Genetics in lymphoedema: Input into daily clinical practice

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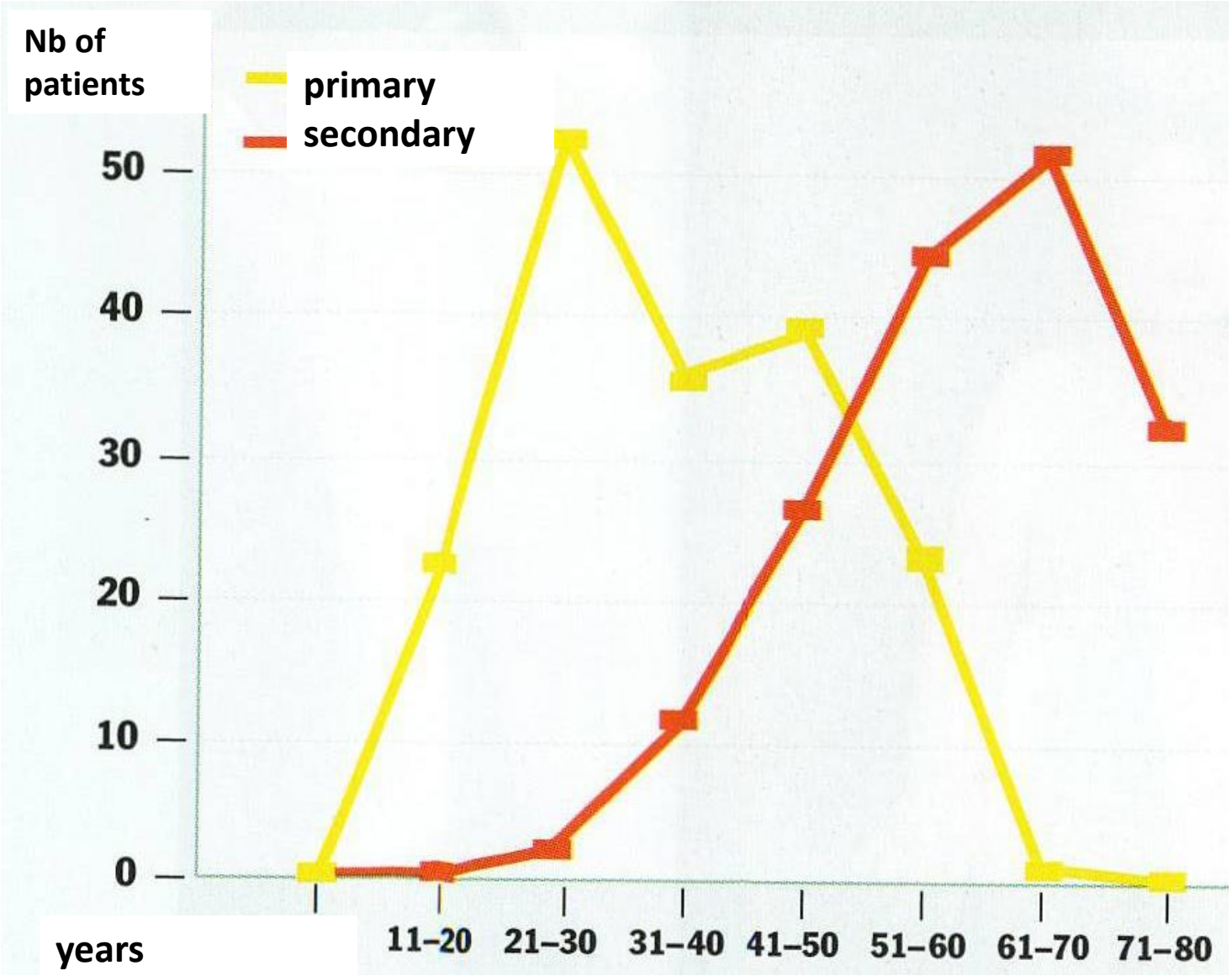
LYMPHOEDEMA



- A prevalence of lymphoedema is 1,33 per 1000 people
- The primary lymphoedema:10 – 20 % of all lymphoedemas
- A prevalence of primary lymphoedema is 1.15 per 100,000 people under 20 years of age

- The primary lymphoedema: sporadic (90%), hereditar (10%) – gens malformation

CLASSIFOCATION OF PRIMARY LYMPHOEDEMAS

- 3 types
- congenital
- precox
- tarda

YESTERDAY

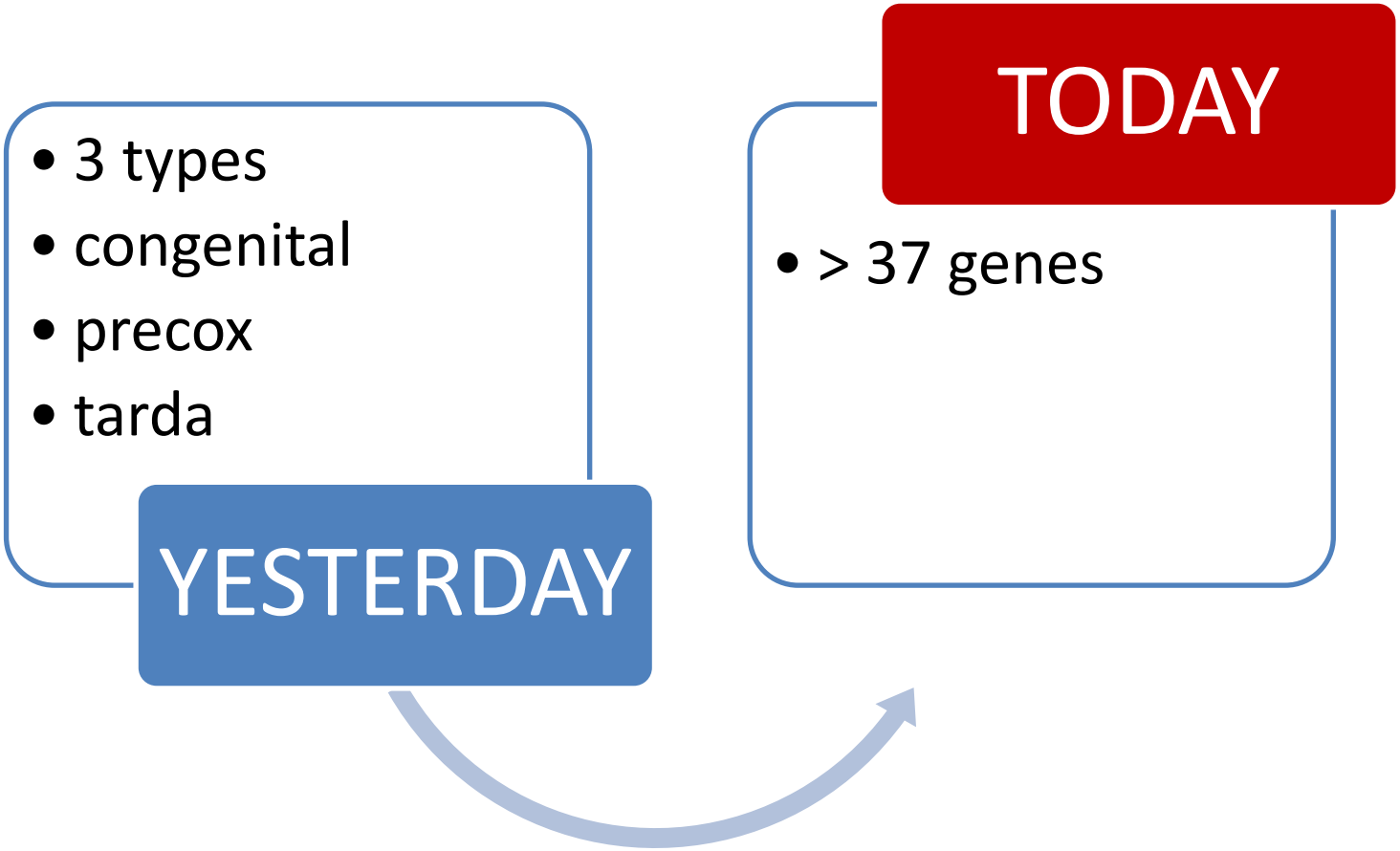
Allen. Classification, aetiology and differential diagnosis: a study of 300 cases. Arch Intern Med 1934; 54: 606-624

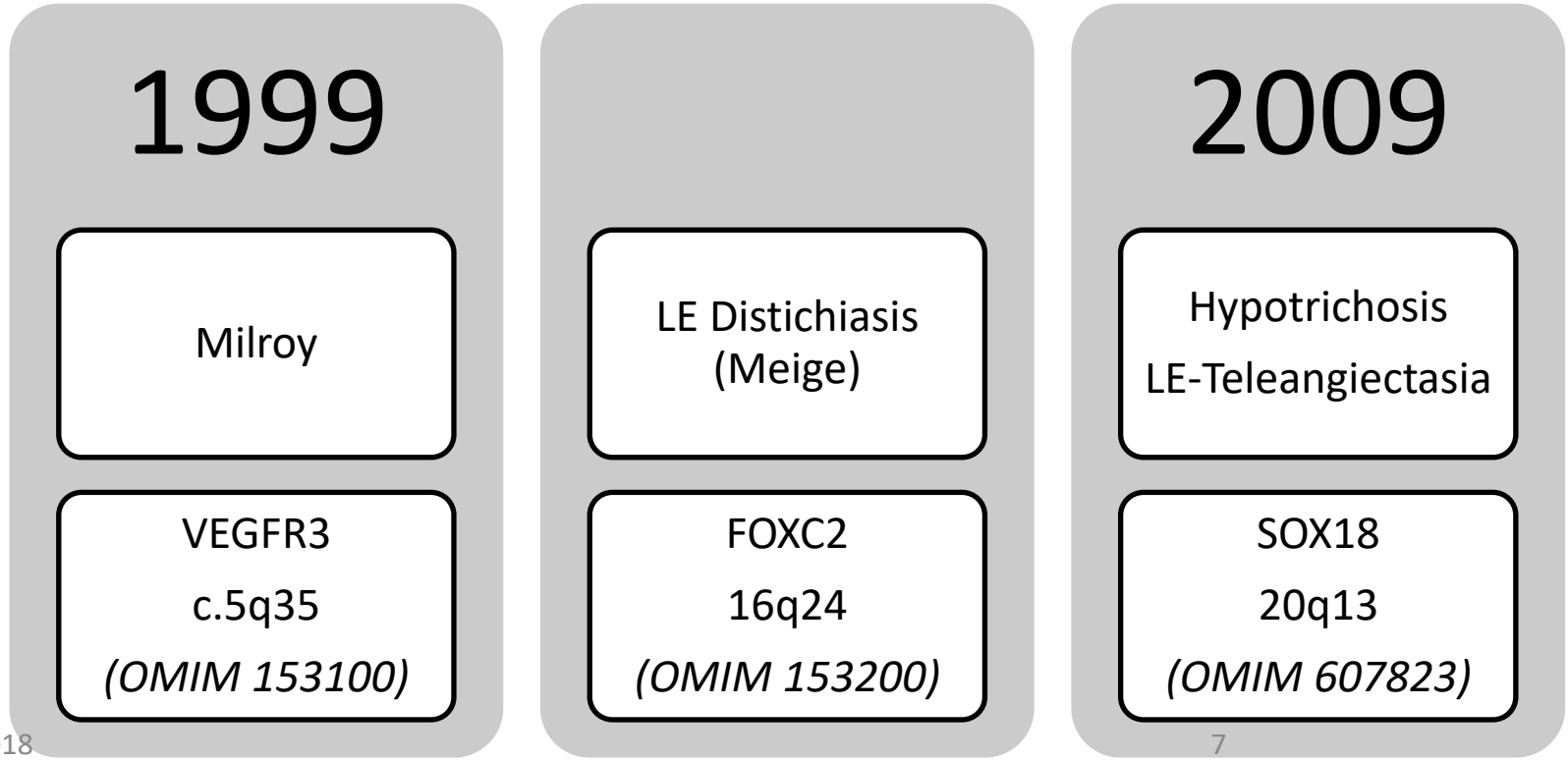
Kinmonth et al. Primary Lymphoedema: clinical and lymphangiographic studies… Br J Surgery 1957; 45: 1-10

LYMPHOEDEMA

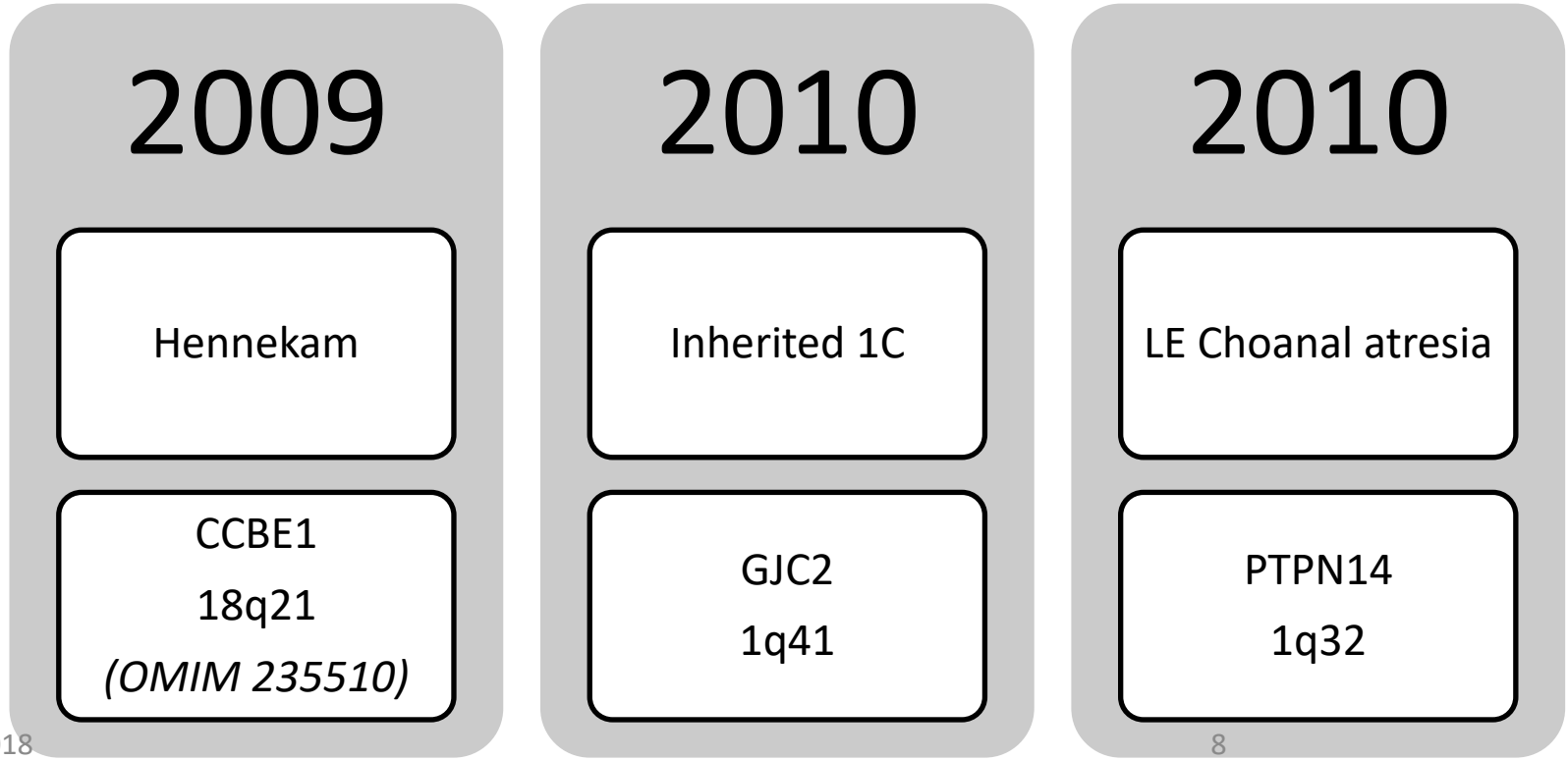
PRIMARY			SECONDARY		
HEREDITARY SPORADIC	SYNDROMS		MALIGNANT	BENIGN	
AT BIRTH CHILD	ADULT	CHILD	PRIMARY TUMOR METASTASES RECURENCES	RADIOTHERAPY SURGERY	INFECTION INJURYS …

CLASSIFICATION OF PRIMARY LYMPHOEDEMAS





Ostergaard et al 2010 ;



Ostergaard et al 2010 ;

LYMPHOEDEMA

- VEGFR3
- FOXC2
- SOX18
- GJC2,
- GATA2
- NEMO (1KBKG)
- CCBE 1
- PTPN11
- TSC1, 2
- KRAS
- RAF1
- VG5Q-AGGF1
- CHD7
- PLOD1
- RELN
- FGD1
- FABP,
- NRP2,
- SOX17
- VCAM1
- SOS1
- NRAS
- BRAF
- Mutation on chrom. X
- and more

Karkkainen et al. 2000 ; Brice G et al. 2005; Mellor et al 2007 ; Ostergaard et al 2010 ; Feingold et al 2010

- Turner sy.
- Klippel Weber Trenaunay sy.
- Noonan sy.
- Melkerson-Rosenthal-Miescherjov sy.
- Bonnevie-Ullrich sy.
- Maffucci sy.
- Yellow nail sy.
- Prader-Labhart-Willi sy.
- »Congenital limb ring constrictions« sy.
- Gorlin-Goltz sy.
- »Lymhoedema-Cholestase« sy.
- Proteus, CLOVE

Ostergaard et al 2014 ;

GENERALISED LYMPHATIC DYSPLASIA

- Intestinal lymphangiectasiae
- Ascytes
- Chylous effusions
- Pulmonary lymphangiectasiae
- Pleural effusions
- Pericardial effusions
- Hydrops fetalis

Ostergaard et al 2014

- **Primary lymphoedema present at birth**
- **Late onset lymphoedema**
- **Syndromic primary lymphoedema**
- **Very rare syndromic primary lymphoedema**
- **Congenital Vascular Malformations with Associated Lymphoedema**
- **Primary or secondary lymphoedema ?**

Primary lymphoedema present at birth

- *Milroy Disease (OMIM 153100)*: mutation in the gene for VEGFR3 (also known as FLT4) which is the receptor for vascular endothelial growth factor C (VEGFC)

Abnormality	Percentage
Oedema of lower limbs usually from birth	90 %
Episodes of cellulitis	20 %
Large caliber leg veins	23 %
Papillomatosis	10 %
Up-slanting toenails	10 %
Hydrocoele	37 % of males

- absence or paucity of lymphatic trunks
- abnormal distribution of collectors
- lymphatic reflux and incompetence
- variable uptake by lymph nodes
- mixed lymphatic and blood vascular disturbances

Meige Disease

• presents in adolescence or adulthood
• the lower limbs and there are no associated abnormalities.
• Because of the uncertainties described here, there is no clear picture of the lymphatic abnormality in Meige disease.
• Aplasia and hypoplasia of the peripheral lymphatic with dilation of lymph trunks has been described.

Lymphoedema Distichiasis Syndrome

The lymphatic abnormality seems to be related to reflux in the lower limb lymphatics with an increased number of vessels apparen

- Distichiasis (92%)
- Early onset varicose veins (49%)
- Ptosis (31%)
- Congenital heart disease (8%)
- Cleft palate (4%)
- Spinal cysts

Four limb late onset lymphoedema

- four limb oedema and varicose veins, but no other associated abnormalities.

Hennekam syndrom

- syndrome with intestinal lymphangiectasia,
- severe lymphoedema of the limbs, genitalia and face
- and severe mental retardation.
- Facial anomalies included flat face, flat nasal bridge, hypertelorism, epicanthal folds, small mouth, tooth anomalies and ear defects.

Syndromic primary lymphoedema

- - ***Turner Syndrome***: a missing or incomplete second X chromosome (X0); partial Xp deletions (region Xp11.4).
  - ***Noonan Syndrome*** *(OMIM 163950):* the mutations in the RAS-MAP-kinase pathway; a mutation of the gene PTPN11 on chromosome 12q24 which encodes for the non-receptor protein tyrosine phosphatase SHP2; a mutation of the SOS1 gene which encodes for a guanine nucleotide exchange factor for Ras- a key regulator of cell growth, and is part of the Ras-MAPK (mitogen-activated protein kinases) signalling cascade. The protein encoded by PTPN11 is also part of this cascade; NRAS, KRAS, RAF1 and BRAF.
  - ***Emberger Syndrome*** *(Primary lymphoedema, myelodysplasia, acute myeloid leukaemia and deafness)*: The causative gene is GATA2.
  - ***Lymphoedema, microcephaly, chorioretinopathy syndrome*** *(OMIM 152950)*
  - ***Tuberous Sclerosis*** *(OMIM 191100)*: the affected genes are TSC1 (on chromosome 9q34) and TSC2 (on chromosome 16p13) encoding hamartin and tuberin respectively. Lymphangioleiomyomatosis (LAM) is a rare lung condition; caused by mutations in TSC2.

Noonan Syndrome

- hypertelorism, down slanting palpebral fissures,
- low set posteriorly rotated ears, short stature,
- short neck with webbing or redundancy of skin,
- cardiac anomalies particularly pulmonary stenosis or hypertrophic cardiomyopathy
- deafness
- and a bleeding diathesis

Emberger Syndrome

- primary lymphoedema of the lower limbs and genitalia in late childhood
- with haematological anomalies (myelodysplasia progressing to acute myeloid leukaemia),
- immunodeficiency with a propensity to warts and deafness.

Prader-Willi Syndrome

- include obesity,
- muscular hypotonia,
- learning difficulties,
- short stature,
- hypogonatrophic hypogonadism
- and small hands a feet

Congenital Vascular Malformations with Associated Lymphoedema

- Klippel-Trenaunay Syndrome (OMIM 149000): mutation in VG5Q (also known as angiogenic factor with G patch and FHA domains 1, AGGF1)
- CLOVE Syndrome (OMIM 612918)
- Wild Syndrome
- Proteus Syndrome (OMIM 176920)

Klippel-Trenaunay Syndrome

- large cutaneous haemangiomata with hypertrophy of the related bones and soft tissues.
- It is often in a “quadrantic” distribution (i.e. involves one limb and adjacent trunk).
- Venous varicosities are present in about 80% but no obvious major arteriovenous fistulae.
- Lymphatic malformations

CLOVE syndrome

- by progressive, complex and mixed truncal vascular malformations,
- disregulated adipose tissue associated with congenital lipomatous overgrowth and epidermal naevi.
- It may be associated with varying degrees of scoliosis and enlarged bony structures.
- Cranial asymmetry and central nervous system manifestations such as generlised seizures, hemimegalencephaly and dysgenesis of the corpus callosum have been described.

Wild Syndrome

- viral Warts,
- a depressed cell-mediated Immunity,
- primary Lymphoedema and
- anogenital Dysplasia

Proteus Syndrome

- a severe disorder of asymmetric and disproportionate overgrowth of body parts,
- connective tissue naevi,
- epidermal naevi and
- disregulated adipose tissue
- vascular malformations.

PRIMARY OR SECONDARY LYMPHOEDEMA?

Primary or secondary lymphoedema ?

- *1. Yellow nail syndrome (OMIM 153300)*
  2. Post-cellulitic lymphoedema
  3. Inguinal node fibrosis
  4. Genetic predisposition to lymphoedema: four candidate genes (FABP, NRP2, SOX17 and VCAM1) mutations and mutations in the HGF/MET pathway
  5. Congenital but secondary lymphoedema (OMIM 217100)

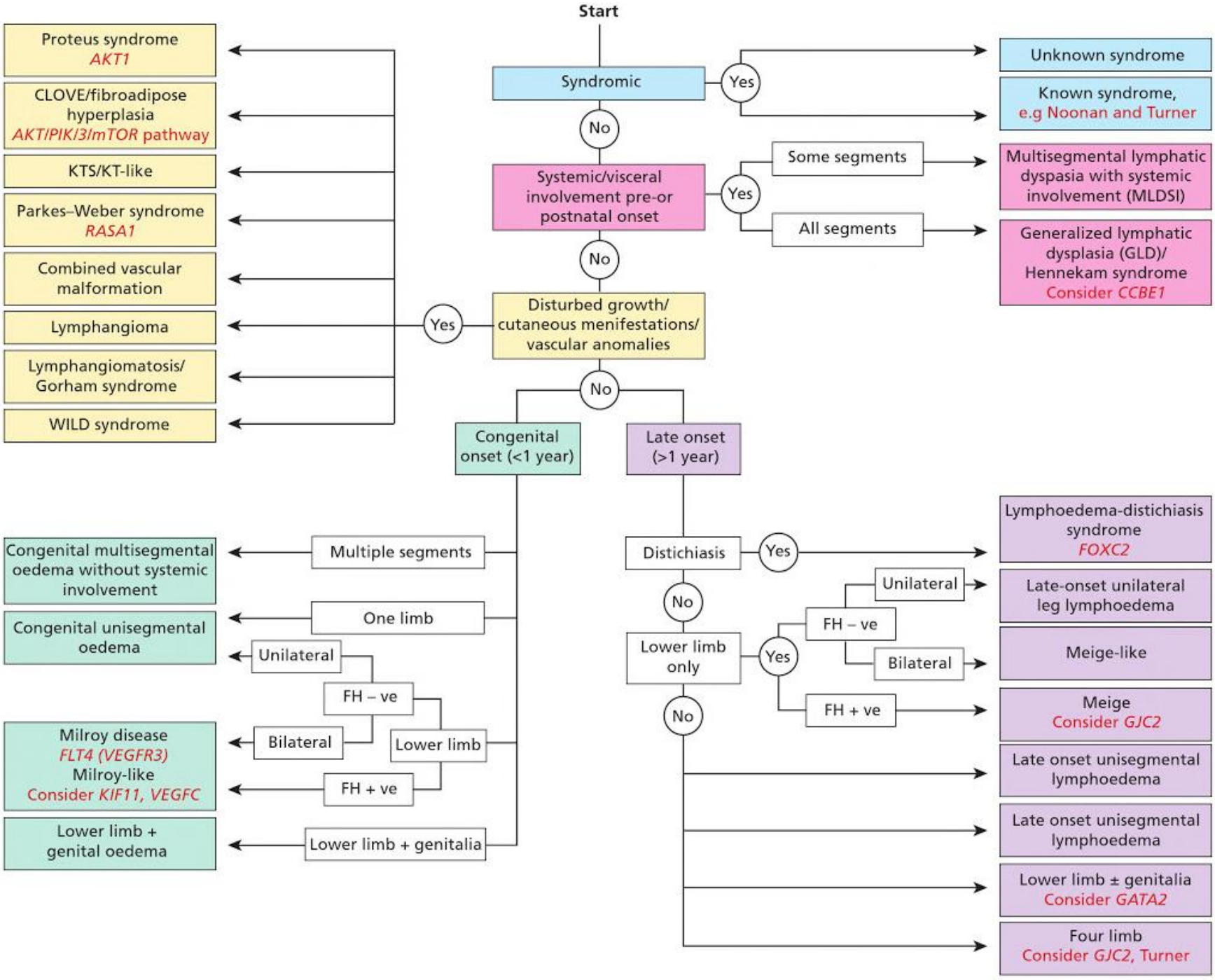
YELLOW NAIL SYNDROME

- thick dystrophic yellow nails which are excessively curved from side to side
- lymphoedema of the legs (in 80% of patients)
- exudative pleural effusions (in 36% of patients)

CONGENITAL BUT SECONDARY LYMPHOEDEMA

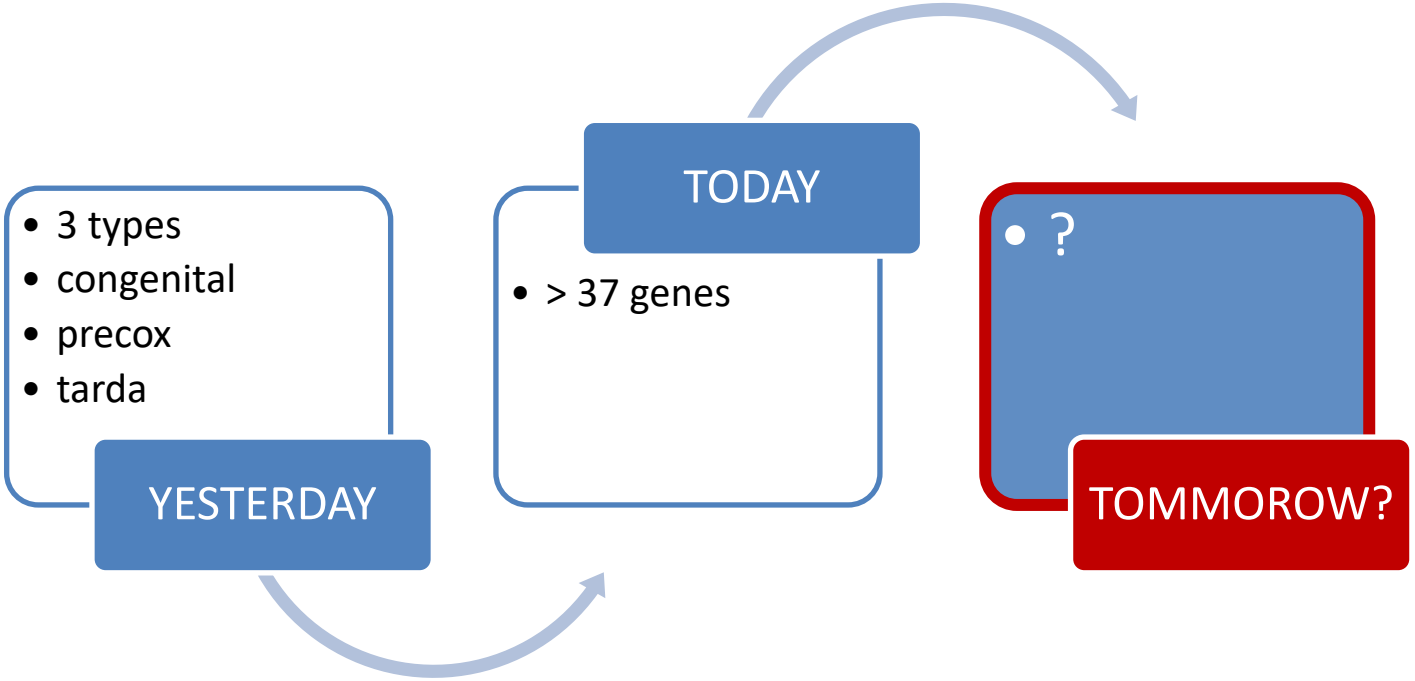
(OMIM 217100)

Constricting amniotic bands may cause amputation of various body parts, but also due to ring constrictions can cause lymphoedema


Start
Syndromic
Yes
Unknown syndrome
Known syndrome, e.g Noonan and Turner
No
Systemic/visceral involvement pre-or postnatal onset
Yes
Some segments
Multisegmental lymphatic dysplasia with systemic involvement (MLDSI)
All segments
Generalized lymphatic dysplasia (GLD)/ Hennekam syndrome Consider CCBE1
No
Disturbed growth/ cutaneous menifestations/ vascular anomalies
Yes
Proteus syndrome AKT1
CLOVE/fibroadipose hyperplasia AKT/PIK/3/mTOR pathway
KTS/KT-like
Parkes–Weber syndrome RASA1
Combined vascular malformation
Lymphangioma
Lymphangiomatosis/ Gorham syndrome
WILD syndrome
No
Congenital onset (<1 year)
Late onset (>1 year)
Multiple segments
Congenital multisegmental oedema without systemic involvement
One limb
Congenital unisegmental oedema
Unilateral
FH – ve
Bilateral
Lower limb
Milroy disease FLT4 (VEGFR3) Milroy-like Consider KIF11, VEGFC
FH + ve
Lower limb + genital oedema
Lower limb + genitalia
Distichiasis
Yes
Lymphoedema-distichiasis syndrome FOXC2
No
Lower limb only
Yes
Unilateral
Late-onset unilateral leg lymphoedema
FH – ve
Bilateral
Meige-like
FH + ve
Meige Consider GJC2
No
Late onset unisegmental lymphoedema
Late onset unisegmental lymphoedema
Lower limb ± genitalia Consider GATA2
Four limb Consider GJC2, Turner

Genetic analysis

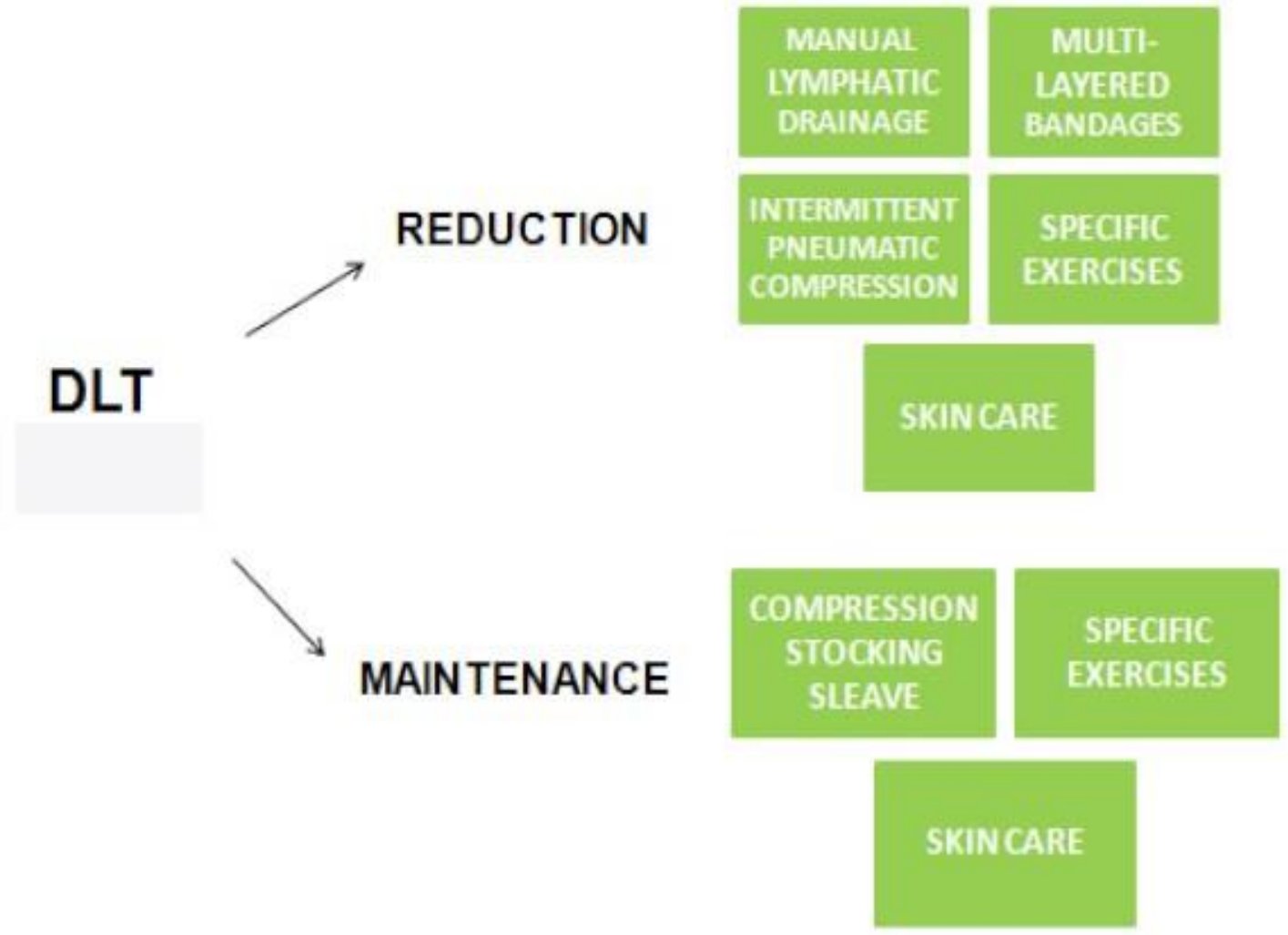
CLASSIFICATION OF PRIMARNY LYMPHOEDEMOAS



Therapy

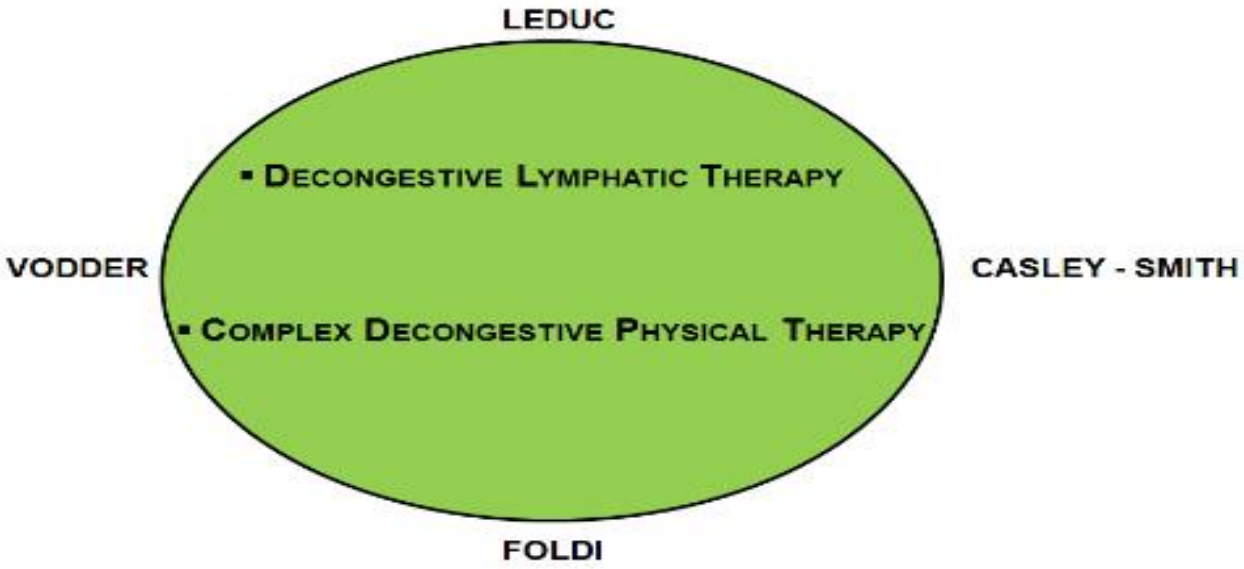
- To prevent complications

Therapy of lymphoedema



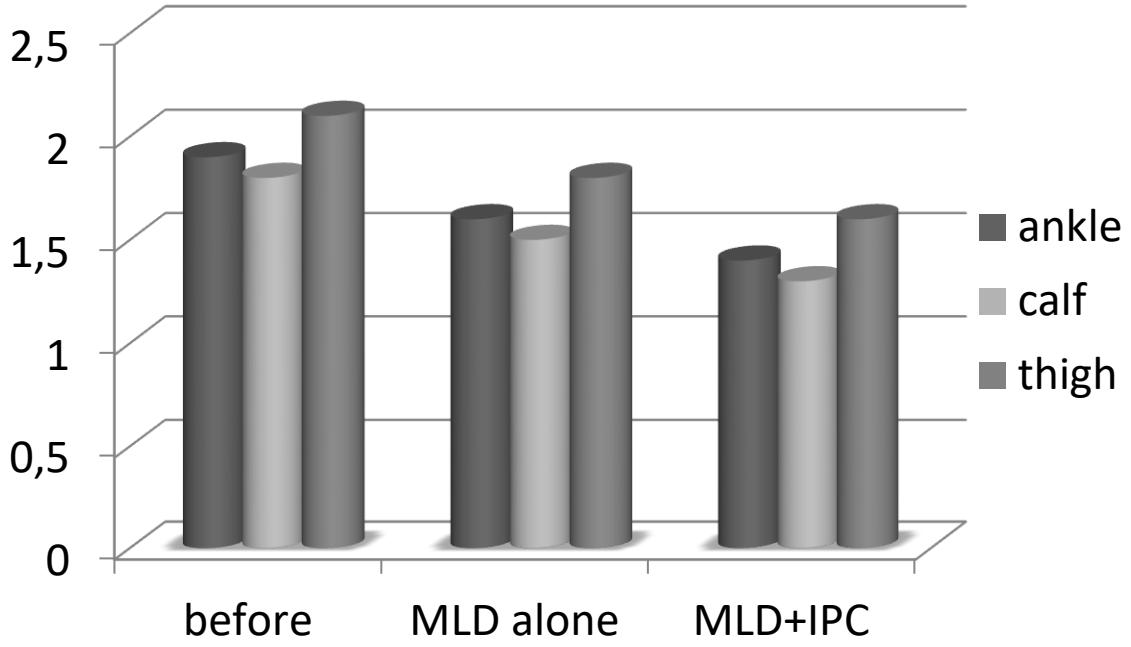
MLD

The four largest lymphoedema schools worldwide share the same philosophies : they suggest different handling on MLD techniques and ways to apply the multilayer bandages, but they all propose a two-stage treatment regime that includes a reduction phase and maintenance phase.



Nuno Duarto, Sophia Jordao dos Santos, 2011

The current evidence from RCTs does not support the use of MLD in preventing or treating lymphoedema



Huang, et al. Effects of manual lymphatic drainage on breast cancer-related lymphoedema: a systematic review and meta-analysis of randomized controlled trials. World journal of surgical oncology 2013

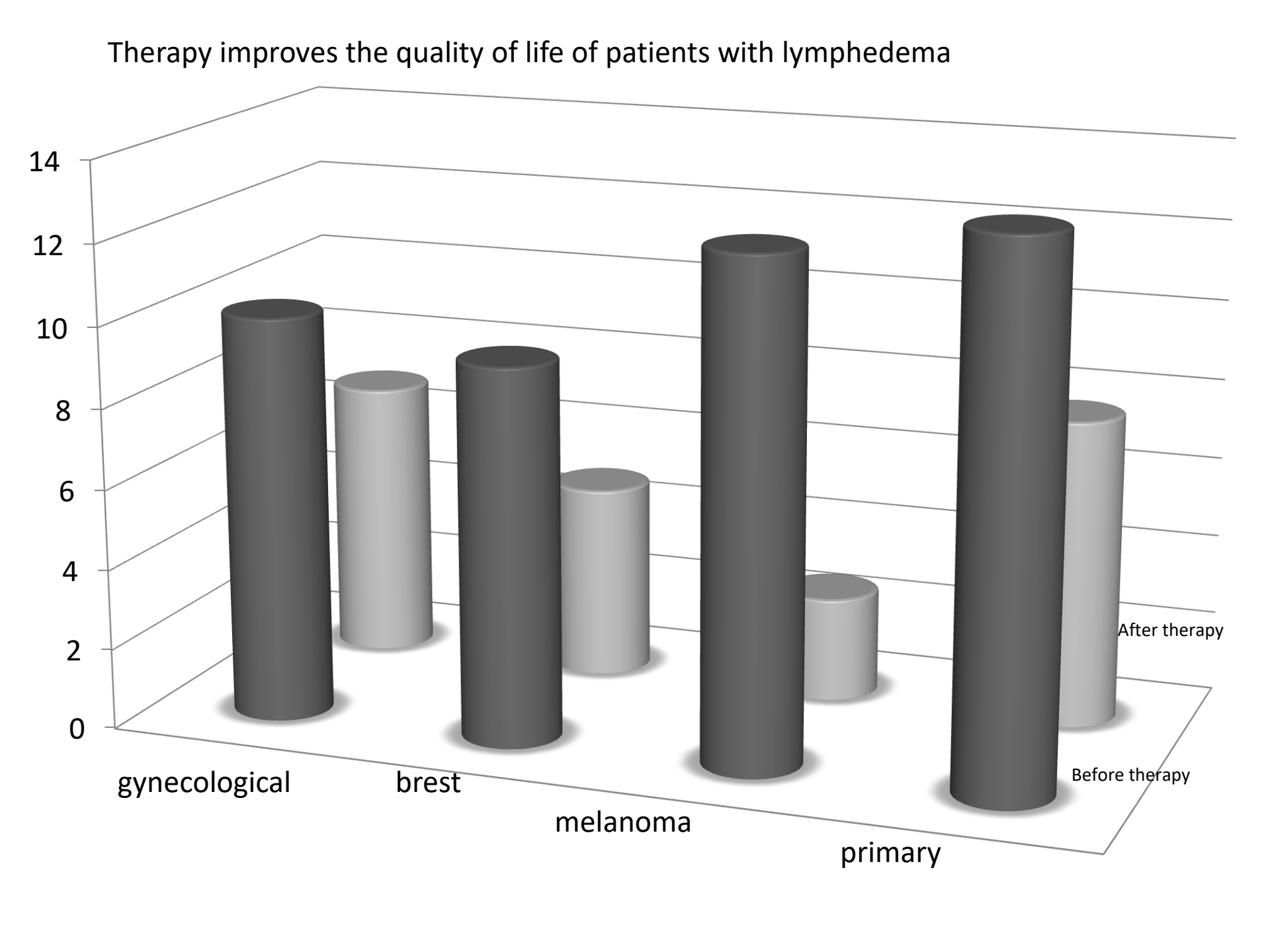
Iker, Glass. How to objectively access results of lymphoedema treatment, ISL congress, 2014

	H2O	Proteins
MLD	+	++
Intermittent Pneumatic Compression	++	+
Multi-Layered Bandages	++	++

Nuno Duarto, Sophia Jordao dos Santos, 2011

stocking	compression	Indication
class I, flat	18 – 21 mmHg	children; toes
class II, round	23 - 33 mm Hg	lymphoedema st.I
class III, round	34 - 46 mm Hg	lymphoedema st. II
class III, flat	34 - 46 mm Hg	lymphoedema st. III
class IV, flat	>46 mm Hg	lymphoedema st. III

sleeves	compression	Indication
class I, round	18 - 22 mm Hg	lymphoedema st. I
class I, flat	18 - 22 mm Hg	lymphoedema st. I at children
class II, round	23 - 33 mm Hg	lymphoedema st. II
class II, flat	23 - 33 mm Hg	lymphoedema st. III
class I (II), flat	18 - 22 mm Hg, (23 - 33 mm Hg)	fingers


Therapy improves the quality of life of patients with lymphedema
14
12
10
8
6
4
2
0
gynecological
brest
melanoma
primary
After therapy
Before therapy

Genetic counseling

For the future: GENS THERAPY

- An understanding of the genetic of primary lymphoedemas is the option of gene therapy for patients with primary and even secondary lymphoedemas.

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