

Genetic Endocrine Tumour Syndromes (MTG4) HCP Meeting

Frederic Castinetti, Antje Redlich, Petra Bruegmann



Funded by
the European Union

MANAGEMENT & COORDINATION



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

5 publications
with at least 2
member
states in 2025

0
Webinar
held in
2025

1 CPMS
case in
2025

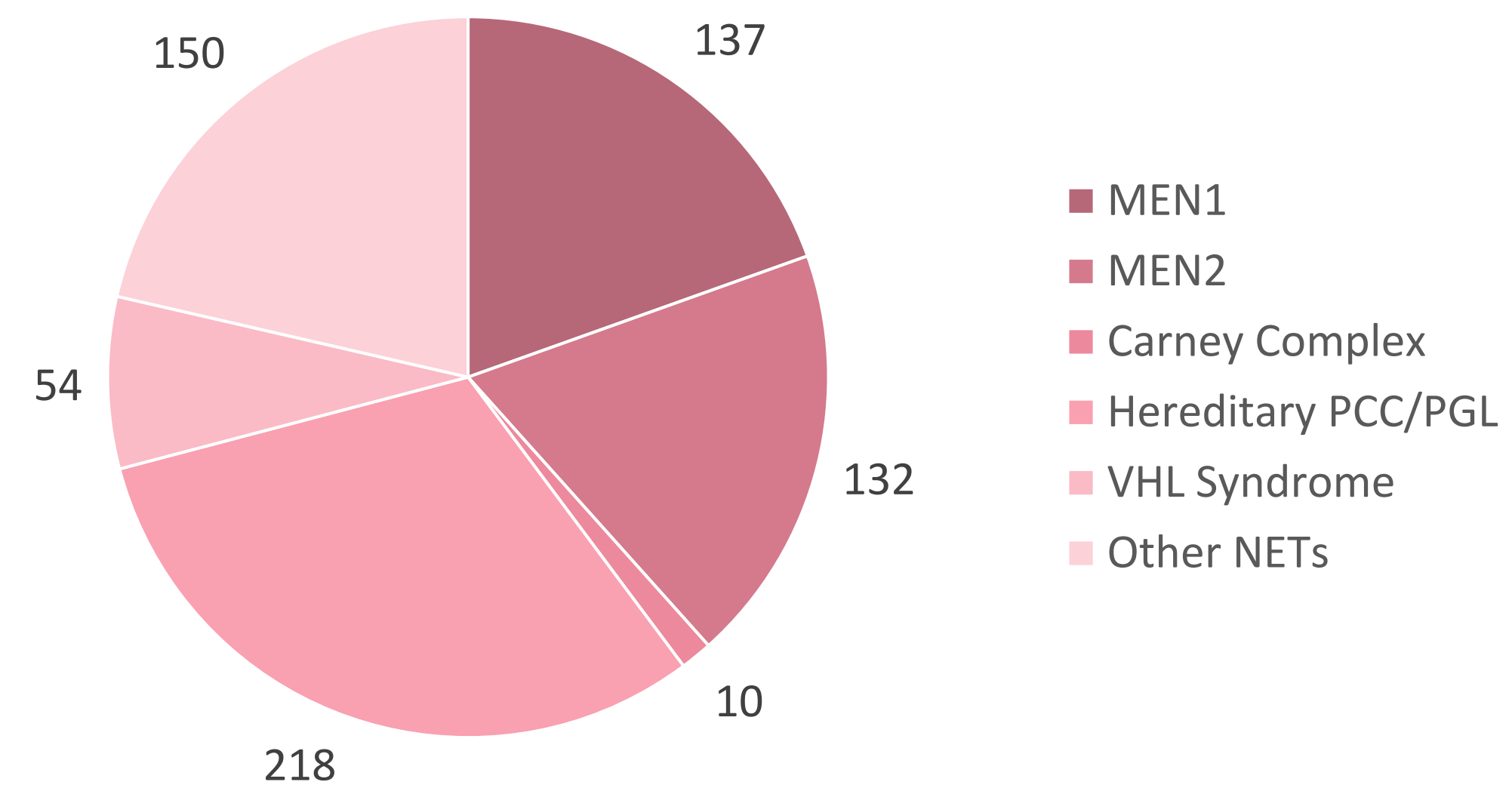


European
Reference
Network

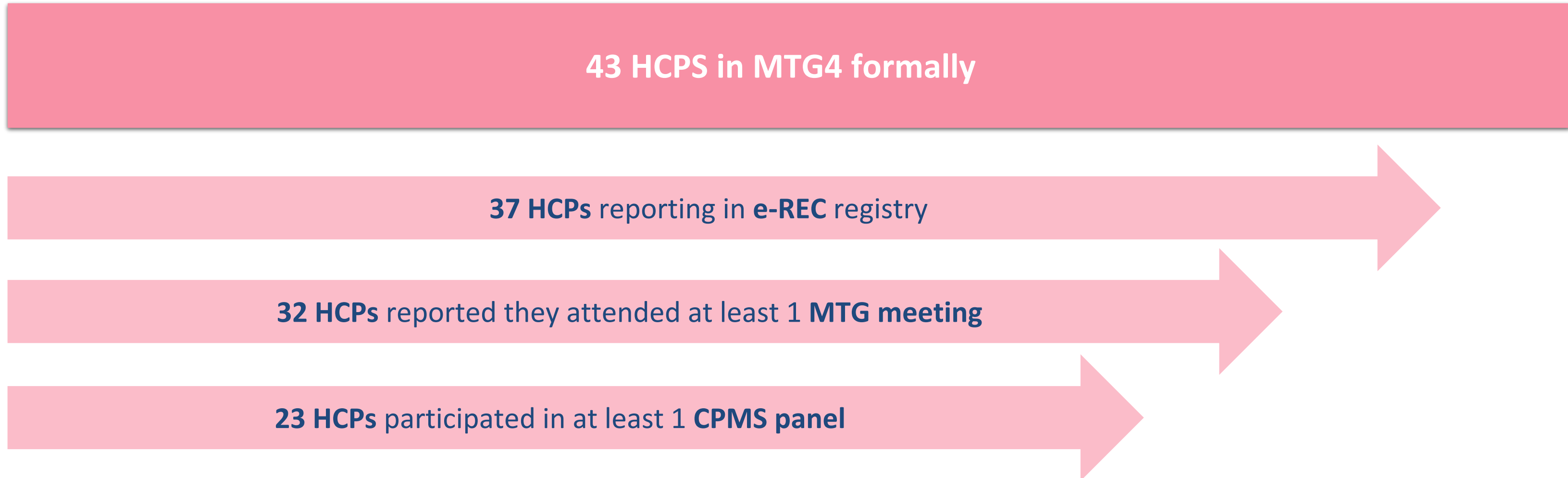


Endo-ERN

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



MTG4 HCPS - 2025 Stats

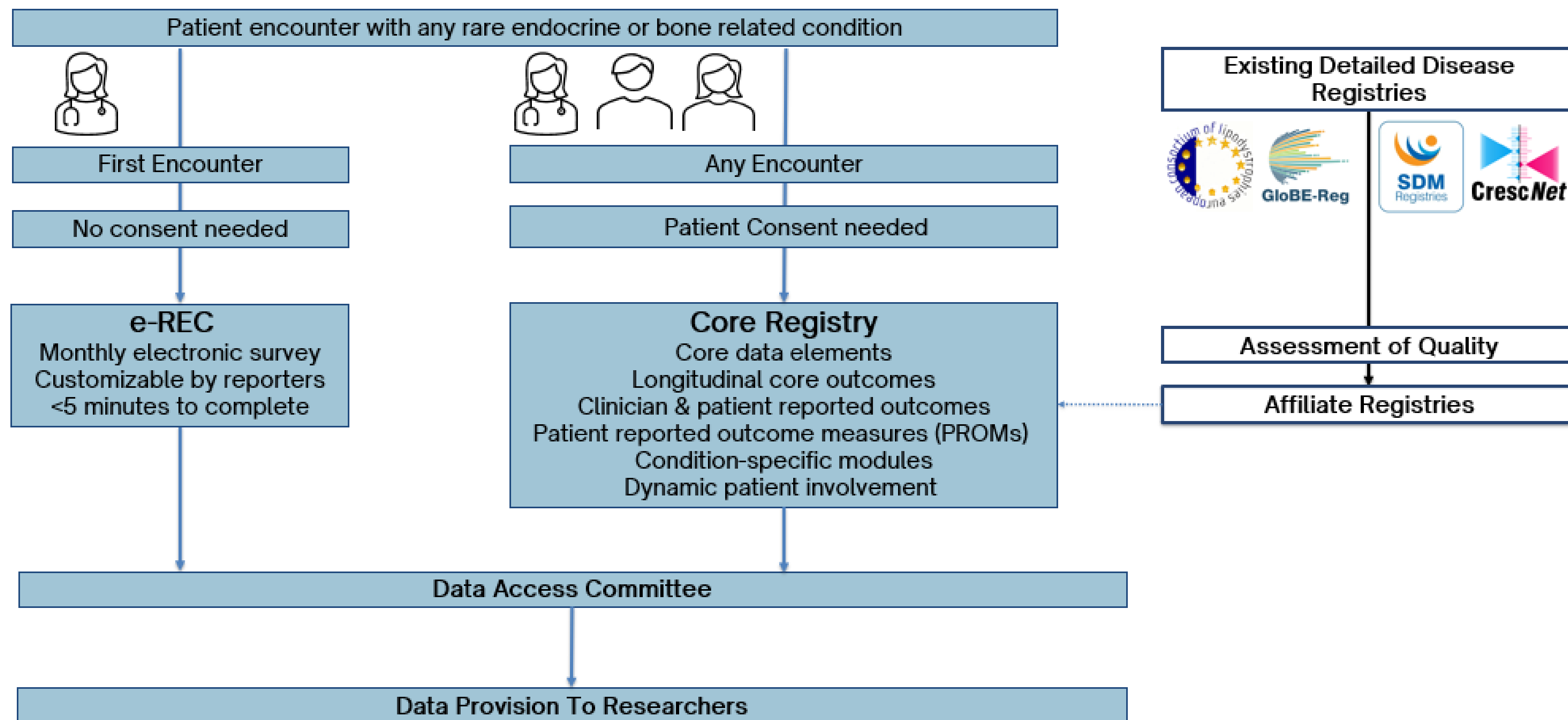


- 33 HCPs have **different** EC & e-REC totals
- 5 HCPs **do not have** Endo-ERN logo/url at their website
- 8 HCPs who did not measure patient satisfaction – this is based on your HCP **NOT your department** usually

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 Brüggmann	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

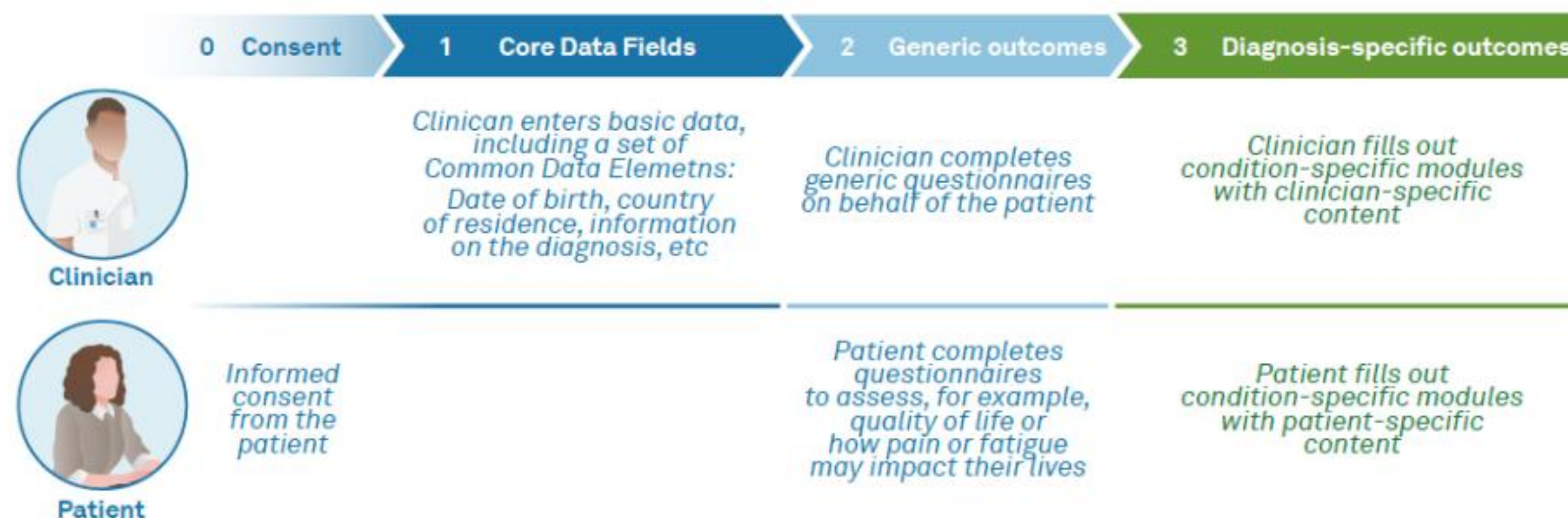
Live version

- Available for users

Patients

Clinicians

Data Entry Flow in the Core Registry



The MEN-1 Condition-Specific Module

Patient history	Genetic testing	Clinical manifestation	Follow up
Assessment Date		?	yyyy-mm-dd
Type of diagnosis			☐ Predictive testing as child of an affected parent ☐ Cascade screening because a new diagnosis of MEN1 in a (first-degree) relative ☐ Genetic testing because of clinical phenotype or a clinical/familial diagnosis ☐ Clinical diagnosis (2 MEN1 main tumors) ☐ One MEN1 main tumor plus a diagnosis of MEN1 in first-degree relative(s)
MEN1 affected first-degree relatives		?	☐ Mother ☐ Father ☐ Brother(s) ☐ Sister(s) ☐ Children ☐ Unknown
First MEN1-related clinical manifestation		?	☐ Primary hyperparathyroidism ☐ Pituitary adenoma ☐ DP neuroendocrine tumours (NET) ☐ Lung NET ☐ Thymus NET ☐ Gastric NET ☐ Distant metastasis from a NET ☐ Adrenal lesions ☐ Skin lesions ☐ Other manifestations (eg, Breast cancer)

The MEN-1 Condition-Specific Module

Patient history

Genetic testing

Clinical manifestation

Follow up

MEN1 sequencing genetic testing

☐ Yes

☐ No, but a relative has been tested

☐ No and no known genetic testing in the family

☒ Unknown

MPLA analysis of MEN1 gene

☐ Not Known

☐ Yes

☐ No

Other genes analyzed?

?

☐ CDKN1B

☐ AIP

☐ CDKN1A

☐ CDKN2C

☐ CDKN2B

☐ CDC73

☐ CASR

☐ Other

Results of other genes analyzed

The MEN-1 Condition-Specific Module

Patient history

Genetic testing

Clinical manifestation

Follow up

Clinical manifestation

Has the patient ever been diagnosed with...?

?

☐ Primary hyperparathyroidism

☐ Pituitary adenoma

☒ DP neuroendocrine tumours (NET)

☐ Lung NET

☐ Thymus NET

☐ Gastric NET

☐ Distant metastasis from a NET

☐ Adrenal lesions

☐ Skin lesions

☐ Other manifestations (eg, Breast cancer)

DP NET

Specify DP NET

?

☐ NF-PanNET

☐ Gastrinoma

☐ Insulinoma

☐ Another functional PanNET

☐ Loco-regional LN metastases from a DPNET

Was the patient operated for this?

☐ Not Known

☐ Yes

☐ No

The MEN-1 Condition-Specific Module

Patient history

Genetic testing

Clinical manifestation

Follow up

Current status

Assessment Date

?

yyyy-mm-dd

Does the patient currently have...?

?

☐ Primary hyperparathyroidism

☒ Pituitary adenoma

☐ DP neuroendocrine tumours (NET)

☐ Lung NET

☐ Thymus NET

☐ Gastric NET

☐ Distant metastasis from a NET

☐ Adrenal lesions

☐ Skin lesions

☐ Other manifestations (eg, Breast cancer)

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



eureb.eu

Research overview e-REC Core Registry ▾ Data Dictionaries Obtaining Registry Data Ethics Approval

Condition Specific Modules

Condition Specific Modules

Active Studies

Condition Specific Modules result from the work of dedicated multidisciplinary **Working Groups**. Condition-specific datasets cover aspects of specific conditions such as diagnosis, therapy, and monitoring. They are built into the **Core Registry** platform for dynamic and longitudinal collection of data. These data can be entered by clinicians and patients.

Want to develop a Condition Specific Module? Please use this [Application Form](#). Have you already created a Condition Specific Module, but want to make changes to the module, please use the [Module Changes Form](#). For minor changes to an existing module you can contact us at registries@lumc.nl.

Once a Condition Specific Module is developed, the module is available for different **Study Groups** to perform a study with data from the module.

If you would like to join or start a Working or Study Group please contact us at: registries@lumc.nl.

Current Modules available:

- Achondroplasia
- Chronic Non-bacterial Osteitis (CNO)
- Fibrous Dysplasia / McCune Albright Syndrome (FD/MAS)
- Gender Incongruence
- Hypoparathyroidism **new module!**
- iPPSD/PHP
- Langerhans Cell Histiocytosis (LCH)
- Melorheostosis
- Multiple Endocrine Neoplasia type 1 (MEN-1)
- Non-Langerhans Cell Histiocytosis (Non-LCH)
- Osteogenesis Imperfecta (OI)
- Parathyroid Carcinoma
- Pediatric Differentiated Thyroid Carcinoma (P-DTC)



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

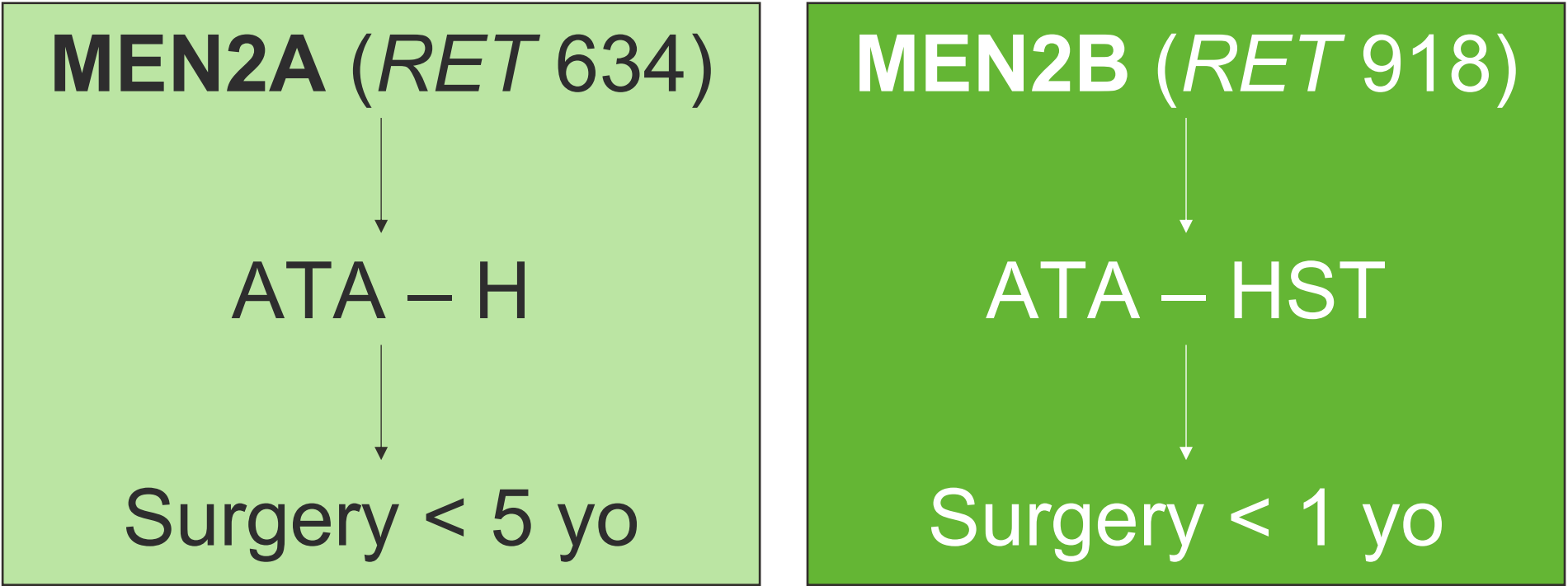
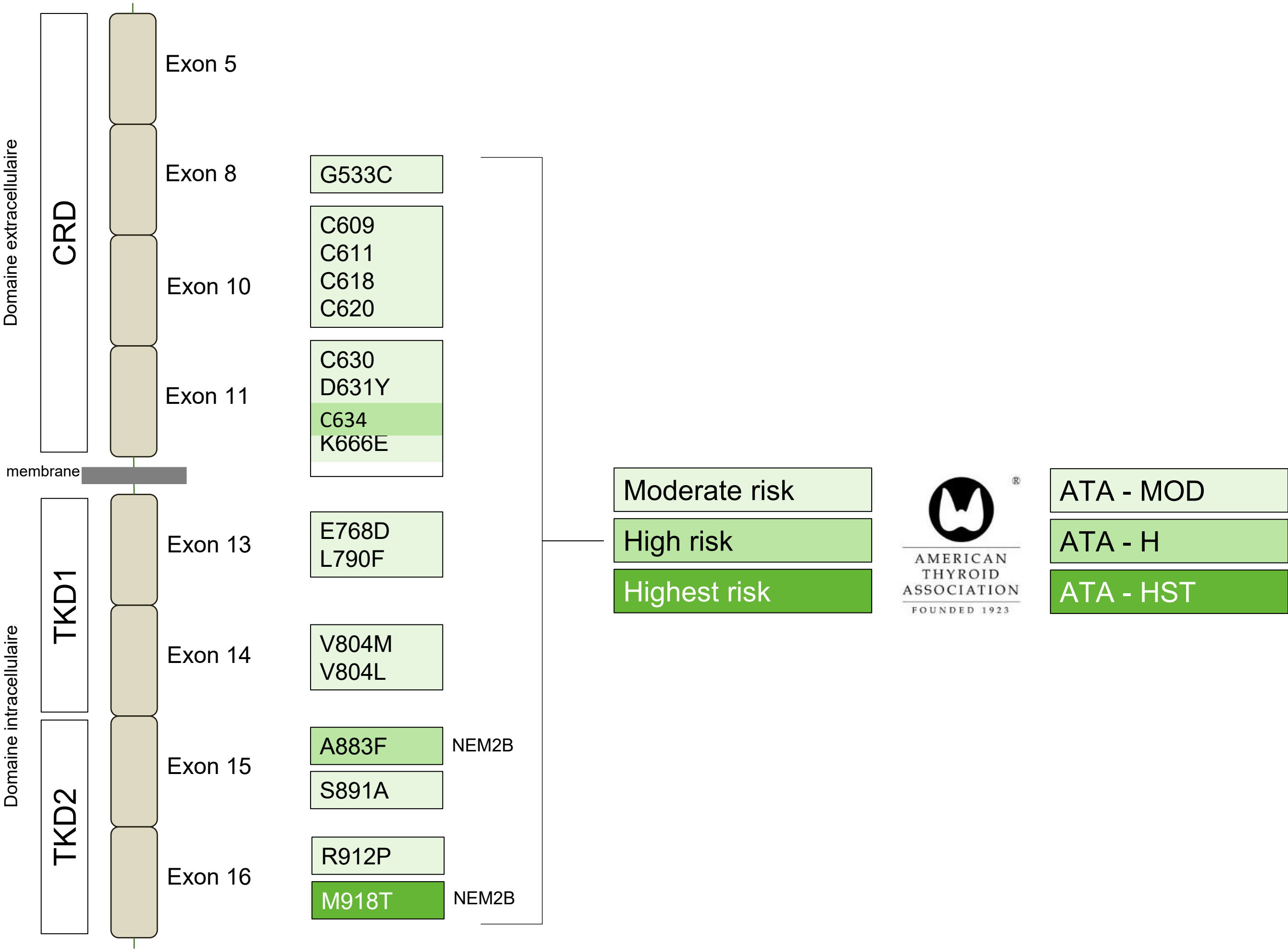
Nicolas SAHAKIAN, MD, Ph.D

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



MEN2 : Genetics

RET mutations

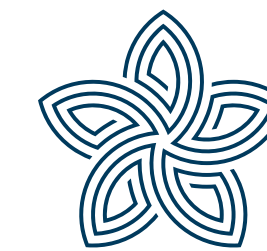


Wells SA et al. Thyroid. 2015 Jun 1;25(6):567–610.

MEN2 FRENCH COHORT



European
Reference
Network



Endo-ERN

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

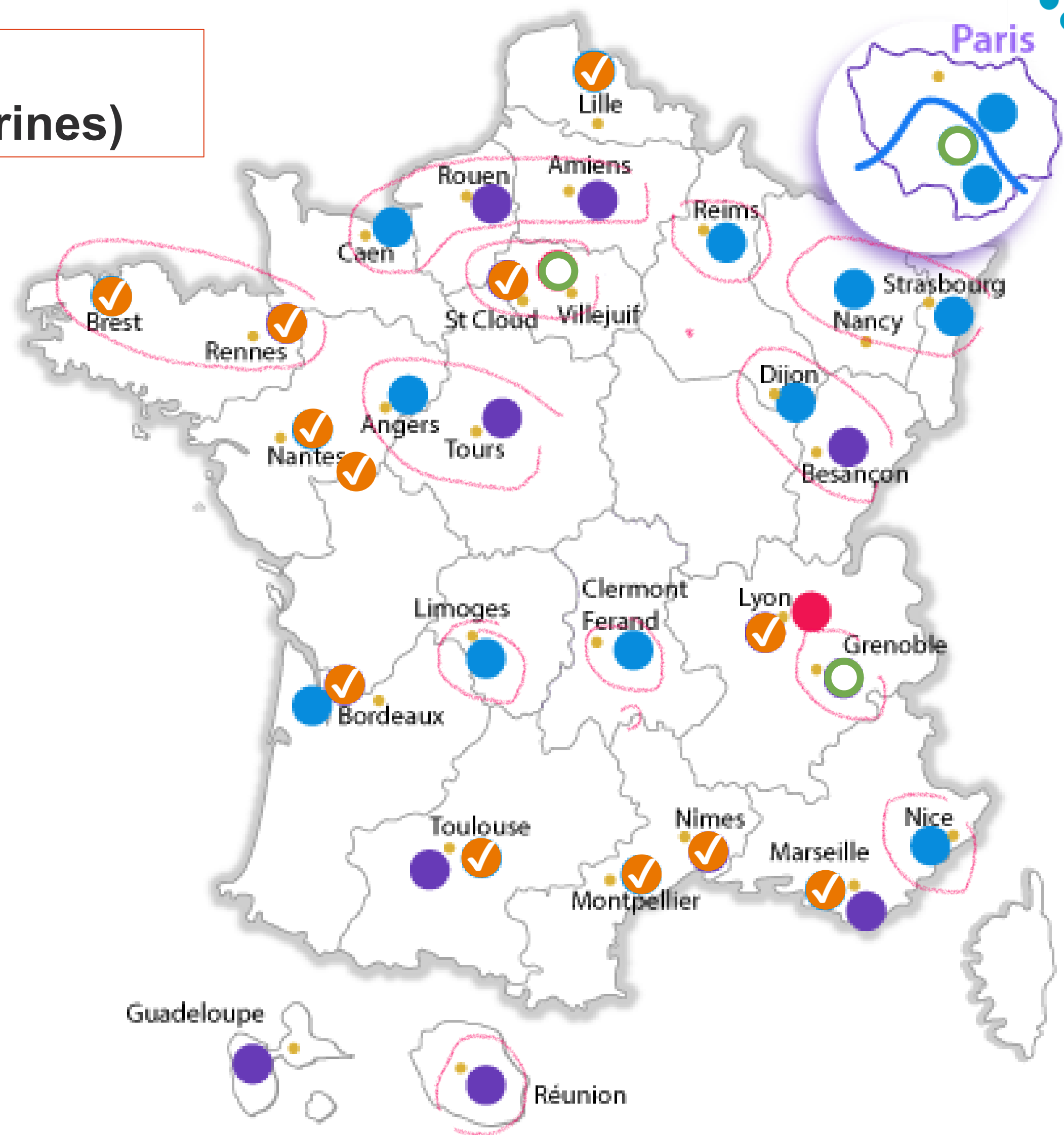
Factors associated with
the natural history of
MEN2? (penetrance,
aggressiveness of the MTC
depending on the variant)

Looking for **protective
factors** in pheo

MEN2 FRENCH COHORT

National database
(Groupe des tumeurs endocrines)

977 patients / Currently
750 with usable data



European
Reference
Network



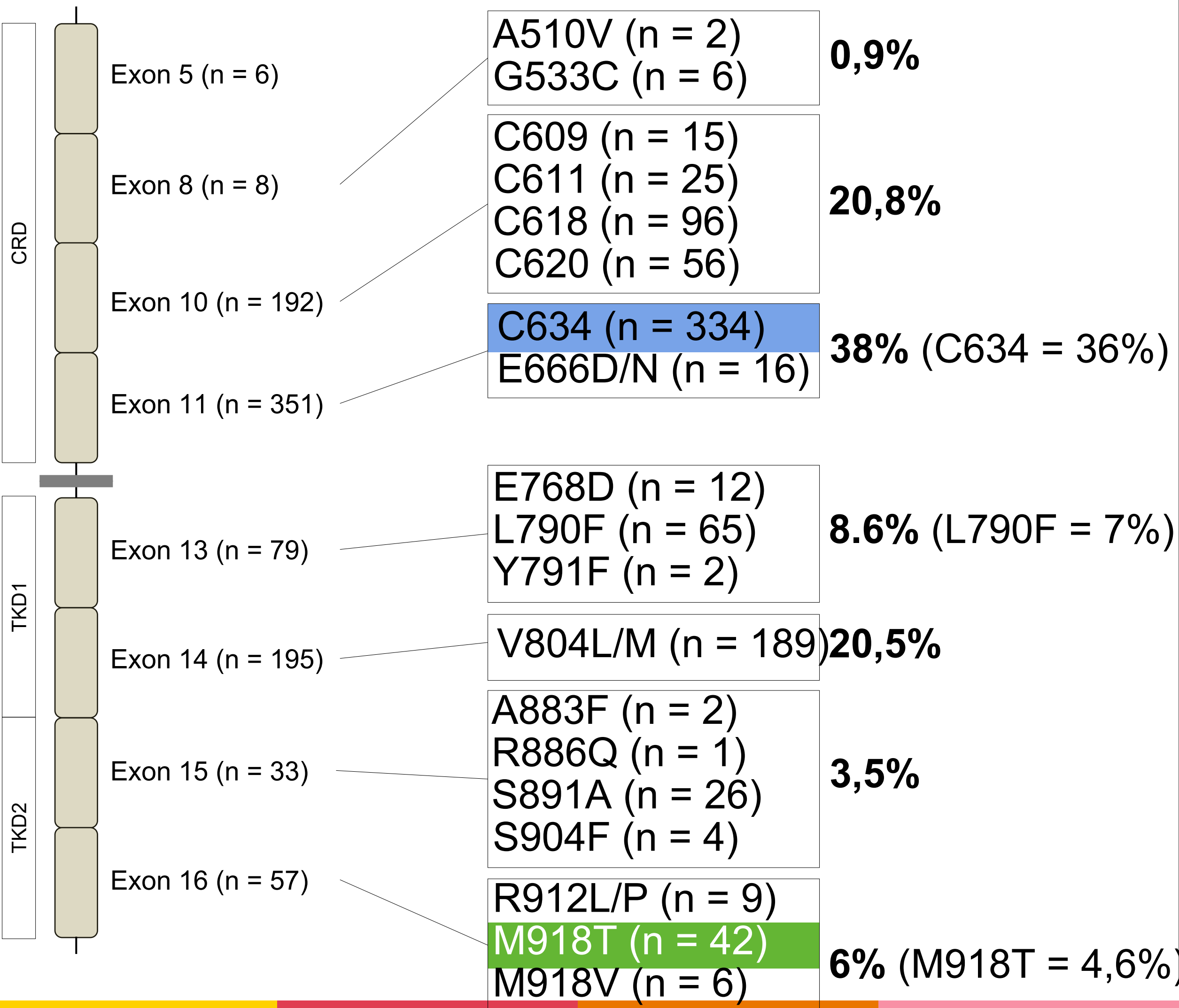
Endo-ERN



Groupe d'étude des Tumeurs Endocrines



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)

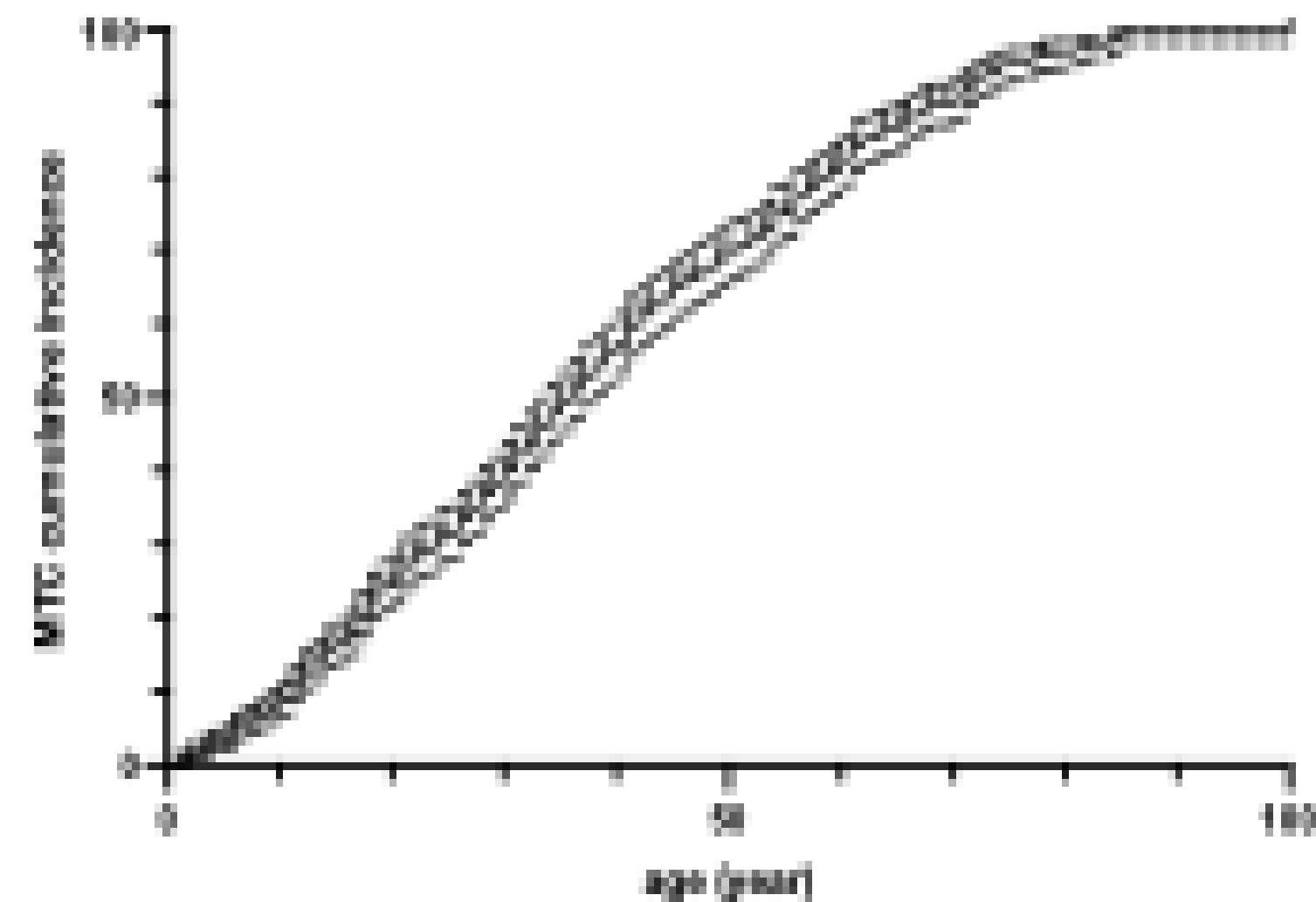
First Disease (n = 874) :

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

Clinical data LFU n = 707

MEN2 FRENCH COHORT: PENETRANCE

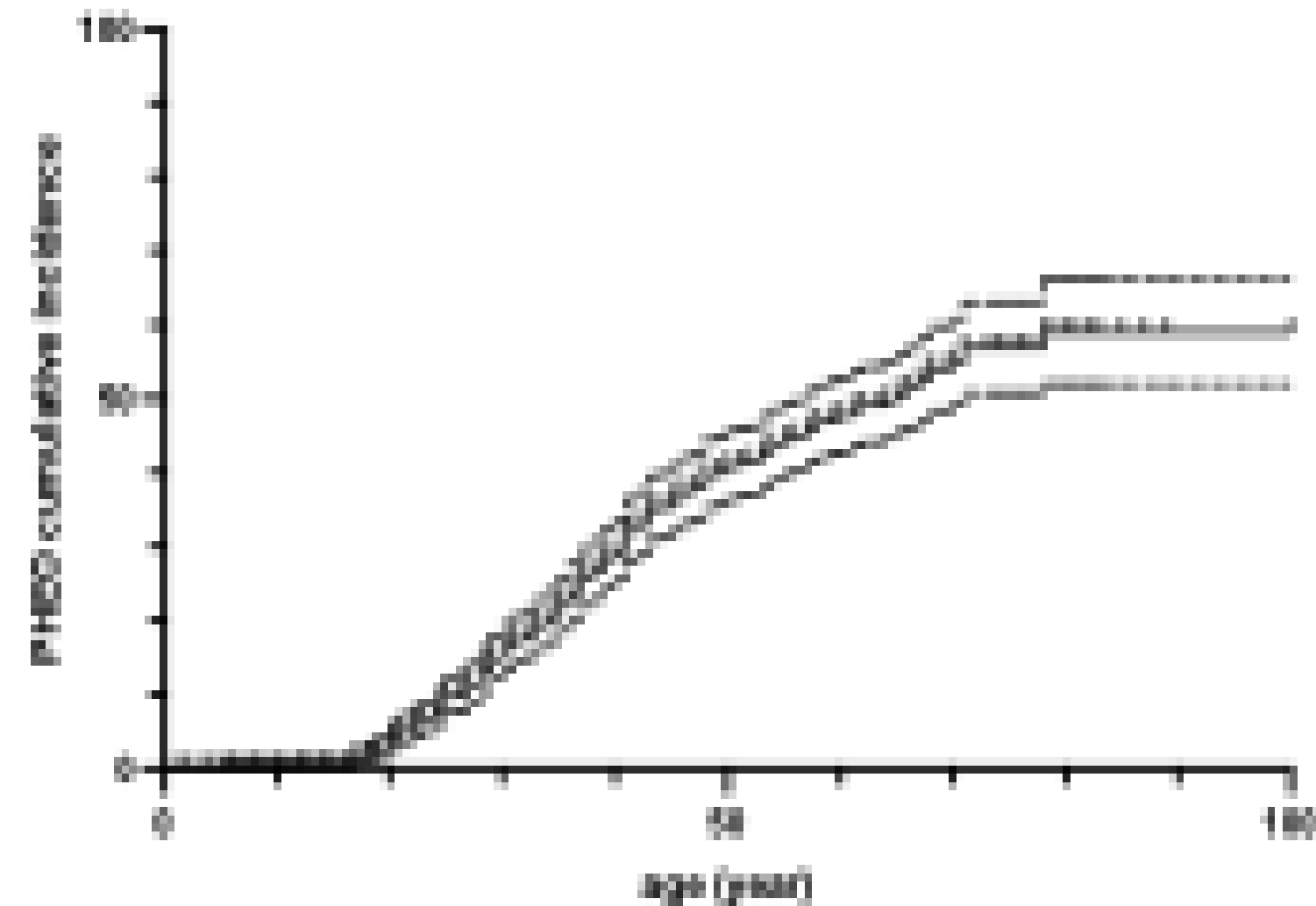
MTC : all (n = 747)



10.000	8.709	2.282	1.827
20.000	28.081	5.380	5.021
30.000	40.137	9.878	9.647
40.000	57.282	3.988	3.908
50.000	70.083	5.713	5.754
60.000	82.387	3.148	3.407
70.000	90.482	2.472	2.907
80.000	98.008	0.504	1.416

MTC
≈ 100%

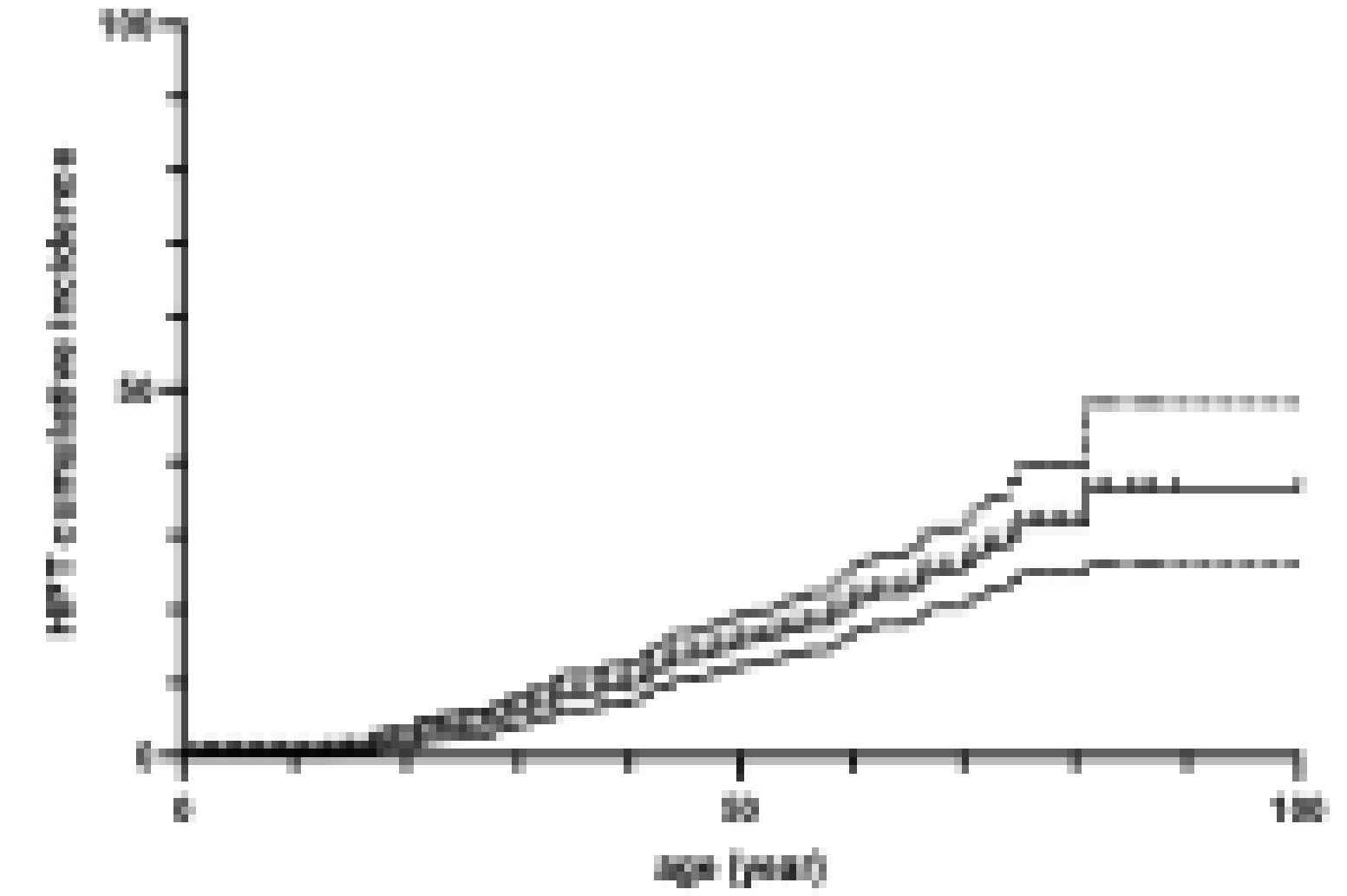
PHEO all (n = 713)



10.000	0.287		
20.000	4.108	1.515	1.515
30.000	16.224	3.388	2.860
40.000	28.338	4.283	3.821
50.000	40.984	4.775	4.451
60.000	47.708	5.138	4.878
70.000	54.981	5.515	5.728
80.000	58.988		

PHEO :
≈ 60%

HPT all (n = 706)



10.000	0.013	1.054	0.383
20.000	3.899	1.905	1.284
30.000	8.884	3.002	2.333
40.000	15.908	3.870	3.188
50.000	21.982	4.821	4.088
60.000	26.324	6.143	5.180
70.000	34.133	12.153	8.830

HPT :
≈ 30%

ATYPICAL NATURAL HISTORY

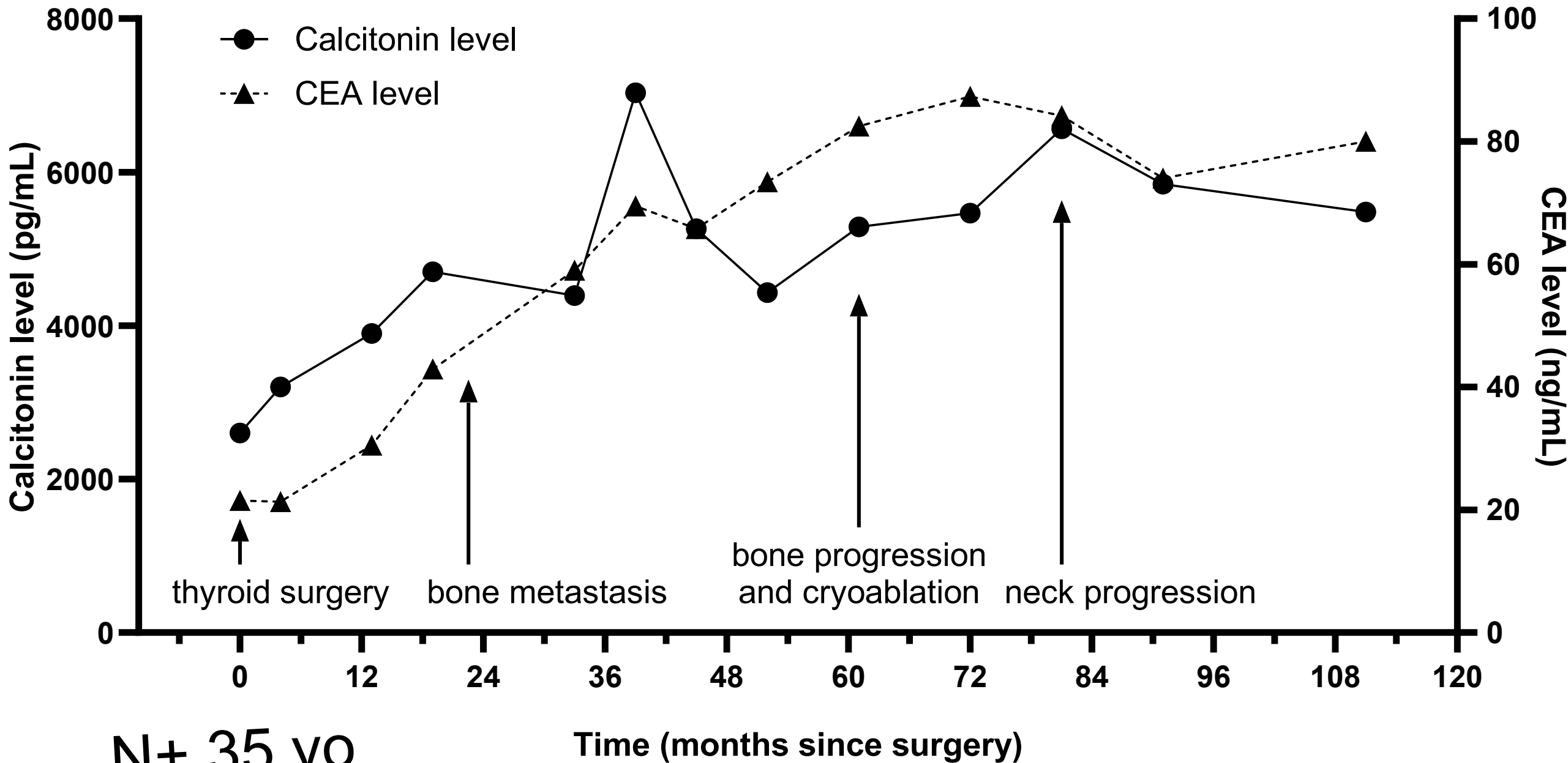


Letter to the editor: The somatic *RET* M918T variant may modify the natural history of germline *RET* L790F MEN2-related medullary thyroid carcinoma

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

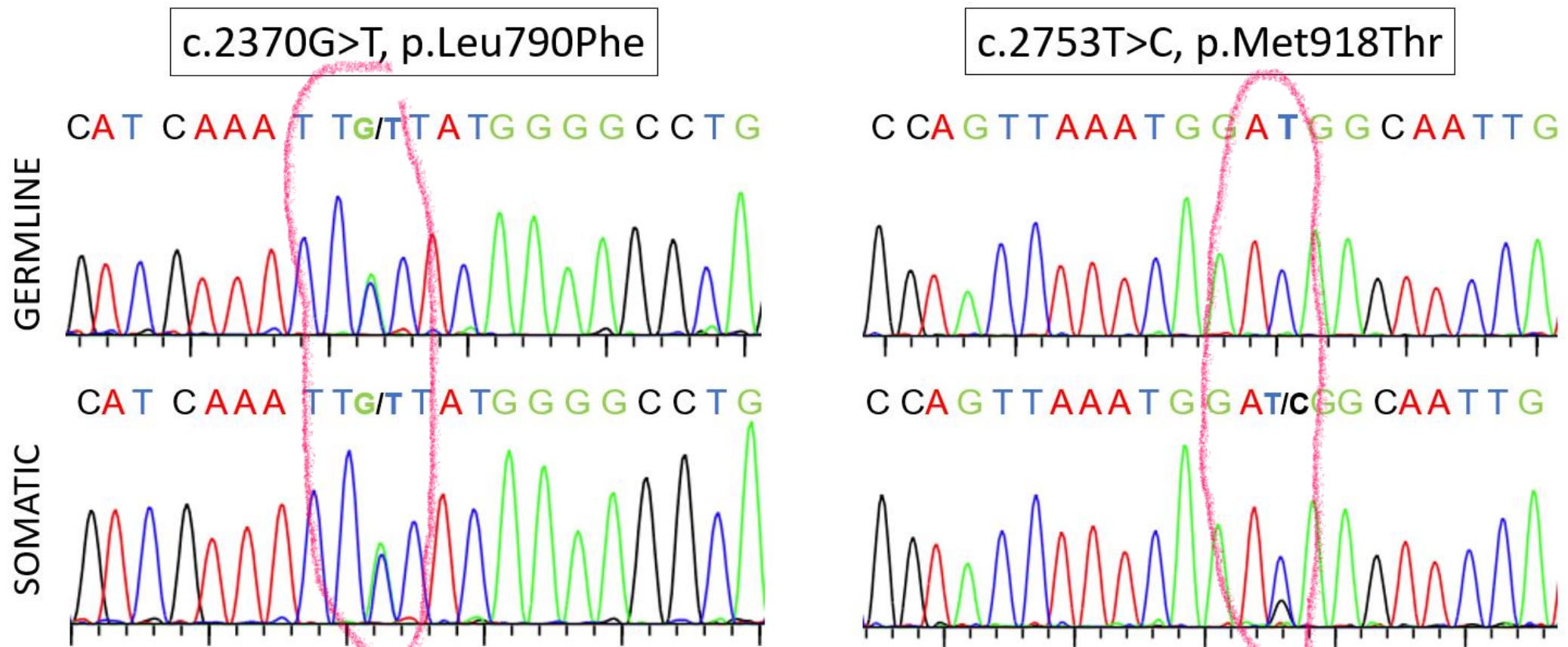
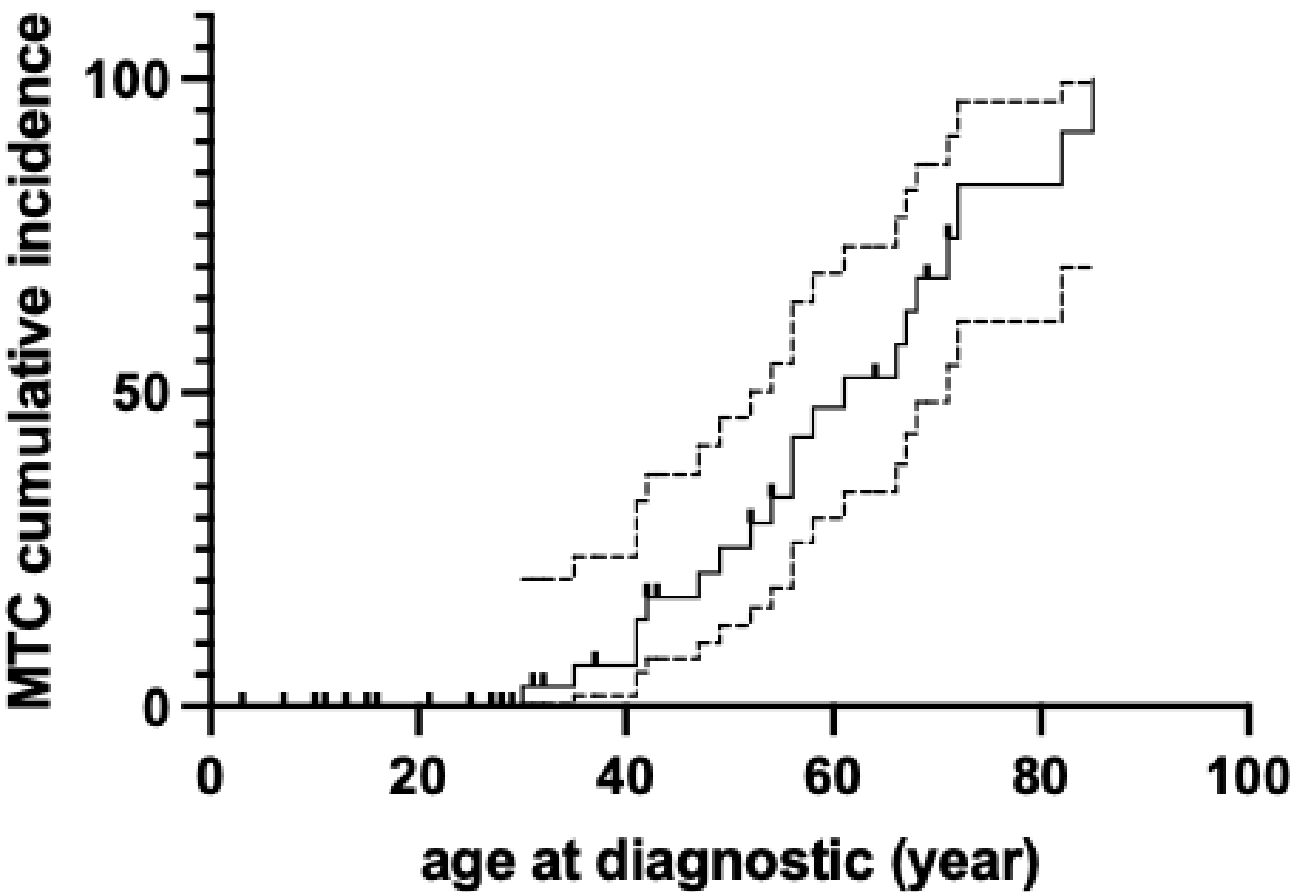


Figure 1: targeted *RET* sanger sequencing on blood and MTC

L790F in our cohort (n = 65)

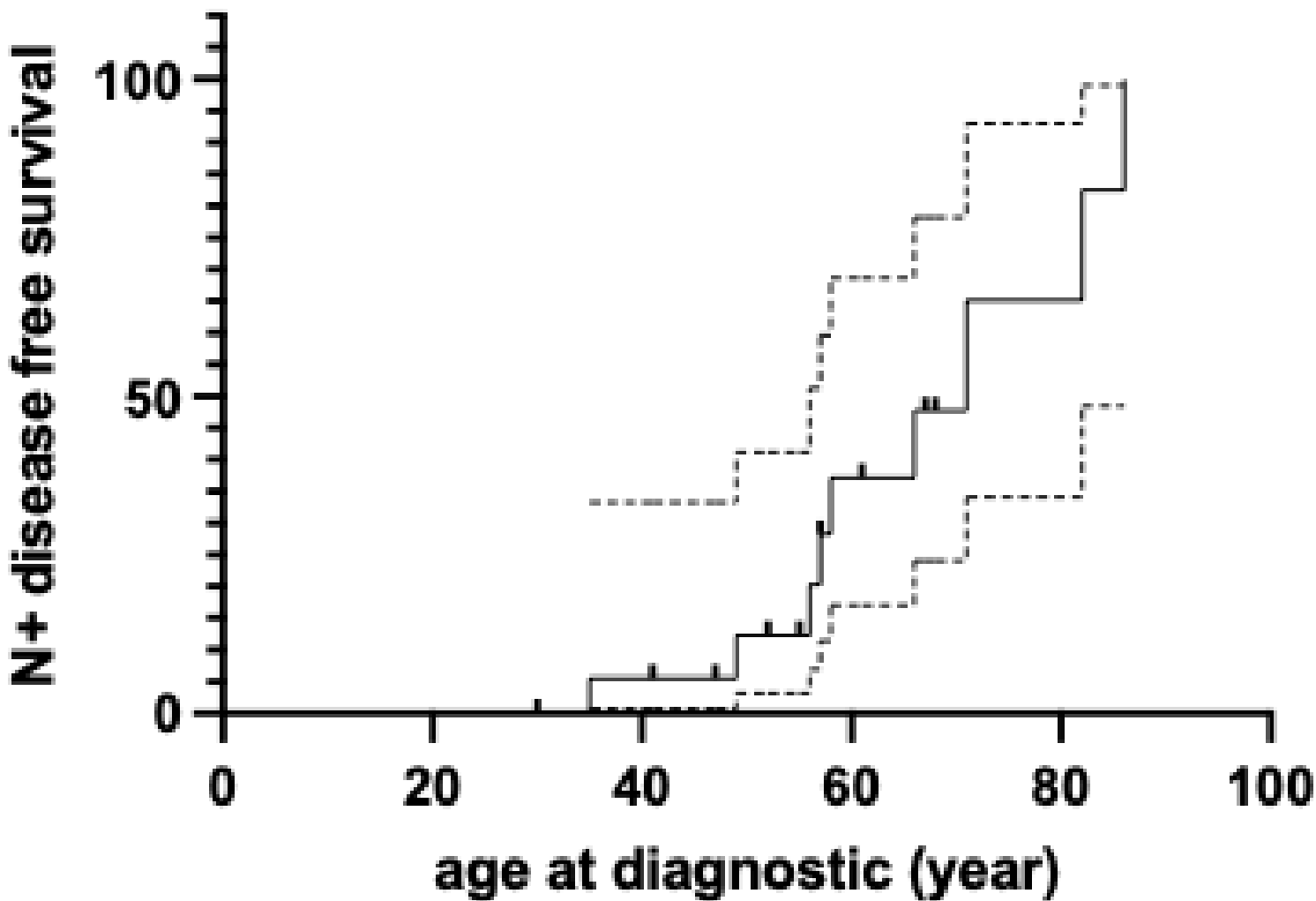


L790F (n = 65)



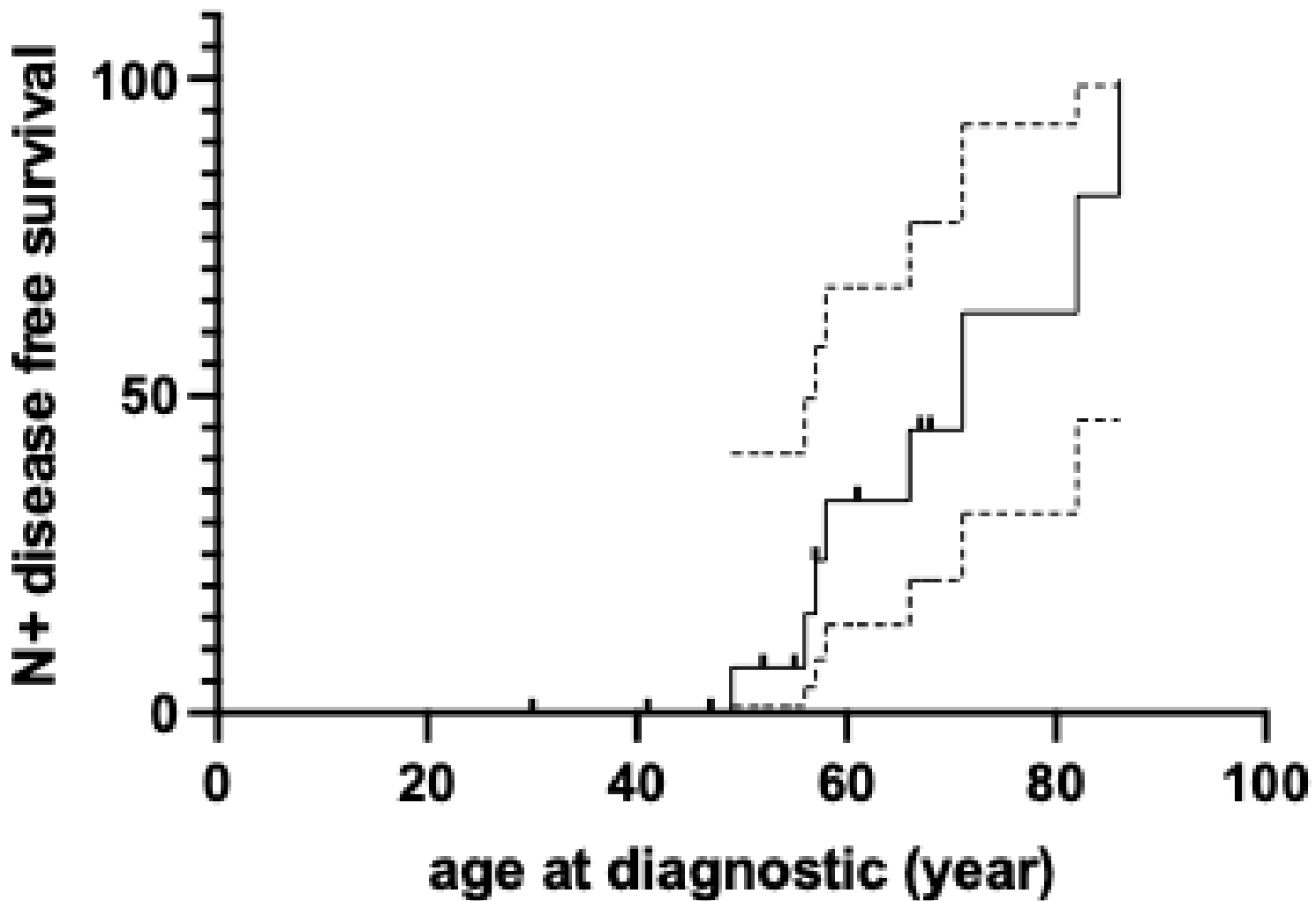
10.000	0.000		
21.000	0.000		
30.000	3.125	17.056	2.679
41.000	13.771	18.959	8.384
52.000	29.169	20.988	13.467
61.000	52.382	20.898	18.276
71.000	74.604	16.309	20.295
82.000	91.535	7.835	21.550

L790F (n = 65)



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

L790F (n = 64 ; sans M918T somatique)

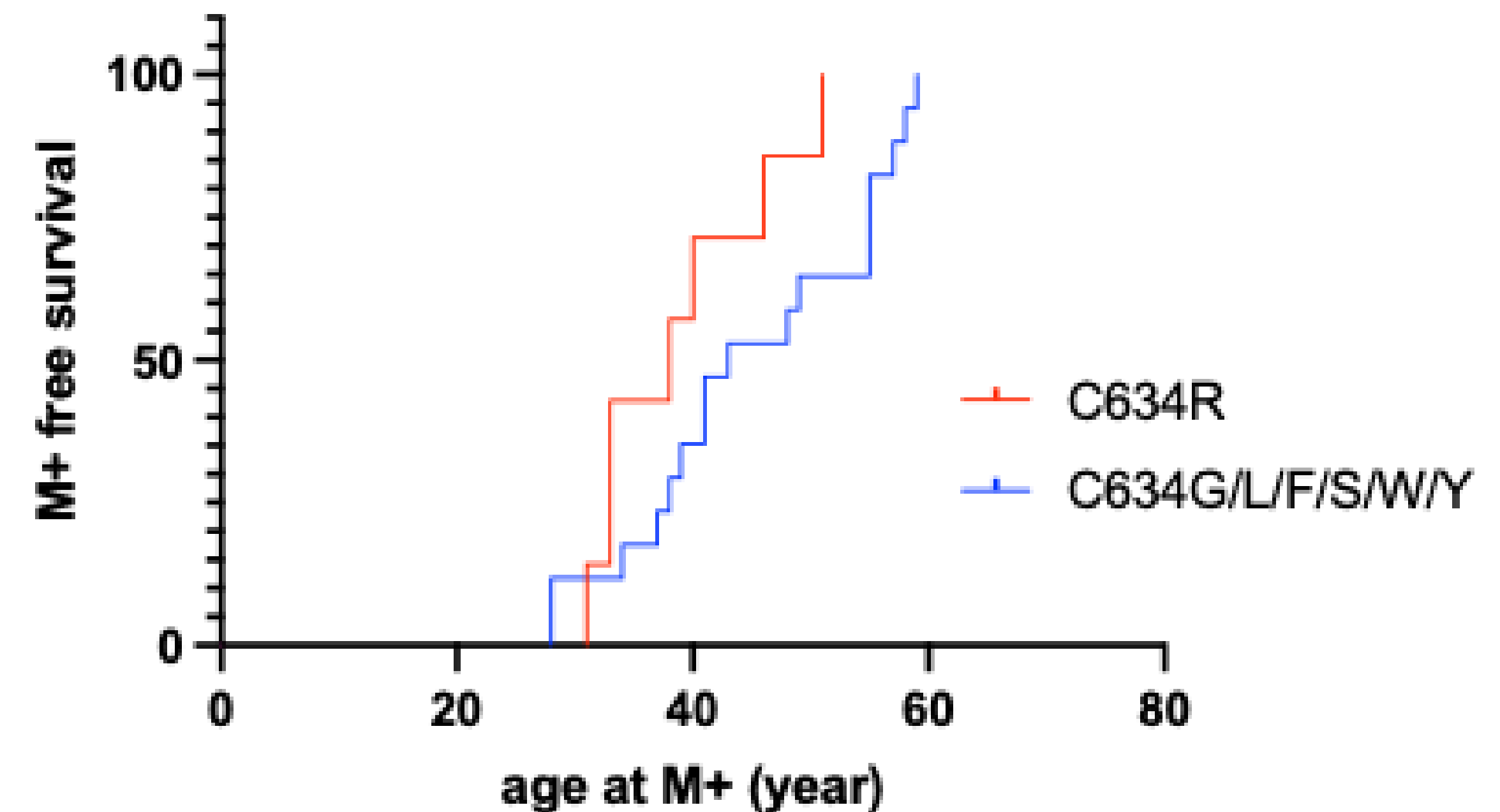
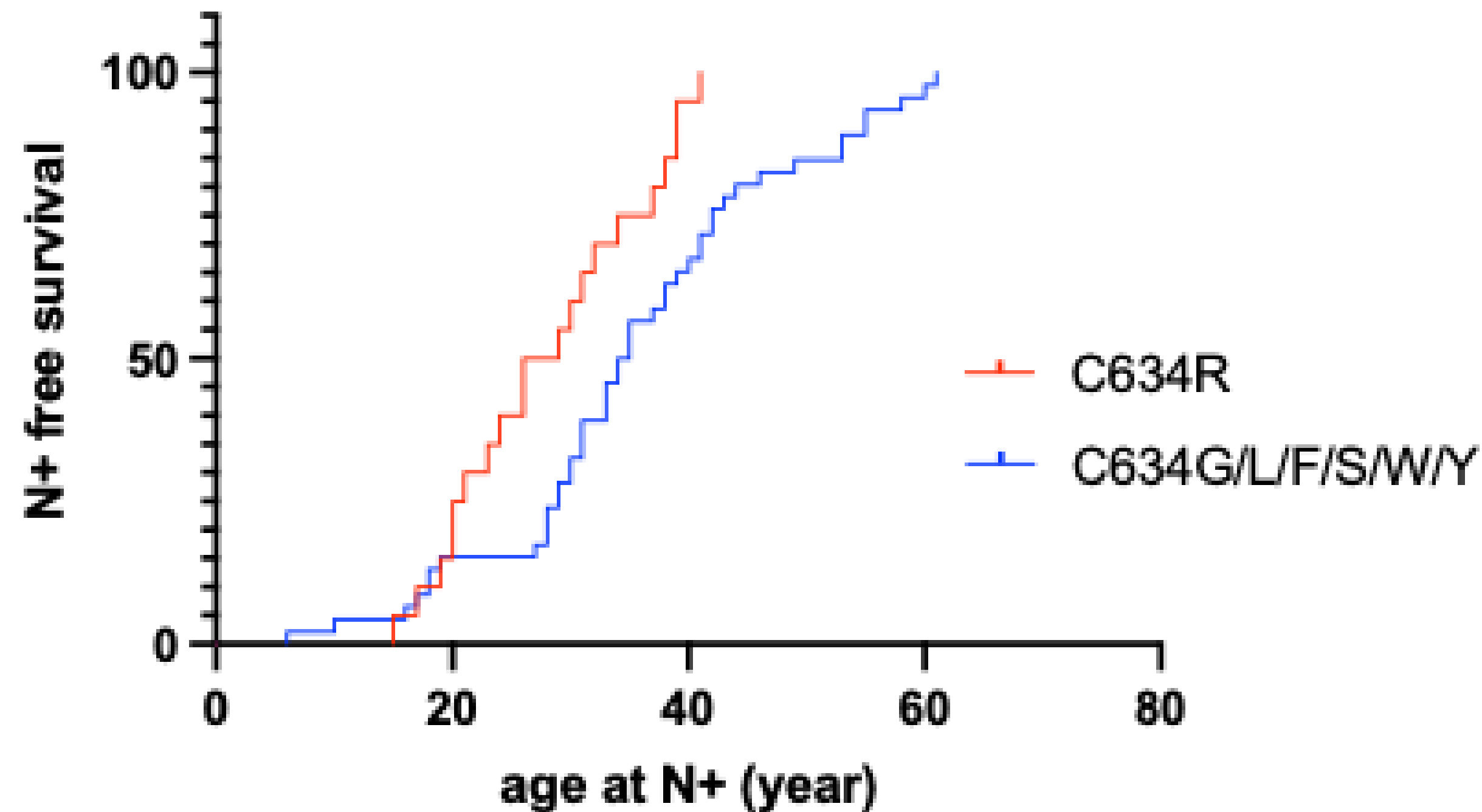


30.000	0.000		
49.000	7.143	33.780	6.105
58.000	33.523	33.583	19.598
71.000	63.068	29.727	31.646

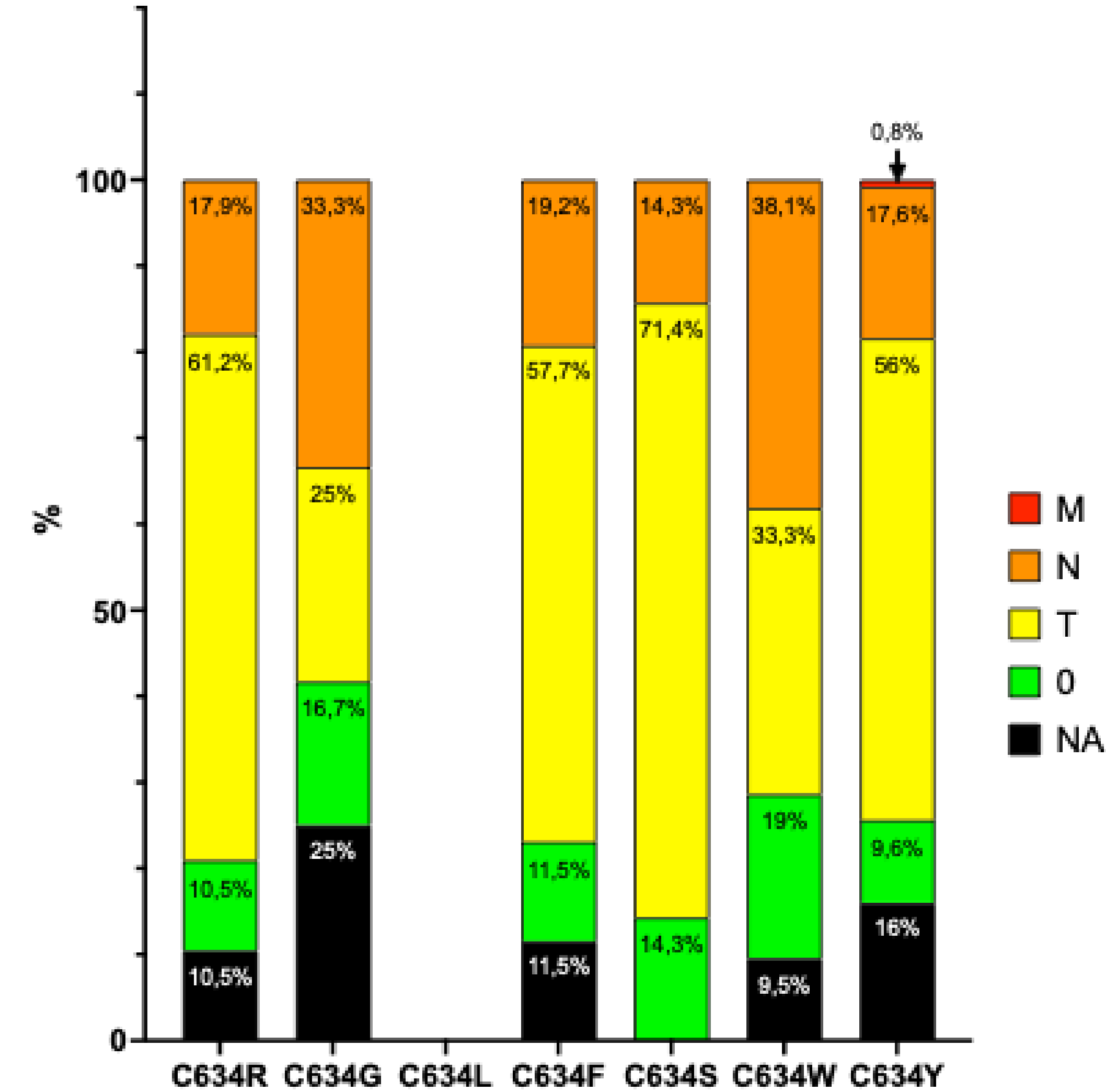
YoungestT : 30 yo (M918T somatique : 35 yo)
Youngest : 49 yo (M918T somatique : 35 yo)
Youngest M : 58 yo (M918T somatique : 38 yo)

AMINO ACID CHANGE IN 634

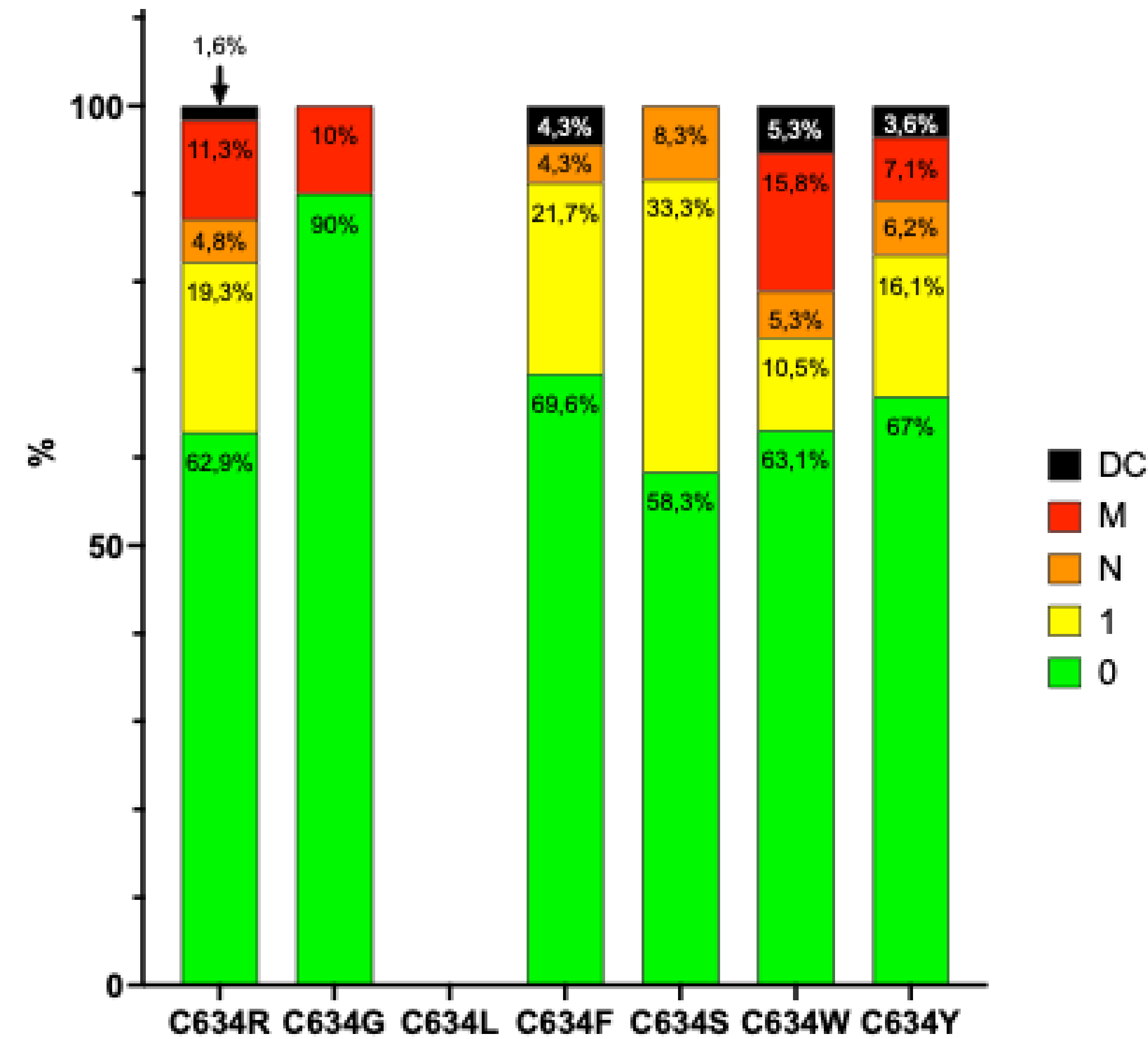
- C634R: n=72
- C634Y: n=125
- C634 G/L/F/S/W: n= 75



AMINO ACID CHANGE IN 634

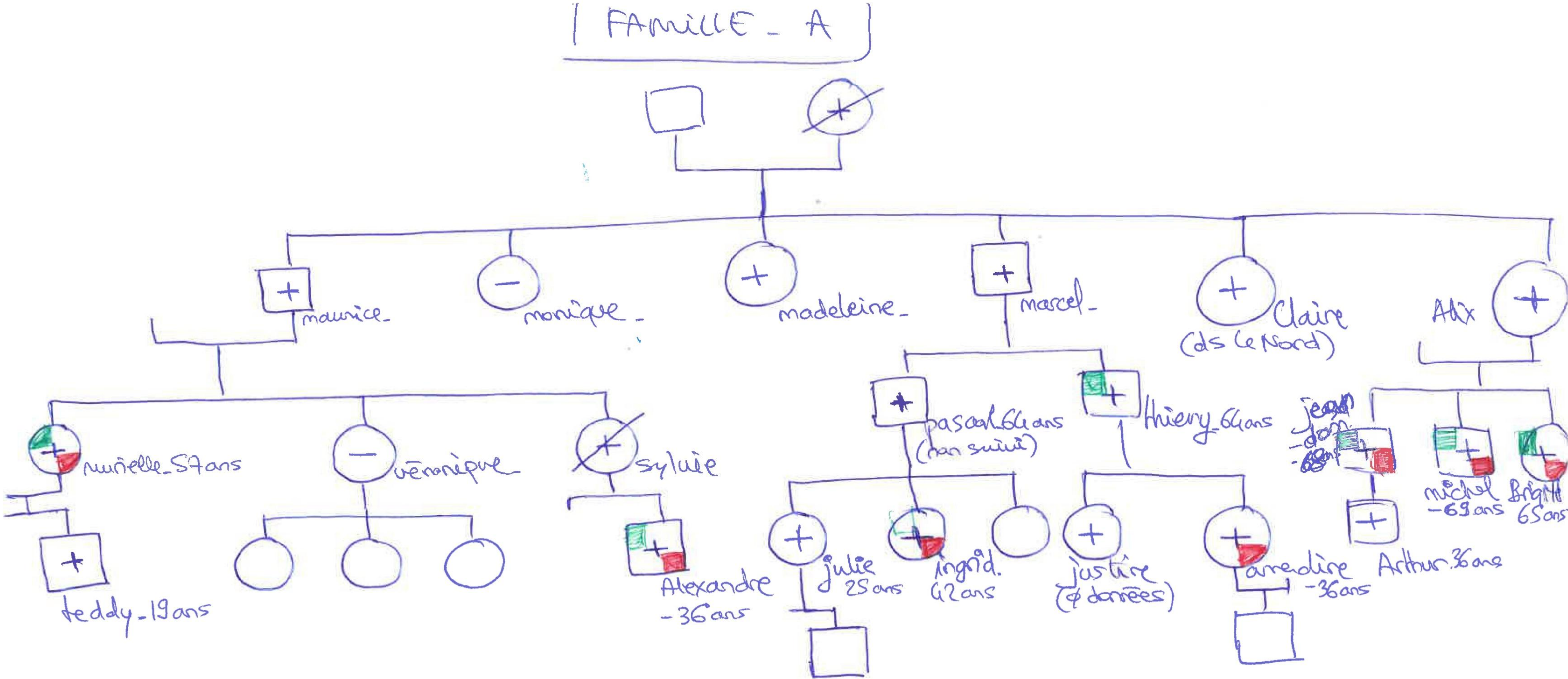


MTC DIAGNOSIS



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 something.

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	

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

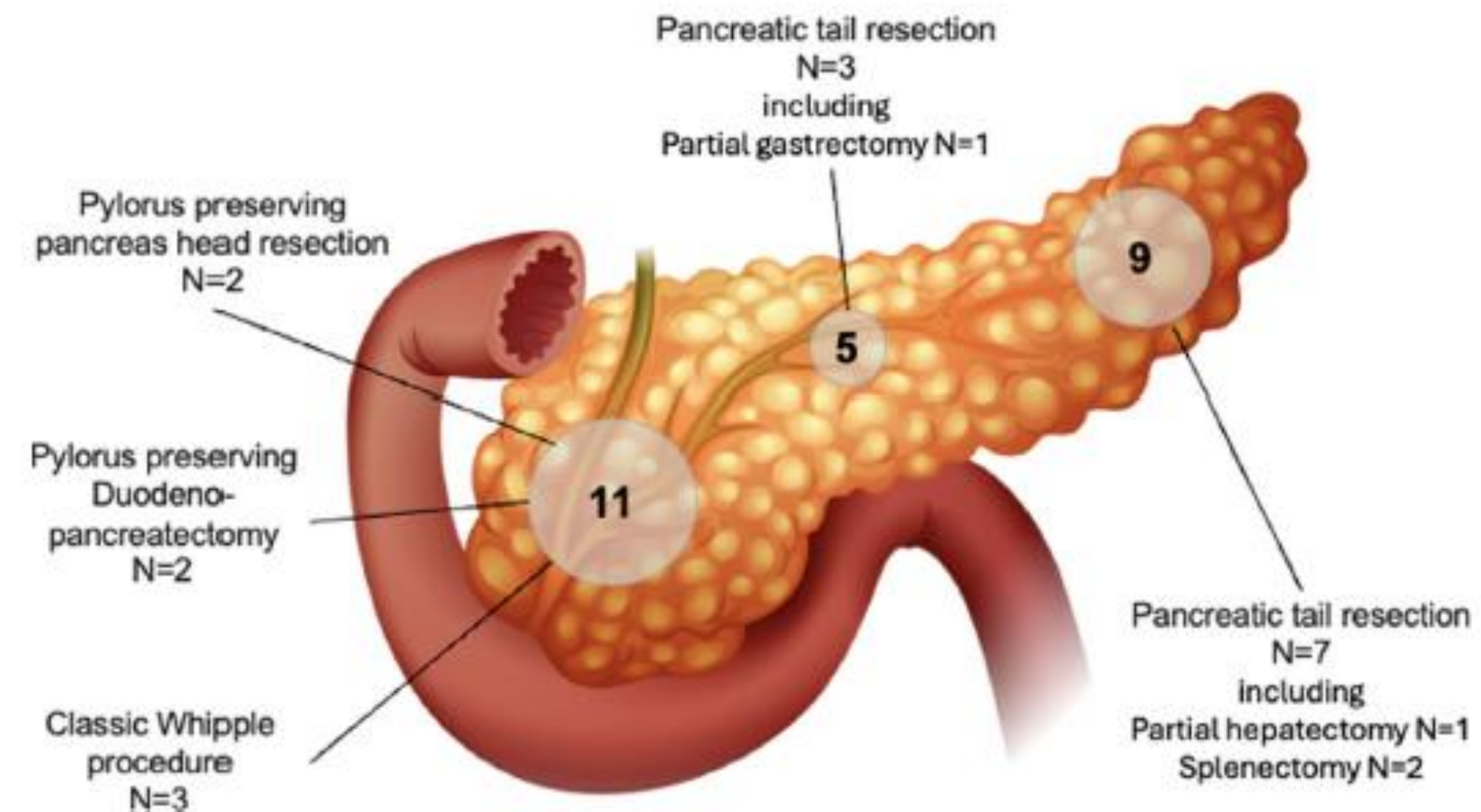
Pancreatic neuroendocrine tumors in children - MET registry



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Karges et al., J Neuroendocrinol, 2025

Pancreatic neuroendocrine tumors in children - MET registry



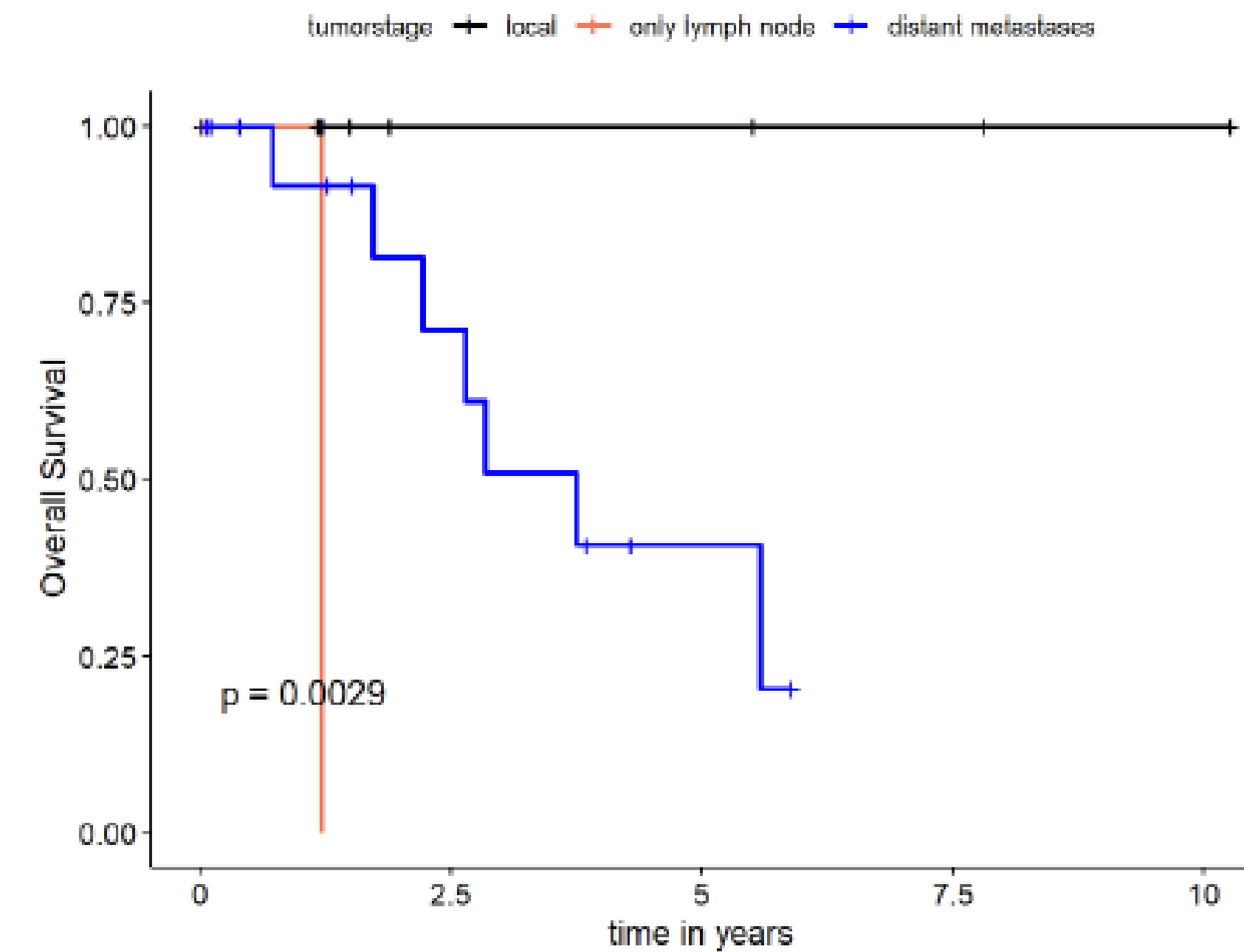
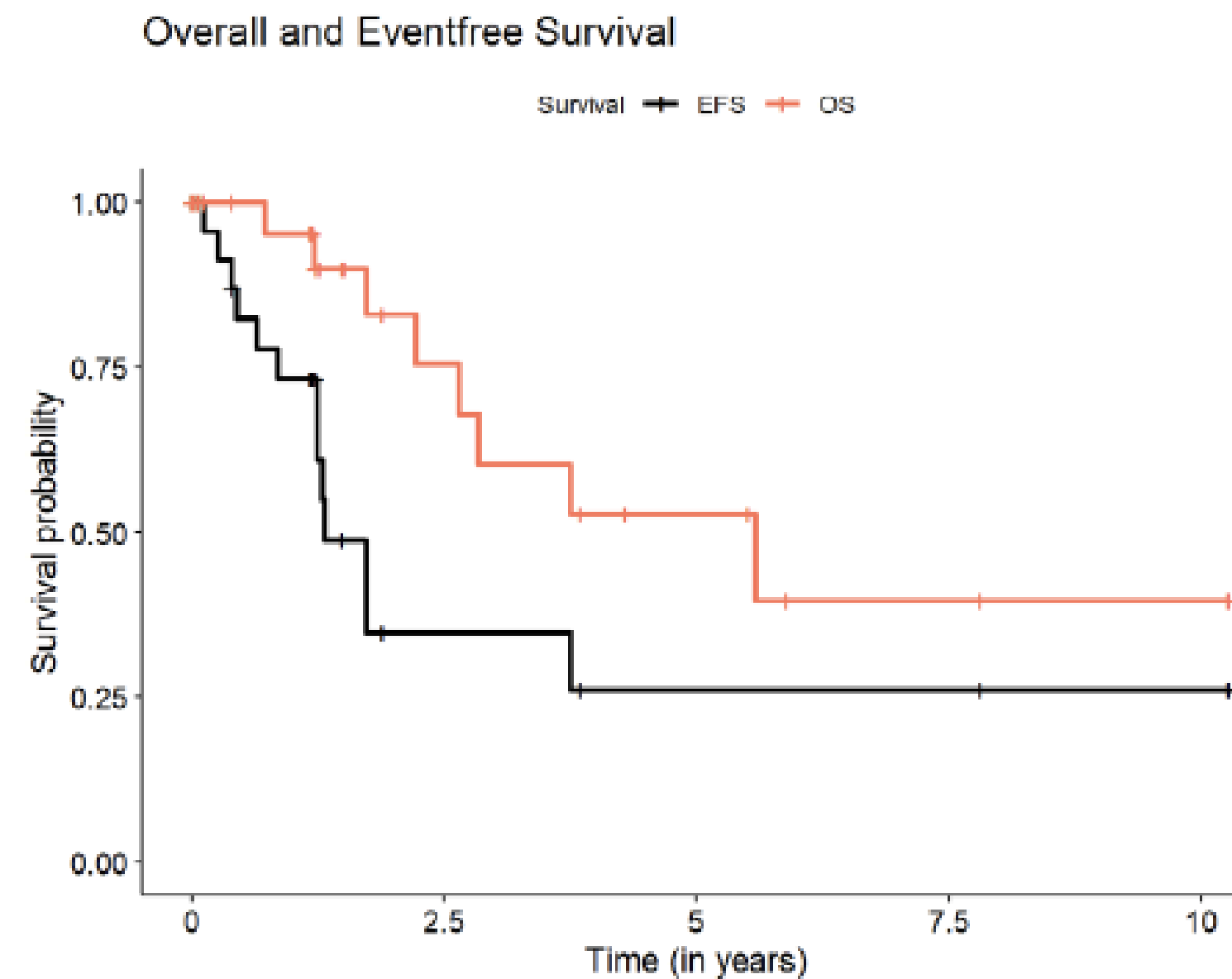
1997-2024

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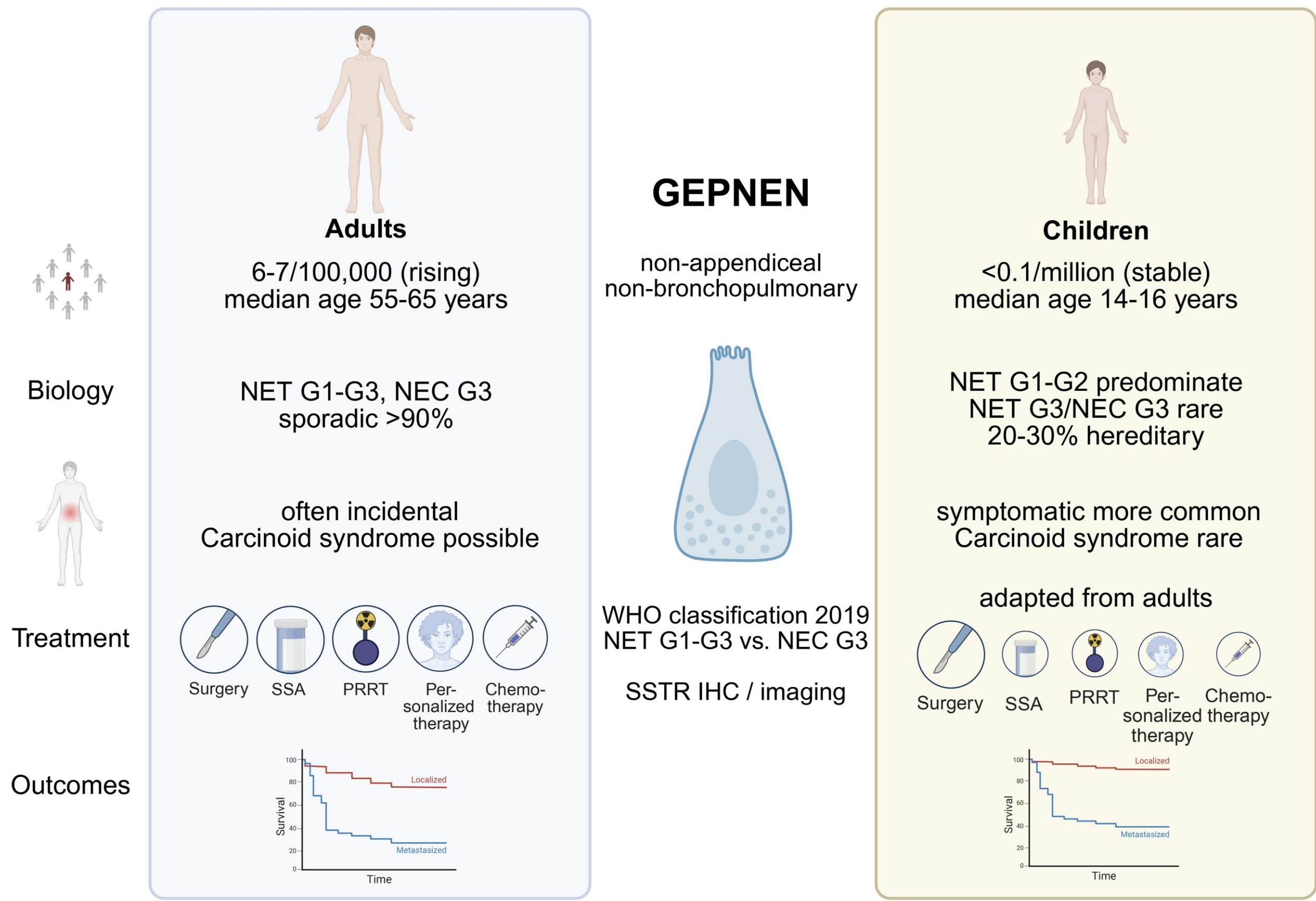
WHO classification of panNET ^{a,b}		
Well-differentiated NET		
G1 (Ki67 <3%, mitotic index <2)	4	14.3
G2 (Ki67 3%–20%, mitotic index 2–20)	12	42.9
G3 (Ki67 >20%, mitotic index >20)	2	11.1
Poorly differentiated NEC		
High (Ki67 >20%, mitotic index >20)	7	25.0
Unknown	3	10.7

Pancreatic neuroendocrine tumors in children - MET registry



Karges et al., J Neuroendocrinol, 2025

Gastrointestinal neuroendocrine tumors in children - MET registry



Gastrointestinal neuroendocrine tumors in children - MET registry



1997-2024

16 Patients (10 male, 6 female)

mean age 15.4 years

MET

SEER registry

GI tract, nos, $n=2/83$

Duodenum, $n=2/16$ vs. $n=4/83$

Jejunum, $n=1/16$ vs. $n=2/83$

Ileum, $n=9/83$

Meckel's diverticulum,
 $n=2/16$ vs. $n=4/83$

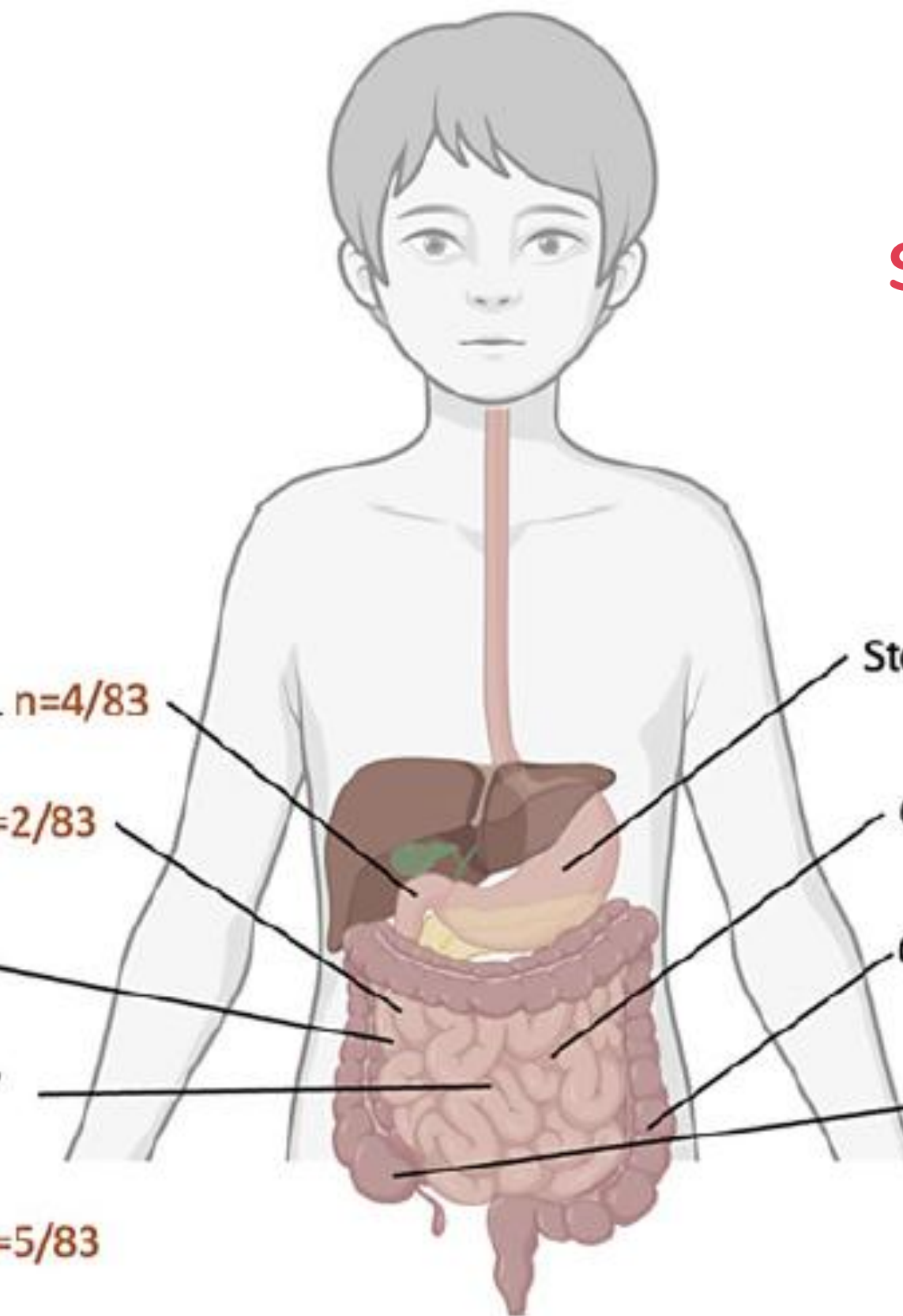
Small intestine, nos, $n=5/83$

Stomach, $n=7/16$ vs. $n=10/83$

Omentum majus, $n=1/16$

Colorectal region, $n=3/16$ vs. $n=45/83$

Cecum, $n=2/83$



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

Gastrointestinal neuroendocrine tumors in children - MET registry

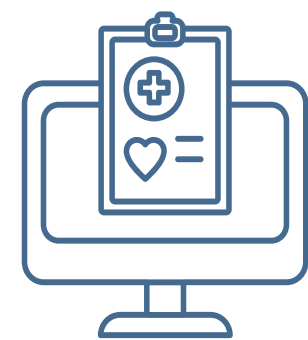
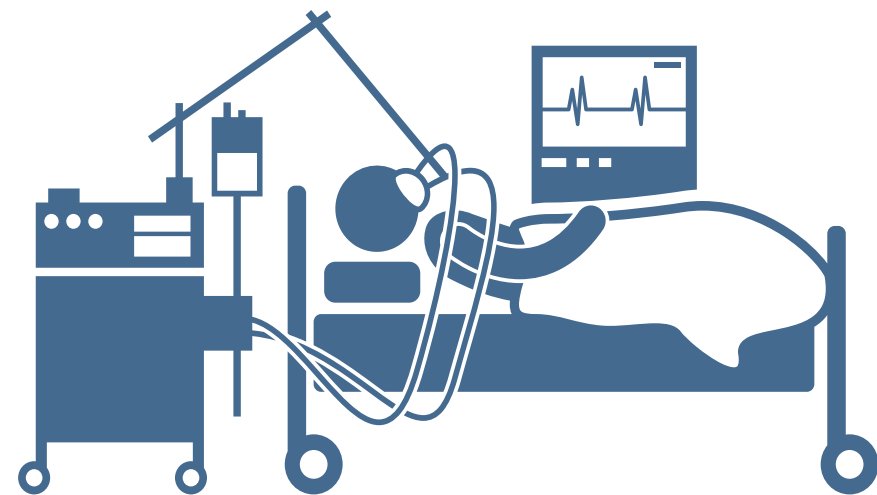


Tumor genetic syndromes
and presentation

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

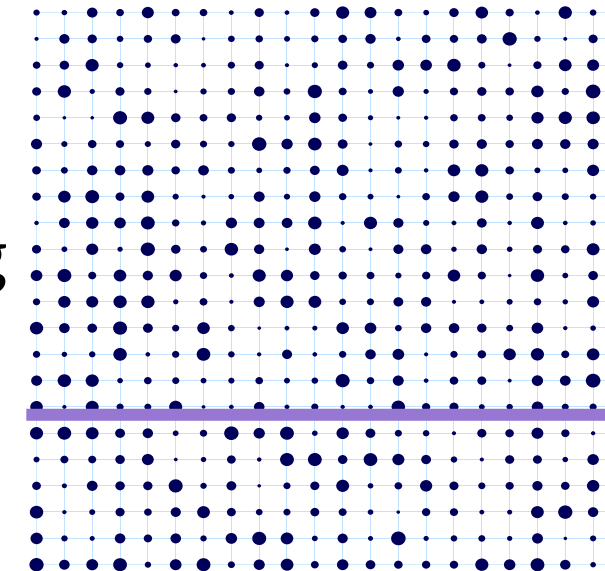
Machine learning

Algorithms and data

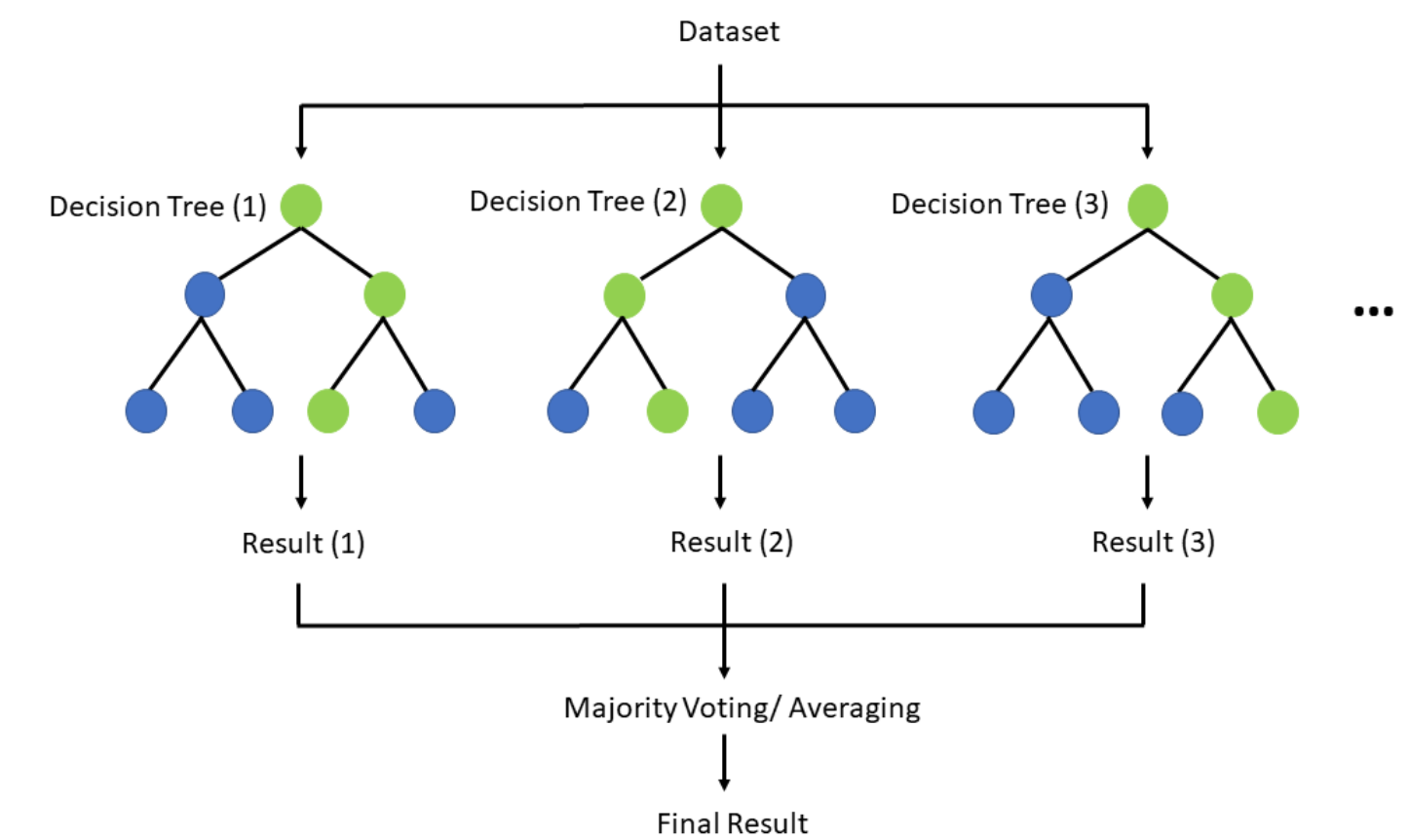


Monitoring
digital health records

80% Training
20% Testing



data
labeled

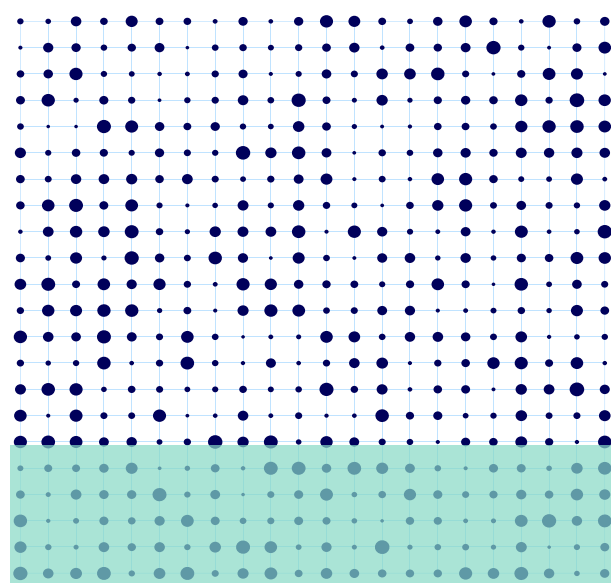


Prediction outcome (nominal) via
features (nominal/continuous)

Adrenocortical Carcinoma in Children: ML Prediction Survival



Data

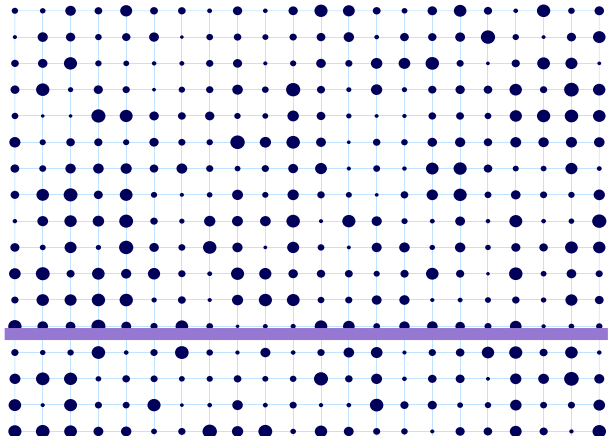


MET Registry
1997-2024
97 ACC/ACx

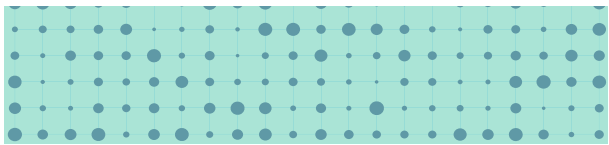
Model evaluation/Feature selection

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)

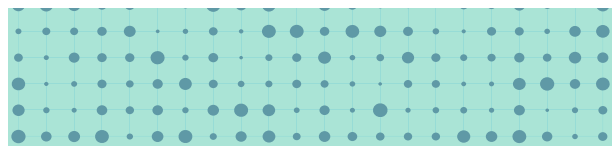
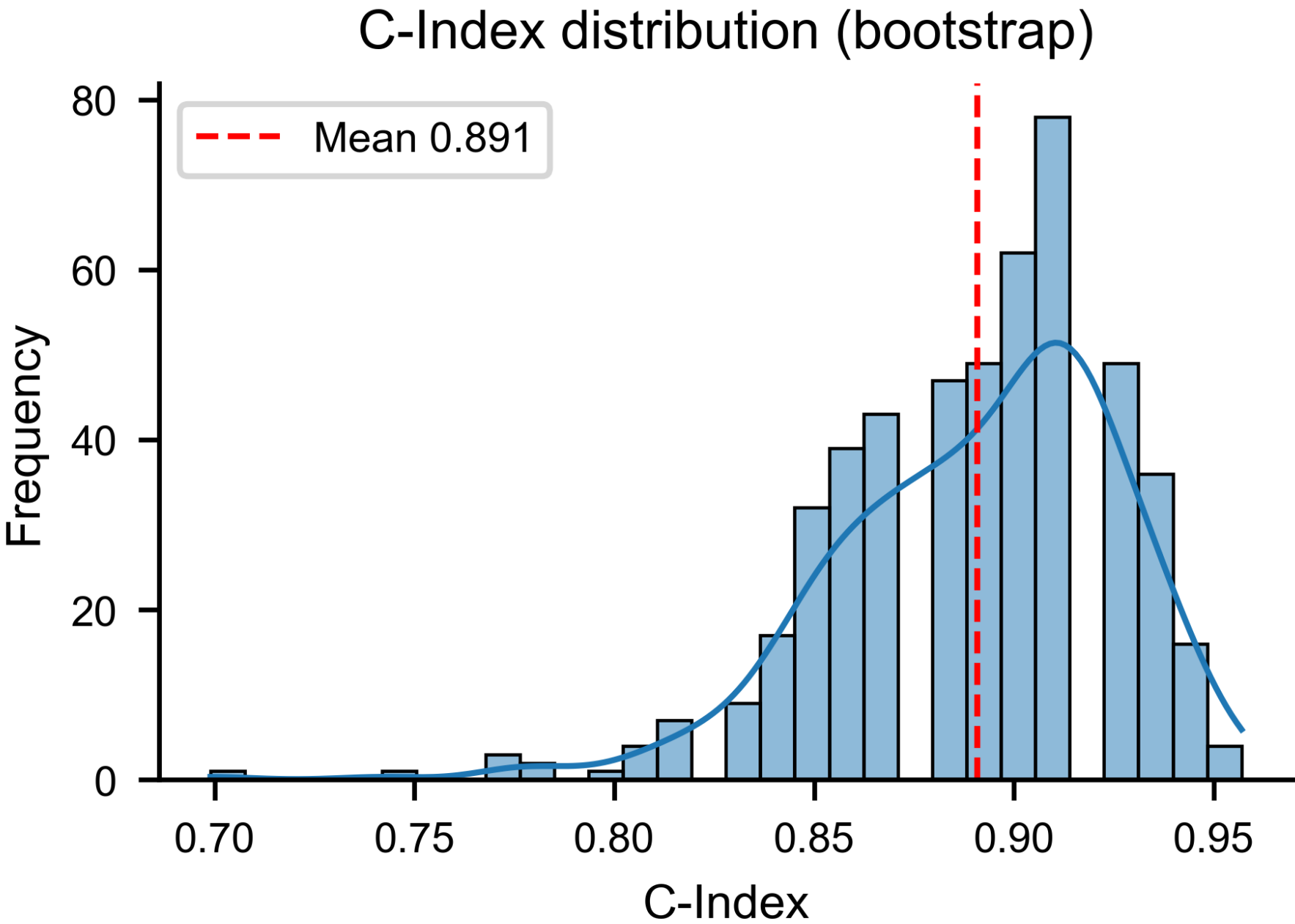


hould out
final model

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Best Model C-Index 0,891

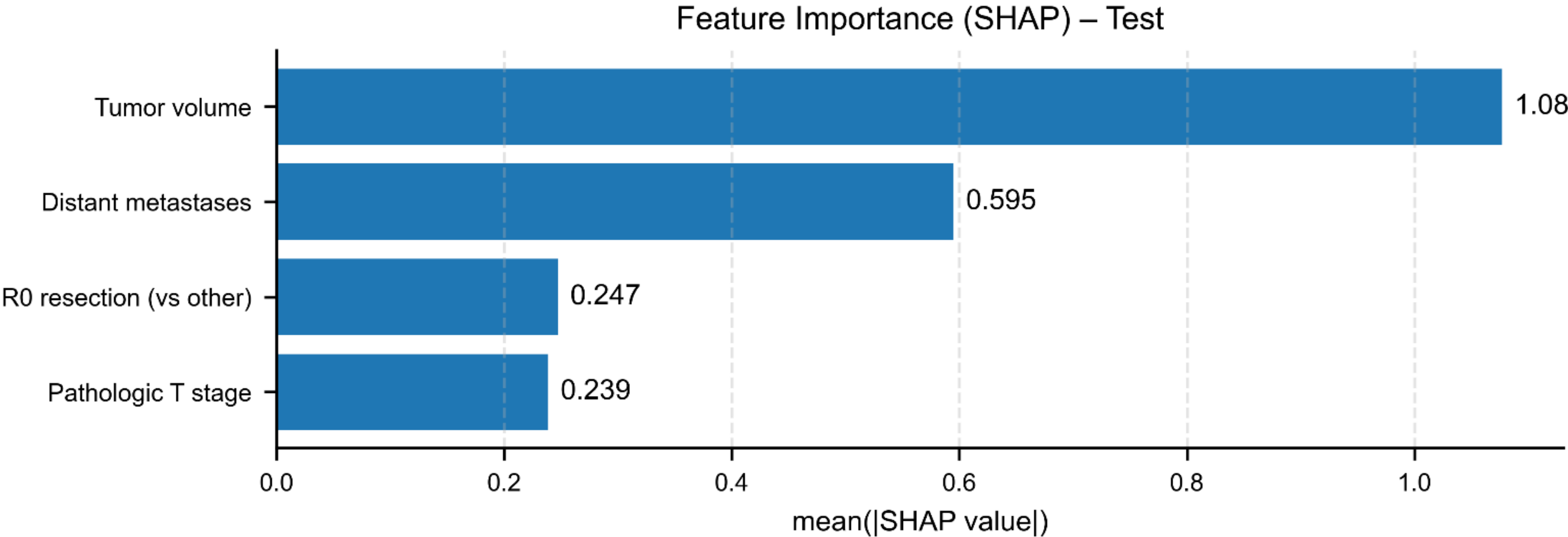


ould out
C-Index 0,925

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

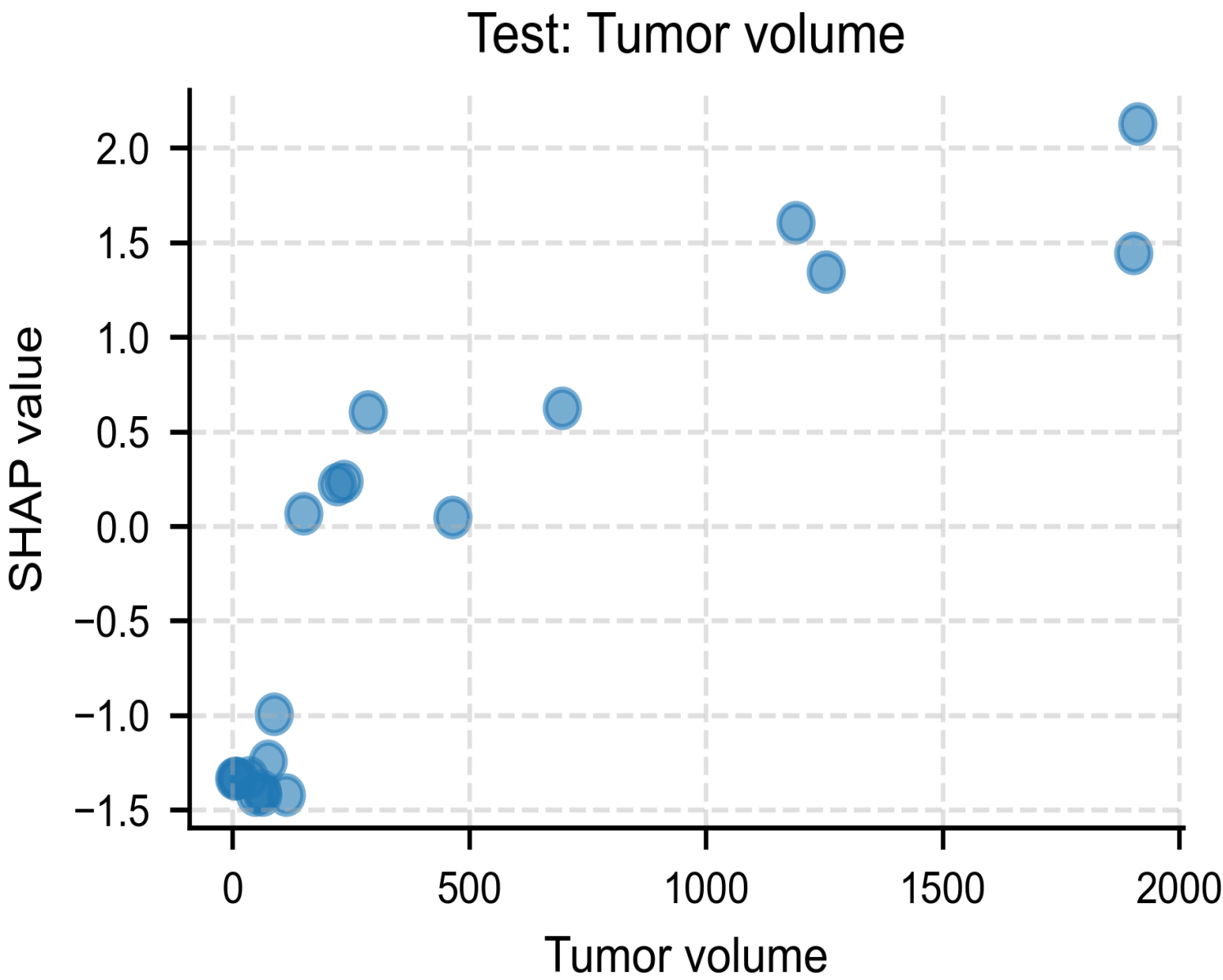
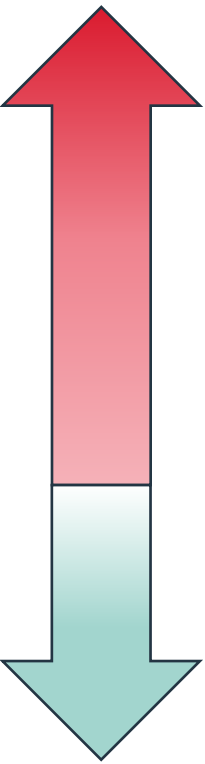
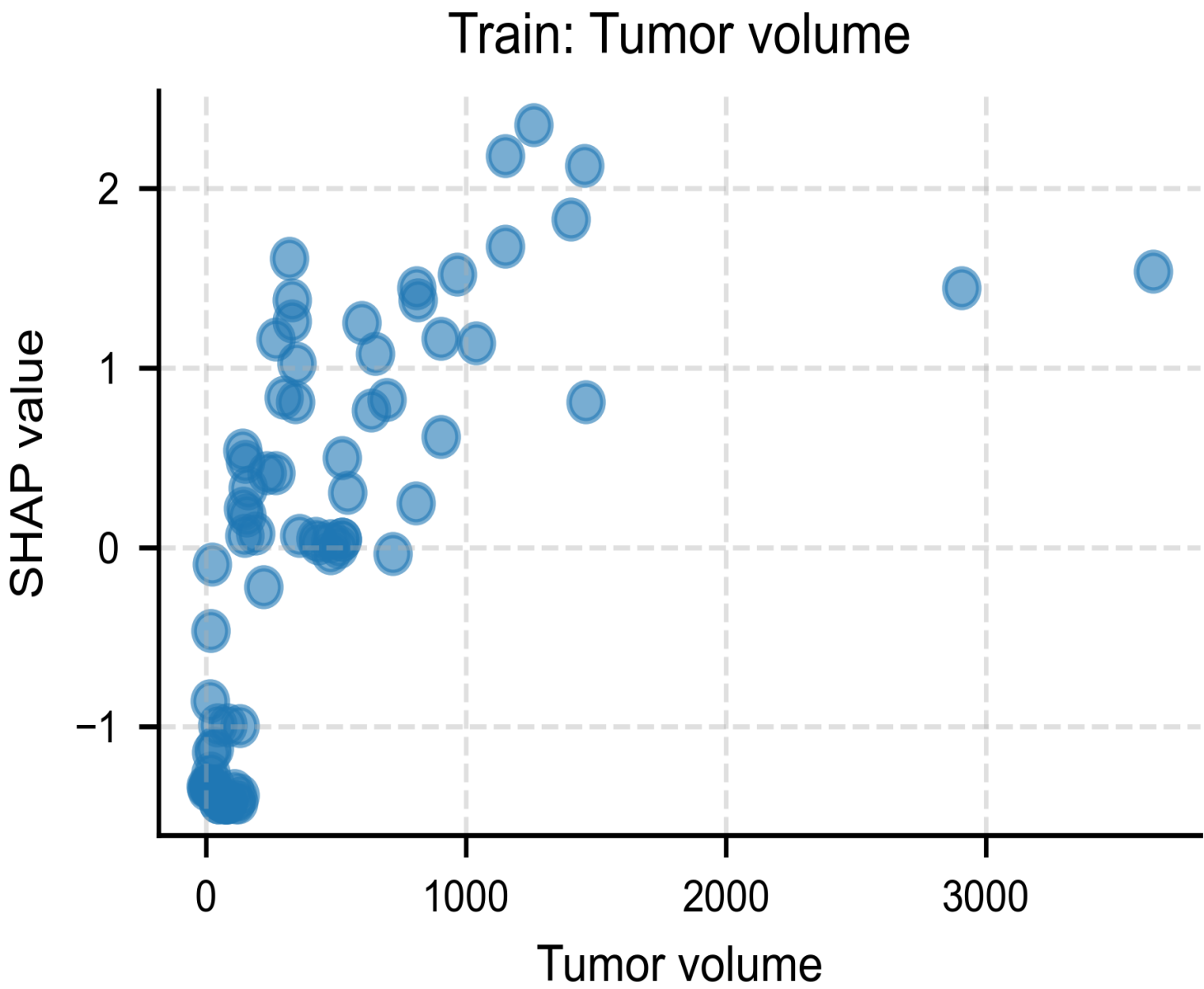


SHAP: 1 ≈ 2,7 Odds

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

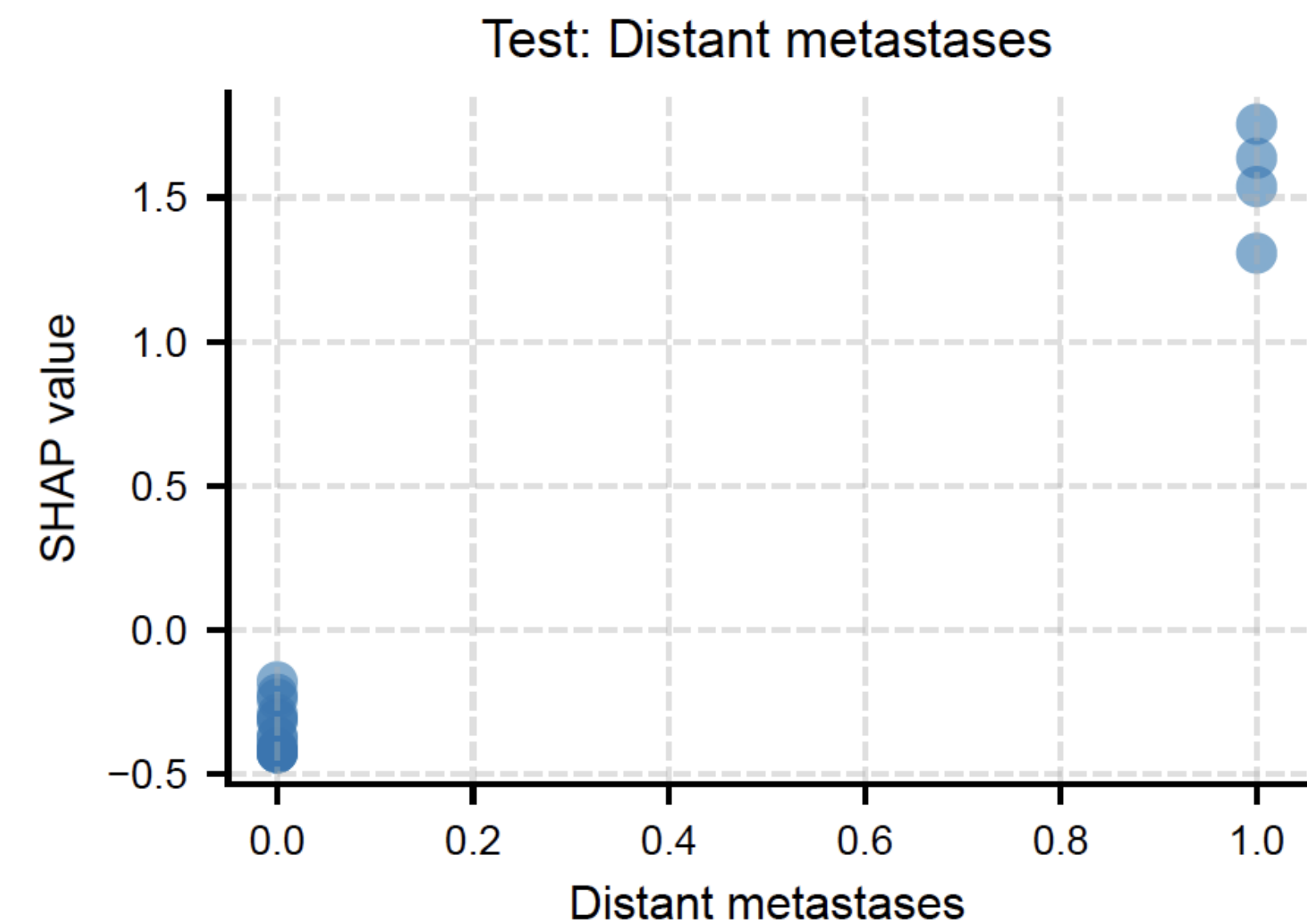
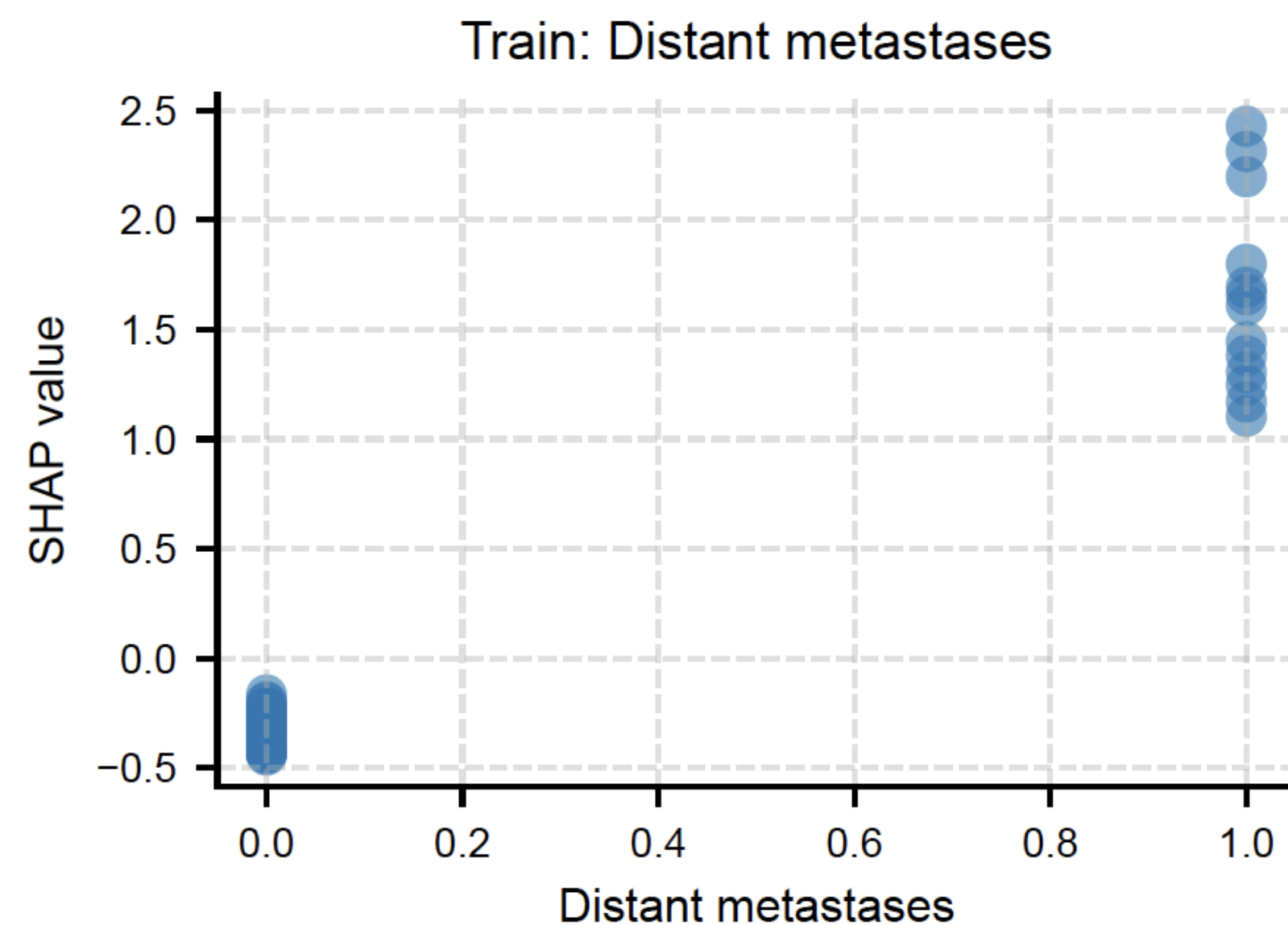


SHAP: 1 $\approx$ 2,7 Odds

Adrenocortical Carcinoma in Children: ML Prediction Survival



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

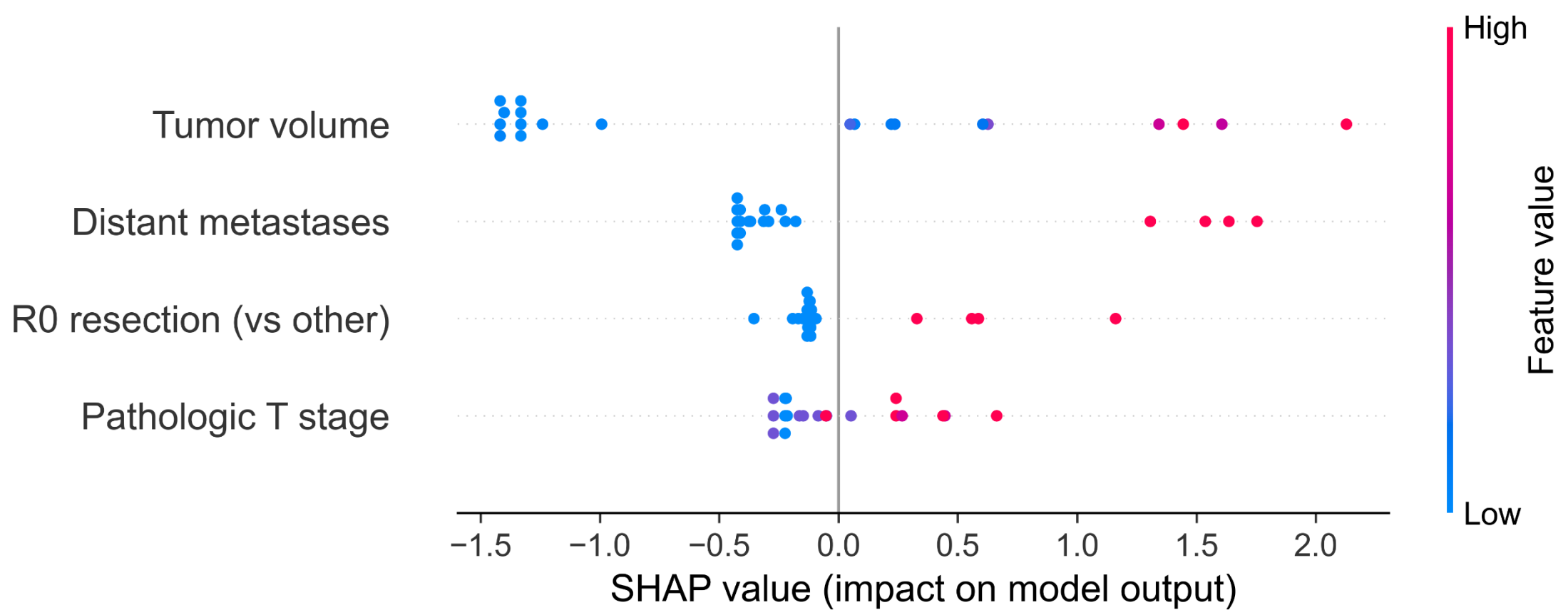
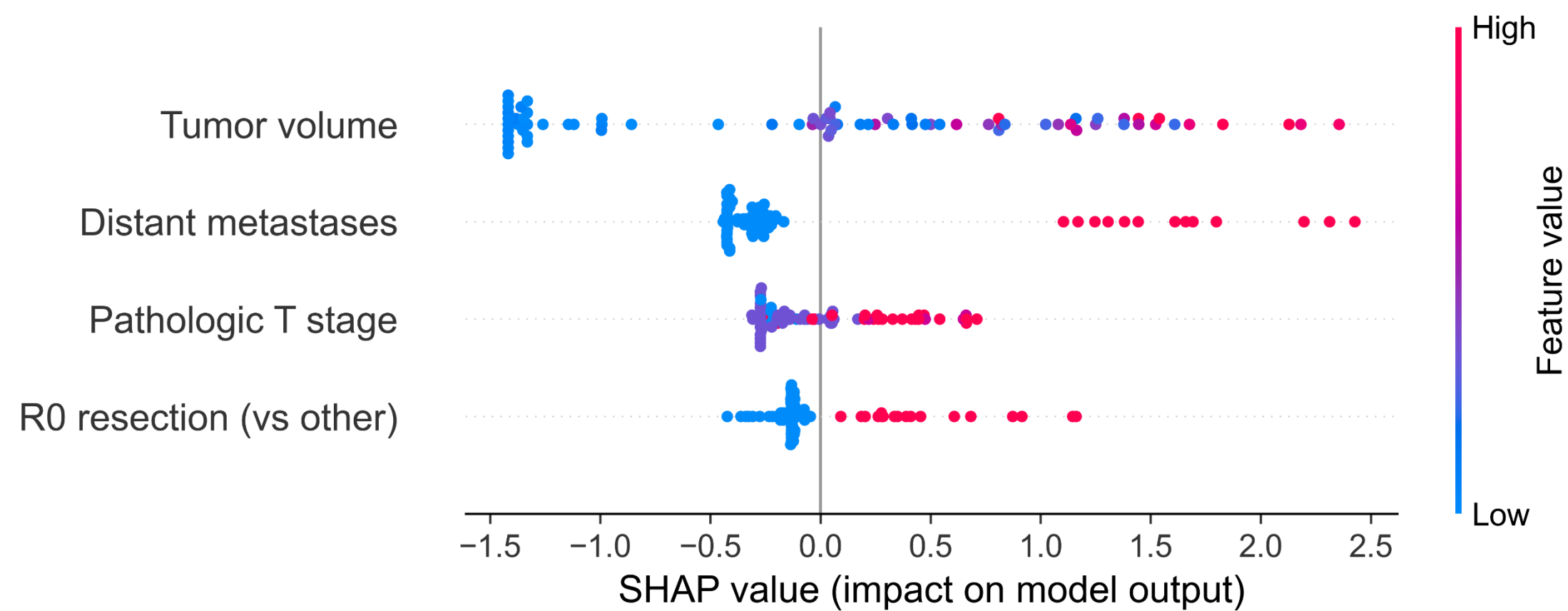
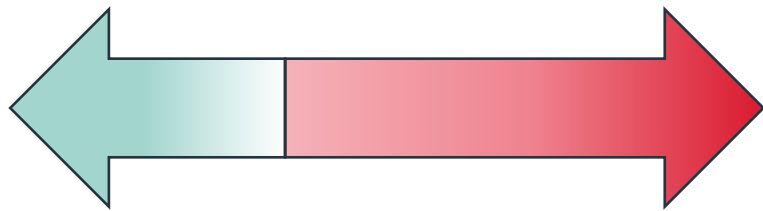
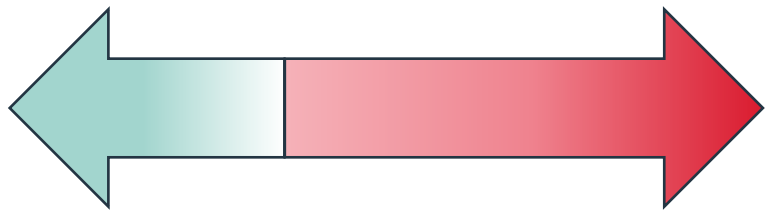


SHAP: 1 $\approx$ 2,7 Odds

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

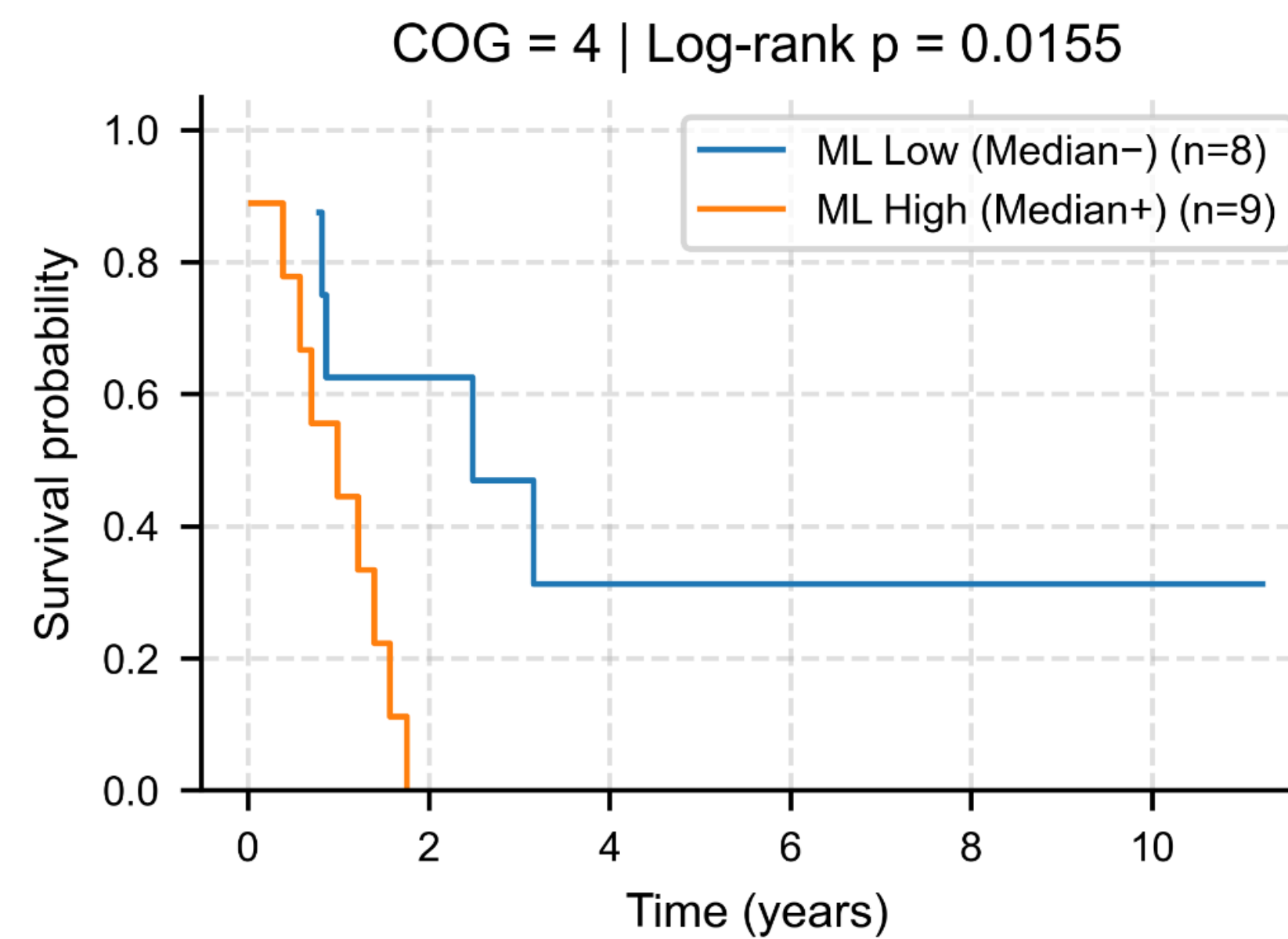
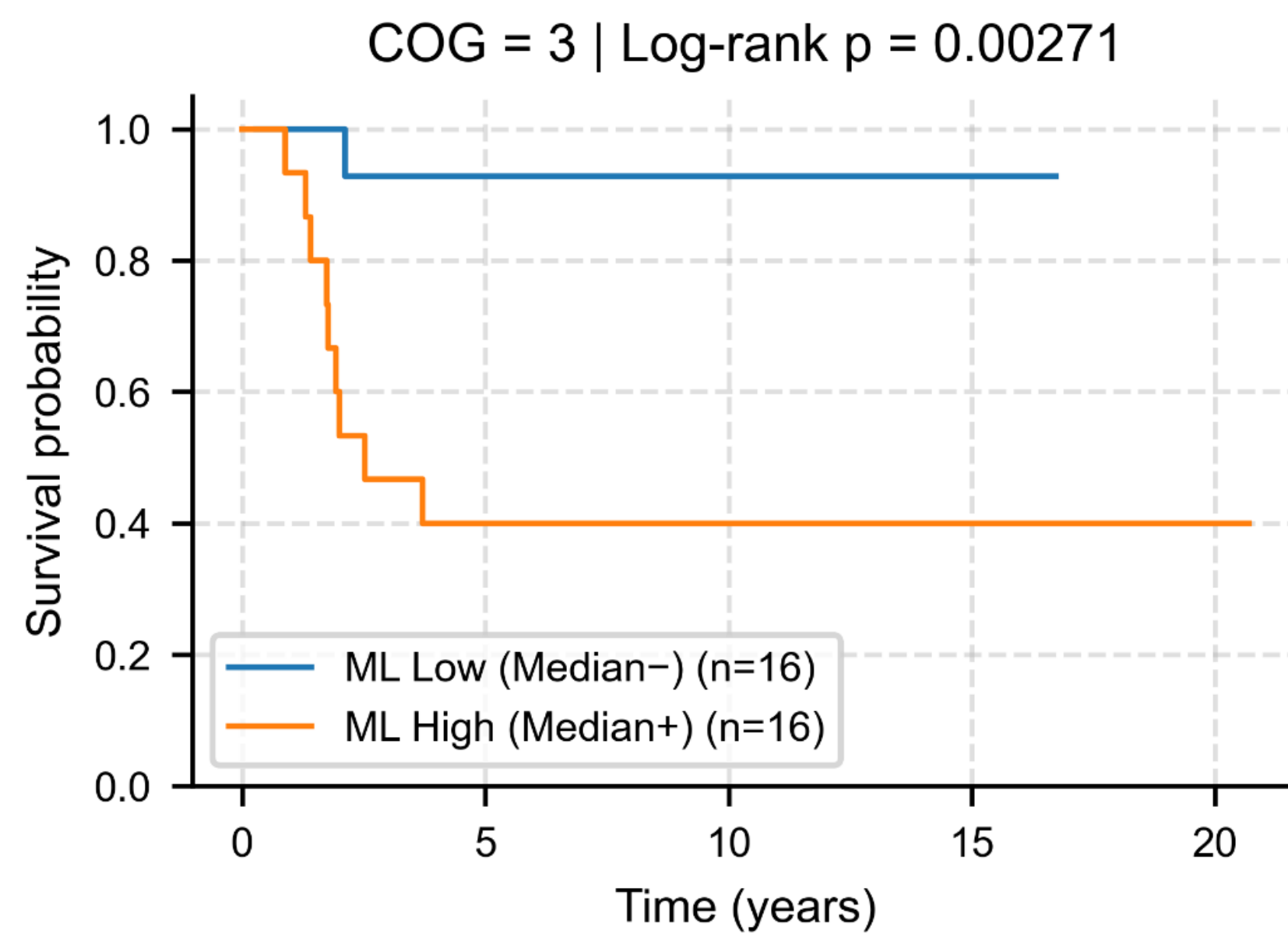


SHAP: 1 $\approx$ 2,7 Odds

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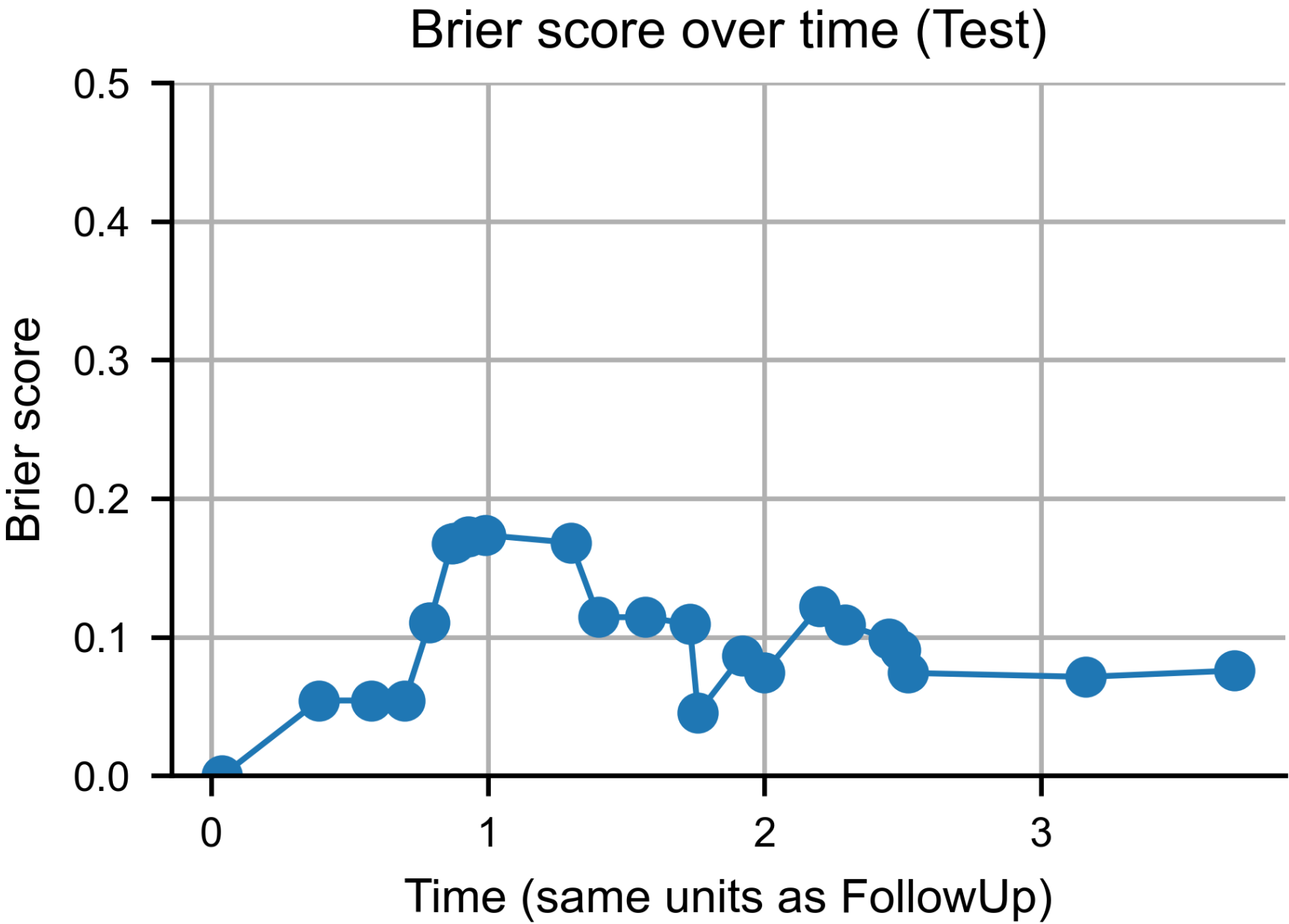
Best model: Tumorvolume, Distant metastases, R-Status, pathologic T stage
better than COG stages



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Brier Score: Squared error over time



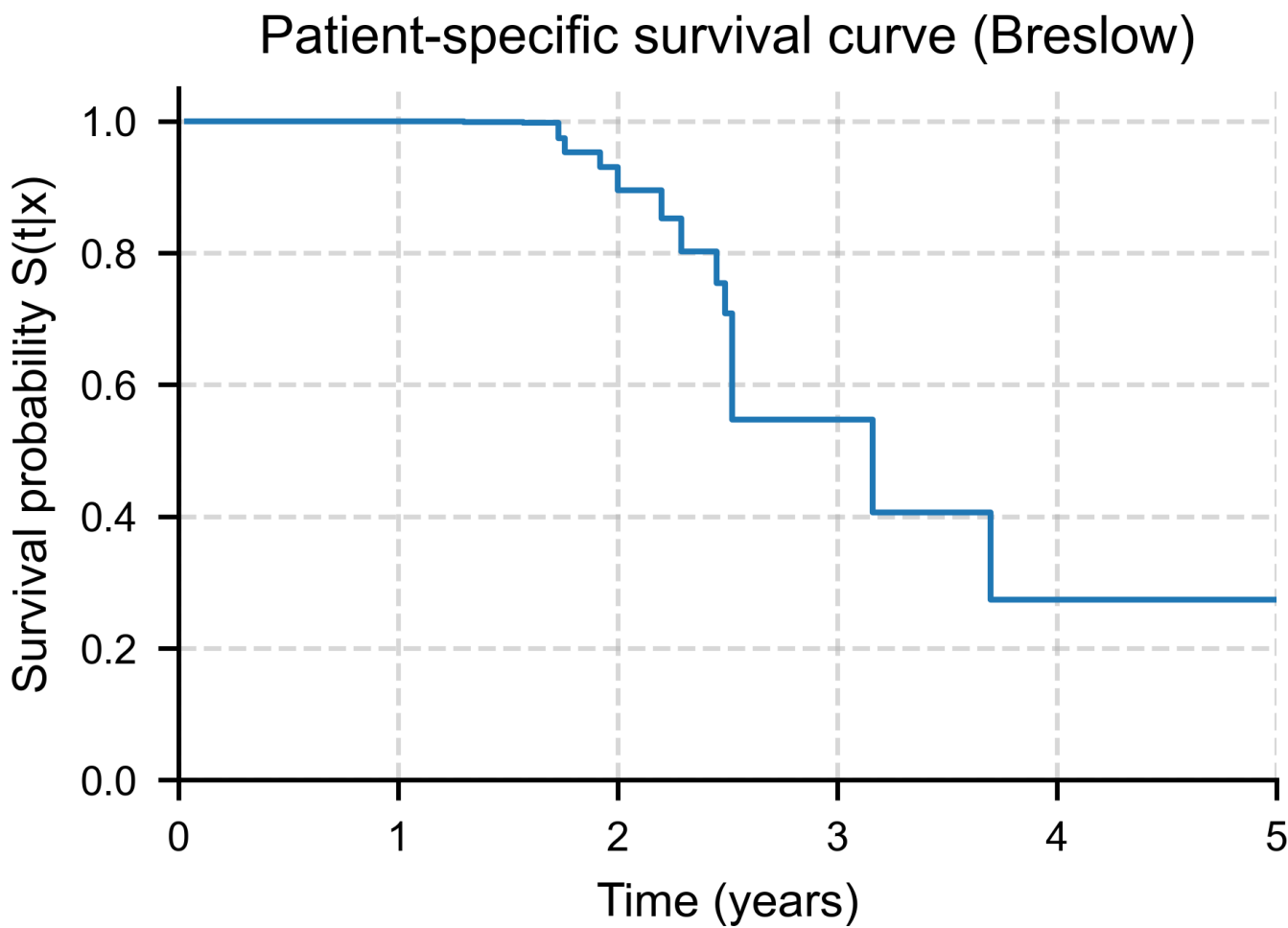
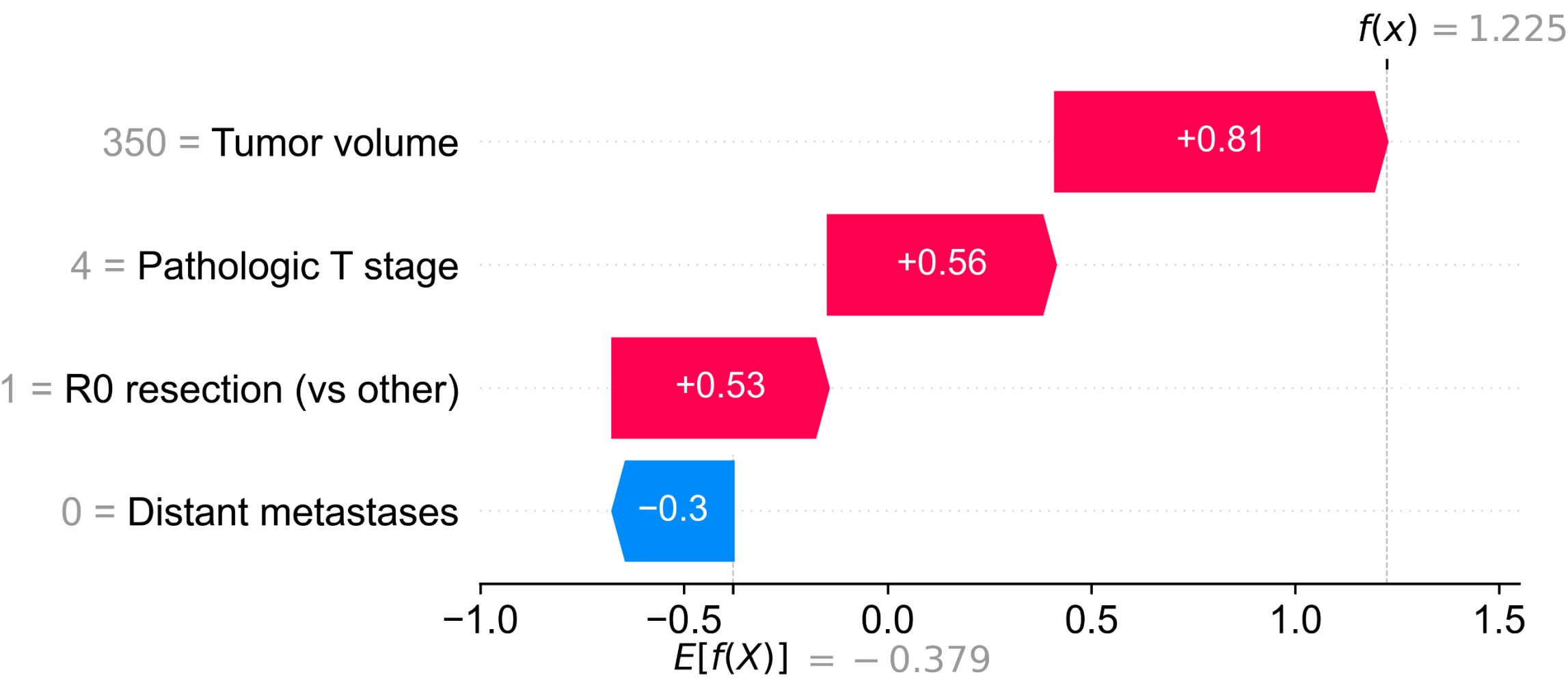
IBS =0,09 (very good!)

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Model: Tumorvolume, pM, R-Status, pT

Individual risk



TRAINING & EDUCATION



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

Tuesday, June, 18th TBC

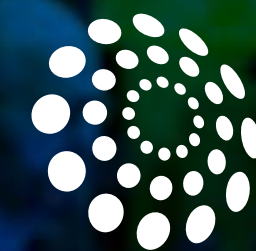
ML Brandi, G. Valk, S. Waguespack

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



European
Reference
Network



Endo-ERN