



# Prospective evaluation of finger two-point discrimination and carpal tunnel syndrome among women with breast cancer receiving adjuvant aromatase inhibitor therapy

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## Abstract

**Purpose** Aromatase inhibitors (AIs) are associated with musculoskeletal symptoms and risk of developing carpal tunnel syndrome (CTS), which can impair quality of life and prompt treatment discontinuation. The incidence of CTS and clinical utility of diagnostic tests such as 2-point discrimination (2-PD) have not been prospectively examined among women receiving AIs.

**Methods** Postmenopausal women with stage 0–III hormone receptor-positive breast cancer who were enrolled in a randomized clinical trial investigating adjuvant AIs (Exemestane and Letrozole Pharmacogenetics, ELPh) underwent prospective evaluation of 2-PD with the Disc-criminator™ (sliding aesthesiometer) and completed a CTS questionnaire at baseline, 3, 6, and 12 months, following initiation of AI. Changes in mean 2-PD were analyzed with multivariable mixed effects modelling. A *p* value < 0.05 was considered statistically significant.

**Results** Of 100 women who underwent baseline 2-PD testing, CTS was identified by questionnaire in 11% at baseline prior to AI initiation. Prevalence of CTS at any time in the first year was 26%. A significant increase in worst 2-PD score was observed from baseline to 3 months (3.7 mm to 3.9 mm, respectively, *p* = 0.03) when adjusted for age, prior chemotherapy, randomized treatment assignment, and diabetes. There were no significant differences in treatment discontinuation due to CTS between the arms.

**Conclusion** For women receiving adjuvant AI, 2-PD scores were significantly worse at 3 months compared to baseline. Studies are required to assess whether change in 2-PD is an adequate objective assessment for CTS with AI therapy. Early diagnosis of CTS may expedite management, improve AI adherence, and enhance breast cancer outcomes.

**Keywords** Breast cancer survivor · Aromatase inhibitor induced musculoskeletal symptoms · Carpal tunnel syndrome · Endocrine therapy · Early detection

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## Introduction

Third-generation aromatase inhibitors (AIs) for 5–10 years represent an integral component of endocrine therapy for postmenopausal women with hormone receptor positive (HR+) breast cancer [1]. Despite substantial benefits of adjuvant AIs in reducing risk of recurrence by about 30% and death by 15% compared to tamoxifen, over 30% of women discontinue the medication due to side effects [2–6]. AIs are associated with common musculoskeletal symptoms such as myalgias and arthralgias, which can severely impact quality of life [7–11]. Initial rates of AI-associated musculoskeletal symptoms reported in randomized trials were 19–39%. However, subsequent series report that up to 58% of women report these symptoms, [3], [12], [13] which usually begin within the first few months of initiating these medications [14–17]. In the Exemestane or Letrozole Pharmacogenomics (ELPh) prospective randomized trial, we reported that 24.3% of women discontinued adjuvant AI therapy within 2 years due to musculoskeletal symptoms, with a median time to treatment discontinuation of 6.1 months [2].

AIs may also be associated with an increased risk of specific pathophysiological conditions such as carpal tunnel syndrome (CTS) [18]. CTS is a pressure-induced entrapment neuropathy caused by compression on the median nerve, which is more prevalent in patients with breast cancer receiving AIs than in those treated with tamoxifen, and surgical release might be necessary in some cases [19]. The association of CTS and AI therapy was not initially recognized in large randomized trials but emerged in subsequent analyses. The investigators from the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial reported CTS in 2.6% of participants in the anastrozole arm compared to 1% in the tamoxifen arm ( $p < 0.0001$ ) [14]. The Intergroup Exemestane Study (IES) investigators reported a similar proportion of CTS (2.8%) to that reported in ATAC ( $p < 0.0001$ ) [20].

The clinical diagnosis of CTS is made with symptoms of pain, weakness, and paresthesias in the affected hand and digits [21]. Numbness in the distribution of the median nerve, nocturnal symptoms, thenar muscle atrophy, positive Tinel's sign, and abnormal sensory testing such as finger 2-point discrimination (2-PD) have been standardized as diagnostic criteria [22]. Ultrasonography and electrodiagnostic studies can help confirm the diagnosis in atypical cases. If missed or neglected, CTS may result in irreversible damage to the median nerve [23].

We aimed to prospectively characterize the prevalence of CTS in postmenopausal women receiving adjuvant AI therapy, and to evaluate whether there is a change in 2-PD over one year. We hypothesized that since 2-PD is one

of the measures that can be used for diagnosing CTS, we would observe a correlation between change in 2-PD and clinical diagnosis of CTS.

## Methods

### Study design and oversight

The parent study titled “A multi-center randomized clinical trial correlating the effects of 24 months of AIs (exemestane or letrozole) on surrogate markers of response with aromatase polymorphisms” enrolled participants at three centers, including Indiana University School of Medicine, University of Michigan Health System and the Johns Hopkins School of Medicine (ELPh trial; clinicaltrials.gov identifier #NCT00228956). Previous publications include details regarding design and enrollment [2]. This sub-study was added to the parent study in 2008 and included all patients enrolled from that time forward. The study was approved by each local Institutional Review Board. All participants signed a written informed consent before participating in the trial. Eligible participants included postmenopausal women with histologically proven HR+ stage 0–III breast cancer and were candidates for adjuvant AI therapy either upfront or following tamoxifen. Participants were randomized to exemestane or letrozole daily for 2 years.

### Assessment of CTS and two-point discrimination

Sub-study participants completed the validated Kamath 9-item CTS survey to determine the presence of CTS at baseline and 3, 6, and 12 months following initiation of the AI [24]. A score of equal to or greater than five (out of a maximum score of 10) is diagnostic of CTS and can be used for referral to a hand surgeon for surgical decompression without the need for confirmatory nerve conduction studies. 2-PD measurements were taken by trained study personnel with the Disc-criminator™ (sliding aesthesiometer) at baseline and 3, 6, and 12 months following AI initiation. Briefly, the sharp ends of the Disc-criminator™ were simultaneously applied at two points to the skin on the volar tip pulp of the index fingers, until the capillary bed in the skin surface beneath the prongs just barely began to blanch. The distance between the two points was varied by the examiner during measurements. The examiner and participant were sitting, the participant with closed eyes and forearm in supination on a desk, and indicated whether she felt one or two points as static measurements were taken. The initial distance between the two points started at 20 mm and was gradually decreased until the participant could not differentiate the two points. The threshold value was determined as the shortest distance between the two points that was differentiated correctly at

least seven out of 10 times and was repeated three times at each index finger for both hands. Average 2-PD was the average of the sum of the 3 measurements on each hand divided by 6. The worst 2-PD was the largest value of the two average 2-PD measurements calculated on each hand.

## Statistical analyses

Baseline descriptive characteristics were examined. Changes from baseline in the average of the 2-PD for the left and right fingers and worst 2-PD were estimated from mixed effects linear regression models with indicators for the time points (3, 6, or 12 months) and a random intercept for each participant, while adjusting for age, prior taxane chemotherapy, randomized treatment assignment, and history of diabetes. This modelling approach allows for all observed data points to be used in the estimation, regardless of whether patients had missing data during follow-up. To check that patients with missing follow-up data were not different from those who continued through the study, we compared their baseline characteristics.

Changes in the probability of having CTS (score of five or higher) over time were estimated similarly using logistic regression. Differential changes in these outcomes according to subgroups (i.e., age, body mass index [BMI], prior chemotherapy, randomized drug assignment) at each time point were assessed with interaction terms in the mixed effects regression models. Differences between participants with CTS at 3 and 6 months were explored using logistic regression models adjusted for randomized drug assignment. The association between CTS (yes/no) over time and 2-PD scores over time was assessed with mixed effects linear regression models with CTS as the outcome and terms for the 2-PD score, time-point, and their interaction, randomized drug

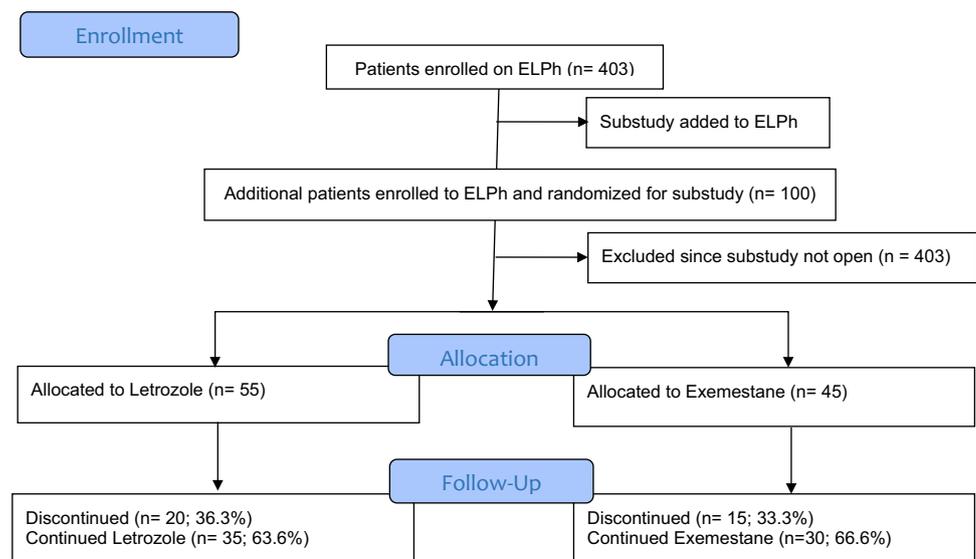
assignment, and a random intercept for each participant. Analyses were completed in R version 3.4.2.

## Results

From 2005 to 2009, 503 participants enrolled in the parent ELPh trial. The sub-study was added in 2008 and included patients who received exemestane or letrozole from 2008 to 2009. A total of 100 women underwent baseline 2-PD testing and were included in the analytical cohort (Fig. 1). Patient characteristics are described in Table 1. Mean age was 59 years, the majority (92%) were Caucasian, 39% received adjuvant taxanes, 76% were overweight or obese, 14.1% had diabetes, and 12% reported prior history of CTS. Those with a self-reported history of CTS were more likely to have CTS on baseline survey (odds ratio = 5.8, 95% CI: 1.4, 24.0,  $p = 0.02$ ) and a higher worst baseline 2-PD (mean difference = 1.3, 95% CI: 0.38, 2.2,  $p = 0.006$ ) than those without a history of CTS.

Prevalence of CTS based on baseline survey was 11% (11/100), compared to 12% after 3 months of AI (10/84;  $p = 0.84$  relative to baseline), 17% after 6 months of AI (13/78;  $p = 0.24$ ), and 15% after 12 months of AI (10/65;  $p = 0.21$ ). The prevalence of CTS at any point in the first year was 26%. Fifteen new cases of CTS were diagnosed with the CTS questionnaire during the study. The AI discontinuation rates in sub-study participants were 19% at 3 months and 53% at 12 months. There was no difference in baseline characteristics between those who continued on study compared to those with missing follow-up data. We observed a statistically significant increase in the worst 2-PD score of 0.3 points at 3 months ( $p = 0.03$ ) when adjusted for age, prior chemotherapy, randomized

**Fig. 1** CONSORT Flow Diagram



**Table 1** Baseline patient characteristics ( $N=100$ )

Age – mean (SD)	58.52 (9.36)
Race – no. (%)	
Asian	3 (3)
Black	5 (5)
White	92 (92)
BMI – mean (SD)	29.76 (5.85)
BMI – no. (%)	
< 25	24 (24)
25–30	35 (35)
30	41 (41)
Tumor size – mean in cm	1.49
Drug assignment – no. (%)	
Exemestane	45 (45)
Letrozole	55 (55)
Stage – no. (%)	
0	8 (8)
I	54 (54)
II	27 (27)
III	11 (11)
Prior chemotherapy – no. (%)	44 (44)
Taxane – no. (%)	39 (41.1)
Platinum – no. (%)	3 (3.2)
Diabetes – no. (%)	14 (14.1) <sup>a</sup>
Thyroid disorder – no. (%)	20 (20.2) <sup>a</sup>
Patient-reported history of CTS – no. (%)	12 (12)
CTS total score – mean (SD)	3 (1.33, 0 to 8)
CTS $\geq 5$ at baseline –no. (%)	11 (11)
2-PD left arm average – mean in mm (SD)	3.17 (1.02)
2-PD right arm average – mean in mm (SD)	3.43 (1.55)
Average of left and right finger 2-PD Score – mean in mm (SD)	3.32 (1.15)
Worst 2-PD Score – mean in mm (SD)	3.64 (1.58)

<sup>a</sup>One patient had missing information regarding diabetes and thyroid history

SD standard deviation; no. number; BMI body mass index; CTS carpal tunnel syndrome; 2-PD 2-point discrimination

drug assignment, diabetes, and history of CTS. We did not observe significant changes in average 2-PD at any time points, incidence of CTS by questionnaire or 2-PD by drug, average of left and right finger 2-PD, or prevalence of CTS at 6 and 12 months (Table 2).

In a subgroup analysis, the worst 2-PD following 3 months of AI therapy deteriorated significantly among women with baseline BMI 25 or higher (change = 0.29 [0.03, 0.56],  $p=0.03$ , Table 3), though this change was not significantly different from those with BMI < 25 (change 0.1, interaction  $p=0.43$ ). The changes in worst 2-PD from baseline to 3 months of AI therapy also did not differ according to age, randomized drug assignment, prior chemotherapy, or history of CTS.

**Table 2** Changes in average (left and right) and worst score for two-point discrimination (2-PD) and carpal tunnel syndrome (CTS) score at 3, 6, and 12 months from baseline

	3 months	6 months	12 months
<b>2-PD Average (mm)</b>			
No. in analysis	81	74	47
Baseline, mean (SD)	3.3 (1.2)	3.3 (1)	3.1 (0.9)
Follow-up, mean (SD)	3.5 (1.4)	3.4 (0.9)	3.2 (0.7)
Follow-up, median (range)	3.1 (1, 12.2)	3 (1, 5.8)	3.1 (2, 5.3)
Change from baseline, mean (SD)	0.2 (1)	0 (0.8)	0.1 (0.7)
P value, change from baseline <sup>a</sup>	0.08	0.47	0.42
<b>Worst 2-PD (mm)</b>			
No. in analysis	81	74	47
Baseline, mean (SD)	3.7 (1.7)	3.6 (1.2)	3.3 (1)
Follow-up, mean (SD)	3.9 (2.2)	3.6 (1)	3.5 (0.8)
Follow-up, median (range)	3.3 (1, 20)	3.3 (1, 7)	3.3 (2, 6)
Change from baseline, mean (SD)	0.3 (1.3)	0 (0.9)	0.1 (0.8)
P value, change from baseline <sup>a</sup>	0.03	0.72	0.55
<b>CTS Total Score</b>			
No. in analysis	84	78	65
Baseline, mean (SD)	3 (1.3)	3.1 (1.3)	3 (1)
Follow-up, mean (SD)	2.9 (1.4)	3.3 (1.3)	3.3 (1.2)
Follow-up, median (range)	3 (–1, 7)	3 (–1, 6)	3 (1, 6)
Change from baseline, mean (SD)	–0.1 (1.3)	0.2 (1.3)	0.3 (1.3)
P value, change from baseline <sup>a</sup>	0.42	0.21	0.2
<b>CTS Score <math>\geq 5</math></b>			
No. in analysis	84	78	65
No. with CTS $\geq 5$ (%)	10 (12)	13 (17)	10 (15)
P value, change from baseline <sup>a</sup>	0.84	0.24	0.21

<sup>a</sup>P values from a single mixed effects linear regression model with a random intercept for each participant. Model-based  $p$  values include adjustment for age, prior chemotherapy, randomized drug assignment, and diabetes (2-PD and CTS total score only)

SD standard deviation

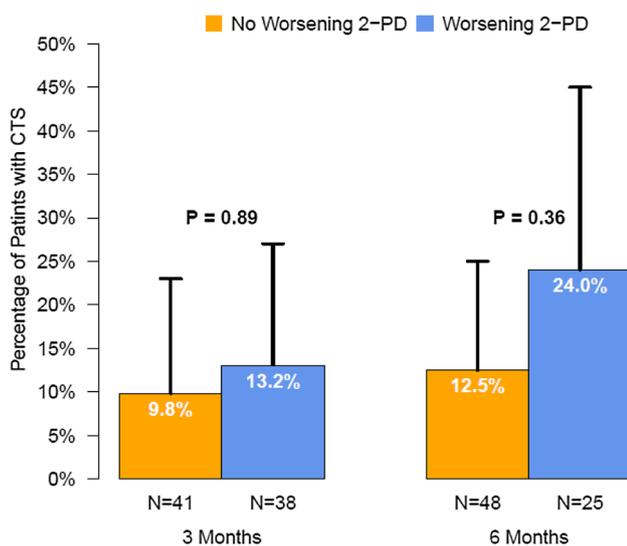
We assessed the association between change in 2-PD and score on the CTS questionnaire (Fig. 2). We found no significant association between the average of the left and right finger 2-PD score and CTS score across all time points, and there was no interaction between individual time points; the same was true for the worst score. While not statistically significant, patients with worsening average 2-PD had a higher prevalence of CTS by questionnaire at 3 months (13.2% vs. 9.8%) and 6 months (24% vs. 12.5%); this was not assessed at 12 months due to diminishing sample size. We found no significant association between mean change in worst 2-PD

**Table 3** Mean changes in worst two-point discrimination (worst 2-PD) score at 3, 6, and 12 months from baseline, by patient subgroups

	Mean in mm (SD), BL	3 m vs. BL	6 m vs. BL	12 m vs. BL	IntP, 3 M	IntP, 6 M	IntP, 12 M
<b>Age</b>							
< 60	3.2 (1.2)	0.23 [−0.09, 0.55], <i>P</i> =0.16	0 [−0.33, 0.33], <i>P</i> =1	−0.02 [−0.42, 0.38], <i>P</i> =0.91			
≥ 60	3.5 (1)	0.34 [−0.15, 0.83], <i>P</i> =0.18	0.15 [−0.37, 0.67], <i>P</i> =0.57	0.05 [−0.56, 0.66], <i>P</i> =0.88	0.94	0.77	0.47
<b>Prior chemo</b>							
None	3.2 (1)	0.26 [−0.01, 0.52], <i>P</i> =0.06	0.07 [−0.2, 0.34], <i>P</i> =0.62	0.13 [−0.19, 0.45], <i>P</i> =0.42			
Yes	3.4 (1.3)	0.22 [−0.14, 0.59], <i>P</i> =0.24	−0.01 [−0.39, 0.37], <i>P</i> =0.97	−0.02 [−0.46, 0.43], <i>P</i> =0.95	0.89	0.74	0.53
<b>BMI</b>							
<25	3 (1.2)	0.1 [−0.27, 0.46], <i>P</i> =0.6	0.09 [−0.28, 0.47], <i>P</i> =0.63	0.22 [−0.2, 0.64], <i>P</i> =0.31			
≥ 25	3.4 (1.1)	0.29 [0.03, 0.56], <i>P</i> =0.03	0.01 [−0.26, 0.28], <i>P</i> =0.92	0.02 [−0.31, 0.34], <i>P</i> =0.91	0.43	0.77	0.49
<b>Drug assignment</b>							
Exemestane	3.1 (0.9)	0.33 [0.02, 0.64], <i>P</i> =0.04	0.24 [−0.09, 0.58], <i>P</i> =0.16	0.12 [−0.25, 0.49], <i>P</i> =0.52	0.47	0.14	0.63
Letrozole	3.5 (1.3)	0.17 [−0.12, 0.46], <i>P</i> =0.26	−0.11 [−0.4, 0.19], <i>P</i> =0.49	0.03 [−0.34, 0.4], <i>P</i> =0.88			
<b>History of CTS</b>							
None							
Yes	3.2 (1)	0.14 [−0.03, 0.3], <i>P</i> =0.11	0.08 [−0.09, 0.25], <i>P</i> =0.36	0.12 [−0.08, 0.33], <i>P</i> =0.24			
	4 (1.9)	0.27 [−0.37, 0.91], <i>P</i> =0.42	−0.03 [−0.7, 0.64], <i>P</i> =0.93	−0.11 [−0.87, 0.65], <i>P</i> =0.78	0.57	0.59	0.34

*P* values for within-group changes and interactions for differential changes by time point and subgroup

*SD* standard deviation; *BL* baseline; *IntP* interaction *p* value, follow-up time points (3, 6, or 12 M) compared to baseline; *BMI* body mass index



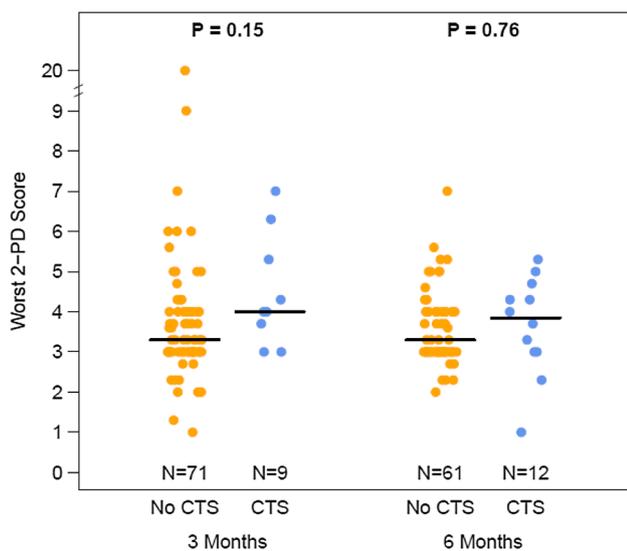
**Fig. 2** Percentage of patients with a diagnosis of Carpal Tunnel Syndrome (CTS) according to whether the worst 2-PD score worsened (increased) at 3 or 6 months compared to baseline

scores and a CTS questionnaire score  $\geq 5$  consistent with a clinical diagnosis of CTS at 3 and 6 months (Fig. 3).

## Discussion

Adjuvant endocrine therapy for 5–10 years is associated with substantial survival benefits. Therefore, clinicians should proactively identify and intervene on symptoms, such as CTS, which can impact daily life activities, impede adherence and ultimately lead to increased morbidity. In our prospective study, we observed a high prevalence of CTS within the first year of starting AIs (26%) and a significant worsening of worst 2-PD at 3 months, suggesting that this condition emerges over time. The incidence of CTS while on AIs reported in our study appears to be higher than that reported in previous studies [25], [26].

With an aging population and earlier diagnosis of breast cancer, the breast cancer survivors and users of AI therapy are likely to increase over the next decade [27]. Therefore,



**Fig. 3** Distribution of the worst two point discrimination (2-PD) for those with and without CTS, at 3 and 6 months, among women receiving adjuvant aromatase inhibitor therapy for breast cancer. The median of the distribution is shown by the horizontal bar

conditions associated with AIs may rise, and healthcare professionals should be able to promptly and accurately recognize and manage emerging symptoms. Understanding risk factors for the development of CTS may be critical to prompt detection and early intervention. In a retrospective analysis of data from the ATAC trial, the prevalence of reported CTS in AI users was seven times that of participants receiving tamoxifen therapy and CTS was significantly increased for women who used prior hormone replacement therapy or received prior chemotherapy. Those who were 60 years of age or older at entry were at lower risk of CTS compared with their counterparts [28]. In the ATAC trial, BMI > 30 kg/m<sup>2</sup> was associated with increased risk of developing AI-associated musculoskeletal symptoms [28]. Excess body mass markedly increases the risk of CTS by 1.5–2 fold [29]. Although the interaction test for a subgroup effect according to BMI (normal weight v. overweight or obese) was not statistically significant, our data suggest that overweight or obese women may be at higher risk of worsening 2-PD.

Adjuvant AI therapy may be associated with significant change in worst 2-PD as early as 3 months; therefore, early diagnosis and treatment might reduce the need for surgery [30]. The management of CTS is based on severity of symptoms and functional consequences. Earlier stages usually respond to analgesics and/or steroids, while advanced cases may need surgical intervention [31]. In a retrospective analysis of data from IES, CTS greatly affected daily-life activities in 36.2% of participants and 69.0% of those affected underwent surgical release [32]. Clinicians should consider

a drug holiday or a change to another endocrine agent and encourage physical activity [33], [34]. Additional research is needed to evaluate whether early detection of CTS and/or 2-PD worsening could lead to reduction in surgical interventions for CTS, or improvement in AI compliance, quality of life, and ultimately survival outcomes.

Several mechanisms by which AI could contribute toward development of CTS have been proposed including local inflammatory response in the tenosynovial structures of the wrist [35–37], profound estrogen deprivation, or mediation of BMI and hand grip strength by growth hormone/insulin like growth factor-I (GH/IGF-I) which is controlled by sex steroids [38]. Single-nucleotide polymorphisms (SNPs) related to cytokines such as the gene (TCL1A) related to cytokine IL-17 may be associated with increased risk of musculoskeletal symptoms from AIs [39].

While our study's main strength is its prospective assessment, there are a few limitations. A small sample size with short follow-up provides limited power to do subgroup analyses. The reason for discontinuation was not collected in this sub-study, and due to the high AI treatment discontinuation rates in the study, the reported prevalence of CTS at each follow-up is likely an underestimation. Finally, we did not evaluate whether early detection of sub-clinical CTS by 2-PD will ultimately influence adherence to AI or survival outcomes.

In conclusion, compared to a clinical questionnaire, 2-PD may provide a reliable and quantitative measure of sensory loss and lead to greater recognition and assessment of CTS as well as the need for intervention. Further research is needed to define a cutoff for predicting CTS before 2-PD assessment can be routinely incorporated into clinical practice. Ultimately, early diagnosis of CTS may improve the quality of life and survival outcomes in women with early HR + breast cancer.

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**Author contributions** VS: concept and design. VS, AMS, DFH, NLH, NLH, GR: investigation. KT, AN, JH, SCJ, JG, GR: collection and assembly of data. ZZ, ALB: data analysis and interpretation. All authors: Manuscript writing. All authors: Final approval of manuscript.

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### Compliance with ethical standards

**Conflict of interest** JS, ALB, RV, GR, JG, SCJ, ZZ, JH, AN, AMS, and KT declare that they have no conflict of interest. AB has received

grants from Biothernostics Inc, Immunomedics, Novartis, Genentech/Roche, Merck, Radius Health, Spectrum Pharma, Innocrin, and Merisana Pharmaceuticals; consultant to Immunomedics, Novartis, Genentech/Roche, Merck, Radius Health, Spectrum Pharma, Taiho Pharma, Biothernostics Inc and Sanofi. GR has received grants from AxoGen and Allergan; patents US PCT/US2009/000,887, Europe 09710338.6-1222, Brazil PI0908087-2, licensed to Aegeria Soft Tissue; patent US 6+2/119,047 issued to Sonavex. DFH has received grants from Pfizer, Novartis and Astra Zeneca; Stock in Oncimmune LLC and Inbiomotion; Consultant/advisory panels with Cepheid, Freenome Inc, Artiman Ventures (CellWorks), CVS Caremark, Agendia Inc.; Sponsored Research with Merrimack Pharmaceuticals, Eli Lilly, Menarini Silicon BioSystems, Puma Biotechnology, Pfizer, Astra Zeneca; Patents US 8790, 878 B2 licensed to Menarini Silicon BioSystems. NLH has received grants from NIH, Pfizer, Novartis, AbbVie, H3 Biomedicine, and Innocrin Pharmaceuticals. VS has received grants from Abbvie, Biocept, Pfizer, Novartis, Medimmune, and Puma Biotechnology; data safety monitoring board for Immunomedics; consultant to Iridium Therapeutics, Inc.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Research involving human and animal participants** This article does not contain any studies with animals performed by any of the authors.

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