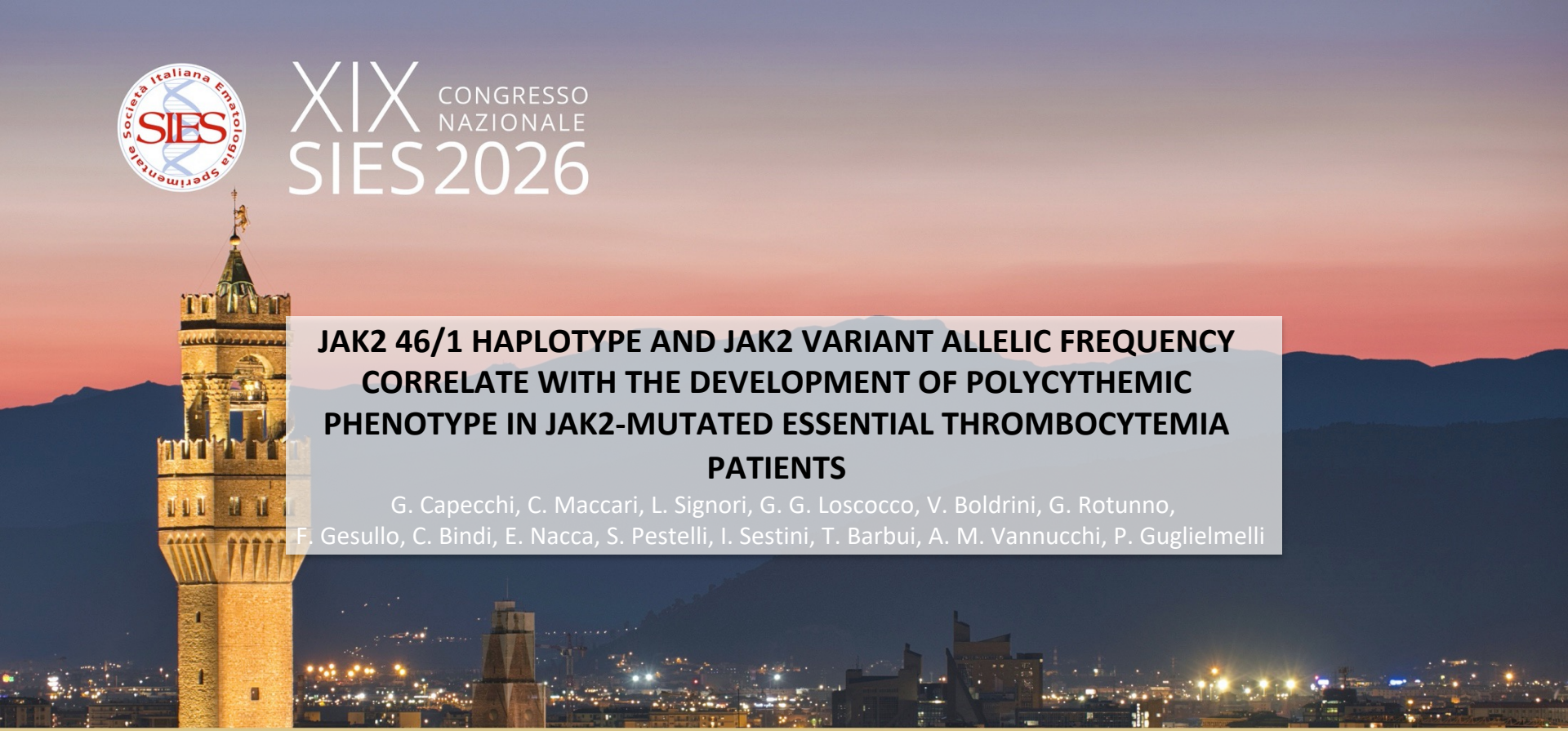


XIX CONGRESSO NAZIONALE SIES 2026

JAK2 46/1 HAPLOTYPE AND JAK2 VARIANT ALLELIC FREQUENCY CORRELATE WITH THE DEVELOPMENT OF POLYCYTHEMIC PHENOTYPE IN JAK2-MUTATED ESSENTIAL THROMBOCYTEMIA PATIENTS

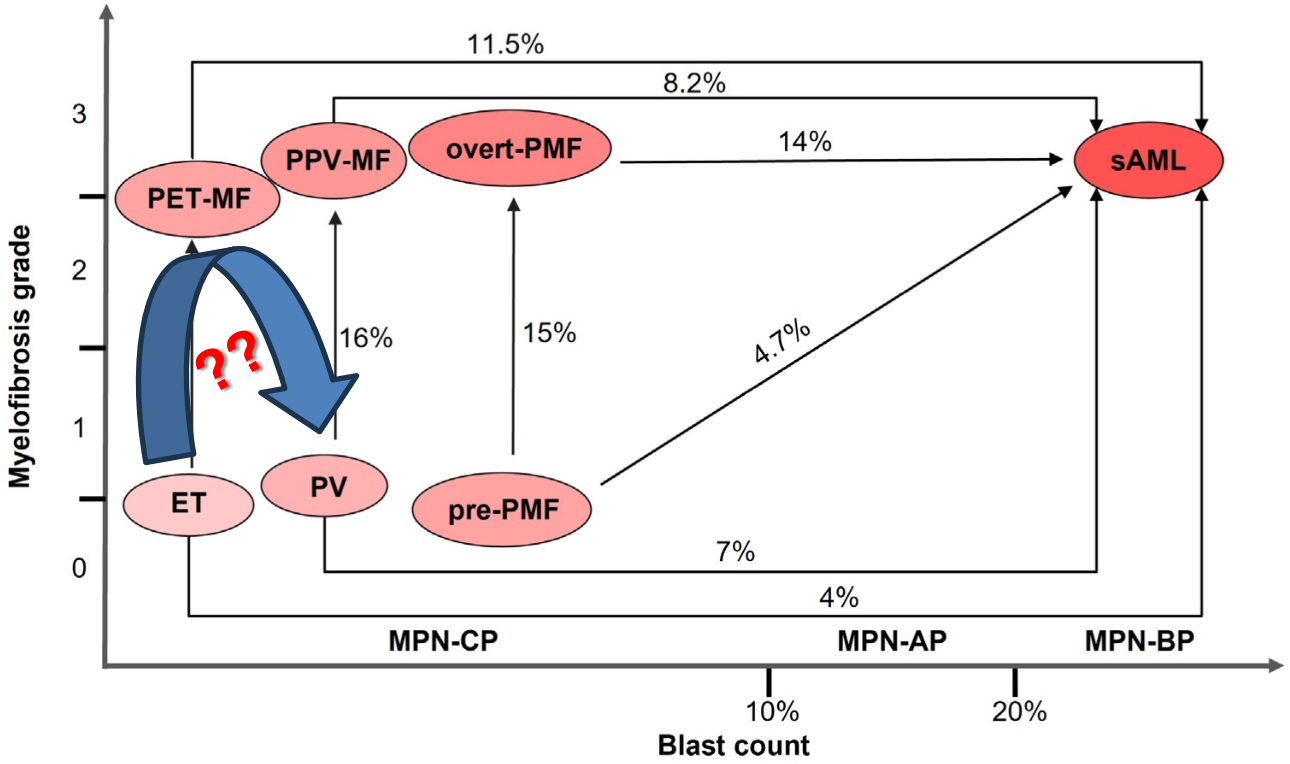
G. Capecchi, C. Maccari, L. Signori, G. G. Loscocco, V. Boldrini, G. Rotunno, F. Gesullo, C. Bindi, E. Nacca, S. Pestelli, I. Sestini, T. Barbui, A. M. Vannucchi, P. Guglielmelli

Firenze | 4-6 marzo 2026
Palazzo degli Affari

Disclosures of Giulio Capecchi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
GSK							x
AOP							x

Clinical plasticity represents an intrinsic property of all MPNs



Aims

- To estimate the incidence of polycythemic phenotype development
- To identify distinctive clinical and molecular features both at diagnosis and during follow up
- To explore potential predisposing factors for the progression of ET to PV

Methods

- **411 *JAK2*-mutated** ET patients from the CRIMM Database were analyzed and compared

Definition of polycythemic phenotype

A second BMB showed features consistent with PV diagnosis (ICC/WHO22)

Persistent elevation of Hb or Hct meeting ICC/WHO22 thresholds for PV

Required therapeutic phlebotomies during follow-up

Persistent elevation of Hb or Hct during follow-up despite cytoreduction or sideropenia

Absence of secondary causes of erythrocitosys

Results from 411 *JAK2*-mutated ET patients – clinical data

We identified **45** patients who developed a polycythemic phenotype, representing **11%** of the population

Variable	Study group (n = 45)	Control group (n = 366)	P value
Age at diagnosis years, median (range)	**47 (17 – 77)**	**63 (19 – 92)**	**< 0 .001**
Age at diagnosis >60 years, n (%)	**6 (13.3)**	**210 (57.4)**	**< 0.001**
Male gender, n (%)	15 (33.3)	118 (32.2)	1.0
WBC x10^9/L, median (range)	8.7 (4.5 – 13.9)	8.7 (4 – 23.4)	0.17
Hb g/dl, median (range)	14.2 (11.3 – 16)	14.5 (10 – 17.5)	0.17
PLT x10^9/L, median (range)	638 (449 – 971)	655 (460 – 1881)	0.21
MF progression, n (%)	2 (4.4)	10 (2.7)	0.63
AML Progression, n (%)	1 (2.2)	9 (2.5)	1.0
Deaths, n(%)	2 (4.4)	52 (14.2)	0.1

Variable	Study group (n=45)	Control group (n=366)	P value
Palpable splenomegaly, n (%)	2 (4.4)	41 (11.4)	0.20
Pruritus, n (%)	**14 (31.1)**	**53 (14.7)**	**0.01**
Constitutional symptoms, n (%)	2 (4.4)	17 (4.7)	1.0
Microvascular symptoms, n (%)	14 (31.1)	110 (30.4)	1.0
JAK2V617F VAF, % (DS)	23 (±12)	23 (± 14)	0.48

We found no significant differences in neither SMF-FS, BP-FS nor OS.

Aims

- To estimate the incidence of polycythemic phenotype development
- To identify distinctive clinical and molecular features both at diagnosis and during follow up
- To explore potential predisposing factors for the progression of ET to PV

Methods

- **411 *JAK2*-mutated** ET patients from the CRIMM Database were analyzed and compared
- 1:3 Propensity score matching was performed to identify **45 cases and 135 matched controls** (Age, FU duration, *JAK2 VAF,* gender)
- *JAK2* VAF, NGS, and SNP analysis were performed

Results from matched analysis – clinical features

No clinical features showed any association with the evolution toward a polycythemic phenotype

Variable	Study group (n = 45)	Matched group (n = 135)	P value
Age at diagnosis, median (range)	47 (17 – 77)	48 (19 – 79)	0.63
Male gender, n (%)	15 (33.3)	49 (36.3)	0.86
WBC x10^9/L, median (range)	8.6 (4.5 – 13.9)	8.2 (3.5 -16.6)	0.79
Hb g/dl, median (range)	14.2 (11.3 – 16)	14.4 (11.7 – 17.2)	0.31
PLT x10^9/L, median (range)	638 (460 – 971)	631 (346 – 1500)	0.94
MF progression, n (%)	2 (4.4)	7 (5.2)	1.0
AML Progression, n (%)	1 (2.2)	4 (3.0)	1.0
Deaths, n (%)	2 (4,4)	11 (8.1)	0.52

Variable	Study group (n = 45)	Matched group (n = 135)	P value
Palpable splenomegaly, n (%)	2 (4.4)	11 (8.1)	0.52
Pruritus, n (%)	14 (31.1)	25 (18.5)	0.09
Constitutional symptoms, n (%)	2 (4.4)	9 (6.7)	0.73
Microvascular symptoms, n (%)	14 (31.3)	51 (37.8)	0.48

We found no significant differences in neither in SMF-FS, BP-FS or OS.

Results from matched analysis – Thrombosis

Patients in the study group experienced **fewer thrombotic events**, particularly after diagnosis

Variable	Study group (n = 45)	Matched group (n = 135)	P value
≥1 Thrombotic event (TE), n (%)	11 (24,4)	50 (37)	0.15
≥1 TE at/before diagnosis, n (%)	9 (20)	27 (20)	1.0
≥1 TE during follow up, n (%)	**4 (8.9)**	**31 (23.0)**	**0.049**
Arterial TE at or before diagnosis, n (%)	8 (17.8)	19 (14.1)	0.63
Arterial TE during follow up, n (%)	3 (6.7)	23 (17.0)	0.14

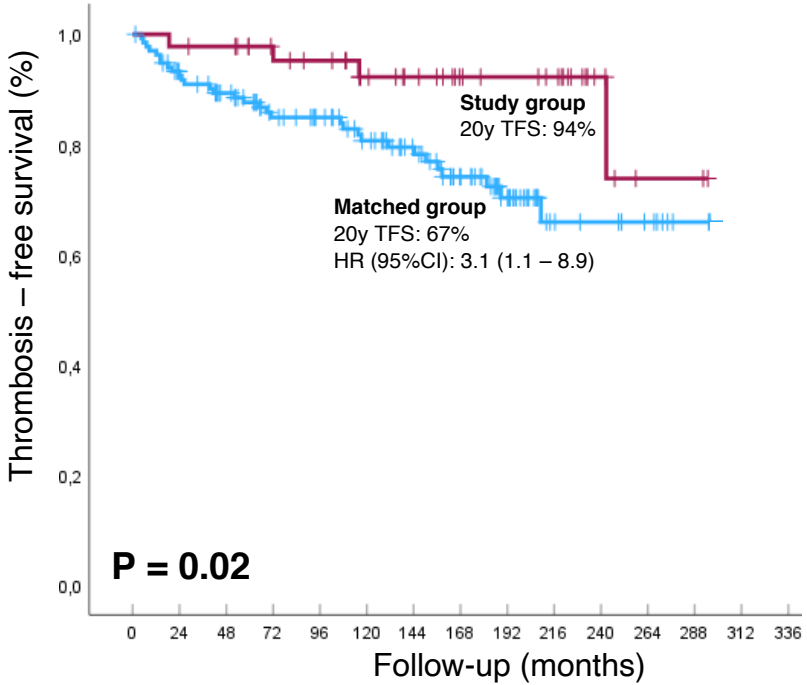
Variable	Study group (n = 45)	Matched group (n = 135)	P value
Venous TE at/before diagnosis, n (%)	1 (2.2)	8 (5.9)	0.45
Venous TE during follow up, n (%)	2 (4.4)	14 (10.4)	0.36
Bleeding events, n (%)	5 (11.1)	31 (23.0)	0.13
Major Bleeding, n (%)	3 (6.7)	13 (9.6)	0.76
Minor bleeding, n (%)	**2 (4.4)**	**23 (17.0)**	**0.044**

Arterial events: AMI (14), stroke (20), SAT (1), angina (1), TIA (5), PAD (19), other (2)
Venous events: DVT (11), SVT (4), Budd-Chiari (7), CVST (1), retinal thrombosis (9), other (1)

We found no differences in the use of **antiplatelet/anticoagulant** prophylaxis (100% vs 98.5% p = 1.0) nor **cytoreductive therapy** (53.3% vs 63.6% p = 0.34).

Results from matched analysis – Thrombosis

Patients in the study group experienced **fewer thrombotic events**, particularly after diagnosis



Results from matched analysis – *JAK2*V617F VAF

Patients in the study group showed a **significant increase in *JAK2V617F* VAF** over time

Variable	Study group	Matched group	P value
Baseline *JAK2*V617F VAF %, median (±SD); n=180	23 (± 12)	20 (±12)	0.85
***JAK2*V617F VAF % on follow up, median (±SD); n=89**	34 (±28)	24 (±17)	**0.035**
***JAK2*V617F VAF % annual increase, median (±SD); n=89**	+ 6.1 (±33)	+ 1.5 (±14)	**0.01**
***JAK2*V617F VAF >50% at baseline, n (%); n=180**	0 (0.0)	3 (2.2)	0.57
***JAK2*V617F VAF >50% at follow up, n (%); n=89**	**12 (30.8)**	**3 (6.0)**	**0.003**

Median time to the second sample was comparable between the two groups 10.9 y vs 8.7 y p = 0.20

Results from matched analysis – *JAK2* 46/1

Patients showed no significant differences in *JAK2* 46/1 allele distribution

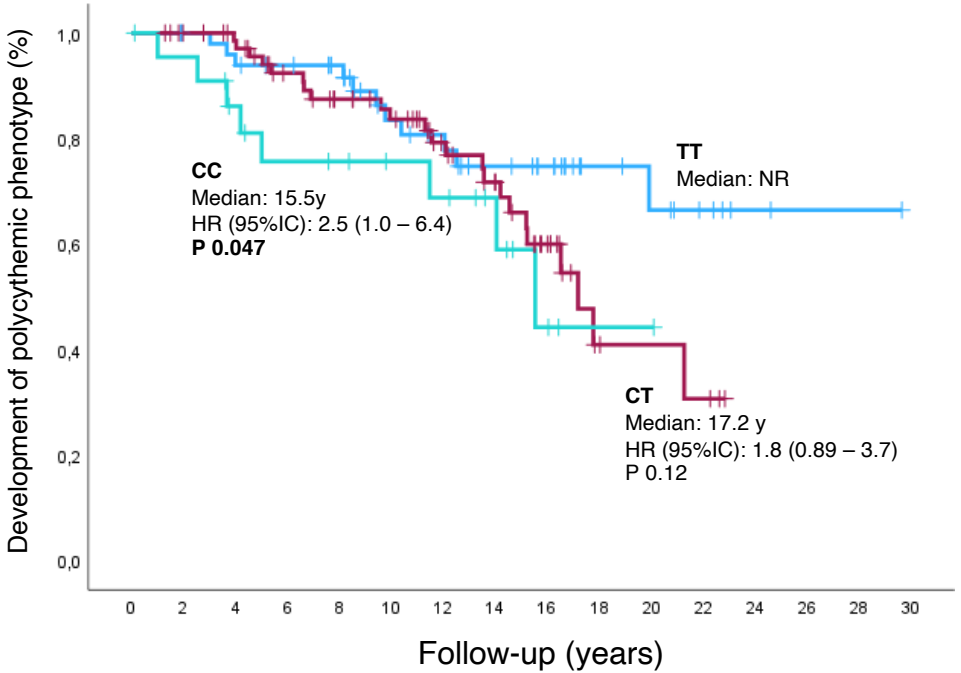
46/1 Status (n = 149)	Study group	Matched group	
TT, n (%)	11 (26.2)	40 (37.4)	P value = 0.4
CT, n (%)	23 (54.8)	52 (48.6)	
CC, n (%)	8 (19.0)	15 (14)	

46/1 Status (n = 149)	Study group	Matched group	P value
Non-TT, n (%)	31 (73.8)	67 (62.6)	0.25
CC, n (%)	8 (19.0)	15 (14)	0.46

- **C** = 46/1 allele
- **T** = non-46/1 allele

JAK2 46/1 correlates – development of polycythemic phenotype

Patients harbouring *JAK2* 46/1 alleles showed a faster development of the polycythemic phenotype



C = 46/1 allele
T = non-46/1 allele

Results from matched analysis – iron metabolism

Patients showed no significant differences evaluated iron parameters

	Study group	Matched group	P value
Ferritin ng/ml, Median (range) n = 140	61.5 (7- 276)	55.5 (9 – 564)	0.29

The HFE SNP rs79220007 has been previously linked to PV in genome-wide association studies.

	Study group	Matched group	P value
HFE variants, n (%) M = 140	1 (2.6)	4 (4.0)	1.0

All 5 patients presented HFE variants in heterozygosity

Results from matched analysis – NGS

Patients in the study presented **fewer additional mutation** at diagnosis

Variable	Study Group (n = 39)	Matched Group (n=26)	P Value
Additional mutation in myeloid gene, n (%);	9 (23.1)	9 (34.6)	0.40

Gene	Study Group (n=39)	Matched Group (n=25)	P value
***ASXL1*, n (%)**	1 (2.6)	2 (7.7)	0.56
***SH2B3*, n (%)**	2 (5.1)	1 (3.8)	1.0
***DNMT3A*, n (%)**	1 (2.6)	2 (7.7)	0.56
***TET2*, n (%)**	2 (5.1)	4 (15.4)	0.21
***BCOR*, n (%)**	1 (2.6)	0 (0.0)	0.5
***SF3B1*, n (%)**	1 (2.6)	1 (3.8)	1.0
***RUNX1*, n (%)**	0 (0.0)	1 (3.8)	0.4

No variants were identified at diagnosis in the following genes: *EZH2, IDH1/2, SRSF2, N/K/H RAS, CBL, TP53, SETPB1, U2AF1, ZRSR2, CSF3R, PTPN11*

Results from matched analysis – paired NGS

Patients in the study presented **fewer additional mutation** at diagnosis, but **clonal progression** was frequent at the development of the polycythemic phenotype

Matched NGS analysis was available in 35 study group patients. **8 (23%) acquired ≥1 mutations** in myeloid genes.

TET2 and ***TP53*** mutations were acquired in 3 patients, ***ASXL1*** mutations in 2 patients and ***SF3B1*** in 1 patient each.
Two of these patients already presented an additional mutation ad ET diagnosis.
One patients acquired more than one gene mutation (*TET2* and *SF3B1*).

Variable	ET diagnosis	Polycythemic phenotype	P Value
Additional mutation in myeloid gene, n (%); n = 35	8 (22.9)	14 (40.0)	0.2

Gene	ET diagnosis	Polycythemic phenotype	P value
***ASXL1*, n (%)**	1 (2.9)	3 (8.6)	0.61
***SH2B3*, n (%)**	2 (5.7)	2 (5.7)	1.0
***TET2*, n (%)**	2 (5.9)	5 (14.7)	0.21
***SF3B1*, n (%)**	1 (2.9)	2 (5.7)	1.0
***TP53*, n (%)**	0 (0.0)	3 (8.6)	0.24

Discussion

- This study investigated the characteristics of a large cohort of *JAK2*V617F-mutated ET patients who developed a polycythemic phenotype.
- The **incidence** of development of a polycythemic phenotype in our study **was 11%,** higher than what is reported in previous works.
- Patients who would develop a polycythemic phenotype **receive MPN diagnosis earlier** than controls, but clinical features are similar, except for **pruritus**.
- In matched analysis, study population experienced **fewer thrombotic events during follow up and longer Thrombosis-FS,** but no differences in clinical features and outcomes were noted

Discussion

- The development of a polycythemic phenotype was followed by an **increase of *JAK2*V617F VAF** with almost than one third of patients raising over 50% of VAF
- Patients harbouring ***JAK2* 46/1 alleles** showed a faster development of the polycythemic phenotype
- **NGS** analysis showed a trend to a lower incidence of additional mutations in the study group, but clonal progression was frequent
- **Iron metabolism** showed no significant differences in the variables under investigation

Special thanks to

Azienda Ospedaliero Universitaria Careggi

Centro Ricerca e Innovazione Malattie Mieloproliferative, AOU Careggi:

- Prof.ssa Paola Guglielmelli
- Prof. Alessandro Maria Vannucchi
- Prof. Francesco Mannelli
- Giuseppe Loscocco
- Valentina Boldrini
- Francesca Crupi
- Lorenzo Fagiolo
- Jessica Caroprese
- Chiara Maccari
- Leonardo Signori
- Elena Nacca
- Francesca Gesullo
- Claudia Bindi