European Reference Network

Endo-ERN

Genetic Endocrine Tumour Syndromes (MTG4) HCP Meeting

Frederic Castinetti, Antje Redlich, Petra Bruegmann

Funded by the European Union

MANAGEMENT & COORDINATION

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Frederic Castinetti Adult chair

Assistance Publique – Hôpitaux de Marseille (Marseille, France)

Frederic Castinetti

Antje Redlich Paediatric chair

University Children's Hospital Magdeburg (Magdeburg, Germany)

Antje Redlich

Petra Bruegmann ePAG representative

German Network of Pituitary and Adrenal Diseases (Fürth, Germany)

Petra Bruegmann

NEXT MEETING TO BE HELD IN OCTOBER 2025 (Date to be confirmed)

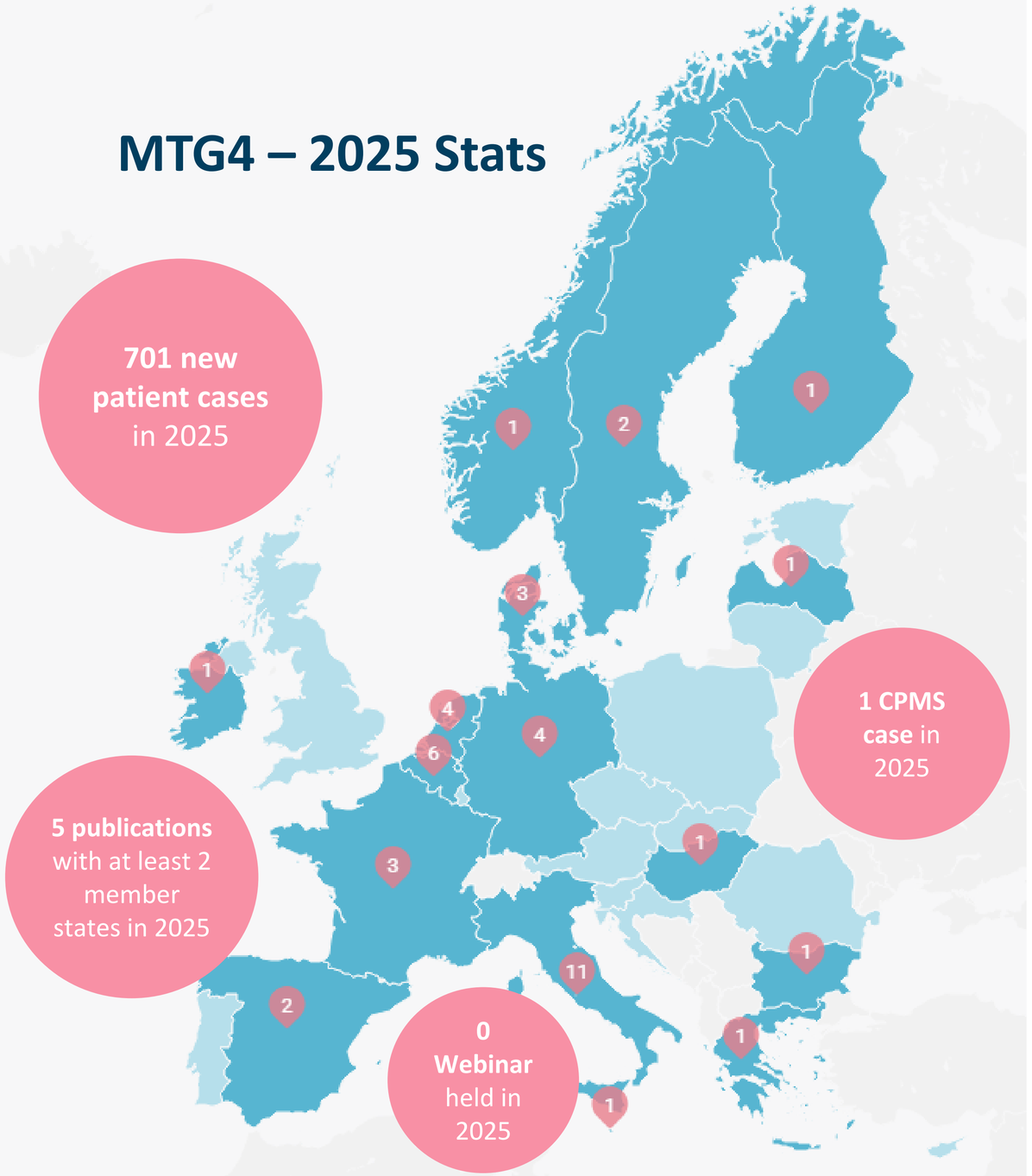
MTG4 – 2025 Stats

701 new patient cases in 2025

1 CPMS case in 2025

5 publications with at least 2 member states in 2025

0 Webinar held in 2025



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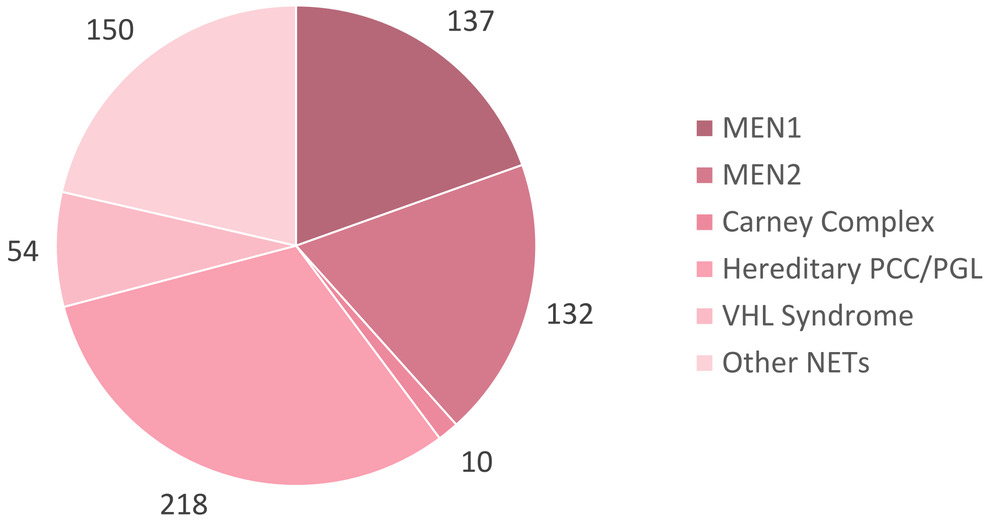
No. of new patients per MTG4 sub thematic area of new patients



MTG4 HCPS - 2025 Stats

43 HCPS in MTG4 formally

37 HCPs reporting in **e-REC** registry

32 HCPs reported they attended at least 1 **MTG meeting**

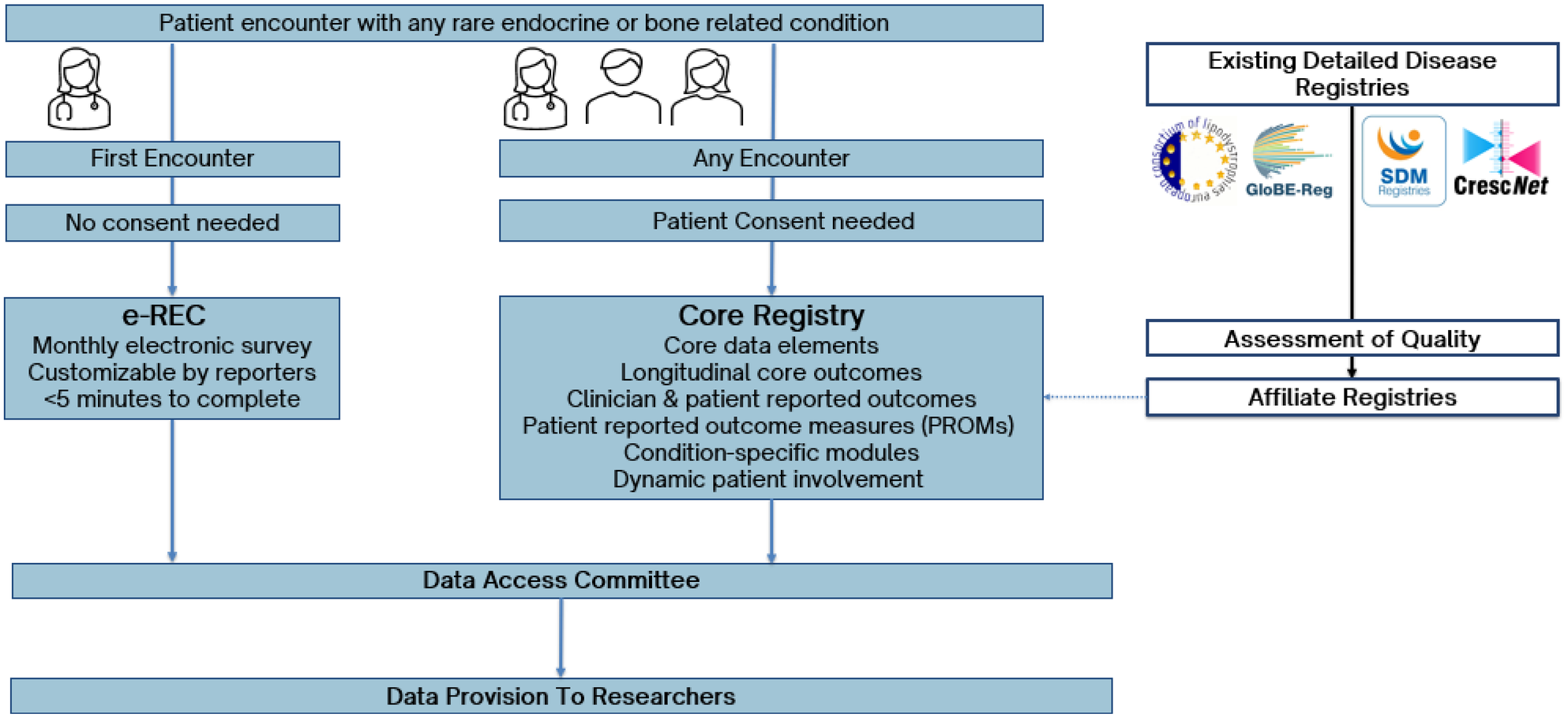
23 HCPs participated in at least 1 **CPMS panel**

- 33 HCPs have **different** EC & e-REC totals
- 5 HCPs **do not have** Endo-ERN logo/url at their website
- 8 HCPs who did not measure patient satisfaction – this is based on your HCP **NOT your department** usually

The EuRREB Registries: Supporting Research within MTG4

Ana Priego
EuRREB Quality Manager

The Registries in a Nutshell



MEN-1 Module Study Group

Name	Expertise / Role	Country
Alberto Pereira	endocrinologist, Endo-ERN coordinator	the Netherlands
Carla Pieterman	endocrinologist	the Netherlands
Cinzia Aurilia	patient representative	Italy
Faisal Ahmed	peadiatric endocrinologist, EuRREB coordinator	United Kingdom
Francesca Marini	endocrinologist	Italy
Francesca Giusti	endocrinologist	Italy
Frederic Castinetti	endocrinologist	France
Gerlof Valk	endocrinologist	the Netherlands
Ludwig Schaaf	endocrinologist	Germany
Maria Luisa Brandi	endocrinologist	Italy
Mariya Cherenko	endocrinologist, EuRREB data manager	the Netherlands
Medard van den Broek	endocrinologist	the Netherlands
Natasha Appelman-Dijkstra	internist-endocrinologist, EuRREB coordinator	the Netherlands
Petra Brügmann	patient representative	Germany

Developing the MEN-1 Condition-Specific Module

Working Group

'Develop a CSM to collect natural history of MEN-1, with a focus on DPNETs, breast cancer, and manifestations of very aggressive forms of MEN-1'

Study Group

Consensus
- Meetings
- Final dataset

Plan
- From the dataset to the platform
- Developments

Build
- Beta version

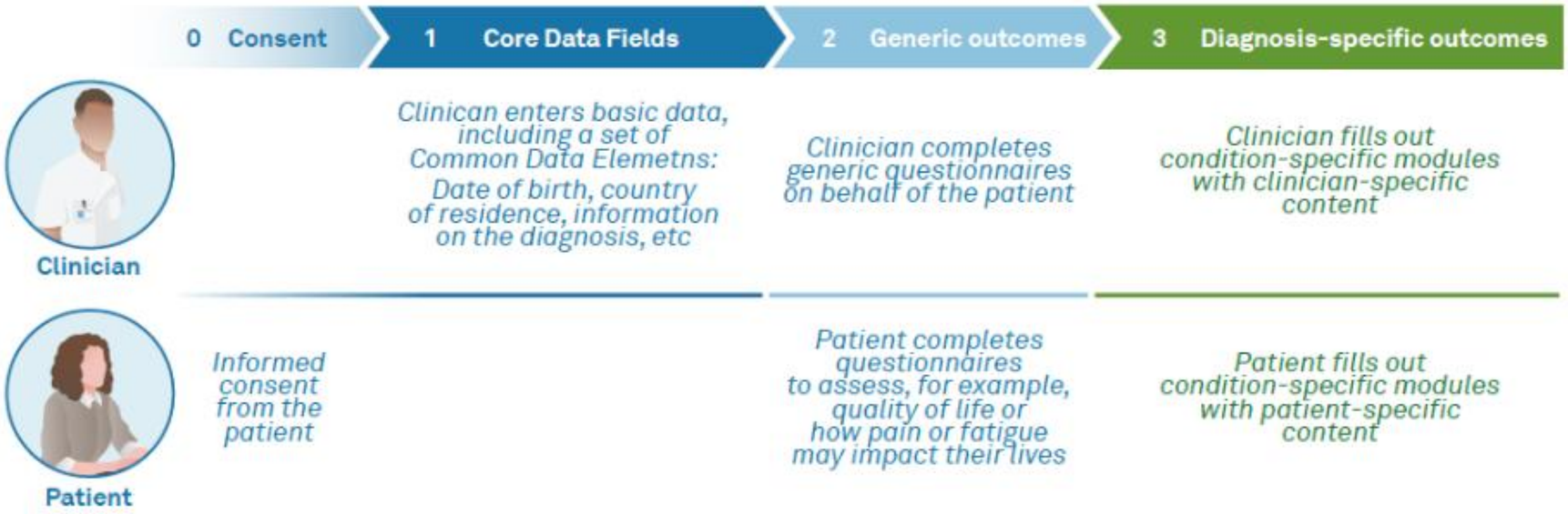
Test
- Feedback
- Final changes

Live version
- Available for users

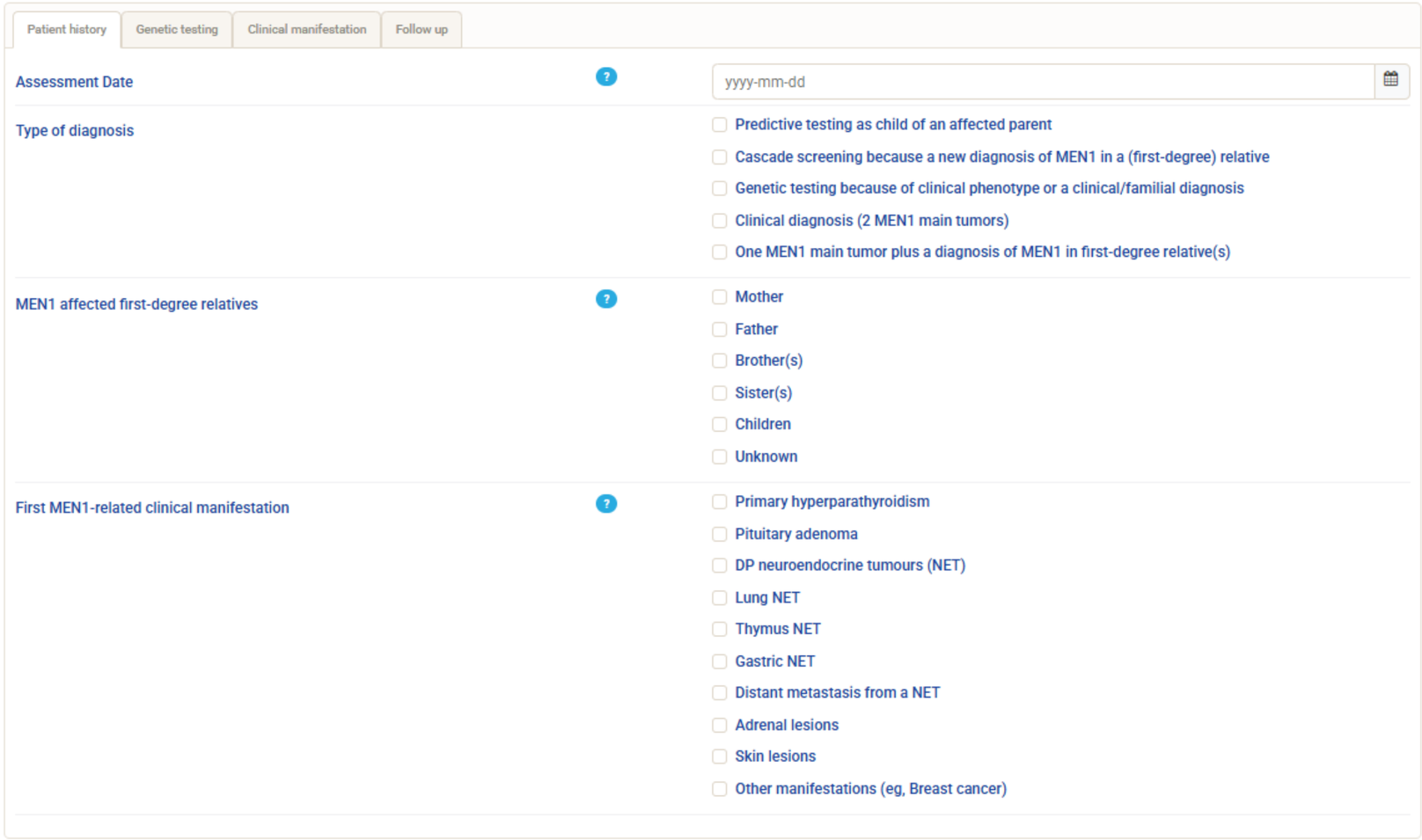
→ Patients

→ Clinicians

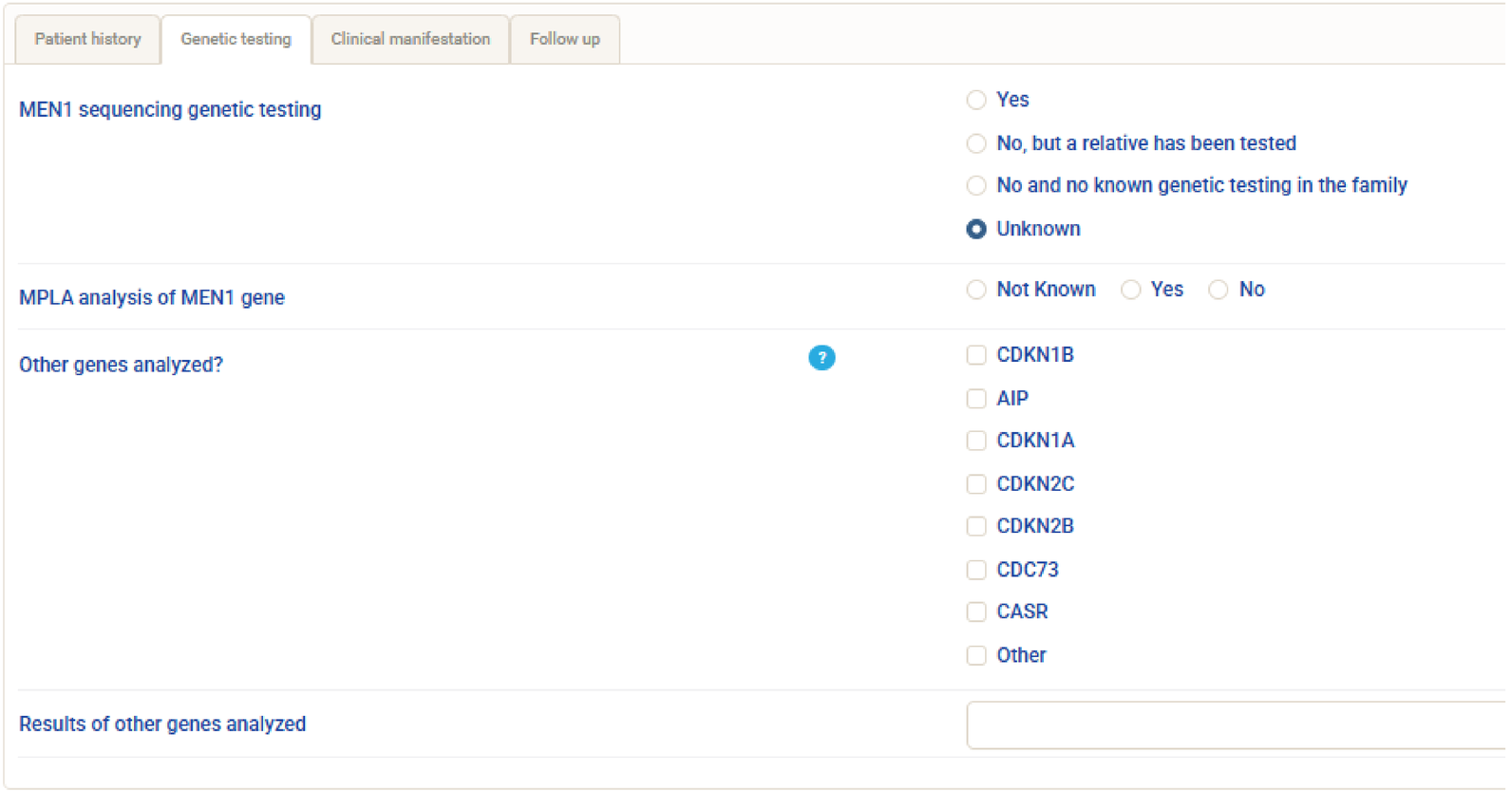
Data Entry Flow in the Core Registry



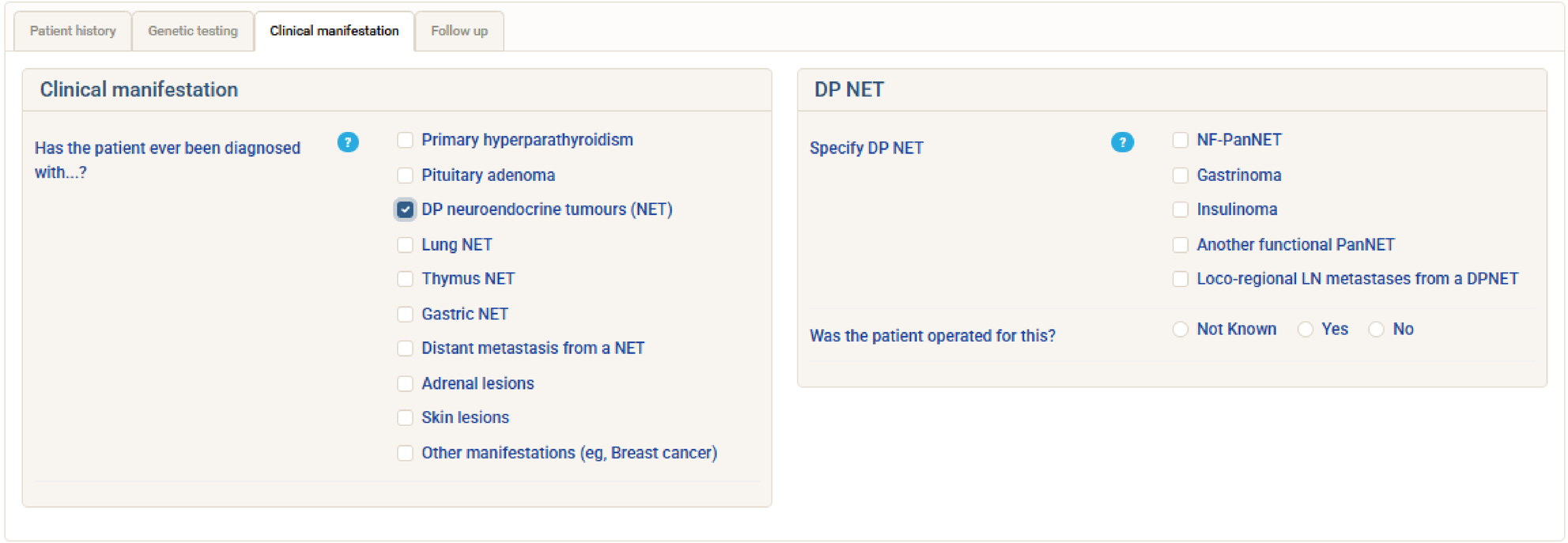
The MEN-1 Condition-Specific Module



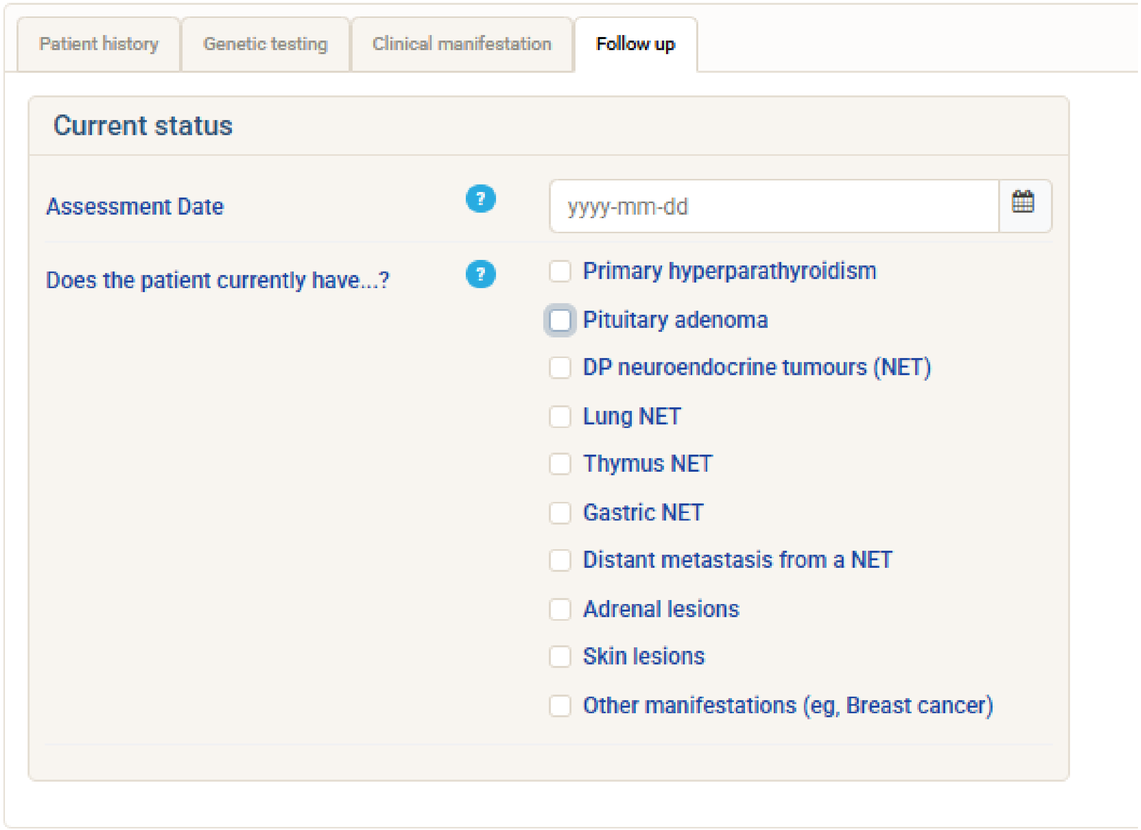
The MEN-1 Condition-Specific Module



The MEN-1 Condition-Specific Module



The MEN-1 Condition-Specific Module



Tools Used in the Module

Currently collected

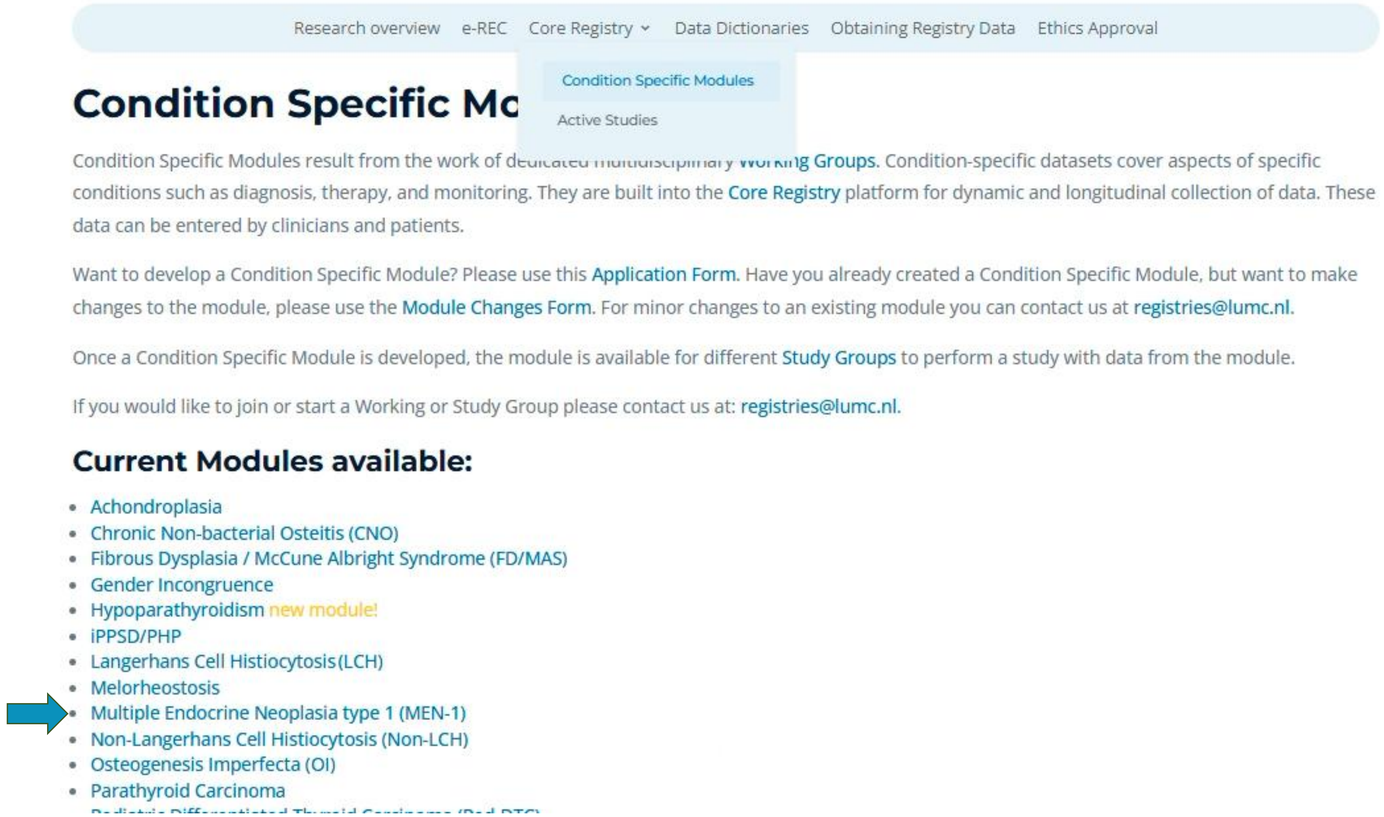
- EQ-5D-5L
- CWS - Cancer Worry Scale

To be included

- HADS – Hospital Anxiety and Depression Scale

The MEN-1 Condition-Specific Module

eurreb.eu



Ways to contact us:

eurreb.eu

registries@lumc.nl

drop-in sessions via Zoom

European Registries for Rare Endocrine and Bone Conditions

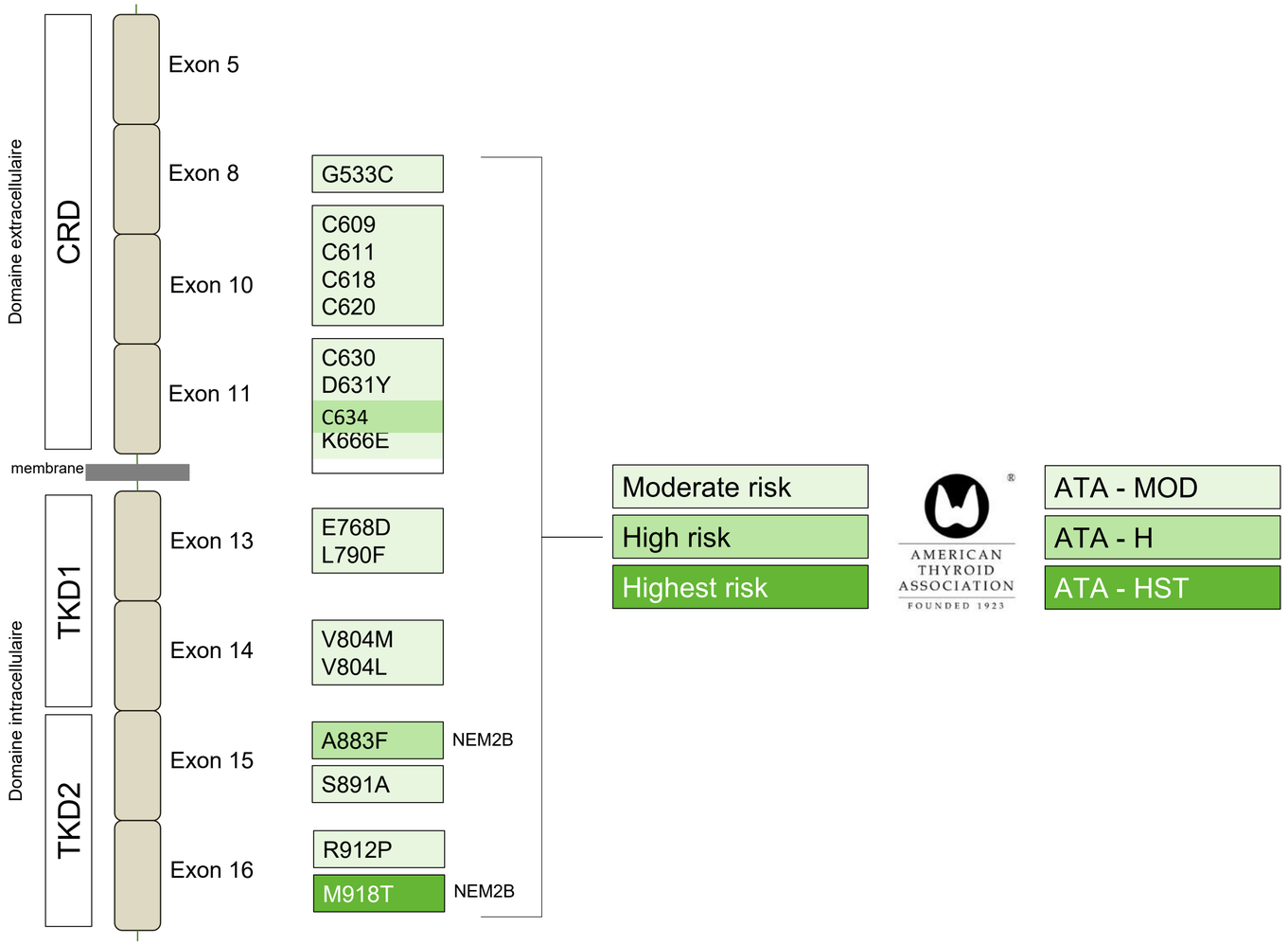
EuRREB
European Registries for Rare
Endocrine and Bone conditions

MEN2 UPDATE FROM A FRENCH COHORT

Nicolas SAHAKIAN, MD, Ph.D
Ph.D supervisors: F. Castinetti and P. Romanet, Aix Marseille University

MEN2 : Genetics

RET mutations



MEN2A (*RET* 634)

↓

ATA – H

↓

Surgery < 5 yo

MEN2B (*RET* 918)

↓

ATA – HST

↓

Surgery < 1 yo

Wells SA et al. Thyroid. 2015 Jun 1;25(6):567–610.

MEN2 FRENCH COHORT

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AIMS:
IMPROVE THE UNDERSTANDING OF MEN2 ATYPICAL NATURAL HISTORIES
IMPROVE THE UNDERSTANDING OF VARIABLE AGGRESSIVENESS
BETTER CHARACTERIZE THE EPIDEMIOLOGY OF MEN2 **IN FRANCE** AS A FIRST STEP

Atypical natural history

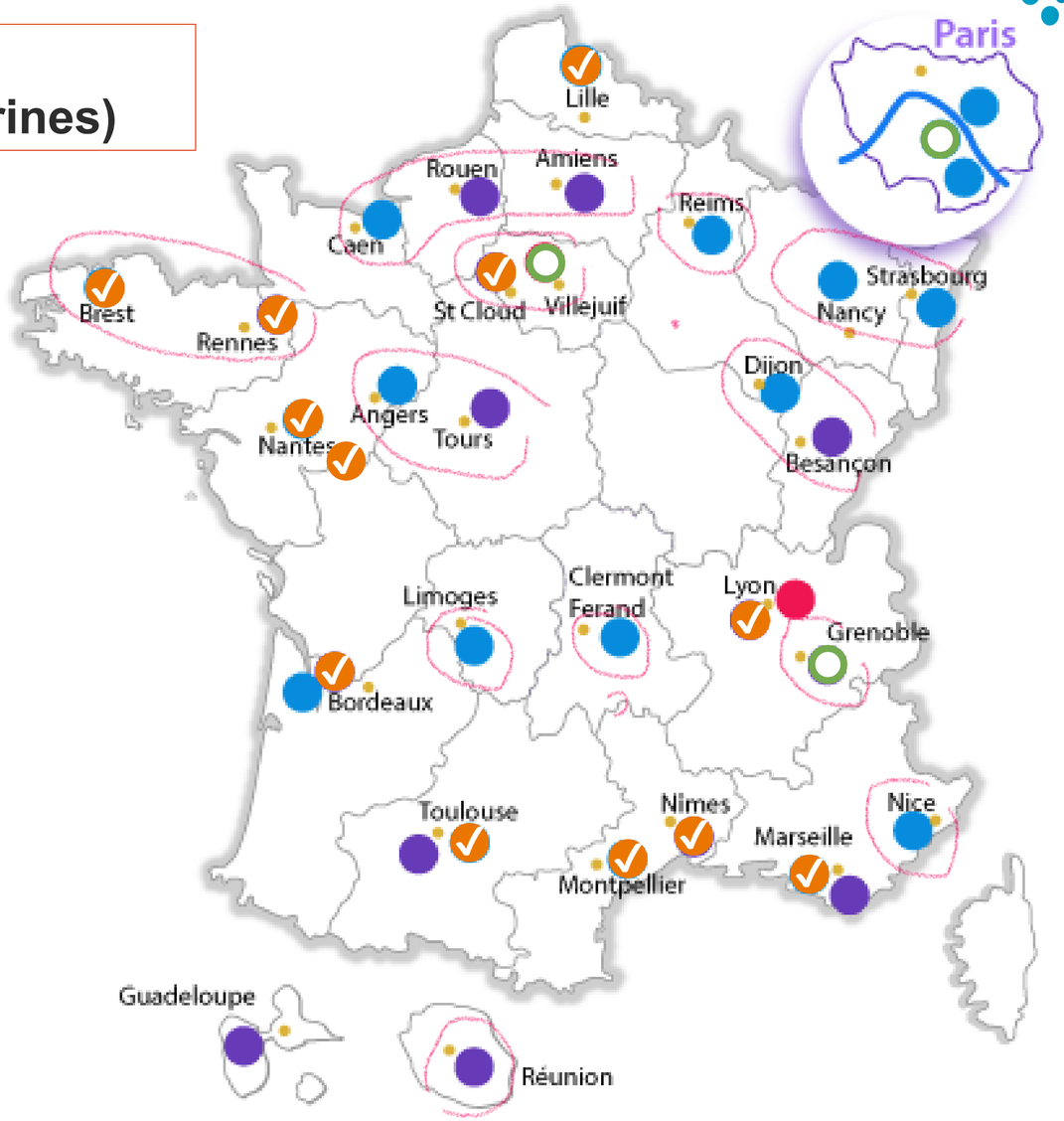
Factors associated with the natural history of MEN2? (penetrance, aggressiveness of the MTC depending on the variant**)**

Looking for **protective factors** in pheo

MEN2 FRENCH COHORT

National database
(Groupe des tumeurs endocrines)

977 patients / Currently
750 with usable data



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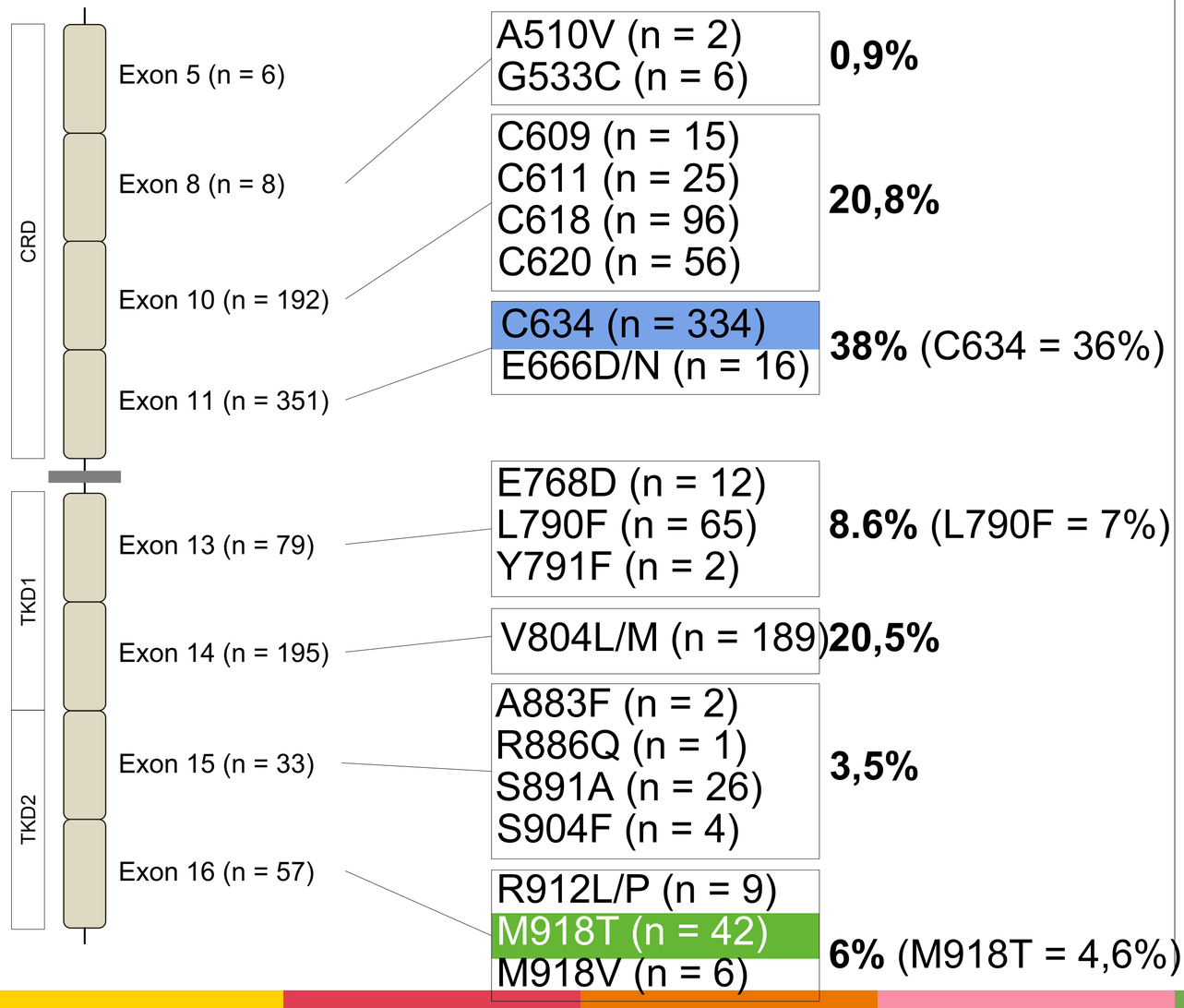
Groupe d'étude des Tumeurs Endocrines

TEN GEN

https://www.tuthyref.com/fr/

MEN2 FRENCH COHORT



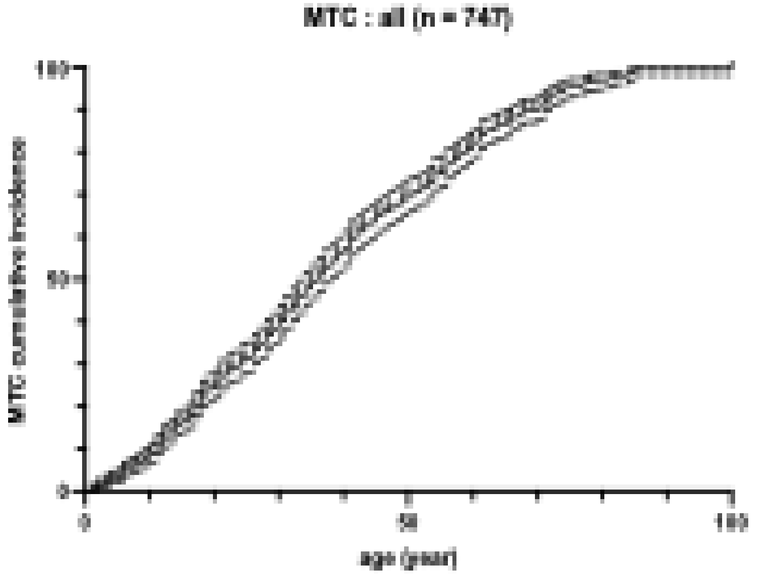
n = 948
Surgery between 1965 – 2025
Genetic data: 921
Index n = 316 / Familial cases n = 418

Data at diagnosis
- MTC n = 759
- PHEO n = 746
- HPT1 n = 742
- HSCR n = 17 (*RET* C609 ; 618 ; 620 ± *1 RET 533*)

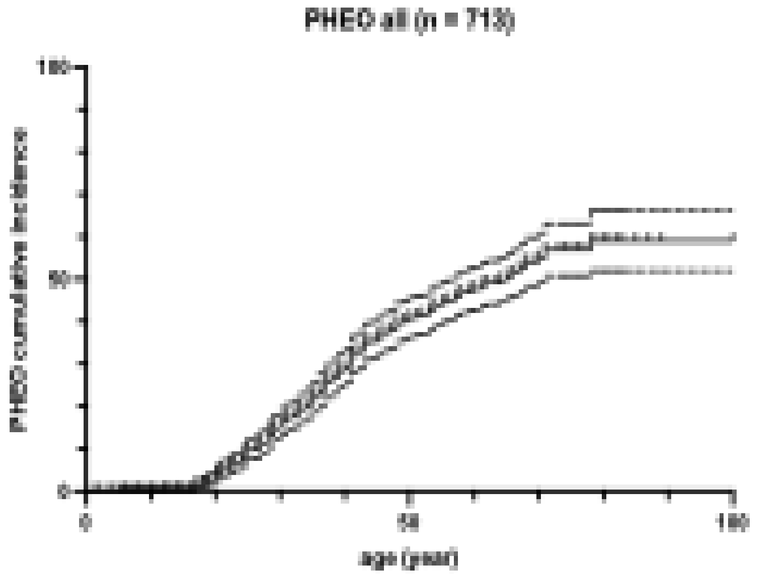
First Disease (n = 874) :
- MTC n = 570
- PHEO n = 69
- HPT1 n = 8
- NA n = 167 (patient sans CMT)

Clinical data LFU n = 707

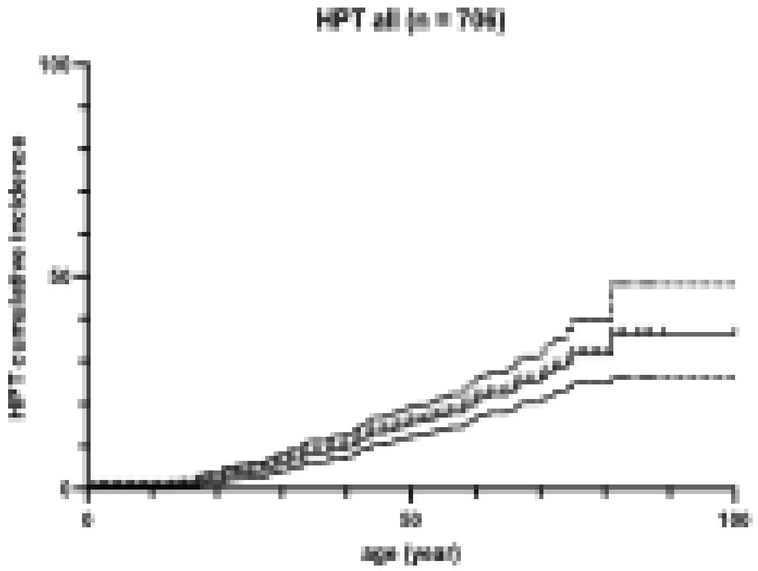
MEN2 FRENCH COHORT: PENETRANCE



10.000	5.709	2.262	1.827
20.000	25.061	3.362	3.051
30.000	40.137	3.878	3.647
40.000	57.262	3.958	3.958
50.000	70.063	3.713	3.794
60.000	82.367	3.148	3.407
70.000	90.462	2.472	2.897
80.000	99.000	0.306	1.416



10.000	0.287		
20.000	4.109	1.915	1.315
30.000	16.224	3.365	2.950
40.000	29.339	4.265	3.931
50.000	40.964	4.775	4.451
60.000	47.709	5.138	4.876
70.000	54.961	5.915	5.726
80.000	58.058		



15.000	0.613	1.014	0.383
25.000	3.899	1.805	1.284
40.000	8.884	3.002	2.333
50.000	15.508	3.870	3.156
60.000	21.092	4.921	4.055
70.000	26.224	6.143	5.193
81.000	36.133	12.113	8.830

MTC
≈ 100%

PHEO :
≈ 60%

HPT :
≈ 30%

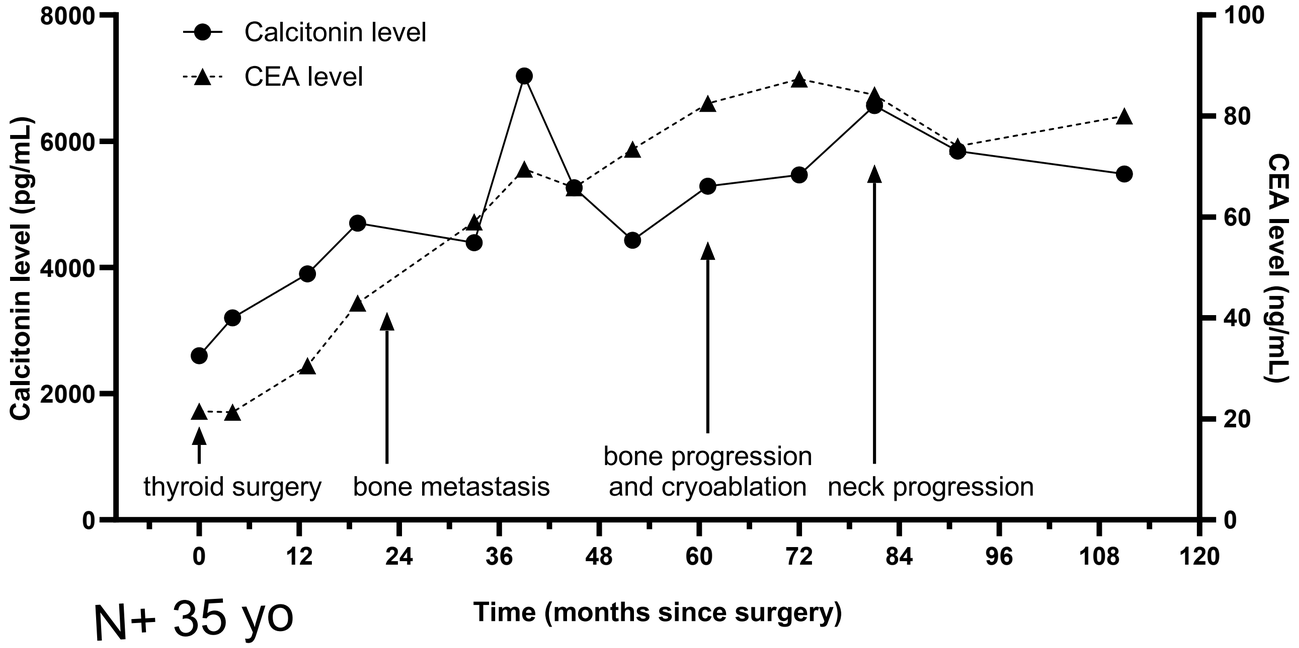
ATYPICAL NATURAL HISTORY

Letter to the editor: **The somatic *RET* M918T variant may modify the natural history of germline *RET* L790F MEN2-related medullary thyroid carcinoma**

Authors: Nicolas Sahakian, Pauline Romanet, Delphine Mirebeau-prunier, Nunzia Cinzia Paladino, Frederic Castinetti, Anne Barlier

♀ 35 yo
CMT pT3N1b

RET exon 13, c.2370G>C, p.L790F



N+ 35 yo

M+ 38 yo

L790F literature	n = 112
T+ / youngest	56 (50%) / 14 yo
N+ / youngest	19 (17%) / 34 yo
M+ / youngest	1 (0,9%) / 57 yo

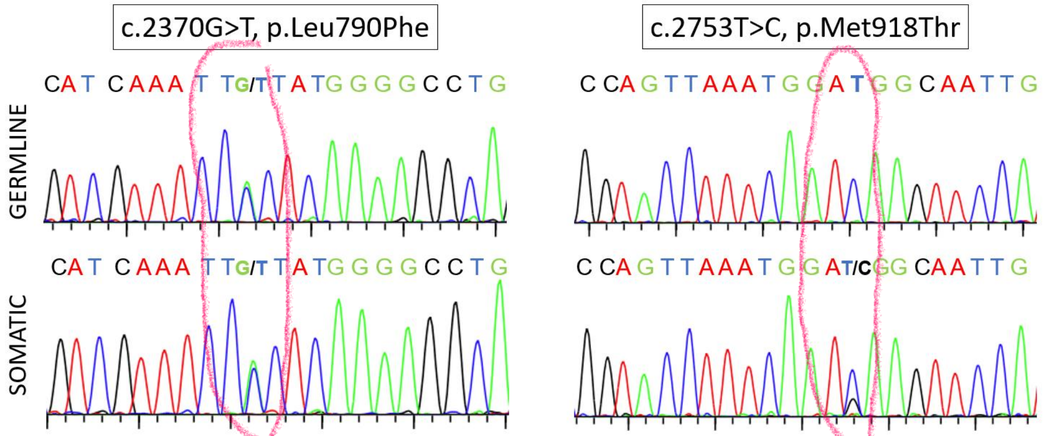
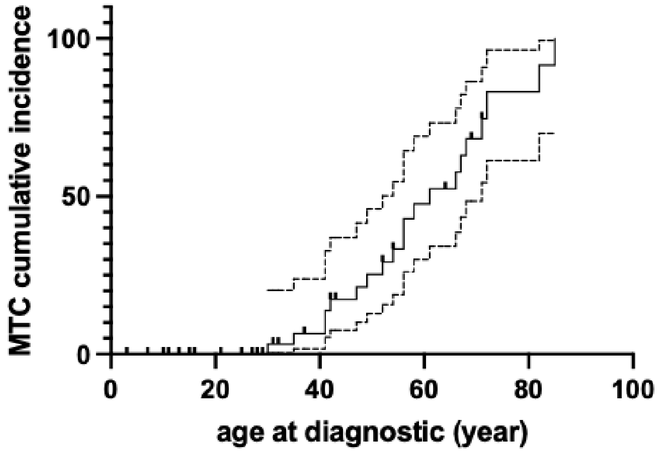
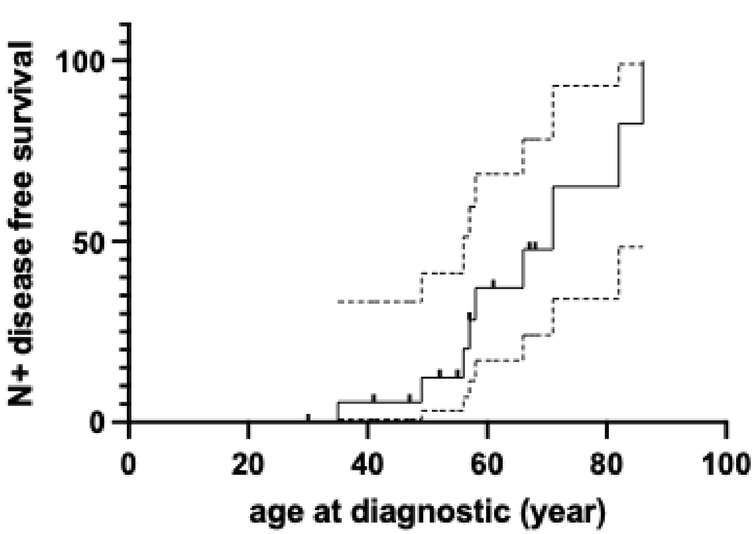


Figure 1: targeted *RET* sanger sequencing on blood and MTC

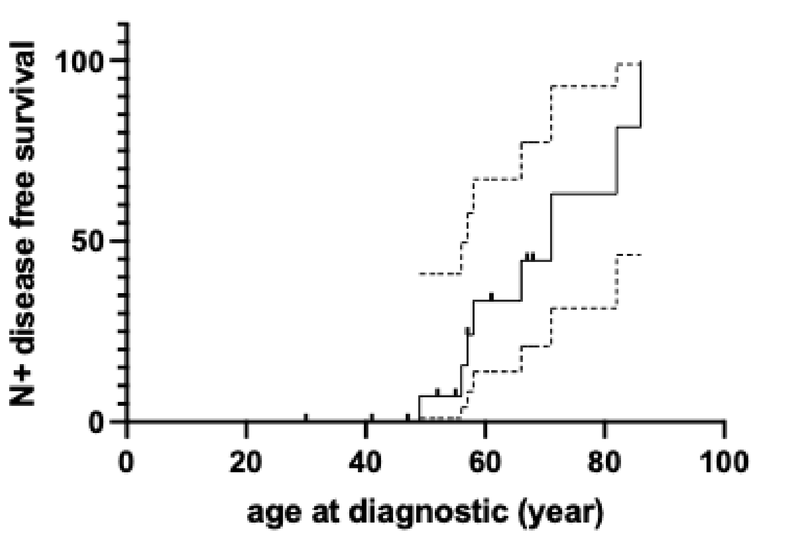
L790F in our cohort (n = 65)



10.000	0.000		
21.000	0.000		
30.000	3.125	17.056	2.679
41.000	13.771	18.959	8.384
52.000	29.169	20.988	13.467
61.000	52.382	20.898	18.276
71.000	74.604	16.309	20.295
82.000	91.535	7.835	21.550



35.000	5.556	27.805	4.754
49.000	12.302	28.901	9.109
56.000	20.274	31.039	13.390
66.000	47.680	30.572	23.633
71.000	65.120	27.849	30.965

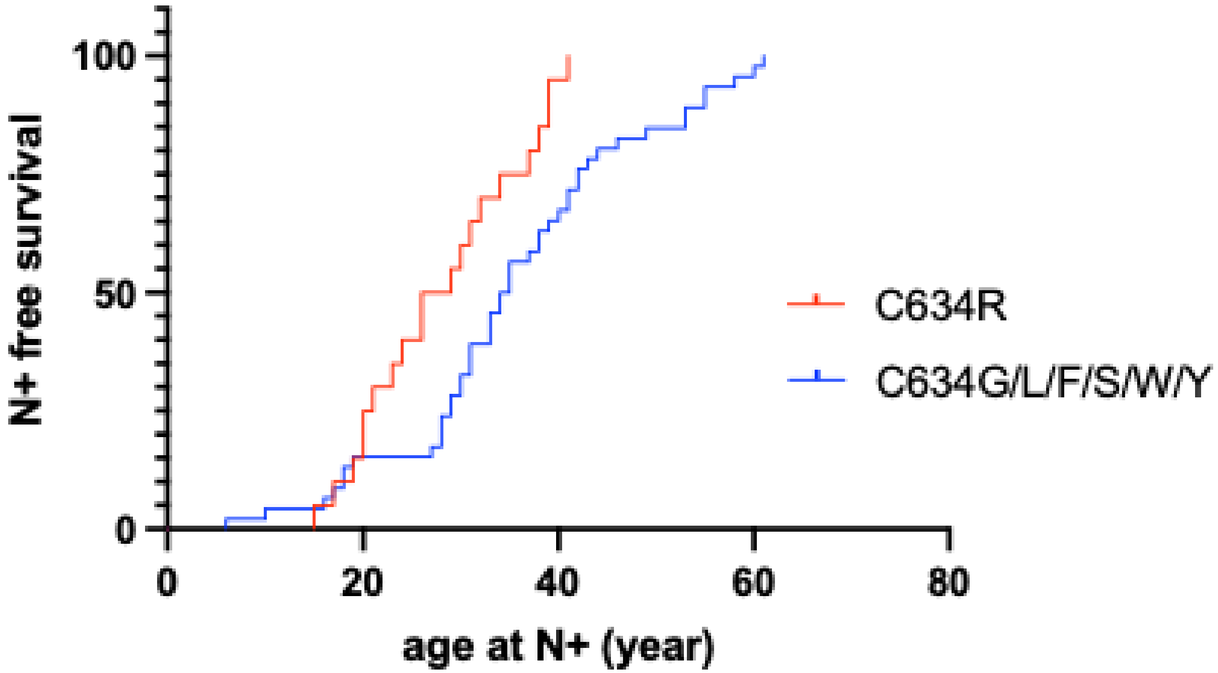


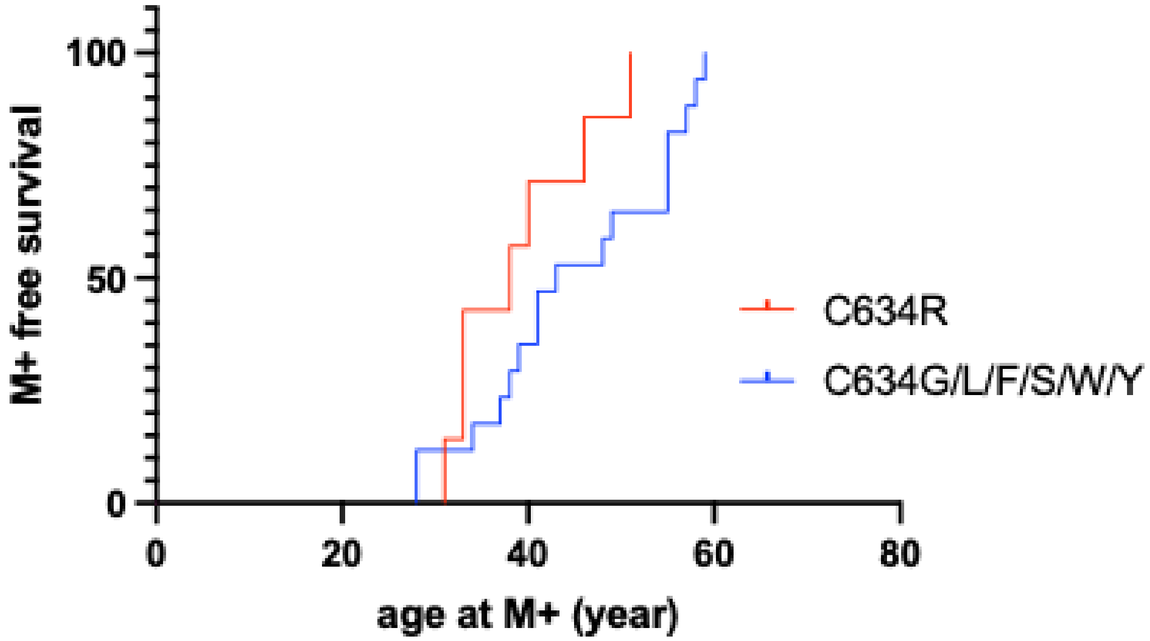
30.000	0.000		
49.000	7.143	33.780	6.105
58.000	33.523	33.583	19.598
71.000	63.068	29.727	31.646

YoungestT : **30** yo (M918T somatique : 35 yo)
Youngest : 49 yo (M918T somatique : **35** yo)
Youngest M : 58 yo (M918T somatique : **38** yo)

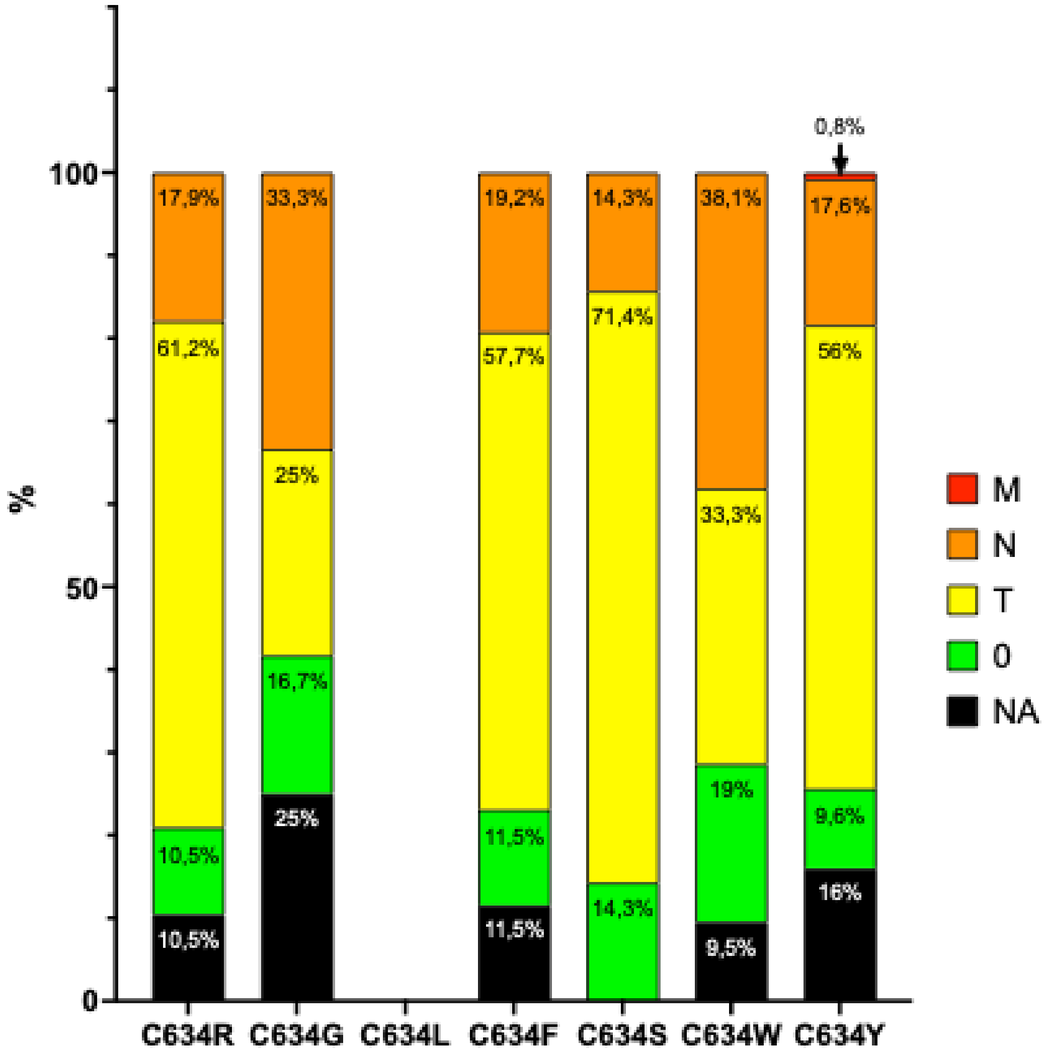
AMINO ACID CHANGE IN 634

- C634R: n=72
- C634Y: n=125
- C634 G/L/F/S/W: n= 75

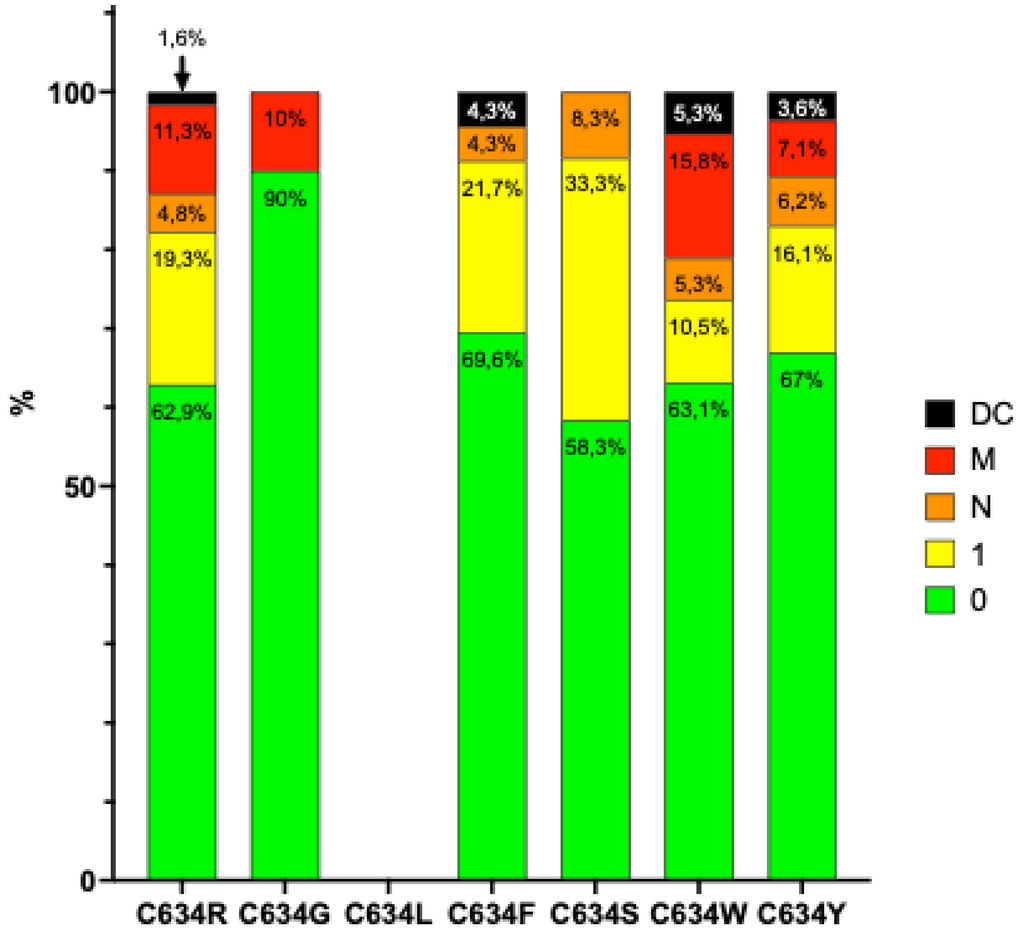




AMINO ACID CHANGE IN 634

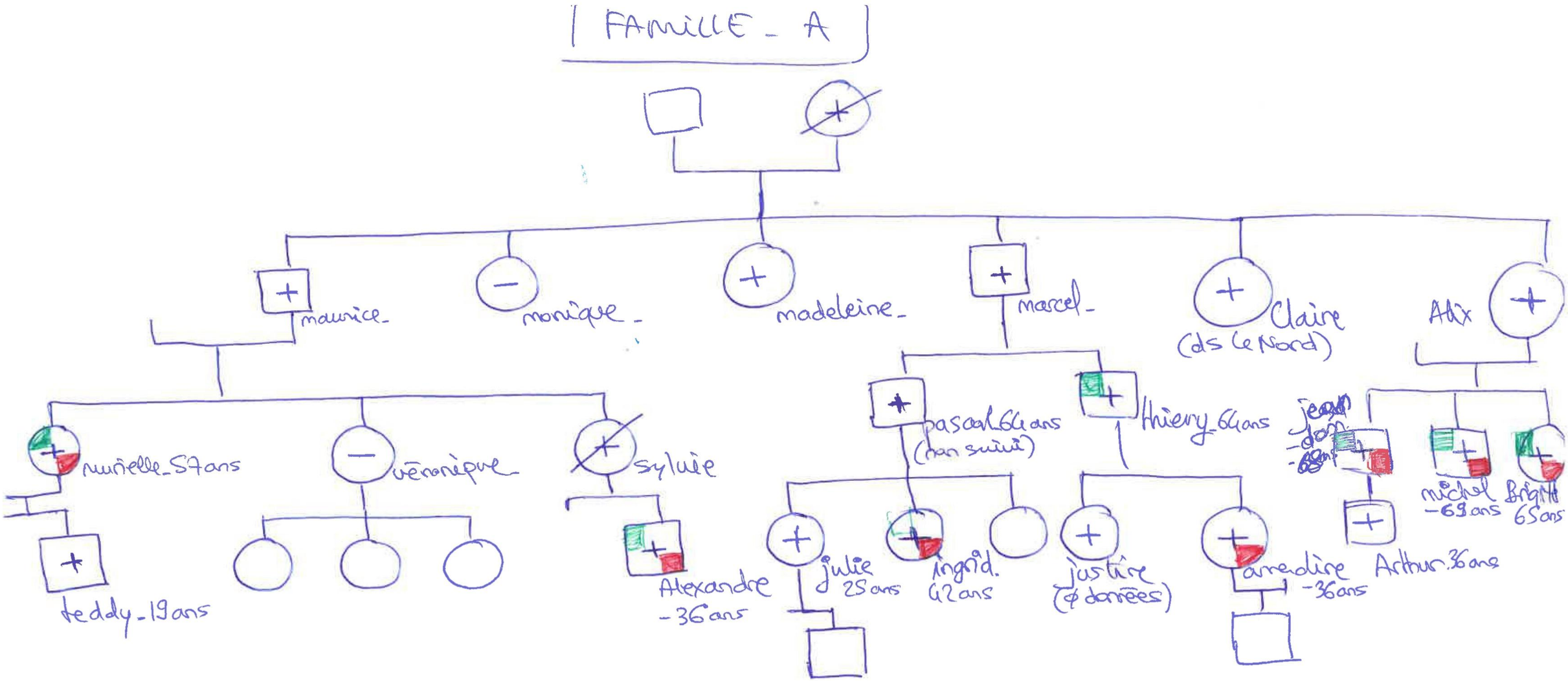


MTC DIAGNOSIS



MTC LAST FOLLOW-UP

SEARCHING FOR PROTECTIVE/WORSENING FACTORS IN PHEO



Pheochromocytoma

WGS

MEN2 FRENCH COHORT: TAKE HOME MESSAGES

1. Gives an epidemiological view of MEN2 in 2/3 of France. Data analysis ongoing.
2. Confirms previous data on amino acid substitution
3. Emphasizes the need to look for « something else » in atypical stories
4. Work in progress … a lot and especially the protective factors history for which we will need collaborations and confirmations by other centers/countries if we find somethng.

Pancreatic neuroendocrine tumors in children - MET registry

1997-2024

28 Patients (10 male, 18 female)

median age 14.7 years (6.2-17.9)

Characteristics	German MET registry	
	Count	Proportion, %
Presenting symptoms		
Abdominal/back pain	21/26	
Weight loss	9/26	
Palpable abdominal resistance	6/23	
Metabolic imbalance	5/25	
Icterus	4/25	
Vomiting	4/26	
Diarrhea	4/26	
Hepatomegaly	4/24	

Karges et al., J Neuroendocrinol, 2025

Pancreatic neuroendocrine tumors in children - MET registry

1997-2024

28 Patients (10 male, 18 female)

median age 14.7 years (6.2-17.9)

Characteristics	German MET registry	
	Count	Proportion, %
Functional/nonfunctional panNET		
Insulinoma	4	14.3
Gastrinoma	1	3.6
Nonfunctional	18	64.3
Unknown/unclear	5	17.9
Cancer predisposition		
MEN1, pathogenic variant	3	10.7
MEN1, no pathogenic variant	5	17.9
Tuberous sclerosis	1	3.6
von Hippel–Lindau syndrome	1	3.6
Unknown	18	64.3

Karges et al., J Neuroendocrinol, 2025

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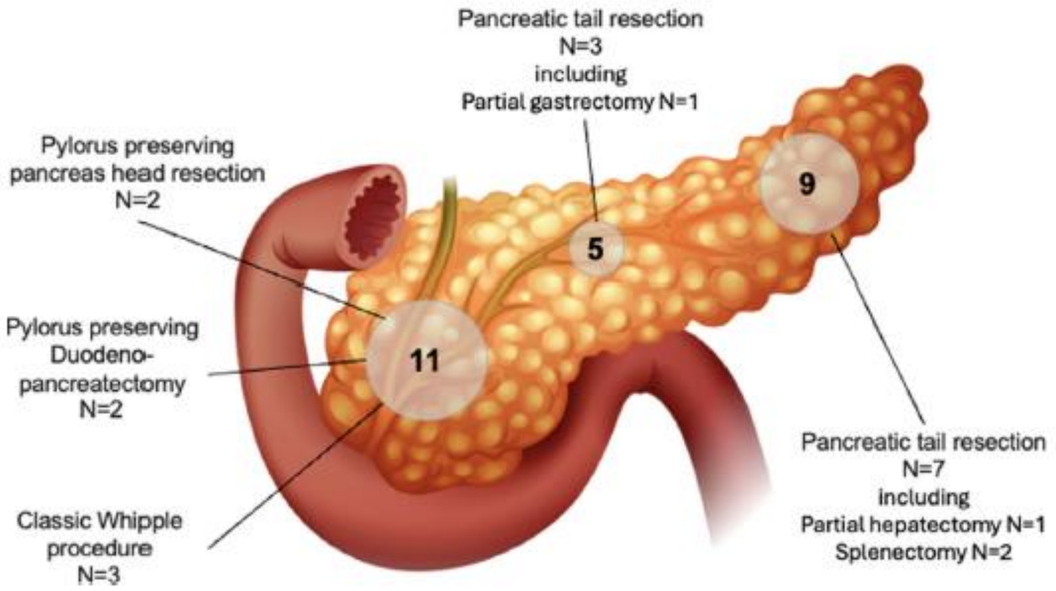

Karges et al., J Neuroendocrinol, 2025

Pancreatic neuroendocrine tumors in children - MET registry

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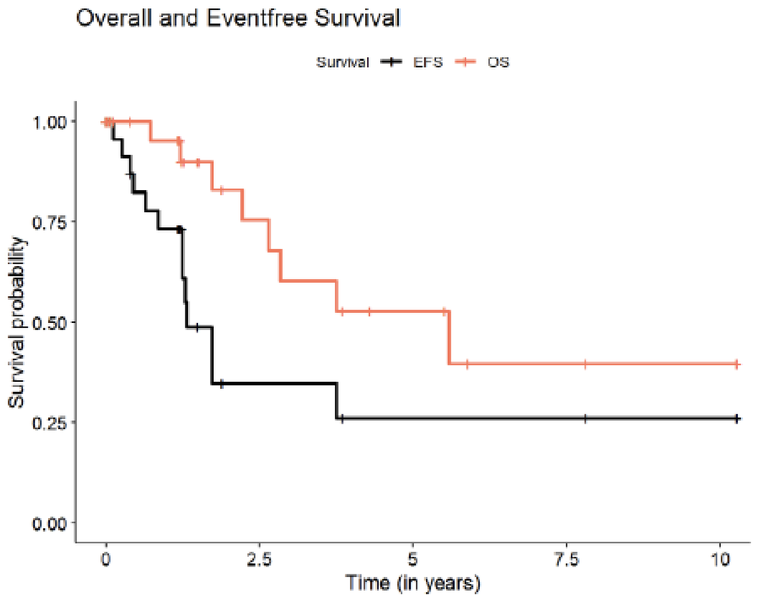
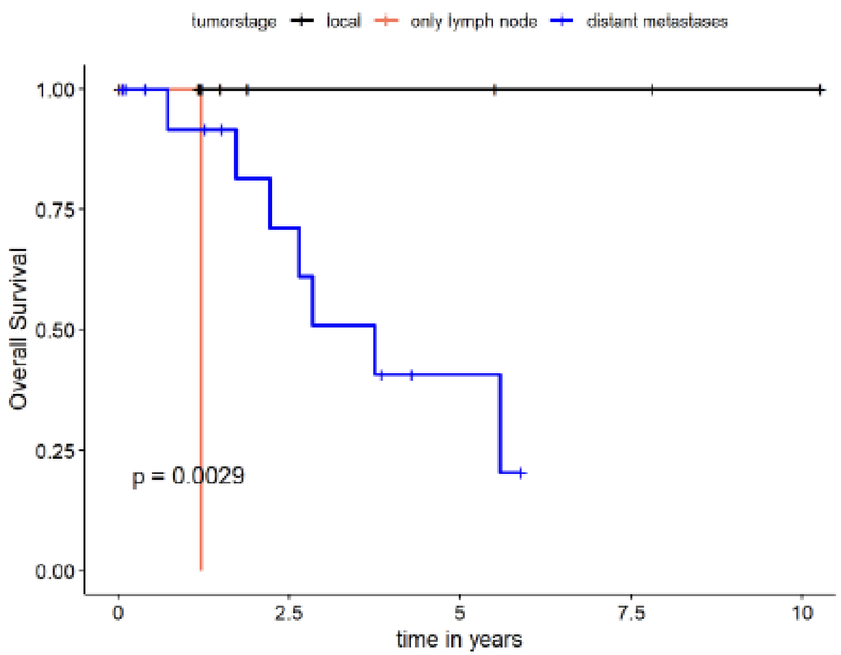
median age 14.7 years (6.2-17.9)

WHO classification of panNET[a,b]		
Well-differentiated NET		
G1 (Ki67 <3%, mitotic index <2)	4	14.3
G2 (Ki67 3%–20%, mitotic index 2–20)	12	42.9
G3 (Ki67 >20%, mitotic index >20)	2	11.1
Poorly differentiated NEC		
High (Ki67 >20%, mitotic index >20)	7	25.0
Unknown	3	10.7

Karges et al., J Neuroendocrinol, 2025

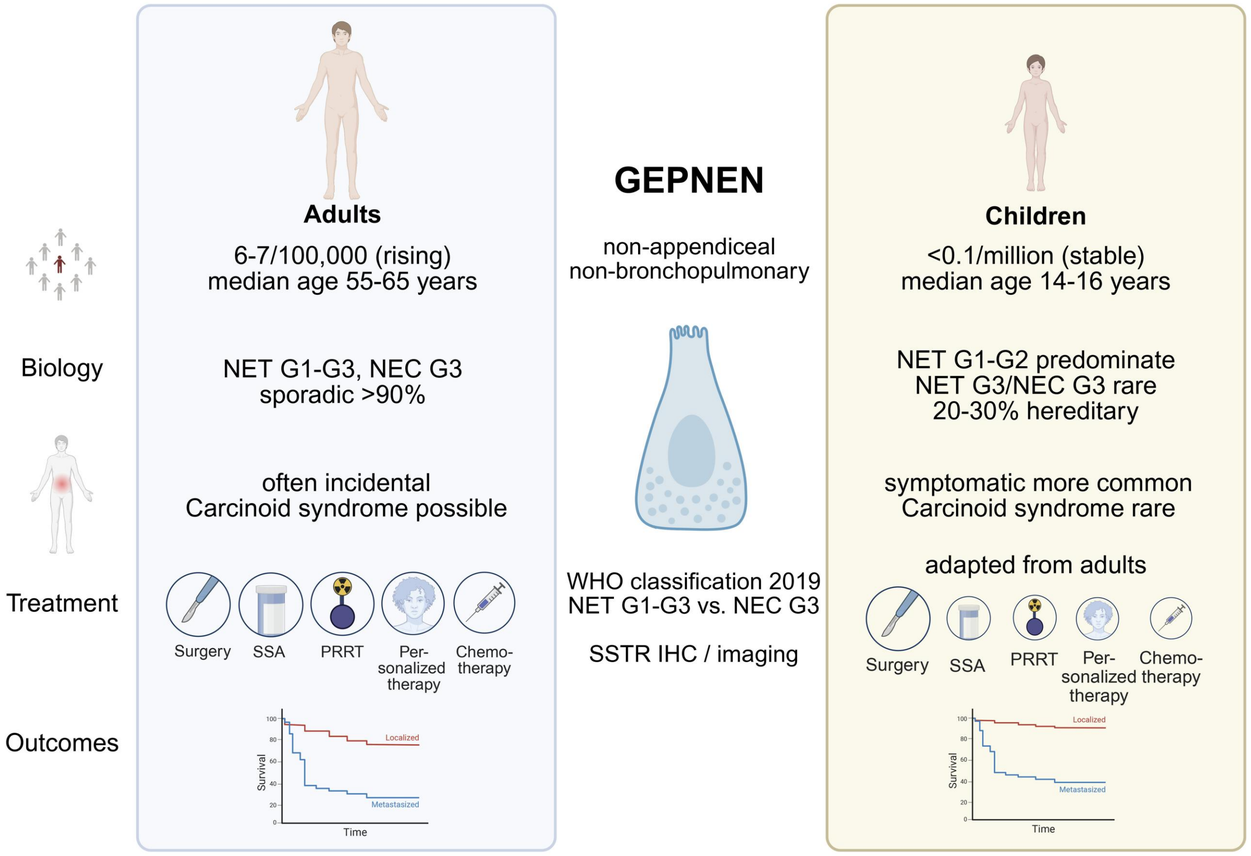
Pancreatic neuroendocrine tumors in children - MET registry





Karges et al., J Neuroendocrinol, 2025

Gastrointestinal neuroendocrine tumors in children - MET registry



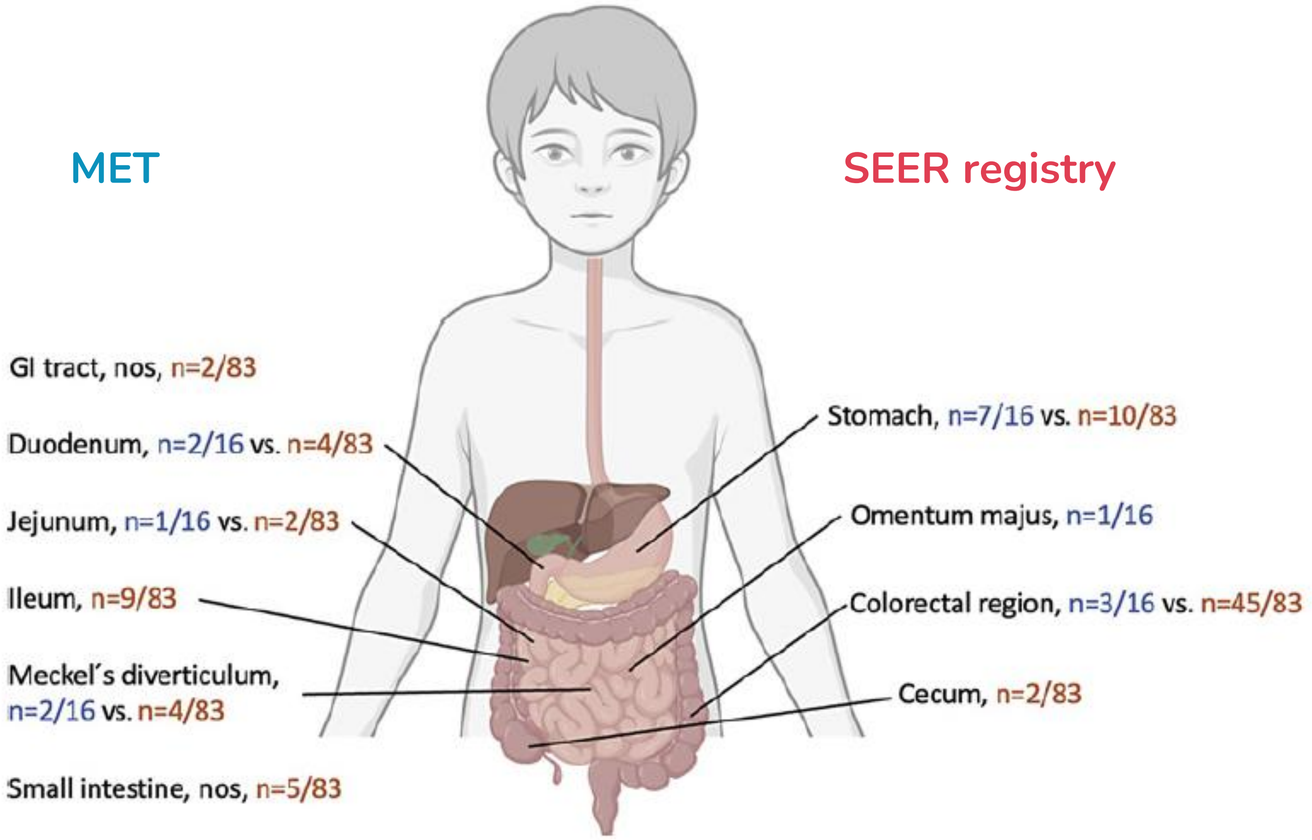
Kuhlen et al., Frontiers in Endocrinol, 2025

Gastrointestinal neuroendocrine tumors in children - MET registry

1997-2024

16 Patients (10 male, 6 female)

mean age 15.4 years



Kuhlen et al., Frontiers in Endocrinol, 2025

Gastrointestinal neuroendocrine tumors in children - MET registry

Tumor genetic syndromes

and presentation

Cancer predisposition		
MEN1	1	6.3
Pacak-Zhuang syndrome	1	6.3
Wolf-Hirschhorn syndrome	1	6.3
Unknown	2	12.5
No	11	68.8
Performance status at diagnosis		
Not impaired/mildly impaired	11	68.8
(Severely) impaired	2	12.5
Unknown	3	18.8
Presenting symptoms		
Abdominal/back pain	10	62.5
Weight loss	3	18.8
Palpable abdominal resistance	2	12.5
Vomiting	5	31.3
Diarrhea	2	12.5
Hematemesis	2	12.5
Melena/hematochezia	5	31.3
(Sub-)ileus	3	18.8
Other symptoms	6	37.5
No symptoms/incidental finding	4	25.0
Unknown	1	6.3
Functional/nonfunctional		
Gastrinoma	4	25.0
Nonfunctional	11	68.8
Unknown/unclear	1	6.3

Kuhlen et al., Frontiers in Endocrinol, 2025

Gastrointestinal neuroendocrine tumors in children - MET registry

European Reference Network

Endo-ERN

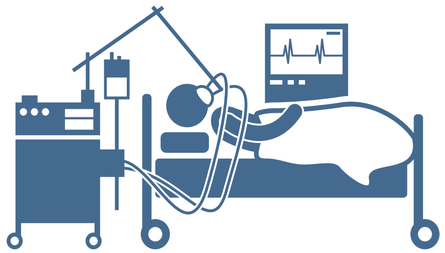
Tumor genetic syndromes

and presentation

c/pM stage		
M0	9	56.3
M1	5	31.3
Unknown	2	12.5
R classification		
R0	6	46.2
R1/R2	4	30.8
Rx	1	7.8
Unknown	2	15.4
Grading		
Well-differentiated NET		
G1 (Ki-67 <3%, mitotic index <2)	7	43.8
G2 (Ki-67 3–20%, mitotic index 2–20)	6	37.5
G3 (Ki-67 >20%, mitotic index >20)	1	6.3
Poorly differentiated NEC		
High (Ki-67 >20%, mitotic index >20)	0	0
Unknown	2	12.5

Kuhlen et al., Frontiers in Endocrinol, 2025

Machine learning Algorithms and data

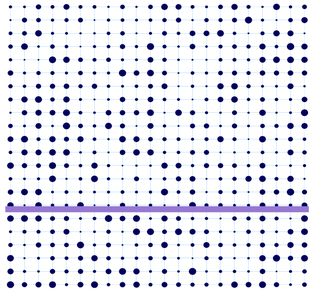


Monitoring

digital health records

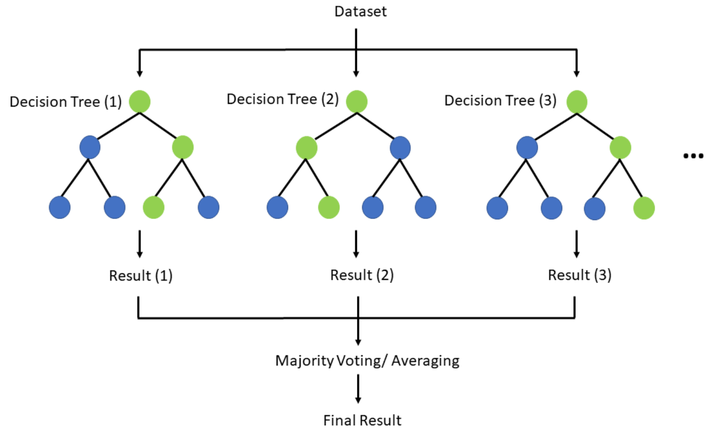
80% Training

20% Testing



data

labeled



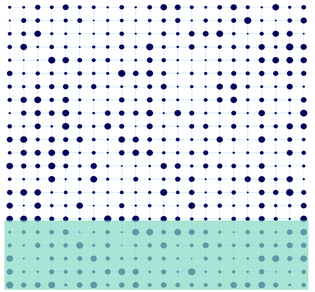
Predicition outcome (nominal) via features (nominal/continous)

Adrenocortical Carcinoma in Children: ML Prediction Survival

European Reference Network

Endo-ERN

Data



MET Registry
1997-2024
97 ACC/ACx

Model evaluation/Feature selection

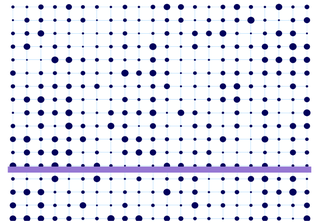
XGBoost Cox (objective="survival:cox")

15 Features, 3-7 Features: **11.737 models**

Bootstrapping for performance evaluation

Target: Maximum C-Index

categorical	continous
Age group (<10, ≥10 years)	Age at diagnosis
Sex (male, female)	Intervall Symptoms-diagnosis
Virilisation, Cushing	Tumorsize, Tumorvolume
pT, p/cN, p/cM	Ki-67 Index
Resection (R0/1/2)	
Necrosis, Vascular invasion	



stratified split

(80 train/20 test)

hould out

final model

Redlich et al., Interpretable Machine Learning Model for Survival Prediction in Pediatric Adrenocortical Tumors, J Endocrine Soc, 2026 accepted

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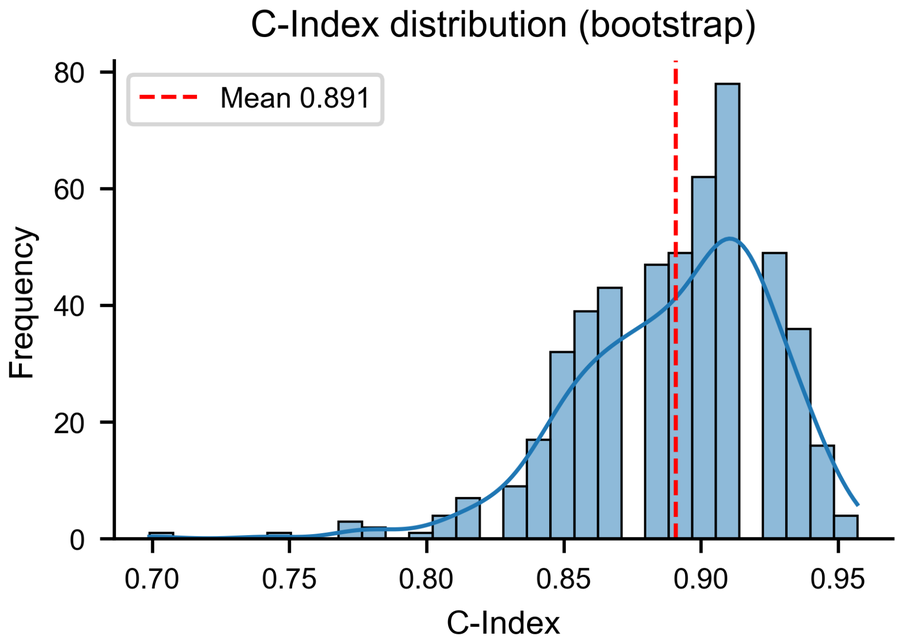
Best Model C-Index 0,891



hould out

C-Index 0,925

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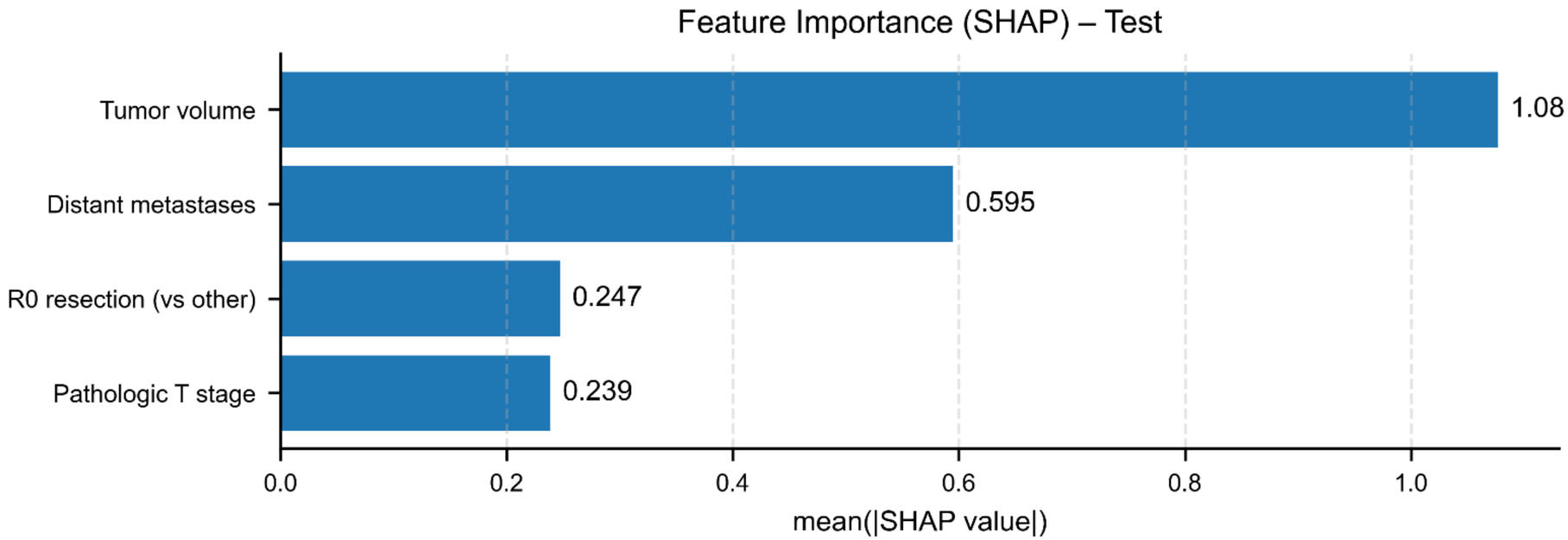
Best model: Tumorvolume, Distant metastases, R-Status, pathologic T stage



SHAP: 1 ≈ 2,7 Odds

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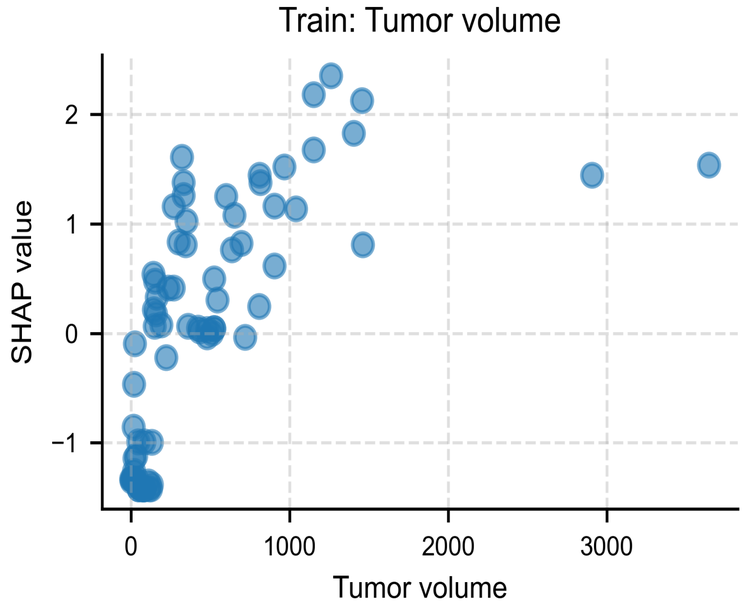

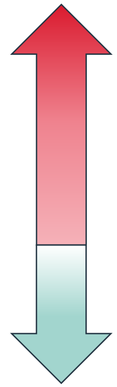

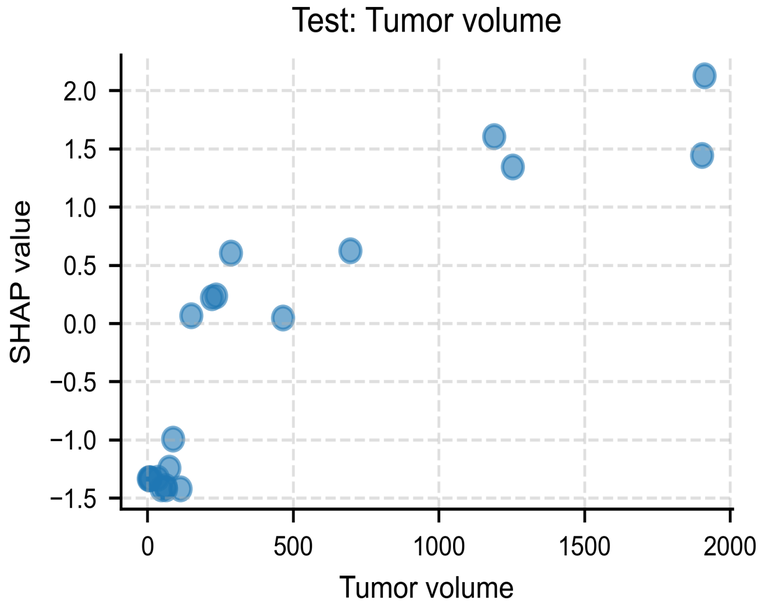

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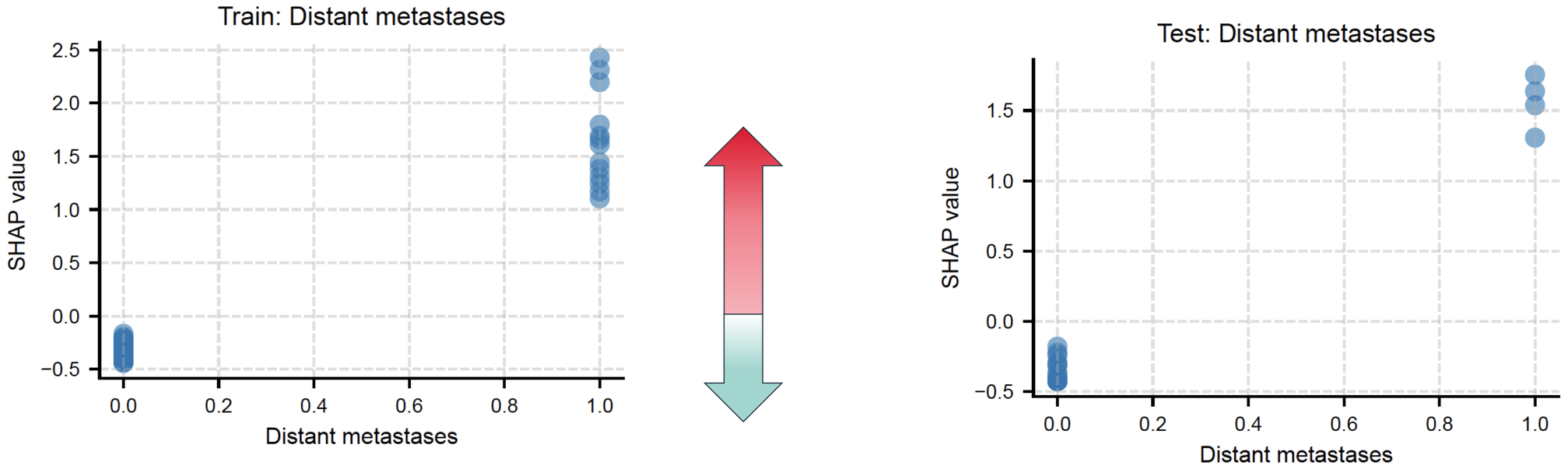

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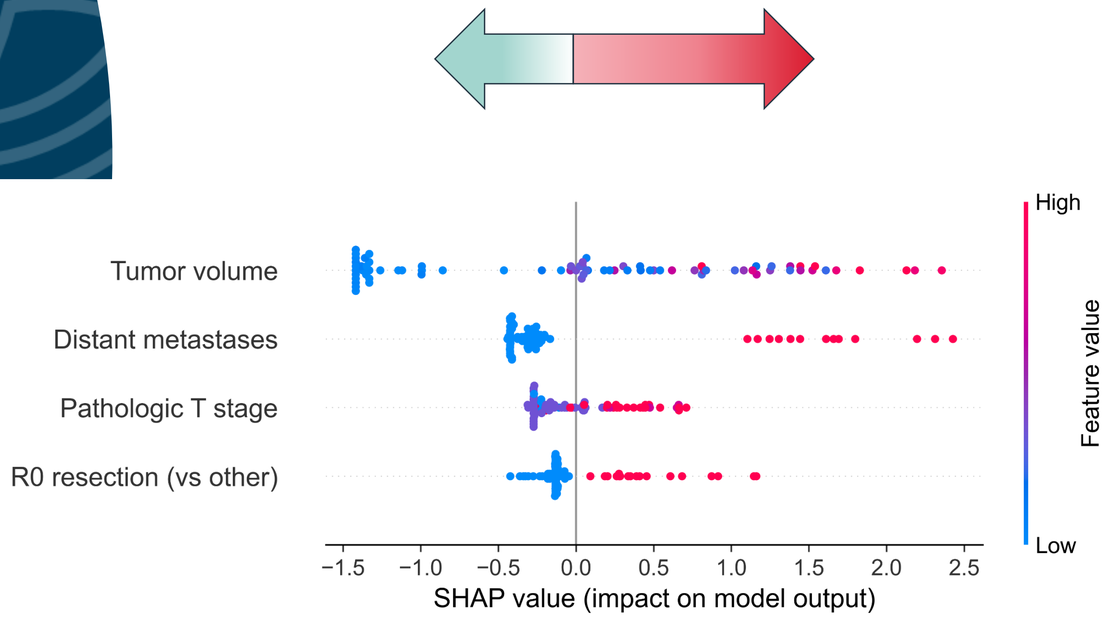
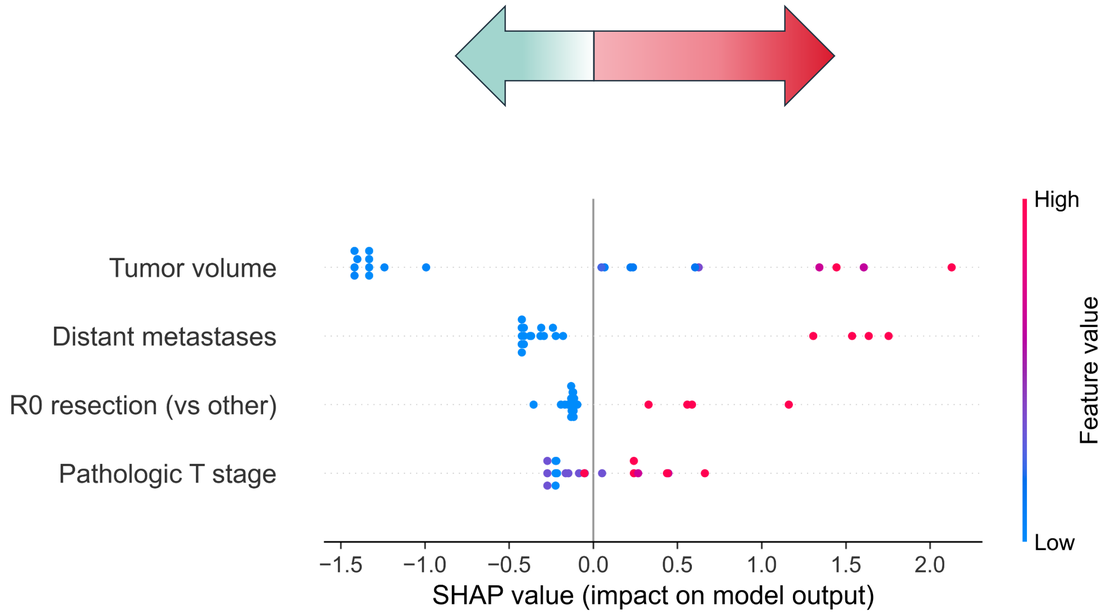
Best model: Tumorvolume, Distant metastases, R-Status, pathologic T stage





SHAP: 1 ≈ 2,7 Odds

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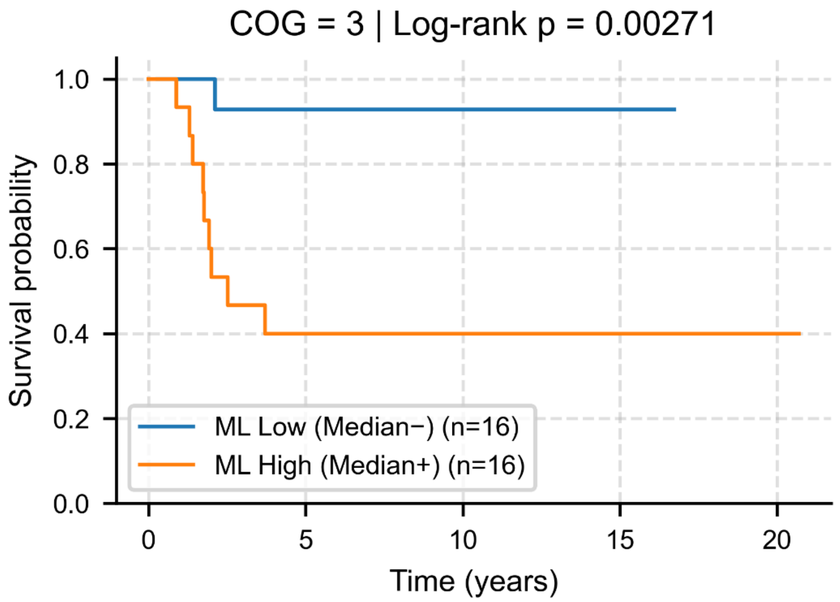
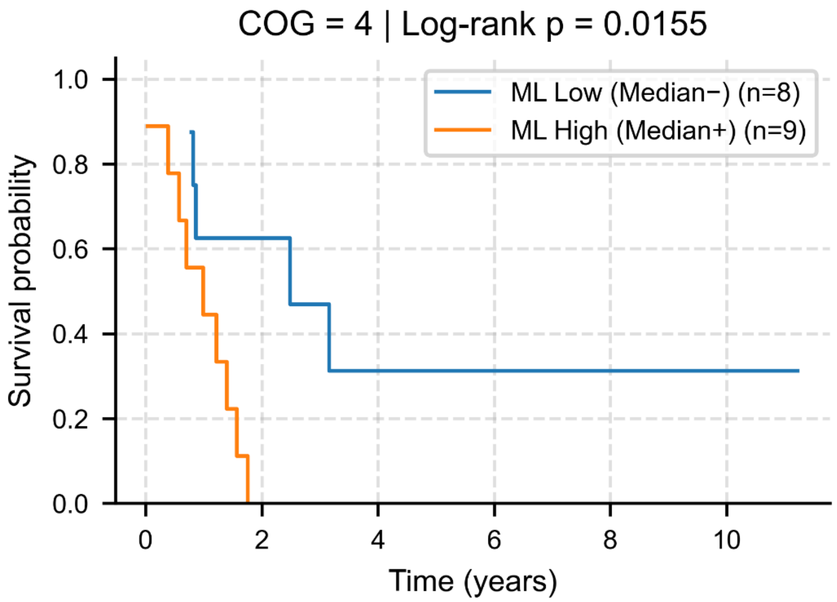
Adrenocortical Carcinoma in Children: ML Prediction Survival

Best model: Tumorvolume, Distant metastases, R-Status, pathologic T stage better than COG stages





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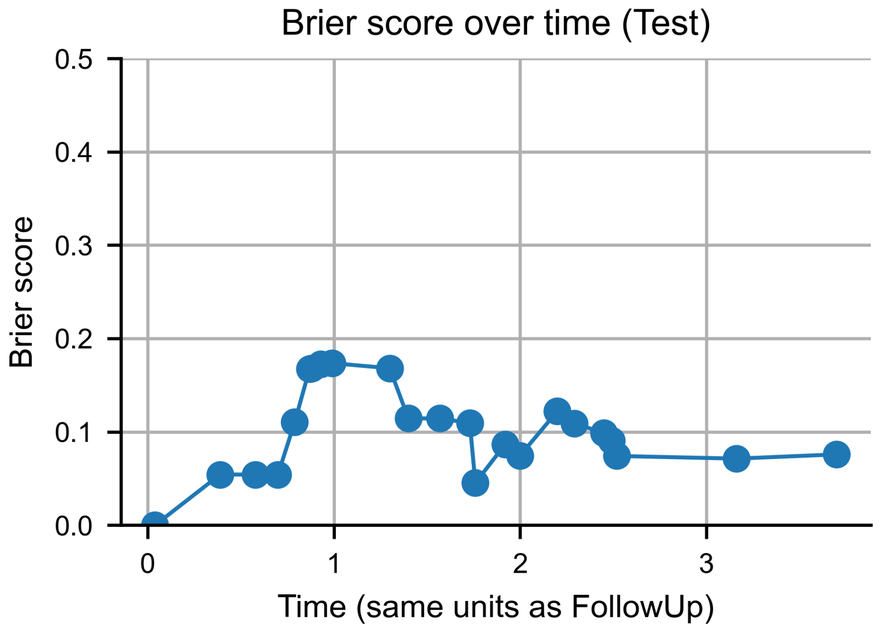
Brier Score: Squared error over time



IBS =0,09 (very good!)

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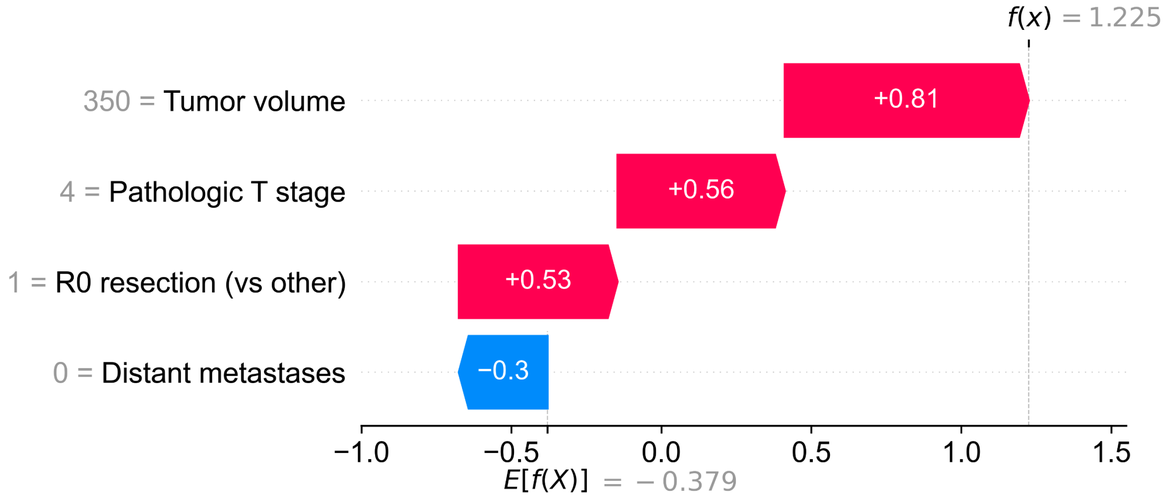
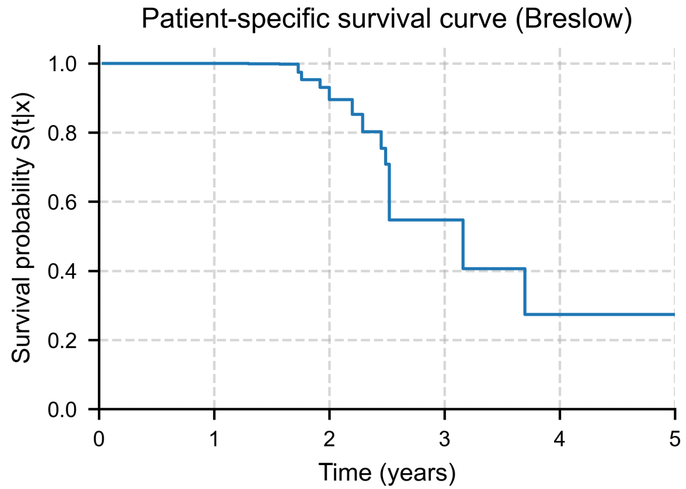
Model: Tumorvolume, pM, R-Status, pT

Individual risk





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TRAINING & EDUCATION

MTG4 Webinar: MEN1: An update from the guidelines across the lifespan

Tuesday, June, 18th TBC

ML Brandi, G. Valk, S. Waguespack

SAVE THE DATE !!!!

We need YOU for suggestions !!!!!! VHL, SDH…
Please send us emails for names and topics ☺

ANY OTHER BUSINESS (AOB)

- Updates from your HCP/Organisation
- Research or information you would like to share


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