Construct Validity and Internal Consistency of Patient-Reported SymptoMScreen in Phase IIIb Trials of Ocrelizumab in Relapsing Multiple Sclerosis (ENSEMBLE and CASTING)

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BACKGROUND

- SymptoMScreen is a patient-reported outcome (PRO) developed to assess severity of limitations associated with symptoms of multiple sclerosis (MS)[1]
  - SymptoMScreen is freely available to the research community (https://www.symptomscreen.org/)
- SymptoMScreen consists of 12 distinct domains commonly affected by MS, which are assessed across a 7-point Likert scale, ranging from 0 (not at all affected) to 6 (total limitation) (**Figure 1**)
  - Domain scores are summed to yield a total score, ranging from 0 to 72, with a higher score indicating more severe symptom limitations
- Previous analyses described baseline SymptoMScreen scores in two ongoing, open-label, single-arm, Phase IIIb clinical trials of ocrelizumab (OCR):[2]
  - ENSEMBLE (NCT03085810): treatment-naive patients with early-stage relapsing-remitting MS (RRMS)
  - CASTING (NCT02861014): patients with RRMS and a prior suboptimal response to disease-modifying treatment (DMT)
- Mean (CI) total SymptoMScreen scores at baseline were lower in ENSEMBLE than in CASTING[2]
- In both ENSEMBLE and CASTING:[2]
  - Fatigue was the domain with the highest score
  - Walking was the domain with the largest differential score between studies
  - Hand function/dexterity was the domain with the lowest domain score

Figure 1. SymptoMScreen patient-reported outcome measure

Please circle **one number that best describes how MS has affected each function.** For example, if it takes you longer to type or text, you might rate your hand function as 'mildly limited' (circle '2'), but if you gave up typing completely, you might rate your hand function as 'very limited' (circle '4')

	0 – not affected at all	1 – very mild limitation / I make minor adjustments	2 –mild limitation / I make frequent adjustments	3 – moderate limitation / I reduced my daily activities	4 – severe limitation / I gave up some activities	5 – very severe limitation / I'm unable to do many daily activities	6 – total limitation / I'm unable to do most daily activities
Walking	0	1	2	3	4	5	6
Hand function/ Dexterity Poor hand coordination, tremors	0	1	2	3	4	5	6
Spasticity & Stiffness Muscle cramping or muscle tightness	0	1	2	3	4	5	6
Bodily Pain Achiness, tenderness	0	1	2	3	4	5	6
Sensory symptoms Numbness, tingling or burning	0	1	2	3	4	5	6
Bladder control Urinary urgency, frequency	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6
Vision Blurry vision, double vision	0	1	2	3	4	5	6
Dizziness Feeling off balance, spinning/vertigo	0	1	2	3	4	5	6
Cognitive function Memory, concentration problems	0	1	2	3	4	5	6
Depression Depressed thoughts, low mood	0	1	2	3	4	5	6
Anxiety Feelings of stress; panic attacks	0	1	2	3	4	5	6

MS, multiple sclerosis.

OBJECTIVES

- Using baseline data from the ENSEMBLE and CASTING studies, the objectives of this poster are to:
  - Demonstrate that SymptoMScreen is a robust fit-for-purpose tool to detect limitations associated with MS
  - Demonstrate the association between SymptoMScreen domains and other clinical outcome assessments capturing similar constructs (construct validity)
  - Demonstrate that SymptoMScreen items are appropriately related and that there is limited redundancy (internal consistency)

METHODS

- SymptoMScreen total scores and individual domain scores at baseline were recorded in ENSEMBLE (n=678) and CASTING[2] (n=680)
  - Expanded Disability Status Scale (EDSS), Multiple Sclerosis Impact Scale (MSIS-29), Work Productivity and Activity Impairment (WPAI) questionnaire and Symbol Digit Modalities Test (SDMT) were collected in both studies
  - 9-hole peg test (9HPT) and timed 25-foot walk (T25FW) were collected in ENSEMBLE only
- Correlations between SymptoMScreen (total/domain scores) with other outcome measures were assessed using the Spearman's rank correlation coefficient
  - Textual gradings (e.g. strong, moderate, weak) were assigned with consideration towards validity coefficients as described by Swank and Mullen *et al* (2017)[3]
- All analyses were run separately for ENSEMBLE and CASTING, to assess whether the psychometrics were broadly consistent across studies
  - Since correlations were consistent between the two studies, analyses were also performed on pooled data
- To assess SymptoMScreen internal consistency among the 12 distinct domains, Cronbach's alpha was calculated

RESULTS

Baseline Characteristics

- Baseline characteristics of patients within ENSEMBLE were reflective of treatment-naive patients with early-onset RRMS, while baseline characteristics in CASTING were reflective of RRMS patients with prior suboptimal response to DMTs (**Table 1a and 1b**)[2]

Table 1a. Baseline characteristics in ENSEMBLE

Parameter	ENSEMBLE (N=678) Treatment naive Early RRMS
Age, mean (SD), years	32.4 (9.1)
Female, n (%)	438 (65)
Caucasian, n (%)	563 (83)
BMI, mean (SD), kg/m²	25.6 (5.8)
Duration since MS symptom onset, mean (SD), years	1.1 (0.8)
Baseline EDSS score	
Mean (SD) score	1.7 (1.0)
Median (range)	1.5 (0.0-4.0)
Number of relapses in last year, mean (SD)[a]	1.5 (0.9)
Enrolled due to, n (%):	
Only MS relapse	104 (15)[b]
Only MRI activity	72 (11)
Both relapse and MRI activity	502 (74)

Table 1b. Baseline characteristics in CASTING

Parameter	CASTING (N=680) RRMS Suboptimal response to prior DMT
Age, mean (SD), years	34.2 (8.6)
Female, n (%)	436 (64)
Caucasian, n (%)	624 (92)
BMI, mean (SD), kg/m²	25.0 (5.4)
Duration since MS symptom onset, mean (SD), years	5.0 (2.7)
Baseline EDSS score	
Mean (SD) score	2.1 (1.1)
Median (range)	2.0 (0.0-6.0)
Number of relapses in last year, mean (SD)[a]	1.2 (0.9)
Enrolled due to, n (%):	
Only MS relapse	238 (35)[b]
Only MRI activity	167 (25)
Both relapse and MRI activity	275 (40)

[a]Annualized relapse rate calculated in the year prior to enrollment; [b]Either ≥1 T1 gadolinium-enhancing lesion(s) or ≥2 new/enlarging T2 lesions.
BMI, body mass index; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

For mean total and individual SymptoMScreen domain scores at baseline, please scan here

Construct Validity

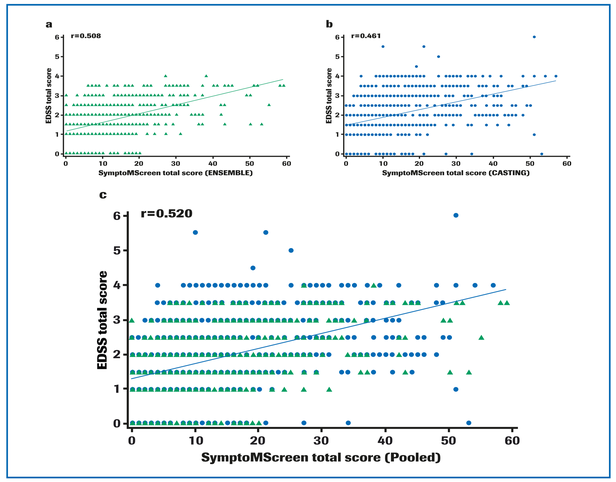
- Correlations between SymptoMScreen and other clinical outcome assessments were broadly consistent between CASTING and ENSEMBLE

Table 2. Spearman correlations between SymptoMScreen scores and clinical assessments

	ENSEMBLE	CASTING	Pooled
Total SymptoMScreen score			
EDSS	**Moderate** r=0.508 (**Figure 2**)	**Moderate** r=0.461 (**Figure 2**)	**Moderate** r=0.520 (**Figure 2**)
MSIS-29 (psychological)	**Strong** r=0.770 (**Figure 3**)	**Strong** r=0.744 (**Figure 3**)	**Strong** r=0.775 (**Figure 3**)
MSIS-29 (physical)	**V Strong** (**Figure 4**) r=0.856	**V Strong** (**Figure 4**) r=0.830	**V Strong** (**Figure 4**) r=0.864
WPAI work time missed	**Moderate** r=0.360	**Moderate** r=0.310	**Moderate** r=0.330
WPAI impairment whilst working	**Strong** r=0.716	**Strong** r=0.656	**Strong** r=0.686
WPAI overall work impairment	**Moderate** r=0.328	**Moderate** r=0.292	**Moderate** r=0.306
WPAI activity impairment	**Strong** r=0.755	**Strong** r=0.758	**Strong** r=0.765
SymptoMScreen walking item			
EDSS ambulation	**Moderate** 0.487	**Moderate** 0.569	**Moderate** 0.551
T25FW	**Weak** r=-0.281	**Weak** NA[a]	**Weak** NA[a]
SymptoMScreen cognition item			
SDMT	**Weak** r=-0.101	**Weak** r=-0.238	**Weak** r=-0.187
SymptoMScreen hand function item			
9HPT	**Moderate** 0.327	NA[a]	NA[a]

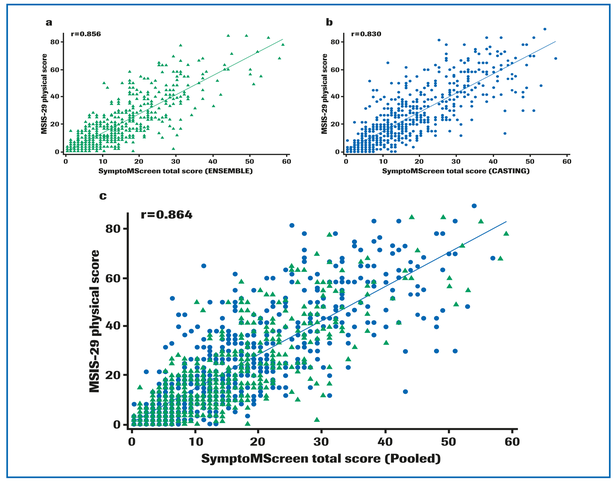
[a]These assessments were collected in ENSEMBLE only. p<0.001 for all correlations.
9HPT, 9-hole peg test; EDSS, Expanded Disability Status Scale; MSIS-29, Multiple Sclerosis Impact Scale; N/A, not applicable; SDMT, Symbol Digit Modalities Test; T25FW, timed 25-foot walk; WPAI, Work Productivity and Activity Impairment.

Figure 2. SymptoMScreen total score correlates with EDSS score



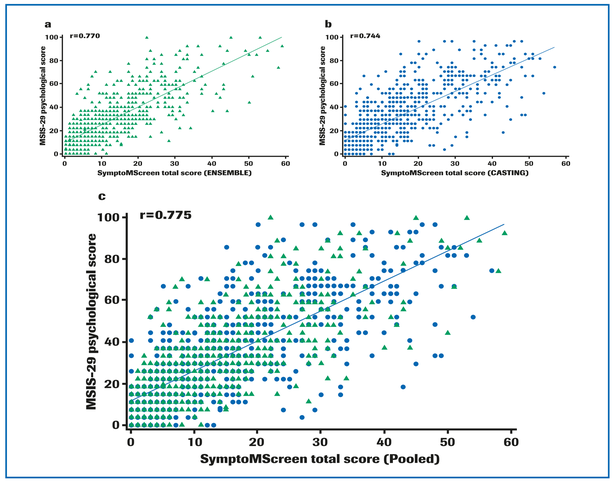
EDSS, Expanded Disability Status Scale.

Figure 3. SymptoMScreen total score correlates with MSIS-29 physical score



MSIS-29, Multiple Sclerosis Impact Scale. Scores are transformed on a 0-100 scale.

Figure 4. SymptoMScreen total score correlates with MSIS-29 psychological score



MSIS-29, Multiple Sclerosis Impact Scale. Scores are transformed on a 0-100 scale.

- Although correlations were observed between individual SymptoMScreen domain scores and counterpart performance assessments, these correlations were weaker (except for EDSS ambulation). Several reasons may exist for this:
  - In the SymptoMScreen, patients evaluate symptoms that lead to symptom-related limitations, as opposed to objective measures of disability like the EDSS
  - The SymptoMScreen cognition item measures symptomatic memory and concentration, which can be affected by many other factors (e.g. fatigue, depression) than true cognitive impairment. The SDMT (to which it was compared) measures information processing speed,[4] which is a single cognitive function domain, rather than a measure of global impairment
  - Symptoms such as hand dysfunction and aspects of lower limb dysfunction are not seen until more advanced stages of MS, whereas patients included in CASTING and ENSEMBLE have low levels of clinical disability (EDSS score ~2.0)

Internal Consistency

- The Cronbach's alpha score among the 12 domains was 0.924, indicating that SymptoMScreen is a consistent and reliable tool to assess MS symptom severity

CONCLUSIONS

- Correlations were consistent across ENSEMBLE and CASTING studies
- SymptoMScreen showed good construct validity in patients with early RRMS
  - Total SymptoMScreen scores correlated with clinical disability (EDSS), patient perceived physical and psychological impact (MSIS-29 physical and psychological domains) and work productivity (WPAI)
  - Individual SymptoMScreen domain scores moderately correlated with objective counterpart assessments
- Preliminary analyses suggest the SymptoMScreen may be a useful tool to assess symptom-related limitations even in ambulatory patients with MS
- Longitudinal follow-up will be valuable to establish sensitivity to change

DISCLOSURES

I Kister has received consulting fees from F. Hoffmann-La Roche Ltd, Biogen and Genentech, and has carried out contracted research using investigator-initiated grants funded by Biogen, Genentech and Genzyme. H-P Hartung has received honoraria for consulting, serving on steering committees and speaking at scientific symposia with approval from the Rector of Heinrich-Heine University Düsseldorf from Bayer, Biogen, F. Hoffmann-La Roche Ltd, GeNeuro SA, Genzyme, MedImmune, Merck Serono, Novartis, Octapharma, Teva and Sanofi. P Vermersch has received honoraria and consulting fees from Bayer, Biogen, Celgene, MedDay, Merck, Novartis, F. Hoffmann-La Roche Ltd, Sanofi Genzyme, Servier, Teva and Almirall, and research support from Bayer, Biogen, Merck, Novartis, F. Hoffmann-La Roche Ltd and Sanofi Genzyme. R Buffels is an employee of F. Hoffmann-La Roche Ltd. R Kuhelj is an employee of F. Hoffmann-La Roche Ltd. S Clinch is an employee of F. Hoffmann-La Roche Ltd. W Wei is an employee of F. Hoffmann-La Roche Ltd. G Cutter is employed by the University of Alabama at Birmingham and President of Pythagoras, Inc., a private consulting company located in Birmingham, AL; has received compensation from AMO Pharmaceuticals, BioLineRx, Horizon Pharmaceuticals, Hisun Pharmaceuticals, Merck, Merck/Pfizer, Opko Biologics, Neurim, Novartis, Orphazyme, Sanofi-Aventis, Reata Pharmaceuticals, Receptos/Celgene, Teva Pharmaceuticals, NHLBI (Protocol Review Committee) and NICHD (OPRU oversight committee) for data and safety monitoring boards; has received compensation for consulting or advisory boards from Atara Biotherapeutics, Axon, Biogen, Argenx, BrainStorm Cell Therapeutics, Charleston Laboratories, Inc., Click Therapeutics, Genzyme, Genentech, GW Pharma, Klein Buendel Inc, MedImmune, MedDay, Novartis, F. Hoffmann-La Roche Ltd, SciFluor, Somahlution, Teva Pharmaceuticals, TG Therapeutics and UT Houston.

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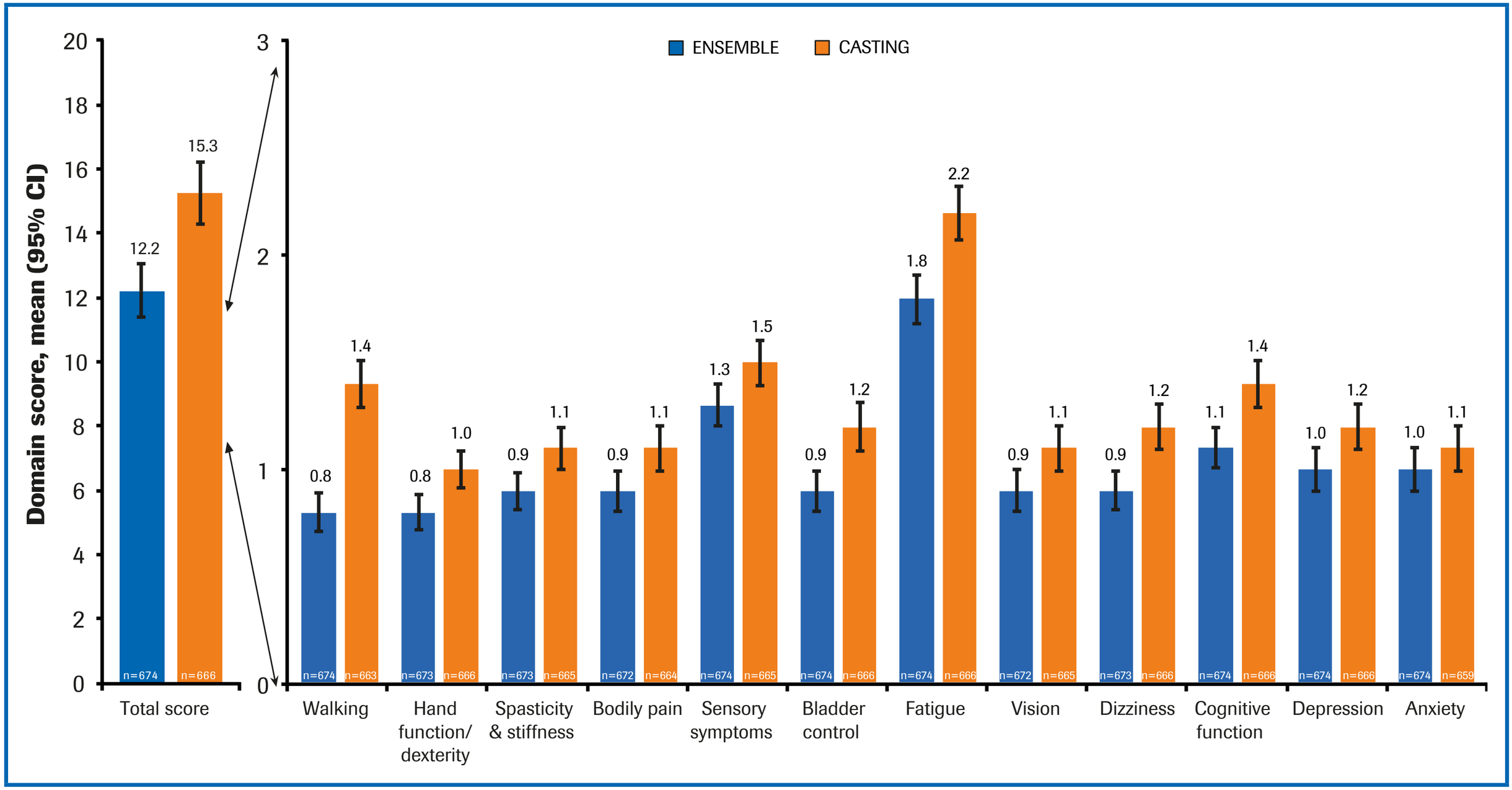
Supplemental Figure 1. Mean total and individual SymptoMScreen domain scores at baseline