

**FDRS 2023 April 14-16**



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RESOURCE SOCIETY

# Looking to the Future: a Roadmap for Lipedema Research

**Guy Eakin, PhD**  
Lipedema Foundation

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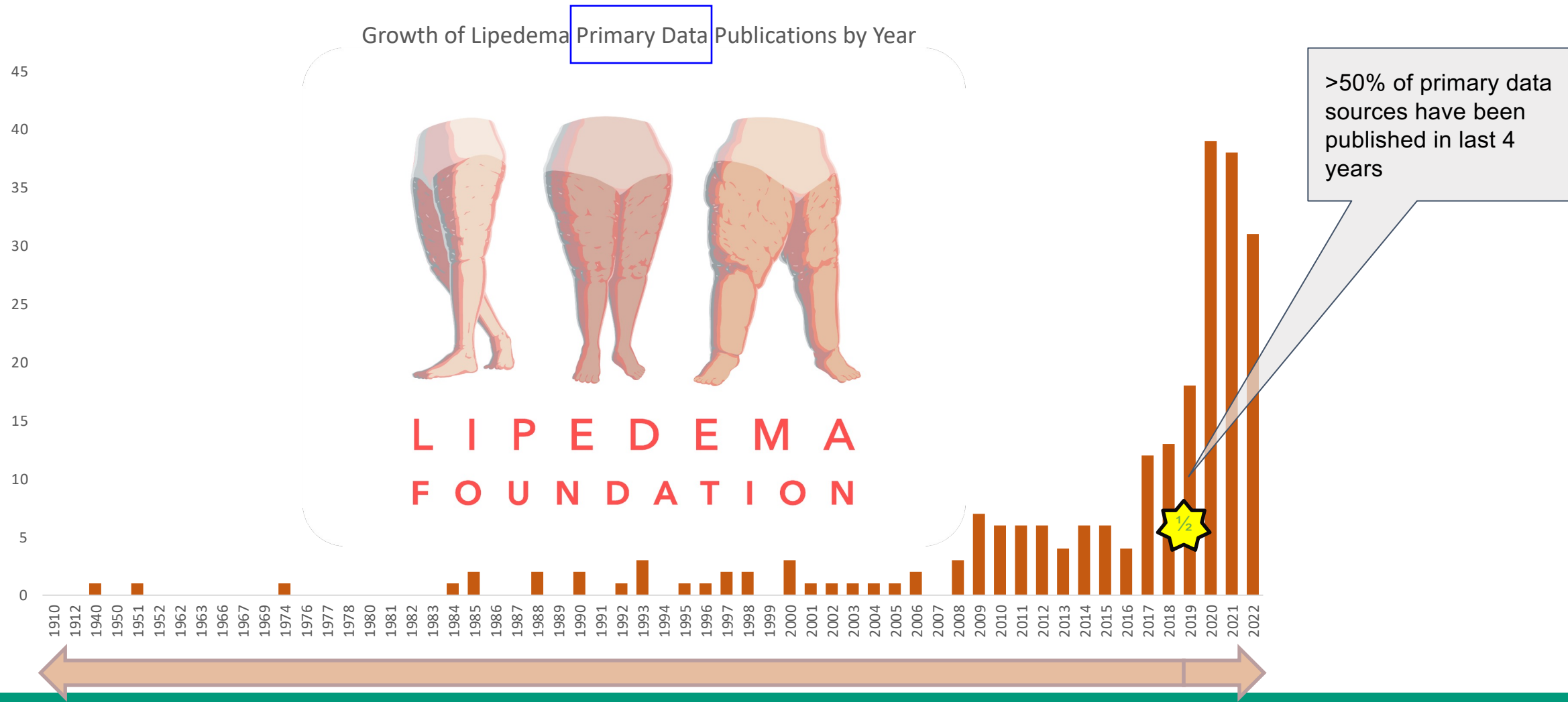
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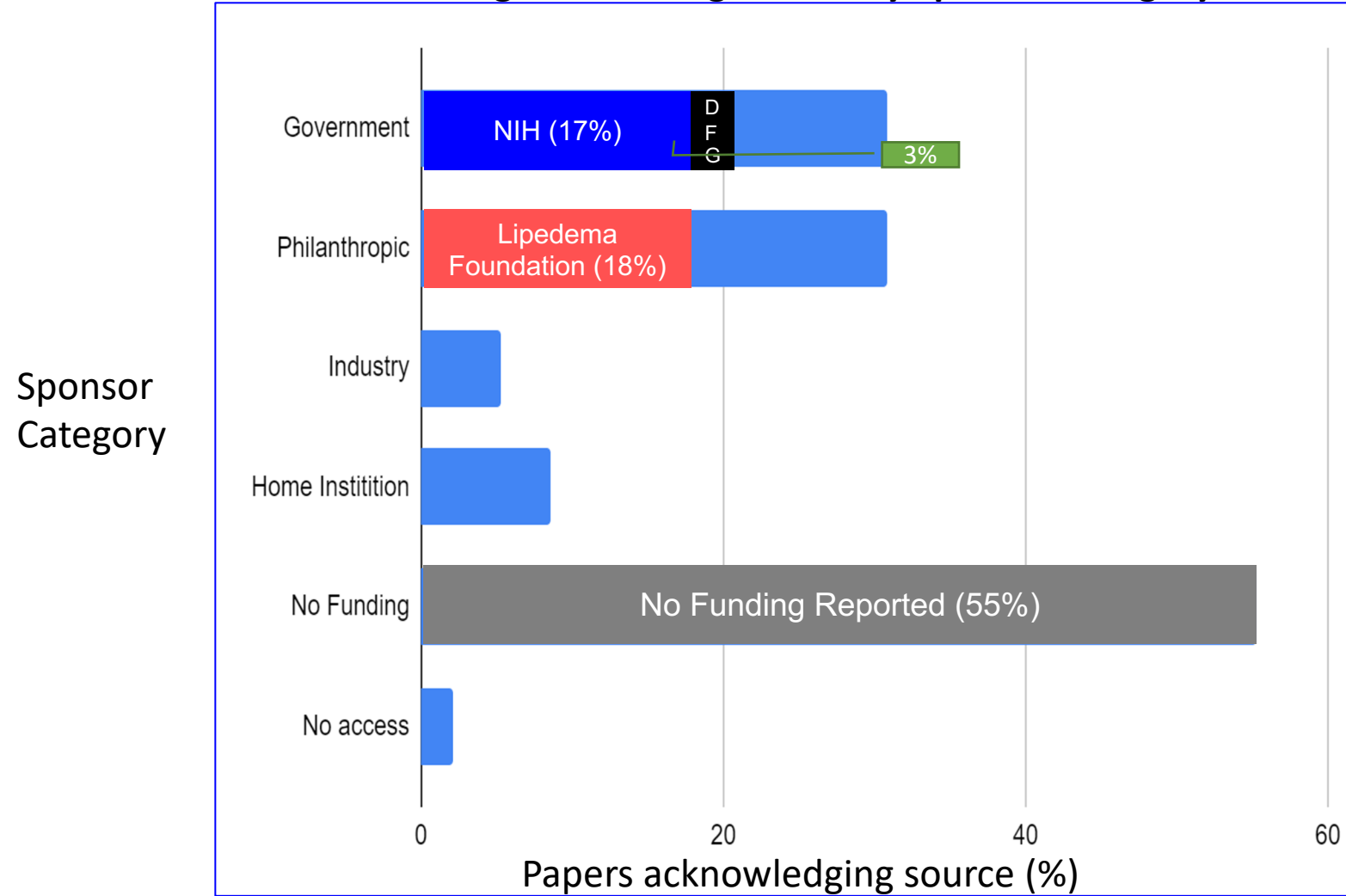
# Is a Renaissance in Lipedema Research Coming?

## Is it already here?



# Few Funders, Few Funded Studies

## Funding acknowledgements by Sponsor Category



N=94 papers examined



# Challenges To Lipedema Research

- **Reliance on a clinical diagnosis**
  - Symptoms vary between patients
  - multiple diagnostic criteria in use.
- **Intrinsic challenges to recruiting study participants**
  - Low awareness of lipedema in patient, clinical, and research communities
- **Lack of natural history knowledge,**
  - especially with respect to demographic and phenotypic diversity
- **Lack of Lipedema-directed funding amongst traditional research funders**
- **Lack of enabling infrastructure**



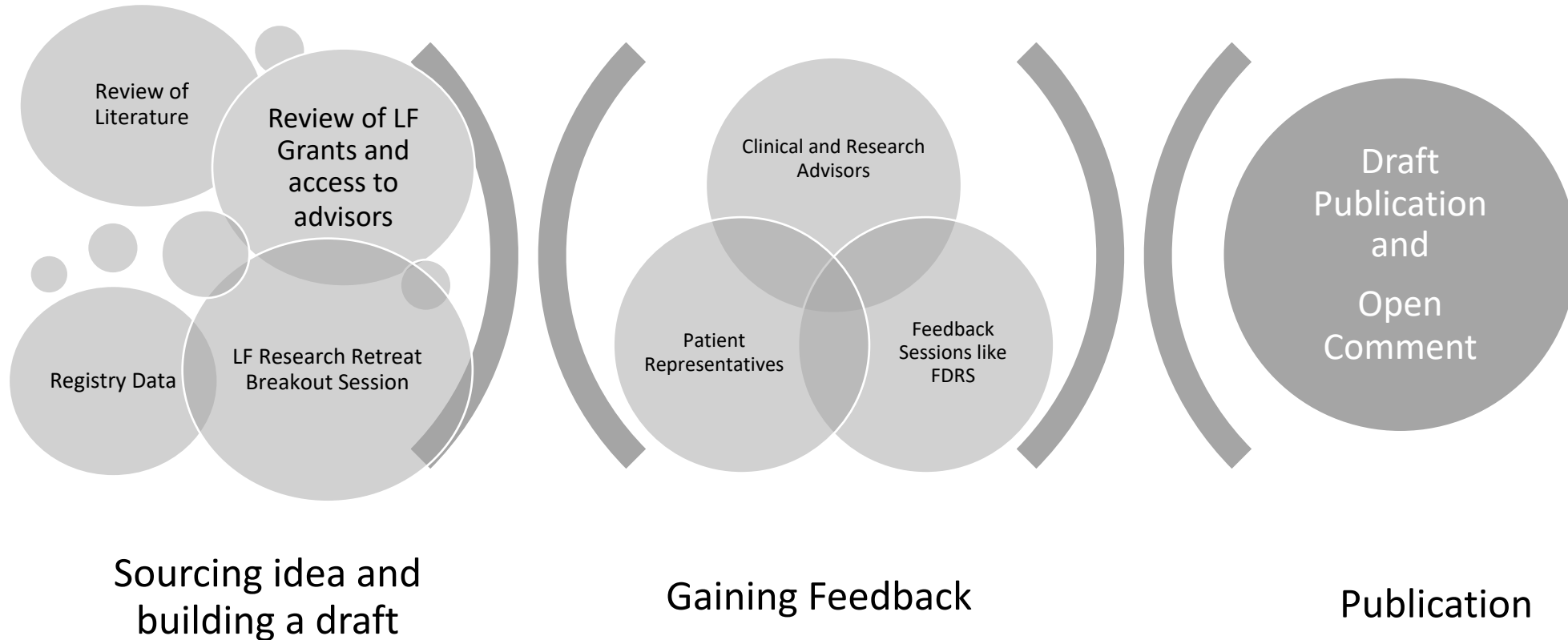
## Summary

- Small Community
- Limited Resources
- Significant Challenges
- Important Mission

Suggests need for coordination of the research agenda – a Lipedema Research Roadmap

- But where to begin?

# The LF Approach to Defining a Multi-Stakeholder Research Roadmap





# Organization of the Roadmap

## Environment

- Build the workforce and infrastructure that (with patients!) will help solve Lipedema

## Developing Standards for the field

- Bring precision to vocabulary, common data elements, SOP

## Develop Diagnostic Tools

- Nurture a pipeline of technologies aimed at improving diagnosis

## Characterize Biology of Disease

- Challenge dogma and better characterize the factors that initiate Lipedema and cause it to progress

## Develop Treatments

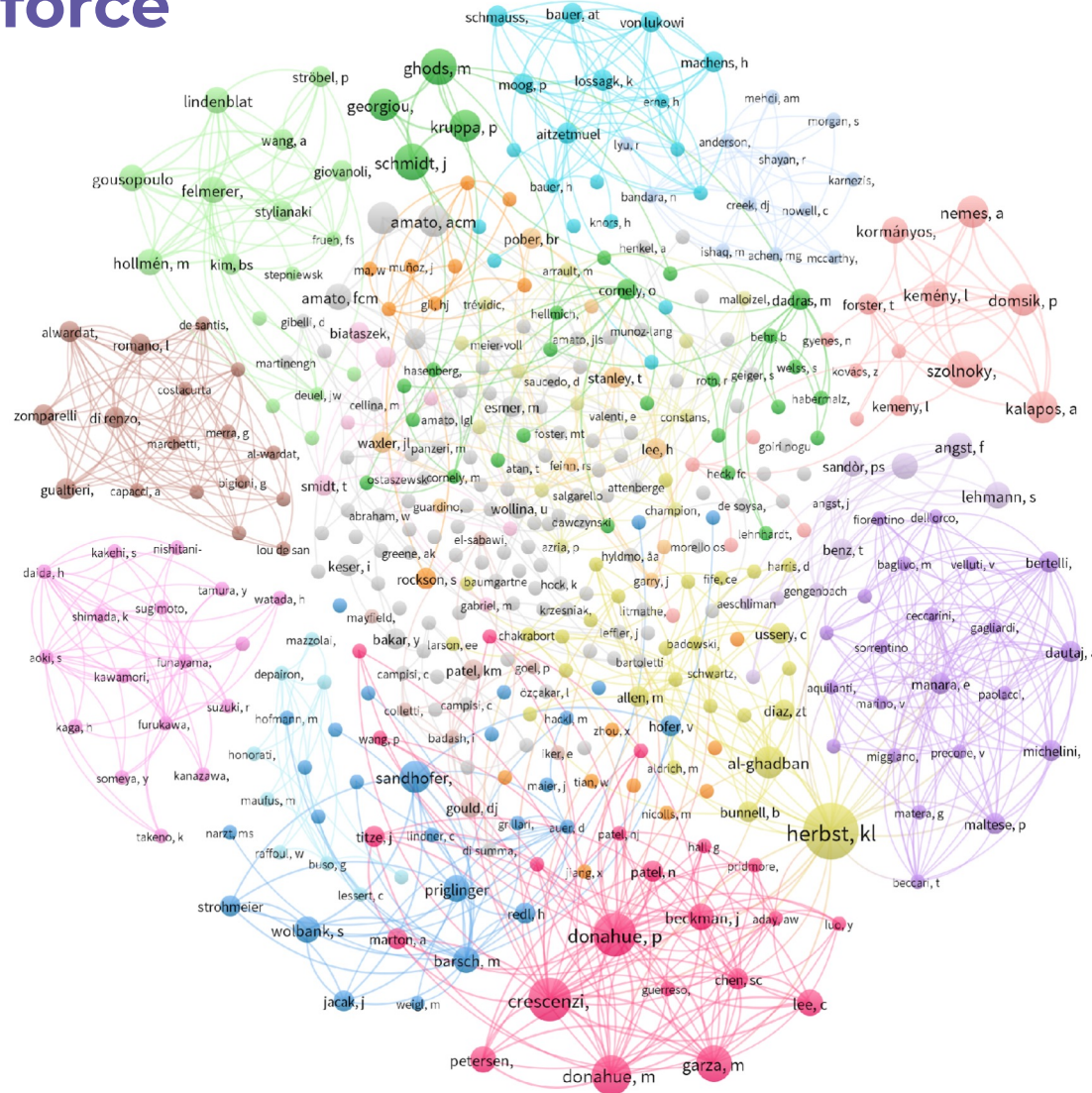
- Gather data on currently used treatments, and ensure that clinical research focuses on outcomes that matter most to people with Lipedema

## Epidemiology

- Broaden concept of epidemiology to more than prevalence of disease



# Lipedema Research Environment: Small and Modestly Integrated Workforce



PubMed Records of **Primary Data** Publications Studying Lipedema

Last 5 years (Jan/2017 – Oct/2022)

89 published papers

N= 408 authors

~40 collaborative clusters





# Lipedema Research Environment: Summary of Challenges and Recommendations

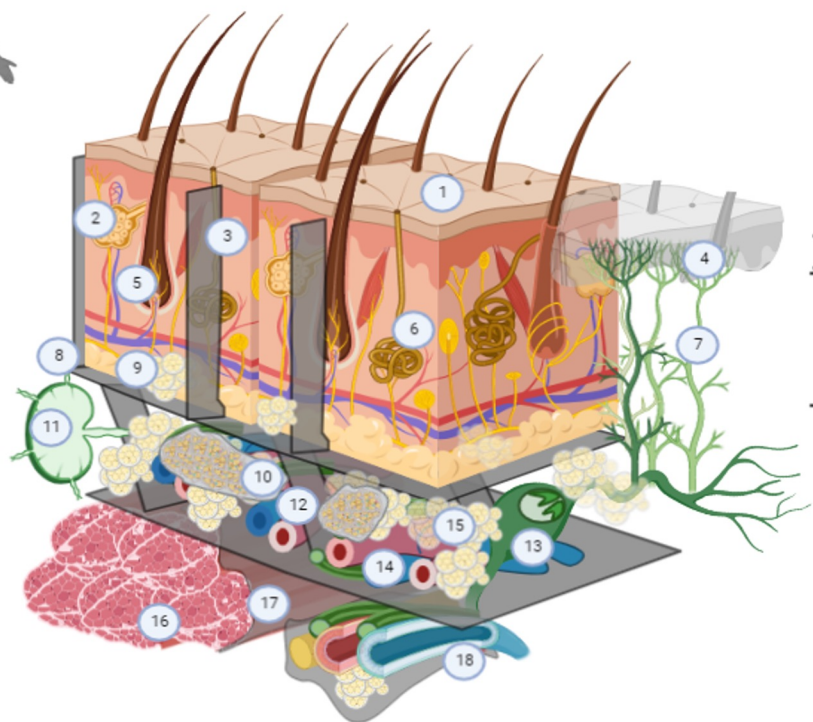
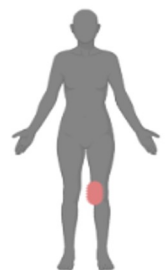
## Challenges to Overcome

- The workforce is small
- Barriers to entry
  - Funding
  - Mentorship and Training
- Comparatively little data in field

## Strategic Recommendations

- Improve the Lipedema Workforce
- Bring new Funding to the field
- Support collaboration and knowledge exchange
- Build and sustain research infrastructure
- Empower and Engage Patients
- Import successful technologies to Lipedema

# Developing Standards for the Field



1. Epidermis
2. Sebaceous gland
3. Skin ligaments, reticulum cutis superficialis
4. Dermal lymphatic capillaries, lymphatic plexus (associated watershed in gray)
5. Follicle
6. Sweat gland
7. Lymphatic precollectors and collectors
8. Subcutaneous fascia, Scarpa's fascia, superficial fascia
9. Subcutaneous adipose tissue (SAT)
10. Dense fibrotic adipose, lipedema-related nodular structures
11. Lymph node
12. Reticulum cutis profundus
13. Lymphangion, lymphatic valve
14. Superficial vascular structures
15. Deep Adipose Tissue (DAT)
16. Muscle
17. Muscular fascia and investing fascia
18. Deep vasculature
19. Dermal layer
20. Hypodermal layer
21. Subcutaneous layer
22. Muscular layer

Created in [BioRender.com](https://www.biorender.com)

## Development of Common Case Report Form

### Basic Demographic Information:

- Sex assigned at birth
- Race
- Ethnicity
- Age
- Height
- Weight
- Waist Measurement
- Hip Measurement
- Calculated fields: BMI, WHtR, WHR

### Clinical information:

- Date of last menstrual cycle
- Menstrual cycle status (before puberty, puberty, menstruating, perimenopausal, menopause, post-menopausal)
- Consider FSH levels

### Stage of Lipedema

- Concomitant medication list

### Medical Conditions or History:

- Obesity
- Diabetes (T1D, T2D)
- Hypertension
- Cholesterol (High Cholesterol, Dyslipidemia, Hyperlipidemia)
- Thyroid dysfunction (hypothyroidism, hyperthyroidism, other thyroid conditions not specified)

### Lymphedema

- MCAS
- POTS
- CVI
- PCOS
- Ehlers Danlos Syndrome – Hypermobility

### Patient History

- Age of onset
- Onset trigger [puberty, pregnancy, menopause, contraceptives, other, I don't know]
- Disease duration (yrs or range)

### Family History & Genetics

### Canonical Symptoms

- Symmetrical involvement
- Disproportionate fat distribution
- Cuffing at ankle or wrist / slender instep
- Spared feet and hands
- Distal fat tendrils of the knee (popliteus)
- None or limited weight loss in affected tissues
- Negative Stemmer's Sign
- Body Region involvement (arms (upper/lower), legs (upper/lower), abdomen, head)

### Swelling or edema

- Bruising
- Pain and/or tenderness to touch
- Fatigue
- Palpable presence of nodules
- Palpable changes to tissue texture

### Other Commonly Cited Symptoms

#### Dermatologic

- Softness
- Plasticity
- Cold/Temperature

#### Cardiovascular/Vascular

- Varicose veins
- Cellulite

#### Musculoskeletal

- Fatigue in limbs
- Heaviness in limbs
- Joint pain
- Range of motion/hypermobility
- Quadricep strength

#### Immunologic and Autoimmune

- Allergies and sensitivities

#### Neuropsychiatric

- Brain fog
- Migraines
- Sleep disturbances
- Depressive disorders
- Anxiety disorders



Illustration of  
Common CRF



# Developing Standards: Summary of Challenges and Recommendations

## Challenges to Overcome

- Studies use different criteria for staging and diagnosis
  - Uncertain how each applies to different patient populations
  - Practice to practice variation
- Reporting of inclusion and exclusion decisions varies across studies
- Publications often use imprecise language

## Strategic Recommendations

- Development of a common diagnostic criteria specifically for research
- Development of a common case reporting form
- Recommending certain field standards and reporting conventions

# Develop New Diagnostic and Biomarker Tools

MORPHOMETRY	Sub category	BMX Type	Measurement & Stage of Development	Modality		
			Ideation → Discovery → Analytic validation → Clinical validation → Qualification			
Body Shape		●●●●	Limb to whole body fat mass ratios	MRI, DEXA, 2D Perometry, 3D Contour Scanning, Bioimpedance		
		●●●●	Gynoid to android ratios			
		●●●●	WHR and WHR relative to BMI			
		●●●●	Circumference measurements			
		●●●●	Trunk to leg ratios			
		●●●●	Fat to water ratios			
		●●●●	Irregular: ankle cuff, popliteus		MRI, DEXA, 3D Contour Scanning	
	Dermal	●●●●	Skin thickness		Ultrasound	
	Adipose Tissue		●●●●		Pre-tibial subcutaneous fat thickness	MRI, DEXA, Ultrasound
			●●●●		Thigh/lateral leg subcutaneous fat thickness	
		●●●●	SAT volume to muscle volume ratios			
		●●●●	Presence of nodular structures			
		●●●●	Stiffness/fibrosis	Ultrasound		
		●●●●	Fascia thickness or fibrous retinacula cutis orientation			
Lymphatic or Vascular		●●●●	Lymphatic vessel: number, diameter, tortuosity	MR lymphangiography, Lymphoscintigraphy, NIRFLI		
		●●●●	Aortic dilation	Echocardiographic		
		●●●●	Blood capillaries: tortuosity	Capillaroscopy		

● Diagnostic ● Risk & Susceptibility ● Monitoring ● Prognostic

BIOMECHANICAL	Sub category	BMX Type	Measurement & Stage of Development	Modality
			Ideation → Discovery → Analytic validation → Clinical validation → Qualification	
Dermal		●●●●	Skin stiffness	Durometry
		●●●●	Skin water concentration	Tissue Dielectric Constant
		●●●●	Skin temperature	Thermography
Tissue		●●●●	Subcutaneous tissue tonometry	Manometer, Indurometer
Fluid & Fluid Flow		●●●●	Lymph flow: pump frequency, strength, synchrony, and efficiency	MR lymphangiography, Lymphoscintigraphy, NIRFLI
		●●●●	Interstitial fluid flow	Biophysical & computation models
		●●●●	Impedance of extracellular fluid	L-Dex, Bioimpedance, Perometry
Mico-Vascular		●●●●	Fragility of capillaries	Angiostereometry
		●●●●	Capillary permeability	Streten test
Physio-logical		●●●●	Joint stability	Knee range of motion
		●●●●	Muscle strength	Isometric strength test, gait/walking test

● Diagnostic ● Risk & Susceptibility ● Monitoring ● Prognostic





# Develop New Diagnostics and Biomarker Tools: Summary of Challenges and Recommendations

## Challenges to Overcome

- Reliance on Clinical Diagnosis, with no “gold standard”
- Lack of meaningful measurements to support diagnosis
- Shared Symptoms with common comorbidities
- Failure to Recognize and Diagnose a “Stage 0” phenotype

## Strategic Recommendations

- Develop the data to support the diagnosis process
  - Consider graded scoring that conveys confidence in a diagnosis
- Adopt a biomarker development framework that emphasized specific biomarker goals
- Advance a pipeline of approaches for biomarker based tests with prioritization

# Characterizing the Biology of Lipedema

Canonical Symptoms	Reports examined	Range of prevalence
Symmetrical involvement	5	100%
Upper arm involvement	4	15.2-100%
Spared Feet	3	89.2-100%
Fat pads around the knees	3	53.3-85%
Negative Stemmer's Sign	5	80.7-100%
Pain and/or tender to touch	10	62-100%
Bruising	11	28.1-93.3%
Swelling or edema	7	14.5-79%
Heaviness	2	69%
Fatigue	3	15-66.7%
Hypermobility	4	17.8-58%
Fibrosis	4	6.5-58%
Cold skin	5	41.3-94%
Pes plantus or flat feet	3	15.2-96%
Spider veins	4	23.9-89.9%
Altered gait	2	60-81%
Family History	5	14.9-89.2%







# Characterizing Biology of Lipedema: Summary of Challenges and Recommendations

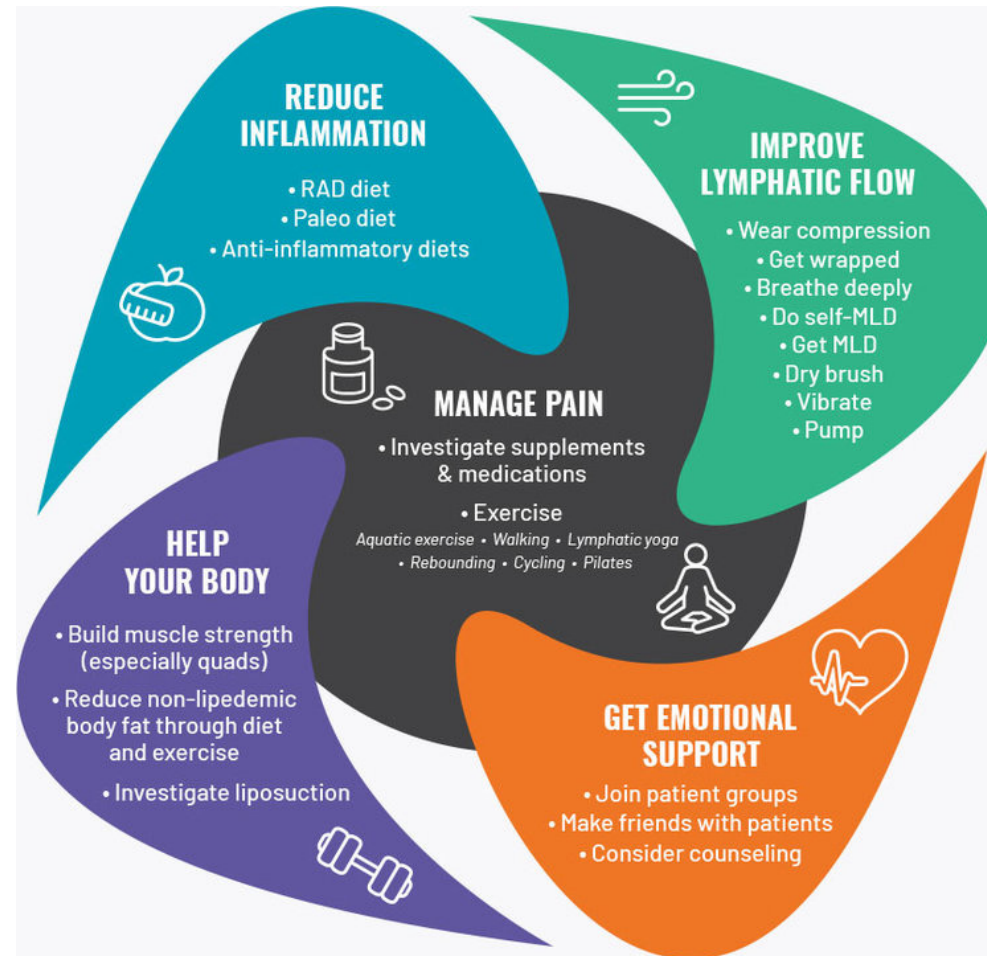
## Challenges to Overcome

- Immature field
  - suggestive, but rarely confirmatory data
- Many specific symptoms are poorly characterized
- Initiation and progression triggers are largely unknown
- Lack of suitable animal and other model systems

## Strategic Recommendations

- Need for careful clinical phenotyping
- Identify genetic and non-hormonal contributions driving initiation and progression
- Understand progression to support development of disease modifying therapies
- Support research that accounts for changes in multiple tissues or areas of the body
- Develop appropriate animal, in vitro, and clinical models

# Developing New Therapies



<https://www.fatdisorders.org/treatments-summary>





# Developing New Therapies: Summary of Challenges and Recommendations

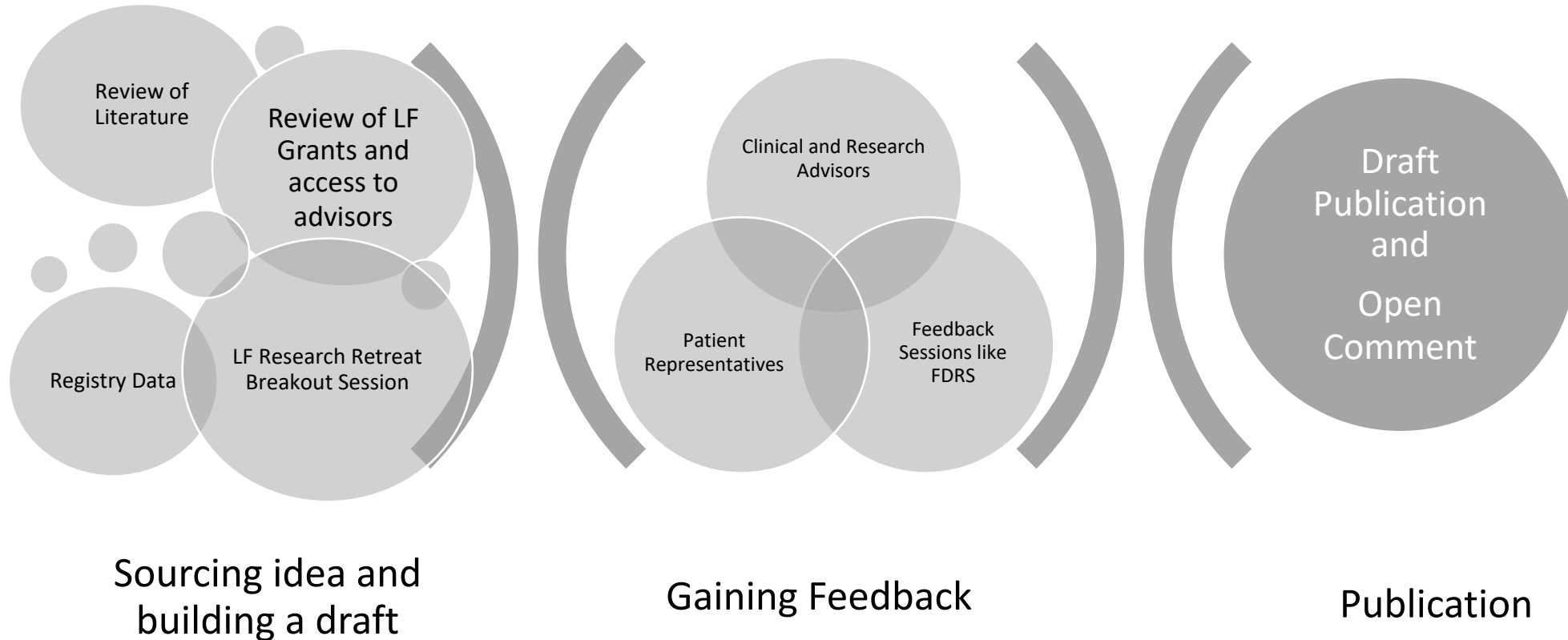
## Challenges to Overcome

- Little known about disease progression
- Evidence on efficacy and safety of existing treatments is minimal
- Little understanding of which outcomes are most meaningful to patients

## Strategic Recommendations

- Explore near term opportunities to improve data behind the most common clinical and at-home treatments
- Support better understanding and statistical validation of clinical research outcomes
- Monitor and support a therapeutic pipeline

# The LF Approach to Defining a Multi-Stakeholder Research Roadmap



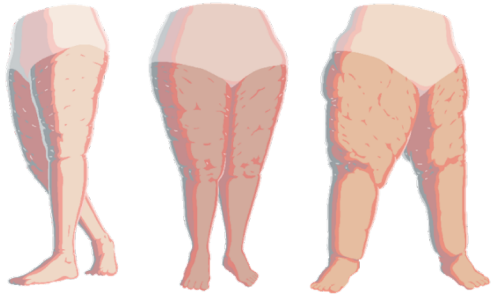
# What's coming and how to learn more

- **Get Connected in Research**
  - **Dip your toes:**
    - LF blogs
    - Legato – Research Library
    - Engage on Social Media
    - Sign up for the Lipedema Foundation Newsletter
  - **Jump in:**
    - Join the Lipedema Foundation Registry
    - Explore Legwork: Clinical Trial Finder



2022 Lipedema Foundation Research Retreat





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