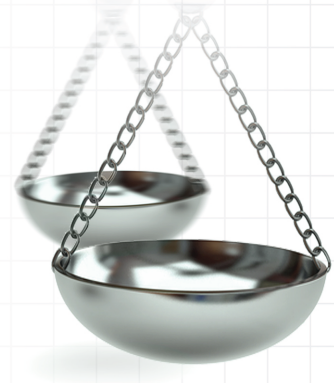
Letter to the Editor



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Letter in reply

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Letter in Reply to Letter to the Editor, Hannouf MB, Muzzey D, Kronenwett R & Lancaster JM. *J. Comp. Eff. Res.* 8(5), 289–304 (2019).

We appreciate the comments from Hannouf *et al.* that allow for elaboration on the analyses and implications. Several queries concern the incidence of distant recurrence among women not prescribed chemotherapy, clinically referred to as prognosis. Across multiple large-cohort studies and control arms of clinical trials of chemotherapy, the average 10-year incidence of distant recurrence in node-negative tumors for all women receiving endocrine therapy varies between 6.4 and 14.8% [1–10]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported a 10-year incidence of distant recurrence of 11% among a cohort of women with node-negative tumors in whom 32% underwent chemotherapy (Table 1 & Figure 2A in [11]); they remark that "*. . . the risk of recurrence after 5 years may well be somewhat lower in women who receive contemporary chemotherapy than among those in our study*" [11]. Based on these data, we assumed across all multigene assays an average 10-year incidence equal to 11% if a woman receives endocrine therapy alone.

The EndoPredict® (EP) assay uses 12-genes to derive a risk score; EPclin also incorporates nodal status and tumor size to compute a risk score between 0 and 15. The incidence of distant recurrence stratified by risk score was reported for EP and EPclin in 2016, showing EPclin had a higher 10-year incidence for high-risk patients relative to EP [10]. We applied almost the same incidence as recently reported by Hannouf *et al.*, which had a monthly incidence of 0.15%, computing into a 16.1% incidence at 10 years assuming a constant hazard rate [12]. Our meta-analyses systematically summarized the published evidence on how physicians use multigene assays to affect chemotherapy recommendations and decisions [13]. Fallowfield *et al.* is the only published study of effects of EPclin on real-world decision making [14]. In seven hospitals in the UK, EPclin increased the use of chemotherapy from 61 to 62 patients among 149 tested patients. Moreover, axiomatically (adhering to mathematical consistency), a higher incidence of distant recurrence results in more distant recurrences overall, unless there is an offsetting chemobenefit among women with high-risk versus low-risk tumors. Chemobenefit has only been demonstrated for the 21-gene Oncotype DX Breast Recurrence Score® test (see below for more details). A higher incidence also correlates with more resources to manage metastatic disease and higher costs. Due to the high cost of managing metastatic cancer, applying the higher incidence rate increases the cost – relative to no testing – from $41M with EP to more than $100M with EPclin. Even if physicians exhibited greater confidence to prescribe chemotherapy only to women with a high-risk score by EPclin, it would not offset its lack of proven chemobenefit. Notably, NCCN Guidelines® refer to '12-gene (EndoPredict)' assay, but also cite the cutpoint associated with EPclin; by contrast, the American Society of Clinical Oncology (ASCO) guidelines refer to '12-gene risk score' only [15]. It seems reasonable thus to highlight the differences between EP and EPclin in outcomes and cost consequences. Both are costly relative to no testing, driven mostly by lack of proven chemobenefit. Given current evidence, treating according to EP is less costly than treating according to EPclin.

The validation of chemobenefit is no longer informed by only the NSABP B-20 trial [2]. A more confident inference about chemobenefit can be achieved if interpreted within the context of findings from both the EBCTCG meta-analyses of more than 100 trials and the TAILORx trial [11,16–18]. The EBCTCG meta-analysis showed an approximately 30% relative reduction in the incidence of distant recurrence across the entire spectrum of women

eligible for testing; that is, women choosing between endocrine therapy alone or also adding chemotherapy (Webappendix, p11 [18]). TAILORx found that among the 6496 women with Recurrence Score® (RS) results 11–25, 691 (10%; 476 with age <50 years and RS 21–25 and 215 with age <50 years, RS 16–20 and high clinical risk) had an absolute reduction greater than 6% in 9-year incidence of distant recurrence with chemotherapy (Table 2 [16]). Assuming as did the investigators when designing TAILORx that little if any chemobenefit exists for women with RS <11 [19], the reduction in incidence with chemotherapy observed in the EBCTCG meta-analyses must be due almost exclusively to the reduced incidence with chemotherapy among women with RS >25; that is, a relative risk reduction of chemotherapy greater than 70%. Together the results of the EBCTCG and TAILORx align with, if not confirm, the findings of the NSABP B-20 analyses by Paik *et al.* [2]. The preponderance of compelling evidence that RS uniquely identifies women who do and do not derive chemobenefit also suggests that additional studies are needed for physicians and patients to have confidence that similar outcomes will occur with other proposed non-genomic and multigene assays.

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