Patient-No*:_____male☐ female☐ **Year of birth** _____
(*Will be given by study center)

Referring Center:_____ **Case Manager***_____

***Tel.-No.:** _____ ***Email:**_____

Date of questionnaire: _____

Prerequisites:

A) Clinical signs raising the suspicion of NF1 or Legius syndrome

1) Café au lait spots (CALS), hyperpigmented skin areas: yes☐ no☐

   Typical NF1-associated CALS: no. > 1cm [ ] max. size (cm) [ ]

   Typical NF1-associated CALS: no. < 1cm [ ] max. size (cm) [ ]

   Macules with irregular boarders and/or pigmentation: no. > 1cm [ ] max. size (cm) [ ]

   Body distribution of CALS/hyperpigmented macules: segmental☐ generalized☐

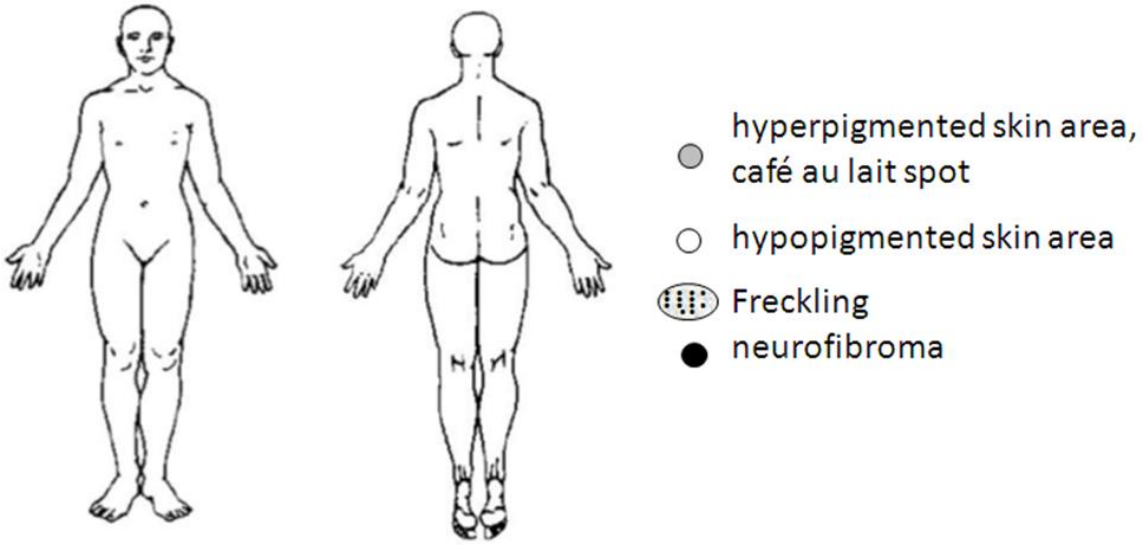
2) Other signs of NF1 ☐ yes ☐ no Specify (number) _____

   _____

Describe the localization and type of cutaneous and pigmentary alterations or indicate in the body scheme below:

_____

_____



B) *NF1* and *SPRED1* mutation analysis

(may be filled retrospectively by laboratory performing analysis)

1) *NF1* mutation analysis performed: yes ☐ no ☐

Specify lab that performed the analysis and method used:_____

_____

mention all methods applied: e.g. massive parallel sequencing of gene panel (NGS, incl./excl. CNV analysis), RNA-analysis by cDNA sequencing, CNV-analysis by MLPA, other

Mutation or variant of unknown significance (VUS) found: yes ☐ no ☐

If yes, specify mutation or VUS:_____

name mutation/VUS at cDNA and protein level

2) *SPRED1* mutation analysis performed: yes ☐ no ☐

Specify method used:_____

mention all methods applied: e.g. massive parallel sequencing of gene panel (NGS, incl./excl. CNV analysis), RNA-analysis by cDNA sequencing, CNV-analysis by MLPA, other

Mutation or variant of unknown significance (VUS) found: yes ☐ no ☐

If yes, specify mutation or VUS:_____

name mutation/VUS at cDNA and protein level

C) Absence of diagnostic NF1 sign(s) in both patents

1) Diagnostic NF1 sign(s) in **mother**: yes ☐ no ☐ not assessed ☐
Status was *:
   a. assessed by physical examination by referring physician ☐
   b. self reported upon interrogation ☐
   c. reported by partner/close releative upon interrogation ☐

*tick only one

2) Diagnostic NF1 sign(s) in **father**: yes ☐ no ☐ not assessed
Status was *:
   a. assessed by physical examination by referring physician ☐
   b. self reported upon interrogation ☐
   c. reported by partner/close releative upon interrogation ☐

*tick only one

Additional features, at least one (either in the family or in the patient) is required

***In the family*:**

1) Consanguinity of parents*: yes ☐ _____ no ☐ unknown ☐
   *as reported by parents — specify relationship

2) Both parents come from a population with known MMR gene founder mutations: yes ☐ no ☐

   If yes, specify population and known MMR gene founder mutation _____

3) Sibling with diagnostic NF1 sign(s): yes ☐ no ☐

   If yes, [ ] no. of siblings, specify signs _____
   (e.g. >5 CALM Ø > 1cm; 1 plexiform neurofibroma; etc.)

   Status was *:

   a. assessed by physical examination of sibling by referring physician: ☐

   b. reported by parent/close releative upon interrogation: ☐

   *tick only one

4) A (deceased) sibling with any type of childhood malignancy: yes ☐ no ☐

   If yes, specify malignancy and age at diagnosis: _____

5) Genetic diagnosis of Lynch syndrome in one or both of the parental families yes ☐ no ☐

   If yes, specify: paternal ☐ maternal ☐ : MMR gene and mutation _____

6) A carcinoma from the Lynch syndrome spectrum* before the age of 60 years in first-degree or second-degree relative: yes ☐ no ☐

   If yes, specify relationship to patient, carcinoma and age at diagnosis: _____

   _____

   *colorectal, endometrial, ovarian, gastric, small bowel, bile duct or gall bladder, pancreatic, urothelial carcinoma

***In the patient*:**

7) Hypopigmented skin areas (ash-leave spots): yes ☐ no ☐

   If yes, no. of macules > 1cm [ ] max. size (cm) [ ];

   body distribution segmental ☐ generalized ☐

8) Atypical CALMs (irregular borders and/or pigmentation)*: yes ☐ no ☐
   (*If yes, also fill question A1 and body scheme on page 1)

9) Pilomatricoma (=calcifying epithelioma of Malherbe) yes ☐ no ☐

   If yes; no. [ ]; age at diagnosis in years [; ;]; localisation: _____

10) Other cutaneous alterations (e.g. hemangioma, hairy naevi, Lupus erythematosus etc.)

yes ☐ _____ no ☐
(specify)

11) Congenital brain anomalies*: yes ☐ _____ no ☐ not known[a] ☐
(specify*)

[a] tick when no brain MRI was performed;

Other congenital anomalies*: yes ☐ _____ no ☐ not known ☐
(specify*)

*Brain anomalies, e.g. multiple developmental vascular anomalities (DVAs) in separate regions of the brain, brain cavernoma, agenesis of corpus callosum +/- gray matter heterotopia;
Other anomalies, e.g. syndactyly; urinary tract or genital parts; heart and vessel; dysmorphic features; other

CMMRD testing results

1) Mismatch repair mutation analysis performed, please tick which genes were analysed:

MLH1	☐	MSH2	☐
MSH6	☐	PMS2	☐
EPCAM	☐	No MMR sequencing was performed	☐

Specify lab that performed the analysis and method used:_____

_____

mention all methods applied: e.g. massive parallel sequencing of gene panel (NGS, incl./excl. CNV analysis), RNA-analysis by cDNA sequencing, CNV-analysis by MLPA, other

Mutation(s) or variant(s) of unknown significance (VUS) found: yes ☐ no ☐

If yes, specify mutation or VUS:_____

2) Functional analyses performed: yes ☐ no ☐
If yes, please specify method:

gMSI according to Ingham et al. ☐
Methylation tolerance testing according to Bodo et al. ☐
High-sensitivity microsatellite instability assay according to Gonzalez-Acosta et al. ☐
High-sensitivity microsatellite instability assay according to Gallon et al. ☐
Other, please specify: _____

Fuctional testing results indicated CMMRD: yes ☐ no ☐
If yes, please specify results:_____

Send a copy of the completed form to study center: email: katharina.wimmer@i-med.ac.at, Institut für Humangenetik, Medizinische Universität Innsbruck, Peter-Mayr-Str 1, 6020 Innsbruck, Austria

Evaluation whether C4CMMRD criteria for testing are fulfilled

Summary table which can be used at your own discretion to summarize whether the patient meets the testing criteria. It is *not* required to fill out this table to enter the patient in the study/database. Patient fulfills criteria for CMMRD testing when all three prerequisites are fulfilled and at least one additional feature (either in the family or in the patient) is present:

Criteria for CMMRD testing fulfilled: yes ☐ no ☐

Criteria for CMMRD counselling and testing in a child suspected to have NF1/Legius syndrome without malignancy		
Prerequisites fulfilled:	**yes**	**no**
Suspicion of NF1 due to the presence of at least one diagnostic NF1 feature*, including at least two hyperpigmented skin patches reminiscent of CALMs		
No *NF1* and *SPRED1* germline mutations detected using comprehensive and highly sensitive mutation analysis protocols.		
Absence of diagnostic NF1 sign(s) in both parents.		
Additional features in the family:		
Consanguineous parents.		
Sibling with diagnostic NF1 sign(s)		
A (deceased) sibling with any type of childhood malignancy		
Genetic diagnosis of Lynch syndrome in one or both of the parental families		
Carcinoma(s) from the Lynch syndrome spectrum[a] before the age of 60 years in first-degree or second-degree relative		
Additional features in the patient:		
Atypical CALMs (irregular borders and/or pigmentation)		
Hypopigmented skin patches		
One or more pilomatricoma(s) in the patient		
brain MRI in the patient: multiple developmental vascular abnormalities (DVAs) in separate regions of the brain		
agenesis of the corpus callosum		
non-therapy-induced cavernoma		

* Neurofibromatosis conference statement.(1)

[a] colorectal, endometrial, ovarian, gastric, small bowel, bile duct or gallbladder, pancreatic, urothelial cancer

1. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol. 1988;45(5):575-8.