

The 5-Domain Niemann-Pick Disease Type C Clinical Severity Scale (NPCCCSS)



The Niemann-Pick Disease Type C Clinical Severity Scale (NPCCSS)



NPC is a progressive disease and the
NPCCSS IS AN NPC-SPECIFIC,
CLINICIAN-REPORTED TOOL
to characterize and quantify disease progression¹

The original NPCCSS has

17 DOMAINS:
9 MAJOR and 8 MINOR¹

[Click here for the 17 DOMAINS >>](#)



A shorter form of the NPCCSS containing the most
clinically relevant domains would allow clinicians to
FOCUS ON THE **CORE SYMPTOMS**
of the disease²

An abbreviated

5-DOMAIN NPCCSS

has been created to focus on domains identified
by patients, caregivers, and NPC experts as the most
clinically relevant when assessing disease progression²⁻⁴

[Click here for the abbreviated 5 DOMAINS >>](#)



The 5-Domain Niemann-Pick Disease Type C Clinical Severity Scale (NPCCSS)

Validating the 5-domain NPCCSS

The **5-domain NPCCSS** has demonstrated:



High correlation with the 17-domain NPCCSS (excluding the hearing domains)^{4,5}

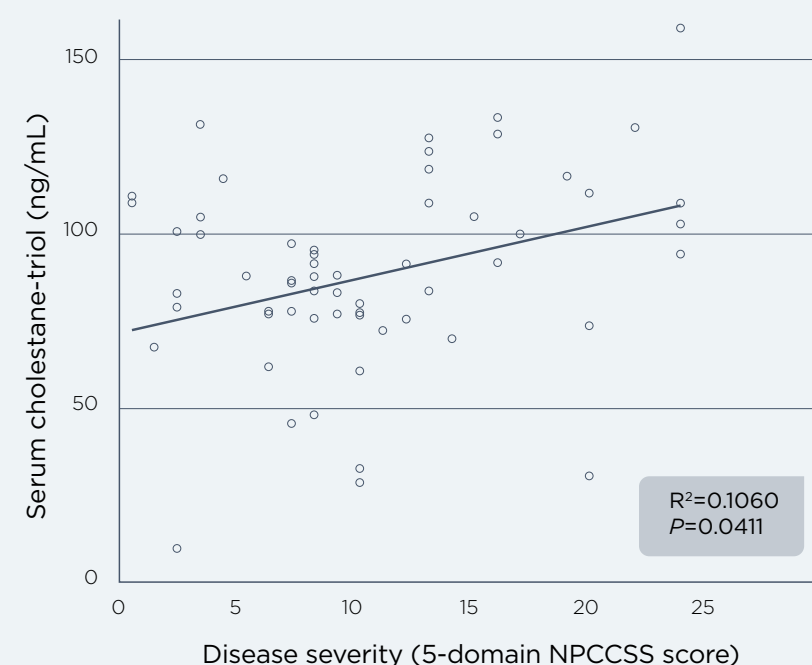
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Strong intra-rater and inter-rater reliability²

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Correlation of Serum Cholestane-triol, a Lipid Biomarker, With 5-Domain NPCCSS Scores²



- In clinical practice, cholestane-triol is frequently used as a biomarker to support diagnosis, as the levels correlate with NPC disease severity and age of disease onset^{6,7}
- In the NPC-001 study, cholestane-triol levels significantly correlated at the population level (Spearman's correlation coefficient=0.265, $P=0.0411$), with disease severity as measured by the 5-domain NPCCSS²

A Delphi study of 19 international NPC experts evaluated the utility of 6 clinical severity scales^{*8}

- There was consensus agreement ($\geq 70\%$) that the 5-domain NPCCSS should be used for the evaluation of disease in clinical practice
- The 5 domains within this scale are the 5 most clinically relevant domains to measure



*The 6 clinical severity scales evaluated were the 17-domain NPCCSS, 5-domain NPCCSS, NPC-specific disability scale, Disease-specific disability scale, NPC-cdb scale, and the Functional disability scale.⁸
cdb, clinical database; NPC, Niemann-Pick disease type C; NPCCSS, NPC Clinical Severity Scale.



The 5-Domain Niemann-Pick Disease Type C Clinical Severity Scale (NPCCSS)

Using the 5-domain NPCCSS



DOMAINS

- The 5 domains evaluate ambulation, fine motor skills, swallow, cognition, and speech⁵



SCORING

- Each domain is rated on a scale of 0–5 based on clinical assessments, observations, and interviews with patients/caregivers^{1,5}
- The clinician assigns a score for each domain based on his or her assessment of that particular symptom⁵



TOTAL SCORE

- The patient will have a score from 0–25, with a higher score indicating more severe clinical impairment⁵
- The total score is a composite of the 5 domains that reflects the full impact of NPC on patients' functioning. No single domain can be viewed as the most clinically relevant^{2,5}

CONSIDERATIONS

- NPC is a heterogeneous, progressive disease and patients may have wide variability between the scoring of the different domains^{1,2}
- The progressive nature of NPC is highly variable. For example, a patient may be stable over a period of time and then they may progress quickly in certain domains^{1,4}
- Additional care should be given to assessing patients aged 2–4 years due to the potential for interference of normal child development with the interpretation of the domain scores⁵



The 5-Domain Niemann-Pick Disease Type C Clinical Severity Scale (NPCCSS)

Interpreting the 5-domain NPCCSS⁵

- NPC is a progressive disease and patients and caregivers view any change in any domain as clinically meaningful and a signal that the disease is progressing and worsening⁵
- Most NPC experts view a 1-category change as clinically meaningful, corresponding to a 1- or 2-point change within the total score⁵

Domain	Score					
	0	1	2	3	4	5
Ambulation	Normal	Clumsy	Ataxic unassisted gait or not walking by 18 months		Assisted ambulation or not walking by 24 months	Wheelchair dependent
Fine motor skills	Normal	Slight dysmetria/dystonia (independent manipulation)	Mild dysmetria/dystonia (requires little to no assistance; able to feed self without difficulty)		Moderate dysmetria/dystonia (limited fine motor skills; difficulty feeding self)	Severe dysmetria/dystonia (gross motor limitation; requires assistance for self-care activities)
Swallow	Normal, no dysphagia	Cough while eating •Intermittent dysphagia* +1=with liquids +1=with solids •Dysphagia* +2=with liquids +2=with solids			Nasogastric tube or gastric tube for supplemental feeding	Nasogastric tube or gastric tube feeding only
Cognition	Normal	Mild learning delay; grade appropriate for age		Moderate learning delay; individualized curriculum or modified work setting	Severe delay/plateau; no longer in school or no longer able to work; some loss of cognitive function	Minimal cognitive function
Speech	Normal	Mild dysarthria (easily understood)	Severe dysarthria (difficult to understand)	Nonverbal/functional communication skills for needs		Minimal communication

Click on any domain to expand

Click here for an example scoring sheet

⁵Score is additive (to the “cough while eating” score of 1) within the 2 subsections of intermittent dysphagia and dysphagia.
NPC, Niemann-Pick disease type C.



References: **1.** Yanjanin NM et al. *Am J Med Genet B Neuropsychiatr Genet.* 2010;153B:132-140; **2.** Mengel E et al. *Orphanet J Rare Dis.* 2020;15:328; **3.** The Ara Parseghian Medical Research Fund. Niemann-Pick disease type C patient and caregiver voices: externally-led, patient-focused drug development meeting. March 18, 2019. Accessed December 30, 2020. <https://nnpdf.org/files/2019/09/NPC-PFDD-Voice-of-the-Patient-report-09162019.pdf>; **4.** Cortina-Borja M et al. *Orphanet J Rare Dis.* 2018;13:143; **5.** Orphazyme Data on File; **6.** Patterson MC et al. *Neurol Clin Pract.* 2017;7:499-511; **7.** Porter FD et al. *Sci Transl Med.* 2010;2:56ra81; **8.** Niemann-Pick UK (NPUK). NP-C Clinical Severity Scales – Delphi Study: NPUK Interactive Workshop. September 25, 2020; **9.** Patterson MC et al. *WORLD Symposium 2021*; Poster 190.



9 MAJOR DOMAINS¹

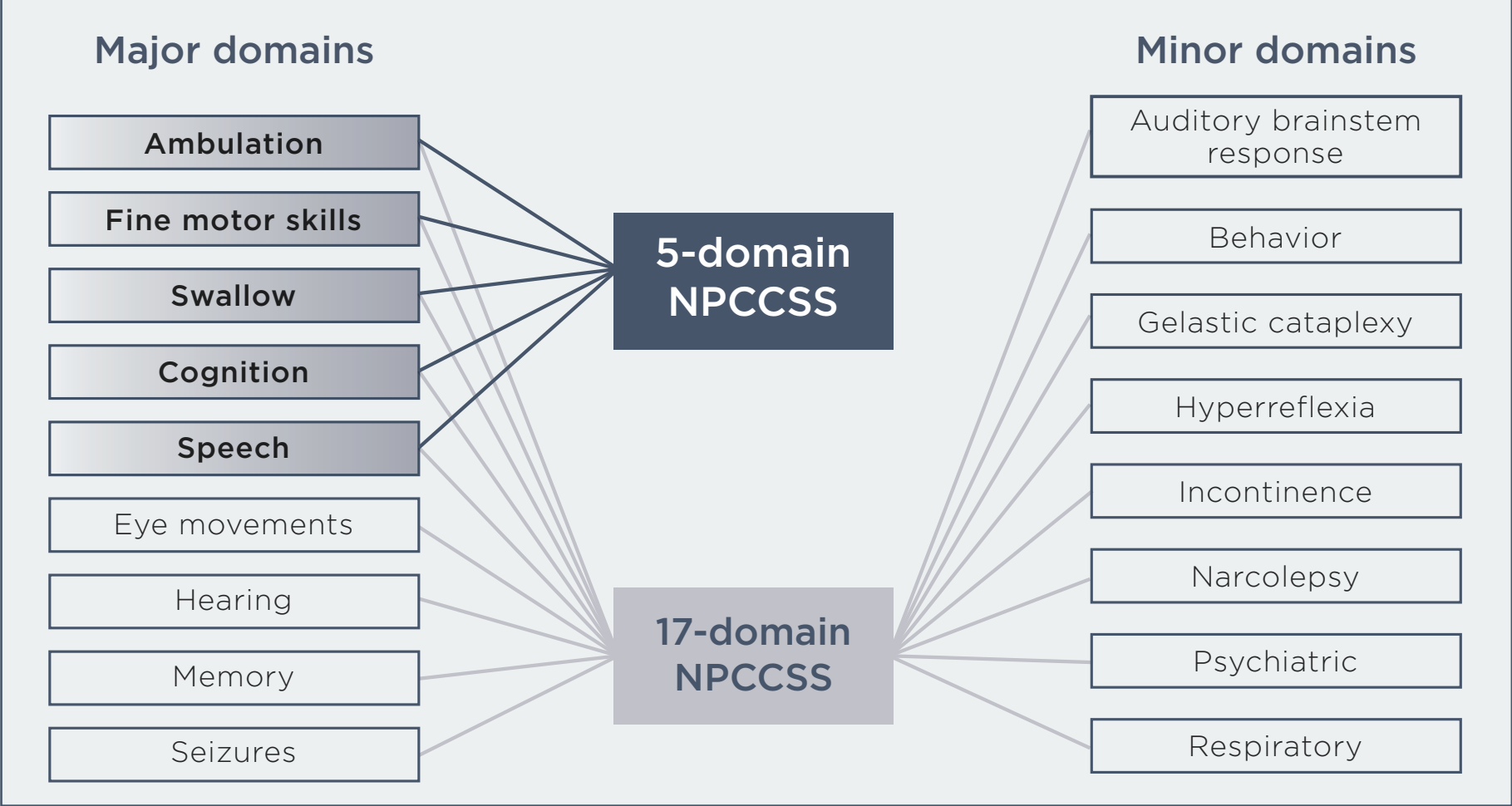
Ambulation	Cognition	Hearing
Fine motor skills	Speech	Memory
Swallow	Eye movements	Seizures

8 MINOR DOMAINS¹

Auditory brainstem response	Behavior	Gelastic cataplexy
Hyperreflexia	Incontinence	Narcolepsy
Psychiatric	Respiratory	

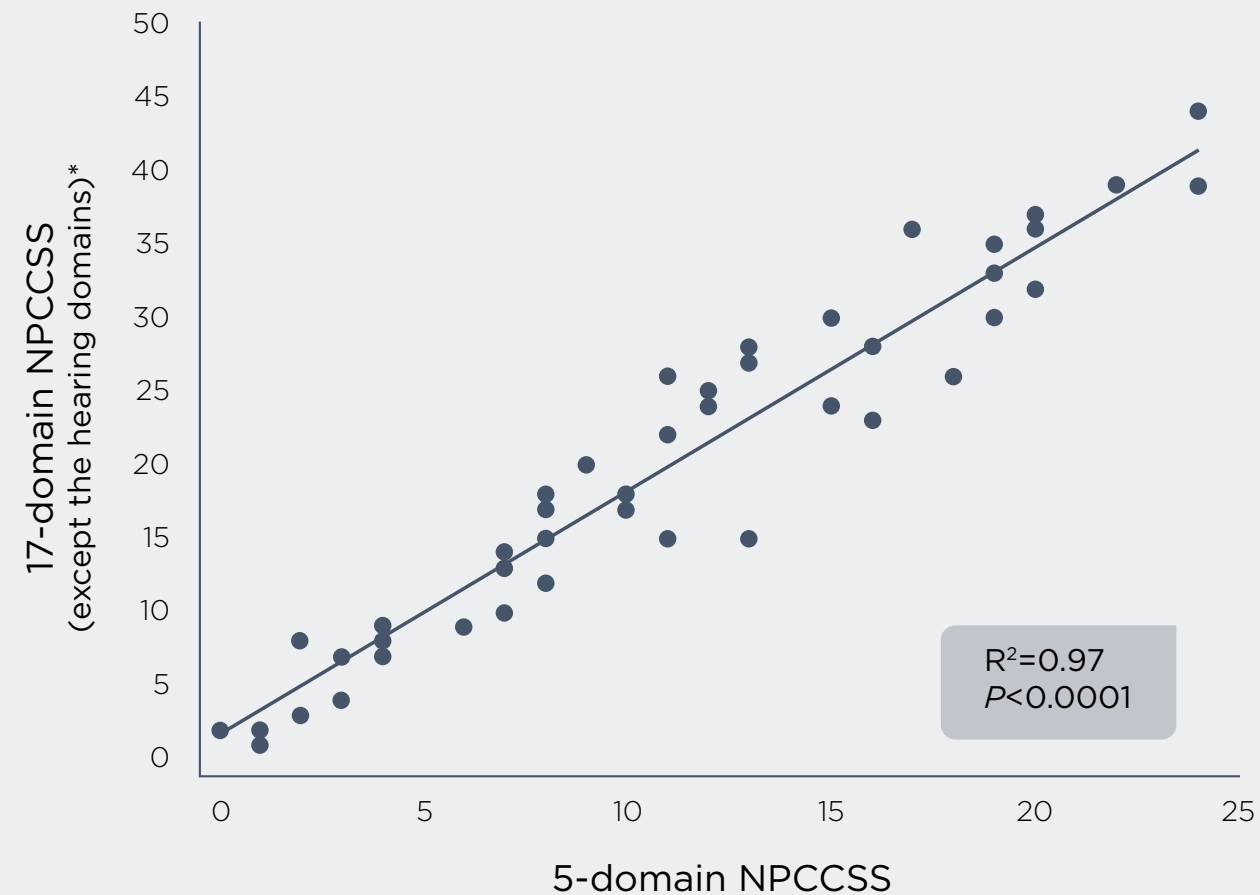


Domains of the NPC Clinical Severity Scales²



NPC, Niemann-Pick disease type C; NPCCSS, NPC Clinical Severity Scale.

5-Domain NPCCSS Score vs 17-Domain NPCCSS Score
(Except the Hearing Domains)* at Baseline of the NPC-002 Study⁵



*The excluded domains are the major domain of hearing and the minor domain of auditory brainstem response.^{2,5}

High correlation between the 5- and 17-domain NPCCSS (except the hearing domains)^{*5}

- Spearman's correlation=0.97

NPC, Niemann-Pick disease type C; NPCCSS, NPC Clinical Severity Scale.



Reliability of the 5-Domain NPCCSS ²		
Domain	Kappa Coefficient of Concordance	
	Initial rating	Repeat rating
Ambulation	0.785	0.681
Cognition	0.917	0.883
Fine motor skills	0.763	0.723
Speech	0.954	0.949
Swallow	0.813	0.858

- The 5-domain NPCCSS showed high ICC agreement in inter- and intra-rater reliability (ICC=0.995 and ICC=0.937, respectively)²
- This reliability study supports use of the 5-domain NPCCSS as an abbreviated alternative to the 17-domain NPCCSS on the most relevant domains of NPC²

ICC, intraclass correlation coefficient; NPC, Niemann-Pick disease type C; NPCCSS, NPC Clinical Severity Scale.

cdb, clinical database; NIH, National Institutes of Health; NPC, Niemann-Pick disease type C.

²The 6 clinical severity scales evaluated were the 17-Domain NPCCSS, 5-Domain NPCCSS, NPC-Specific Disability Scale, Disease-Specific Disability Scale, NPC-cdb Scale, and the Functionality Disability Scale.⁶

The 5-Domain NPCCSS: Ambulation⁵

Domain	Score					
	0	1	2	3	4	5
Ambulation	Normal	Clumsy	Ataxic unassisted gait or not walking by 18 months		Assisted ambulation or not walking by 24 months	Wheelchair dependent

Return to the full table

- **Ambulation is rated on a scale of 0 to 5**, from normal to wheelchair bound⁵
- The domain of **ambulation** is frequently chosen as the most important domain by NPC patients and caregivers⁹
- **Ambulation** is identified as a key domain due to the importance to patients of being able to move independently or not relying on someone to be mobile, and concerns about risks of falling or the greater health impacts associated with losing the ability to walk⁹

⁵NPCCSS, Niemann-Pick disease type C Clinical Severity Scale.

The 5-Domain NPCCSS: Fine Motor Skills⁵

Domain	Score					
	0	1	2	3	4	5
Fine motor skills	Normal	Slight dysmetria/dystonia (independent manipulation)	Mild dysmetria/dystonia (requires little to no assistance; able to feed self without difficulty)		Moderate dysmetria/dystonia (limited fine motor skills; difficulty feeding self)	Severe dysmetria/dystonia (gross motor limitation; requires assistance for self-care activities)

Return to the full table

- **Fine motor skills are rated on a scale of 0 to 5**, from normal to severe dysmetria/dystonia⁵
- **Fine motor skills** is identified as a key domain due to the impact of hand tremors or difficulty coordinating hands has on patients' everyday activities, like eating, writing, and caring for themselves⁹

NPCCSS, Niemann-Pick disease type C Clinical Severity Scale.

The 5-Domain NPCCSS: Swallow⁵

Domain	Score					
	0	1	2	3	4	5
Swallow	Normal, no dysphagia	Cough while eating <ul style="list-style-type: none">• Intermittent dysphagia +1=with liquids +1=with solids• Dysphagia +2=with liquids +2=with solids			Nasogastric tube or gastric tube for supplemental feeding	Nasogastric tube or gastric tube feeding only

Return to the full table

- **Swallow is rated on a scale of 0 to 5**, from normal to requiring a nasogastric tube or relying on gastric tube feeding only⁵
- **Swallow** is identified as a key domain due to the possible risks of choking, aspiration, pneumonia, and even death⁹
- Under the **swallow** category, the “cough while eating” score of 1 has additive symptoms. Intermittent dysphagia or dysphagia with liquids or with solids is additive⁵
 - For example, for intermittent dysphagia with solids and dysphagia with liquids, a score of 4 applies (1+1+2)

The 5-Domain NPCCSS: Cognition⁵

Domain	Score					
	0	1	2	3	4	5
Cognition	Normal	Mild learning delay; grade appropriate for age		Moderate learning delay; individualized curriculum or modified work setting	Severe delay/ plateau; no longer in school or no longer able to work; some loss of cognitive function	Minimal cognitive function

Return to the full table

- **Cognition is rated on a scale of 0 to 5**, from normal to minimal cognitive function⁵
- **Cognition** is identified as a key domain due to the impact on patients’ education or work⁹

The 5-Domain NPCCSS: Speech⁵

Domain	Score					
	0	1	2	3	4	5
Speech	Normal	Mild dysarthria (easily understood)	Severe dysarthria (difficult to understand)	Nonverbal/ functional communication skills for needs		Minimal communication

Return to the full table

- **Speech is rated on a scale of 0 to 5**, from normal to minimal communication⁵
- **Speech** is identified as a key domain due to the importance communication has in everyday life, especially in expressing patients' needs or wants⁹

Sample Clinician Scoring Sheet for 5-Domain NPCCSS⁵



5-domain NPCCSS (Clinician Reported)

Date completed: _____ Patient ID: _____

Please refer to the 5-domain NPCCSS Scoring Guidelines on how to score.

Indicate the correct score (circle the appropriate number).

Ambulation	Score
Normal	0
Clumsy	1
Ataxic unassisted gait or not walking by 18 months	2
Assisted ambulation or not walking by 24 months	4
Wheelchair dependent	5
Fine Motor Skills	Score
Normal	0
Slight dysmetria/dystonia (independent manipulation)	1
Mild dysmetria/dystonia (requires little to no assistance; able to feed self without difficulty)	2
Moderate dysmetria/dystonia (limited fine motor skills; difficulty feeding self)	4
Severe dysmetria/dystonia (gross motor limitation; requires assistance for self-care activities)	5

Swallow	Score
Normal, no dysphagia	0
Cough while eating Intermittent dysphagia* with liquids +1 with solids +1 Dysphagia* with liquids +2 with solids +2 *To be added to "cough while eating" score of 1.	1
Nasogastric tube or gastric tube for supplemental feeding	4
Nasogastric tube or gastric tube feeding only	5
Cognition	Score
Normal	0
Mild learning delay; grade appropriate for age	1
Moderate learning delay; individualized curriculum or modified work setting	3
Severe delay/plateau; no longer in school or no longer able to work; some loss of cognitive function	4
Minimal cognitive function	5

Speech	Score
Normal	0
Mild dysarthria (easily understood)	1
Severe dysarthria (difficult to understand)	2
Nonverbal/functional communication skills for needs	3
Minimal communication	5

Completed by: _____

Signature: _____