

The Swiss Narcolepsy Scale (SNS) and its Short Form (sSNS) for the discrimination of narcolepsy in patients with hypersomnolence: A cohort study based on the Bern Sleep-Wake Database

Panagiotis Bargiotas^{1*}, Anelia Dietmann^{1*}, Alan G. Haynes², Ulf Kallweit^{1,3}, Marta Garcia Calle¹, Markus Schmidt¹, Johannes Mathis¹, Claudio Bassetti¹

¹Sleep Wake Epilepsy Center and Dept. of Neurology, University Hospital (Inselspital) and University of Bern, Switzerland

²Clinical Trials Unit (CTU), University of Bern, Switzerland

³Clinical Sleep and Neuroimmunology, Institute of Immunology, University of Witten/Herdecke, Witten, Germany

*Authors have equally contributed

Corresponding Author:

Dr. med. Panagiotis Bargiotas
Department of Neurology
Inselspital, Bern University Hospital
Freiburgstrasse 18
3010 Bern, Switzerland
Telefon: +41 (0)31 632 30 66
Email: panagiotis.bargiotas@insel.ch

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1 ABSTRACT

2 Previous studies reported high sensitivity and specificity of the Swiss Narcolepsy Scale (SNS) for the
3 diagnosis of narcolepsy type 1. We used data from the Bern Sleep-Wake Database to investigate the
4 discriminating capacity of both the SNS and the Epworth Sleepiness Scale (ESS) to identify narcolepsy
5 type 1 and type 2 in patients with central disorders of hypersomnolence (CDH) or sleepy patients with
6 obstructive sleep apnea (OSA). In addition, we aimed to develop a simplified version of the SNS.
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8 We created the two-item short-form SNS (sSNS), based on the discriminative capability of the models
9 including all possible combinations of the five questions of the SNS.
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11 Using the previously published co-efficiencies, we confirmed the high capacity of the SNS in
12 identifying narcolepsy type 1. The updated SNS (based on new co-efficiencies and cut-off) and the
13 sSNS showed high capacity and were both superior to ESS in identifying narcolepsy type 1. The sSNS
14 correlated significantly with the SNS ($r = -0.897$, $p < 0.001$). No scale showed sufficient discrimination
15 for narcolepsy type 2.
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17 This is the largest cohort study that confirms the discriminating power of SNS for narcolepsy type 1 in
18 patients with hypersomnolence and the first study to assess its discriminative power for narcolepsy
19 type 2. The easy-to-use and easy-to-calculate short-form scale has a high discriminating power for
20 narcolepsy type 1 and may be used as screening tool, especially among general practitioners, to identify
21 patients and accelerate their referral to a center of expertise.
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1 INTRODUCTION

1 2 Narcolepsy belongs to the group of central disorder of hypersomnolence (CDH) and is clinically
2 3 characterized by excessive daytime sleepiness (EDS), cataplexy (in narcolepsy type I, NT1),
3 4 hypnagogic or hypnopompic hallucinations, sleep paralysis and sleep fragmentation[1].

4 5 Narcolepsy has an estimated prevalence of 0.05% and symptom onset typically peaks during the second
5 6 decade of life[2,3].

6 7 There is evidence for a delayed referral of patients with narcolepsy to a specialized center[4] and
7 8 delayed diagnosis of narcolepsy[5,6] often due to lack of recognition of signs and symptoms and lack
8 9 of knowledge about CDH in a broad medical community[4].

9 10 The correct diagnosis of narcolepsy is based on clinical features and objective measures including
10 11 multiple sleep latency test (MSLT), polysomnography, and/or measurement of decreased or absent
11 12 hypocretin in cerebrospinal fluid supported by HLA DQB1*0602 testing. Questionnaires such as the
12 13 Ullanlinna Narcolepsy Scale (UNS)[7], Narcolepsy Severity Scale[8] and the Epworth Sleepiness
13 14 Scale (ESS)[9,10] are frequently used in screening of EDS as well as evaluation of treatment effects in
14 15 narcolepsy, but have a limited discriminative capability especially among patients with
15 16 hypersomnolence[9-12]. ESS allows calculating a score that quantifies daytime sleepiness, respectively
16 17 how likely participants fall asleep in different passive situations. It consists of 8 items with a 4-step
17 18 rating scale. Total score ranges from 0 to 24. Excessive daytime sleepiness is defined by an ESS value
18 19 ≥ 10 [13,14].

19 20 In 2004, we introduced a new scale, the Swiss Narcolepsy Scale (SNS)[12] aiming to develop a simple,
20 21 short and specific screening questionnaire for identifying patients with narcolepsy. The SNS is a self-
21 22 administered narcolepsy screening instrument which contains five questions and assesses the following
22 23 parameters: (1) the inability to fall asleep; (2) feeling unrefreshed in the morning; (3) taking a nap at
23 24 noon; (4) weak knees/buckling of the knees during emotions such as laughing, happiness, or anger and
24 25 (5) sagging of the jaw during emotions such as laughing, happiness, or anger. A calculated value (with
25 26 defined multipliers) of < 0 is indicating the presence of narcolepsy[12].

26 27 This initial study compared the SNS with the UNS in 57 patients with NT1, 56 with non-narcoleptic
27 28 hypersomnolence, and 40 healthy controls, and reported high sensitivity (96%) and specificity (98%)
28 29 for NT1 compared to a similar sensitivity (98%) but lower specificity (56%) of the UNS[12]. This
29 30 initial study and a recent validation study[15] focused mainly on the diagnostic accuracy of SNS in
30 31 detecting NT1 against other types of hypersomnolence. Studies comparing the discriminating power
31 32 of SNS and ESS for NT2 among patients with hypersomnolence are lacking.

32 33
33 34 In the current study, we aim 1) to assess the capacity of the SNS and the ESS in discriminating NT1
34 35 and NT2 in a larger cohort of new patients with disorders of hypersomnolence, 2) to provide an update

1 version of the SNS based on new scoring coefficients and optimal cut-off point and 3) to develop a
 1 2 simplified short-form of the SNS to increase practicability in a daily practice of a broad community of
 2 3 physicians. In an effort to increase applicability of the SNS and mainly of the sSNS in a general
 4 4 practitioner's usual practice, we additionally assessed the discriminative power of the scales in an
 5 5 expanded cohort that included also patients suffering from obstructive sleep apnea, one of the most
 6 6 common causes of excessive sleepiness among patients who visit a general practitioner.

11 **METHODS AND PATIENTS**

12 8 This is a retrospective cohort study based on data from the Bern Sleep-Wake Database (Dietmann et
 13 9 al submitted). The protocol for the establishment of the database for clinical and research purposes was
 14 10 approved by the local ethics committee (Kantonale Ethikkommission Bern, 2016-00409). For this
 15 11 study, data sets collected between 2001 and 2016 for clinical purposes were used. Patients have been
 16 12 admitted to the Sleep-Wake-Epilepsy Center, Department of Neurology, Inselspital, University
 17 13 Hospital Bern, Bern, Switzerland for evaluation of suspected disorder of hypersomnolence. Patients
 18 14 underwent clinical routine work-up including clinical consultations and electrophysiological
 19 15 examinations (polysomnography, multiple sleep latency test, maintenance of wakefulness test,
 20 16 psychovigilance test and actigraphy), all patients filled in a set of questionnaires related to sleep-wake-
 21 17 disorders. Final diagnosis was reviewed for this study by two independent sleep specialists (A.D. and
 22 18 M.G.C.) according to the International Classification of Sleep Disorders (ICSD-3)[16] using medical
 23 19 history from hospital records, laboratory data, electrophysiological work-up of subjective complaints
 24 20 (including PSG, MSLT, MWT and actigraphy) and a battery of sleep-wake questionnaires. Patients
 25 21 included in this study were diagnosed with narcolepsy (type 1 and 2) or other disorder of
 26 22 hypersomnolence, including idiopathic hypersomnia, hypersomnolence due to a medical disorder,
 27 23 hypersomnolence associated with a psychiatric disorder, insufficient sleep syndrome, long sleepers,
 28 24 EDS of unknown origin and sleepy (ESS>10) patients who have completed the SNS scale and were
 29 25 diagnosed with obstructive sleep apnea (Apnea-Hypopnea Index, AHI>5/h).

28 **Clinical Assessment**

29 29 The assessment of the clinical and epidemiological sleep-wake profile of the patients was based on the
 30 30 "Bern Sleep Questionnaire". The questionnaire contains 110 questions about demographics, reasons
 31 31 for referral to sleep laboratory, general information about sleep-wake habits and sleep problems,
 32 32 breathing and circulation, parasomnias and potential trigger factors, dreaming, waking-up, tiredness
 33 33 and sleepiness, cataplexy, hallucinations, stress, well-being, drugs, medication, neurological,
 34 34 psychiatric and other comorbidities, as well as information on family history. Furthermore, all
 35 35 questions included in the ESS, SNS and UNS are included in the Bern Sleep Questionnaire.

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2 **Statistical model**

3 To assess the diagnostic accuracy of the SNS, sensitivity and specificity were calculated for the cut-
4 off value of 0. Additionally, logistic regression was used to model the effect of the SNS on the
5 probability of NT1 and NT2 separately. Model coefficients of the individual questions in the SNS were
6 also re-assessed using logistic regression. The Hosmer-Lemeshow goodness-of-fit test and the Brier
7 score were subsequently calculated to test for calibration and agreement between diagnosis and
8 prediction, respectively. Complete cases analyses were performed.

9 To derive the new short-form SNS (sSNS), logistic regression and AUC for all combinations of
10 questions was used to rank the discriminative ability of the combinations of questions. Although
11 models with four and five questions typically showed higher discriminative abilities, a two question
12 model (including at least one question on cataplexy and one question on awakening) was desirable.

13 The best two-question model was chosen for further analyses. The cut-off for predicting narcolepsy
14 was selected by summing the sensitivity and specificity for each possible predicted value from the
15 model and selecting the cut-off with the largest sum. Cut-offs reported are on the linear predictor scale.

16 Validation of the sSNS for NT1 and the re-parameterized SNS to predict NT1 was assessed via internal
17 bootstrap validation to estimate the optimism in the AUC, Brier score and calibration plot slope and
18 intercept. Briefly, a training sample was drawn and the model was refit in that sample, with Briers
19 score and a test of calibration plot intercept and slope calculated for the training sample. The statistics
20 from that training model were then compared to the original sample for an estimate of the test
21 performance. Optimism was then calculated based on the difference between training and test
22 performance. This procedure was performed 2000 times and the average optimism subtracted from the
23 statistics from the original model to derive a corrected performance.

24 As an exploratory analysis, the best cut-off for ESS to determine NT1 and NT2 was assessed by
25 calculating sensitivity and specificity at each possible cut-off (each value between the minimum and
26 maximum), summing the sensitivity and specificity and determining the cut-off with the highest sum.

27 AUC was also calculated.

28 Analyses were performed in Stata 15.1 and R 3.4.2

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1 RESULTS

1 2 Patients

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3 3 In our data set, we identified 299 individuals with a disorder of hypersomnolence who have completed
4 4 the SNS scale. The final cohort consisted of patients with NT1 (30%), NT2 (7%), idiopathic
5 5 hypersomnia (15%), hypersomnolence due to a medical condition or a substance (5%),
6 6 hypersomnolence associated with a psychiatric disorder (26%) and hypersomnolence of unknown
7 7 origin (17%). Mean age was 33 years (range 23-48) and the male/female ratio was 1.45. For NT1 and
8 8 NT2 mean age was 31 (range 23-42) and 25 years (range 19-34), and the male/female ratio was 2.0
9 9 and 2.2 respectively. Table 1 presents the demographic and clinical characteristics of the patients with
10 10 CDH.

11 11 Expanding the cohort of patients who completed the SNS and including not only patients with CDH
12 12 but also sleepy (ESS>10) patients with obstructive sleep apnea (AHI >5/h) we could identify 473
13 13 individuals.
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15 The discriminating power of the SNS for NT1 and NT2

16 16 In our cohort, the SNS showed a sensitivity of 86% and a specificity of 88% in detecting NT1 against
17 17 other types of hypersomnolence using the previously published scoring coefficients and the published
18 18 cut-off of zero[12]. A Brier score of 0.87 indicated relatively poor agreement between observed and
19 19 predicted outcome (NT1), although the Hosmer-Lemeshow test (p=0.70) was not statistically
20 20 significant suggesting a normal calibration (Table 2). For the detection of NT2 against other types of
21 21 hypersomnolence the SNS showed a sensitivity of 25% and a specificity of 71% (Table 2). The
22 22 distribution of the SNS values in patients with NT1 are shown in Figure 1.
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24 The discriminating power of the updated SNS for NT1 and NT2

25 25 Based on this new cohort, we recalculated the published model coefficients for scoring SNS and
26 26 determined a new cut-off point of -1.83. The parameterization of the model to predict NT1 (rather than
27 27 not-NT1, as in the original parameterization) resulted in the following formula:
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$$29 Q1 \times (-0.47) + Q2 \times (-0.83) + Q3 \times 0.58 + Q4 \times 0.56 + Q5 \times 1.45 - 2.75 \geq -1.83$$

30 30 The sensitivity of the updated SNS for detecting NT1 against other types of hypersomnolence was 91%
31 31 and the specificity 82%. Brier score was 0.07, indicating good agreement between observed and
32 32 predicted outcomes (NT1). The Hosmer-Lemeshow test was also non-significant (p=0.39) suggesting
33 33 a normal calibration (Table 2).
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1 The updated SNS showed a sensitivity of 63% and a specificity of 70% in detecting NT2 against other
 1 2 types of hypersomnolence, using the revised scoring coefficients and the revised cut-off of -2.75 (Table
 2 3 2).

7 5 **The discriminating power of the simplified form SNS (sSNS) for NT1 and NT2**

9 6 The 2-item simplified form from the SNS (sSNS) was created based on the discriminative capability
 10 of the models including all possible combinations of the five SNS questions. Among them, the
 11 7 combination of SNS question 2 (feeling of being unrefreshed in the morning) and question 5 (reports
 12 8 of episodes with muscle weakness in the face/neck related to emotions) showed the highest
 13 9 discriminative capability for NT1 (supplementary table 1 and supplementary table 2). The accuracy for
 14 10 the sSNS in detecting NT1 was comparable to that of the SNS reaching 80% sensitivity and 92%
 15 11 specificity (Table 2). Brier score was 0.08, indicating good agreement, and the Hosmer-Lemeshow test
 16 12 was non-significant (p= 0.26), suggesting a good calibration. The sSNS score correlate significantly
 17 13 with the updated SNS (r = -0.89, p <0.001).

25 26 15 Based on the sensitivity and specificity of the models to predict NT1 we determined a cut-off point of
 27 -0.68 for the sSNS. The parameterization of the model to predict NT1 resulted in the following formula:

$$31 17 \quad Q2 \times -0.82 + Q5 \times 1.70 - 0.74 \geq -0.68$$

33 34 18 The distribution of the sSNS values in patients with NT1 are shown in Figure 2. Model parameters are
 35 19 presented in Table 2.

37 38 20 We used the above formula to create an easy-to-use grid, based on the possible answers in sSNS (Q2
 39 and Q5 of the SNS), in order to assess probability of NT1 diagnosis against other disorders of
 40 21 hypersomnolence (Figure 3).

42 23 None of the combinations among SNS questions showed sufficient capacity in discriminating NT2
 43 24 within the cohort of patients with hypersomnolence (data not shown).

50 51 25 **The discriminating power of the original SNS, the updated SNS and the sSNS for NT1 among patients with CDH or OSA**

52 53 28 We then assessed the discriminating capability of SNS, updated SNS and sSNS to discriminate NT1
 54 29 among patients with CDH or sleepy patients with obstructive sleep apnea (OSA).

1 The original SNS, using the previously published scoring coefficients and the published cut-off of
 1 2 zero[12], showed a sensitivity of 83.3% (95% CI 73.1 – 90.2%) and a specificity of 90.6% (95% CI
 2 3 86.9 – 93.2%) in detecting NT1 among patients with CDH or OSA.

4 4 The sensitivity of the reparametrized SNS for detecting NT1 among patients with CDH or OSA was
 5 6 93% (95% CI 84.8 – 97.0%) and the specificity 82.3% (95% CI 77.9 – 86.0%).

8 6 The sensitivity of the sSNS for detecting NT1 among patients with CDH or OSA was 83% (95% CI
 9 7 72.9 – 89.7%), and the specificity 82.6% (95% CI 78.6 – 86.0%).

13 **The discriminating power of the ESS for NT1 and NT2**

15 10 In our cohort, the sensitivity of ESS score, using the typical cut-off of sleepiness ($ESS \geq 10$) was 68%
 16 11 and specificity was 56% for the identification of NT1 against other disorders of hypersomnolence
 17 12 (Table 3). By using various ESS cut-off's, finally applying the one ($ESS \geq 18$) with the best AUC, the
 18 19 sensitivity (51%) and specificity (78%) for identifying NT1 remained low.

21 14 Similarly, by using various ESS cut-off's, applying the one ($ESS \geq 10$) with the best AUC, the
 22 23 sensitivity for identifying NT2 against other disorders of hypersomnolence was 93% but specificity
 24 25 was very low (17%).
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1 DISCUSSION

1 2 This is the largest known retrospective cohort study to assess the discriminative capacity of the SNS
 2 3 for narcolepsy. Our data confirmed the previously reported high capacity of the SNS in identifying
 4 4 NT1 against other types of hypersomnolence[12]. In addition, we updated the SNS by recalculating the
 5 5 model coefficients for scoring SNS and defining new cut-off scores for the scale. The capacity of the
 6 6 updated SNS for discriminating NT1 against other disorders of hypersomnolence was comparable to
 7 7 the capacity of the original SNS.

8 8 There is ample evidence for a delayed diagnosis of narcolepsy often due to the absence or lack of
 9 9 recognition of common narcolepsy symptoms, especially cataplexy. Therefore, the implementation of
 10 10 simple, easy-to-use, and reliable questionnaires on the symptom-based suspicion of narcolepsy and its
 11 11 subtypes in primary care may significantly increase the referral accuracy and improve resource
 12 12 utilization by narrowing the differential diagnosis upon referral. In an effort to increase its
 13 13 practicability, we aimed to simplify the SNS and introduced a simplified form (sSNS) which contains
 14 14 only two questions.

15 15 The sSNS correlated with the full SNS and demonstrated comparable validity with the SNS in detecting
 16 16 NT1 against other types of hypersomnolence. We created an easy-to-use grid, based on the sSNS
 17 17 formula, to simplify further the prediction of NT1, by selecting the relevant cell.

18 18 We then applied the original SNS, the updated SNS and the sSNS in a larger cohort of patients
 19 19 including sleepy patients with obstructive sleep apnea (OSA). The discriminative power of all scales,
 20 20 including the two-questions sSNS, remained satisfactory. This increases the applicability of the SNS
 21 21 and mainly of the sSNS in a general practitioner's usual practice, as OSA is one of the most common
 22 22 causes of pathological level of sleepiness among patients who visit a general practitioner.

23 23 Our data from the sSNS suggest that the combined reports of episodes with muscle weakness in the
 24 24 face/neck related to emotions and the subjective feeling of restorative night time sleep can better predict
 25 25 the NT1 among patients with hypersomnolence. Indeed, the cataplectic attacks and the restorative
 26 26 nature of sleep are considered, among sleep specialists, typical symptoms for NT (and specifically for
 27 27 NT1), in contrast to the absence of cataplexy in NT2 or to the non-restorative nature of sleep in other
 28 28 CDH such as idiopathic hypersomnia. However, often these two important sleepiness features are not
 29 29 implemented in the standard first-line screening of a sleepy patient.

30 30 Furthermore, we compared the capability of the SNS, the sSNS and the ESS to discriminate NT1
 31 31 against other disorders of hypersomnolence. Our data further support the superiority of SNS and sSNS
 32 32 against ESS in identifying NT1, even if these higher cut-off ESS scores were used.

33 33 Finally, this is the first study to report the poor discriminative capacity of SNS for NT2. Both SNS and
 34 34 the updated SNS, showed low capacity in identifying NT2 against other disorders of hypersomnolence.

35 35 No combination of the five SNS questions showed a satisfactory discriminative ability. Similarly, ESS

1 showed low validity in identifying NT2 against other disorders of hypersomnolence even if the higher
2 cut-off ESS scores were used. These findings are consistent with previous data showing that the
3 distinction between narcolepsy without cataplexy (NT2) and other disorders of hypersomnolence
4 (mainly the idiopathic hypersomnia) remains ambiguous, not seldom due to a diagnosis change over
5 the time[17].
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8 The retrospective approach and the small N number of patients with NT2 consist two important
9 limitations of our study. Due of the retrospective design of the study, not all patients with CDH have
10 completed the SNS, and therefore had to be excluded from the analysis. In addition, the small sample
11 size of NT2 patients may have limited our ability to detect the discriminative power of the scales for
12 NT2 in this cohort. Prospective cohort studies would overcome these limitations.
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15 16 17 18 19 **CONCLUSIONS**

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21 The SNS is a useful and valid complementary tool for the diagnosis of NT1 against other types of
22 hypersomnolence. In this study, we introduce its short form (sSNS), a two-questions, simple, easy-to-
23 use, easier-to-calculate and reliable questionnaire in particular to be used in primary care as a screening
24 tool for narcolepsy in patients with hypersomnolence. This could decrease the delay and increase the
25 accuracy of referral of patients with hypersomnolence to a specialized sleep center for narcolepsy
26 specific diagnostic. Finally, our data suggest that SNS and ESS are not the ideal tools for the
27 discrimination of NT2 against other disorders of hypersomnolence.
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30 Although further confirmatory studies and most importantly prospective studies on clinical biomarkers
31 for disorders of hypersomnolence are needed, our data could be used for the improvement of diagnostic
32 processes in these conditions and the development of more specific screening scales in the future.
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6 "Jazz pharmaceuticals holds a royalty-bearing non-exclusive license to the SNS from the University of
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8
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1 FIGURES CAPTIONS

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4 **Figure 1.** Distribution of the SNS for NT1. Black points indicate correct predictions, grey points
5 4 indicate incorrect (false negative) predictions. Sensitivity and specificity values are shown.

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7 5 NT1, narcolepsy type 1; SNS, swiss narcolepsy scale

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12 7 **Figure 2** Distribution of the sSNS score for NT1 patients. Black points indicate correct predictions,
13 8 grey points indicate incorrect (false negative) predictions. Sensitivity and specificity values are shown.

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15 9 NT1, narcolepsy type 1; sSNS, short-form swiss narcolepsy scale

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20 11 **Figure 3** Grid to predict NT1. Black regions suggest the possibility of NT1. Values in the cell represent
21 12 probability of NT1 against other types of hypersomnolence.

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24 13 P: probability; NT1, narcolepsy type 1

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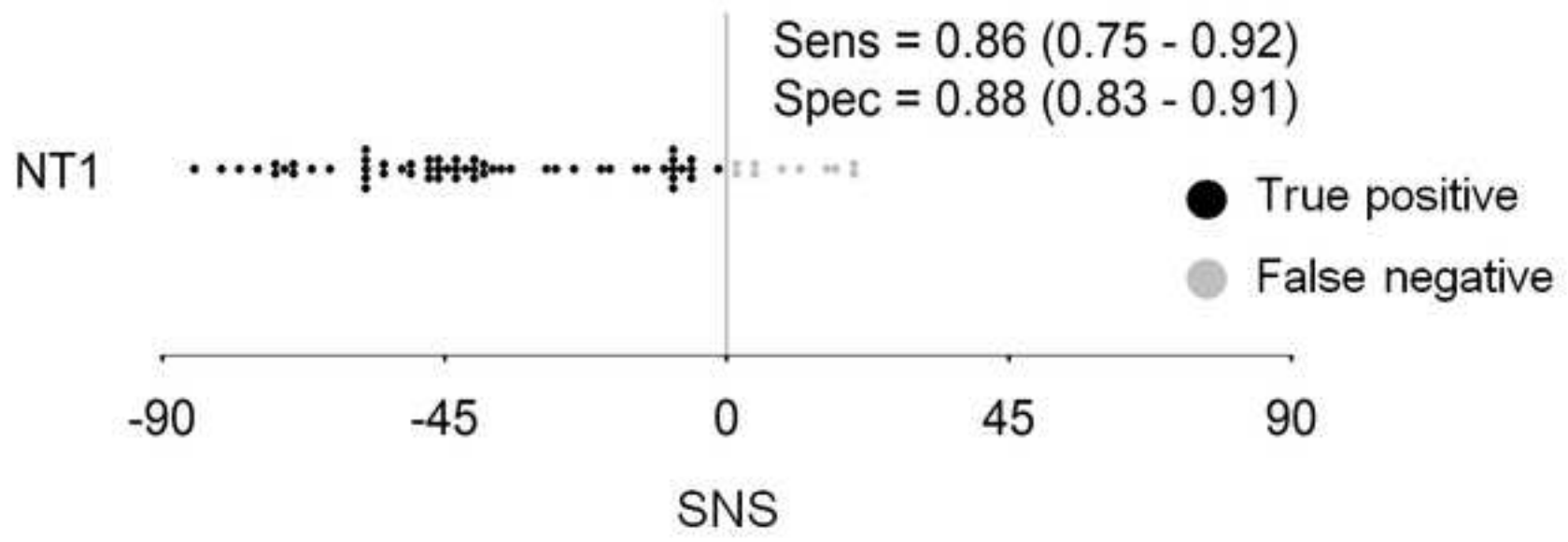
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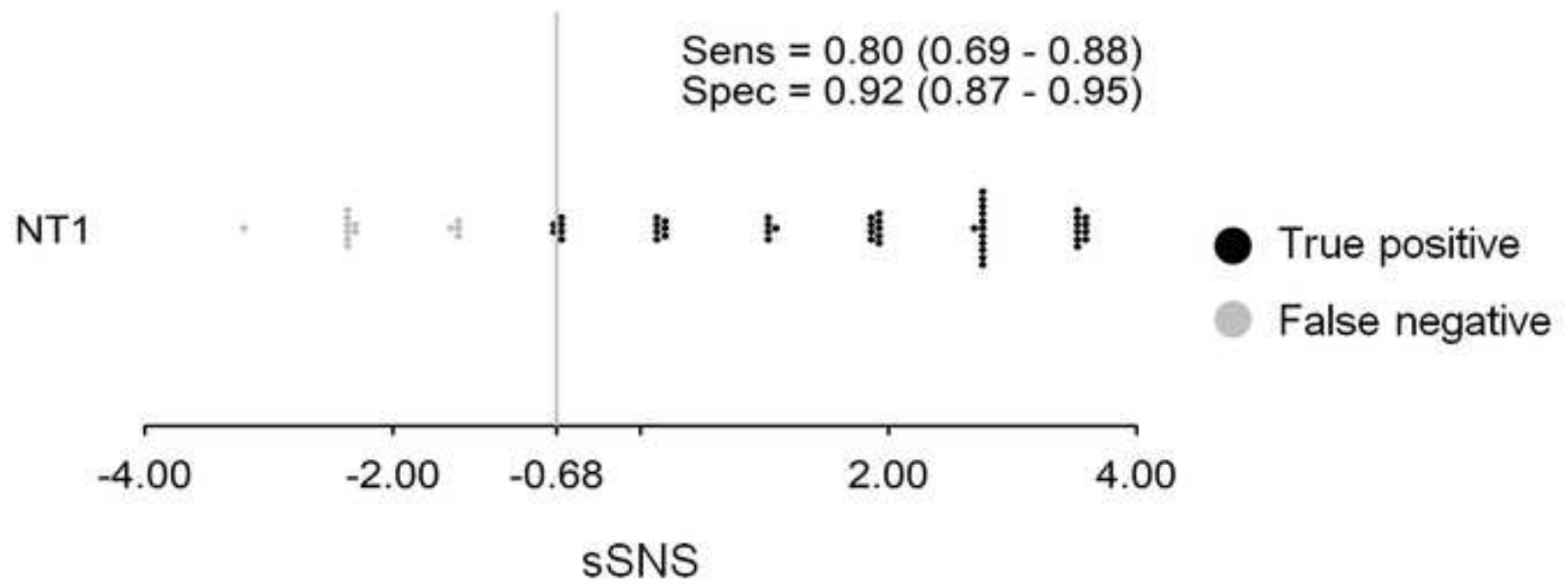
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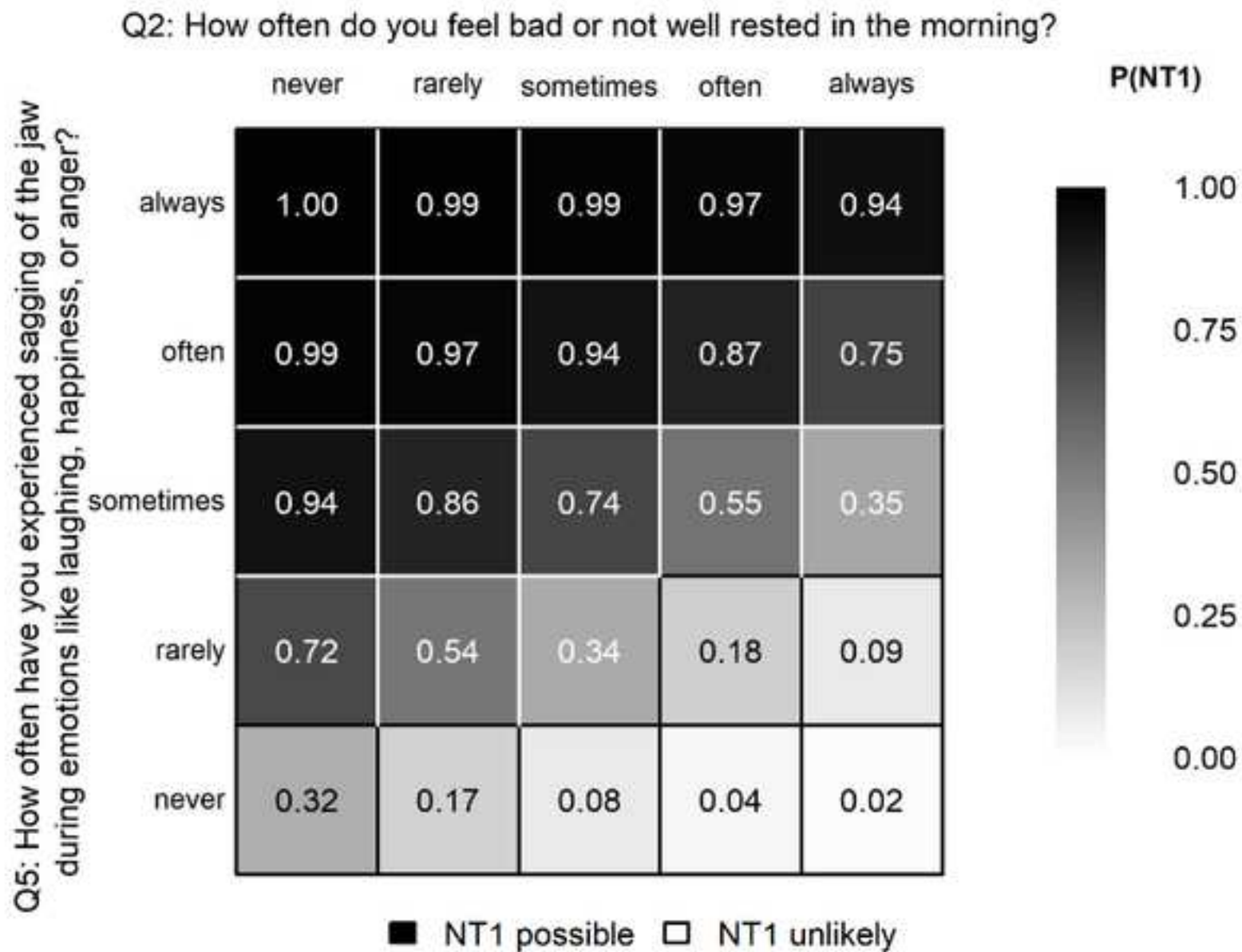
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Demographic and clinical characteristics	n (%) or median (lq, uq)
Age	32.9 (22.8, 47.7)
Gender	
male	177 (59%)
female	122 (41%)
ESS mean score (\pm SD)	11.6 (\pm 6.8)
Disorders of hypersomnolence	299 (100%)
NT1	69
NT2	16
Idiopathic hypersomnia	35
Hypersomnia due to a medical disorder	12
Hypersomnia due to a medication or substance	2
Hypersomnia associated with a psychiatric disorder	59
Insufficient sleep syndrome	91
Long sleeper	10
EDS unclear etiology	35
Table 1 Demographic and clinical characteristics of the cohort	
LQ, lower quartile; UQ, upper quartiles; SNS, swiss narcolepsy scale; NT1, narcolepsy type 1; NT2, narcolepsy type 2, EDS: excessive daytime sleepiness	

Table 2

	SNS*		Updated SNS**		sSNS	
	NT1	NT2	NT1	NT2	NT1	NT2
Cut-off	0	0	-1.83	-2.75	-0.68	-2.26
Sensitivity (95% CI)	0.86 (0.75 - 0.92)	0.25 (0.10 - 0.49)	0.93 (0.84 - 0.97)	0.63 (0.39 - 0.82)	0.80 (0.69 - 0.88)	0.44 (0.23 - 0.67)
Specificity (95% CI)	0.88 (0.83 - 0.91)	0.71 (0.65 - 0.76)	0.82 (0.76 - 0.86)	0.70 (0.64 - 0.75)	0.92 (0.87 - 0.95)	0.83 (0.78 - 0.87)
Hosmer-Lemeshow goodness-of-fit	0.70	0.02	0.39	0.28	0.26	0.00
Brier score	0.87	0.87	0.07	0.05	0.08	0.22
AUC	0.95	0.54	0.96	0.68	0.92	0.82

Table 2 Sensitivities and Specificities of SNS and its short-form (sSNS) in discriminating NT1 and NT2 in a cohort of individuals with hypersomnolence

NT1, narcolepsy type I; NT2, narcolepsy type II; CI, confidence interval; AUC, area under the estimated curve; SNS, swiss narcolepsy scale; sSNS, Short form SNS.

*SNS in the current cohort based on the previously published scoring coefficients(Sturzenegger and Bassetti, 2004)

**SNS in the current cohort based on the updated scoring coefficients.

Table 3

	ESS	
	NT1	NT2
Sensitivity (95% CI)	0.56 (0.46 – 0.65)	0.96 (0.82 – 0.99)
Specificity (95% CI)	0.68 (0.61 – 0.75)	0.07 (0.05 – 0.11)
Hosmer-Lemeshow goodness-of-fit	0.288	0.225
Brier score	0.210	0.093
AUC	0.681	0.501

Table 3 Sensitivities and Specificities of ESS in discriminating NT1 and NT2 in the cohort of patients with hypersomnolence.

ESS Epworth Sleepiness Scale; NT1, narcolepsy type I; NT2, narcolepsy type II; CI, confidence interval; AUC, area under the curve