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70TH ESCVS CONGRESS
& 7TH IMAD MEETING
20 I 23 JUNE 2022

Genetic Bechet disease in THE HUGHES-STOVIN SYNDROME: new findings and successful treatment.

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Brit. J. Dis. Chest (1959) **53**, 19

SEGMENTAL PULMONARY ARTERY ANEURYSMS WITH PERIPHERAL VENOUS THROMBOSIS

By J. P. Hughes and P. G. I. Stovin

From the London Hospital, E.1

Pulmonary arterial aneurysms are not common and have been classified by Brenner (1935) into four groups: mycotic, congenital, syphilitic and traumatic.

The infecting source of the mycotic aneurysms is usually obvious (Stengel and Wolferth, 1923; Brenner, 1935). It is, however, probable that infected pulmonary emboli or secondarily infected infarcts produce pulmonary abscesses (Davison, 1958) more often than aneurysms. In a few cases, such as those reported by Fowler (1933), Carroll (1950), and Boucher, Protar and Bertein (1951), pulmonary embolus from infected thrombus resulted neither in aneurysm nor abscess formation.

Hughes-Stovin Syndrome

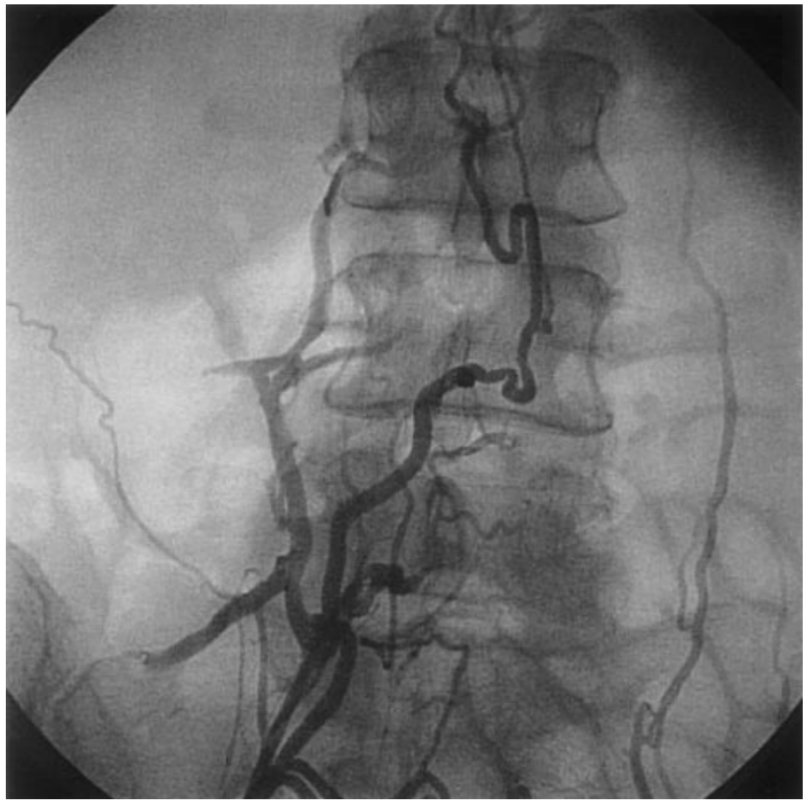

Figure 1. Injection of dye through a right femoral access shows occlusion of both the iliac veins and the inferior caval vein. Blood is drained by a collateral circulation of pelvic and lumbar veins (see Movie I).

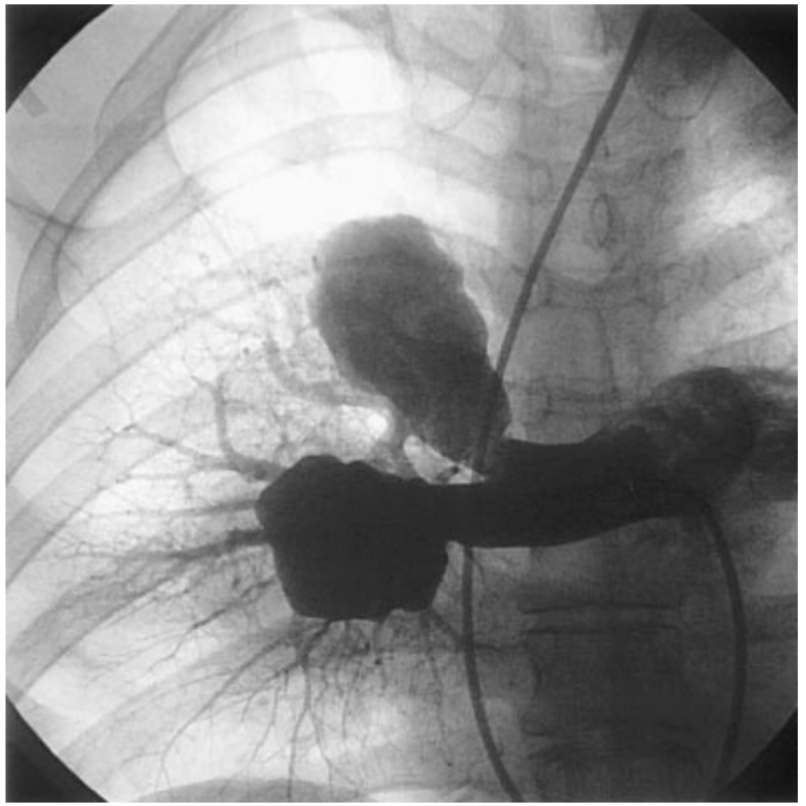

Figure 2. Right-sided pulmonary angiography. Two large aneurysms originating from the upper lobe and intermediate pulmonary arteries. Marked hypoperfusion of the right upper and lower lobe is evident (see Movie II).

M Kindermann et all. Images in Cardiovascular *Circulation.* 2003;108:e156

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Rare case of multiple pulmonary artery aneurysms with caval thrombosis — Hughes-Stovin syndrome

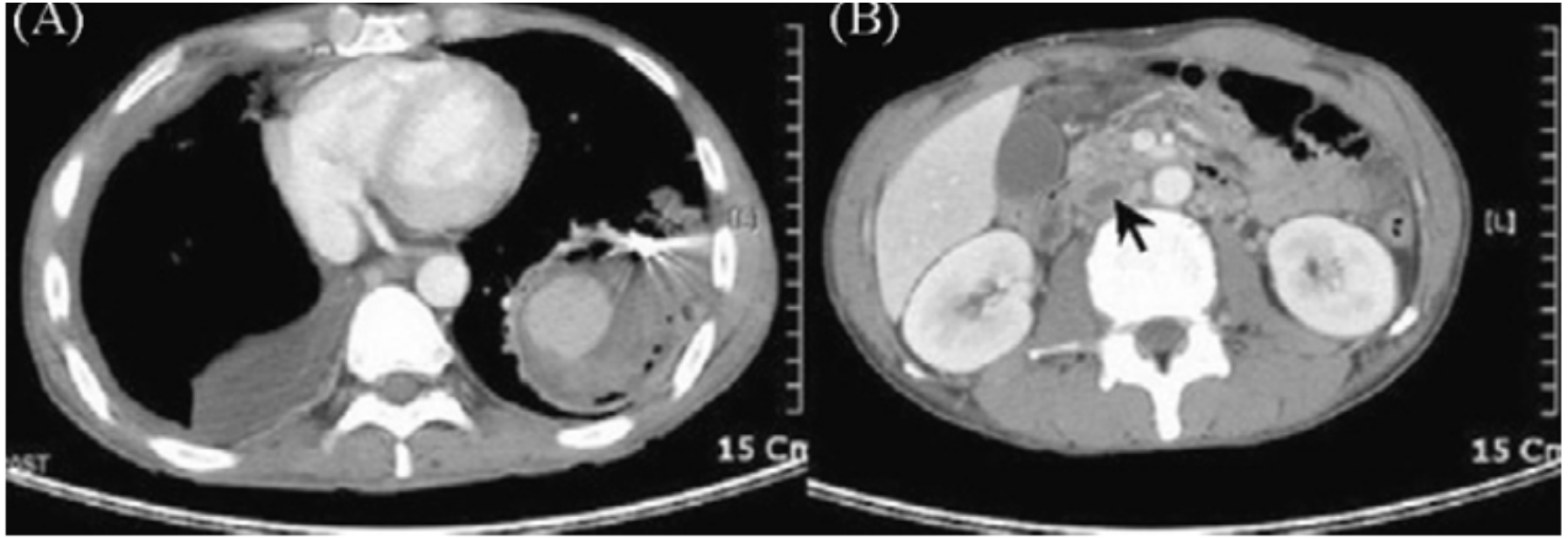

Fig. 2. (A and B) Follow up chest CT shows other pulmonary artery aneurysms with a mural thrombus in the left lower lobe and inferior vena. (Arrow).

Jung Tae Kim, Tae Yun Oh *, Woon Ha Chang Eur J of Cardio-thorac Surgery 31 (2007) 561—562

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THE HUGHES-STOVIN SYNDROME

The ethiology of Hughes-Stovin syndrome is still unknown:

- Infections
- Angiodysplasia
- Genetic
- Environmental
- Immunological
- Endothelial

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Ethiology
Infectious agents involved theory

Agents	Pertinent rationale or refutation for involvement in Behcet's disease
Hepatitis A, B, C, E viruses	Serological evidence of previous HAV, HCV and HEV infections showed no significant difference in patients with Behcet's disease compared to controls. Previous HBV infection, however, seen in a remarkably lower number of patients with Behcet's disease as compared with healthy controls.
Herpes simplex virus (HSV)	Anti-HSV-1 antibodies were found more commonly in patients with Behcet's disease than controls. DNA of HSV was detected in genital and intestinal ulcers but not in oral aphthous ulcers.
Parvovirus B19	Parvovirus B19 IgG antibodies were reported more in patients with Behcet's disease as compared to controls
Helicobacter pylori	Almost the same proportion of patients with Behcet's disease and controls were found to have *H. pylori* infection following eradication therapy.
Chlamydia pneumoniae	IgG seropositivity for *C. pneumoniae* between cases and controls was not significantly different. However, the proportion of seropositive cases with higher IgG titres was greater.
Streptococcus sanguis, *Streptococcus mitis* and *Streptococcus salivarius*	Decline of skin and arthritic involvement in Behcet's disease after antibiotic administration. Hypersensitivity to cutaneous streptococcal antigens was reported. Aggravation of symptoms after dental procedures. Treatment of chronic oral infections positively impacts long term prognosis of disease.
Saccharomyces cerevisiae	Unclear role, distribution and pathogenetic relationship of ASCA antibodies in patients with Behcet's disease
Heat shock proteins	Heat shock proteins of mycobacteria and streptococci were suggested to have a role in Behcet's disease. Model of molecular mimicry thought to be responsible for manifestations of Behcet's disease.

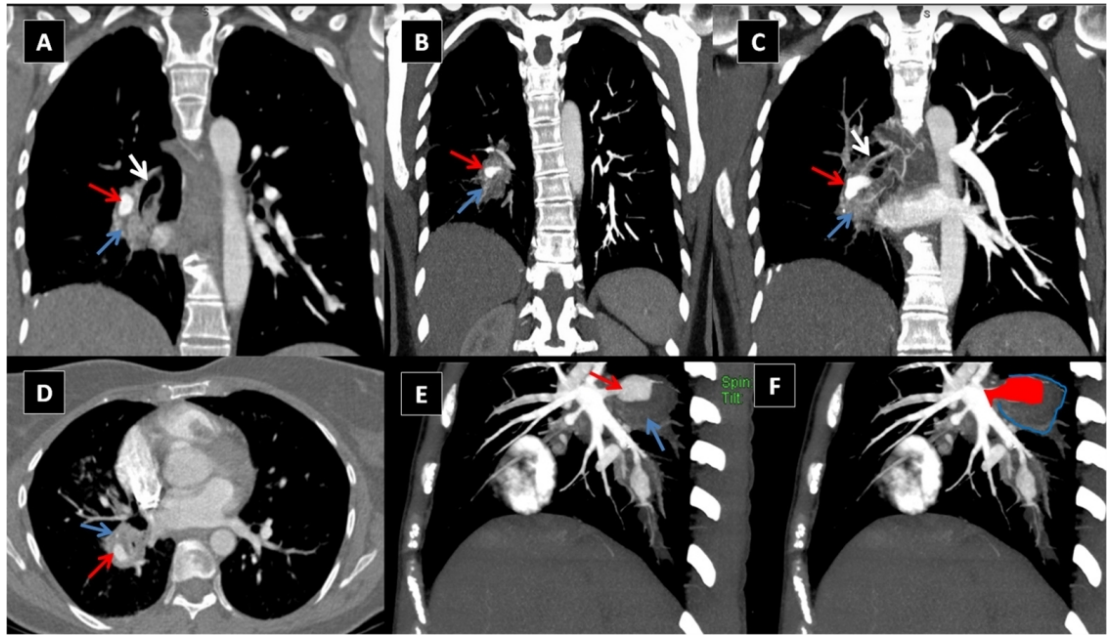
Umair and Taimur Orphanet J. Rare Dis. 6 (2011) 15

Ethiology
Angiodysplasia theory

structural changes in brochial artery impaired the provision of adequate nutrition to the pulmonary artery trought the vasa vasorum

these events led to inflammation, damage to the elastic tissue and aneurysm creation

The occlusion of the pulmonary arteries causes increased flow and pressure in the bronchial artery wich predispose to the formation of bronchial artery aneurysm



Umair and Taimur Orphanet J. Rare Dis. 6 (2011) 15

Ethiology

Genetic

Genetic susceptibility loci associated with Behçet's disease at GWAS level of significance ($p < 5 \times 10^{-8}$).

Reported gene	Chr	SNPs	Candidate genes	References
IL12RB2, IL23R	1	rs10889664, rs6660226, rs1495965, **rs924080**		(13, 14, 22, 24)
IL10	1	**rs1518111**, rs1518110, rs3024490, rs1800871		(13, 14, 23, 24)
IL1A, IL1B	2	**rs3783550**	*IL37*	(23)
TFCP2L1	2	**rs17006292**		(16)
STAT4	2	**rs7574070**, rs897200		(16, 17)
CCR1, CCR3	3	**rs7616215**, rs2087726	*CCR2, RTP3, FYCO1*	(17, 24)
IL12A-AS1, IL12A	3	rs76830965, **rs17753641**, rs17810546, rs1874886	*SCHIP1, IQCJ-SCHIP1*	(21–24)
ERAP1	5	**rs17482078**	*CAST*	(17)
HLA-A	6	rs9260997, rs112166594, **rs114854070**	*HLA-F, RNF39, TRIM31, PPP1R11*	(14, 18, 19)
HLA-B, MICA	6	rs4959053, rs4947296, rs79556279, rs9266490, rs1050502, rs2848713, rs7770216, rs2442736, **rs116799036**	*POU5F1*	(13–23)
HLA-C	6	**rs12525170**		(18)
IFNGR1	6	**rs4896243**		(24)
RIPK2	8	**rs2230801**		(23)
Intergenic LNCAROD/DKK1	10	**rs1660760**		(24)
ADO, EGR2	10	**rs224127**, rs12220700		(23, 24)
Intergenic JRKL/CNTN5	11	**rs2848479**		(22)
KLRC4	12	**rs2617170**	*KLRC3, KLRC2, KLRC1, KLRK1*	(17)
LACC1	13	rs2121034, **rs2121033**	*CCDC122*	(23, 24)
IRF8	16	**rs7203487**		(23)
IRF8	16	**rs11117433**		(23)
FUT2	19	**rs681343**	*RASIP1, IZUMO1, NTN5*	(20)
Intergenic CEBPB/PTPN1	20	**rs913678**		(23)

Lead SNPs (or the most significant SNP in each genetic region in the largest single cohort for each associated locus) are highlighted in bold. Candidate genes suggested by functional annotation are also included.

Ortiz-Fernández[1] and Sawalha ·Front Med 2021; 8: 625710.

Ethiology

Genetic

Human Leukocyte Antigen (HLA) B51

prevalance

Pat n° 4800

Contr n° 16289

HLA-B51/B5 and the risk of Behçet's disease: a systematic review and meta-analysis of case-control genetic association studies

Pooled estimates for overall and subgroup meta-analyses for *HLA–B51/B5* carriage and its association with BD risk[*]

Subgroups	Populations, no.	Pooled prevalence for *HLA–B51/B5*[†] BD cases (95% CI)	Controls (95% CI)	OR (95% CI)	I^2 (%)	P_{het}	P_{cov}
Overall	80	57.2 (53.4–60.9)	18.1 (16.1–20.3)	5.78 (5.00–6.67)	60.6	0.0001	
By geographic area							0.31
Eastern Asia	25	55.0 (49.8–60.1)	19.6 (16.0–23.7)	5.18 (4.15–6.47)	52.2	0.001	
Middle East/North Africa	27	63.5 (58.8–68.0)	21.7 (18.2–25.7)	6.25 (4.87–8.03)	70.4	0.0001	
Southern Europe	15	60.6 (51.9–68.7)	16.8 (13.3–21.0)	7.20 (4.89–10.62)	57.2	0.003	
Northern/Eastern Europe	11	39.0 (28.2–51.1)	11.2 (8.1–15.3)	5.31 (3.35–8.40)	55.6	0.013	
North America[‡]	2	34.2 (6.0–80.8)	18.0 (7.6–37.1)	2.35 (0.56–9.82)	57.0	0.13	
By genotype							0.81
HLA–B51	50			5.90 (4.87–7.16)	66.8	0.0001	
HLA–B5	30			5.64 (4.57–6.95)	45.1	0.005	
By genotyping technique							0.07
Serologic	49			6.31 (5.23–7.60)	59.3	0.0001	

[*]BD = Behçet's disease; 95% CI = 95% confidence interval; OR = odds ratio; P_{het} = P values for heterogeneity statistics; P_{cov} = P values for significance of corresponding covariates in the pooled genetic effect (calculated by random-effects meta-regression).

[†]Pooled prevalence values were calculated using random-effects normal-logistic models.

[‡]Two studies combined in the North American group had distinctly different ethnicities.

de Menton all Arthritis Rheum 2009 Oct 15;61(10):1287-96.

Genetic perspective

- It is perhaps not too distant in the future that data obtained from large-scale genetic studies can be routinely applied to health care of individual patients. Nevertheless, there is still much to be learned about the genetics of Behcet's disease and, importantly, how the associated genetic variants lead to pathogenic consequences predisposing to the disease

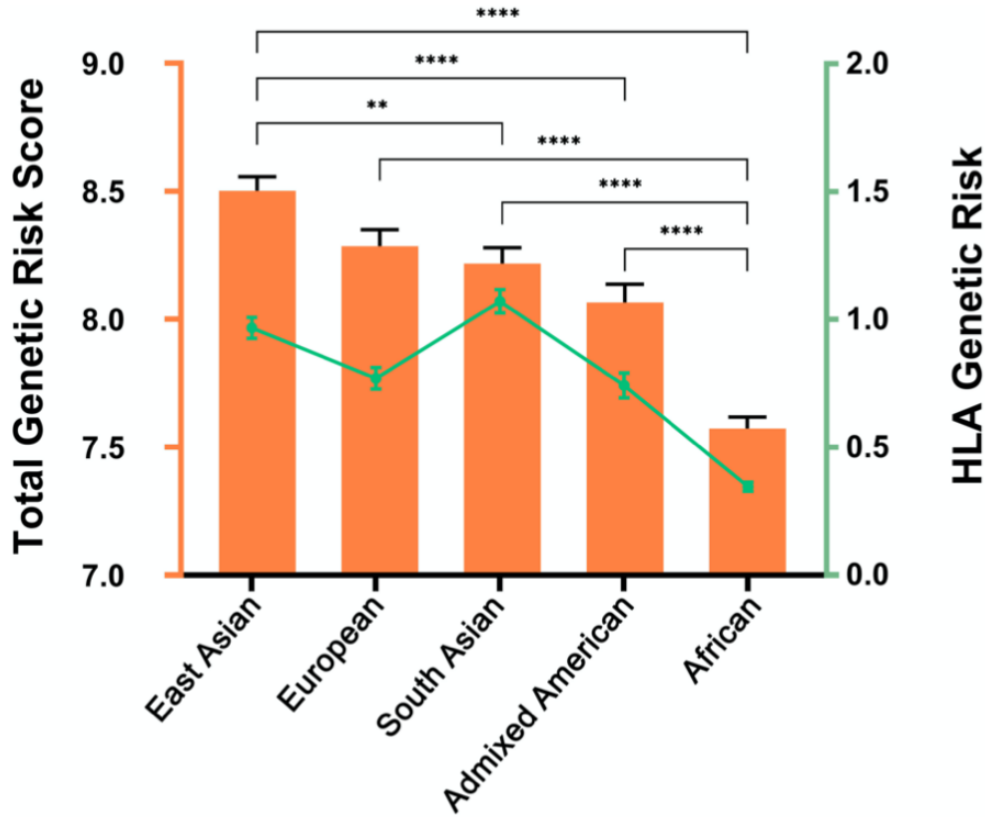


FIGURE 3 | Genetic Risk Score (GRS) for Behçet's disease across the five major populations included in the 1000 Genomes Project. Data were used from the 1000 Genomes Project, phase 3 release. African, $n = 661$; Admixed American, $n = 347$; East Asian, $n = 504$; European, $n = 503$; South Asian, $n = 489$. The orange color illustrates the total GRS including all the genetic susceptibility loci. Columns represent the mean and standard error of mean (error bars) for each population. One-way ANOVA p-value was <0.0001 for both total GRS and for HLA genetic risk. Pair-wise differences were evaluated using Tukey's multiple comparisons tests and p-values depicted represent analysis using total GRS. **, $P < 0.01$; ****, $P < 0.0001$. The green color corresponds with the GRS considering only the HLA region. Mean and standard error of mean (error bars) are depicted for each population.

Ortiz –Fernandez and Sawalha, Frontiers in Medicine Feb 2021; 8: 1-12

Ethiology

- Environmental

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Materials and methods

- Period in which patients were considered 1911-2020
- Period in which paper was selected 1957-2020
- Paper selected 57
- Paper excluded 7 (Insufficient data or repeated cases)
- Patients n° 40
- Classification for geographic site:
  - 5 case
  - 3-5 cases
  - < 3 cases

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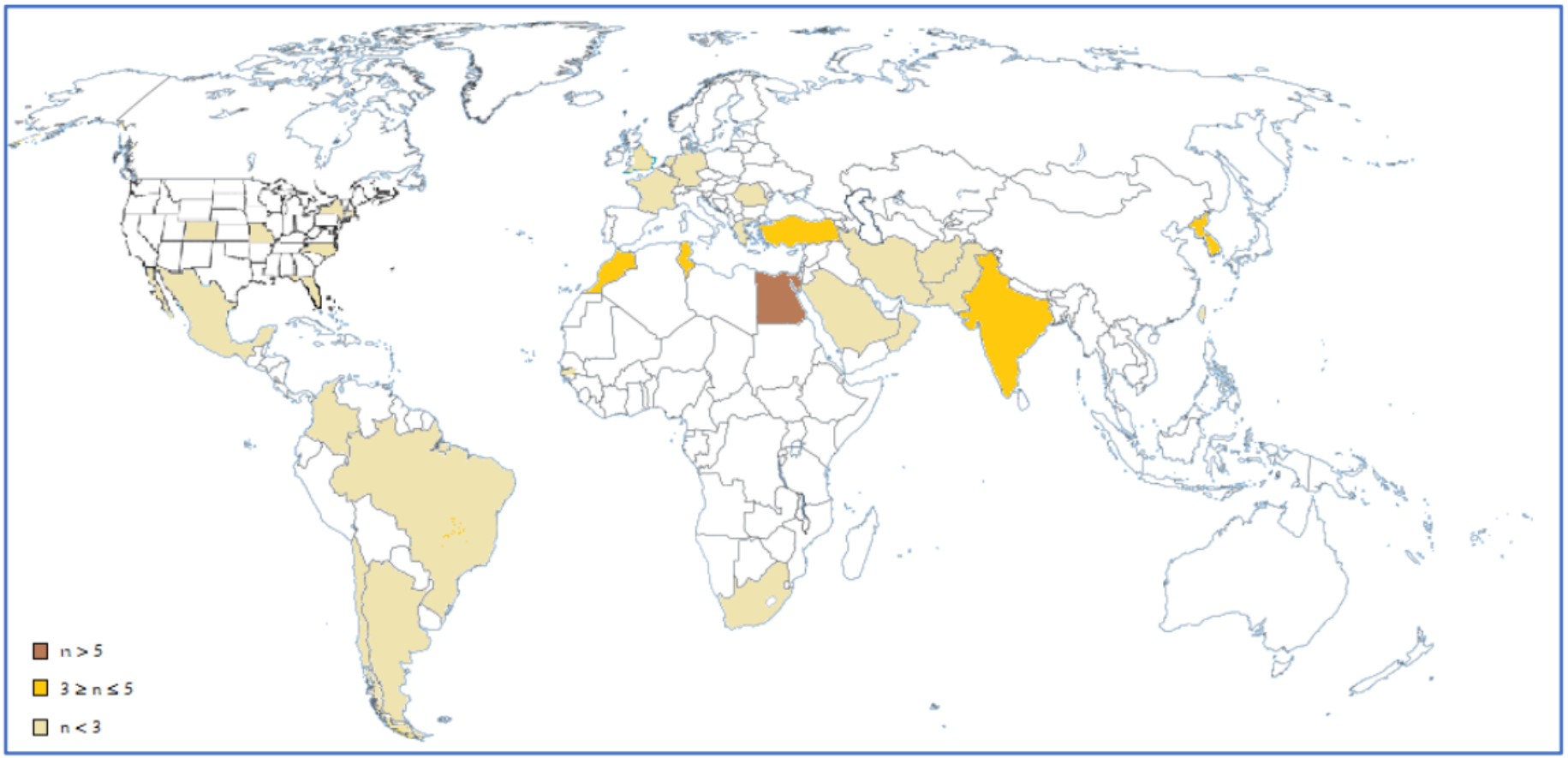
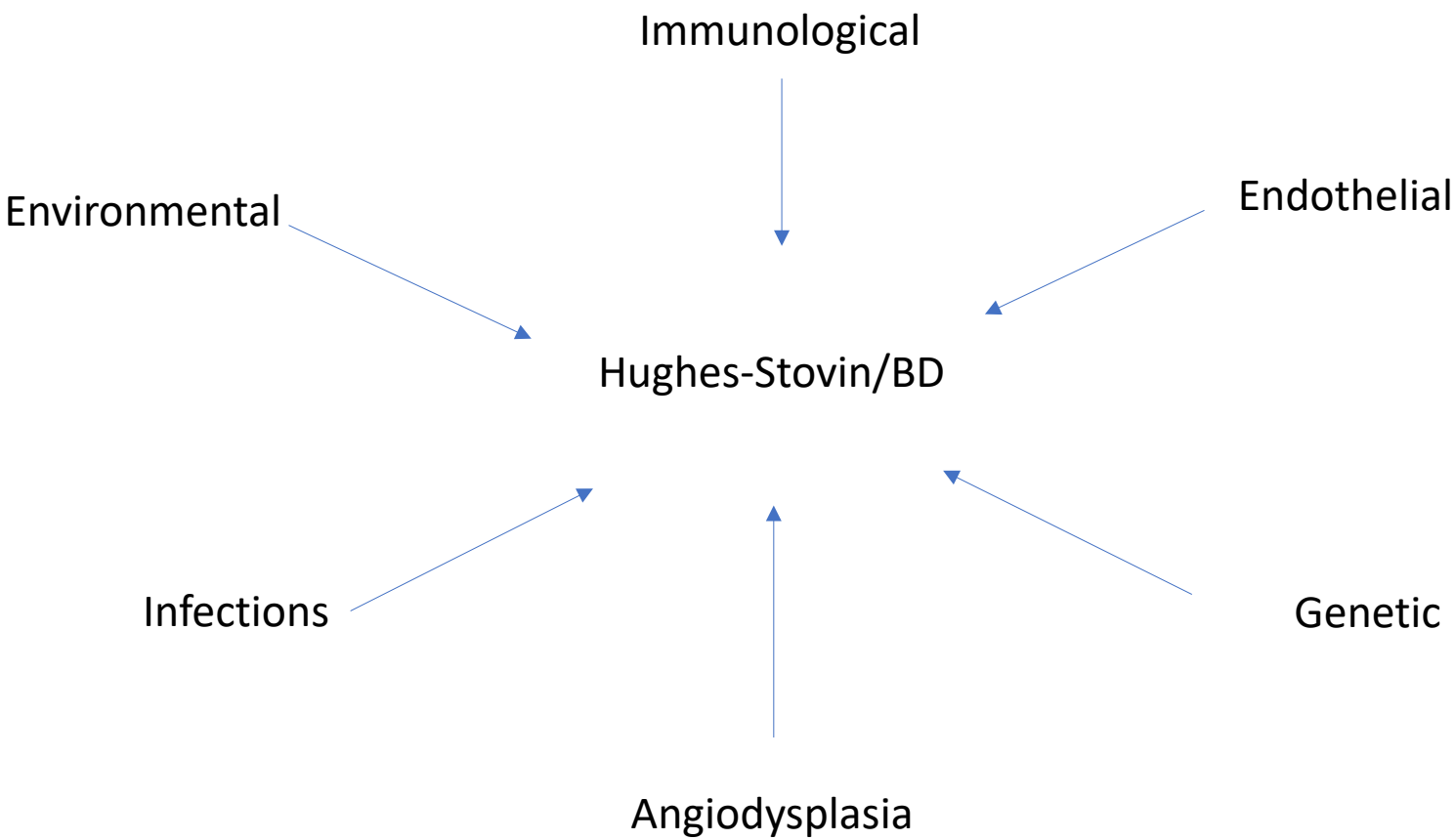
GEOGRAPHICAL DISTRIBUTION

Number of confirmed cases of HSS reported by geographic area.



THE HUGHES-STOVIN SYNDROME

The ethiology of Hughes-Stovin syndrome is mutifactorial



TREATMENT

- IMMUNOSUPPRESSION
- SURGICAL RESECTION OR ENDOVASCULAR TREATMENT OF HIGH-RISK LESIONS
  - Lobectomy, Segmentectomy
  - Pneumectomy
  - Ligature of carotid false aneurysm and posterior tibial artery
  - Exeresis of pulmonary mass
  - Repeated embolization of bronchial artery
  - Resection of pulmonary aneurysm
  - Lung transplantation
  - Embolization of pulmonary aneurism or bronchial artery
  - Chest drainage
  - Atrial mass removal
- THE USE OF ANTICOAGULANTS IS STILL DEBATED IN HSS

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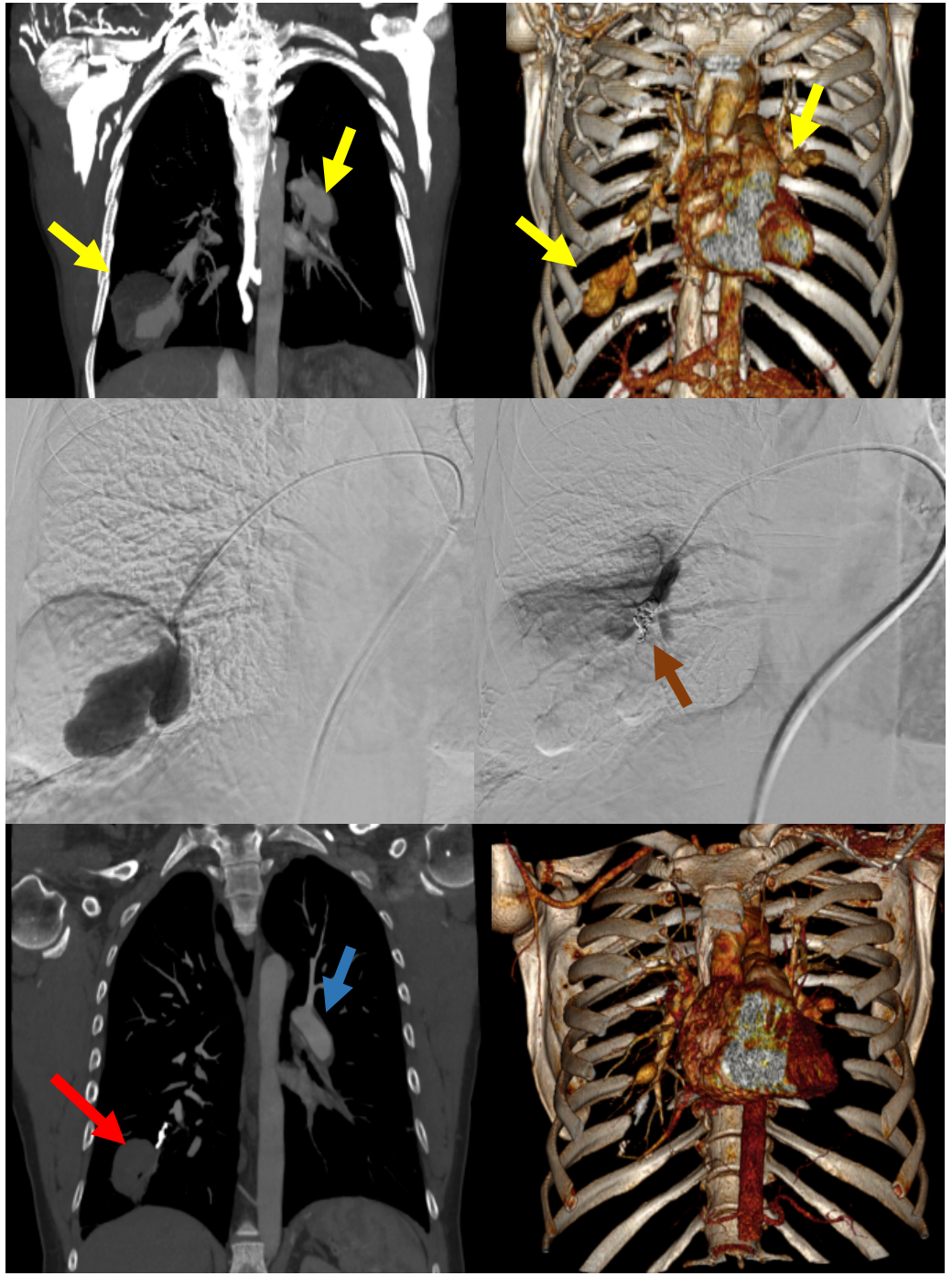
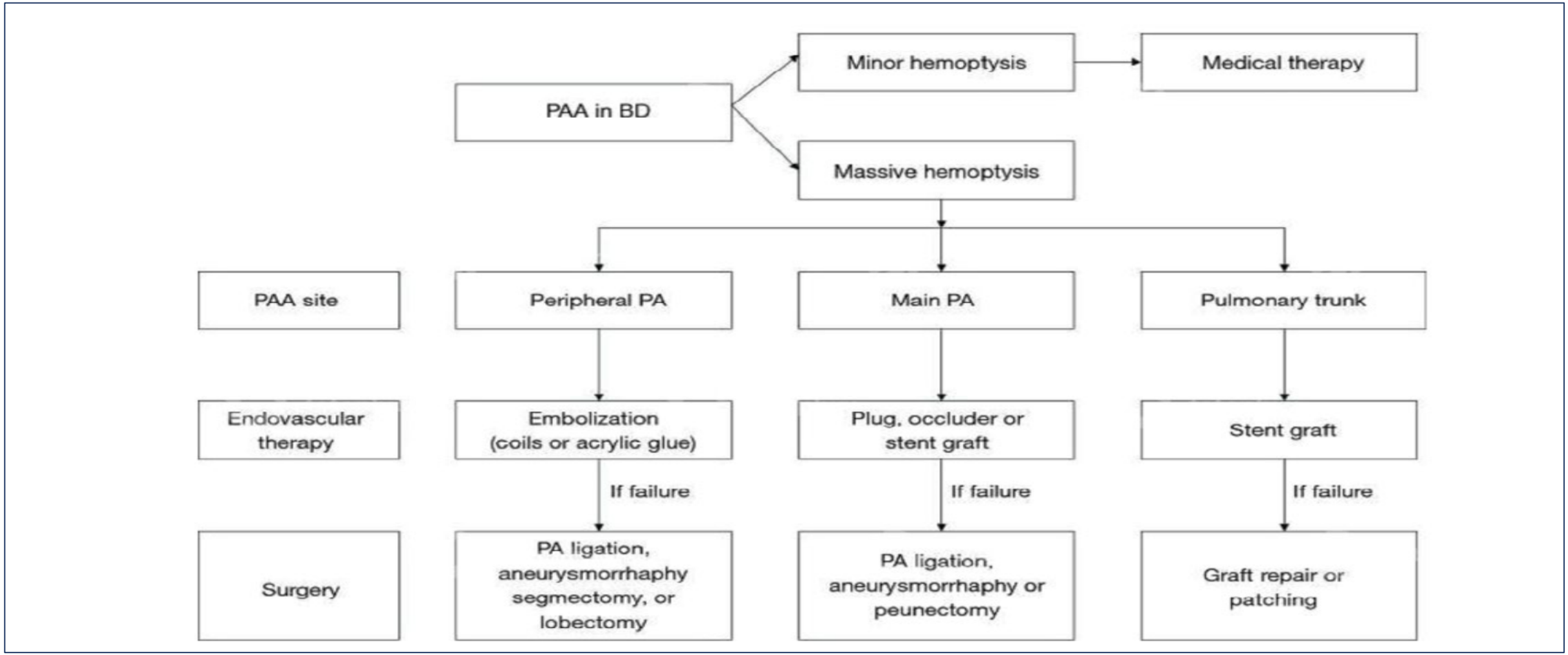
A) Preoperative image CT MIP and SSD reconstruction showing pulmonary aneurysms: patent right great aneurysm and little left aneurysm (yellow arrows)
B) Intraoperative selective angiography confirming the non-ruptured aneurysm and successful coil embolization (brown arrow) with aneurysm exclusion
C) Postoperative image CT MIP and SSD reconstruction showing complete right aneurysm exclusion (red arrow) and unmodified left aneurysm (blue arrows)



Managment protocol of PAA in BD according to degree of hemoptysis and presenting clinical condition: open surgery and endovascular treatment

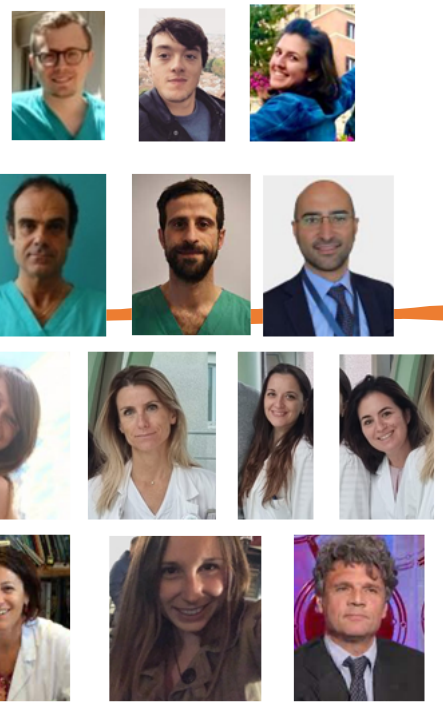


Journal of Surgery 16:4; 2020 Abd Alkader

CONCLUSION

- Further functional studies can be prioritized to relevant cell types involved to elucidate the molecular effects of disease- associated genetic variants
- A complete understanding of the genetic contribution to the development of Behcet's disease, the pathways and cell types involved, and the resulting functional disturbances, will help to achieve better management strategies in this complex disease.
- New therapeutic options make treatment less invasive lead to better prognosis, in multisciplinary approach.

Thank you



- Vascular surgery: Fabio Massimo Oddi, Federico Pennetta, Alice de Giorgi and Arnaldo Ippoliti
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- Cardiac surgery: Lorella Belvivere
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- Genetic: Federica Sangiuolo
- Internal medicine: Ilaria Coccia, Manfredi Tesauro