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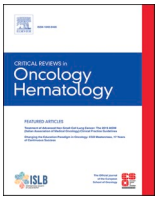

Gene expression signatures in older patients with breast cancer: A systematic review

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ABSTRACT

Background: Gene expression signatures have emerged to predict prognosis and guide the use of adjuvant therapy in patients with hormone receptor-positive breast cancer. The objective of this systematic review was to evaluate the prognostic and predictive value of commercially available gene expression signatures as a tool in adjuvant treatment decision-making in older patients with breast cancer.

Methods: PubMed, MEDLINE, Embase, Web of Science, Cochrane Library, and Emcare were reviewed for relevant articles published before December 2021. Eligible studies were randomised trials and cohort studies that externally validated commercially available gene expression signatures in patients aged 65 years and older, including studies that presented subanalyses of this age group. Data extraction and risk of bias assessment was performed independently by two investigators.

Results: Fifteen studies were included. Most studies investigated Oncotype DX, while results from other gene expression signatures were limited. Several studies underlined the prognostic performance of Oncotype DX and Prosigna Risk of Recurrence in older patients. Moreover, Oncotype DX was predictive for older patients with an intermediate-risk recurrence score; chemotherapy could be spared in both lymph node-positive and lymph node-negative disease.

Conclusions: Prognostic performance has been demonstrated in older patients for several gene expression signatures. However, additional validation in patients with high-risk tumours is needed before gene expression signatures can be implemented in clinical practice as a prediction tool for adjuvant chemotherapy decision-making in the older age group.

1. Introduction

The incidence of breast cancer increases with age, with more than half of all patients aged 65 years and older at the time of diagnosis (DeSantis et al., 2017). Ageing increases the exposure to age-related diseases, resulting in a heterogeneous older population with large differences in fitness and frailty (Piccirillo et al., 2008). Older patients are particularly susceptible to side effects associated with therapy. Therefore, accurate identification of patients with a high risk of recurrence and selecting the optimal therapy for each patient, whilst avoiding negligible treatment, is advocated.

Traditionally, guidelines for breast cancer treatment are based on classification systems, which consider tumour size, histological grade, human epidermal growth factor-2 receptors (HER2), oestrogen receptors (ER), progesterone receptors (PR), lymph node involvement, and young age. PREDICT and Adjuvant! Online are examples of online tools that predict prognosis and treatment benefit with these traditional clinicopathological parameters (Wishart et al., 2010; Ravdin et al., 2001). However, their ability to predict individual outcomes in a heterogeneous older population is limited and this is due to competing risks for mortality, depending on individual frailty and comorbidity (Wasif et al., 2019; Derks et al., 2018; de Glas et al., 2016a, 2014). The novel Prediction of Outcome, Risk of toxicity and quality of life in older patients TREaTed for breast cancer (PORTRET) tool compensates for this limitation by integrating comorbidity and geriatric predictors into the prediction model (van der Plas-Krijgsman et al., 2021).

Over the past decades, gene expression signatures have emerged to predict prognosis and guide the use of adjuvant therapy in patients with

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hormone receptor-positive disease (Andre et al., 2022). An important distinction has been made between prognostic and predictive gene expression signatures. A prognostic signature solely provides the prognosis of the patient in terms of tumour recurrence or survival, while predictive gene signatures have the capacity to predict the beneficial effect from therapies. Unfortunately, the use of gene expression signatures is expensive with a lack of criteria for selecting patients who would potentially benefit. As it is currently difficult for physicians to tailor treatment for the older population, the role of gene expression signatures might be of considerable importance. In older patients, competing mortality may influence the prognostic and predictive value of these tests. The aim of this systematic review was to evaluate the prognostic and predictive value of commercially available gene expression signatures as a tool in adjuvant treatment decision-making in older patients with breast cancer.

2. Materials and methods

On the 7th of December 2021, a literature search was conducted in the PubMed, MEDLINE, Embase, Web of Science, Cochrane Library, and Emcare databases. The search strategy included the following terms and its equivalents: "Breast Neoplasms", "Gene Expression Profiling", "Recurrence", "Treatment Outcome", and "Disease-Free Survival". The full search strategy is presented in detail in the Supplementary Appendix. Cross-referencing was performed to retrieve relevant articles that might have been missed. This systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines (Moher et al., 2009).

2.1. Study selection

Eligible studies were external validation studies of commercially available gene expression signatures that included patients with breast cancer and performed a (sub)analysis of patients of at least 65 years or older. Outcomes of interest were distant recurrences, breast cancer-specific mortality (BCSM), non-breast cancer-specific mortality (non-BCSM), breast cancer-specific survival (BCSS), relapse-free survival, disease-free survival, overall survival (OS) and response. The studies reviewed included randomised clinical trials, cohort studies, and case-control studies. Two investigators independently selected the studies by reading the title, abstract, and full text. Any disagreement was resolved by a third author.

2.2. Data extraction and risk of bias assessment

The following data were extracted independently: study characteristics (i.e., first author, journal, year of publication, inclusion period, study design, number of patients, median follow-up, statistical analysis, and adjustment for confounders), clinicopathological characteristics (i.e., age, definition of 'old' used, and type of breast cancer), type of gene expression signature, and clinical outcome.

Risk of bias was assessed by two investigators using the Quality in Prognostic Factor Studies (QUIPS) tool for prognostic studies (Riley et al., 2019). For prediction studies, the Cochrane Collaboration's tool was used for randomised controlled trials, and the Risk Of Bias In Non-randomised Studies – of Interventions-I (ROBINS-I) tool for cohort and registry studies (Supplemental Tables A–C) (Higgins et al., 2011; Sterne et al., 2016). Discrepancies in classification of study bias were resolved through consensus discussions between the investigators. Due to the study designs, high risk of bias, and heterogeneity of the included

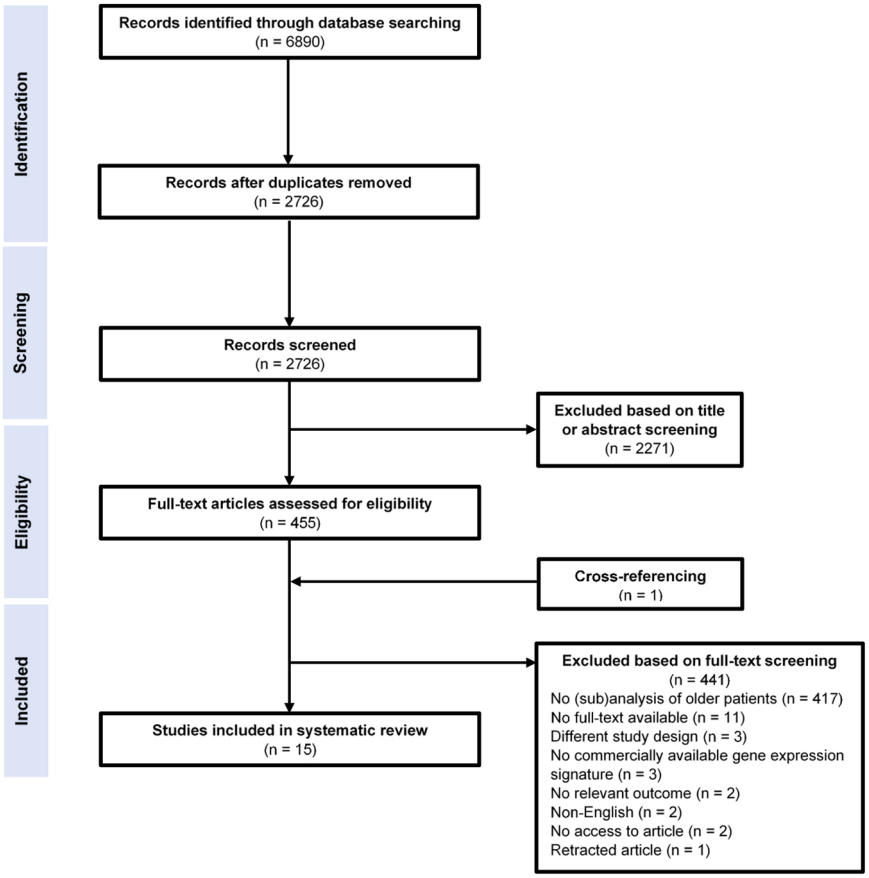

Fig. 1. Flowchart.

studies, a meta-analysis was not considered feasible.

3. Results

A total of 6.890 publications were identified, which resulted in 2.726 unique studies after removal of duplicates (Fig. 1). Of these, 2.287 were identified in PubMed, 0 in MEDLINE, 136 in Embase, 269 in Web of Science, 31 in the Cochrane Library, and 3 in Emcare. After title and abstract screening, full text of 455 studies was reviewed, of which 14 publications were eligible and included in this review. Cross-referencing identified another study, which resulted in a total of 15 included articles.

A description of the included studies is provided in Supplemental Table D. Ten studies were cohort studies and the others were (deducted from) prospective trials. Most studies investigated the prognostic and/or predictive feature of Oncotype DX. The two-gene expression ratio composed of the homeobox gene HOXB13 and the interleukin-17B receptor IL17BR (HOXB13:IL17BR), and the Prosigna Risk of Recurrence were both described once. There were no (sub)analyses of older patients of other commercially available gene expression signatures (e.g. Mammaprint and EndoPredict). The age cut-off used to define older patients varied in the included studies. In eight studies, the definition of older patients was 65 years of age and older, in one study 66 years of age and older, in one study 68.2 years and older and five studies used 70 as cut-off. Regarding the quality assessment, most of the included publications regarding the prognostic value were deemed to be at moderate risk of bias, while studies about the predictive value were mainly judged as high risk of bias (Supplemental Tables A–C).

3.1. Prognostic value of gene expression signatures in older patients with breast cancer

3.1.1. Lymph node-negative disease

Four studies evaluated the prognostic performance of Oncotype DX in older patients with hormone receptor-positive, lymph node-negative breast cancer and they were all assessed as moderate risk of bias (Table 1a and Supplemental Table A). All four studies were retrospective registry studies (Stemmer et al., 2019, 2017a; Wu et al., 2019; Zhou et al., 2020). Two studies reported on distant recurrences and two on BCSS. All four studies showed a positive correlation between the recurrence score (RS) and distant recurrences or BCSS in older patients (Stemmer et al., 2019, 2017a; Wu et al., 2019; Zhou et al., 2020). Using the traditional thresholds (i.e., < 18, 18–30, > 30), Oncotype DX accurately estimated 5-year recurrence rates in 322 patients of 70 years and older (Stemmer et al., 2017a). The association between the RS and 10-year distant recurrence rates was found in a study of 218 patients aged 70 years and older using the Trial Assigning Individualised Options for Treatment (TAILORx) thresholds (i.e., < 11, 11–25, >25) (Stemmer et al., 2019). Two retrospective registry studies using both the traditional and TAILORx thresholds, showed that the RS was significantly prognostic for 5-year BCSM in 8.524 and 18.456 patients aged 65 years and older, which retained in a competing-risk model (high-risk versus low-risk RS: Hazard Ratio (HR) 4.78, 95 % Confidence Interval (CI) 2.68–8.61, $p < 0.001$) and after propensity score matching for age, tumour grade and stage, PR status, race, surgery, chemotherapy, and radiotherapy (Wu et al., 2019; Zhou et al., 2020).

Table 1a
Studies investigating the prognostic value of Oncotype DX in older patients with hormone receptor-positive, lymph node-negative breast cancer.

Author	Year of publication	Multigene assay	Type of study	Age cut-off	Number of older patients	Results	Conclusion	Risk of bias
Stemmer et al., 2019	2019	21-gene RS (Oncotype DX)	Retrospective, from Clalit Health Services registry	≥ 70	218	**Log-rank test, Cox proportional hazards model:** 10-year distant recurrence for RS < 11: 3.0 %, 95 % CI 0.4–19.6; RS 11–25: 12.5 %, 95 %CI 7.0–21.7; RS > 25: 18.2 %, 95 %CI 9.0–35.0 (p = 0.042)	10-year distant recurrence rates between RS groups did differ	Moderate[a]
Stemmer et al., 2017a	2017	21-gene RS (Oncotype DX)	Retrospective, from Clalit Health Services registry	≥ 70	322	**Log-rank test, Cox proportional hazards model:** 5-year distant recurrence for RS < 18: 0.6 %, 95 % CI 0.1–3.9; RS18–30: 3.8%, 95 %CI 1.4–9.8, RS ≥ 31: 8.3 %, 95 %CI 2.8–23.7 (p = 0.003)	5-year distant recurrence rates significantly differed between RS risk-groups	Moderate[a]
Wu et al., 2019	2019	21-gene RS (Oncotype DX)	Retrospective, from SEER	≥ 65	18.456	**Multivariate Cox proportional hazards model**: 5-year BCSS before propensity score matching RS17–29 versus RS < 18: HR 1.87, 95 %CI 1.31–2.68, p = 0.001; RS > 30 versus RS < 18: HR 6.11, 95 %CI 4.09–9.13, p < 0.001. After propensity score matching RS17–29 versus RS < 18: HR 2.21, 95 %CI 1.27–3.84, p = 0.005, RS > 30 versus RS < 18: HR 8.02, 95 %CI 4.53–14.19, p < 0.001	RS was prognostic for 5-year BCSS, also after matching for age, race, radiotherapy, histology subtype, stage and chemotherapy	Moderate[a]
Zhou et al., 2020	2020	21-gene RS (Oncotype DX)	Retrospective, from SEER	≥ 65	8.524	**Multivariate Cox proportional hazards model:** BCSM for RS > 25 versus RS< 11: HR 1.56, 95 %CI 1.18–2.06, p = 0.002. **Fine and Gray competing-risks model:** BCSM RS > 25 versus RS < 11: sdHR 4.78, 95 %CI 2.68–8.61, p < 0.001. Comparable BCSM was found between patients who had a RS11–25 and a RS < 11 in both models	The RS was independently associated with BCSM	Moderate[a]

Abbreviations: RS – recurrence score; HR – hazard ratio; sdHR – subdistribution hazard ratio; CI – confidence interval; BCSS – breast cancer-specific survival; BCSM – breast cancer-specific mortality; SEER – Surveillance, Epidemiology, and End Results database.

[a] Using the Quality in Prognostic Factor Studies (QUIPS) tool.

3.1.2. Lymph node-positive disease

The prognostic value of three different gene expression models (HOXB13:IL17BR, Prosigna Risk of Recurrence, and Oncotype DX) was studied in older patients with lymph node-positive tumours or in studies with a combination of lymph node-positive and negative tumours (Table 1b). Two of these studies were retrospective analyses with tumour tissues obtained in the context of randomised clinical trials. The other two were retrospective cohort studies based on registry data. One study (Goetz et al., 2006) had a high risk of bias and the other three had a moderate risk of bias (Table 1b and Supplemental Table A). In a retrospective analysis of a randomised controlled trial with more than 600 older patients, Oncotype DX RS and Prosigna Risk of Recurrence were both associated with distant recurrences, but not after adjustment for age, nodal status, grade, tumour size and treatment received (Sestak et al., 2016). Another study of patients aged 70 years and older with lymph node-positive breast cancer showed no statistically significant association between Oncotype DX RS and 5-year distant recurrences (Stemmer et al., 2017b). However, the sample size was small (N = 136) with very few events. Kizy et al. showed a statistically significantly worse OS in more than 11.400 patients aged 70 years and older with a high-risk Oncotype DX RS when compared to patients with a low-risk RS (HR 1.47, 95 % CI 1.15–1.90, p = 0.003) (Kizy et al., 2019). In this study, 82 % of patients had lymph node-negative disease. HOXB13:IL17BR was not able to give an accurate prognosis on relapse-free survival, disease-free survival and OS (Goetz et al., 2006).

Table 1b
Studies investigating the prognostic value of HOXB13:IL17BR, Prosigna, and Oncotype DX in older patients with hormone receptor-positive, lymph node-positive or mixed lymph node-status breast cancer.

Author	Year of publication	Multigene assay	Type of study	Age cut-off	Number of older patients	Lymph node-status	Results	Conclusion	Risk of bias
Goetz et al., 2006	2006	HOXB13:IL17BR	Retrospective analysis of a randomised trial	≥ 65	96	N +	**Log-rank test and Cox proportional hazards model:** Relapse-free survival, disease-free survival and OS do not differ with respect to the HOXB13/IL-17BR expression ratio; p = 0.217, p = 0.148 and p = 0.148, respectively	No prognostic effect of HOXB13/IL-17B ratio on relapse-free survival, disease-free survival and OS	High[a]
Kizy et al., 2019	2019	21-gene RS (Oncotype DX)	Retrospective, from SEER	≥ 70	11.426	Mixed, 82 % N0, 18 % N +	**Cox proportional hazards model:** OS in RS 11–25 versus RS < 11: HR0.97, 95 %CI 0.77–1.23, p = 0.81. OS in RS > 25 versus RS < 11: HR1.47, 95 %CI 1.15–1.90, p = 0.003	Patients with a high-risk RS have a statistically significantly worse OS, compared to patients in the low-risk RS group	Moderate[a]
Sestak et al., 2016	2016	21-gene RS (Oncotype DX) and Prosigna Risk of Recurrence score (ROR)	Retrospective analysis of a randomised trial	> 68.2	626	Mixed	**Cox proportional hazards model, univariate:** distant recurrence by Risk of Recurrence and RS in patients aged > 68.2 years: HR 1.83, 95 %CI 1.28–2.60 and HR 1.38, 95 %CI 1.11–1.73, respectively. **Cox proportional hazards model, bivariate:** distant recurrence by Risk of Recurrence and RS in patients aged > 68.2 when corrected for the Clinical Treatment score, including nodal status, grade, tumour size, age, and treatment received: HR 1.33, 95 %CI 0.92–1.93 and HR 1.26, 95 %CI 1.00–1.58, respectively	ROR and RS were in a univariate model associated with distant recurrence, but not after adjustment for age, nodal status, grade, tumour size and treatment received	Moderate[a]
Stemmer et al., 2017b	2017	21-gene RS (Oncotype DX)	Retrospective analysis of prospectively designed registry	≥ 70	136	N +	**Log-rank test, Cox proportional hazards model:** 5-year distant recurrence: RS < 18: 5.3 %, 95 %CI 2.0–13.6, RS18–30: 11.3 %, 95 %CI 4.9–25.1, RS ≥ 31: 7.1 %, 95 %CI 1.0–40.9 (p = 0.458)	5-year distant recurrence rates between RS risk-groups did not differ	Moderate[a]

Abbreviations: N – nodal status; RS – recurrence score; ROR – Risk of Recurrence; HR – hazard ratio; CI – confidence interval; OS – overall survival; SEER – Surveillance, Epidemiology, and End Results database.

[a] Using the Quality in Prognostic Factor Studies (QUIPS) tool.

3.2. Predictive value of gene expression signatures in older patients with breast cancer

3.2.1. Adjuvant chemotherapy in lymph node-negative disease

The predictive ability of Oncotype DX in older patients with lymph node-negative disease was addressed in four studies (Zhou et al., 2020; Cheng et al., 2020; Choi et al., 2020; Sparano et al., 2018, 2019). Two publications by Sparano et al. were based on the same prospective randomised controlled trial, and three studies were based on retrospective analyses of registry data (Table 2a). In the prospective trial, with a moderate risk of bias, patients with hormone receptor-positive, HER2-negative, lymph node-negative breast cancer who had an

Table 2a
Studies investigating the predictive value of response to chemotherapy of Oncotype DX in older patients with hormone receptor-positive, lymph node-negative breast cancer.

Author	Year of publication	Type of study	Age cut-off	Number of older patients	Results	Conclusion	Risk of bias
Sparano et al., 2018, 2019	2018, 2019	Randomised controlled trial	> 65	950	**Cox proportional hazards model:** Distant recurrence-free interval for endocrine therapy alone versus chemoendocrine therapy, RS11–15: HR0.73, 95 %CI 0.15–3.44; RS16–20: HR0.93, 95 %CI 0.29–2.94; RS21–25: HR1.07, 95 %CI 0.40–2.86. Relapse free interval for endocrine therapy alone versus chemoendocrine therapy with RS11–15: HR0.60, 95 %CI 0.16–2.22; RS16–20: HR0.91, 95 %CI 0.37–2.21; RS21–25: HR1.02, 95 %CI 0.39–2.70. Invasive disease-free survival for endocrine therapy alone versus chemoendocrine therapy with RS11–15: HR1.36, 95 %CI 0.78–2.39; RS16–20: HR0.97, 95 %CI 0.58–1.62; RS21–25: HR1.07, 95 %CI 0.59–1.95. **Cox proportional hazards model (n = 628):** no statistically significant difference in 9-year distant recurrence-free interval and invasive disease-free survival between patients who had a RS16–25 treated with endocrine therapy and patients treated with additional chemotherapy	In patients with an intermediate-risk RS, endocrine therapy alone was not inferior to chemotherapy in addition to endocrine therapy regarding distant recurrence-free interval, invasive disease-free survival, and relapse free interval	Moderate[a]
Cheng et al., 2020	2020	Retrospective, from SEER	≥ 66	12.634	**Log-rank test:** better OS in patients aged 66–80 years who received chemotherapy compared to those not receiving chemotherapy/unknown who had a RS11–25 (p = 0.031), a RS26–100 (p = 0.042), and a RS0–10 (p = 0.870). Patients > 80 years with a RS0–10 had a worse OS when receiving chemotherapy than those not or unknown (p = 0.002), which was also seen in patients with a RS11–25 and a RS26–100, but not statistically significant (p = 0.261, p = 0.071, respectively)	Patients aged 66–80 years who had an intermediate- or high-risk RS receiving chemotherapy had a better OS than patients not receiving chemotherapy or unknown. In patients aged > 80 years who had a low-risk RS, OS was worse for patients receiving chemotherapy compared to those not or unknown, which was also seen for intermediate- and high-risk RS groups, but not significant	High[b]
Choi et al., 2020	2020	Retrospective, from SEER	> 65	2.609	**Log-rank test and Cox proportional hazards model after propensity score matching based on year of diagnosis, age at diagnosis, race, T category, tumour grade, hormone receptor-status, and use of radiotherapy:** BCSM in patients with RS11–25 receiving chemotherapy versus no chemotherapy: HR1.31, 95 %CI 0.64–2.65, p = 0.459	Patients with an intermediate-risk RS receiving chemotherapy did not have a decrease in BCSM compared to patients not receiving chemotherapy	High[b]
Zhou et al., 2020	2020	Retrospective, from SEER	≥ 65	8.524	**Multivariate Cox proportional hazards model:** BCSM in patients not receiving chemotherapy versus patients receiving chemotherapy who had a RS11–25: HR1.03, 95 %CI 0.69–1.53, p = 0.90; RS> 25: HR0.76, 95 %CI 0.56–1.05, p = 0.099. **Fine and Gray competing-risks model:** BCSM in patients not receiving chemotherapy versus patients receiving chemotherapy with a RS11–25: sdHR1.45, 95 %CI 0.68–3.08, p = 0.335; RS> 25: sdHR1.04, 95 %CI 0.67–1.62, p = 0.864	Patients who had an intermediate- or high-risk RS did not have a reduced BCSM when treated with chemotherapy	High[b]

Abbreviations: RS – recurrence score; HR – hazard ratio; sdHR – subdistribution hazard ratio; CI – confidence interval; OS – overall survival; BCSM – breast cancer-specific mortality; SEER – Surveillance, Epidemiology, and End Results database.

[a] Using the Cochrane Collaboration's tool.

[b] Using the Risk Of Bias In Non-randomised Studies – of Interventions-I (ROBINS-I) tool.

intermediate-risk RS according to the TAILORx thresholds were randomly assigned to receive either endocrine therapy alone or chemotherapy in addition to endocrine therapy (Sparano et al., 2018, 2019). The trial demonstrated no benefit from the addition of chemotherapy in patients aged 65–75 years of age with an intermediate-risk RS in terms of distant recurrence-free interval, invasive disease-free survival, and relapse free interval. One of the retrospective studies, with a high risk of bias, showed that patients aged 66–80 years had a better OS when treated with chemotherapy compared to those who did not receive chemotherapy, for both the intermediate-risk RS ($p = 0.031$) and high-risk RS groups ($p = 0.042$), but not in patients over 80 years of age (Cheng et al., 2020). The other two retrospective studies, with a high risk of bias, showed no beneficial effect of chemotherapy on BCSM in patients who had an intermediate- and high-risk RS, when using the TAILORx thresholds (Zhou et al., 2020; Choi et al., 2020).

3.2.2. *Adjuvant chemotherapy in lymph node-positive disease*

Three studies investigated the predictive value of Oncotype DX in patients with lymph node-positive disease. One study was a randomised controlled trial and two studies were retrospective studies based on registry data (Table 2b). In the prospective RxPONDER trial (Clinical Trial RX for Positive Node, Endocrine Responsive Breast Cancer), Kalinsky and co-workers investigated the effect of chemotherapy on invasive disease-free survival in patients of at least 18 years of age with hormone receptor-positive, HER2-negative breast cancer with one to three positive lymph nodes and a RS of ≤ 25 (Kalinsky et al., 2021). Patients were randomly assigned to receive either chemotherapy in addition to endocrine therapy or endocrine therapy alone. A subgroup analysis of approximately 1.100 patients aged 65 years and older who had either a low-risk or intermediate-risk RS, showed no statistically significant difference in 5-year invasive disease-free survival between the two treatment strategies (HR 1.05, 95 % CI 0.75–1.47). The two retrospective studies, with a high risk of bias, included patients with a high-risk RS who had either lymph node-negative or lymph node-positive disease (Kizy et al., 2019; Gulbahce et al., 2021). One study showed that patients aged 65 years and older receiving adjuvant chemotherapy had a decrease in BCSM compared to patients not receiving chemotherapy (HR 0.63, 95 %CI 0.60–0.67, $p < 0.001$) (Gulbahce et al., 2021). The number of older patients with lymph node-negative disease was not mentioned, but 70 % of the whole cohort (including the younger patients) had negative lymph nodes. The other retrospective study by Kizy et al. found no BCSS and OS advantage of chemotherapy for patients aged 70 years and older. Eighteen percent of patients had lymph node-positive disease (Kizy et al., 2019).

3.3. *Adjuvant endocrine therapy in lymph node-negative disease*

One retrospective registry study, with high risk of bias, assessed the predictive performance of Oncotype DX for the response to adjuvant endocrine therapy in patients with hormone receptor-positive, HER2-negative, ≤ 3 cm in size, lymph node-negative breast cancer (Weiser et al., 2021). Around 8.800 patients of 70 years and older were included, all with a low-risk RS or intermediate-risk RS according to the TAILORx thresholds. Upon multivariate analysis, patients aged 70 years and older receiving endocrine therapy demonstrated a 5-year OS advantage for both the low-risk RS (HR 2.14, 95 % CI 1.41–3.24, $p < 0.001$) and intermediate-risk RS groups (HR 1.71, 95 % CI 1.20–2.44, $p = 0.001$).

Table 2b
Studies investigating the predictive value of response to chemotherapy of Oncotype DX in older patients with hormone receptor-positive, lymph node-positive or mixed lymph node-status breast cancer.

Author	Year of publication	Type of study	Age cut-off	Number of older patients	Lymph node-status	Results	Conclusion	Risk of bias
Kalinsky et al., 2021	2021	Randomised controlled trial	> 65	1.180	N1	**Cox proportional hazards model:** 5-year invasive disease-free survival in patients with a RS ≤ 25 treated with endocrine therapy alone versus chemoendocrine therapy: HR1.05, 95 %CI 0.75–1.47	Patients who had a RS ≤ 25 receiving chemotherapy did not have an increased 5-year invasive disease-free survival compared to patients who did not receive chemotherapy	Low[a]
Gulbahce et al., 2021	2021	Retrospective, from SEER	≥ 65	236.355	Mixed	**Cox proportional hazards model:** BCSM in patients with a RS > 25 receiving chemotherapy versus no chemotherapy: HR0.63, 95 %CI 0.60–0.67, p < 0.001. Stratification for race: Non-Hispanic White: HR0.65, 95 %CI 0.61–0.70, Asian/Pacific Islander: HR0.71, 95 %CI 0.42–0.73, Hispanic: HR0.56, 95 %CI 0.45–0.69, American Indian/Alaskan Native: HR0.83, 95 %CI 0.32–2.16	Patients who had a high-risk RS receiving chemotherapy had a lower hazard of BCSM compared to a similar group without chemotherapy	High[b]
Kizy et al., 2019	2019	Retrospective, from SEER	≥ 70	11.426	Mixed, 82 % N0, 18 % N +	**Kaplan-Meier:** BCSS for chemotherapy versus no chemotherapy in patients who had a RS > 25 did not differ (no numbers available). **Kaplan-Meier:** OS for chemotherapy versus no chemotherapy in patients who had a RS > 25 did not differ. **Cox proportional hazards model:** overall mortality for chemotherapy versus no chemotherapy in patients who had a RS > 25: HR1.35, 95 %CI 0.94–1.95, p = 0.11	Chemotherapy did not improve BCSS and OS in older patients who had a high-risk RS	High[b]

Abbreviations: N – nodal status; RS – recurrence score; HR – hazard ratio; CI – confidence interval; OS – overall survival; BCSS – breast cancer-specific survival; BCSM – breast cancer-specific mortality; SEER – Surveillance, Epidemiology, and End Results database.

[a] Using the Cochrane Collaboration's tool.

[b] Using the Risk Of Bias In Non-randomised Studies – of Interventions-I (ROBINS-I) tool.

3.4. Adjuvant radiotherapy in lymph node-negative disease

One retrospective registry study of Wu et al., with high risk of bias, investigated whether Oncotype DX could identify risk-groups for whom postoperative radiotherapy could be beneficial in patients aged ≥ 65 years with ER-positive, tumour size ≤ 5 cm (T1-T2), lymph node-negative breast cancer (Wu et al., 2019). This study showed that in around 18.000 older patients, those with an intermediate-risk RS who had been treated with breast conserving surgery followed by radiotherapy had a better BCSS when compared to patients who had not been treated with postoperative radiotherapy before (HR 0.47, 95 %CI 0.28–0.77, p = 0.003) and after propensity score matching (HR 0.39, 95 %CI 0.18–0.85, p = 0.017). This was not the case in patients with low-risk and high-risk RS tumours (Wu et al., 2019). The use of endocrine therapy was unknown for all patients.

4. Discussion

We found, in accordance with results from younger patients, adequate evidence of the clinical validity of the prognostic performance of Oncotype DX RS and Prosigna Risk of Recurrence in older patients with hormone receptor-positive, lymph node-negative and lymph node-positive breast cancer. In addition, studies on the predictive performance of gene expression signatures were scarce in the older age group and they have only been prospectively validated for the Oncotype DX RS.

Gene expression signatures are particularly useful if they have the capacity to predict when an older patient would benefit from therapy, while avoiding treatment that has negligible benefit with high risk of toxicity. In the current review, no beneficial effect of adjuvant chemotherapy was observed in older patients with negative lymph nodes who had an intermediate-risk RS with regard to invasive disease-free survival, distant recurrence-free interval and/or relapse free interval (Sparano et al., 2018, 2019). Another included trial by Kalinsky and co-workers found no benefit from adjuvant chemotherapy in older patients with lymph node-positive disease and a low- or intermediate-risk RS (Kalinsky et al., 2021). In contrast, a benefit from chemotherapy was observed in younger patients (Sparano et al., 2018, 2019; Kalinsky et al., 2021; Piccart et al., 2021). Whether the findings of these trials underline the importance of tumour type, decreasing benefit of chemotherapy in older patients or indicate malperformance of gene expression signatures in the older population is currently unclear (Peto et al., 2012; (EBCTCG) EBCTCG, 2005; Battisti et al., 2022).

There is a lack of evidence of chemotherapy benefit in high-risk tumours as defined by gene expression signatures in older patients. Two previous trials showed additional benefit from the addition of adjuvant chemotherapy in high-risk, ER-positive tumours with both negative and positive lymph nodes (Paik et al., 2006; Albain et al., 2010). In these trials, around thirty percent of the patients were older (i.e. ≥ 60 years of age), but unfortunately the authors did not perform a subanalysis of the older age group. Chemotherapy benefit was assessed in some retrospective studies of older patients with high-risk tumours (Zhou et al., 2020; Kizy et al., 2019; Cheng et al., 2020; Gulbahce et al., 2021). However, retrospective studies do not randomise patients to treatment and are therefore highly susceptible to confounding by indication. The results of these studies cannot be used for solid conclusions about the predictive performance of gene expression signatures. The only results of chemotherapy benefit specifically in older patients with high-risk tumours as determined by gene expression signatures, may be deducted from a simulated model designed by Chandler et al. (2020). They designed a model of patients aged 65–89 years with early-stage, ER-positive, HER2-negative lymph node-negative breast cancer. The aim was to estimate benefits and harms of chemotherapy in addition to endocrine versus endocrine therapy alone by age and comorbidity level in patients with an Oncotype DX RS of 26 or greater. The authors showed that, breast cancer mortality rates decreased with the addition of chemotherapy to endocrine therapy, regardless of age or comorbidity. However, the results should be interpreted with caution because the authors did not include real patients. Currently, the ASTER 70s phase III trial (EudraCT 2011-004744-22) investigates the effect of the addition of adjuvant chemotherapy to endocrine therapy on OS in patients aged 70 years and older with a high genomic grade, ER-positive, lymph node-positive or lymph node-negative breast cancer, and incorporates competing risks for mortality and geriatric characteristics (Brain et al., 2012). With a median follow-up of 5.8 years, the authors showed no significant OS benefit for older patients at high genomic risk from the addition of chemotherapy to endocrine therapy (Brain et al., 2022).

It is essential to consider the impact of competing risk of mortality when tailoring treatment for older patients. Most studies in the current review investigated BCSS and recurrences, which may not be the most relevant endpoints in older individuals with limited life expectancy. Therefore, it is important to incorporate comorbidity and other age-associated characteristics into prediction tools as they are highly predictive of other cause mortality (Derks et al., 2018, 2019). Specific statistical methods could be used to adequately address the role of competing mortality, such as the Cumulative Incidence Competing Risks Method or the Fine and Gray model (de Glas et al., 2016b). Unfortunately, only one of the included studies took competing risks into account, whilst none of the studies adjusted for other geriatric characteristics (Zhou et al., 2020).

Another important consideration in older patients is the increased risk of chemotherapy toxicity and treatment-related mortality when compared to younger patients, due to comorbidities and reduced organ function (Muss et al., 2007; Colleoni et al., 1999). This is important, because toxicity could interfere with important treatment outcomes, including maintenance of quality of life and functional independence. Treatment strategies should, therefore, not be based on tumour biology alone, but rather on a personalised risk estimation.

To our knowledge, this is the first review that has evaluated the current knowledge on the prognostic and predictive value of commercially available gene expression signatures in older patients with breast cancer. This review also has its limitations. First, retrospective studies examining the predictive value of gene expression signatures were highly susceptible to confounding by indication and results from these studies could, therefore, not be used in the evaluation. Second, the reliability of the outcome data from the included randomised controlled trials may be limited as it is well known that older patients included in randomised controlled trials are generally fitter and have a higher socioeconomic status than the general population (van de Water et al., 2014). Third, we only included studies that performed (sub)analyses of patients aged 65 years and older. Thus, studies that included older patients without a specific subanalysis were excluded from this review. Although there is no consensus on the ideal age cut-off to begin defining an older person, we included patients of at least 65 years or older to include as many studies as possible. Unfortunately, this relatively low age cut-off resulted in the inclusion of mainly young older patients (i.e. between 65 and 75 years), which may not reflect the true older population. Furthermore, different study types (i.e., observational and experimental), different age cut-off values and multiple gene expression signatures with different RS thresholds (i.e., traditional versus TAILORx), have limited the generalisability of their conclusions. Finally, the effect sizes of the included studies varied so that, although statistically significant, some results may be clinically less relevant.

5. Conclusion

Gene expression signatures have been developed and validated mainly in large, relatively young, homogeneous groups of patients. Except for some validation studies that included subanalyses of older patients, very few studies focussed specifically on the older population. We presented evidence of the clinical validity of the prognostic performance of Oncotype DX and Prosigna Risk of Recurrence in older patients

with hormone receptor-positive, lymph node-negative and lymph node-positive breast cancer. Although our review found Oncotype DX to be predictive for older patients with an intermediate-risk recurrence score in both lymph node-positive and lymph node-negative disease, most studies included relatively young (i.e. between 65 and 75 years of age) older patients, which may not reflect the true older population. Further research in older patients with high-risk tumours and integration of geriatric characteristics is required before gene expression signatures could be implemented in clinical practice as a prediction tool for adjuvant chemotherapy decision-making.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Competing interests

The remaining authors declare no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2022.103884.

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