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1 **Diagnosis of Alzheimer’s disease patients with Rapid Cognitive**
2 **Decline in clinical practice: interest of the Deco questionnaire.**

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1 **Abstract**

2

3 *Background:* Patients with Alzheimer’s disease (AD) who deteriorate rapidly are likely to
4 have a poorer prognosis. There is a clear need for a clinical assessment tool to detect such a
5 decline in newly diagnosed patients.

6 *Objective:* To identify the predictive factors of rapid cognitive decline (RCD) in a cohort of
7 patients with mild to moderate AD ; and to validate a self-questionnaire for caregivers as a
8 diagnostic tool for rapid decline.

9 *Design and analysis:* an open-label, observational, 12-month, multicenter, French study.

10 Physicians were asked to record data of three eligible rivastigmine naïve (or on rivastigmine
11 for < 1 year) AD patients. Risk factors of RCD and the detection power of the Détérioration
12 Cognitive Observée scale (Deco), a 19 item self-questionnaire for caregivers, were assessed at
13 endpoint using regression analyses.

14 *Results:* Out of the 361 patients enrolled in the study, 91 (25.2%) were excluded due to loss of
15 follow-up. Among subjects using cholinesterase inhibitors or memantine, 161 (59.6%)
16 experienced a stabilization (29.2%) or an improvement (30.4%) in global functioning as
17 measured by the CGI-C. Sixty of the remaining 204 patients retained for analysis (29.6%, CI
18 95% [23.4; 35.8]) lost three or more points on the MMSE score between the inclusion and one
19 of the follow-up visit. In the multivariate logistic regression analysis, institutionalization,
20 higher level of education and the loss of 3 points or more on the MMSE were found to be
21 significant predictors of a rapid cognitive loss in this population. The threshold which
22 maximizes the predictive values of the Deco score as a diagnostic tool of rapid cognitive
23 decline was significantly different according to the age of the patient (below or over 75 years
24 old). A score below 16 for patients < 75 years old and below 14 for patients \geq 75 years old
25 consistently predicted a RCD within the next year.

26 *Conclusion:* The Deco test appears to be a simple tool to alert the physician to the possibility
27 of an aggressive course of the disease which warrants particular management.

28

29 **Key words: Alzheimer’s disease, rapid cognitive decline, diagnostic tool**

1 **INTRODUCTION**

2 Neurodegenerative dementias such as Alzheimer Disease (AD) are characterized by a
3 progressive cognitive decline. However, the rate of progression can be highly variable from
4 one patient to another [1] and some patients could have a more rapid cognitive decline (RCD).
5 These patients are likely to have a poorer prognosis, with a higher mortality rate or a lower
6 survival rate without severe dementia, than those with slower progression rates [1-3].

7 A prospective observational study performed in a population of 455 AD patients
8 followed for at least one year, demonstrated that the risk of deterioration was significantly
9 decreased in patients taking cholinesterase inhibitors (ChEIs) for at least one year compared
10 to untreated patients [4]. To date, rivastigmine is the only drug which has been specifically
11 studied in patients with RCD. A meta-analysis of four 6-month, double-blind, placebo-
12 controlled phase studies [5] showed that patients who experienced rapid decline, i.e. a decline
13 of at least 4 points of the ADAS-cog score, during 26 weeks of placebo treatment, improved
14 significantly more after 12 weeks of rivastigmine therapy than those who had declined by less
15 than 4 points in the first 26 weeks. Thus, identifying AD patients at risk of RCD is important
16 as these patients might benefit from specific primary or secondary care including more
17 frequent clinical and neuropsychological evaluations, more frequent adaptation of drug
18 treatment and more effective support for the caregiver.

19 Several factors may predict RCD in AD patients: cognitive status, presence of Extra-
20 Pyramidal Signs, psychotic symptoms and hallucinations, prominent sub-cortical pathology
21 with attention and executive deficits and poor nutrition [6; 7]. However many of these factors
22 are of limited interest in a clinical setting for individual patients as it is difficult to obtain
23 valid information about most of them during the time of a consultation. There is thus a clear
24 need for a simple clinical assessment tool, drawing on caregiver input, to detect RCD in
25 recently diagnosed patients. The “Détérioration Cognitive Observée” (Deco) scale is a 19-item
26 questionnaire administered to a person with at least a monthly contact with the patient. Its aim
27 is to evaluate the change in cognitive functioning of the patient over the previous year. This
28 instrument has been shown to be highly sensitive to early changes in cognitive functioning in
29 previous studies [8].

30 The objectives of the prospective study we report here were to identify the predictive factors
31 of RCD in a cohort of patients with mild to moderate AD ; and to analyze the predictive value
32 of a self-questionnaire for caregivers (the Deco score) as a simple diagnostic tool for RCD.

33
34

1 PATIENTS AND METHODS

2 *Study Design*

3 EXPLORE was an open label, observational cohort study, 12-month, multicenter,
4 French study for which 350 neurologists, geriatricians and psychiatrists were contacted in
5 order to finally include 250 of them. Each was asked to record data of three eligible patients.
6 Eligibility criteria included: outpatients with AD over fifty years old, satisfying the criteria of
7 the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for
8 dementia and those of NINCDS-ADRDA Work Group; with Mini-Mental State Examination
9 (MMSE) [9] scores between 10 and 26; initiating therapy for the first time with rivastigmine
10 or having already received rivastigmine for less than one year; with a planned follow-up visit
11 within 12 months of enrolment and a caregiver's burden assessment; with an available
12 informant. Patients not treated according to the product labeling, patients involved in a
13 clinical trial or patients treated by an experimental drug within the previous 4 weeks were
14 excluded. Investigators were advised to follow product labeling.

15 The Steering Committee, the French National Council of Medical Practitioners Order (CNO)
16 and the National Council of Informatics and Freedom (CNIL) approved the study. All the
17 patients were given a study information sheet.

18 For the present analysis, only subjects followed during twelve months were considered
19 (n=204). Figure 1 is a detailed flow chart of patients 'selection and exclusion.
20

21 *Study assessments*

22 At study entry, a detailed medical history of each patient was taken and baseline and
23 follow-up assessments of cognitive performances was performed.
24 Rapid cognitive decline was defined as a decline of at least three points of MMSE during the
25 one year of follow-up. The following potential predictive factors of RCD were collected at
26 baseline: MMSE, presence of behavioral disorders reported by the patient or his family
27 (delusions, hallucinations, agitation/aggression), presence of extrapyramidal signs, lack of
28 autonomy for the key Instrumental Activities of Daily Living (IADL) items (budget, phone,
29 drugs, transport) [10], lack of stabilization with previous IChE or memantine treatment, Body
30 Mass Index (BMI) and level of education. The clock drawing test[11], the 5-word test[12] and
31 a verbal fluency test were also taken into account.

32 The 19-item caregiver questionnaire, the Deco score was collected at the end of the 12-
33 month follow-up.

1 Safety (vital signs, adverse events and a physical examination) regarding the use of
2 IChE was assessed throughout the study as needed.

4 *Data analysis*

5 Characteristics of the patients who were seen at the 12-month visit were compared to
6 those of all subjects enrolled in the study by appropriate univariate statistical tests.
7 Using simple and multiple logistic regressions, we studied the risk of RCD according to
8 baseline characteristics of the patients. The multivariate analysis included all variables
9 significantly associated with the risk in the univariate analysis at a p-value < 0.10. Moreover,
10 we compared mean values of the Deco score according to some baseline characteristics of the
11 patients. We used student t-test for the comparison.

12 In addition, we ran a Receiver Operating Characteristic (ROC) analysis to detect the best
13 threshold of diagnosis of RCD for the Deco score. Sensitivity, specificity, positive and
14 negative predictive values were calculated for the best thresholds found from the observed
15 ROC curve. We systematically sought for interactions between age and Deco score on the risk
16 of RCD. Indeed, the risk of rapid decline is higher among younger subjects so we
17 hypothesized that the predictive value of Deco might have a differential association with RCD
18 according to age. SAS statistical software version 9.2 was used to perform analyses.

21 **RESULTS**

22 *Patients*

23 Three hundred and sixty one patients were enrolled in the study by 152 neurologists,
24 geriatricians and psychiatrists. Among subjects using ChEI or memantine, 161 patients
25 (59.6%) experienced a stabilization (29.2%) or an improvement (30.4%) in global
26 functioning, as measured by the CGI-C. One hundred and fifty seven patients (25.2%) were
27 excluded from analysis because of loss of follow-up between baseline and the 12-month
28 follow-up (n=151) or missing value on MMSE (n=6) (figure 1). Baseline characteristics of the
29 analyzed and enrolled populations were comparable (Table 1). In the analyzed population, 89
30 patients (43.6%) had received prior ChEI treatment and 115 (56.4%) were de novo patients.
31 Of the 89 patients who had received prior ChEI treatment, 63 patients were already treated by
32 rivastigmine and 26 discontinued from a previous treatment by another ChEI.

1 There were more women than men (58.3% versus 41.7%) and the mean age was
2 approximately 78 years (range 51-102 years). At baseline, patients included in this analysis
3 had a mean MMSE score of 19.7 ± 4.4 .
4 For patients who had been previously treated by ChEIs, the mean duration of treatment before
5 starting the study was 14.0 ± 14.3 months with a mean MMSE decrease of 2.1 ± 3.0 ($-1.1 \pm$
6 2.6 for rivastigmine; -4.1 ± 2.8 for donepezil and -3.6 ± 3.0 for galantamine).
7 For the analyzed population, the MMSE decrease within the previous year was only known
8 for 101 patients (i.e., data missing for 103).
9 The mean follow-up period was $377.6 (\pm 61.2)$ days.

10

11 *Predictive factors of cognitive decline*

12 Sixty of the 204 patients retained for analysis (29.4%, 95%CI [23.4; 35.8]) were
13 qualified as rapid cognitive decliners as they lost three or more points on the MMSE score
14 between the inclusion and the 12-month follow-up visit.

15 Table 2 shows that the demographic and neuropsychological characteristics
16 significantly associated with RCD by univariate analysis are: living in an institution and a
17 high level of education (p-value < 0.03). In addition, a weaker level of autonomy and the loss
18 of 3 points or more on the MMSE during the year prior to inclusion tended to be associated
19 with RCD (p-value < 0.07). As there was a high number of missing values for the variable
20 “loss of 3 points or more on the MMSE during the year prior inclusion”, two multivariate
21 models were performed to analyze the risk of RCD (table 3). Model 1 included residential
22 status, level of education and loss of autonomy. In this model, only the level of education
23 remained significantly associated with RCD (OR = 2.21, 95%I.C. (1.12 – 4.37)). The second
24 model (model 2) was further adjusted for the loss of more than 3 points on MMSE prior
25 inclusion. In this model, the level of education and the loss of more than 3 points on MMSE
26 were significant predictors of rapid decline.

27

28 *The Deco questionnaire*

29 The mean Deco questionnaire score was 19.0 ± 8.8 . It was significantly different
30 between rapid decliners (15.5 [13.6; 17.5]) and slow decliners (20.3 [18.8; 21.8]) (p for
31 difference = 0.001) (table 4).

32 Table 4 displays the mean of the Deco score according to baseline characteristics of
33 the patients. No significant association was found for socio-demographic characteristics.

1 Significant lower values of Deco scores were observed for subjects with low level of (p-value
2 = 0.07).

3 Figure 2 shows the ROC curve of the predictive value of RCD according to the Deco
4 score. Visually, the threshold which maximizes the specificity and the sensitivity of the score
5 seems to be between 16 and 18. Table 5 reports the risks of RCD as well as the results from a
6 sensitivity/specificity analysis for three thresholds (a Deco score ≤ 16 , ≤ 17 or ≤ 18). The
7 best model in terms of risk was observed for the threshold of 16. The risk of RCD for a
8 patient having a score ≤ 16 for the Deco questionnaire was three times higher than for a
9 patient scoring over 16 (p=0.002). However, we found an interaction between age and the
10 threshold of 16 on the risk of RCD. For this threshold, the risk of RCD was significantly
11 increased among younger subjects (age < 75) but not among older ones (respectively OR =
12 6.7, 95% C.I. (1.8-25.1) and OR = 2.1, 95% C.I. (0.9-4.8)). As a consequence we ran new
13 analyses to evaluate the best predictive thresholds of RCD according to age-group (below or
14 over 75). Results are reported in table 6. We found that a threshold of 16 among subjects aged
15 below 75 years old and a threshold of 14 for subjects older than 75 years old maximized the
16 predictive values of the Deco score. Sensitivity, specificity and predictive values were
17 consistently better than in the analysis pooling the two age-groups.

18

19 **DISCUSSION**

20 In this one year observational study we found that 29.4% of patients with AD lost 3
21 points or more at the MMSE score and were thus classified as rapid decliners over the study
22 period. Living in an institution, having a high educational level and being impaired for at least
23 two activities in daily living were significantly associated with RCD. Finally, the Deco score
24 was differently related to the occurrence of RCD according to the age of the patient. A
25 threshold of 16 was found to be the best diagnostic tool for RCD among subjects aged < 75
26 years old while a threshold of 14 was found for subjects aged ≥ 75 years old.

27 In our study we found a relatively low proportion of rapid decliners compared with
28 other studies. Although other definitions of cognitive decline have been proposed [3; 13], a
29 decline of 3 points or more of the Mini-Mental State Examination (MMSE) over one year is a
30 commonly used definition of RCD. Indeed, several clinical or population-based studies have
31 shown that this threshold of decline was strongly linked to mortality or entry in an institution
32 [2; 14]. Moreover, the use of MMSE compared to other neuropsychological tests is the only
33 one to fit with clinical practice. In addition, all our patients were using ChEI so the low

1 proportion of rapid decliners found is consistent with the fact that rivastigmine, which is the
2 only therapy studied in this population, has been shown to reduce the risk of rapid cognitive
3 decline in patients using ChEI [4; 15].

4 As AD patients with RCD have a poorer prognosis, they warrant particular attention
5 from the clinician. Previous efforts have been made to identify risk factors of rapid decline
6 which could be targeted for timely introduction of preventive actions [6; 7; 16; 17] . In our
7 study, demographic factors as living in institution and high level of education, and previous
8 rapid decline appear as independent factors correlated with a rapid disease progression, while
9 the usual clinical predictors as poor nutritional status, psychotic or extrapyramidal signs were
10 not found to be correlated. While this lack of correlation could be attributed to the greater
11 benefits of rivastigmine in this population [5; 7], the low proportion of patients in our study
12 with such clinical symptoms at baseline should also be taken into account.

13 Even if certain factors may be good predictors of rapid decline, available data remain
14 contradictory [18] and are not sufficient or relevant in routine practice for clinical-decision
15 making, especially for newly diagnosed patients. In this respect, we aimed to assess the
16 capacity of a new scale to evaluate the one-year change in cognitive functioning of patients
17 according to their caregiver (or a person in contact with them). The Deco questionnaire used
18 in this study appeared to be a valuable clinical tool for the detection of RCD. Indeed, when
19 taking into account the age of the patients, thresholds of detection were strongly associated
20 with RCD. A Deco score of less than 16 among patients under 75 years old, and of less than
21 14 among patients over 75 years old, was found to be strongly associated with RCD. The risk
22 of being a rapid decliner was 3 to 6 times higher among patients whose caregiver scored less
23 than the threshold found for the Deco score. Moreover, the positive predictive value was close
24 to 50% in the younger age-group which is a relevant value for clinical decision making.
25 Indeed, it indicates that if an informant reports a score lower than 16 for a patient, there is
26 50% chance that this subject has actually encountered a rapid decline within the previous
27 year. Preventive care for these subjects appears necessary and will be useful for one patient
28 out of 2. In addition, it is to be noted that the predictive values of the Deco score were better
29 in the younger group of patients. This finding may be explained by the fact that older patients
30 complain less than younger ones and they, as well as their caregivers, may attribute their
31 changes in cognitive performances to age rather than to a pathological process. They may
32 report less frequently little cognitive changes. Hence, the Deco questionnaire could represent
33 a simple way of detecting patients with a high probability of rapidly progressing symptoms
34 and thus to adapt disease management accordingly.

1 While our results are promising, this study does have some limitations. It remains
2 merely a historical comparison and no definitive conclusion can be drawn. Moreover, only a
3 low number of neurologists finally recruited patients. Together with the fact that a quarter of
4 the patients were lost to follow-up, this could have introduced a bias. Our sample may not be
5 fully representative of the AD population and thus our results should be interpreted with
6 caution. Nonetheless, when enrolled patients' baseline characteristics were compared to those
7 of the finally analyzed population, no difference was found, especially in the items of level of
8 autonomy and cognitive impairment.

9 Overall this study suggests that AD patients at risk of RCD can be identified in the
10 setting of a regular consultation by means of the Deco questionnaire. Once alerted to the
11 possibility of an aggressive disease course, the physician could pay particular attention to
12 these patients and adapt disease management accordingly.

13

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17

1 Table 1 – Comparison of baseline characteristics of enrolled and analyzed patients
 2

	Enrolled Population N = 361	Analyzed population N = 204
Age (years), m ± SD	77.9 ± 7.55	78.0 ± 7.5
Sex (female)	215 (59.6%)	119 (58.3%)
Level of education		
* long secondary school	92 (25.6%)	53 (26.0%)
Residential status (out-patients)	302 (83.7%)	169 (82.8%)
Duration of the disease (years) , m ± SD	1.8 ± 1.5	1.8 ± 1.4
Psychotropic drugs	170 (47.1%)	106 (52.0%)
* neuroleptics	31 (8.6%)	20 (9.8%)
* antidépressive drugs	98 (27.1%)	60 (29.4%)
Previous treatment by ChEI		
* none	214 (59.3%)	115 (56.4%)
* rivastigmine	97 (26.9%)	63 (30.9%)
* other ChEI	50 (13.8%)	26 (12.7%)
Memantine	26 (7.2%)	10 (4.9%)
MMSE score, m ± SD	19.6 ± 4.6	19.7 ± 4.4
mini-Zarit score, m ± SD	3.1 ± 1.7	3.1 ± 1.7
4-IADL score (≥ 2 activities)	225 (62.4%)	123 (60.3%)
5 words test , m ± SD	5.6 ± 2.3	5.7 ± 2.3
Verbal fluency, m ± SD	10.7 ± 5.5	10.5 ± 5.1

3 Figures are given as n and % unless otherwise specified
 4 SD: Standard Deviation

1 Table 2. Association between baseline characteristics of patients and the risk of rapid
 2 cognitive decline. Univariate logistic regression.

	Rapid cognitive decline		OR (95%I.C.)	p-value
	Yes n=60	No n=144		
Sex				
Male	25 (29.4)	60 (29.4)		
Female	35 (70.6)	84 (70.6)	n.a	
Age				
<75 years old	16 (26.7)	43 (29.9)	1.00	
>= 75 years old	44 (73.3)	101 (70.1)	1.17 (0.60-2.30)	0.647
Residential status				
Out-patients	44 (73.3)	125 (86.8)	1.00	
Institution	16 (26.7)	19 (13.2)	2.39 (1.13-5.06)	0.022
Level of education				
primary or short secondary school	22 (36.7)	31 (21.5)	1.00	
long secondary school	38 (63.3)	113 (78.5)	2.11 (1.09-4.08)	0.026
BMI				
< 18.5 kg/m ²	9 (23.1)	30 (20.8)	0.68 (0.26-1.78)	0.432
18 <= BMI < 25 kg/m ²	15 (30.6)	34 (23.6)	1.00	
>= 25 kg/m ²	36 (60.0)	80 (55.6)	1.02 (0.50-2.10)	0.957
MMSE				
>=20	35 (58.3)	78 (34.2)	1.00	
<20	25 (41.7)	66 (45.8)	0.84 (0.46-1.55)	0.586
Verbal fluency				
>=15	12 (20.3)	27 (18.9)	1.00	
<15	47 (79.7)	116 (81.1)	0.91 (0.43-1.95)	0.811
5 words				
>=8	10 (16.7)	36 (25.2)	1.00	
<8	50 (83.3)	107 (74.8)	1.68 (0.77-3.66)	0.190
Clock				
>2	22 (37.9)	48 (35.6)	1.00	
<=2	36 (62.1)	95 (66.4)	0.83 (0.44-1.56)	0.557
Symptoms				
Agitation	13 (21.7)	22 (15.3)	1.72 (0.76-3.93)*	0.194
Hallucination	9 (15.0)	16 (11.1)	1.64 (0.65-4.18)*	0.298
Strolling	6 (10.0)	13 (9.0)	1.35 (0.46-3.92)*	0.584
Depression	14 (23.3)	38 (26.4)	1.08 (0.50-2.31)*	0.851
EPS	6 (10.0)	18 (12.5)	0.97 (0.35-2.73)*	0.959
Loss of autonomy for at least 2 activities				
No	18 (30.0)	63 (43.8)	1.00	
Yes	42 (70.0)	81 (56.2)	1.81 (0.95-3.45)	0.069
Previous ChEI treatment				
No	32 (53.3)	83 (57.6)	1.00	
Yes	28 (46.7)	61 (42.4)	1.19 (0.65-2.18)	0.572
Loss >= 3 points on MMSE in the previous year				
No	10 (29.4)	33 (49.3)	1.00	
Yes	24 (70.6)	34 (50.8)	2.33 (0.97-5.61)	0.060

* Compared with none trouble

Table 3. Risk of rapid decline in two multivariate logistic regression analyses

	Model 1 (n = 204)		Model 2 (n = 101)	
	OR (95%I.C.)	p-value	OR (95%I.C.)	p-value
Residential status				
Out-patients	1.00		1.00	
Institution	1.95 (0.89 - 4.31)	0.097	2.88 (0.97 - 8.59)	0.057
Level of education				
Primary or short secondary school	1.00		1.00	
long secondary school	2.21 (1.12 - 4.37)	0.022	4.94 (1.83 - 13.32)	0.002
Loss of autonomy for at least 2 activities				
No	1.00		1.00	
yes	1.71 (0.86 - 3.40)	0.124	0.72 (0.26 - 2.01)	0.529
Loss >= 3 points on MMSE in the previous year				
No			1.00	
yes			2.81 (1.03 - 7.65)	0.043

Table 4. Association between baseline characteristics of patients and the Deco score

	m	sd	p-value
Sex			
Male	18,5	9,1	0,618
Female	19,2	8,7	
Age			
<75 years old	19,1	8,8	0,803
>= 75 years old	18,8	8,9	
Residential status			
Out-patients	18,8	8,8	0,727
Institution	19,6	9,6	
Level of education			
Primary or short secondary school	19,1	9,1	0,388
long secondary school	18,3	8,1	
Loss of autonomy for at least 2 activities			
No	20,3	8,6	0,071
yes	17,9	8,9	
Rapid decline between inclusion and 12-month visit			
No	20,2	8,9	0,0008
yes	15,1	7,4	

Table 5. Predictive power of 3 thresholds of the Deco score. Univariate logistic regression.

		RCD		OR (95%I.C.)	p-value	Se	Sp	PPV	NPV
	Yes	No							
DECO > 16	17 (37.8)	85 (64.4)	1.00						
DECO ≤ 16	28 (62.2)	47 (35.6)	2.98 (1.46-6.00)	0.002	62.2	64.4	37.3	83.3	
DECO > 17	16 (35.6)	79 (64.4)	1.00						
DECO ≤ 17	29 (59.9)	53 (40.2)	2.70 (1.34-5.46)	0.006	64.4	59.9	35.4	83.2	
DECO > 18	15 (33.3)	72 (54.6)	1.00						
DECO ≤ 18	30 (66.7)	60 (45.5)	2.40 (1.18-4.87)	0.015	66.7	54.6	33.3	82.8	

RCD states for rapid cognitive decline, Se for sensitivity, Sp for specificity, PPV for positive predictive value, NPV for negative predictive value

Table 6. Best predictive thresholds of the Deco score according to age-groups. Univariate logistic regression.

	RCD		OR (95%I.C.)	p-value	Se	Sp	VPP	VPN
	Yes	No						
Age < 75 yrs old								
DECO > 16	4 (26.7)	29 (70.7)	1.00					
DECO <= 16	11 (73.3)	12 (29.3)	6.65 (1.76-25.1)	0.005	73.3	70.7	47.8	87.9
Age >= 75 yrs old								
DECO > 14	14 (17.5)	66 (82.5)	1.00					
DECO <= 14	16 (39.0)	25 (61.0)	3.02 (1.29-7.08)	0.011	57.8	74.2	43.3	83.8

RCD states for rapid cognitive decline, Se for sensitivity, Sp for specificity, PPV for positive predictive value, NPV for negative predictive value

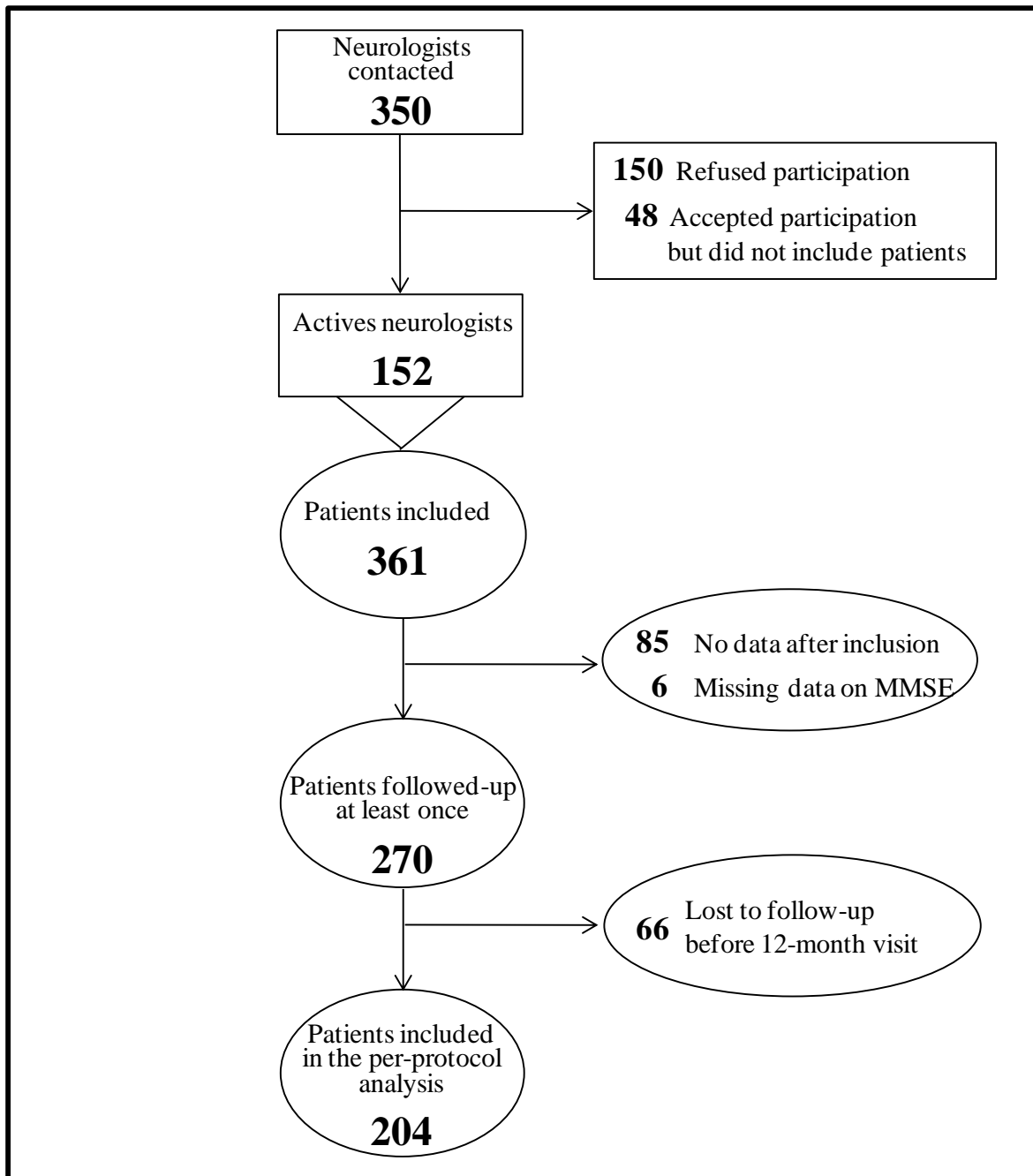


Figure 1: Flow chart of the patients' selection for the per-protocol analysis

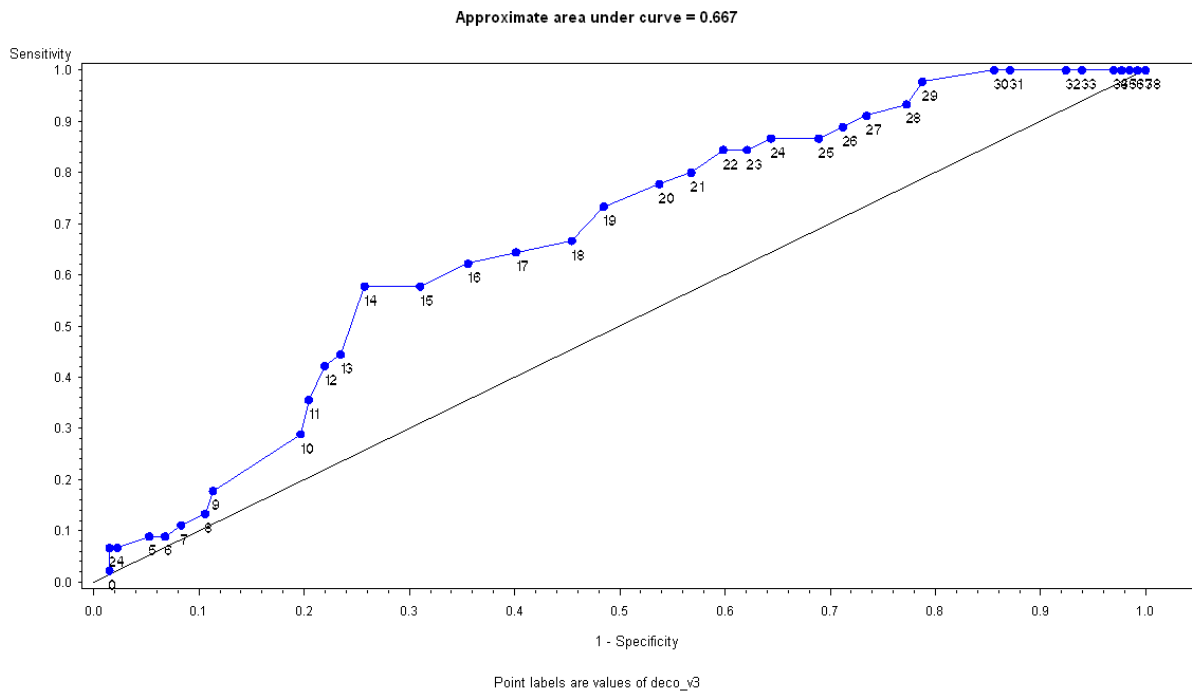


Figure 2: ROC curve for the prediction of rapid cognitive decline according to DECO scores