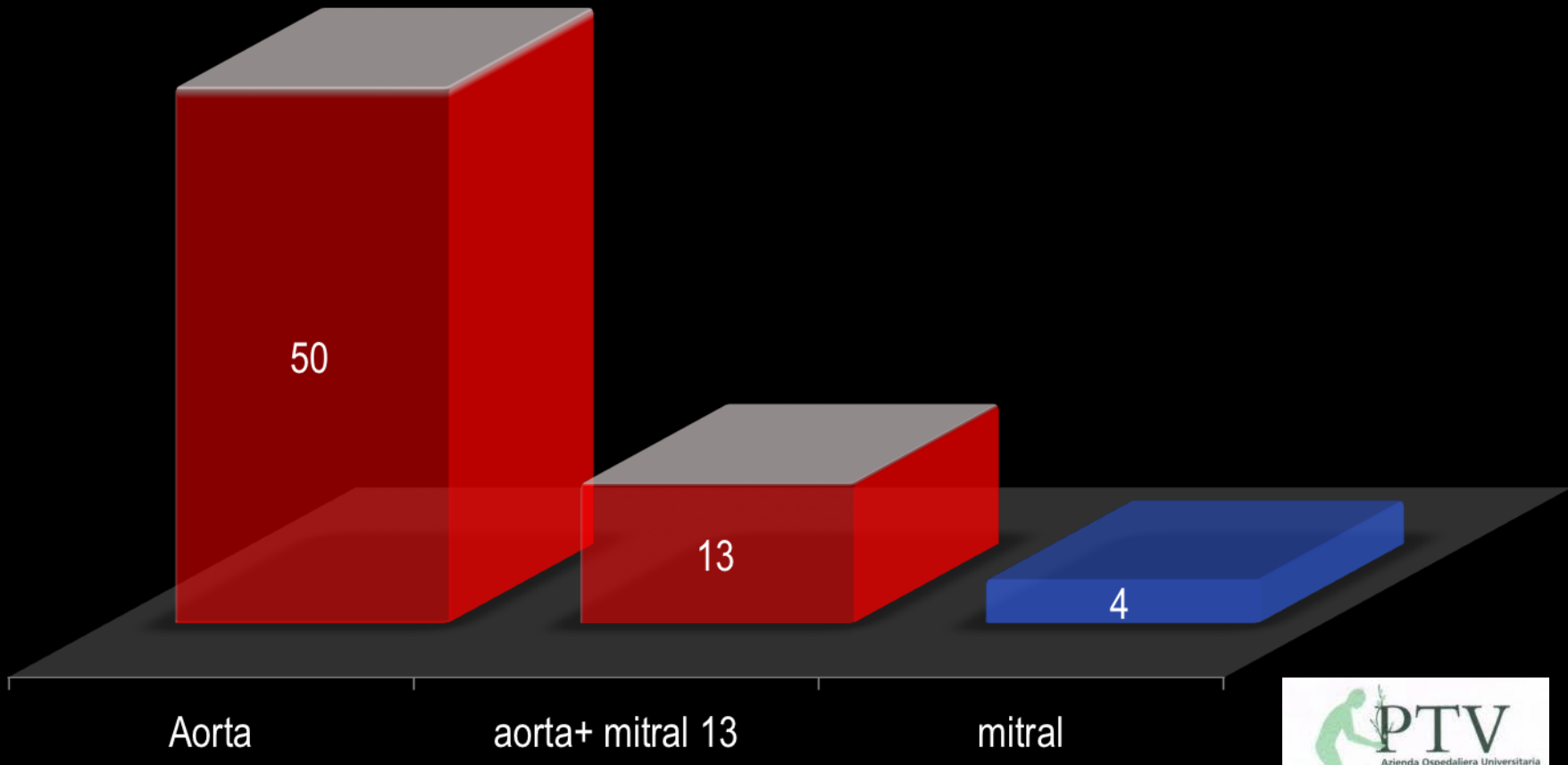
Presidio per la sindrome di Marfan e patologie correlate
Direttore Prof. Luigi Chiariello

Susanna Grego, U.O.C. Cardiochirurgia

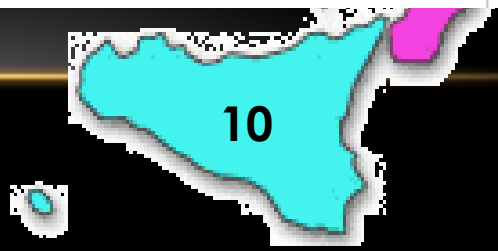
38% OF PATIENTS HAD CARDIAC SURGERY

54/141



PLAN PRIME VISITE

PERCORSO A:			PERCORSO B:		
		8.00			8.00
I VISITA	Pediatria	8.00			
II VISITA	Oculistica	8.30	I VISITA	Cardiochirurgia/Ortopedia	8.30
III VISITA	Cardiochirurgia/Ortopedia	9.30	II VISITA	Genetica	9.30
IV VISITA	Genetica	11.30	III VISITA	Oculistica	11.30
V VISITA	Odontoiatria	12.30	IV VISITA	Odontoiatria	12.30
PEDIATRICI :			ADULTI :		



MS is inherited as a dominant trait.

Each parent with the condition has a 50% risk of passing the genetic defect on to any child due to its

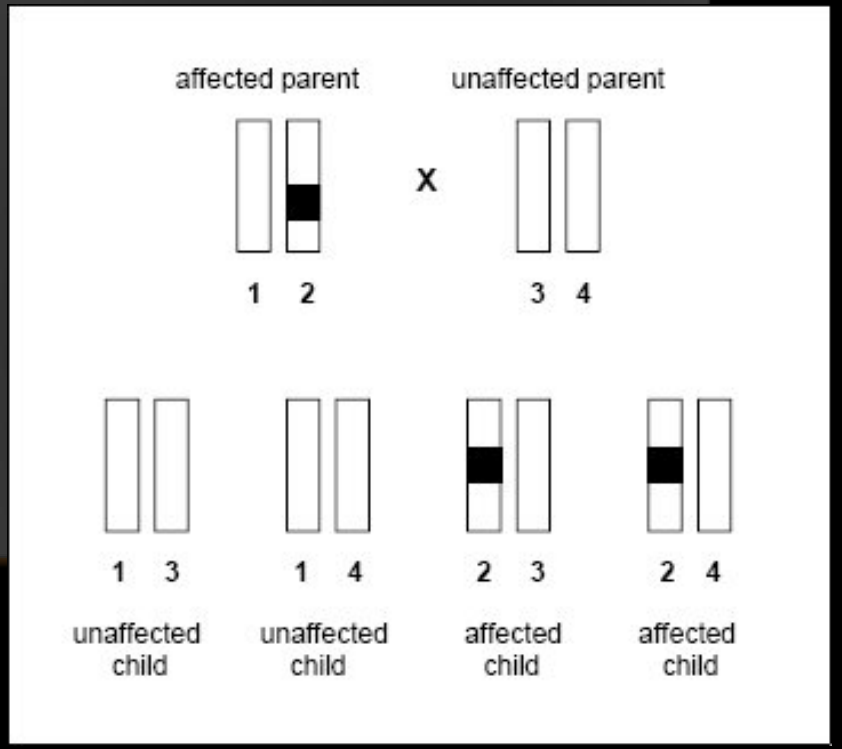
It appears as a de novo mutation in 25% of cases

Marfan syndrome affects males and females equally and the mutation shows no ethnic or geographical bias.

2:10.000

In Italy 15-18.000/60.000.000

Lazio 1.500



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The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Genetic Linkage of the Marfan Syndrome, Ectopia Lentis, and Congenital Contractural Arachnodactyly to the Fibrillin Genes on Chromosomes 15 and 5

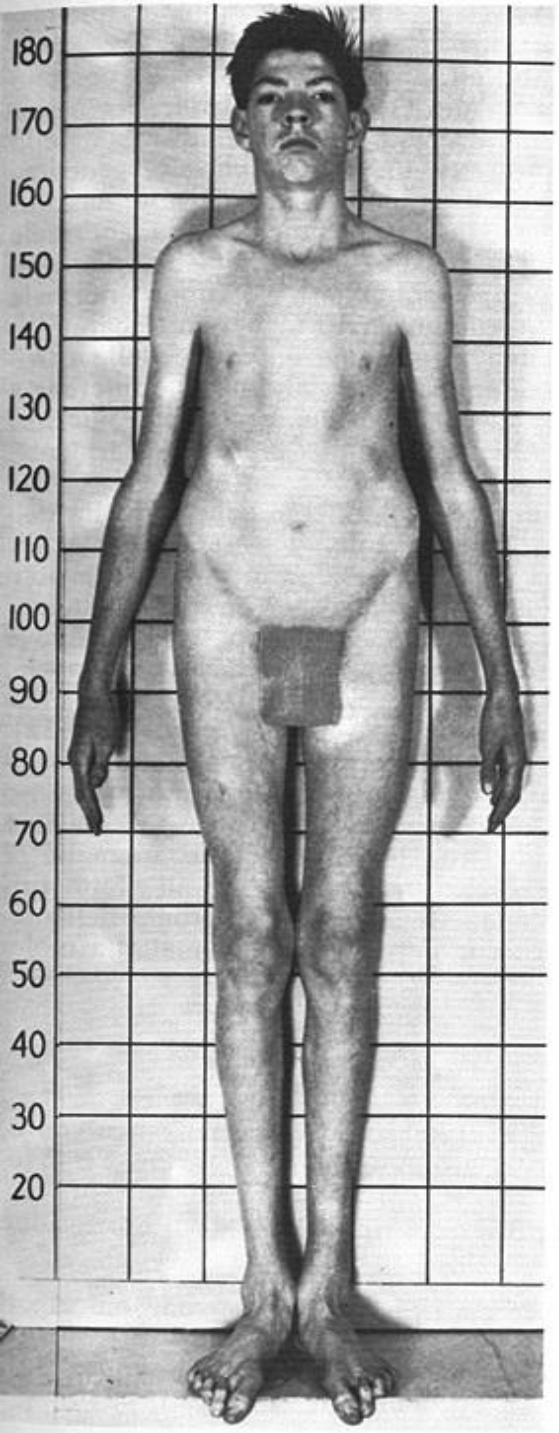
Petros Tsipouras, M.D., Richard Del Mastro, Ph.D., Mansoor Sarfarazi, Ph.D., Brendan Lee, Ph.D., Emilia Vitale, Ph.D., Anne H. Child, M.D., Maurice Godfrey, Ph.D., Richard B. Devereux, M.D., Duncan Hewett, B.Sc., Beat Steinmann, M.D., Denis Viljoen, M.D., Bryan C. Sykes, Ph.D., Michael Kilpatrick, Ph.D., Francesco Ramirez, Ph.D., and the International Marfan Syndrome Collaborative Study*

N Engl J Med 1992; 326:905-909 | April 2, 1992 | DOI: 10.1056/NEJM199204023261401

It is caused by mutation in the FBN1 gene on chromosome 15 (15q21) which encodes the glycoprotein fibrillin 1

more than 1,000 *FBN1* have been identified. Most of the mutations change a single protein building block (amino acid) in the fibrillin-1 protein. The remaining *FBN1* gene mutations result in an abnormal fibrillin-1 protein that cannot function properly.

missense or in-frame deletions/insertions versus nonsense or out-of-frame deletions/insertions


180
170
160
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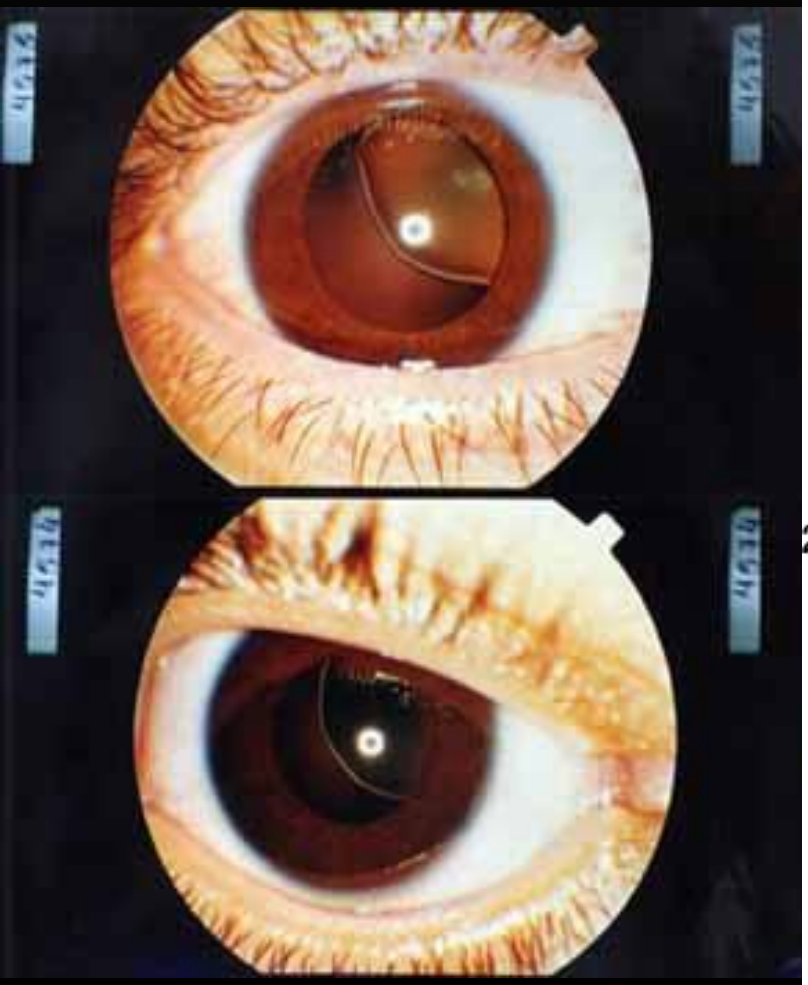
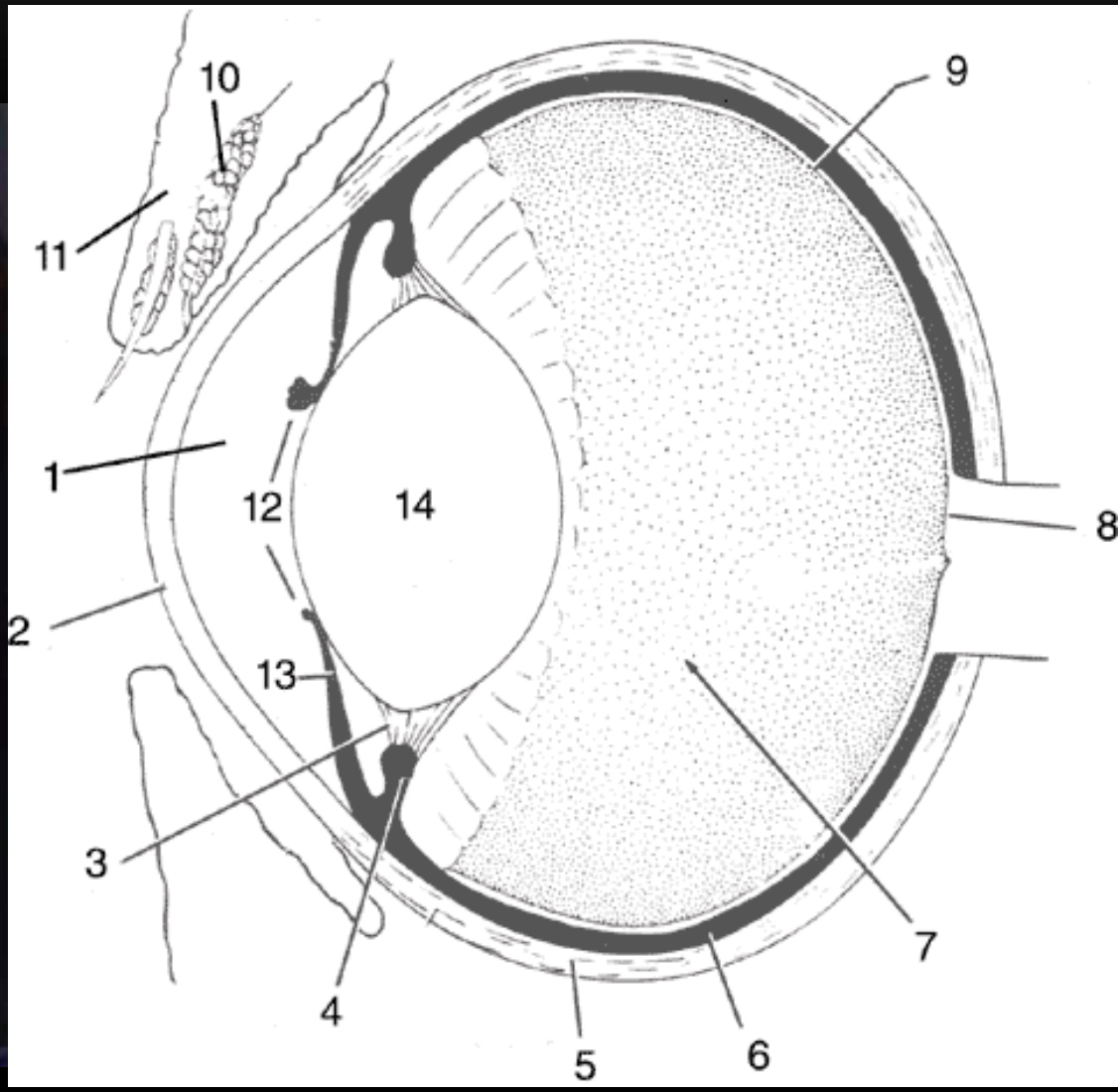
THE ECTOPIA LENTIS AND LENS SUBLUXATION





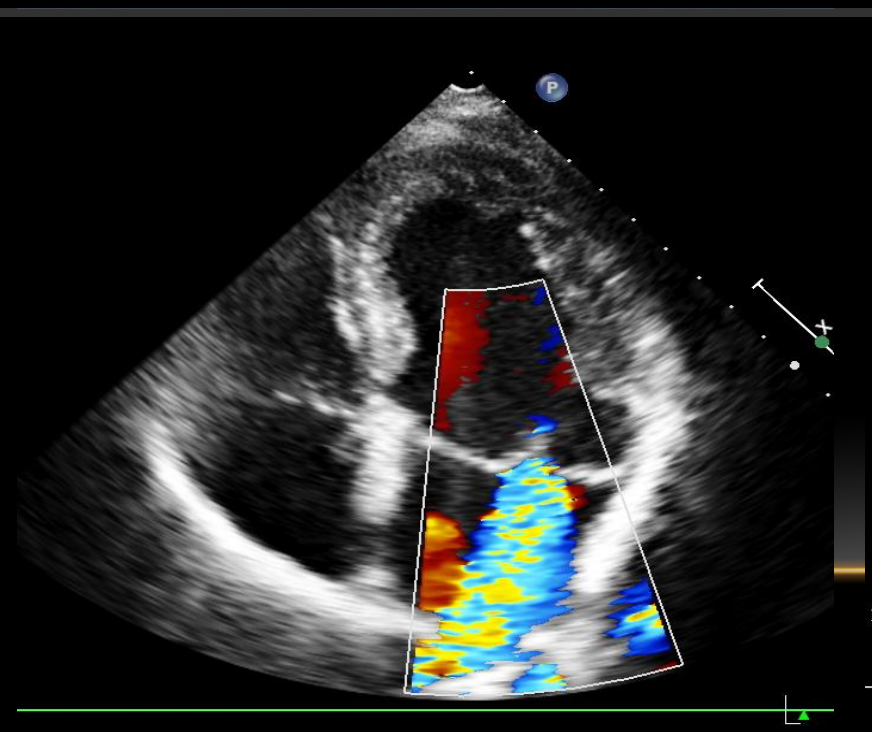
Original article

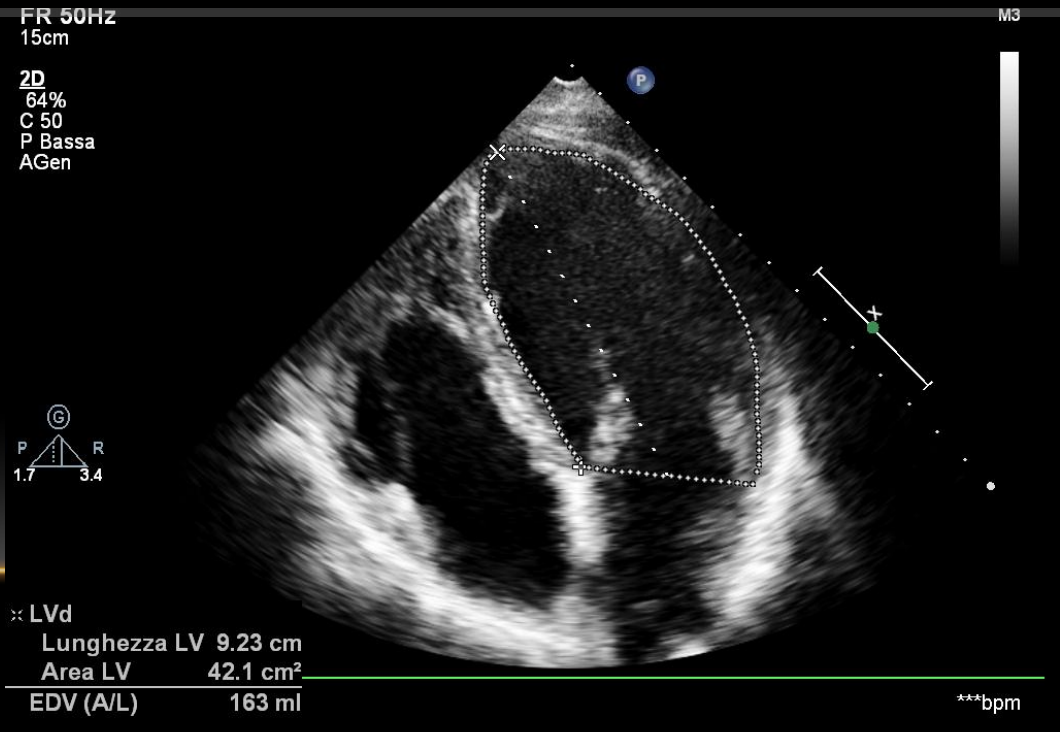
The revised Ghent nosology for the Marfan syndrome

Bart L Loeys,[1] Harry C Dietz,[2] Alan C Braverman,[3] Bert L Callewaert,[1] Julie De Backer,[1] Richard B Devereux,[4] Yvonne Hilhorst-Hofstee,[5] Guillaume Jondeau,[6] Laurence Faivre,[7] Dianna M Milewicz,[8] Reed E Pyeritz,[9] Paul D Sponseller,[10] Paul Wordsworth,[11] Anne M De Paepe[1]

J Med Genet 2010;**47**:476–485. doi:10.1136/jmg.2009.072785

The heart in Marfan syndrome





The history of Marfan syndrome

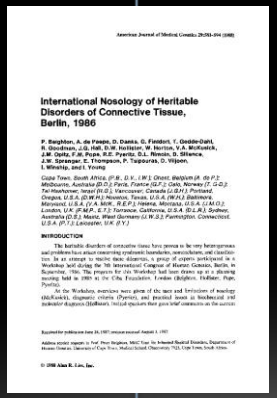
1° description by Antoine Marfan

1896

CLASSIFICATION OF CONNECTIVE TISSUE DISORDER VICTOR MCKUSICK

1955

The Berlin nosology



International Nosology of Heritable Disorders of Connective Tissue, Berlin, 1986

1986

FBN1 mutation identification

1991

1° Ghent nosology

1996

2° Ghent nosology

The revised Ghent nosology for the Marfan syndrome

2010

Original article

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Marfan syndrome is associate with a high risk of aortic dissection

It can be detrimental to diagnose MFS in patients without such a risk

Misdigagnosis leads to
Restriction of career aspiration
No access to insurance benefits
Anxiety or depression
Unfounded marital or reproductive decision
Exercise and sport restriction

Diagnosi → Prognosi

System	Major	Minor
Family/genetic history	Having a first-degree relative (parent, child, or sibling) who meets these diagnostic criteria independently Presence of a mutation in FBN1 known to cause the Marfan syndrome Presence of a haplotype around FBN1, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family	None
Skeletal	Presence of at least 4 of the following manifestations: Pectus carinatum Pectus excavatum requiring surgery Reduced upper-to-lower segment ratio or arm span-to-height ratio greater than 1.05 Wrist and thumb signs Scoliosis > 20 degrees or spondylolisthesis Reduced extensions at the elbows (< 170 degrees) Medial displacement of the medial malleolus causing pes planus Protrusio acetabulare of any degree (ascertained on radiographs)	Pectus excavatum of moderate severity Joint hypermobility Highly arched palate with crowding of teeth Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slating palpebral fissures)
Ocular	Ectopia lentis (dislocated lens)	Abnormally flat cornea (as measured by keratometry) Increased axial length of globe (as measured by ultrasound)
Cardiovascular	Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva or dissection of the ascending aorta	Mitral valve prolapse with or without mitral valve regurgitation Dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause in patients age < 40 years Calcification of the mitral annulus in patients age < 40 years Dilatation of dissection of the descending thoracic or abdominal aorta in patients age < 50 years
Pulmonary	None	Spontaneous pneumothorax Apical blebs (ascertained by chest radiography)
Skin and integument	None	Stretch marks not associated with marked weight changes, pregnancy, or repetitive stress Recurrent incisional hernias
Dura	Lumbosacral dural ectasia as demonstrated by computed tomography or magnetic resonance imaging scans	None

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Richard B Devereux[4], **Yvonne Hilhorst-Hofstee**[5], **Guillaume Jondeau**[6], **Laurence**
Dianna M Milewicz[8], **Reed E Pyeritz**[9], **Paul D Sponseller**[10], **Paul Wordsworth**[11], **Anne M De Paepe**[1]

+ Author Affiliations

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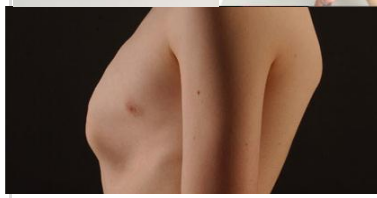
Received 26 August 2009
Revised 16 December 2009
Accepted 17 December 2009

Abstract

The diagnosis of Marfan syndrome (MFS) relies on defined clinical criteria (Ghent n
outlined by international expert opinion to facilitate accurate recognition of this gene
aneurysm syndrome and to improve patient management and counselling. These G
criteria, comprising a set of major and minor manifestations in different body systems
proven to work well since with improving molecular techniques, confirmation of the d
is possible in over 95% of patients. However, concerns with the current nosology are
some of the diagnostic criteria have not been sufficiently validated, are not applicabl
children or necessitate expensive and specialised investigations. The recognition of
clinical expression and the recently extended differential diagnosis further confound
diagnostic decision making. Moreover, the diagnosis of MFS—whether or not establ
correctly—can be stigmatising, hamper career aspirations, restrict life insurance opp
and cause psychosocial burden. An international expert panel has established a rev
Ghent nosology, which puts more weight on the cardiovascular manifestations and i
aortic root aneurysm and ectopia lentis are the cardinal clinical features. In the abse
family history, the presence of these two manifestations is sufficient for the unequivo
diagnosis of MFS. In absence of either of these two, the presence of a bonafide *FBN*
or a combination of systemic manifestations is required. For the latter a new scoring

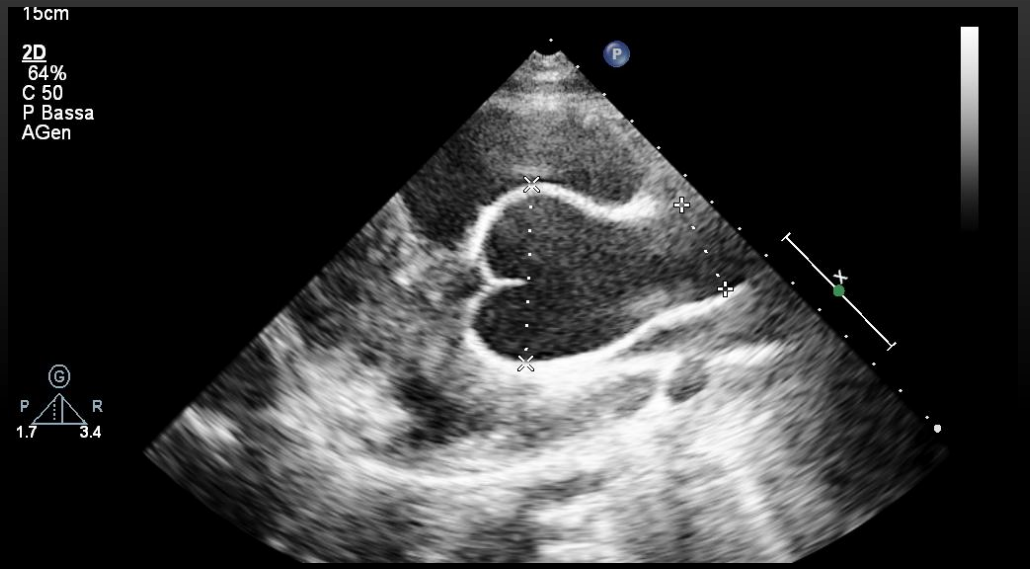
Prognosi → Diagnosi

Feature		Value
Wrist AND thumb sign	visita	3
Wrist OR thumb sign		1
Pectus carinatum deformity		2
Pectus excavatum or chest asymmetry		1
Hindfoot deformity		2
Plain flat foot (pes planus)		1
Pneumothorax	anamnesi	2
Dural ectasia	RMN	2
Protrusio acetabulae	RX	2
Reduced upper segment / lower segment AND increased arm span/height ratios		1
Scoliosis or thoracolumbar kyphosis	RX e visita	1
Reduced elbow extension	visita	1
3 of 5 facial features		1
Skin striae		1
Myopia	Visita oculistica	1
Mitral valve prolapse	Ecocardiogramma	1
Total	Positive if ≥7	

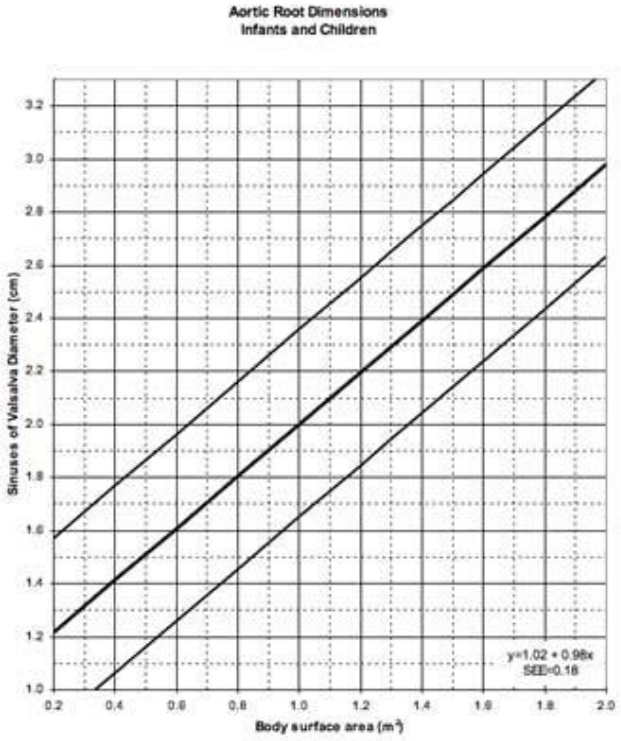


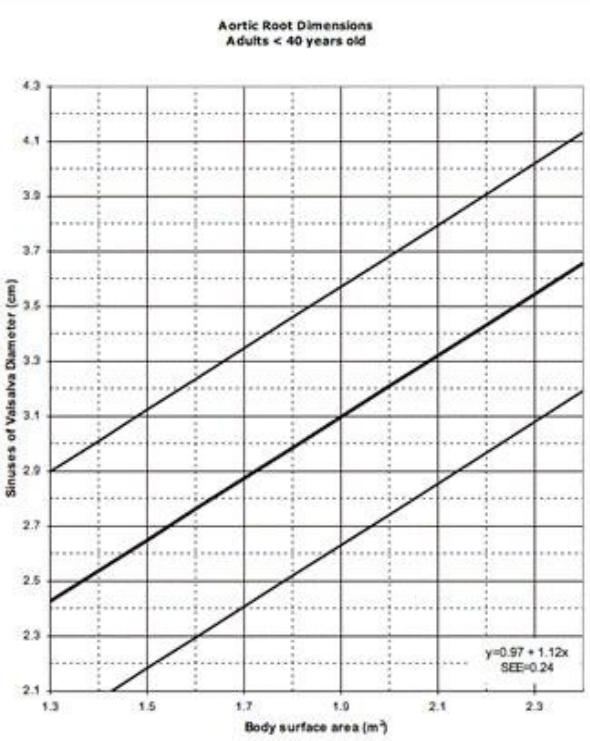
A Systemic Score calculator and a complete description of each component evaluation can be found at the National Marfan Foundation Web site.

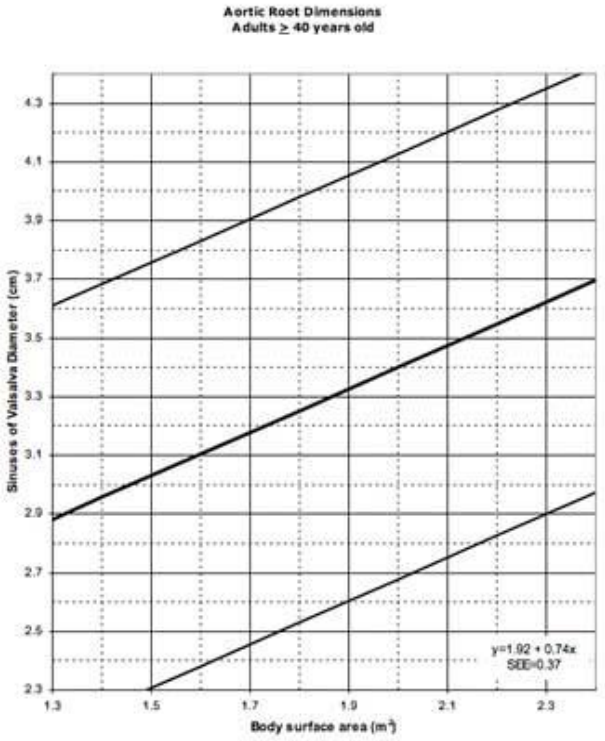
AORTIC Z-SCORE CALCULATION



(Charts refer to "4.Cornell data-based formulae...")







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In the absence of family history	In the presence of family history
Ao (Z≥2 or 3) and ectopia lentis = MFS *	EL and FH of Marfan syndrome = MFS
Ao (Z≥2 or 3) and FBN1 = MFS	Systemic score ≥7 and FH = MFS*
Ao (Z≥2 or 3) and systemic score ≥7 = MFS*	Ao (Z≥2 or 3) and FH = MFS*
Ectopia lentis and FBN1 with known Ao = MFS	Z-score > 3 in children

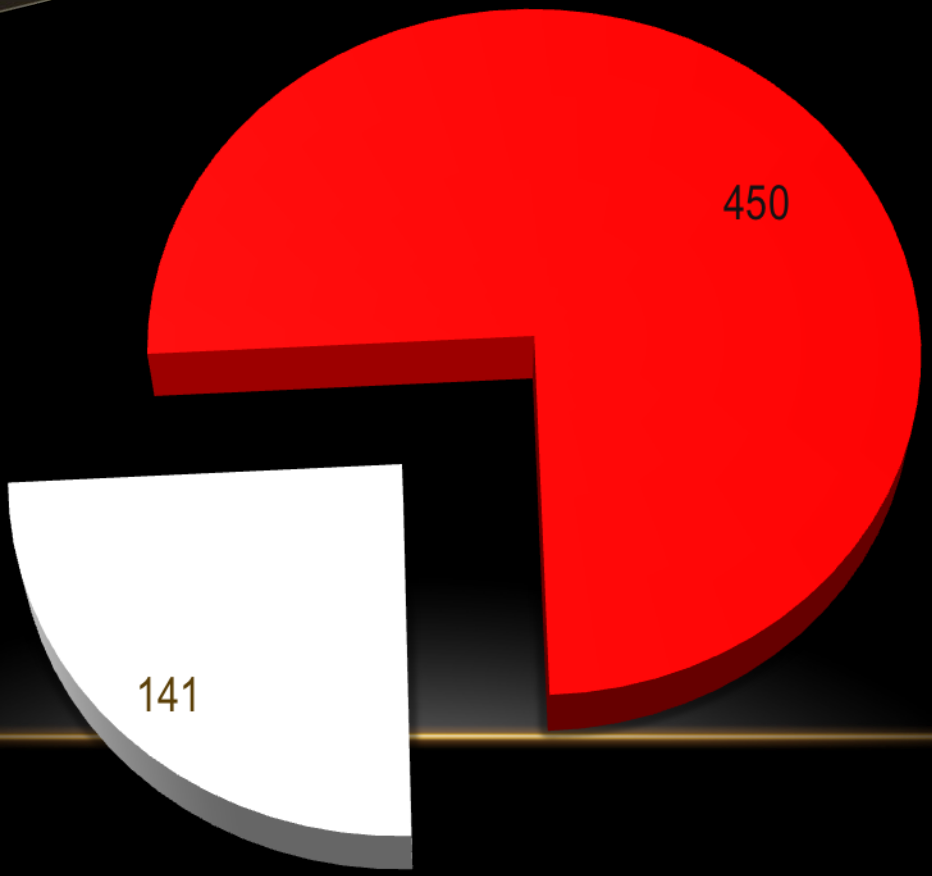
MASS phenotype is an autosomal dominant condition that can be caused by heterozygous mutations in *FBN1*. The acronym MASS stands for **m**itral valve prolapse, myopia, borderline and non-progressive **a**ortic enlargement, and nonspecific **s**kin and **s**keletal findings that overlap with those seen in Marfan syndrome. One is most confident in this diagnosis when concordant manifestations are seen in multiple generations in a given family. Still, it remains unclear whether some individuals in such a family may be predisposed to more severe vascular involvement, and a regimen of intermittent cardiovascular imaging should be maintained. It is difficult to distinguish MASS phenotype from "emerging" Marfan syndrome when assessing an isolated individual, especially during childhood. This phenotypic designation is appropriate if the aortic root Z-score is less than 2.0, there is no ectopia lentis, and the systemic score is at least 5. This diagnosis can only be established for individuals age 20 years or older [Loeys et al 2010a].

Mitral valve prolapse syndrome, an autosomal dominant condition that associates mitral valve prolapse and (often subtle) skeletal features reminiscent of the Marfan syndrome, can be caused by mutations in *FBN1*. This phenotypic designation is appropriate in the presence of MVP if the aortic root Z-score is less than 2.0, there is no ectopia lentis, and the systemic score is less than 5. This diagnosis can only be established for individuals age 20 years or older [Loeys et al 2010a].

Ectopia lentis syndrome is an autosomal dominant condition that associates ectopia lentis and variable skeletal manifestations that are reminiscent of the Marfan syndrome. The condition is often caused by heterozygous mutations in *FBN1*. It remains unclear whether some individuals in affected families are destined to show later onset of progressive aortic enlargement. A regimen of intermittent cardiovascular imaging should be maintained. This phenotypic designation is appropriate if the aortic root Z-score is less than 2.0 and the patient does not have an *FBN1* mutation previously associated with aortic enlargement irrespective of the systemic score. This diagnosis can only be established for individuals age 20 years or older [Loeys et al 2010a].

FBN1 mutation can be present

PATIENTS WITH MARFAN SYNDROME PTV EXPERIENCE 2008-2012



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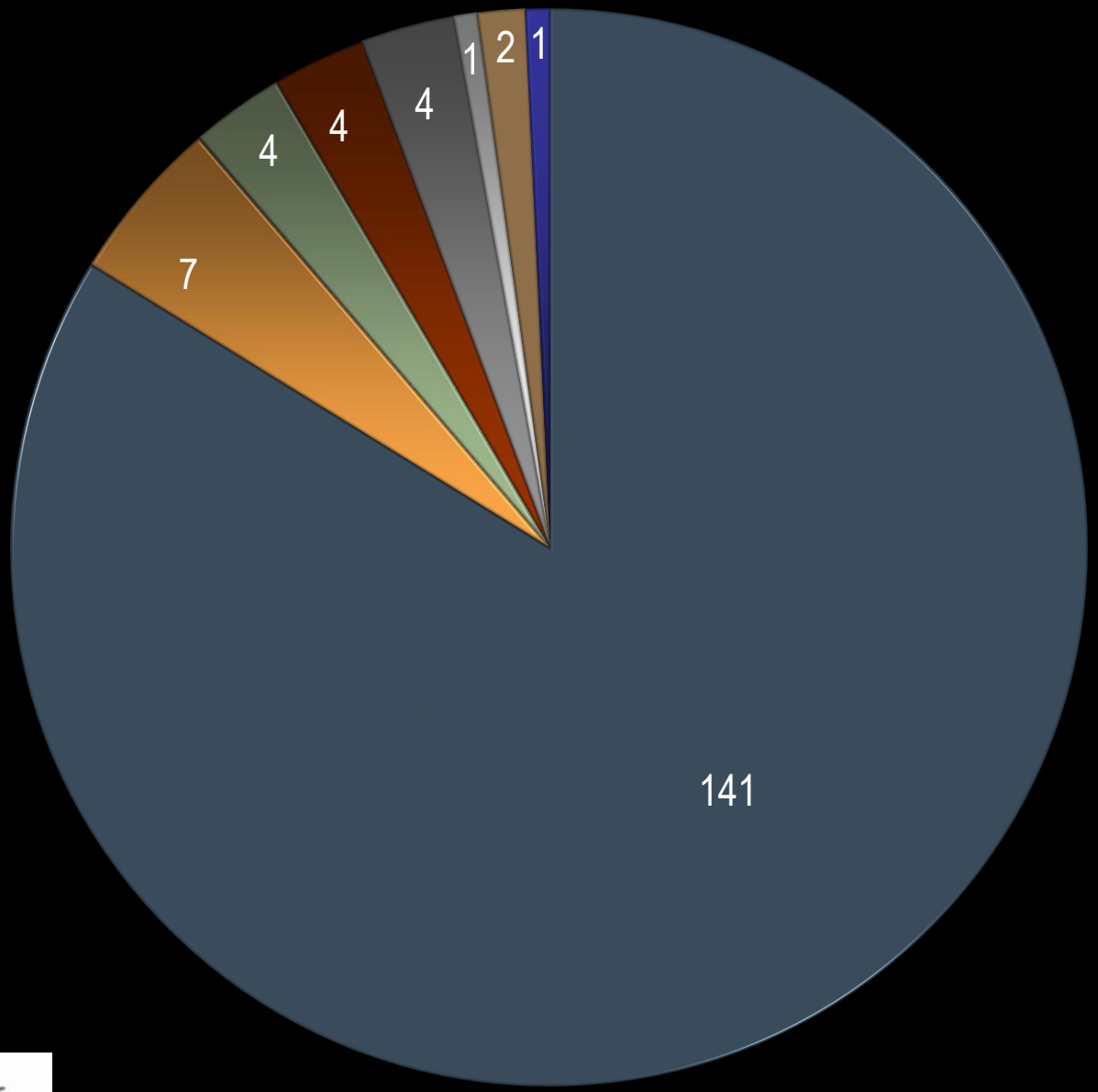

Marfan
MASS
SPM
LOEYS-DIETZ
ECTOPIA LENTI
DI.L AORTA
emerging
potentally

PTV
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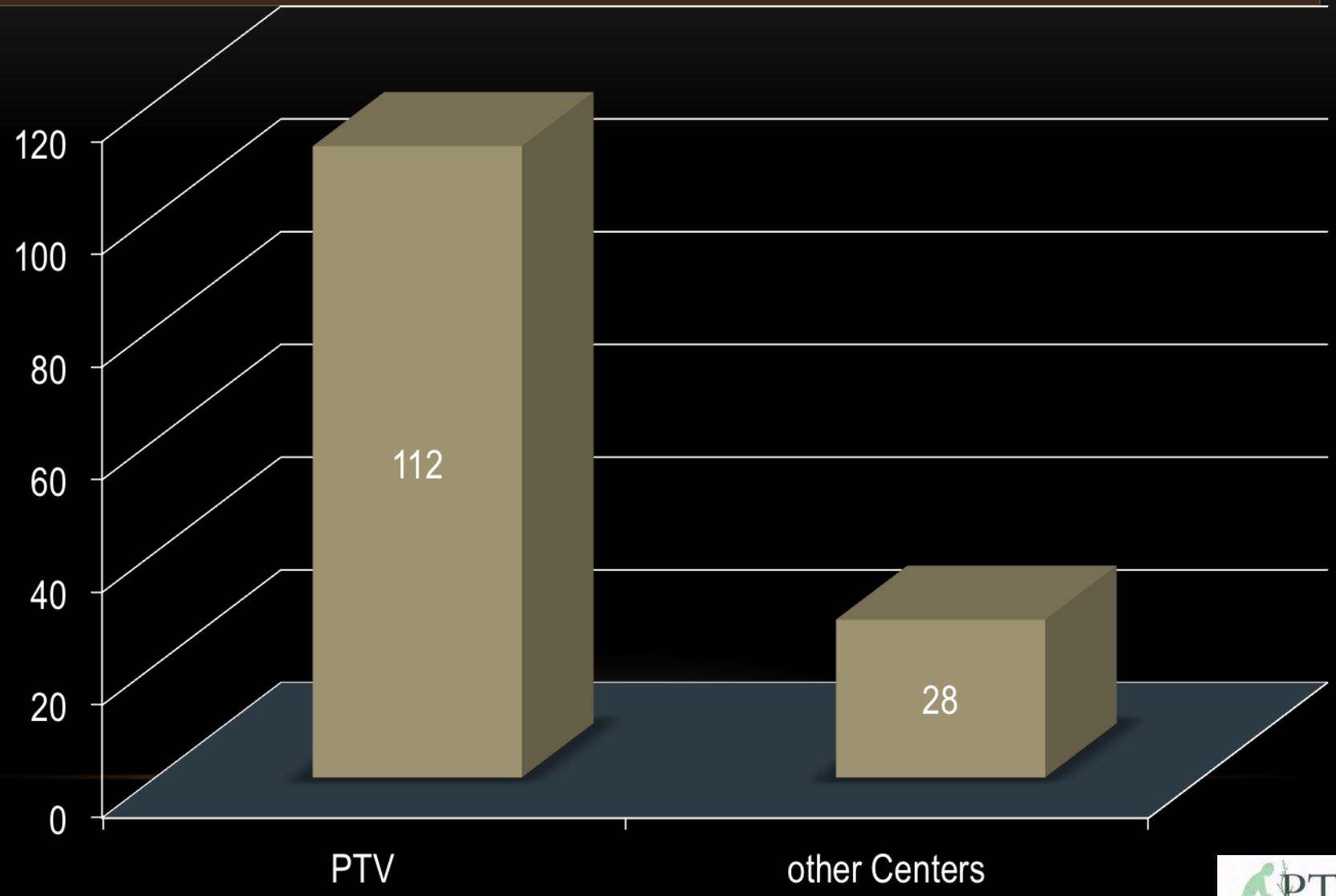
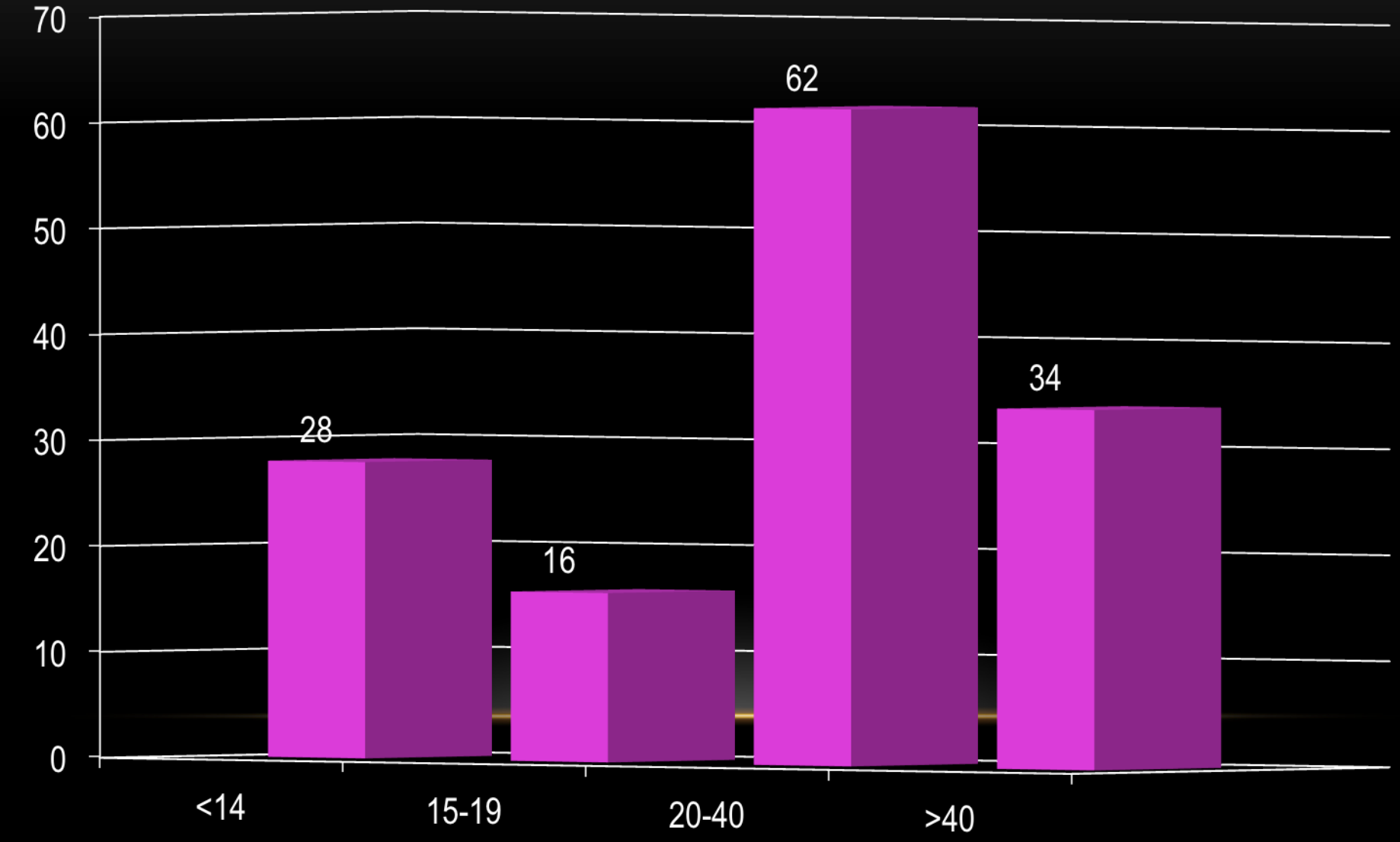
POLICLINICO TOR VERGATA

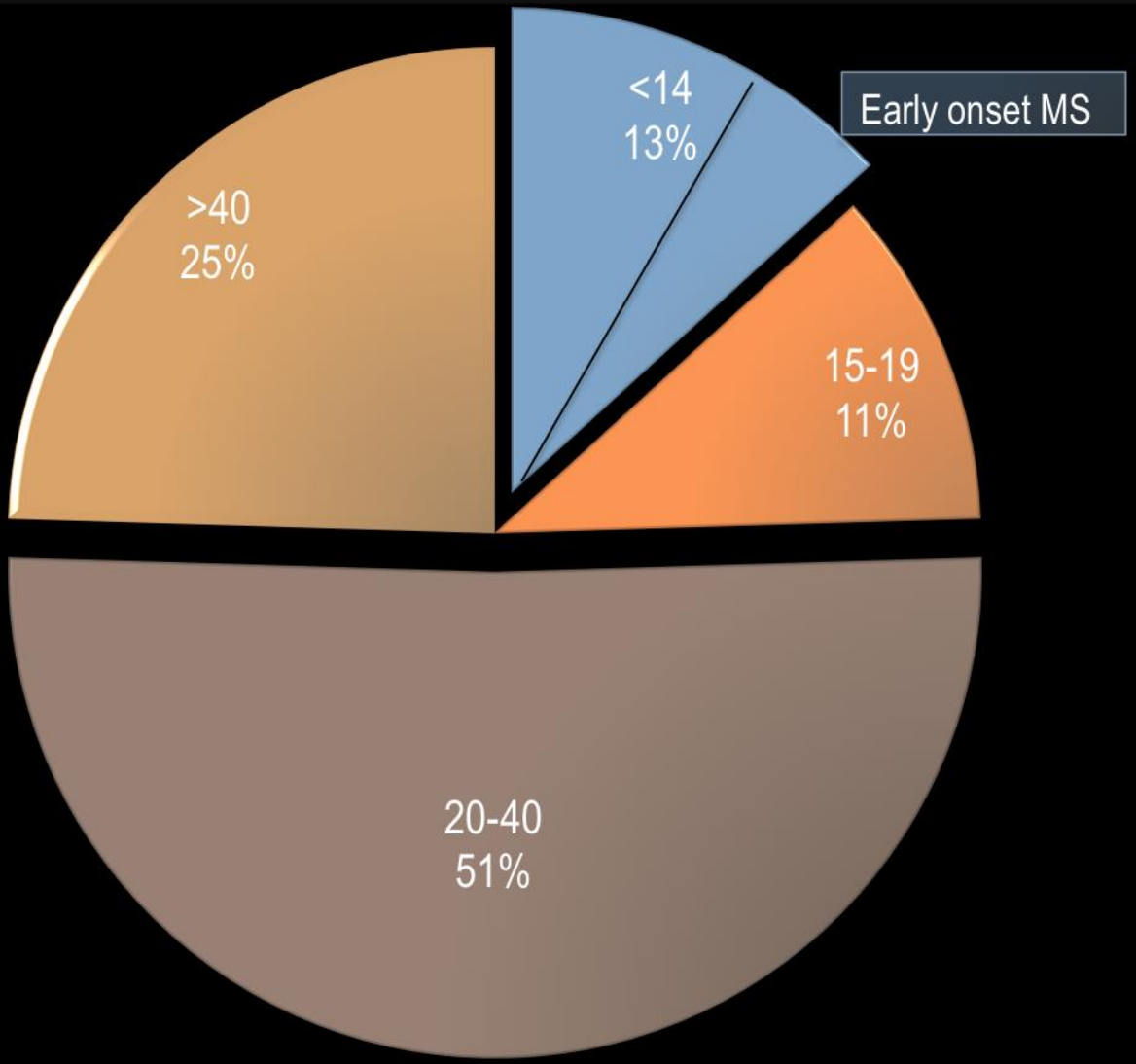
THE DIAGNOSIS OF MARFAN SYNDROME
141 PATIENTS



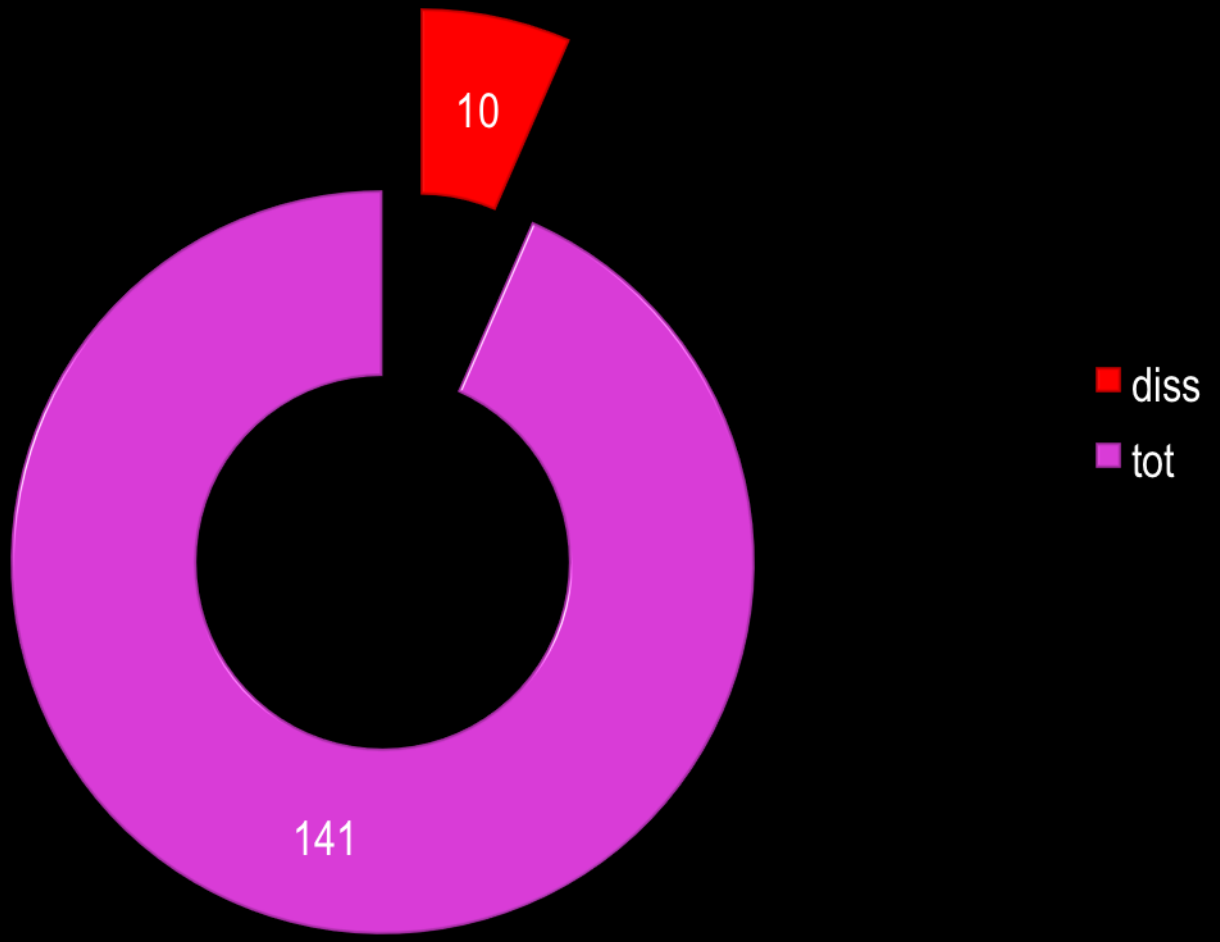
First screening: age

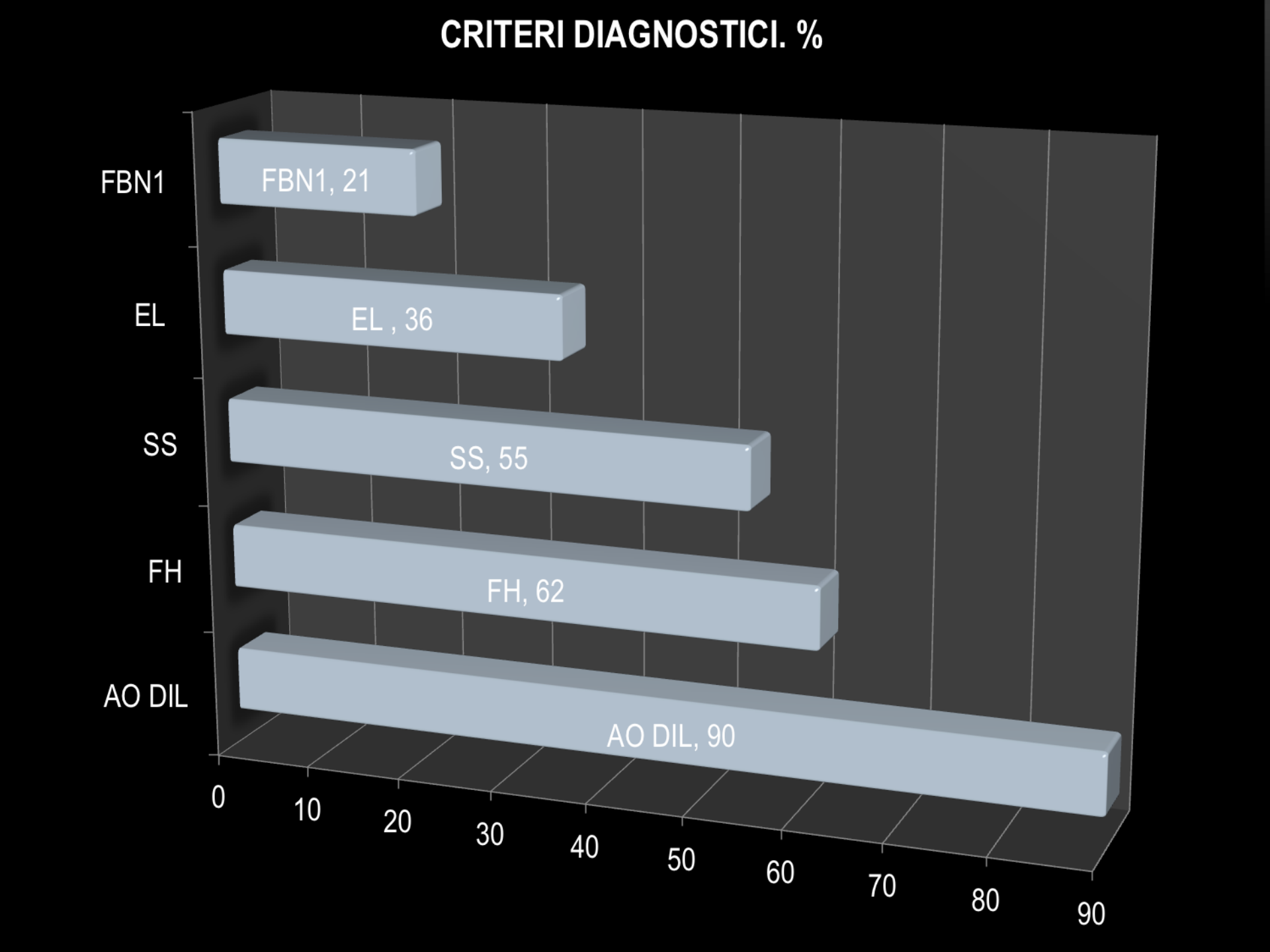


Age of first cardiac surgery

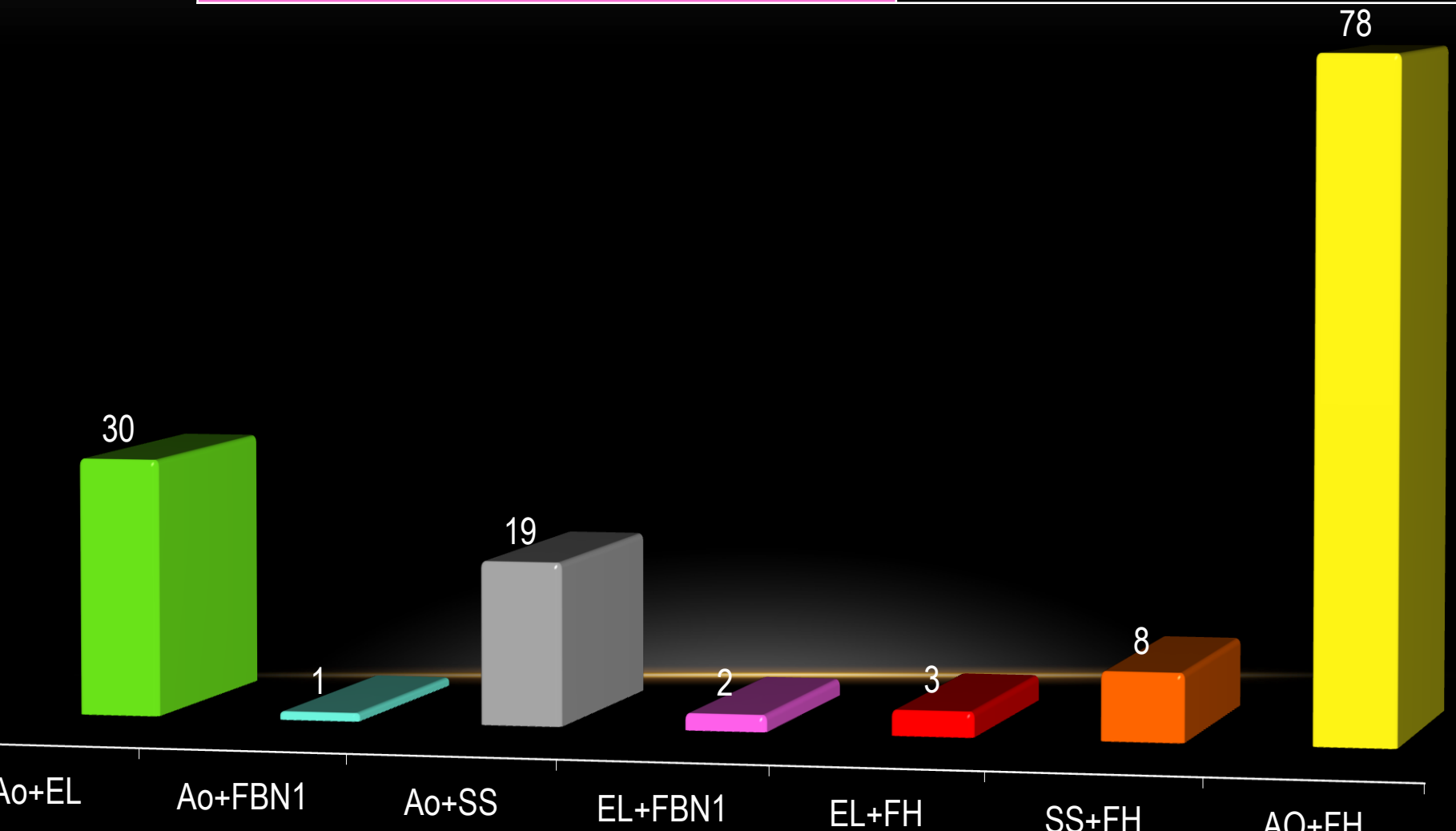


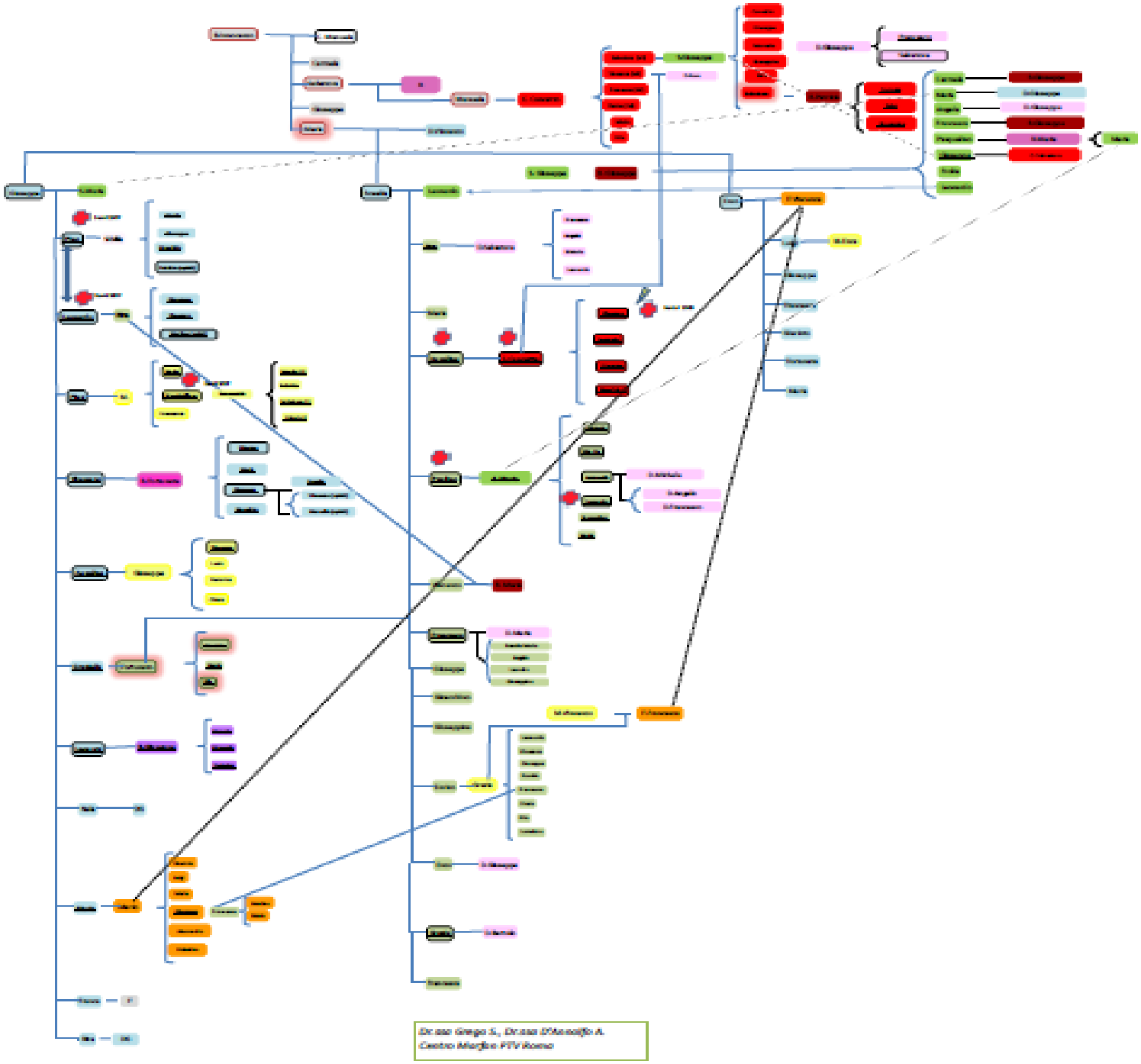
AORTIC DISSECTION INCIDENCE IN PTV MARFAN POPULATION (7%)




CRITERI DIAGNOSTICI. %
FBN1
EL
SS
FH
AO DIL
FBN1, 21
EL , 36
SS, 55
FH, 62
AO DIL, 90
0
10
20
30
40
50
60
70
80
90

In the absence of family history	In the presence of family history
Ao (Z>2) and ectopia lentis = MFS *	EL and FH of Marfan syndrome = MFS
Ao (Z>2) and FBN1 = MFS	Systemic score and FH = MFS*
Ao (Z>2) and systemic score = MFS*	Ao (Z>2 or 3) and FH = MFS*
Ectopia lentis and FBN1 with known Ao = MFS	

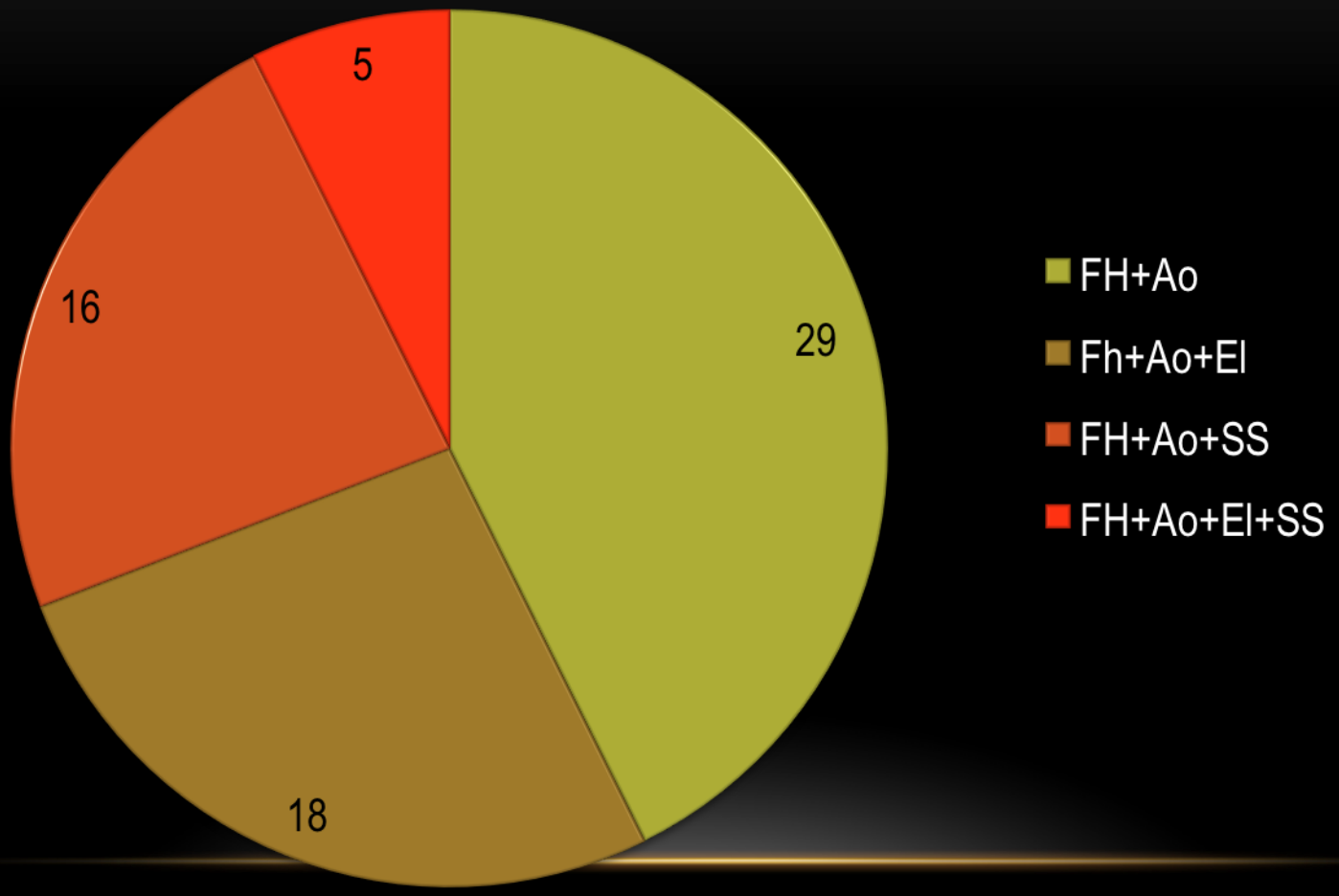


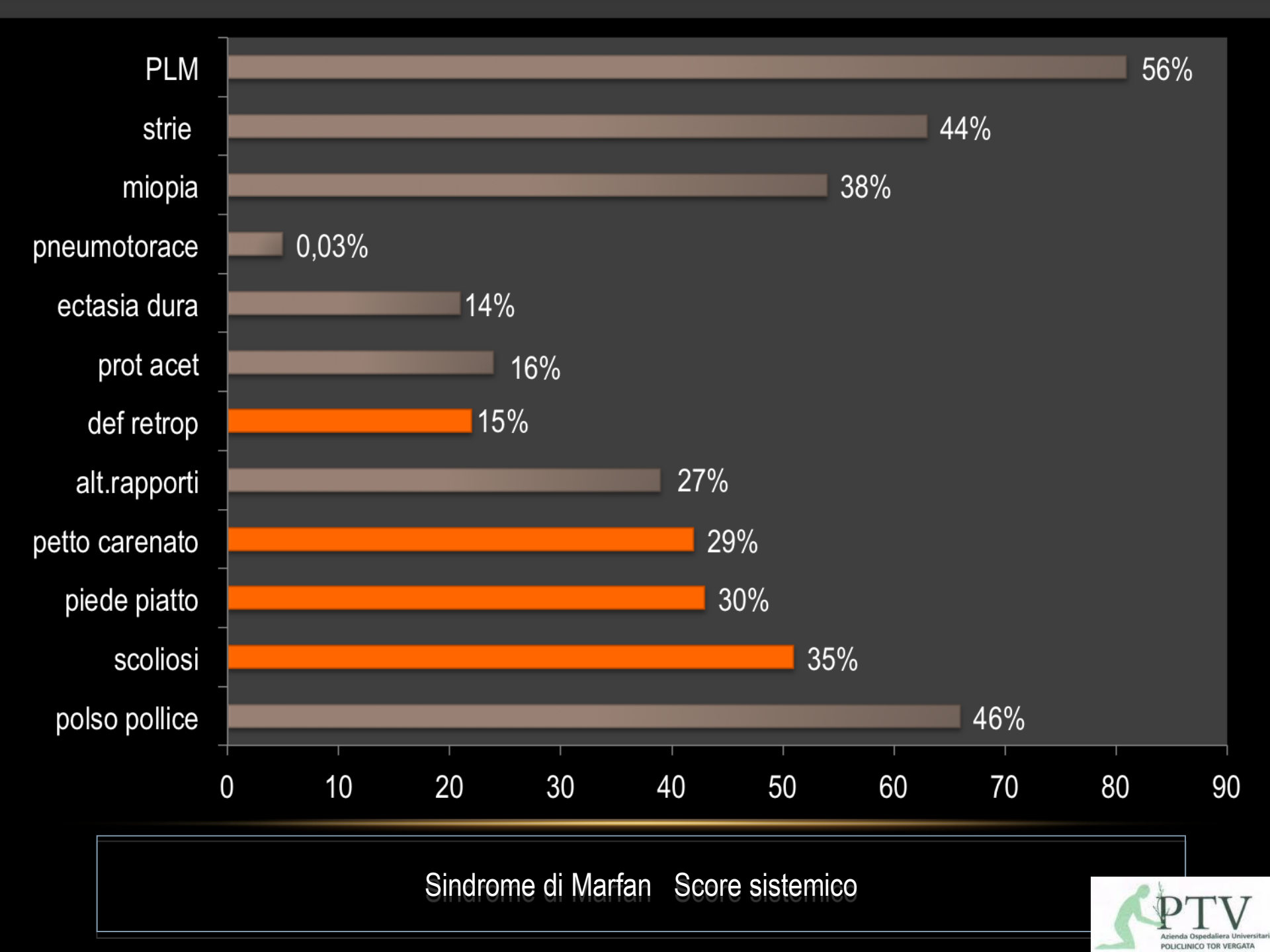


32/77

41%

Incidenza delle diverse manifestazioni della sindrome nei pazienti con familiarità accertata ed aorta dilatata




PLM
strie
miopia
pneumotorace
ectasia dura
prot acet
def retrop
alt.rapporti
petto carenato
piede piatto
scoliosi
polso pollice
56%
44%
38%
0,03%
14%
16%
15%
27%
29%
30%
35%
46%
0
10
20
30
40
50
60
70
80
90
Sindrome di Marfan Score sistemico

1. La prevalenza della malattia è stata messa in discussione o rivalutata con la revisione più precisa e restrittiva dei criteri Ghent?

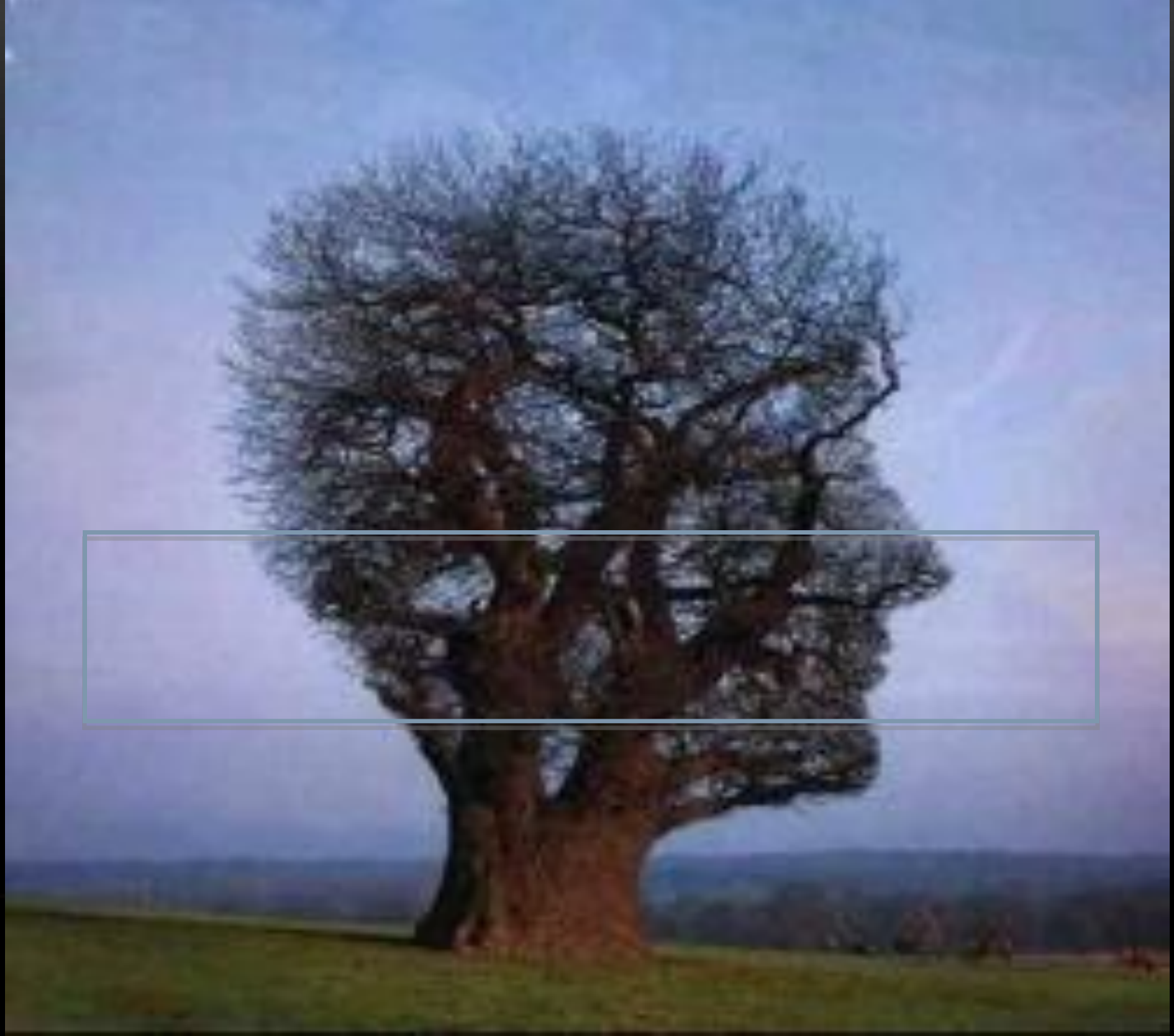
2. I nostri risultati consentono di confermare l'efficacia della diagnosi clinica della sindrome di Marfan

3. E' possibile limitare le indagini più costose ai casi effettivamente dubbi

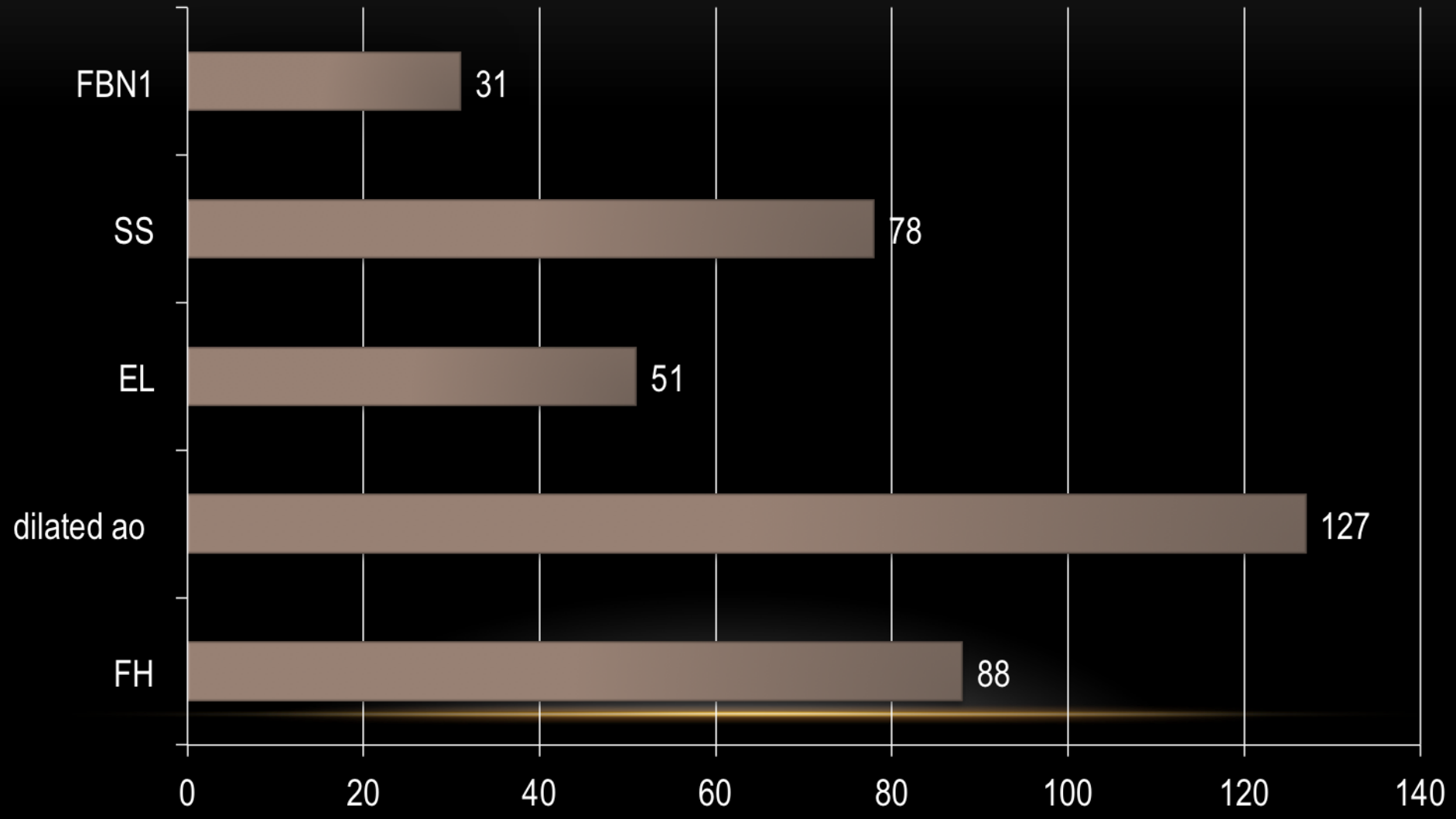
4. E' opportuno valutare uno scambio di informazioni tra registro e centro

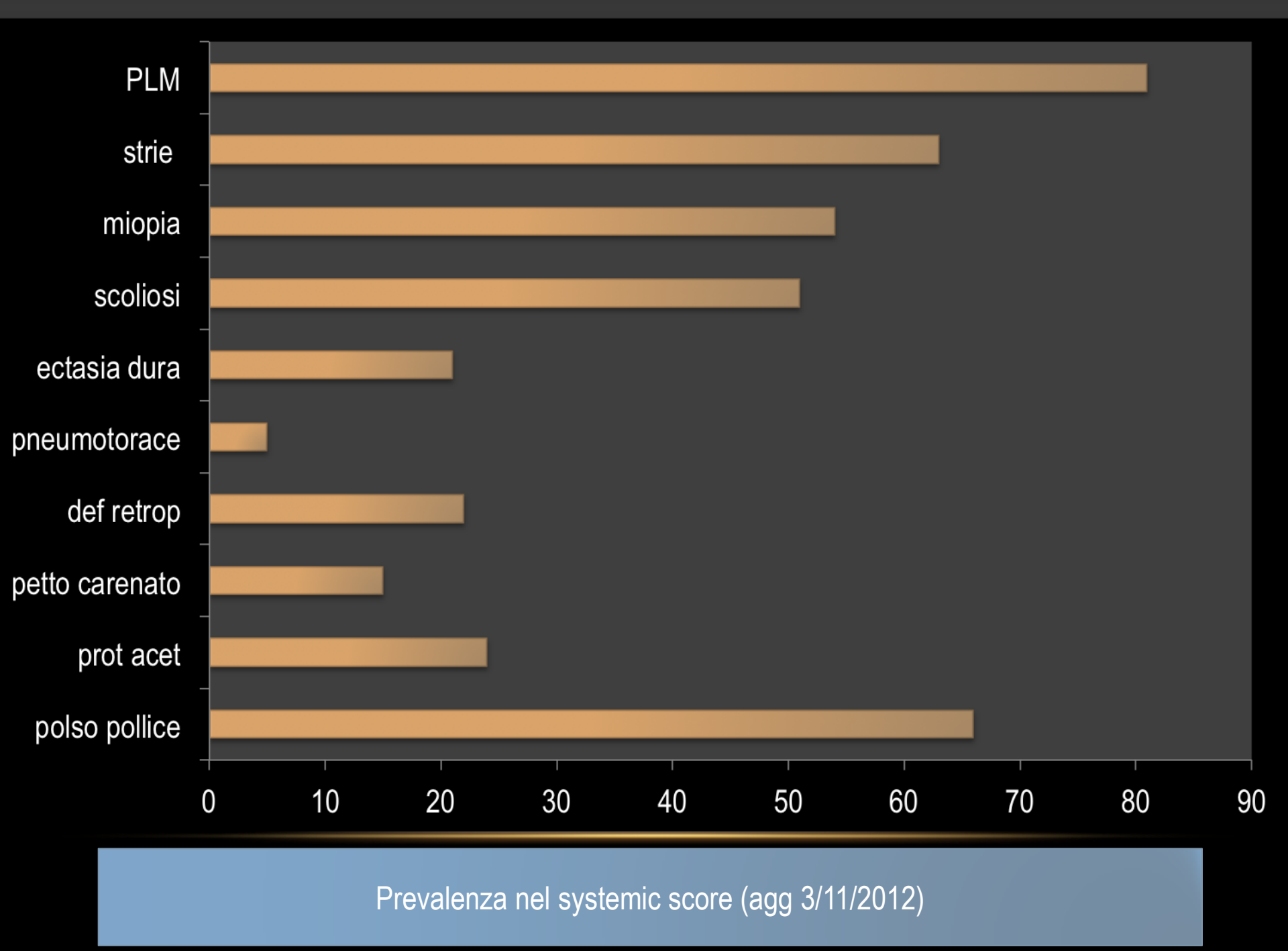
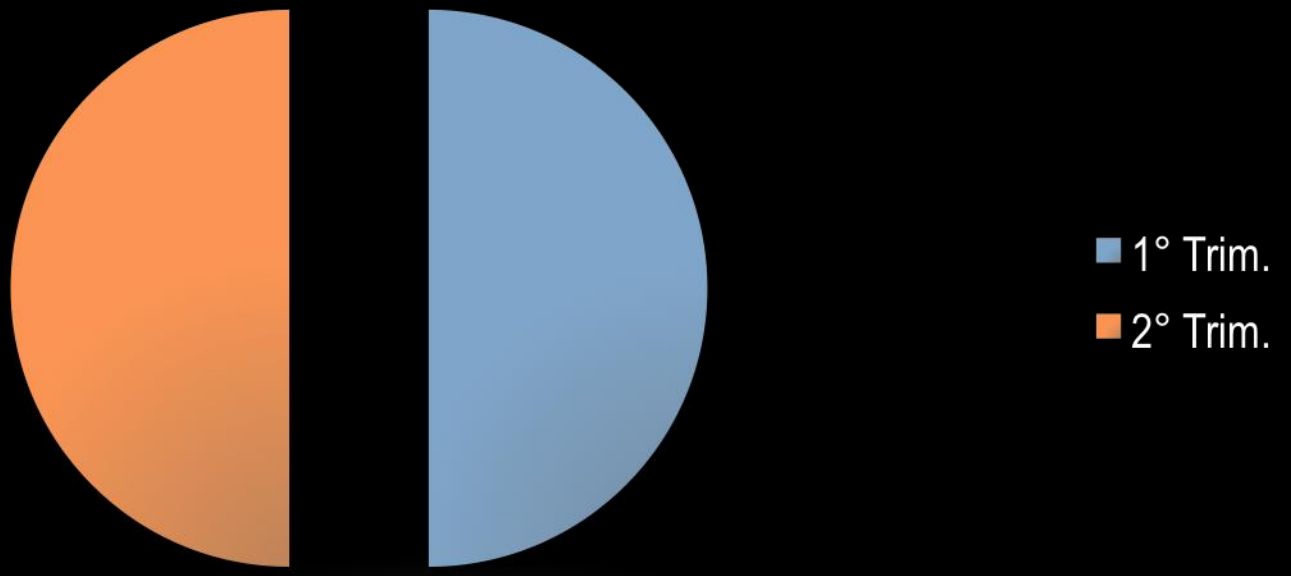
5. Le informazioni inserite dal centro possono essere più specifiche e servire ad una pianificazione della spesa regionale per ogni patologia.

CONCLUSIONI E CONSIDERAZIONI



PTV MARFAN PATIENTS DIAGNOSTIC CRITERIAS AGGIORNATO IL 3/11/12




PLM
strie
miopia
scoliosi
ectasia dura
pneumotorace
def retrop
petto carenato
prot acet
polso pollice
0
10
20
30
40
50
60
70
80
90
Prevalenza nel systemic score (agg 3/11/2012)

47% MASCHI E 53% FEMINE