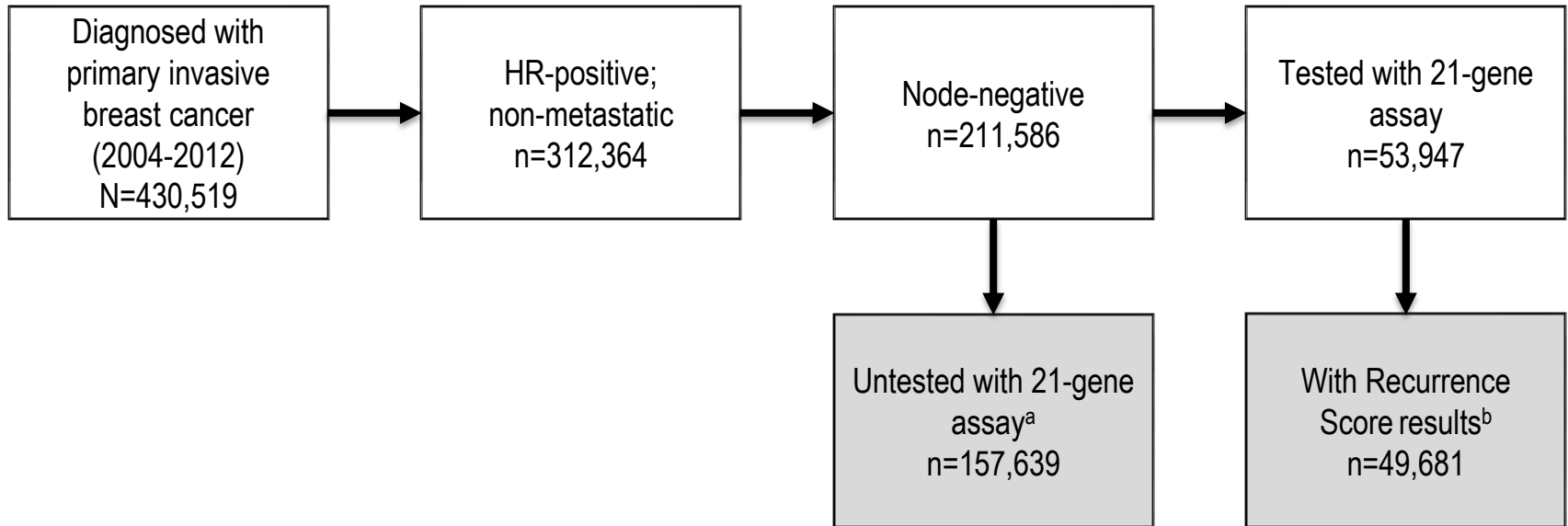
3. IMS, Inc., Calverton, MD, USA

4. University of California, San Francisco, San Francisco, CA, USA

Methods

- ♦ SEER demographics, tumor characteristics, reported CT use, and BCSM available through 2013
- ♦ Genomic Health provided RS electronically to SEER, per registry operations
- ♦ Analysis population: N0, HR+ (by SEER and RT-PCR), HER2-negative (by RT-PCR), diagnosed between January 2004 and December 2012
 - ♦ Excluded: N+, prior invasive tumors, or concurrent multiple tumors
- ♦ RS groups standard cutpoints (18, 31)
- ♦ Actuarial estimates of survival (cause-specific and overall) and BCSM computed through 5 years with 95% CI
- ♦ The log-rank test was used to compare the three RS groups

SEER Population - STROBE Diagram



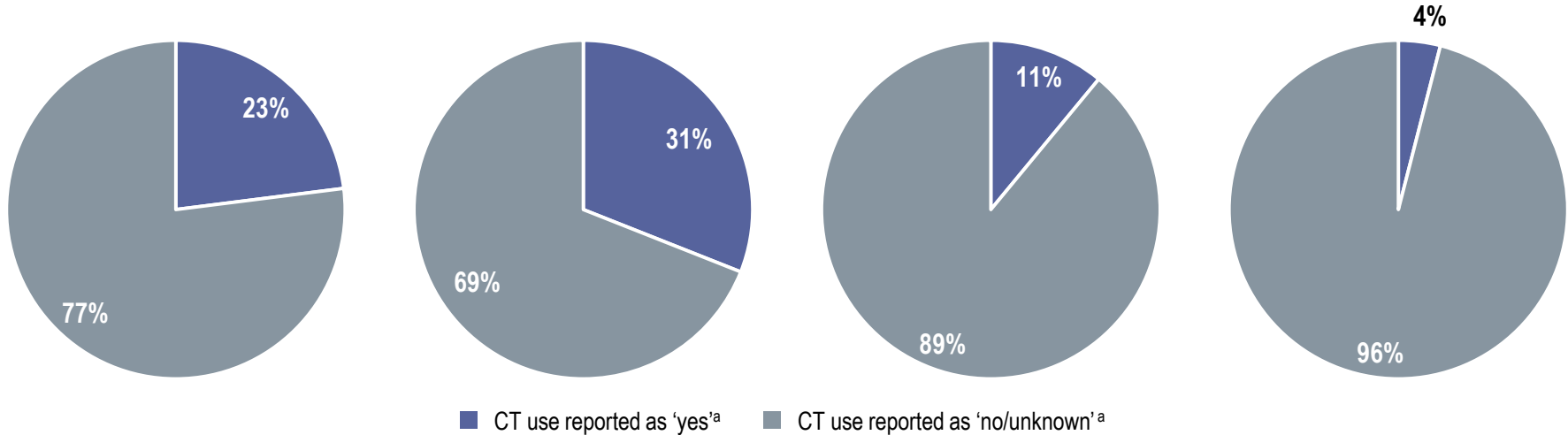
Patient Testing and Demographics

		Age <70 years		Age ≥70 years	
		Tested (N=43,693)	Not Tested (N=100,519)	Tested (N=5,988)	Not Tested (N=57,120)
		%	%	%	%
Sex ^a	Female	99	99	99	99
Race	White	84	81	87	87
	Black	8	9	7	7
	Asian or Pacific Islander	8	10	5	6
	Am. Indian/Alaska Native	<1	<1	<1	<1
Socioeconomic status, quintile	Lowest SES	11	13	15	14
	Second lowest SES	15	17	17	18
	Middle SES	19	20	21	21
	Second highest SES	23	23	23	22
	Highest SES	32	28	25	25

- Almost 6,000 patients ≥70 years with RS results
- Testing occurred 3.2 times less frequently in patients ≥70 years compared to <70 years
- Testing rates were similar by race and socioeconomic status

Reported Chemotherapy (CT) Use

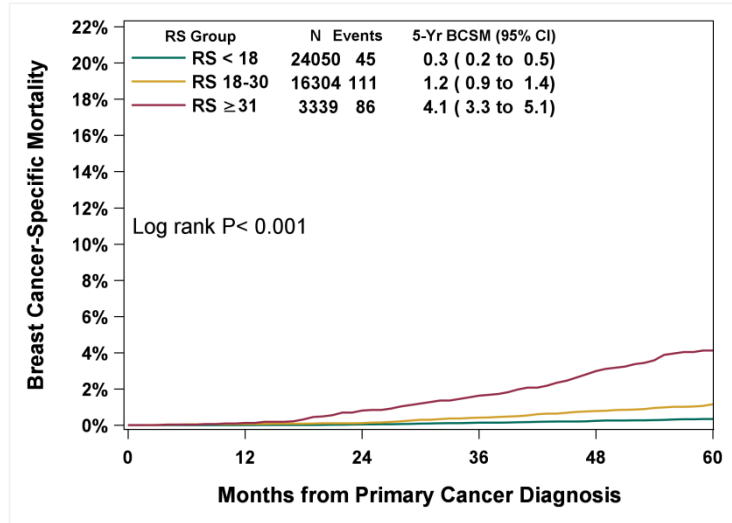
Age <70 years		Age ≥70 years	
Tested (N=43,693)	Not Tested (N=100,519)	Tested (N=5,988)	Not Tested (N=57,120)



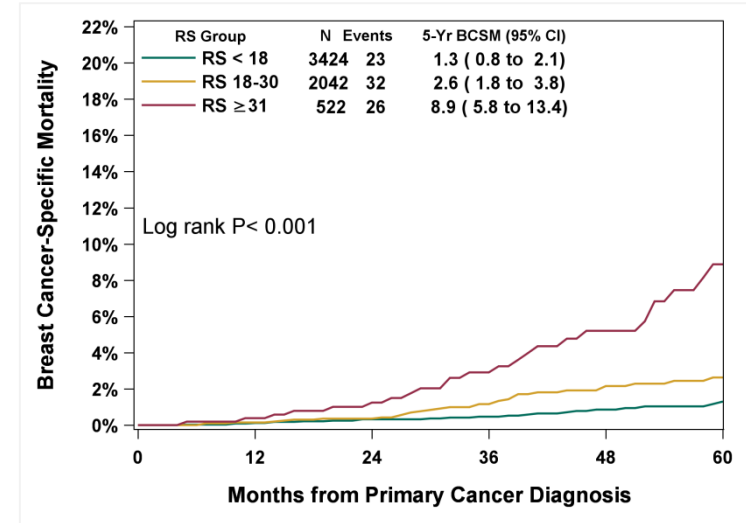
- CT use was lower in patients ≥70 years, in both RS-tested and untested cohorts

5-year BCSM by Age and RS Group

Age <70 y



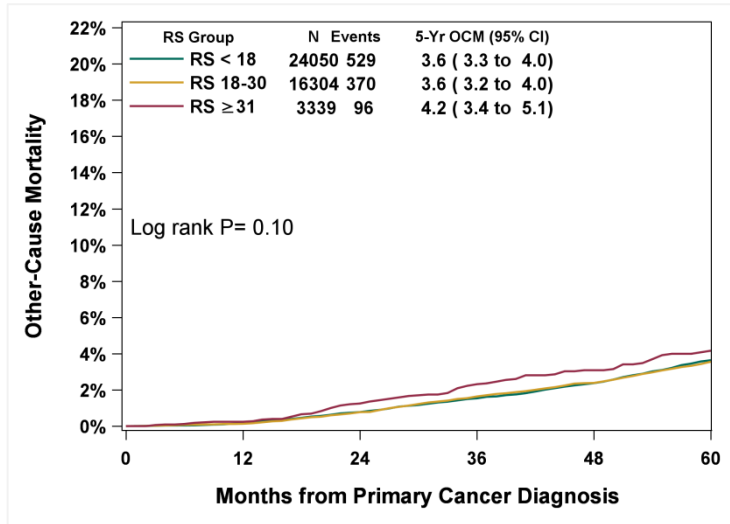
Age ≥70 y



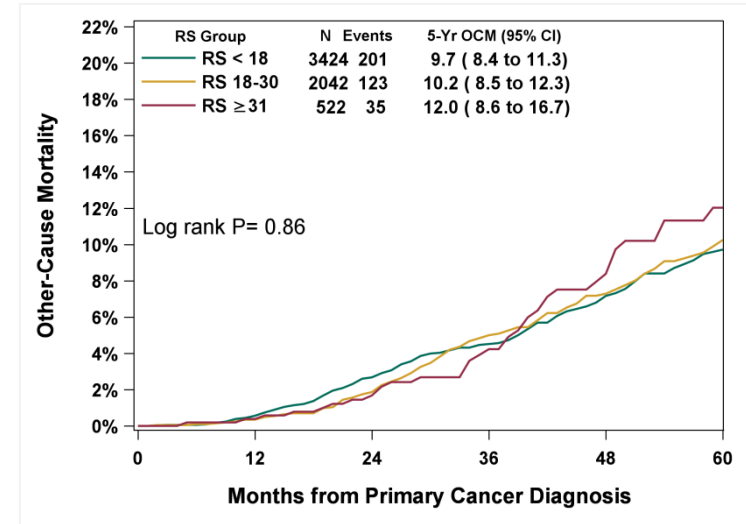
- RS predicts BCSM in both age groups ($p < 0.001$)
- Low 5-y BCSM was observed with RS < 18 in both age groups
- Higher 5-y BCSM was observed with RS 18-30 and RS ≥ 31 in older patients

5-year Other-Cause Mortality by Age and RS Group

Age <70 y



Age ≥70 y



- As expected, RS group does not predict other-cause mortality (p=NS)
- As expected, higher other-cause mortality was observed in older patients

5-year BCSM (95% CI) by Age in Tested and Untested Patients

	RS < 18			RS 18-30			RS ≥31			Untested		
	N	CT Use ^a (% of N)	5-y BCSM (95% CI)	N	CT Use ^a (% of N)	5-y BCSM (95% CI)	N	CT Use ^a (% of N)	5-y BCSM (95% CI)	N	CT Use ^a (% of N)	5-y BCSM (95% CI)
<70 y	24050	7%	0.3% (0.2%, 0.5%)	16304	37%	1.2% (0.9%, 1.4%)	3339	73%	4.1% (3.3%, 5.1%)	100519	31%	2.3% (2.2%, 2.4%)
≥70 y	3424	2%	1.3% (0.8%, 2.1%)	2042	14%	2.6% (1.8%, 3.8%)	522	52%	8.9% (5.8%, 13.4%)	57120	4%	5.5% (5.2%, 5.7%)
70-74 y	2116	2%	1.1% (0.6%, 2.0%)	1245	17%	2.4% (1.4%, 3.9%)	320	61%	6.2% (3.2%, 11.9%)	17647	8%	2.8% (2.6%, 3.2%)
75-79 y	968	2%	1.9% (0.9%, 4.0%)	590	11%	2.4% (1.1%, 5.2%)	142	43%	11.6% (5.5%, 23.8%)	16445	4%	4.3% (4.0%, 4.7%)
≥80 y	340	1%	1.0% (0.2%, 4.5%)	207	6%	4.8% (2.3%, 9.9%)	60	32%	20.5% (9.6%, 40.6%)	23028	2%	8.6% (8.2%, 9.1%)

- Notably, 5-y BCSM is relatively high in untested patients at all ages; this deserves further study

5-year BCSM by Age and RS Group in Nottingham Prognostic Index (NPI) >3.4

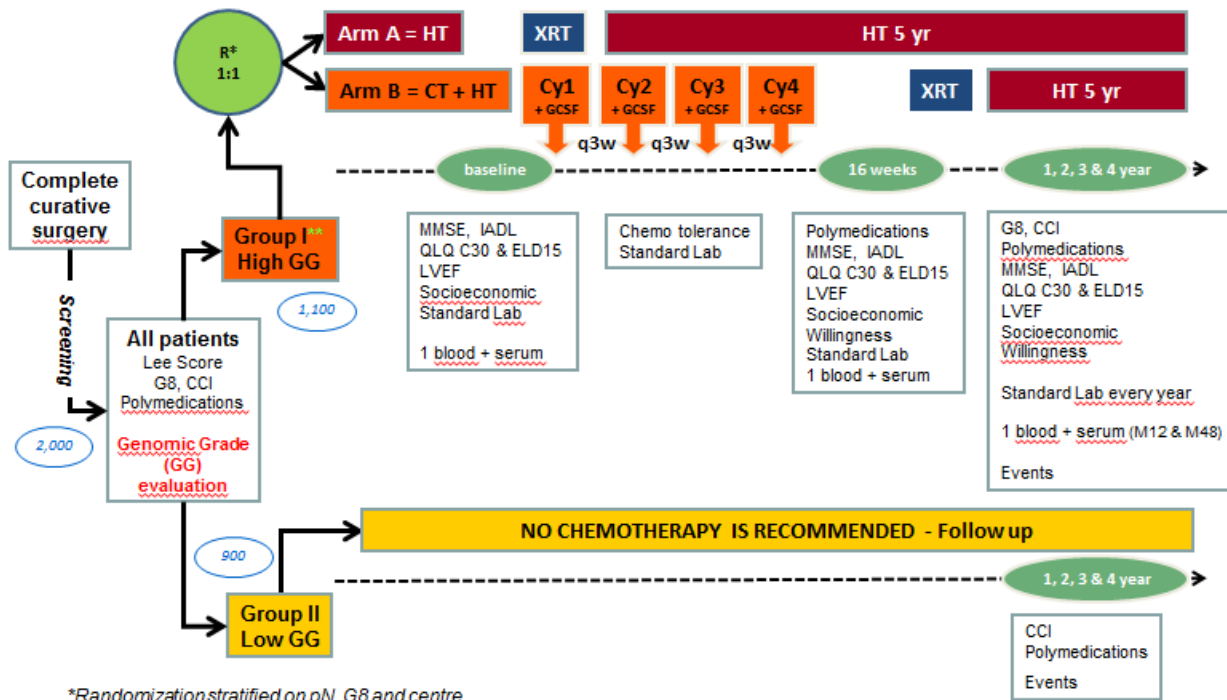
	RS <18			RS 18-30			RS ≥31		
	N	CT Use ^a (% of N)	5-y BCSM (95% CI)	N	CT Use ^a (% of N)	5-y BCSM (95% CI)	N	CT Use ^a (% of N)	5-y BCSM (95% CI)
<70 y	4727	12%	0.7 (0.4, 1.2)	4959	48%	2.1 (1.6, 2.8)	2236	75%	4.7 (3.6, 6.0)
≥70 y	940	2%	1.4 (0.5, 3.6)	821	20%	3.6 (2.2, 5.9)	377	52%	8.5 (5.1, 14.0)

- RS predicts BCSM in both age groups (p<0.001)
- Similar results were seen for NPI >3.2 and ≤3.4

Adjuvant chemotherapy

ASTER 70s (EUDRACT N° 2011-004744-22, PHRC national 2011, NCT01564056)

ER+ (ongoing study)



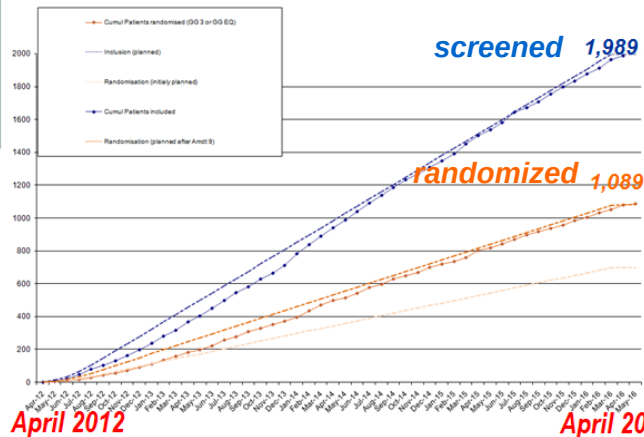
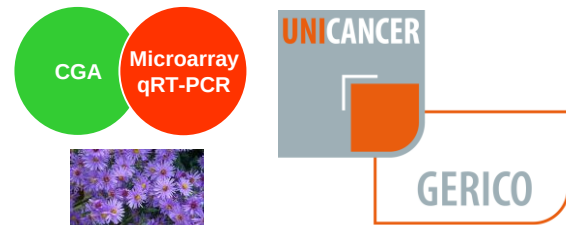
*Randomization stratified on pN, G8 and centre

**Group I include both high and equivocal GG cases

time

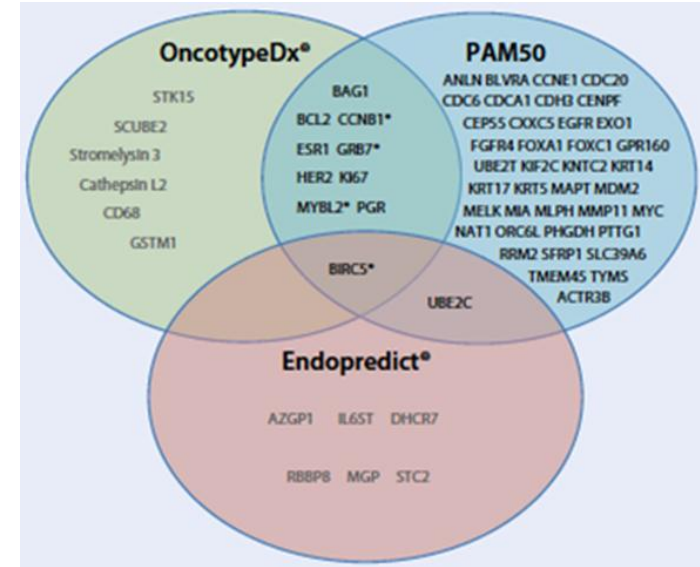
Chemo = 4 TC or 4 AC or 4 MC

Hypothesis $B > A \Delta +7.5\%$ (A 80% vs B 87.5%) HR 0.60 $\alpha 5\% \beta 10\%$ 4-yr OS



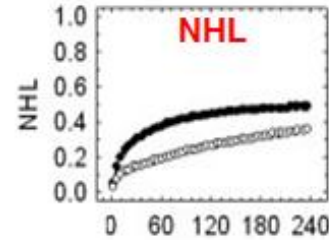
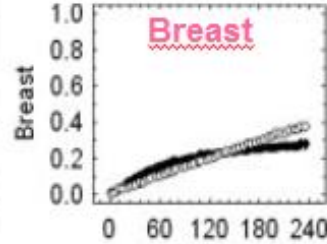
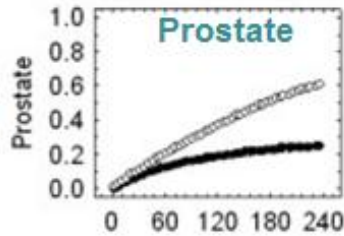
Comparing Breast Cancer Multiparameter Tests in the OPTIMA Prelim Trial: No Test Is More Equal Than the Others

- Prospective study on 313 patients
- Risk of relapse
 - OncotypeDx 82.1%
 - Prosigna 65.5%
 - Mammaprint 61.4%
- Only 39% agreement
- Prosigna+Blueprint → 40% discordant
- Risk estimates are close at the population level but individual differences

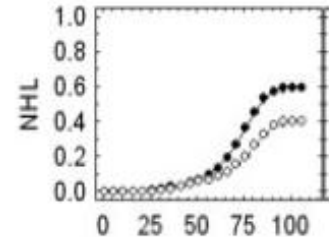
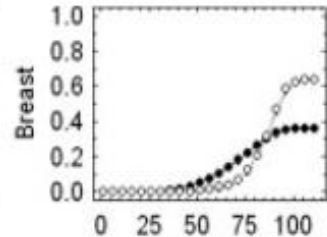
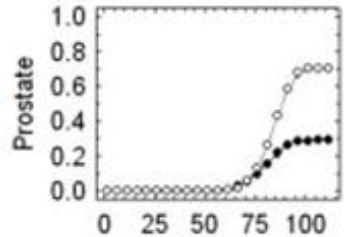


Competing causes for mortality

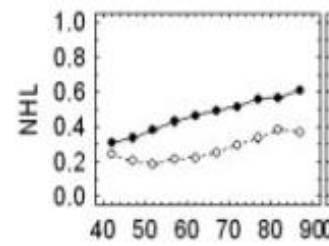
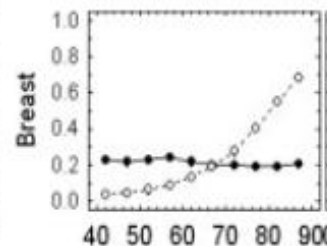
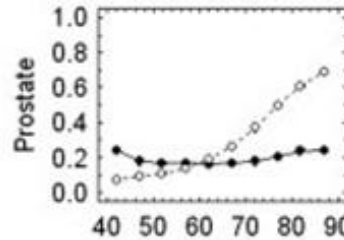
*Cumulative
probability of death /
time of diagnosis*



*Cumulative
probability of death /
attained age*



*Log/log plot of
probability of
comorbid death vs
corresponding
probability for
cancer-specific
death*



Deaths attributed to the primary cancer (solid dots) and those attributed to comorbidity (open circles)

Kendal Cancer 2008

Two worlds confronting one another?

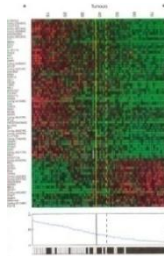
- **Young patient**

- Social and family obligations
- Quantity of life +++

- **Oncology**

- Therapies and interventions
- Toxicity, response
 - RECIST
 - NCI CTC v4.0
 - Survival (DFS, PFS, DOR)
- Fast-moving world
- "Molecular portrait" of patient &

GEP



**Genomic
defect
targeted
therapy**

versus

**or
+
?**

CGA

**CGA
defect
targeted
geriatric
intervention**

- **Elderly patient**

- QoL+++
- Independence
- Staying at home
- **Geriatrics**
- Symptoms, diagnosis
- Quality of survival, i.e. amount of life with good QoL

- Cognition
- Functional status
- QoL
- Nutrition, etc.

Requiring time

"Global portrait" of patient &

CGA

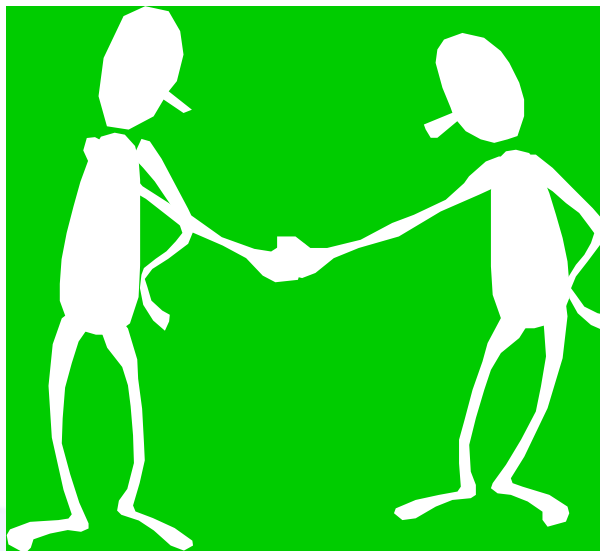
FEC, AACR, FAC, ASCO, anti-PDL1, anti-PD1, CMF, SABCS, PD-1, PDL1, DXR, PK/PD, CEX, 5FU CDDP, Calvert AUC, ESMO, Chatelut AUC, CTC, TILs, population PK, EORTC, FOLFIRI, ctDNA, FOLFOX 7, CPA, DFS, CALGB, DDFS, OS, TTP, NCI, CYP P450, JCO, JNCI, HER2, PI3K, mTOR, Phase 0, ECCO, ib and ab, Unicancer, EORTC, SWOG, CALGB, etc.

Charlson, CIRSG, CGA, AD, MCI, MNA, GDS, MMS, ADL, IADL, GFI, CMR2, JAGS, EUGMS, G8, CARG, Oncodage, VES-13, TRFs, JGO, NIA, SoFOG, Walter's score, Lee's score, CRASH, etc.





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FEC, FAC, SoFOG, ADL, IADL, CMF, SABCS, DXR, PK/PD, CEX, G8, EORTC, 5FU CDDP, MCI, Calvert and Chatelut AUC, CARG, GDS, population PK, AD, FOLFIRI, MMS, FOLFOX, CPA, CRASH, SWOG, DFS, OS, TTP, NCI, GERICO, TILs, CARG, anti-PDL1, anti-PD1, EORTC TFE, JCO, JNCI, Charlson, JGO, CIRSG, PD-1, PDL-1, ctDNA, EGS, EGA, MNA, GFI, Unicancer, Lee's score, JAGS, etc.

**To be practice changing,
let us be practice sharing!**

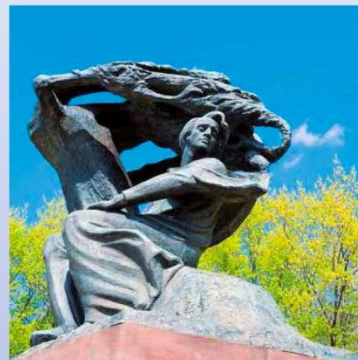
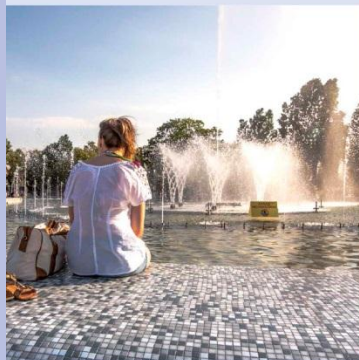
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