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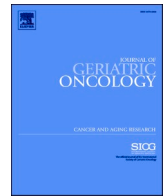
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Validation of the 70-gene signature test (MammaPrint) to identify patients with breast cancer aged ≥ 70 years with ultralow risk of distant recurrence: A population-based cohort study.

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ABSTRACT

Introduction: When risk estimation in older patients with hormone receptor positive breast cancer (HR + BC) is based on the same factors as in younger patients, age-related factors regarding recurrence risk and other-cause mortality are not considered. Genomic risk assessment could help identify patients with ultralow risk BC who can forgo adjuvant treatment. However, assessment tools should be validated specifically for older patients. This study aims to determine whether the 70-gene signature test (MammaPrint) can identify patients with HR + BC aged ≥ 70 years with ultralow risk for distant recurrence.

Materials and Methods: Inclusion criteria: ≥ 70 years; invasive HR + BC; T1-2N0-3M0. Exclusion criteria: HER2 + BC; neoadjuvant therapy. MammaPrint assays were performed following standardized protocols. Clinical risk was determined with St. Gallen risk classification.

Primary endpoint was 10-year cumulative incidence rate of distant recurrence in relation to genomic risk. Subdistribution hazard ratios (sHR) were estimated from Fine and Gray analyses. Multivariate analyses were adjusted for adjuvant endocrine therapy and clinical risk.

Results: This study included 418 patients, median age 78 years (interquartile range [IQR] 73–83). Sixty percent of patients were treated with endocrine therapy. MammaPrint classified 50 patients as MammaPrint-ultralow, 224 patients as MammaPrint-low, and 144 patients as MammaPrint-high risk. Regarding clinical risk, 50 patients were classified low, 237 intermediate, and 131 high. Discordance was observed between clinical and genomic risk in 14 MammaPrint-ultralow risk patients who were high clinical risk, and 84 patients who were MammaPrint-high risk, but low or intermediate clinical risk. Median follow-up was 9.2 years (IQR 7.9–10.5). The 10-year distant recurrence rate was 17% (95% confidence interval [CI] 11–23) in MammaPrint-high risk patients, 8% (4–12) in MammaPrint-low (HR 0.46; 95%CI 0.25–0.84), and 2% (0–6) in MammaPrint-ultralow risk patients (HR 0.11; 95%CI 0.02–0.81). After adjustment for clinical risk and endocrine therapy, MammaPrint-high risk patients still had significantly higher 10-year distant recurrence rate than MammaPrint-low (sHR 0.49; 95%CI 0.26–0.90) and MammaPrint-ultralow patients (sHR 0.12; 95%CI 0.02–0.85). Of the 14 MammaPrint-ultralow, high clinical risk patients none developed a distant recurrence.

Discussion: These data add to the evidence validating MammaPrint's ultralow risk threshold. Even in high clinical risk patients, MammaPrint-ultralow risk patients remained recurrence-free ten years after diagnosis. These findings justify future studies into using MammaPrint to individualize adjuvant treatment in older patients.

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1. Background

As the general population ages, breast cancer is increasingly becoming a disease of older women. A third of all patients diagnosed with breast cancer are aged ≥ 70 years, and in this growing population two specific age-related issues arise [1].

Firstly, with higher age, the proportion of hormone receptor positive (HR+) tumors increases, and these tumors are characterized by late recurrences. Two-thirds of distant recurrences present after five years, and the recurrence risk accumulates until 20 years after diagnosis [2,3]. However, in older patients, the recurrence risk is inversely correlated to their age and the competing risk of other-cause mortality [4]. Secondly, older patients are usually more frail than younger patients, may experience more adverse events of cancer treatment, and are at higher risk of hospitalization and long-term loss of quality of life [5,6].

Nevertheless, most older women with breast cancer are treated according to standard treatment guidelines [7]. Age-specific factors are often not taken into account, which may lead to significant overtreatment in this population [8]. Thus, new tools are needed, that accurately estimate recurrence risk in older patients with breast cancer.

The 70-gene signature test (MammaPrint, MP) is a genomic risk profile based on microarray gene expression. Previous studies showed that MammaPrint may be used to de-escalate the use of chemotherapy and endocrine therapy (ET) in genomic low and ultralow risk patients, respectively [9–11]. However, these trials did not routinely include patients aged ≥ 70 years. This study aims to determine if MammaPrint can be used to accurately estimate recurrence risk within the older population, where breast cancer is increasingly common.

2. Methods

Details on the FOCUS cohort (Female breast cancer in the elderly: Optimizing Clinical guidelines USing clinic-pathological and molecular data) have been described previously [12]. Briefly, it is a retrospective population-based observational cohort, which included all consecutive women aged ≥ 65 years and diagnosed with breast cancer between 1997 and 2004 in the West region of the Comprehensive Cancer Center of the Netherlands. The FOCUS cohort was approved by the scientific committee of the Netherlands Comprehensive Cancer Registry, waiving the need for informed consent because all data has been anonymized.

Data on patient, tumor and treatment characteristics, adverse events, recurrences, and death were recorded from medical charts. Tumor samples were collected from biopsies and excised material from surgery. Sections were formalin-fixed paraffin-embedded (FFPE) and stored in the research laboratory of the department of Pathology, Leiden University Medical Center.

A subset of patients from this cohort was analyzed to examine the prognostic ability of MammaPrint in older women with HR+ breast cancer.

Inclusion criteria for this analysis were: aged ≥ 70 years; invasive breast cancer; T1-2N0-3M0; any histological tumor grade. Exclusion criteria were: HR negative; human epidermal growth factor receptor 2 positive (HER2+); neoadjuvant therapy. Tumor specimens had to be available for genomic profiling.

FFPE tumor samples of eligible patients were analyzed according to standardized protocols and blinded to clinical characteristics. Samples were categorized as MP-ultralow risk (MammaPrint Index [MPI] ≥ 0.355), MP-low risk ($0 < \text{MPI} < 0.355$), or MP-high risk ($\text{MPI} \leq 0$) of developing distant recurrences. These thresholds have been previously developed and validated [9,10].

Determination of patients' clinical risk was based on the St. Gallen risk classification [13]. Briefly, patients were low risk if they had T1a-

bN0 grade 1–2, or T1cN0 grade 1 disease. Patients were intermediate risk with T1cN0 grade 2 disease, T2N0, T1N1, or grade 3 disease, and high risk with T2N1 or N2 disease (Supplementary Fig. S1).

The primary endpoint was 10-year cumulative incidence rate of distant recurrences (DR). Secondary endpoints were 10-year overall mortality rate, defined as death of any cause, and multivariate analyses adjusted for clinical risk, and use of adjuvant ET.

2.1. Statistical Analyses

For comparison of baseline characteristics between risk groups, Fisher's exact tests were used. Cumulative incidences of DR were estimated using competing risk survival analyses, in which DR were the event of interest, and death before recurrence was considered a competing event. The association between genomic risk and DR rate was assessed by performing univariate and multivariate Fine and Gray competing risk regression analyses, and the effects were expressed as subdistribution hazard ratios (sHR) with corresponding 95% confidence intervals (CI) [14]. The Fine and Gray analysis is a proportional hazards model that is analogous to the Cox proportional hazard model, except that it models a hazard function from a cumulative incidence function instead of Kaplan-Meier survival estimates.

Overall mortality was estimated from Kaplan-Meier survival analyses, and *P*-values were derived from log-rank tests. Hazard ratios (HRs) and corresponding 95% CI were estimated from univariate and multivariate Cox regression models. Two models were used for multivariate analyses; model 1 was adjusted for clinical risk, and model 2 was also adjusted for HR status and use of adjuvant ET. *P*-values less than 0.05 were considered statistically significant. Analyses were performed using SPSS version 24.0 and STATA/SE version 16.

3. Results

Between 1997 and 2004, 2095 women aged ≥ 65 years were diagnosed with any stage breast cancer in the West region of the Comprehensive Cancer Center of the Netherlands and were included in the FOCUS cohort. Of those patients, 1195 were excluded from this study because they were younger than 70 years, had T3 or T4 tumors, had metastatic disease at diagnosis, had HR- or HER2+ tumors, or had received neoadjuvant therapy. Of the 900 eligible patients, 482 did not have sufficient tumor material for genomic testing, and thus the 418 remaining patients were included in this study (Fig. 1). No significant differences were observed in age, HR expression, and adjuvant treatment strategy between the 418 included patients and the 482 excluded but eligible patients. Excluded patients did have significantly smaller tumors, lower histological grade, less lymph node involvement, and more often did not undergo surgery than included patients (Supplementary Table S1). Specifically, the smaller tumor size and less extensive surgery may explain why these patients did not have sufficient tumor material for genomic testing.

Baseline characteristics of the included patients are described in Table 1. Median age was 78 years (interquartile range [IQR] 73–83). Local treatment was a mastectomy in 272 patients (65%), breast conserving surgery (BCS) with radiotherapy in 99 patients (24%) and BCS without radiotherapy in 32 (8%). Fifteen patients (3%) did not undergo any surgery. Most patients ($N = 252$; 60%) were treated with adjuvant ET, only 22 patients (5%) received adjuvant chemotherapy, and 164 patients (39%) did not receive any systemic treatment. Approximately 39% of patients aged 70–75 years ($N = 58/149$) had screening-detected cancers. National guidelines in the Netherlands discourage routine breast cancer screening in women aged ≥ 76 years [15]. Median follow-up was 9.2 years (IQR 7.9–10.5).

MammaPrint classified 144 patients (34%) as MP-high risk, 224 patients (54%) as MP-low risk, and 50 patients (12%) as MP-ultralow risk. Patients with MP-ultralow risk tumors were less often treated with adjuvant ET than patients with MP-low and MP-high risk tumors (52% vs 54% vs 72%, respectively). The distribution of MammaPrint risk categories was similar in screening-detected versus symptom-detected tumors and also to what is reported in the literature (Table 1) [16].

Ten years after diagnosis, 17% (95%CI 11–23) of MP-high risk patients developed DR. The 10-year DR rate in MP-low risk patients was 8% (4–12; HR 0.46, 95%CI 0.25–0.84), and 2% (0–6; HR 0.11, 95%CI 0.02–0.81) in MP-ultralow risk patients (Table 2; Fig. 2A). These differences remained statistically significant in multivariate analyses adjusted for clinical risk and use of adjuvant ET (Table 2). Death without recurrence occurred at similar rates throughout the genomic risk groups. Overall mortality was significantly higher for MP-high risk patients (68%) than for MP-low and MP-ultralow risk patients (52% and 49%, respectively; $P = 0.001$; Fig. 3).

When applying the St. Gallen risk classification, 50 patients were deemed clinically low risk, 237 were clinically intermediate risk, and 131 were clinically high risk. Discordance was observed between clinical and genomic risk in 14 MP-ultralow risk patients who were deemed clinically high risk, and 84 patients who were MP-high risk, but clinically low or intermediate risk.

Among clinically high-risk patients, MP-high risk patients had a higher 10-year DR rate (22% [95%CI 12–32]) than MP-low risk (9% [2–16]; HR 0.39, 95%CI 0.14–1.10) or MP-ultralow risk patients (0%, HR 0; Fig. 2B). In clinically low and intermediate risk patients, the 10-year DR rate was 13% (95%CI 6–20) in MP-high risk patients, 8% (4–12; HR 0.57, 95%CI 0.26–1.28) in MP-low risk patients, and 3% (0–8; HR 0.20, 95%CI 0.03–1.55) in MP-ultralow risk patients (Supplementary Table S2; Fig. 2C).

4. Discussion

Genomic risk assessment tools like the 70-gene signature test can be used to accurately estimate DR risk in patients with breast cancer aged ≥ 70 years. MammaPrint-ultralow risk patients had excellent clinical

outcome up to ten years after diagnosis, despite 48% not receiving any systemic therapy. Significantly more MP-high risk patients developed DR, even though 72% of MP-high risk patients did receive adjuvant ET. Multivariate analyses adjusted for ET usage still showed significantly lower 10-year DR rates for MP-ultralow risk patients.

This is the first study examining a gene-expression profile in the older population. Our data show that genomic ultralow risk patients had excellent long-term outcomes even if clinically high risk. This may be explained by the discontinuation of routine screening at the age of 75. With increasing age, breast cancer is more often diagnosed at a higher clinical stage as women participate at reduced rates in routine screening [17]. Therefore, larger tumors and more elaborate regional spread may not be signs of aggressive tumor biology, but rather of late diagnoses. Thus, using only clinical parameters to determine recurrence risk for older patients may result in inaccurate risk estimation. Our data show that the 70-gene signature test provides more accurate risk assessment, and it seems reasonable to suggest that all older patients with ultralow risk breast cancer could forgo adjuvant endocrine therapy. This would apply to patients with a high risk of competing events, but also to those who are relatively fit, since the risk of developing a distant recurrence seems extremely low. Prospective randomized trials should examine whether MammaPrint can indeed be used to decide if these older patients can safely forgo adjuvant ET.

The use of other genetic profiling tools, such as the Breast Cancer Index, PAM50, Prosigna and Endopredict as prognostic or predictive tools in the older patient population has not been validated as of yet, either [18]. The prognostic ability of the Oncotype Dx has been validated in older patients with HR+ breast cancer [19]. However, it remains unresolved whether Oncotype Dx can be used to influence decisions regarding chemo- and endocrine therapy [20]. Our study presents an important addition to the evidence of using genetic profiling in this specific patient population.

Limitations of this study are the retrospective nature of the FOCUS cohort and the small sample size. Adjuvant treatment was decided by the treating physician, which may have introduced confounding by indication. Furthermore, due to adhering to Dutch treatment guidelines, the use of endocrine therapy was low when compared to other European

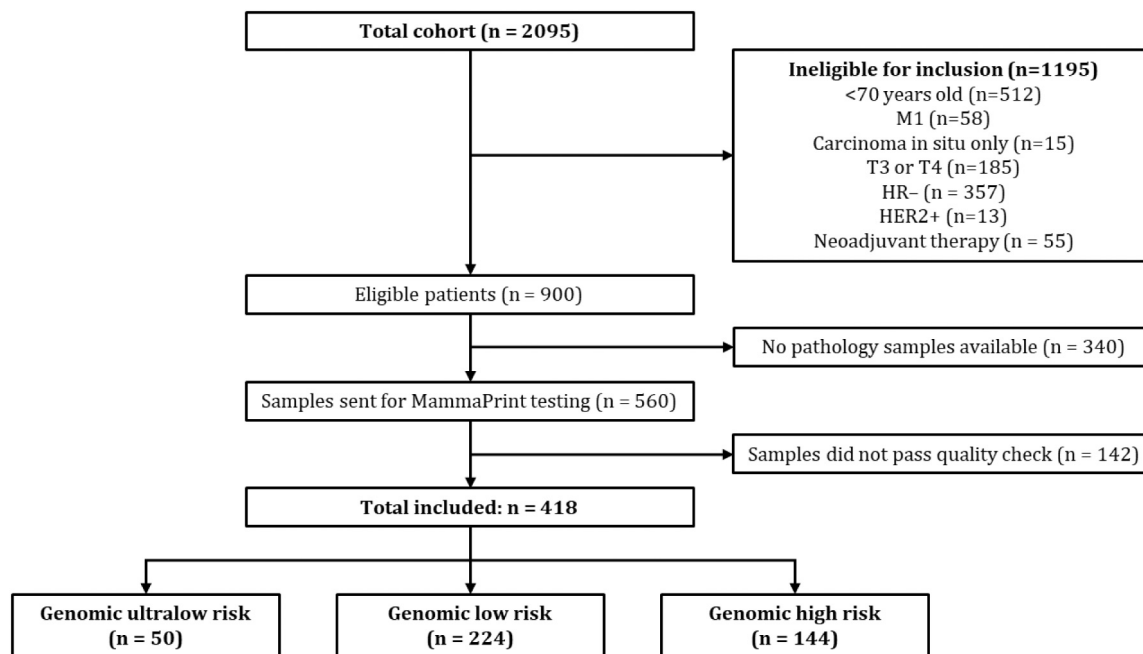


Fig. 1. CONSORT diagram.

HR- = hormone receptor negative. HER2+ = human epidermal growth factor receptor 2 positive.

countries [8]. Consequently, caution should be used when extrapolating these results to patient populations outside of the Netherlands, and these results should be confirmed in prospective trials.

Nonetheless, this study presents unique and valuable results for geriatric oncology practice, as it is the first analysis of the 70-gene signature test in patients aged ≥ 70 years. Another clear strength of this study is the use of real-life data from a population based cohort, which provides more accurate representation of patients in clinical practice than a trial population [21].

5. Conclusion

This analysis adds to the growing body of data demonstrating the validity of MammaPrint's ultralow risk threshold. Women with ultralow risk, regardless of clinical stage or grade, had an extremely low risk of recurrence. These data are especially relevant for clinicians working

with older patients, who may be frailer and more susceptible to adverse effects of treatment.

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The MammaPrint tests performed for these analyses were supplied by Agendia.

Author Contributions

IN, EB, NdG, and MK were involved in the conceptualization, data curation, formal analysis, validation, writing - original draft, writing - review & editing.

JS, LE, JW, JK, and JP were involved in the supervision, writing -

Table 1
Baseline characteristics of included patients from the FOCUS cohort.

	Included patients (N = 418)	Genomic high risk (N = 144)	Genomic low risk (N = 224)	Genomic ultralow (N = 50)	P value
Age, N (%), years					0.103
70–74	131 (31)	46 (32)	70 (31)	15 (30)	
75–79	117 (28)	46 (32)	57 (25)	14 (28)	
80–84	88 (21)	19 (13)	60 (27)	9 (18)	
85–89	57 (14)	22 (15)	28 (13)	7 (14)	
≥ 90	25 (6)	11 (8)	9 (4)	5 (10)	
Age, median (IQR), years	78 (73–83)	77 (73–84)	78 (73–83)	78 (73–84)	0.353
Year of diagnosis, N (%)					0.236
1997–2000	182 (44)	70 (49)	94 (42)	18 (36)	
2001–2004	236 (56)	74 (51)	130 (58)	32 (64)	
Cancer detection method, N (%)					0.094
Screen-detected	61 (15)	13 (9)	40 (18)	8 (16)	
Symptom-detected	252 (60)	89 (62)	130 (58)	33 (66)	
Unknown	105 (25)	42 (29)	54 (24)	9 (18)	
Tumor stage, N (%)					0.009
T1	181 (43)	53 (37)	111 (50)	17 (34)	
T2	236 (56)	90 (63)	113 (50)	33 (66)	
Unknown	1 (0)	1 (1)	0	0	
Nodal status, N (%)					0.006
N0/N0(i+)	238 (57)	65 (45)	140 (63)	33 (66)	
N1	133 (32)	62 (43)	56 (25)	15 (30)	
N2	26 (6)	9 (6)	16 (7)	1 (2)	
N3	12 (3)	5 (3)	7 (3)	0	
Unknown	9 (2)	4 (3)	5 (2)	1 (2)	
Histological tumor grade, N (%)					<0.001
1	55 (13)	5 (3)	39 (17)	11 (22)	
2	155 (37)	42 (29)	92 (41)	21 (42)	
3	85 (20)	53 (37)	31 (14)	1 (2)	
Unknown	123 (29)	44 (31)	62 (28)	17 (34)	
Histological subtype, N (%)					0.267
Ductal	326 (78)	120 (83)	170 (76)	36 (72)	
Lobular	45 (11)	10 (7)	29 (13)	6 (12)	
Other	47 (11)	14 (10)	25 (11)	8 (16)	
Hormone receptor status, N (%)					0.014
ER+/PR+	251 (60)	71 (49)	145 (65)	35 (70)	
ER+/PR-	98 (23)	45 (31)	46 (21)	7 (14)	
ER-/PR+	7 (2)	5 (3)	1 (0)	1 (2)	
Unknown	62 (15)	23 (16)	32 (14)	7 (14)	
Most extensive surgery, N (%)					0.222
None	15 (3)	6 (4)	5 (2)	4 (8)	
Breast conserving with RT	99 (24)	28 (19)	62 (28)	9 (18)	
Breast conserving without RT	32 (8)	13 (9)	16 (7)	3 (6)	
Mastectomy	272 (65)	97 (68)	141 (63)	34 (68)	
Adjuvant chemotherapy, N (%)					0.421
No	396 (95)	135 (94)	215 (96)	46 (92)	
Yes	22 (5)	9 (6)	9 (4)	4 (8)	
Adjuvant endocrine therapy, N (%)					0.001
No	166 (40)	40 (28)	102 (46)	24 (48)	
Yes	252 (60)	104 (72)	122 (54)	26 (52)	

P-values are derived from Fisher's exact tests and Mann-Whitney U tests. IQR = Interquartile Range. ER = Estrogen Receptor. PR = Progesterone Receptor. RT = Radiotherapy.

Table 2
Multivariate analysis of primary and secondary endpoints in all patients.

	Genomic low risk		Genomic ultralow risk	
	HR (95%CI) ^a	HR (95%CI) ^b	HR (95%CI) ^a	HR (95%CI) ^b
Any recurrence	0.46 (0.27–0.78)	0.49 (0.28–0.84)	0.17 (0.04–0.69)	0.17 (0.04–0.71)
Locoregional recurrence	0.48 (0.20–1.14)	0.57 (0.24–1.38)	0.24 (0.03–1.87)	0.30 (0.04–2.21)
Distant recurrence	0.49 (0.26–0.90)	0.49 (0.26–0.93)	0.12 (0.02–0.85)	0.12 (0.02–0.82)
Death without recurrence	0.87 (0.63–1.21)	0.84 (0.60–1.19)	1.10 (0.67–1.79)	1.05 (0.63–1.74)
Overall mortality	0.63 (0.48–0.84)	0.61 (0.46–0.82)	0.63 (0.40–0.99)	0.61 (0.39–0.97)

The genomic high-risk group is used as reference. Subdistribution hazard ratios (sHR) for recurrence rates and corresponding 95% confidence intervals (CI) are derived from Fine and Gray analyses. HR for mortality are derived from Cox regression models. Bold values represent statistical significance.

^a Model 1 is adjusted for clinical risk based on St. Gallen criteria.

^b Model 2 is adjusted for hormone receptor status and use of adjuvant endocrine therapy.

review & editing

AS, CS, and SE were involved in the conceptualization, methodology, writing - review & editing

The corresponding author (GJL) was involved in the conceptualization, data curation, formal analysis, funding acquisition, supervision, writing - original draft, writing - review & editing, and had final

responsibility to submit for publication.

Declaration of Competing Interest

MK is an employee of Agendia.

All remaining authors have declared no conflicts of interest.

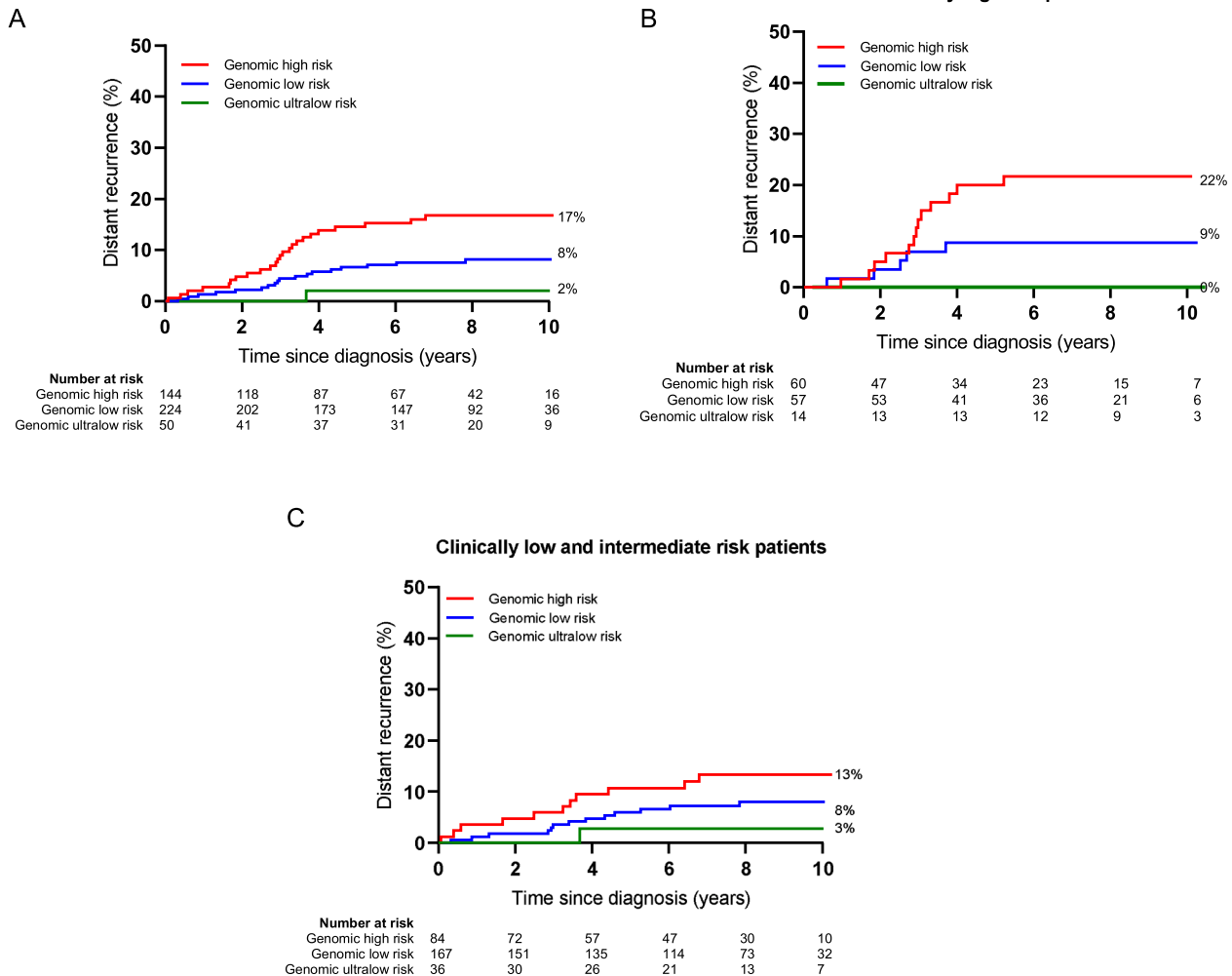


Fig. 2. Distant recurrences in all (A), clinically high (B), and low and intermediate risk (C) patients. Percentages represent the cumulative incidence rate of distant recurrences in each group.

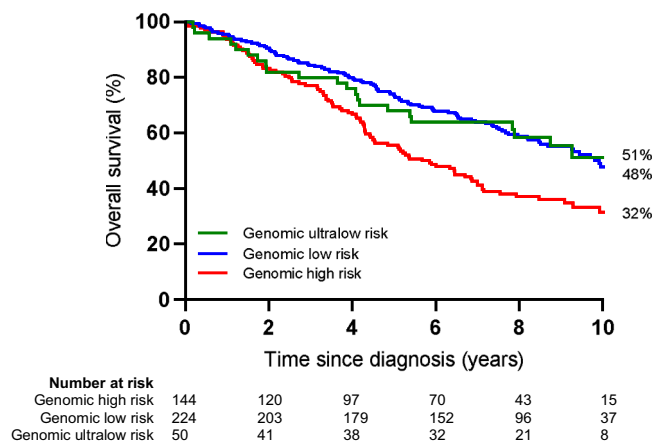


Fig. 3. Kaplan-Meier estimates of overall survival. Percentages represent the overall survival rate in each group.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jgo.2022.07.006>.

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