Prospective observational study on the impact of the 21-gene assay on treatment decisions and resources optimization in breast cancer patients in Lombardy: The BONDX study

Alberto Zambelli [a], [*], Edda Simoncini [b], Monica Giordano [c], Nicla La Verde [d], Gabriella Farina [e], Valter Torri [f], Giorgio Colombo [g], Giulia Piacentini [a], Vittoria Fotia [a], Lucia Vassalli [b], Palma Pugliese [c], Paola Poletti [a], Elena Rota Caremoli [a], Carlo Tondini [a]

[a] USC Oncologia, ASST Papa Giovanni XXIII, Bergamo, Italy
[b] Breast Unit, Oncologia, ASST Spedali Civili, Brescia, Italy
[c] USC Oncologia ASST Lariana Ospedale S. Anna, Como, Italy
[d] USC Oncologia ASST Fatebenefratelli Sacco, PO Sacco, Milano, Italy
[e] USC Oncologia ASST Fatebenefratelli Sacco, PO Fatebenefratelli, Milano, Italy
[f] Lab Metodologia per La Ricerca Clinica, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy
[g] S.A.V.E. Studio Analisi Valutazioni Economiche, Milano, Italy

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ABSTRACT

Purpose: Adjuvant treatment decisions in early breast cancer (eBC) have traditionally been driven by risk stratification based on clinical and pathological risk factors. The 21-gene Oncotype DX® assay has been validated as a predictive test for benefit from adjuvant chemotherapy (CT), hence assessing its impact in clinical decisions is of high interest. The objective of this study was to estimate the rate of adjuvant treatment decision modification impacted by the Recurrence Score® result, and the consequent budget impact.

Methods: The study was a multicentre, prospective, real-life experience in Lombardy (Italy) including consecutive patients with T1—T3, N0—N1a, and ER+/HER2-eBC with clinical-pathologic "intermediate risk" of relapse. The change in treatment recommendations was assessed before and after availability of Recurrence Score result. A budget model evaluated the implications of 21-gene testing in the study population.

Results: The overall proportion of CT recommendations was reduced from 24.6% to 15.2% after 21-gene testing, with a major impact in patients initially considered for CT plus hormone therapy (CHT). In these patients, the total budget was reduced, leading to a net saving of -€81,017. The greater the physician propensity to prescribe CHT, the higher the potential savings for the health system from sparing CT in most tested patients.

Conclusions: Our real-life experience suggests that all intermediate-risk ER+/HER2-eBC patients who are initially deemed candidates for CHT should be tested with the 21-gene test. The potential to spare CT in at least half of them offers relevant advantages for patients and national health services.

1. Introduction

Breast cancer is the most common cancer in women and resulted in almost 12,000 deaths in Italy in 2018 [1]. Although adjuvant chemotherapy (CT) improves outcomes in early breast cancer (eBC), the related potential toxicities and the negative impact on quality of life may outweigh the benefits for some patients [2]. Traditionally, clinicians stratify the risk of relapse and extrapolate a potential CT benefit according to clinical and biological risk factors (e.g. patient's characteristics, extent of the disease, hormone receptor [HR] status, nuclear grade, growth labeling index, human epidermal growth factor receptor 2 [HER2] expression) [3,4]. Nowadays, the 21-gene assay can more specifically identify

patients who are predicted to derive marginal or no benefit from adding CT to hormonal therapy (HT) [5–9].

The Oncotype DX Breast Recurrence Score® assay (Genomic Health, Inc., Redwood City, CA, USA) is a 21-gene assay that calculates a Recurrence Score (RS) result and is established as both prognostic and predictive of benefit from CT when added to HT (CHT) in patients with HR+/HER2-eBC [8]. It has been validated in retrospective-prospective analyses using archived samples in node-negative (N0) (NSABP B-14 and B-20 studies) [9] and node-positive patients (TransATAC and SWOG-8814 studies) [10,11]. In addition, the prospective study Plan-B from the West German Study group has shown that node-positive patients with Recurrence Score results 0 to 11 had excellent outcome when treated with endocrine therapy alone [12]. Recently, the results of the prospective, randomized TAILORx trial confirmed overall no CT benefit for N0, HR+/HER2-eBC patients with a RS result 11 to 25 [13].

Based on these comprehensive clinical evidences, the 21-gene test is now recommended in Lombardy as an option to guide CT decisions in patients with HR+/HER2-eBC who are at intermediate risk of recurrence based on clinical-pathological features. Use of 21-gene testing is included in the guidelines of ASCO [14], NCCN [15], ESMO [16], St. Gallen [17] and NICE [18]. The AJCC [19] also incorporates 21-gene testing as a tool for more accurate eBC staging.

To support the eBC molecular testing in Italy, the Associazione Italiana di Oncologia Medica in 2018 invoked "a regulation that governs the accessibility, the quality and the use of the molecular testing in eBC, along with a robust cost-analysis for an effective and efficient health policy" [20]. Thus, it has been suggested that clinial practice data should be collected to verify the utility of the tests. The first Italian study on the use of the 21-gene test (in the Veneto region) evaluated the clinical impact of the test in a cohort of selected eBC patients [21]. The aim of the present study is to further evaluate the impact of 21-gene testing on CT decision-making in a larger cohort of consecutive, unselected patients with estrogen receptor-positive (ER+)/HER2-eBC with intermediate risk of recurrence based on classical clinical-pathological features, with the intent to better estimate the clinical and budget impact of the test in a real-life setting in the Lombardy region.

2. Methods

2.1. Aims of the study

The primary objective of this study was to estimate the rate of adjuvant treatment decision modification dictated by the RS results. The secondary objective was to estimate the budget impact of clinical decision modifications after 21-gene testing based on a pharmaco-economic analysis from the point of view of the payer.

2.2. Study design

The study was a multicentre, prospective, real-life experience, involving the Breast Units of four major hospitals in Lombardy (Azienda Socio-Sanitaria Territoriale [ASST] Papa Giovanni XXIII in Bergamo, ASST Spedali Civili in Brescia, ASST Lariana in Como, and ASST Fatebenefratelli in Milano) and was approved by local Ethical Committees. The study design is reported in Fig. 1.

After written informed consent, all consecutive patients with T1–T3, N0 or up to three positive axillary nodes (N1a), no multi-focal/multicentre disease, and ER+/HER2-eBC with clinical-pathologic "intermediate risk" of relapse were registered in the study. The clinical-pathologic "intermediate-risk" definition included all patients who were considered neither at very low nor at higher clinical-pathologic risk. Very low clinical-pathologic risk

was defined by the presence of ≥4 of the following 5 favorable features: Grade [G] 1, pT1a–pT1b, Ki67 < 15%, N0, ER > 80%. Higher clinical-pathologic risk was defined by the presence of ≥4 of the following 5 unfavourable features: G3, pT2 or higher, Ki67 > 30%, N1, ER < 30%. Eligible patients were evaluated in a multidisciplinary setting for adjuvant treatment recommendation before and after 21-gene testing. The following data were collected: recommendation of adjuvant treatment (HT or CHT) before and after 21-gene testing, RS results and treatment actually received. Initial recommendations were re-evaluated after the RS results with general advice for possible modification as follows: HT for patients with RS < 18; CHT for those with RS > 30; the initial recommendation was usually maintained for those with RS 18–30. This study was conducted prior to the publication of the TAILORx study, which clarified N0 patients' stratification into two groups: those benefiting from CHT (RS 26–100) vs. those not benefiting from CHT (RS 0–25) [13].

2.3. Statistical plan

A total sample size of 400 consecutive eBC patients was required to demonstrate a 25% treatment-change rate, both in N0 (estimated 270 patients) and in N1 (estimated 130 patients), with 95% confidence intervals of 11% and 16%, respectively. Statistical analyses were performed using SAS® software, version 9.4. The χ^2 test was used to investigate the changes in recommendations before and after RS results. Patient and tumour characteristics, including nodal status (N0 and N1) and RS group were described, reporting pre-RS result recommendations and the rate of change with relative 95% CI. McNemar test was used for comparing pre-RS with post-RS result in terms of recommendations and actual treatment received. All hypothesis tests were conducted at a two-sided alpha level of 0.05.

2.4. Budget impact analysis

A budget model was implemented to evaluate the implications of 21-gene testing in the study population of interest. The calculation captured the costs of the assay, based on published commercial list price, costs of annual HT and CT (considering the regimens with anthracycline/taxanes), average costs related to adverse event management and savings from reductions in CT, based on costs previously reported [22]. The budget model assumed that all patients proposed for CT, in the absence of 21-gene testing, would eventually receive such treatment.

3. Results

3.1. Recurrence score results and clinical-pathological factors

Patient enrolment took place from January 2017 to August 2018. 394 out of 402 enrolled patients underwent 21-gene testing and were evaluable for results. Patient characteristics are reported in Table 1. The RS distribution was as follows: 237/394 (60%) were classified as RS < 18, 133 (34%) as RS 18–30 and 24 (6%) as RS > 30. Applying the TAILORx categories that set a threshold of RS result of 25 between patients benefiting or not from CT, the RS distribution was as follows: 341 (86%) had RS 0–25, and 53 (14%) had RS > 25. As shown in Fig. 2 and Table S1 of the supplementary material RS > 30 was more common in patients with the poorest prognostic factors nuclear grade, progesterone receptor (PgR) status, and Ki67 labeling. No differences in RS distribution were observed according to nodal involvement (N0 vs. N1a).
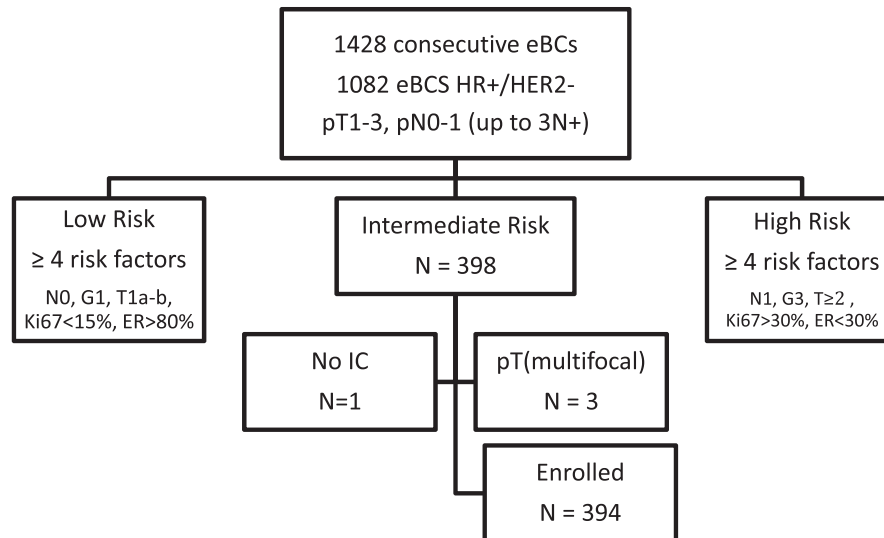
eBC, early breast cancer; ER, oestrogen receptor; CT, adjuvant chemotherapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry.

Fig. 1. Study design. eBC, early breast cancer; ER, oestrogen receptor; CT, adjuvant chemotherapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry.

Table 1
Patient characteristics.

Baseline characteristic	Status
Total number of patients	N = 394
Age, years, median (range)	62 (34−80)
Menopausal status, n (%)	
Premenopausal	108 (27.5)
Postmenopausal	285 (72.5)
Histotype, n (%)	
Ductal	336 (85.3)
Lobular	42 (10.7)
Other	16 (4)
Grading, n (%)	
G1	17 (4.3)
G2	271 (69)
G3	105 (26.7)
pT (mm), n (%)	
pT1a	2 (0.5)
pT1b	45 (11.4)
pT1c	232 (58.9)
pT2	112 (28.4)
pT3	3 (0.8)
pT (mm), median (range)	16 (1−70)
pN, n (%)	
pN0	267 (67.8)
pN1	127 (32.2)
Ki67 (%), median (range)	20 (2−80)
ER (%), median (range)	95 (10−100)
PgR (%), median (range)	80 (0−100)

ER, oestrogen receptor; PgR, progesterone receptor.

3.2. Treatment recommendation before 21-gene testing

MDT recommendations before testing were: HT alone in 297 (75.4%) cases and CHT in 97 (24.6%). CHT recommendations before 21-gene testing were more frequent in N1a patients than N0 patients (38% vs. 18%, respectively; $P < 0.0001$). Other clinical-pathologic factors significantly associated with CHT recommendation included young age, large tumour size, higher nuclear grade, high Ki67 (Table S2 of the supplementary material).

3.3. Treatment recommendation after 21-gene testing

Overall, after 21-gene testing, the final MDT recommendations changed in 15.5% of cases (61/394), with most changes (80%) towards sparing CT (Table 2). All patients received the treatment recommended by the final MDT.

Of the 297 clinical-pathologic intermediate-risk patients who received an initial recommendation of HT, treatment was confirmed for 285 patients (96%) after RS results were available. For the remaining 12 patients (4%), who had a higher RS result, CHT was eventually prescribed. Conversely, of the 97 patients who received the initial recommendation for CHT, the treatment was maintained after 21-gene testing for 48 patients (49.5%), while for the 49 patients (50.5%) who had lower RS results, the initial CHT recommendation was de-escalated to HT alone. Of note, 3/204 patients (1.2%), despite their low RS result, eventually received CHT. Overall, the integration of 21-gene testing in clinical practice resulted in CT sparing for approximately half of the patients initially recommended CHT (Fig. 3).

In the entire study population, the proportion of CT recommendations was reduced from 24.6% to 15.2% after 21-gene testing, with a net reduction in CT use of 9.4% ($P < 0.0001$). The change in treatment recommendation was more frequent in N1a than N0 patients (18% vs 14%, respectively, $P = 0.319$), leading to net reduction in CT use of 18.1% and 5.2% respectively.

3.4. Budget impact

Since the major impact of 21-gene testing was observed in the cohort of patients initially recommended CHT, we focussed the budget impact analysis on this population of special interest (97/394 patients). In the base-case, among the 97 patients who would
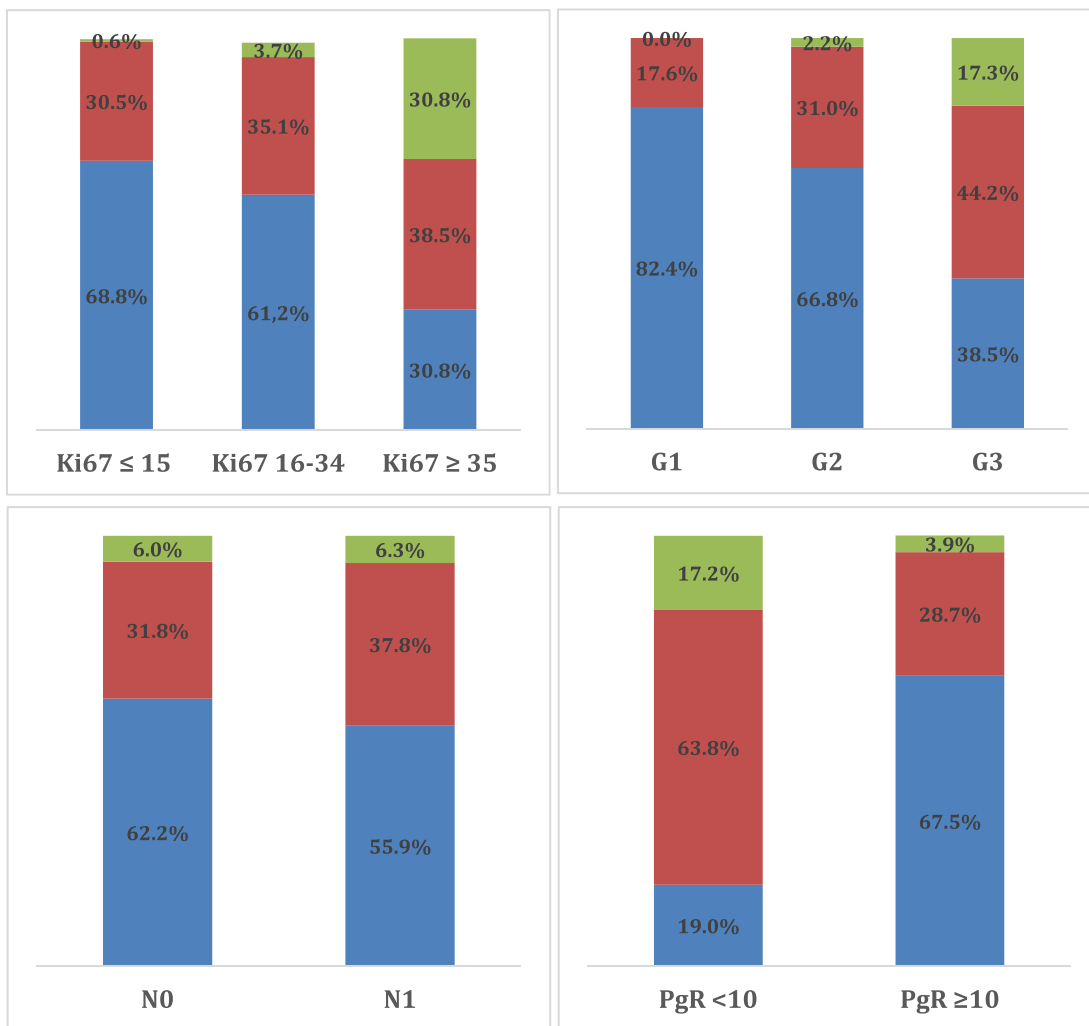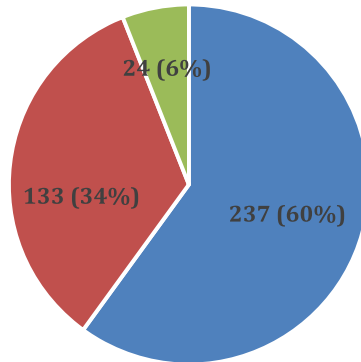
PgR, progesterone receptor; RS, recurrence score.

Fig. 2. Recurrence Score results distribution according to clinical-pathological factors. PgR, progesterone receptor; RS, recurrence score.

Table 2
Change in treatment recommendation after 21-gene test Recurrence Score result.

Change in treatment recommendation	Recurrence Score results							
	Total		RS < 18		RS 18–30		RS > 30	
	N	%	N	%	N	%	N	%
All patients	**394**		**237**		**133**		**24**	
No change	**333**	**84.5**	**204**	**86.1**	**111**	**83.5**	**18**	**75.0**
HT→HT	285	85.6	201	98.5	82	73.9	2	11.1
CHT→CHT	48	14.4	3	1.5	29	26.1	16	88.9
Any change	**61**	**15.5**	**33**	**13.9**	**22**	**16.5**	**6**	**25.0**
HT→CHT	12	19.7	0	0.0	6	27.3	6	100.0
CHT→HT	49	80.3	33	100.0	16	72.7	0	0.0
N1a patients	**127**		**71**		**48**		**8**	
No change	**104**	**81.9**	**57**	**80.3**	**39**	**81.2**	**8**	**100.0**
HT→HT	79	76.0	56	98.2	23	59.0	0	0.0
CHT→CHT	25	24.0	1	1.8	16	41.0	8	100.0
Any change	**23**	**18.1**	**14**	**19.7**	**9**	**18.8**	**0**	**0.0**
HT→CHT	0	0.0	0	0.0	0	0.0	0	0.0
CHT→HT	23	100.0	14	100.0	9	100.0	0	0.0
N0 patients	**267**		**166**		**85**		**16**	
No change	**229**	**85.8**	**147**	**88.6**	**72**	**84.7**	**10**	**62.5**
HT→HT	206	90.0	145	98.6	59	81.9	2	20.0
CHT→CHT	23	10.0	2	1.4	13	18.1	8	80.0
Any change	**38**	**14.2**	**19**	**11.4**	**13**	**15.3**	**6**	**37.5**
HT→CHT	12	31.6	0	0.0	6	46.2	6	100.0
CHT→HT	26	68.4	19	100.0	7	53.8	0	0.0

CHT, adjuvant chemotherapy plus hormone therapy; HT, hormone therapy; RS, Recurrence Score.
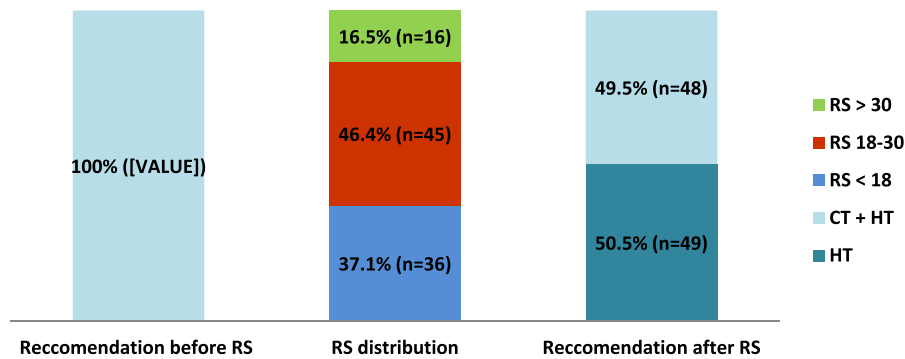
CT, adjuvant chemotherapy; HT, hormone therapy; RS, recurrence score.

Fig. 3. Change in treatment recommendation after Recurrence Score testing in patients initially recommended CHT. CT, adjuvant chemotherapy; HT, hormone therapy; RS, recurrence score.

have received CHT, 48 patients eventually received CHT and 49 cases (51%) were spared CT. Overall, in the target population, the total cost of adjuvant treatments was estimated at €731,380 without 21-gene testing and at €650,363 intergating RS testing,

Table 3
Budget impact analysis with and without Recurrence Score testing for the 97 patients considered initially for CHT.

	Unit cost (€)	Cost without RS (€)	Cost with RS (€)
Oncotype DX® test	2.862	0	277.614
Annual HT	221	21.437	21.437
Adjuvant CT	6287	609.839	301.776
CT induced AEs	1032	100.104	49.536
TOTAL COSTS €		731.380	650.363
Delta			- 81.017

AE, adverse event; CT, adjuvant chemotherapy; HT, hormone therapy; RS, Recurrence Score.

with net savings of -€81,017 (Table 3).

The rate of CT recommendation for patients at intermediate risk based on clinical-pathological features pre-testing was 25% in our study. The general trend in Italy is towards a wider use of CT in this population [24]. A sensitivity analysis was therefore performed with the hypothesis of pre-test CHT recommendations for 50% of patients. In such a hypothetical cohort of 197 patients, the total treatment cost without 21-gene testing was estimated at €1,485,380 and at €1,320,840 intergating 21-gene testing. Therefore, the greater the physician propensity to prescribe CHT, the higher the potential savings for the health system from sparing CT.

4. Discussion

This is the largest prospective study conducted in Italy to evaluate the clinical and budget impact of the 21-gene test in a consecutive cohort of ER+/HER2-eBC patients with intermediate

risk of relapse according to clinical-pathologic factors. A previous study by Dieci et al. [21] evaluated the impact of 21-gene testing in a similar cohort of 250 patients with eBC and found that the use of the 21-gene assay contributed to sparing CT, especially for N1a eBC patients.

The present study enrolled 394 eBC patients representing a consecutive and unselected population of eBCs from four large general hospitals in the Lombardy region. The definition we adopted for clinical "intermediate risk" relies on clinical-pathological characteristics, derived from the St. Gallen Consensus Guidelines [17], and empirically combines nuclear grade, tumour size, Ki67, nodal involvement and ER level [21]. In this setting, uncertainty exists about CT use for optimal adjuvant treatment and the 21-gene test may impact the clinical decision-making process.

In our study, only about one out of four clinical-pathologic intermediate-risk patients was initially recommended to receive adjuvant CHT. This may be considered a conservative attitude, compared with the higher average rate in recommending adjuvant CHT reported at the national level [26]. After 21-gene testing, the recommendation changed in 16% of cases, with CT sparing more pronounced than CT addition.

Although this is in line with previous experiences, the overall treatment change is lower than expected according to literature and protocol assumptions in both the N0 and N1a settings, likely due to our initial conservative attitude in CHT recommendations. Overall, 21-gene testing contributed to significantly reduce the CHT use from 18% to 13% after testing in N0 and from 38% to 20% in N1a.

A pooled analysis of European studies [23] showed that the use of 21-gene testing led to a considerably higher change in treatment recommendations than in our study (31.9% vs 15.5%). Although G3 tumours were more represented in our study than in the pooled analysis (26.7% vs. 13.3%), the pre-test indication of HT alone was higher (75.4% vs. 54.6% respectively). In the subgroup of N1a patients, the reduction of CT use of 20% in our study is consistent with the results of the BreastDX study [21]. The net proportion of CHT recommendation after 21-gene testing was similar to previous reports [24,25], supporting the notion that differences observed in the rate of treatment change are mainly related to the discrepancies in the pre-test recommendations.

In the context of limited resources, the identification of an optimal cost-benefit ratio for the test is crucial. It is therefore relevant to identify the subgroup of patients with the highest rate of change in treatment recommendation after RS results. The number needed to test (NNT), an epidemiological measure that describes the effectiveness of a health-care diagnostic intervention, is the reciprocal of the absolute rate of the clinical impact of the test. NNT represents the number of patients that need to be tested to result in one treatment recommendation change. In our study, the NNT was 7 for the entire population. It was 25 for patients who were initially recommended for HT alone, but it was 2 for patients who were initially recommended CHT. The 25% of initial CHT recommendation in the intermediate-risk setting we reported is quite low, compared with the average of 40–50% observed in Italy [26]. Hence, the potential magnitude of CT spared may be even more pronounced, because the higher the rate of CHT recommendation, the greater the clinical impact of 21-gene testing. Moreover, the application of the new TAILORx results may further improve the cost-benefit of testing because the majority of patients (86% in our experience) at clinical-pathologic intermediate risk would then be classified in the RS 0–25 group with a substantial opportunity to spare CT. This results in a very strong case from the health economic perspective: 1 out of 2 chemotherapies can be spared with the precision brought by the 21-gene test; given that CT costs widely exceeds the costs of 21-gene testing, as reported in the budget

impact calculation, we can validate the cost-effectiveness of the test. A limitation of our analysis is related to the choice and cost of supportive treatments and chemotherapies as this can differ in other institutions and practices. While we based the definition of "intermediar risk" on empiric guidance from the St Gallen guidelines from 2017, it is notable there is to date no clear consensus on this definition and St Gallen committee in 2019 changed to recommend genomic testing for stage 1 T1c and stage 2 as defined in AJCC guidelines.

5. Conclusions

The BONDX trial is a pragmatic real-life experience in the Lombardy region of Italy using the 21-gene test to inform optimal adjuvant eBC treatment recommendation for the clinical-pathologic intermediate-risk ER+/HER2-population. The major clinical utility of 21-gene testing appears to be in sparing CT (one out of two patients tested). In conclusion, according to our data, all intermediate-risk ER+/HER2-eBC patients who are initially deemed candidates for CHT should be tested with the 21-gene test, with the potential to spare CT in at least half of them, with relevant advantages for the patients and for the national health services. Based on the growing evidence available and according to the results of this real-life regional experience, the Lombardy region in July 2019 approved the use and reimbursability of multi-gene classifiers for prognostication and treatment effect prediction among patients eBC HR+/HER2-patients at clinical intermediate risk of relapse.

Declaration of competing interest

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.talanta.2020.120862

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