LIPEDEMA FOUNDATION

Lipedema
Research Roadmap

2023

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Acknowledgements & Contributions

An important part of developing this Roadmap was gathering the input of more than 60 global stakeholders, who participated in brainstorming sessions and as reviewers. Participants included researchers, patients, surgeons, physicians, therapists, and funders.

The authors would especially like to thank the external reviewers, who offered more than 1,300 revisions and comments during a collaborative review process.

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Their contributions were invaluable and made this document more representative of the interests of people with Lipedema and the broader field.

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Foreword

During the past decade, Lipedema, which occurs almost exclusively in women, has evolved from an esoteric condition that only a handful of health care professionals had ever heard of—let alone treated—to a legitimate disease that is distinct from obesity, lymphedema, cellulite, and other adipose conditions.

Awareness has skyrocketed, particularly among patients, from small Facebook groups a few years ago to hundreds of millions of social media views and tremendous search volume today (Figure 1). The time spent by a patient searching for clues about why her body is different has shortened from months to mere seconds; a search today for "big legs" or "fat arms" immediately returns images of Lipedema along with clinical definitions, potential treatments, and even advice on how to dress for one's body shape. Patient support groups have become sustainable, producing libraries of videos, photos, and patient experiences, and regularly holding high-quality conferences in the United States, United Kingdom (UK), Australia, and Germany.

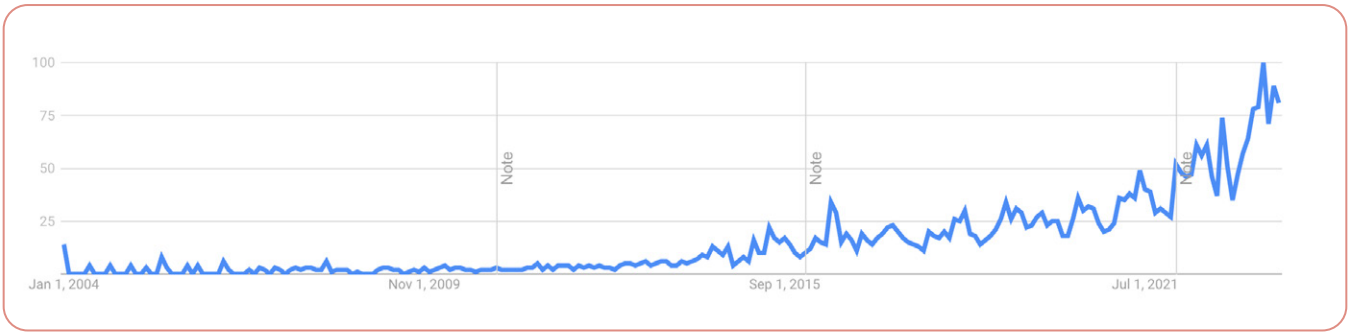

Figure 1. Growth in search volume for the term "Lipedema" on Google over time.
Note from Google Analytics: Numbers represent search interest relative to the highest point on the chart for the given region and time. A value of 100 is the peak popularity for the term. A value of 50 means that the term is half as popular. A score of 0 means there was not enough data for this term.

Anecdotal reports suggest awareness among clinicians is also increasing, albeit at an inadequate pace that lags patient awareness. Consequently, many people with Lipedema continue to self-diagnose, experiencing an epiphany upon reading about the condition and other patients' stories. Yet some doctors show skepticism and are reluctant to diagnose a condition with which they are unfamiliar and that has no confirmatory diagnostic test. Some doctors even dismiss the condition as merely an issue of aesthetics or weight.

With data suggesting the condition affects 5 to 12% of post-adolescent women as well as some percentage of adolescent girls, this medical response puts enormous stress on many patients.[1–3] Patients report being repeatedly dismissed and disbelieved by healthcare professionals, and the long road to receiving a diagnosis is traumatic. Many women experience body shame, daily pain, poor quality of life (QOL), disrupted social interactions, and feared and actual loss of their mobility—all of which lead to psychological distress and mental health impacts.* Some patients at the advanced stages reach a state of helplessness; anecdotal reports have linked suicide to Lipedema.

* This document employs language around biological sex that primarily considers Lipedema as it presents in people designated female at birth. The document does not currently include nuanced discussion of the condition in transgender populations. Likewise, the Roadmap does not consider in depth the presence of Lipedema in people designated male at birth, although there are scattered references in the existing literature. It is anticipated that this discussion will evolve and be added to this document over time.

Lipedema research also lags patient awareness, but appears to be at an inflection point. The number of scientists interested in clinical and basic science research is growing—along with the number of research papers, with 50% of papers published in the past 5 years (Figure 2).

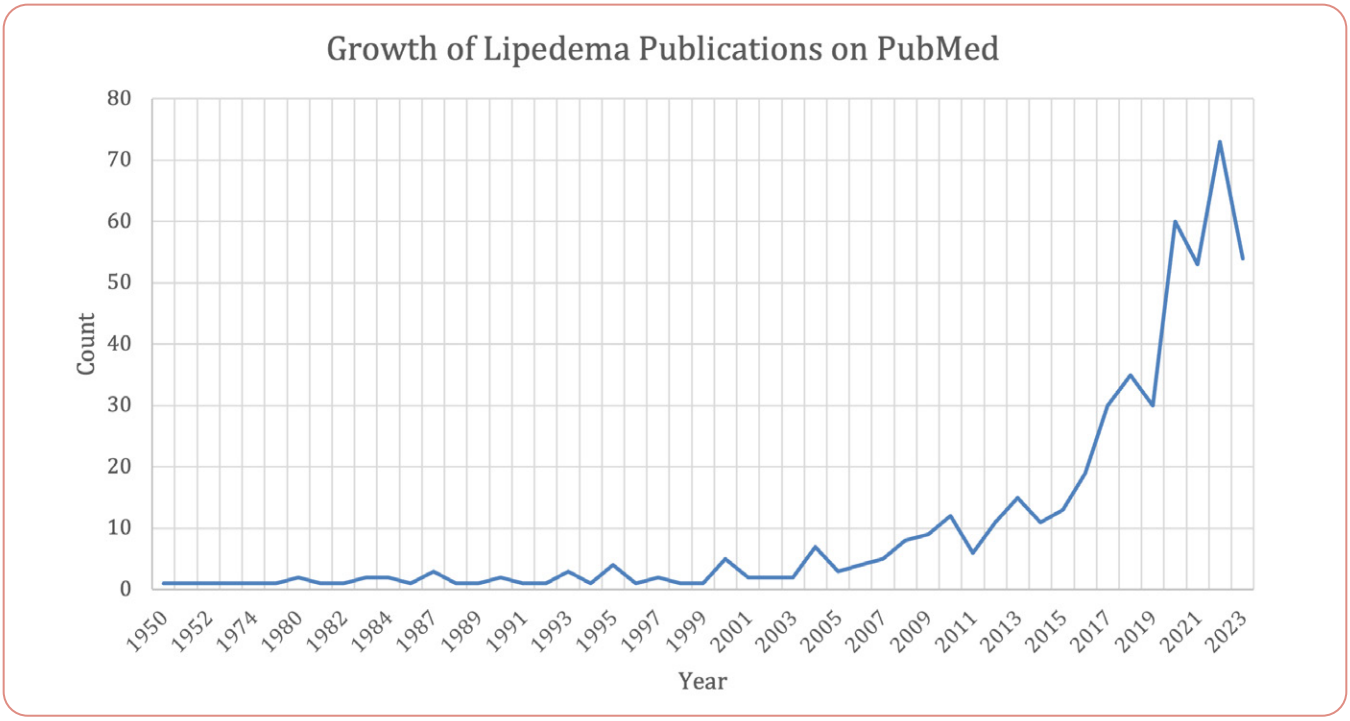

Figure 2. Growth of Lipedema publications on PubMed.

In the next 10 years, we predict the research field will accomplish much more.

However, certain critical factors in the fight against Lipedema are missing:

- Enough aware and trained physicians who are knowledgeable about Lipedema and confident enough to diagnose it
- Consensus on diagnostic criteria and tests to increase diagnostic accuracy
- Sufficient evidence-based treatment options
- Enough well-funded basic and clinical research performed on a larger scale

In the next 10 years, we predict the research field will accomplish much more. We envision large studies that consider more subpopulations of patients, including people with common comorbid conditions, and across all comparator groups. Study participants will be more diverse in terms of race, sex, age, and other demographics, more accurately representing the actual patient population. Estimations of prevalence will improve and longitudinal studies will begin.

The research field should formulate testable hypotheses and design meticulous studies to answer central questions that are relevant to both patients and clinicians, including the following:

- How should a diagnosis be made and ideally by which medical specialty?
- Does the patient population in fact tend toward lower incidence of metabolic complications such as high low-density lipoprotein (LDL; "bad" cholesterol), high blood pressure, insulin resistance, and diabetes, despite increased adiposity?
- Why are the hands and feet spared?
- Why hasn't the field agreed on whether edema exists?
- What explains the unusual texture and palpable nodular structures that many clinicians and people with Lipedema report, and are they linked to fibrosis?
- Should pain be required for a diagnosis?
- What is the relationship between Lipedema and obesity and how can the conditions be easily distinguished from each other in the clinic?
- Why is associated pain described using 30 different adjectives?
- How does Lipedema begin, and what are its cellular, hormonal, and molecular drivers?
- Is Lipedema an inflammatory disease?
- Does a very early prodromal stage that is not currently perceivable to clinicians and patients (sometimes called "stage zero" in the patient community) exist?
- Is the condition progressive? If so, what are the risk factors for developing it and progressing to severe stages?
- What is the relationship between Lipedema and lymphedema and does lymphedema occur in the absence of comorbid obesity?
- What percentage of patients are hypermobile, including those with hypermobility spectrum disorder/hypermobile Ehlers Danlos syndrome?
- Are there different clinical types (e.g., "Allen and Hines" versus "rusticanus Moncorps" type)? If so, how do clinical signs and outcomes differ between phenotypes?
- When there is a family history, how is Lipedema passed between generations?
- What is the relationship between age and Lipedema?
- How prevalent is the condition in pediatric populations?
- Which outcomes (e.g., reducing pain, improving mobility, decreasing limb volume) should be prioritized in research, with deference to patients and the goal of improving overall patient health, participation, and functioning?

More importantly, there should be progress toward real answers about treatments:

- Which therapies are most effective and safe?
- If the condition is progressive, how can progression be stopped, prevented, or reversed?
- How can pain best be managed?
- Can Lipedema be prevented or even cured? If so, what might be the unintended consequences, given that the condition may protect patients from some negative metabolic outcomes?
- Which treatments work best for which subgroups (segmented by demographics, genetic variance, clinical features, etc.) of affected people?
- Which treatments work best for people with comorbid† conditions, including obesity and lymphedema?

As with other underrecognized conditions, in recent years patients and forward-thinking clinicians have led the way in advancing awareness of Lipedema as a legitimate condition. It is our hope that this Research Roadmap can set the stage for increasing recognition among the research and clinical communities and for facilitating significant research advances in the decade to come.

The Authors

† The terms "comorbid" and "comorbidity" are used imprecisely and often ambiguously in medical literature. For the purposes of this document, the authors employ the definition proposed by Feinstein: "Any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study." The authors do not imply any causal link between Lipedema and common comorbid conditions, including obesity and lymphedema. Questions about any common pathophysiology among these conditions, and how these conditions may interact with each other, remain underexplored in the research literature. For more on the use of these terms in medicine and research, see Valderas.[4]

Introduction

Lipedema represents a paradox. Research is experiencing a period of rapid growth and recent advances have generated enough data to formulate a broad array of open questions. Research on the relationship of canonical signs and symptoms of the condition and on methods to objectively differentiate Lipedema from obesity and lymphedema offers tremendous near-term opportunity to improve patient lives. Validation of patient diversity—through studies on the basis of age, sign and symptom severity, duration, and comorbidities, or through the lenses of race, ethnicity, culture, and socioeconomic variables—promises to inform our understanding of the causes of disease and determinants of successful treatment regimens. The field has begun to build some of the foundational infrastructure and resources that may enable future breakthroughs (Box 1). These developments should excite and encourage innovation.

Yet Lipedema research also faces long-standing structural, financial, and societal barriers that hinder our ability to explain the disease's fundamental causes and most frequent patient concerns (Box 2). The field remains disappointingly small considering the significant health burden faced by affected women. A lack of awareness in patient, clinical, and research communities lessens the likelihood of a diagnosis and creates barriers to designing and recruiting for large and potentially confirmatory studies. Although half of known studies have been published within the past 5 years, half of these manuscripts cite no funding source, pointing to financial barriers (Figure 3). As one consequence of underfunding, the field struggles to recruit participants—both patients and controls—which impacts the quality of research and opportunities for innovation.

As Lipedema research advances in an under-resourced environment, the field must focus its attention on specific disease-associated questions that are the most likely to attract human, financial, and infrastructural resources.

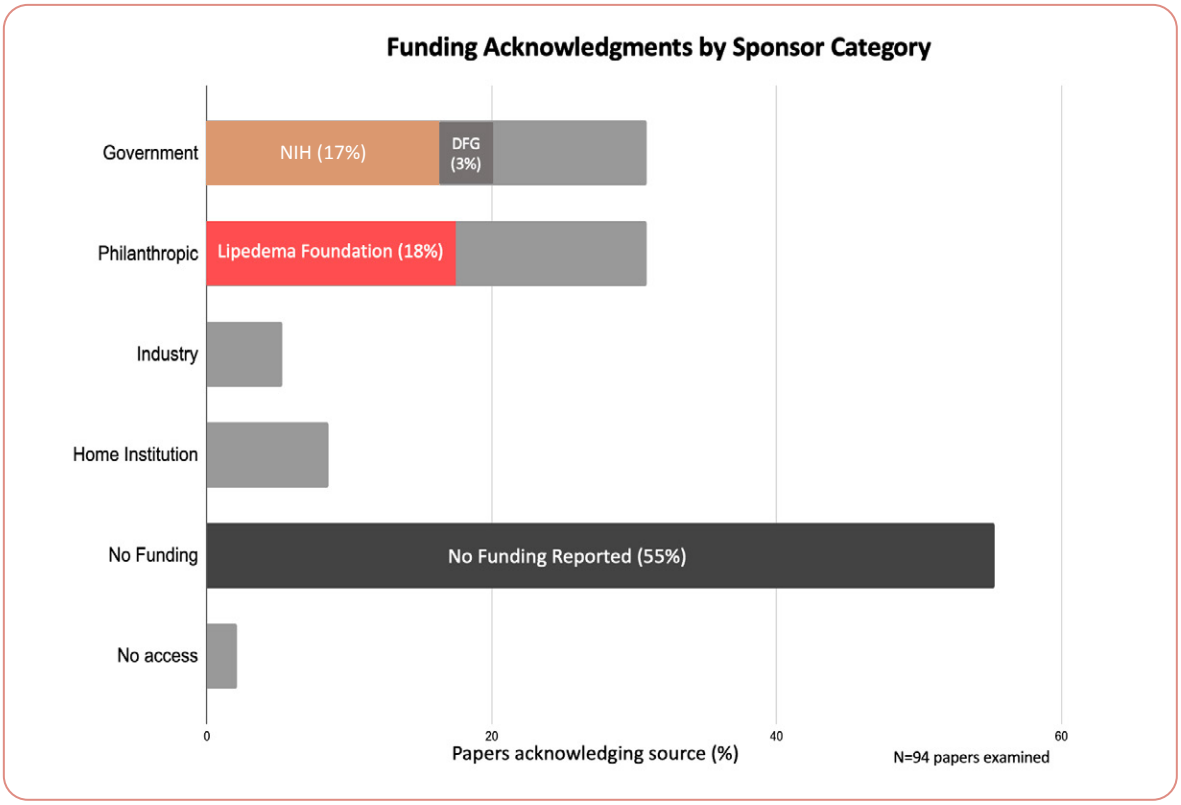

Figure 3. Funding Acknowledgements by Sponsor Category

Purpose of This Document

This document presents a Roadmap to serve the interests of a broad range of stakeholders and aims to achieve the following goals:

Primary Goals

- Identify and communicate Strategic Recommendations to the existing and future medical and research workforce.
- Reduce barriers to entry—especially lack of knowledge about the condition and the current state of research—for new researchers, therapists, clinicians, surgeons, and mental health specialists.
- Facilitate an open, unbiased, and logical exchange of ideas and a mechanism to track progress over time.
- Advance best practices for a field that has lacked coordination and consistency.
- Educate medical societies, governmental agencies, and funders: Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), Food and Drug Administration (FDA), medical education/credentialing organizations such as the American Medical Association and American Physiological Society, and analogous foreign entities.

Ancillary Goals

- Enable patient understanding of and conversations about what is known, suspected, and yet to be understood.
- Motivate patient participation in research.
- Create career and personal opportunities for female, junior, and minoritized/underrepresented researchers to impact a very prevalent condition.

Development of the Roadmap was guided by four principal ideas that can foster research impact:

- **Reach:** Studies that expand Lipedema to new research disciplines will support commensurate expansions in both the research workforce and available funding.
- **Recognition:** Increased awareness and development of tools that help recognize the condition, and reduce reliance on subjective and inconsistent clinical diagnosis, will facilitate better participant recruitment and stronger research.
- **Responsiveness:** Attention to patient needs and experiences should inform research and drive meaningful improvement in patient lives. This orientation toward real-world health outcomes can drive both interest and effective action among funders and researchers.
- **Representation:** With past clinical studies limited to a small number of sites worldwide, representation and knowledge of diversity are limited. Studies lack representation in terms of race (i.e., American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander), ethnicity (i.e., Hispanic or Latino), and sex and gender (i.e., male identifying individuals and members of the trans community). Further, research has not explored how the condition may affect individuals and communities differently by socioeconomic status, education level, and other common demographic criteria. More diverse recruitment, better reporting, and an intentional focus on sub-populations will inform a better, more equitable understanding of the condition's presentations and disparate impacts.

Lipedema Research Roadmap Objectives

1. **Create an Environment Conducive to High-Quality Research**
2. **Develop a Standard Lexicon and Best Practices**
3. **Develop Diagnostic and Biomarker Tools**
4. **Characterize Biology of the Disease**
5. **Develop Treatments**
6. **Cultivate Greater Epidemiology Understanding**

Scope and Process

The creation of the Roadmap relied on a multi-stakeholder process to document and prioritize a wide array of questions in the field. It is conceptualized as a multi-document approach:

Lipedema Research Roadmap (This Document)

This document presents a forward-looking summary of gaps in knowledge and opportunities for research and development, sourced from "Lipedema: A Current Understanding of Its Pathology and Natural History"[3] (described below) and input from the authors and advisors, including researchers, clinicians, and patients. Specific recommendations are organized into six chapters covering key objectives: fostering the research environment, developing reporting standards and best practices, improving diagnosis, broadening understanding of the biology of the disease, identifying potential treatments, and enhancing epidemiology.

Review and prioritization of this document was conceptualized in three stages. Organization and collection of initial draft recommendations were prepared by the Lipedema Foundation (LF) and informed by breakout sessions conducted during the Foundation's December 2022 Research Retreat (Appendix A). These sessions provided specific recommendations regarding improving access to patients, developing appropriate measurements, connecting basic biology to clinical research, addressing infrastructure needs, and enhancing approaches to epidemiology.

A draft was circulated among advisors for editing and feedback (Appendix B). Reviewers provided more than 1,300 revisions and comments on the draft. Follow-up with select reviewers occurred to gather further input or to clarify comments prior to incorporation. The authors reviewed each proposed revision, deliberated, and incorporated most of the feedback.

Advisors were also asked to complete a review form to vote for recommendations they believed should be prioritized. If a reviewer did not complete a review sheet, the authors analyzed the sentiment of their comments about specific recommendations to impute their strongest recommendations in each section. This voting and imputed data, plus contributions from the authors, determined a list of top recommendations, which appear before the full list of recommendations in each chapter.

To gather feedback from the greater field of researchers, patients, clinicians, and other stakeholders, an open comment period will follow publication of the draft Roadmap. Upon completion of the open comment period, the authors intend to publish anonymized feedback collected during this period alongside the Research Roadmap.

In general, the content is both strategic and prospective in nature and, as such, represents ideas and judgements rather than peer-reviewed data. In many cases, advancement in areas detailed here will be required before recommendations related to subject areas such as prevention, public health, or dissemination and implementation of new technologies can be thoroughly explored.

Periodic progress updates will be made as the research landscape evolves.

Lipedema: A Current Understanding of Its Pathology and Natural History (Separate Document)

Prior to drafting the Research Roadmap, a narrative review of Lipedema research, focused on natural history and pathophysiology, was performed to identify and critically assess the state of the science. The resulting document, "Lipedema: A Current Understanding of Its Pathology and Natural History," by Guy Eakin and Stephanie Peterson, is published as a "preprint" on the LF website alongside this Research Roadmap document. See Appendix C for references identified in this review that are cited herein.

Specific attention was given to investigating and where necessary correcting citation of original primary data sources. When prominent ideas could not be traced to published works, references were provided to conference presentations, unpublished data, and non-peer reviewed literature, including patient-reported surveys.

Emails for clarification or corrections are welcome [roadmap@lipedema.org].

Lipedema Research Idea Database (Separate Resource)

An Idea Database (still to be created as of the time of publication) is envisioned as (1) a living tool that enables interested parties to view questions, ideas, and hypotheses that have arisen during the LF's tenure and (2) a mechanism for submission of new ideas.

Audience and Stakeholders

Execution of the Roadmap is not the job of one entity but requires the input and effort of an array of stakeholders.

The primary audiences for this document are Lipedema researchers and the international research funding communities. Although we hope that the content will resonate with current Lipedema researchers, the document recommends hypotheses and field standards to support the broader community of researchers and others who may be interested in entering the field.

A secondary audience is research-oriented healthcare professionals, including physicians, surgeons, therapists, and other allied professionals. Many of the recommendations in this document are oriented toward strengthening networks of healthcare professionals who will undoubtedly play a vital role in advancing research.

The Roadmap is written for the above technical audiences. However, we hope that patients find it to be instructive and representative of their interests, and suggestive of ways in which they might help to advance the research field.

Box 1. Resources Available Now

1. **Existing workforce** of researchers, clinicians, therapists, surgeons, nonprofits, and patient experts, including both those vetted by the LF and unvetted lists of providers such as that of the Lipedema Project

2. Mechanisms to obtain and analyze **new patient input**

Lipedema Foundation Registry (LFR) with researcher access and ability to send out new surveys

Other patient groups' surveys, survey question sets, and publications, for example, Lipoedema UK's surveys

3. Significant social media and digital resources enabling **access to patients and methods of recruitment**

Social media influencers

Facebook groups (e.g., Lipedema Sisters USA)

LF Resources: Lipedema.org, LF Newsletter, Instagram, Facebook, LinkedIn, SmugMug, LF Blog, and LF Brochure

4. **Literature reviews** and key papers

- Duhon et al., 2022
- Ernst et al., 2023
- Kruppa et al., 2020
- Poojari et al., 2022
- Lipedema Foundation, 2023

Visit LF's website to view these and other key papers.

Access to existing literature through LF LEGATO Library, PubMed, and Google Scholar

Clinical trial finders: LEGWORK Clinical Trial Finder and ClinicalTrials.gov

Research conferences: Lipedema World Congress and LF Scientific Retreats

Patient conferences: FDRS, Lipoedema UK, Lipoedema Australia, as well as the unique ability to **perform research during FDRS Conferences**

Alliances between LF, FDRS, LipoedemaUK, and Lipoedema Australia

LF Request for Proposals (For updates on future **RFPs**, sign up for LF Newsletter.)

FDRS's YouTube library and corresponding clinician **continuing medical education (CME)**

Box 1. Resources Available Now, continued

5. Existing and future **biobanks**

Lipedema Biobank of the University Hospital Zurich. Contact: Dr. Gousopoulos, epagousopoulos@gmail.com

Leipzig Obesity Biobank. Contacts: Dr. Anne Hoffmann: anne.hoffmann@helmholtz-munich.de and Prof. Matthias Blüher: matthias.blueher@medizin.uni-leipzig.de Website

Lipedema Biorepository at Vanderbilt Medical Center funded by LF; Contact forthcoming

Berlin Institute of Health at Charité – Universitätsmedizin Berlin, BIH Center for Regenerative Therapies "Lymphovascular Medicine and Translational 3D-Histopathology" Laboratory Biobank. Contact: Rose Behncke, Rose.Behncke@charite.de

Paraffin embedded subcutaneous tissue samples from Dr. Manuel Cornely are being stored at the Institute of Clinical and Functional Anatomy. To discuss sample availability, contact Dr. Erich Brenner at erich.brenner@i-med.ac.at or Dr. Cornely at info@cornely.org.

Box 2. High-Level Barriers to Research

Some fundamental barriers, listed below, impede progress across all areas. The consequences of these barriers include poor research quality (i.e., small and underpowered studies, lack of well-characterized participants and controls, poor knowledge of risk factors other than female sex and family history, and poor understanding of prevalence and burden of illness), as well as substandard, delayed, and expensive/unreimbursed treatment for patients.

- Reliance on a clinical diagnosis with no agreed-upon pathognomonic characteristic, lack of consensus around differing diagnostic criteria, and use of inconsistent and sometimes confusing language
- Challenges to recruiting study participants, including both patients and well-defined comparator populations, for a condition that is poorly recognized across patient, clinical, and research communities
- Lack of highly relevant animal and other nonclinical models
- Difficulty in attracting interest in Lipedema, given stigma around obesity and underinvestment in women's health research and care
- Lack of natural history knowledge, including demographic and phenotypic diversity
- Lack of implementation of consistent medical coding, for example, International Classification of Diseases (ICD) codes, in many countries, presenting barriers to both research and reimbursement
- Limited Lipedema-directed funding among traditional research funders
- Lack of enabling infrastructure supporting development of Lipedema as a mature field of study

OBJECTIVE 1.

Create an Environment Conducive to High-Quality Research

Introduction

The maturity of any research field depends on its human and financial resources. Lipedema clinical and basic science research is driven by a nascent but growing workforce with inconsistent access to funding and critical resources such as tissue samples. Nonetheless, because Lipedema is a complex and poorly understood condition, many "niches" are available for researchers to explore the field, advance their careers, and achieve international recognition and leadership.

The recommendations below support growth of the workforce through training and incentives, with an eye toward engagement of multidisciplinary teams and stronger integration with clinical and patient stakeholders. Establishment of research networks with access to pooled data, tissues, and expertise is oriented toward elevating the capacity of the field to execute high-quality research.

Challenges to Progress

Small Workforce

- The clinical and basic science research workforce is small and globally distributed (Figure 3). Estimates by the LF suggest that in the past 5 years the primary data publications were produced by fewer than 50 research groups, representing only around 400 contributing individuals worldwide.
- Formal training for Lipedema is not mandated or prioritized in most medical specialties and no one specialty "owns" the diagnosis and treatment of the condition. This gap limits the size of the research workforce and hinders interdisciplinary collaboration.
  - Exceptions in the United States are the American Board of Obesity Medicine, which includes questions about Lipedema in its certification exam question bank, and the American College of Cardiology, which includes knowledge of Lipedema among the competencies that are expected of practicing vascular medicine specialists. In Germany, the German Society of Plastic, Reconstructive and Aesthetic Surgeons includes Lipedema in its required specialty knowledge.
- Opportunities for Continuing Medical Education (CME) directed at understanding and diagnosing the condition are limited.
- The lack of robust data to support clinical guideline development and reimbursement policy creates uncertainty for clinical practices, which creates a barrier to entry to clinical teams that might otherwise care for people with Lipedema.

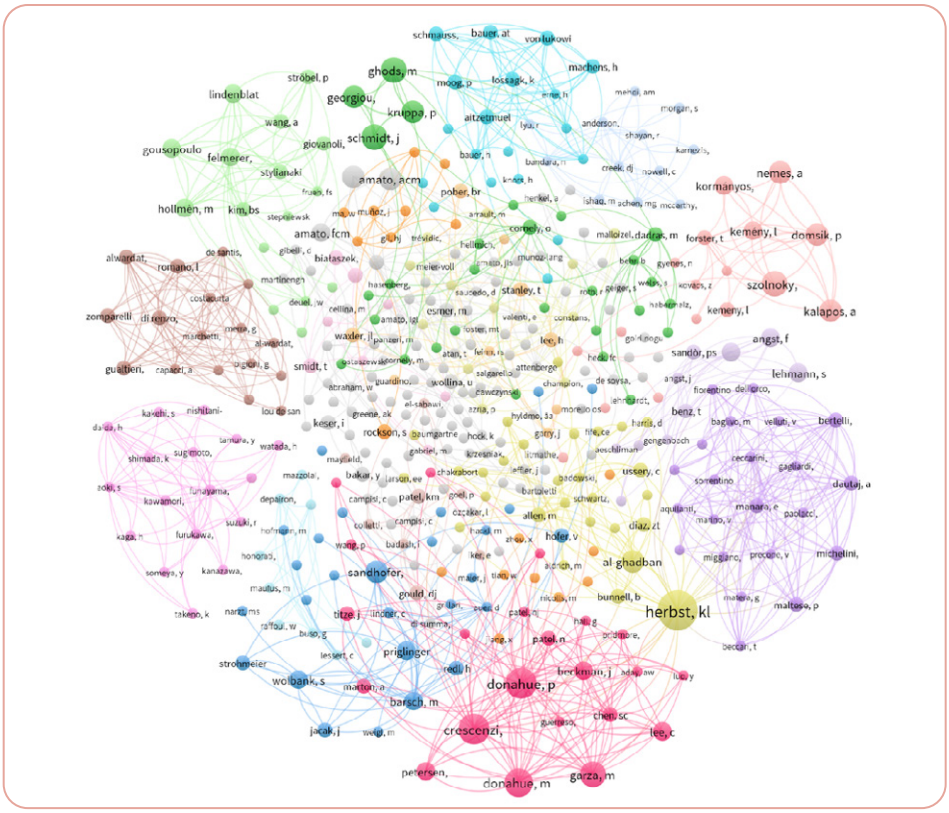

Figure 4. Current active Lipedema research workforce, as evidenced by publication records. Note: 408 authors of 89 primary data and case report manuscripts published within the past 5 years, visualized as 43 collaborative clusters, the largest 2 each comprising 28 networked authors.[5]

Limited Collaboration, Networks, Knowledge Translation, and Exchange

- Successful approaches to Lipedema research will need to be collaborative and multidisciplinary. Any one lab is unlikely to possess the range of expertise needed to generate breakthroughs.
- The existing workforce is fragmented, with practical and philosophical barriers to effective collaboration between working groups (e.g., differing opinions about issues such as the presence of edema, whether pain must be required for a diagnosis, and whether and how to include patients in research or guideline design). In addition, funding to support early-stage collaborations is limited.
- The field currently lacks coordinated mechanisms for collaboration, network building, and knowledge exchange that are present in more mature fields.
  - To date, the only consistently held research conference is the annual Fat Disorders Resource Society conference, which as a patient-focused conference does not primarily serve a research audience.
  - Lipedema is not on the agenda of the most important adipose tissue meetings, such as Gordon Research Conferences or Keystone Symposia.
  - The American Vein and Lymphatic Society (AVLS) conference and International Federation for Adipose Therapeutics and Science (iFATS) conference have periodically included sessions on Lipedema research and a Lipedema World Congress will convene in 2023 in Potsdam, Germany. These developments are promising, although many more are needed.

Insufficient Research Infrastructure and Participant Recruitment

- Research is slowed by difficulties accessing biological samples from well-characterized patients and controls, and often lacks the necessary clinical information to evaluate whether the sample(s) can be pooled or added to ongoing or prospective research studies.
- Inadequate professional awareness and diagnosis reduce the relative pool of patients interested in and eligible for participation in research.
- The settings and situations where patients can readily be recruited for research yield very specific populations of study participants—for example, those presenting at lymphology or plastic surgery clinics or those with access to health insurance or significant financial resources. This situation likely leads to participants who are less representative of the broader patient population.
- Whole tissue samples are particularly challenging to source, compared to lipoaspirate and remnant materials. Often tissue samples are gathered from less invasive

procedures such as punch biopsies that capture only superficial tissue.

- Access to and alignment on definitions of control patients and tissues are challenging.
- These recruitment and infrastructure challenges lead to small, underpowered studies; impediments to data sharing and comparison across studies hinder pooling of data and meta-analysis.
- Patient registries capturing patient-entered data offer great potential but will require more work to structure and launch follow-on studies.

Lack of Patient Empowerment and Engagement

- People with Lipedema are the source of invaluable perspective, information, and ideas about the condition. For example, work on the role of tissue sodium was initially sparked by conversations with patients. Yet these perspectives are often dismissed in clinical and research environments.
- Patient engagement is rarely incorporated in the literature, including in consensus documents. People with Lipedema are excluded from research strategy, study design and execution, and analysis and contextualization of results.
- Engaging people with lived experience as partners in research offers great promise but can be challenging and time consuming, and people may find it difficult to participate in some areas without a background in biology or medicine.
- Little work has been done to date to understand patient prioritization of research questions, funding, and outcomes. Patient reviewers of this document advocated for prioritizing QOL issues and near-term research on treatments, although work is needed to examine patient preferences and tradeoffs in a structured way.

Insufficient Capacity to Leverage Technology

- Leveraging cutting-edge and promising technologies at scale is challenging given their rapid pace of development and the current state of the workforce and funding. Examples of such technology include gene editing; artificial intelligence and machine learning; single- and multi-omics approaches; high throughput single-cell and single-nucleus sequencing; single-cell imaging; organ on a chip, adipose tissue organoids, and other innovative model systems.

Strategic Recommendations

Objective 1. Top Recommendations

- Recruit researchers and clinicians from fields not well represented in the current workforce.
- Work with professional societies to raise awareness about diagnosis, treatment, and career opportunities. Advocate for inclusion in medical curricula and licensure requirements.
- Build researcher capacity to secure available funding.
- Increase government funding support for Lipedema, especially for longer-term projects.
- Establish Lipedema biobanks and encourage better sharing of resources across labs, especially tissue.
- Engage patients to help set the course of Lipedema research.
- Work to implement Lipedema-specific ICD coding, which was adopted by the World Health Organization in 2019 as part of its 11th revision (ICD-11).

Develop the Workforce

1.1 Conduct outreach to and partner with medical and research professional societies to raise awareness about diagnosis and treatment. Advocate for inclusion in medical curricula and licensure requirements. Outreach should focus on pediatricians, general practitioners, and OB/GYNs, because those clinicians are likely to first encounter the largest numbers of Lipedema patients. Other priority fields include obesity research, bariatric medicine, dermatology, and vascular medicine.

1.2 Create, update, disseminate, and incentivize CME and medical training to increase the number of clinicians who can diagnose Lipedema. This effort will increase the number of clinicians able to partner with researchers on studies. Tactics may include hosting CME courses at major specialty conferences (e.g., endocrinology, obesity medicine, cardiology).

1.3 Recruit researchers and clinicians from specialty fields that are not well represented in the current workforce but are expected to have research commonality to Lipedema based on current knowledge of signs, symptoms, and pathogenesis. Research fields may include adipose, stem cell, hormone, extracellular biology, connective tissue and fascia, tissue texture, and fibrosis. Clinical disciplines may include pediatrics, rheumatology, endocrinology, nutrition and dietetics, mental health, weight management, allergy and immunology, physical and obstetrics/gynecology, dermatology, and vascular surgery.

1.4 Build awareness of and provide opportunities for participation in research for allied health professionals, including nurses, nurse practitioners, dieticians, physical and occupational therapists, and others. These professionals are often the first to recognize the condition and may make important contributions to research on treatments (e.g., compression, physical therapy, diet, and exercise).

1.5 Foster pathways for trainees to receive education from Lipedema investigators during their graduate studies, including research, clinical shadowing opportunities, and job opportunities.

Foster Collaboration

1.6 Foster the development of formal and informal research networks across stakeholder groups, including patients, caregivers, mental health experts, therapists, clinicians, surgeons, researchers, relevant government partners, industry, and other specialists such as dietitians.

1.7 Incentivize collaboration.

- **1.7.1** Consider Lipedema-specific collaboration grants with lower dollar values and barriers to entry. Such grants may benefit from being structured to specifically support practical aspects of collaboration (e.g., motivating inter-laboratory staff interactions and travel).
- **1.7.2** Consider larger virtual consortium grants (e.g., NIH ViCTER grant program).
- **1.7.3** Conduct intentional matchmaking between complementary researchers.

1.8 Create and publicize opportunities for researchers to network and share research through:

- **1.8.1** Formal channels (e.g., larger dedicated Lipedema conferences, sessions at relevant adipose tissue research conferences such as Gordon and Keystone, LF research retreat, virtual meetings, dedicated journal(s), and special issues in relevant existing journals such as *Adipocyte* and *Arteriosclerosis, Thrombosis, and Vascular Biology*).
- **1.8.2** Informal channels (e.g., journal clubs, wikis, Slack channels).

1.9 Build clinical research networks to promote standardization, reduce duplication of effort, build connections and serve as the foundation for future quality improvement and clinical trial networks.

- **1.9.1** Establish and leverage research Centers of Excellence (CoEs).

1.9.2 Support near-term learning and exchange of best practices.

1.9.3 Explore the potential of quality improvement networks as a forum for codifying and sharing best practices, codes of conduct, standard rules, guidelines, policies, and procedures.

1.10 Create clinical trial networks and supporting resources.

1.10.1 Establish a reliable directory of physicians focused on diagnosing and treating Lipedema.

1.10.2 Share common definitions and standard operating protocols to accelerate launch of new clinical trials.

1.11 Create and implement FDA-style "master protocols."

Build Research Infrastructure

1.12 Expand and enhance patient registries.

1.12.1 Leverage the LFR as a contact registry to support recruitment to studies.

1.12.2 Integrate the LFR with future biobanks.

1.12.3 Expand the LFR to conduct follow-on surveys. Priorities include studies that contribute to understanding of patient perceptions and beliefs, development of patient-reported outcomes, and assessments of health and financial burden. Over the long term, these materials could be translated into additional languages to increase participant diversity.

1.13 Establish Lipedema biobanks.

1.13.1 Create large biorepositories to store and disseminate high-quality specimens from enough well-diagnosed patients and controls to support current and future research. Specimens should include lipoaspirate, punch biopsies (including superficial subcutaneous adipose tissue [SAT]), blood, saliva, urine, and genetic material (e.g., DNA), and samples from all disease stages and a wide range of ages.‡

1.13.2 Consider increasing the types of samples routinely collected and housed in the biorepositories—for example, deep SAT, fresh adipose tissue from various fat depots in locations other than the thigh, subcutaneous and visceral adipose tissue, and whole-body cadavers.

1.13.3 Create complementary biobanks with international representation in the United States and abroad.

1.13.4 Enhance data collected alongside biological samples (e.g., clinical phenotype, QOL, medical history, imaging data). (See Box 4 for a proposed common case report form [CRF].)

1.13.5 Integrate systems, operating protocols, and data collection and reporting standards across biobanks to facilitate reproducibility and streamline common processes. Elements to standardize include sample storage requirements and international data- and sample-sharing agreements (e.g., the Uniform Biological Material Transfer Agreement).

1.13.6 Create and enforce databasing and data sharing standards for biobank participants (e.g., common data dictionaries, return of data, publishing of protocols and datasets). Explore dedicated server(s) for depositing high-throughput data from different researchers.

‡ Several existing or imminent biobanks include samples from Lipedema patients. See the "Resources Available Now" in the Introduction.

1.14 Encourage research labs and others to share clinical expertise and other resources.

1.14.1 Pool and share resources—especially tissue samples—between labs while ensuring patient privacy. Several reviewers of this document noted that they receive large solid fat samples from surgery in more volume than they can use. There should be increased efforts to make connections between labs with excess samples and those in need.

1.14.2 Encourage research collaborations that can bring academic and private practice clinical specialists to projects that otherwise lack this expertise. Consider engaging knowledgeable clinicians to train others interested in research on how to perform competent diagnoses.

1.14.3 For larger clinical practices, start to analyze and share electronic health record (EHR)[§] data on Lipedema either individually or in coordination as a precursor to the development of future clinical research networks. The feasibility of connecting data across practices would improve with the widespread implementation of the new Lipedema-specific ICD code.

1.14.4 Explore the development of a CoE wherein large facilities with concentrations of specialists, relevant technology, and research capacity can be incentivized to focus continuous effort on Lipedema-related questions. This effort may require dedicated longer-term funding to enable sustainability independent of project-specific research awards.

1.15 Implement Lipedema-specific ICD codes.

- As part of its 11th revision (ICD-11), in 2019 the World Health Organization included for the first time a specific ICD code for Lipedema (EF02.2). Although many countries have adopted ICD-11, others, including the United States, have not yet implemented the new revision. Providers in countries still using ICD-10 or earlier revisions are consequently using a range of codes that are not specific to Lipedema.
- Work in this area will enable better retrospective, epidemiologic, and other research using EHRs and will improve comparability across studies, as well as further legitimize the condition, support clinician education, and facilitate prevalence studies. (Germany serves as one exception, with specific codes for each stage of the condition. Retrospective studies of medical record data in Germany may be of particular interest).

Engage and Empower People with Lipedema

1.16 Engage people with Lipedema to help set the course of research through advisory committees and focus groups. Leverage existing scholarship on this topic and examples from industry, government (e.g., FDA's Patient-Focused Drug Development program), academia (e.g., University of North Carolina's Patient Advocates for Research Council and Inclusive Science program), and others.

1.17 Work with patients to generate knowledge and hypotheses. Reviewers suggested including people with Lipedema in research retreats, meetings, and CME workshops.

1.18 Consider emerging approaches to incorporating patient input from other conditions (e.g., the Long Covid Patient-Led Research Collaborative). Prioritizing outcomes and designing QOL studies are ripe for increasing engagement, but other innovative approaches to incorporating patient input into basic research contexts may be equally productive.

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§ Although often used interchangeably, electronic medical record (EMR) and electronic health record (EHR) have different meanings. An EMR is a patient's medical history that is maintained electronically by a single provider, whereas an EHR is a patient's medical history that is maintained electronically by multiple providers. While recognizing these differences, the Foundation elects to align with the Office of the National Coordinator for Health Information Technology's approach to almost exclusively use EHR to emphasize the concept of health. Learn more at https://www.healthit.gov/buzz-blog/electronic-health-and-medical-records/emr-vs-ehr-difference.

1.19 Aggregate patient perception data from registries and surveys to support hypothesis development. Consider questionnaires that combine patient input with clinician perspective, such as the Ly.search Lipedema Form PST (Germany).

1.20 Prioritize outcomes measures according to patient preferences. Use best practices and methodology from other stakeholders and programs (e.g., Patient-Centered Outcomes Research Institute], European Alliance of Associations for Rheumatology PARE program).

1.21 Engage patient partners and support groups to recruit for studies and resources (e.g., biobanks).

1.22 Coordinate knowledge exchange among existing international patient advocacy groups, funders, and researchers. Consider working with patient ambassadors.

Leverage Existing Technology

1.23 Recruit top researchers from complementary fields who could apply their deep expertise in specific technologies and techniques to the study of the condition.

1.24 Consider participant monitoring/tracking/health and wellness devices and apps, as resources for research.

Need for Dedicated Funding

Very few authors have committed greater than 10% of their publications to Lipedema research, likely because of a historical absence of dedicated research funding, including from traditional government funders such as NIH. Yet funder interest in this research topic is growing: Lipedema proposals can be submitted to NIH under lymphatic grants programs, including a new Notice of Special Interest (NOSI) for lymphatic diseases, and at least one R01 was recently awarded for Lipedema research.

Although most research fields could benefit from additional funding, specific improvements in environmental parameters are critical to developing the data and advocacy necessary to support increased funding for Lipedema research. Recommendations to expand the types and amounts of available funding are presented below.

1.25 Researchers and advocates should make concerted efforts to publicize existing funding opportunities.

- **1.25.1** Publicize information on existing U.S. and International government grant mechanisms relevant to Lipedema research, especially mid-career and longer-term funding (e.g., 3-4 year) opportunities. Researchers should be encouraged to apply for funding through existing grant mechanisms targeting lymphatic disorders (e.g., lymphedema) and obesity.
- **1.25.2** Monitor and disseminate time-sensitive Lipedema-relevant grant opportunities such as the U.S. Congressionally Directed Medical Research Program, Department of Defense Peer Reviewed Medical Research Program, and European Union and European Commission rare disease funding opportunities.
- **1.25.3** Research, collect, and disseminate information on private-sector grant opportunities in adjacent spaces such as obesity, endocrine, and lymphatics, including funding for related technology development, for which Lipedema researchers might be qualified.

1.26 Increase government support for Lipedema research.

- **1.26.1** Advocate for other funders to offer Lipedema-specific grant opportunities and/or explicitly acknowledge the condition in existing funding opportunities. Continue to educate key decision makers around government funding (e.g., study section participants).

1.27 Attract additional private-sector funding.

- **1.27.1** Advocate for additional funders—including private, public, and corporate funders—to consider Lipedema-specific funding. Explore matching grants to incentivize new funders.
- **1.27.2** Consider new private-sector grant mechanisms for early- and mid-career investigators.
- **1.27.3** Provide "shovel ready" research opportunities for other social-sector actors, creating a menu of options.
- **1.27.4** Experiment with new vehicles for philanthropic giving (e.g., donor-advised funds, field of interest funds, social impact bonds).

1.28 Build researcher and medical professional capacity to secure available funding.

- **1.28.1** Build grantsmanship skills (e.g., host grant writing bootcamps, provide paid grant review support). Focus these opportunities on Lipedema-specific challenges and reference recommended infrastructure and field standards described in this Roadmap.
- **1.28.2** Provide junior investigators with mentorship opportunities with senior investigators to gain training on contemporary issues and challenges.

OBJECTIVE 2.

Develop a Standard Lexicon and Best Practices

Introduction

Lipedema researchers and clinicians have not reached consensus on the definition and reporting of the condition. Inconsistency is apparent in communications, published literature, and the diagnostic criteria adopted by different countries, which complicates professional communication. As a major consequence, researchers cannot easily compare results across studies, and attempts to do so can sow confusion. Additional challenges arise when incorrectly or self-diagnosed patients are enrolled in studies, or when different studies include or exclude different subpopulations (e.g., some exclude patients without pain or with central obesity), introducing analysis errors and impeding generalizability of findings.

Common terminology, diagnostic criteria, and reporting standards must be developed and implemented. Progress on this Roadmap objective will start the field on the path toward speaking the same language, training healthcare professionals, and enabling comprehension and comparison of data and conclusions across studies.

Challenges to Progress

Inconsistent Reporting

- Studies use different criteria for diagnosing and staging patients.
- New publications often fail to report the criteria used for diagnosis and staging. Some clinicians make one stage assessment per study participant ("whole body") and others assess stage by individual body part.
- Clinical diagnosis requires an in-depth knowledge of how Lipedema presents, feels, and differs from common overlapping symptomatology of obesity and lymphedema, and other conditions such as lipodystrophy, Lipohypertrophy, and pelvic venous disease.
  - Uncertainty exists about whether current diagnostic and staging criteria apply equally to all patient populations. Existing criteria are untested for validity and reliability in any population and fail to address potential variability across aging and diverse populations or sub-populations.
- The clinical diagnostic criteria and their implementation vary across standards of care and geographies.
  - There is untested variability between practices. "The path to diagnosis can vary greatly from physician to physician."[6]

  - The relative value of any particular clinical sign, or constellation of specific signs and symptoms, in determining a diagnosis is undocumented.
  - Lipedema presents in the clinic with significant heterogeneity in signs and symptoms, and experts have posited that different subtypes might exist. This heterogeneity may pose additional challenges to diagnosis and reporting.
- Published research papers vary in their transparency and precision in reporting definitions of controls, inclusion and exclusion criteria, and other clinical measures.
- Publications rarely describe methods with sufficient detail to enable understanding and reproducing of the anatomical location of procedures and observations.

Inconsistent Terminology

- The condition's name and direct translations (e.g., Lipoedema, Lipödem, Lipœdème) as well as historical and proposed alternate names (e.g., Lipohyperplasia Dolorosa, Lipalgia Syndrome, Lipedema Syndrome) can challenge efforts to identify relevant studies in online databases.
- Contemporary proposals to rename the condition could further complicate this situation.
- Whether Lipedema should be considered a disease, disorder, or syndrome is an ongoing topic of debate. Notably, these terms are not precisely defined or used in broader medical literature.[7]
- Authors use varying language to describe and define signs, symptoms, and other characteristics, especially edema, inflammation, texture, and nodules.
- Other similar-sounding terms can confuse and complicate data analysis using patient health record databases (e.g., "lip edema" [lip swelling], lymphedema, and lipid disorders such as hyperlipidemia or dyslipidemia).

Strategic Recommendations

Objective 2. Top Recommendations

- Convene the research and clinical communities to develop universal diagnostic criteria for the purposes of research.
- Carefully consider and disclose definition of controls and control-matching mechanisms, especially age, body mass index (BMI), and race. Consider other parameters such as comorbid conditions, hormones, and body composition measurements.
- Develop and incentivize a common CRF for research.
- Develop and incentivize publication reporting standards and conventions, especially around diagnosis, common terminology, demographics, and sample anatomical location.

Adopt Common Diagnostic Criteria for Research

2.1 Convene members of the research community to formulate and publish consensus statements around common reporting standards.

2.2 Develop universal diagnostic criteria specifically for the purposes of clinical research (Box 3).

2.2.1 Structure diagnostic criteria to support the analytic needs of clinical research teams and to remain clear, uncomplicated, and workable for clinicians. These criteria might include a point-based system suitable for use in assessing confidence in diagnoses and severity of individual signs and symptoms, and/or distinguishing major and minor criteria.

2.2.2 Incentivize adoption of minimum diagnostic criteria through funding, reporting, and publication requirements.

2.2.3 Where feasible, pursue independent confirmation of the diagnosis by more than one clinician. This research practice is being used by at least one team in Germany. Although this practice could be beneficial, it requires additional time and presents challenges for patients who may struggle to locate—and afford visits to—more than one knowledgeable clinician in their area.

2.3 Endeavor to consistently implement and report staging, even though the approach to staging will likely evolve.

2.3.1 Report, at minimum, definitions of stages and, if used, types of Lipedema.

2.3.2 Where possible, recommend staging primarily (1) by the individual (i.e., one overall stage assessment for each patient ["whole body"]) and secondarily (2) by different body segments (e.g., upper arms, upper legs), focusing on high-frequency body segment tissue sampling areas.

- Because some clinicians stage by body segment, researchers need guidance on how to apply that staging construct to samples that derive from non-localized/circulating biological material such as blood.
- This would be a temporary step while a standardized staging system is pursued.

Develop Common Case Reporting and Control Definitions

2.4 Develop a common CRF to use in the context of research studies. This CRF will enable standardization of a supplemental data table in publications and better comparability across studies. The proposed common CRF (Box 4) lists symptoms and clinical data that likely correlate with high probability signs and symptoms. It should enable deep phenotyping of patient cohorts within studies to better identify subtype populations and support future meta-analyses.

2.4.1 Convene a group of key stakeholders to decide on categories to capture; minimum variables to include within each category; definitions of variables; measurements, response options, and field types for each variable; and variables and metrics that will be monitored in follow-up visits.

2.5 Once the CRF is in use and published as supplemental data, begin to compile and collect data across studies.

2.6 Carefully consider and disclose definition of controls and control-matching mechanisms.

- Current case matching practices typically match study participants by age, sex, and BMI.
  - BMI is especially problematic for Lipedema because it can be complicated by fluid retention or muscularity. In addition, as a whole-body average, BMI does not address the disproportionate weight accumulation associated with the condition. Nevertheless, use of BMI-based matching remains a common practice that enables comparison with not only other Lipedema studies but also studies in adjacent fields and will likely remain important for research until a suitable marker of progression is defined.

Box 3. Proposed Minimal Diagnostic Criteria

Minimal diagnostic criteria for consideration are as follows:

- Bilateral, symmetric fatty enlargement of the limbs with no or minimal involvement of the feet and hands (unless concomitant lymphedema)
- Pain, tenderness on pressure and at other times in the affected fat tissue
- Increased vascular fragility, easy bruising
- Persistent enlargement of the extremities after weight loss; inadequate response to dietary (caloric) restrictions
- Disproportion between upper and lower body, defined as a waist-to-hip ratio (WHR) <0.7 (There is also potential to incorporate waist-to-height ratio (WHtR) reference ranges pending the outcomes of current research.)
- May be otherwise very healthy and/or have "normal" blood work results
- Nodular texture in fat
- Patient history
- Exclusion of other endocrine and fat disorders

Early reviewers of this document suggested that several common criteria that appear in different diagnostic protocols might be considered optional on a list of agreed-upon minimal diagnostic criteria. These include the following:

- No to minimal pitting edema; the Kaposi–Stemmer sign is negative; persistent enlargement after elevation and weight loss; swelling and discomfort worsen with orthostasis especially in summer/heat (Reviewers noted that the presence and role of clinically detectable edema is still a point of debate among clinicians.)
- Family history (Reviewers noted that many patients present without sufficient recall or knowledge of their individual family history.)

Note: Some of these potential criteria might ultimately require a quantitative measurement, for example, "enlargement," vascular fragility, pain on pressure.

Left image: Lipedema is often characterized by a symmetric buildup of adipose tissue in the legs and arms.

Right image: Visualization of a common Lipedema clinical sign: front, side, and rear view of a Lipedema patient's ankle cuffs.

- Matching by sex is considered best practice because the condition is nearly exclusively limited to females. Studies that compare females to male controls may introduce confounding variables.
- Matching by race and ethnicity should be considered as well.

2.7 Explore the use of other parameters that may be valuable to experimentally control, most importantly:

2.7.1 Presence of lymphedema, chronic venous disease, obesity, or other common comorbid conditions.

2.7.2 Menstruation status (specifically pre- and post-menopause) and hormone replacement therapy. This parameter may be better controlled by restricting inclusion criteria to eliminate a particular class of study participant (such as limiting age of enrollment).

2.7.3 WHtR and WHR. However, meaningful cut-off values for these measures have not been determined and should be measured with attention to variation by age or BMI. Clear guidance is needed on defining "waist" and on measuring increased adiposity in the waist region. Furthermore, irregularly shaped skin folds with lobules of adipose complicate taking these measurements. It should also be noted that waist and height measurements change based on the width of the feet apart and change in hip rotation (e.g., pelvic tuck).

2.7.4 Indicators of body composition and metabolic health.

2.7.5 In sex hormone involvement studies, first day of last menstruation.

2.7.6 Other variables such as childbirth, pregnancy history, menstrual regularity, contraceptive use, and history of breast cancer or other gynecological cancers, as well as, especially in studies related to treatments or QOL, measures of functioning as in the International Classification of Functioning, Disability, and Health (ICF).[8]

Identify Field Standards

2.8 Create, disseminate, and incentivize reporting conventions for publication, to include the following:

- Common terminology and definitions.
  - Words such as edema and inflammation require disclosure of the operational definition and whether a precise clinical criterion is in place.
  - Words such as texture and nodules represent imprecise concepts. As understanding of tissue elasticity and fibrosis evolve, reporting of these phenomena should evolve as well.
- Careful description of the study's diagnostic protocol and staging.
- Definition of controls and sample size, including control-matching variables (e.g., age, sex, BMI, WHtR, race, ethnicity).
- Inclusion and exclusion criteria used during recruitment.
- Sources of participants, to disclose potential sampling bias (e.g., sourcing of patients from specialty clinics has inherent biases relative to those sourced from more generalist settings).
- Pain scale used.
- Demographic data related to the cohort under study, including standard variables such as BMI, age, stage, and prevalence of specific signs and symptoms and comorbidities. Data collected through a CRF could ideally be shared for each study as supplementary data.

Box 4. Proposed Common Case Report Form (CRF)

Basic Demographic Information
- Sex for Clinical Use
- Race
- Ethnicity
- Date of Birth
- Height
- Weight
- Waist Measurement
- Hip Measurement
- Calculated fields: Age, BMI, WHtR, WHR

Sample information (if collected)
- Anatomical Location
- Depth

Patient History & Clinical information
- Stage of Lipedema
  - By body segment (legs, arms)
- Date of last menstrual cycle
- Menstrual cycle status
  - (before puberty, puberty, menstruating, perimenopausal, menopause, post-menopausal)
  - Consider FSH levels
- Age of Lipedema onset
- Lipedema Onset trigger
  - [puberty, pregnancy, menopause, contraceptives, other]
- Lipedema Disease duration (yrs or range)
- Concomitant medication list
  - (including immunomodulator and hormonal medication)

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
- Anemia
- Operations or Traumas

Family History & Genetics

Canonical Manifestations
- 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
  - Pitting or non-pitting
- Bruising
- Pain and/or tenderness to touch
- Fatigue
- Palpable presence of nodules
- Palpable changes to tissues texture or fibrosis
- Lateral malleolar fat pad
- Full Achilles sulci

Other Commonly Cited Symptoms
- Dermatologic
  - Softness
  - Plasticity
  - Cold/Temperature
  - Livedo reticulitis
- 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

Daily Functioning Domains
- Mobility
- Self-care
- Activities and Participation

QOL Domains

- Anatomical location (based on anatomical structures) and tissue depth of any procedure or observation. Regarding adipose tissue, care should be taken to characterize location by standard anatomical descriptions (e.g., superficial SAT, deep SAT, and visceral depots as well as different locations on the body).
- In publications using alternative naming, inclusion of "Lipedema" in titles, abstracts, or keywords as well as a statement regarding the synonymous use of an alternative name.
- Explicit acknowledgment of small pilot studies as part of reporting standards. The degree to which such small studies are generalized to broader claims of effectiveness is a concern that must be navigated in a manner that still enables documentation of preliminary findings.
- Note: Some of these field standards are required when submitting studies to frequently used clinical trial databases, such as clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform. The LF requires its awardees to list its funded studies in these databases.

2.9 Encourage best practices for research presentations in the field, particularly for the presentation of unpublished data. In addition to the above conventions for publications, presentations should at a minimum include the following:

- Number of confirmed Lipedema patients included.
- Number of confirmed Lipedema samples included.
- Number of control patients included.
- Number of control patient samples included.
- Descriptions of subgroups included and analyzed.

2.10 Develop and incentivize the adoption of standards around data sharing.

2.10.1 Leverage where possible NIH's efforts to advance data sharing and include the following:

- Maintain comparability of identifiers across samples when pooling samples.
- Include sufficient detail to contextualize images (e.g., depth of tissue taken or imaged, precise stain(s) used).
- Organize data cleanly, including metadata required to interpret data.
- Include associated data required to interpret other data. For example, when including RNA sequencing data, include associated EHR data where possible.
- Disclose statistical packages used and statistical analyses run.

2.11 Encourage data collection and consenting practices that enable options for flexible data sharing (e.g., incorporate the option to re-consent patients).

OBJECTIVE 3.

Develop Diagnostic and Biomarker Tools

Introduction

A timely and accurate diagnosis is vital to Lipedema research. It is necessary to characterize the biology, ensure comparability and reproducibility across studies, and identify which signs and symptoms can inform outcome measures for therapeutic efficacy. Clear and succinct clinical diagnostic criteria and effective diagnostic tools will pave the way for recruitment and stratification of research participants, as well as enable interventions and clinical trials.

Of course, accurate diagnosis is also needed for patient care. Although the research community cannot dictate clinical practice, it can influence conceptions of clinical diagnosis by highlighting knowledge gaps. As these gaps close, accumulating evidence should enable greater levels of standardization of clinical diagnosis and one day, hopefully yield technologies to aid in standard diagnosis and treatment.

One critical element of diagnosis is biomarker development. This chapter proposes a biomarker discovery framework based on categories in the FDA-NIH Biomarker Consortium strategy for the purposes of diagnosis, prognosis, risk assessment, and monitoring. However, the bar for FDA qualification of biomarkers is extremely high, and the authors do not necessarily advocate for pursuing regulatory qualification of biomarkers. This framework is used solely for organizing the pipeline of approaches.

Challenges to Progress

Reliance on a Clinical Diagnosis

- Clinical diagnosis is challenging and complex, relying on a patient's medical history, physical examination, and exclusion of commonly mistaken comorbidities.
- Minimal guidance exists regarding palpation of various adipose depots for the presence of nodules, fibrosis, or abnormal tissue texture during a physical exam.
- There is no "gold standard" clinical diagnosis, study, or test. Thus, the first generation of approaches to a laboratory diagnosis will require voluminous testing against the clinical diagnoses of multiple clinicians, practices, and sites.
- The clinical workforce lacks an adequate number of experienced, trained clinicians to diagnose and differentiate Lipedema from obesity and lymphedema.

Lack of Objective Measurements to Support Diagnosis

- The current diagnostic criteria are subjective and lack precise ways to measure and assess signs and symptoms.
- Clinicians may be less likely to diagnose Lipedema if they lack confidence in the evidence supporting the pathophysiology of the condition and/or recommended therapies.
- The primary sign of Lipedema is adipose accumulation, yet measuring adipose accumulation in specific body regions often relies on imprecise tools (measuring tape) and can be increasingly challenging to measure as adiposity increases, especially in the abdominal regions.
  - Measurement-based body composition calculations other than BMI, such as WHtR or WHR, can be complicated because of variability in the anatomical definition and feasibility of measuring the "waist" or "hip."
- Other commonly reported signs and symptoms, such as a tendency for easy bruising or pain (or untangling interrelated types of pain [chronic versus acute; nociception, neuropathy, central sensitization]) in the affected areas are difficult to assess objectively.
- Tools to assess lymphedema are not designed for the purpose of Lipedema and their performance on people with Lipedema is unclear.
- There is limited research and a very thin pipeline investigating potential biomarkers across different techniques and approaches.

Shared Signs and Symptoms with Common Comorbidities

- Lipedema shares many signs and symptoms with obesity and lymphedema. These conditions are often comorbid in advanced stages, leading to misdiagnosis.
- Differentiating gynoid obesity from Lipedema is difficult because both conditions present with adipose accumulation in similar region(s).
- Differentiating tissue texture, fibrosis, and edema in lymphedema and Lipedema can be difficult, given the absence of longitudinal data describing rates of accumulation in either condition.
- The lack of standard medical billing codes for Lipedema in many countries leads to underdiagnosis, misdiagnosis, and muddled diagnosis.
  - This issue has implications both for determining prevalence and for utilizing EHRs in retrospective studies and impacts any investigation into prescribed therapies.

Failure to Diagnose a Prodromal Stage, and to Understand Risk and Susceptibility

- Identifying early Stage 1, or a prodromal stage, is challenging; however, symptoms often begin at puberty.
- Research has rarely involved minors with potential risk of the condition (e.g., relatives of those with Lipedema).
- Risk factors remain unknown despite family history being commonly reported.
- Basic biology of affected tissues is poorly characterized, with only recently emerging unbiased or "agnostic" approaches to genetics and molecular profiling.

Lack of Tools for Monitoring and Evaluating Progression and Prognosis

- The progression from a presently undefined prodromal stage to a severe stage is insufficiently understood. Whether Lipedema progresses through each stage remains untested. (Refer to Standard Lexicon, Recommendation 2.3, and Recommendations below in this chapter for a nuanced discussion of applications and limitations of the current staging system.)
  - Knowledge of individual differences or triggers that might impact the progression is limited.
  - Monitoring of patients with advanced Lipedema has unique challenges given size limitations of some modalities (i.e., magnetic resonance imaging [MRI]), greater tissue volume, and the unknown biological effects in advanced stages.
- There are likely different clinical sub-groups within the patient population. However, clinical sub-groups are insufficiently characterized or defined (e.g., by demographics, genetic variance, clinical features). This limitation could be important if these sub-groups display different prognoses and treatment responses.

Strategic Recommendations

Objective 3. Top Recommendations

- Survey clinicians to refine key components of diagnosis, to support creation of a standardized clinical diagnosis method.
- Improve the current staging system to account for potential disease progression. Consider severity and impact on QOL.
- In developing diagnostic tools, design studies to understand sensitivity, specificity, and other related measures.
- Adopt a biomarker framework. Prioritize the development of histologic, and secondarily, molecular biomarkers.

Develop and Disseminate a Rigorously Defined Clinical Diagnosis

3.1 Survey clinicians to refine key components of diagnosis and to support creation of a standardized method to diagnose Lipedema.

3.1.1 Conduct a study to investigate inter-rater reliability across clinical sites and use the results to refine diagnostic criteria.

- Focus on patient history collected and patient exam findings.
- Evaluate tissue texture, nodules in affected regions, and differences in fascia with as much specificity and rigor as possible in the clinic (Figure 5).

3.1.2 Partner with clinician organizations to better identify diagnosing clinicians in relevant specialties such as vascular medicine, endocrinology, and internal medicine, as well as general practitioners.

3.2 Resolve key points of disagreement about diagnostic criteria between leading clinical guidelines and consensus statements (U.S. and global), notably presence of pain (including type of pain), nodular structures versus tissue texture, and edema.

3.3 Provide guidelines for differentiating from common comorbid conditions such as obesity, lymphedema, and venous insufficiency.

3.4 Consider inclusion of a composite or graded scoring system that would reflect confidence in diagnosis, enable comparison between practices, and be feasibly employed in a typical clinical visit (e.g., within a 10- to 20-minute appointment typical of healthcare in the United States).

- Examples of such criteria include the Dutch Guidelines9 or those in other disease fields such as myalgic encephalomyelitis/chronic fatigue syndrome.

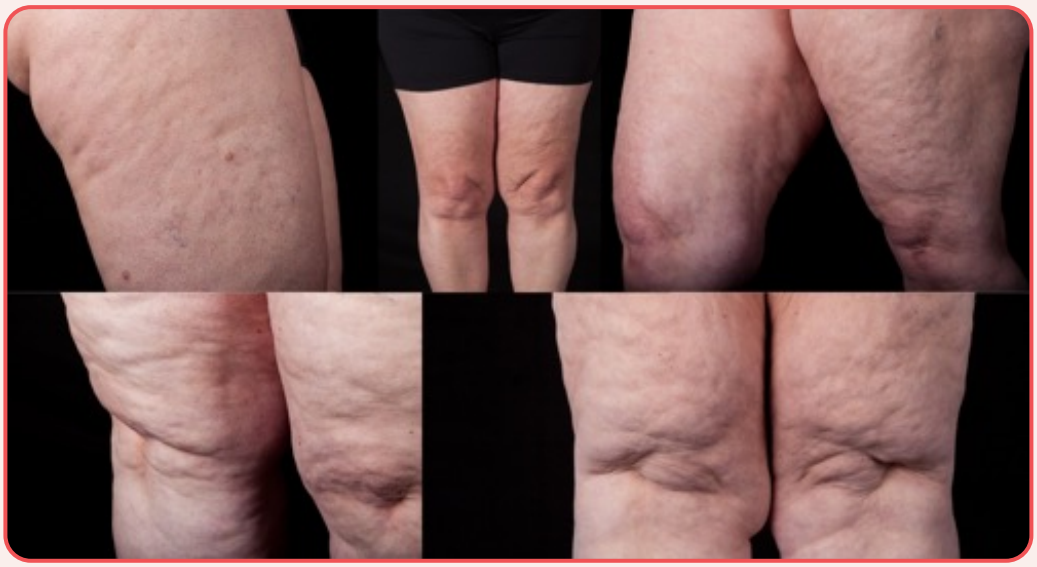


Figure 5. An unusual texture is often present within the fat of Lipedema patients. Lipedema fat can feel like rice, peas, or walnuts beneath the surface of the skin.

3.5 Improve the current staging system to reflect disease progression with an emphasis on severity of signs and symptoms and their impact on QOL (notably pain and mobility). Ideas include the following:

- Rather than develop a Lipedema-specific severity scale, it may be more efficient to conduct clinical research using established measures for each domain of interest, validating these individually within the Lipedema patient community.
- The Dutch guidelines outlined and recommended the use of clinimetrics focusing on limb and waist measurements, pain, mobility, strength, gait, activity levels, and QOL.[9]
- British guidelines suggest development of an outcome-based scoring system to grade patients based on severity along eight dimensions, and to benchmark the numerical score against simple summary terms such as “mild,” “moderate,” and “severe.”[10]
- Approaches from lymphedema may also be informative, including the lymphedema staging system and proposed Leg Lymphedema Complexity Score.[11,12]
- These guidelines have limitations, but they may serve as a useful point of departure for revising the current staging system.

3.6 Encourage adoption of the refined diagnostic criteria among key stakeholders and clinical research sites so that comparisons across studies can begin. Stakeholders include vascular and plastic surgeons, vascular medicine specialists, cardiologists, endocrinologists, rheumatologists, general practitioners, and pediatricians.

3.7 Develop a clinical trial network as a basis for advancing these efforts.

Adopt a Biomarker Framework

3.8 Adapt and employ a biomarker framework in designing and conducting experiments (e.g., BEST framework categories from the FDA-NIH Biomarker Working Group).

- A biomarker is "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions," differentiating them from how an individual "feels, functions, or survives."[13]
- Biomarkers are further categorized along a continuum of use ranging from screening and susceptibility markers and those used for purposes of diagnosis, through assessments of patient progression during or independent of an intervention, and specific markers necessary for the efficient conduct of clinical research.
- Although the BEST framework has seven biomarker categories, this section focuses on the biomarker categories that *define measures of disease presence or status* and does not include the categories that measure aspects of responses to treatments (e.g., predictive biomarkers, response [pharmacodynamic or surrogate endpoint] biomarkers, safety biomarkers).

3.9 Focus and define the context of use when designing experiments targeting biomarkers (e.g., BEST categories as outlined by the FDA-NIH Biomarker Working Group).

3.9.1 Designate the category of biomarker.

- In the context of Lipedema research, the following biomarker categories will be the most relevant: (a) Diagnostic: differentiate those with Lipedema from those without the condition, depending on the context of use; (b) Risk and Susceptibility: identify those with an increased or decreased chance of developing Lipedema; (c) Monitoring of Progression: define changes that occur from stage 1 to 2 and stage 2 to 3; and (d) Prognostic: identify and predict disease course or recurrence.

3.9.2 Identify and define the fit-for-purpose use of the biomarker assay or tool. Fit for purpose is defined as "an evaluation process that is tailored to the degree of certainty required for the use proposed."[14]

3.10 Design studies with a focus on estimating the sensitivity and specificity of the assay in differentiating between comparison groups and demonstrating reproducibility within and between labs and devices (see Table 1 for examples of studies doing this to date). Work to advance this recommendation includes the following:

- Documentation of pre-analytical variables such as specimen collection, processing, storage, shipment, and handling to reproduce experimental design across laboratories, which are inconsistently reported in Lipedema research (see Chapter 2: Develop a Standard Lexicon and Best Practices).
- Experimental protocols should include the "optimization of the pre-analytical variables, core assay performance expectations, and setting minimally acceptable assay performance criteria."[15]
- Determination and definition of the comparison groups necessary to test the specificity and sensitivity of the biomarker assay according to its purpose.
- Given Lipedema's sign and symptom overlap with obesity and lymphedema, experimental designs (at different design phases) should carefully consider the choice of groups for comparison. Important populations include the following:
  - People without Lipedema, obesity, and lymphedema.
  - Obesity without Lipedema.
  - Metabolically healthy obese individuals without Lipedema.

  - Lymphedema without Lipedema, including both primary and secondary lymphedema types.
  - Lipohypertrophy (which is sometimes argued to be a painless prodromal stage of Lipedema, although a recent paper calls this into question).[16]
  - Other comparative groups such as Mast Cell Activation Syndrome without Lipedema, Dercum's without Lipedema, and Lipedema with comorbid lymphedema (i.e., lipolymphedema).
- An acceptable within-subjects control of an "unaffected" versus "affected" tissue specimen from a Lipedema patient, with the corresponding locations from another comparative control group if possible (reviewers noted that this may be challenging).
  - "Affected" tissue locations include thigh, calf, upper arm, or an area with tissue texture change and nodules present.
  - "Unaffected" tissue locations may include the abdomen, although whether this location is truly unaffected is debated in the field. Other experts suggest the dorsal scapula area. Current RNA sequencing work may help further clarify this issue.
  - For pain and sensitization tests, the dorsal aspect of the hand or foot is often used as an internal control.
- Stratification of the Lipedema sample population by stage to determine whether the biomarker assay can adequately detect an early-stage patient or is fit for purpose in measuring progression within Lipedema.
- Stratification of the Lipedema sample based on treatment status of the sampled area, because many patients have already tried surgery (e.g., liposuction, bariatric surgery) or may be well-managed with physical therapy. "Treated, affected" tissue may be important to compare with "Untreated, affected" tissue or "Untreated, unaffected" tissue with "Untreated, affected" tissue.

3.11 Understand the biological rationale or plausibility of biomarkers by conducting experiments that explore the relationship between biomarker measurements made in models, *ex vivo* studies, and *in vivo* studies.

3.11.1 Demonstrate consistency of correlation between the biological rationale and biomarker change with repeated studies across multiple testers and across manufacturers or different compounds.

3.12 Convene stakeholders, including subject matter experts, to provide guidance on sensitivity, specificity, and predictive values that would be required for different use cases. Related concepts include area under the curve (AUC), receiver operating characteristic (ROC) curve, proportion with event at different thresholds, and positive and negative predictive values.

Table 1. Lipedema Research Studies Examining Diagnostic Markers with Receiver Operating Characteristics

Marker	Modality	Cohort n	AUC	95% CI	Cut off	Sensitivity	Specificity	Reference
Legs FM/total FM	DXA	74(33.3) Lipedema 148 (66.7) Control	0.90	(0.86-0.94)	0.383	0.95	0.73	Buso[17]
Legs and arms FM/Total FM	DXA	74(33.3) Lipedema 148 (66.7) Control	0.91	(0.87-0.94)	0.505	0.87	0.80	Buso[17]
Trunk/legs ratio	DXA	74(33.3) Lipedema 148 (66.7) Control	0.88	(0.84-0.93)	1.276	0.93	0.93	Buso[17]
Pre-tibial region thickness (dermal + subcutaneous)	Ultrasound	62 Lipedema 27 Control	0.9079 R 0.9092 L	-- --	11.6 11.8	0.96 0.92	0.96 0.92	Amato[18]
Supramalleolar thickness (dermal + subcutaneous)	Ultrasound	62 Lipedema 27 Control	0.7888 R 0.7670 L	-- --	7.1 7.0	0.73 0.61	0.73 0.61	Amato[18]
PF4 levels in plasma exosomes	Blood-Plasma	15 Lipedema 12 Control	0.95		>9.71	0.9091	0.9091	Ma[19]
Tissue dielectric constant	Moisture Meter D	10 Lipedema 9 Untreated lower limb lymphedema 10 Control	--	--	40	0.90	0.90	Birkballe[20]

Advance a Pipeline of Technologies and Approaches for Biomarker Testing

The FDA guidance on biomarkers separates them into radiographic, molecular, physiological, and histological categories. To reduce duplication of measurements among modalities and categories, we have substituted morphometry and biomechanical categories in place of radiographic and physiological categories until there is a more robust and advanced pipeline of markers. We have integrated radiographic and physiological approaches, where appropriate, into the other categories.

For this Roadmap, we have emphasized the following categories:

- Morphometry biomarkers, defined as depth and volumetric analyses of specific anatomical regions or structures.
- Biomechanical biomarkers, defined as reactions of biological components to internal and external physical forces or stimuli.
- Histological biomarkers, defined as cell size and counts and assessment of the microstructure of tissue.

- Molecular biomarkers, defined as measurements leveraging the presence or concentration of specific molecular entities.

In all cases, attention is placed on the feature being measured rather than specific technologies used to provide the measurement. Although individual technologies or users may have different rates of success, the potential of any one marker is considered to be an aggregate of available techniques and supporting publications.

Morphometry biomarker advancement

Because there is broad consensus among all stakeholders that Lipedema presents with disparity in adipose deposition between limbs (extremities) and trunk, or between the lower half and upper half of the body, morphological biomarkers seek to aid in the quantification of these clinical observations and would be a natural extension to aid in diagnosis and monitoring of progression (Figure 6).

3.13 Promote research to further progress the pipeline of morphological biomarkers toward clinical use.

3.14 Further validate and standardize biomarkers related to morphology for diagnosing Lipedema.

3.14.1 Consider prioritizing morphological biomarker advancements relative to their ease of integration within clinical care and their respective sensitivity and specificity in distinguishing Lipedema from comorbid conditions.

3.15 Evaluate the use of WHtR and WHR instead of BMI[21] as a more sensitive measurement of adipose distribution, exploring the utilization of better tools capable of handling and controlling for the variability of increased adiposity of the abdominal region.

3.16 Encourage testing of more reproducible measurement tools such as a perometer or 3D camera with algorithm (e.g., LymphaTech) for capturing and monitoring circumference measurements, to better evaluate progression in clinical settings.

3.17 Promote research to standardize identification of the presence of nodules, abnormal tissue texture, and fibrosis that clinicians and patients feel, using a variety of modalities.

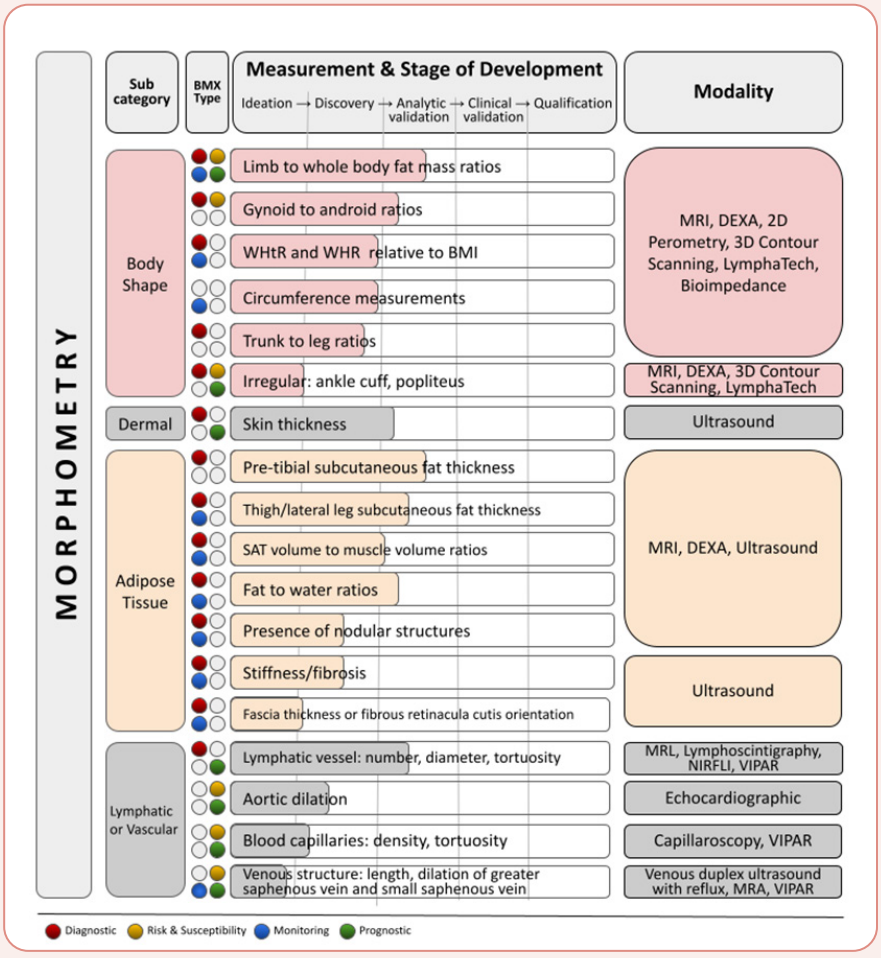


Figure 6. Morphometry biomarker discovery efforts in Lipedema and their progression toward clinical use.

Biomechanical biomarker advancement

The association of edema (presence of fluid, especially orthostatic edema) early in the identification of Lipedema[22] led to study of the structure and function of the lymphatics. In addition, it became important to differentiate Lipedema from lymphedema using these techniques. Another symptom, easy bruising, has led to the investigation of vascular issues such as capillary fragility and permeability.[23] (See Figure 7.)

3.18 Further investigate and determine whether there are unique patterns in fluid dynamics such as lymphatic pump frequency, strength, synchrony, and/or efficiency.

3.19 Promote research on the correlation between fluid accumulation and functional deficiencies with progression, with a particular focus on controlling for BMI and other weight-associated parameters.

3.20 Continue to investigate the potential of microvascular alterations and tissue fibrosis for both providing diagnostic capabilities and monitoring progression.

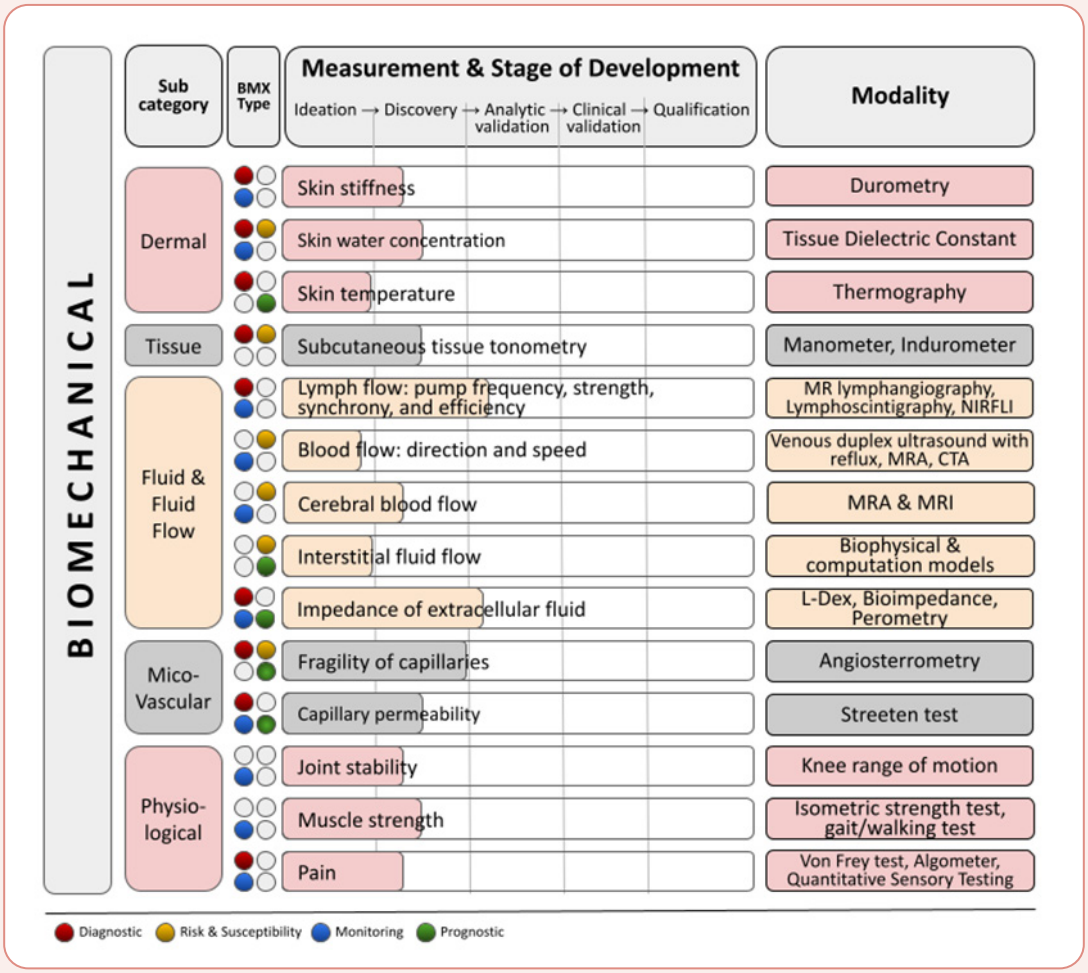


Figure 7. Biomechanical biomarker discovery efforts in Lipedema and their progression toward clinical use.

Histological biomarker advancement

In hopes of better distinguishing Lipedema from its common comorbidities (obesity and lymphedema) and tying biomarkers to biological processes, researchers have explored histological biomarkers. Initial histological measurements are focused on characterizing the structure and pathophysiological differences of adipose tissue, lymphatics, and blood microvasculature (Figure 8).

3.21 Promote research to expand the pipeline of histological biomarkers, including exploring extracellular matrix (ECM), immune cell, and mitochondrial visualization techniques.

3.22 Further validate adipocyte hypertrophy and hyperplasia in Lipedema samples and control group samples for diagnosis.

3.23 Propose examining the biogenesis of lipid droplets in adipocytes as a potential mechanism in explaining hypertrophy in Lipedema.[24,25]

3.24 Explore various adipose depots and layers of adipose tissue for histological characterization techniques.

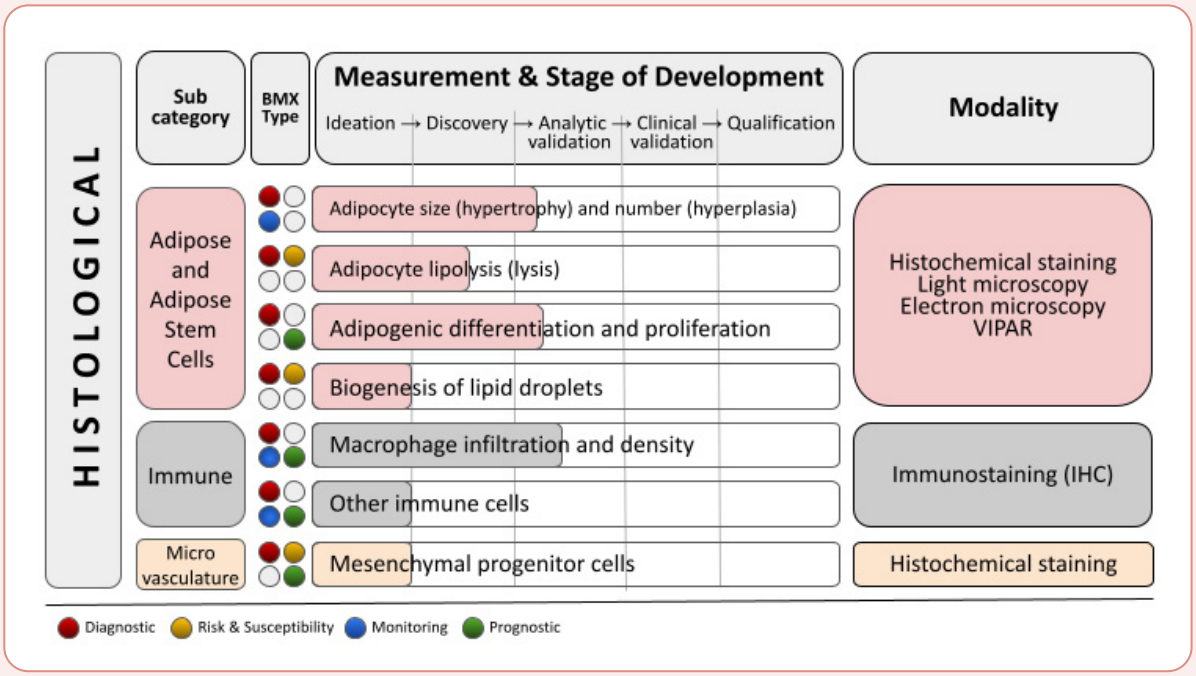


Figure 8. Histological assessments of microstructure in Lipedema and their progression toward clinical use.

Molecular biomarker advancement

The use of a variety of modalities using high-capacity analysis of genes, proteins, transcripts, lipids, metabolites, and other biological molecules to identify potential molecular markers is being explored (Figure 9).

3.25 Support continued research on genetics, including functional validation of genes identified in existing genetic studies.

3.26 Promote research on the correlation between molecular biomarkers, such as exosomal vesicle biomarkers, and other non-molecular modalities (e.g., imaging, histological).

3.27 Further validate and standardize tissue sodium concentrations for diagnosis and monitoring of progression.

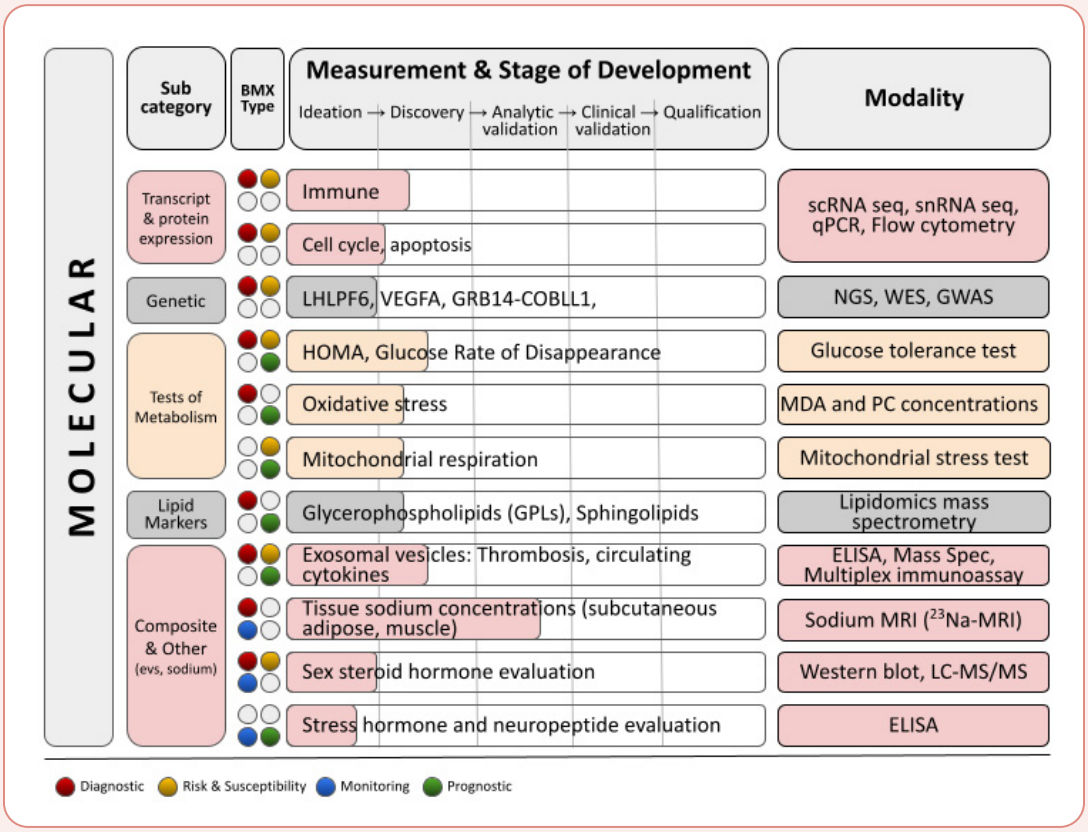


Figure 9. Molecular biomarker discovery efforts in Lipedema and their progression toward clinical use.

3.28 Promote research expanding the pipeline of tests assessing metabolism, including glucose intolerance, oxidative stress, and mitochondrial health.

Prioritize Biomarker Measurements for Translational Research

3.29 Convene subject area experts in the biomarker categories outlined above to provide guidance, strategy, and prioritization of the best biomarker measurements to pursue for diagnosis.

- Specific efforts should identify which biomarkers can progress to the translational research studies (T2, T3, T4) necessary to implement them in clinical practice.[26]

3.30 In prioritization efforts, discuss the trade-offs between adoption in the clinical setting (including primary care settings), the need for a highly trained workforce, and the standardization required to produce accurate and reliable measurements and ensure clinical robustness.

- As biomarker candidates emerge, retrospective studies should be conducted leveraging data repositories from obesity, lymphedema, and other conditions yet to be determined.

3.31 Consider developing and testing wearables, smart devices, and applications for remote assessment of presentation of clinical signs, their severity, and change over time. These methods would need to be employed alongside traditional assessment methods to validate their utility in clinical settings. Common behavioral markers from wearables, such as activity level and gait, and overall usage could be used for this remote assessment.

OBJECTIVE 4.

Characterize Biology of the Disease

Introduction

Discovery sciences play an essential role in advancing healthcare options for people with any disease. Studies of fundamental biological questions about Lipedema, such as the underlying basis for the condition(s) that lead to the disease, or the effect of Lipedema on the adipose and its environment will likely pay dividends across the entire field, from screening to prevention to treatment.

Science does not proceed in a linear fashion, and it is difficult to know in advance which investments of time, energy, and resources in specific projects will most likely generate breakthroughs. To increase the chance of discoveries that can lead to new diagnostic aids and disease-modifying therapies, the field must allocate resources strategically.

To prioritize potential approaches, this chapter draws on other literature reviews.[3,24,27–29] Some areas of basic science are prioritized because of the number of "doors" that focused study in those areas might open in the near term—for example, because they are traditionally well-funded or have significant existing therapeutic opportunities. Such fields might afford access to resources, such as funding, skilled investigators, and tools and techniques that can be repurposed.[¶]

A note about the level of detail in this section: There was diversity in reviewer feedback, with some praising the level of detail as useful to generate ideas for research and others advocating for less detail and direction. The authors have erred on the side of more detail, with the belief that researchers will pursue diverse ideas and approaches stemming from their own expertise and interests.

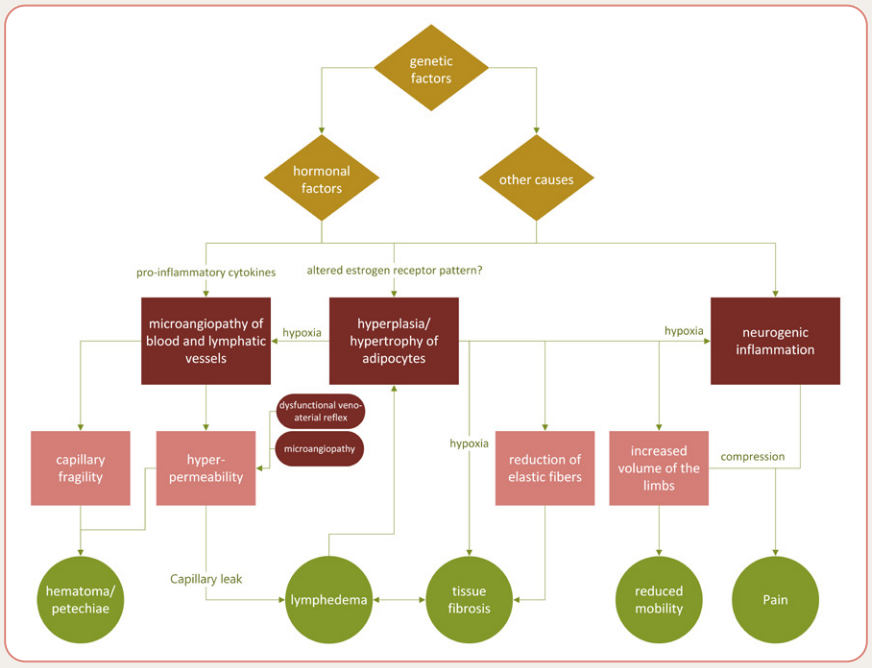
Challenges to Progress

- Challenges in recruiting sufficient patient populations and controls or identifying Lipedema patients in large medical databases contribute to the lack of large sample studies available to research including many modern genetic or -omic approaches.
- Clinical understanding and therefore the practical scope and focus of basic sciences is limited by significant gaps in documentation of signs and symptoms, their prevalence, the relative timing of their appearance, and multiple subtypes or phenotypes.

¶ Because Lipedema research is in an early state, questions and hypotheses about various aspects of the biology outnumber the answers. Many ideas are integrated in the "strategic recommendations" section of this chapter, and many more will be included in the companion Idea Tracker Database resource described in the introduction of this Roadmap. Generally, ideas with substantial field interest or preliminary data suggesting their plausibility have been included in this Roadmap document, while more speculative ideas will be tracked in the companion resource.

Box 5. Hypotheses about Pathogenesis

Those new to the field may benefit from understanding big picture hypotheses about etiology and pathogenesis that have been proposed to date. The excellent review article "Lipedema—Pathogenesis, Diagnosis, and Treatment Options" elaborates on several of the below ideas about natural history.29 In particular, a figure reproduced from that article, "Hypotheses about pathogenesis," summarizes leading theories about natural history as of the time of that article's publication, including ideas around genetics, hormonal factors, inflammation and fibrosis, vascular issues, adiposity, hypoxia, mobility and pain.



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In addition, other proposed and notable hypotheses about pathogenesis, still to be investigated, include:

Lipedema as chronic compartment syndrome. It has been hypothesized that the condition may be related to a form of subclinical chronic compartment syndrome, related especially to dysfunction in the saphenous compartment.[30,31]

Glycosaminoglycan (GAG) hypothesis. In this hypothesis, the glycosaminoglycans of the endothelial and adipocyte glycocalyx may be perturbed by increased presence of sodium ions, creating an environment that has the potential to cause microangiopathy and inflammation. Such conditions would also be predicted to contribute to microedema.[32–34]

Lymphatic dysfunction. Though gross morphological deficiencies have not to date been demonstrated in Lipedema, one hypothesis is that there may be deficiencies in lymphatic micro-architecture that could correspond to suboptimal lymphatic function. As failure to clear lymphatic fluid has been demonstrated to lead to adipose deposition[35], this proposed mechanism could represent a potential pathogenic role of the lymphatic system in Lipedema. It is also possible that lymphatic dysfunction and adipose deposition could work together in a feedback loop that causes disease progression.

Adipose stem cell involvement. In the adipose tissue niche of Lipedema patients, the adipocyte stem cells (ASCs) have been shown to be altered by the disease. Research to date suggests that the ASCs are stimulated by a plethora of inflammatory factors, resulting in enhanced adipogenesis and angiogenesis.[36,37] These phenomena in turn contribute to endothelium dysfunction, fibrosis, and ECM remodeling of tissue.

- Where documented, many specific symptoms (e.g., pain and fatigue) have not been sufficiently characterized. For example, while studies record prevalence of the pain symptom, few studies adequately explore and report nuanced aspects of this pain (e.g., location, duration, type of pain, pain assessment method used). This lack of detailed definition, data gathering, and nuance complicates researchers' ability to hypothesize and identify pathogenic mechanisms and understand their causality.
- Specific mechanisms resulting in initiation and progression are largely undocumented. Sex hormone change is frequently cited as coincident with signs and symptoms but has not yet been mechanistically linked to Lipedema. Genetic or environmental factors may suggest alternative mechanisms leading to initiation or progression of the condition.
- Translational goals of discovery sciences have been slow to progress because of the absence of a fundamental understanding of the disease.
- The relative lack of suitable animal and in vitro model systems, in part due to poor understanding of Lipedema's biological underpinnings, has similarly challenged the ability to test hypotheses under controlled experimental conditions.

Strategic Recommendations

Objective 4. Top Recommendations

- Understand initiation and exacerbation events (e.g., hormonal, genetic, cellular) to characterize the risk of developing Lipedema, and suggest potential prevention strategies.
- Understand progression to develop disease-modifying therapies that reduce the likelihood that a patient will develop severe Lipedema.
- Support rigorous deep phenotyping efforts to carefully describe the diverse phenotypic characteristics present in people with Lipedema.
- Explore the menstrual cycle's relationship to signs and symptoms. Analyze, in particular, circulating sex hormones.
- Utilize simple medical tests, such as urinalysis, to understand variations in the condition.
- Understand the adipose system and adipose environment as a driver of primary disease as well as disease progression.
- Profile immune cells and cytokines in peripheral blood and adipose tissue.
- Conduct studies that confirm the prevalence of different cognitive symptoms and investigate potential biological causes (e.g., brain fog).
- Characterize the adipose microenvironment in affected areas, with attention to lobule organization and fibrosis.

Prioritize Pre-Clinical Research

4.1 Support rigorous deep phenotyping efforts to carefully describe phenotypic characteristics. This will enable a systemic view of changes to the body that are statistically associated with Lipedema.

- Cohorts should be appropriately sized to assess statistical associations between individual phenotypes, comorbidities, and demographic variables. Such comparisons may suggest underlying etiological mechanisms.
- Despite 80 years of study, the depth and anatomic location of Lipedema-affected adipose are not well characterized or understood. There are clear gaps in understanding of differences between adipose locations including the superficial SAT, deep SAT, and visceral depots, as well as different locations on the body. Likewise, questions remain about the degree to which the condition is limited to limbs versus the possibility of signs (e.g., abnormal tissue texture, fibrosis, nodularity) in other areas of the body.

4.2 Understand initiation and exacerbation events to characterize the risk of developing Lipedema and suggest potential prevention strategies.

4.2.1 Identify genetic contributions to risk and establish heritability through population- and family-based studies, including longitudinal studies.

4.2.2 Investigate the hormonal trigger hypothesis. Rare examples of Lipedema in young children force consideration of non-hormonal initiation events that may represent an alternative pathway (e.g., immune response, genetics, trauma, environmental factors, stress).

4.2.3 Consider exploration of signs and symptoms in male relatives of carriers as well as trans females in families where Lipedema seems to be common.

4.2.4 Determine the cell type(s) that drive fundamental disease processes (including differentiated cells such as adipocytes, fibroblasts, and endothelial cells as well as relatively undifferentiated cell types (stem and progenitor), such as adult pluripotent stem cells and others) through live cell imaging and other analysis methods. Understand the interplay between different cell types.

4.2.5 Measure transcriptional changes in all cells in Lipedema adipose tissue compared to lean and control adipose tissue, including single-cell sequencing of intact adipose tissue.

4.2.6 Determine the extracellular and intracellular proteome of tissue using spatial transcriptomic (CyTOF) techniques.

4.2.7 Investigate post-translational modification and signaling events.

4.2.8 Understand the metabolic and inflammatory milieu in tissue.

4.2.9 Explore the potential role of other epigenetic factors as initiating or exacerbating factors (e.g., lifestyle, psychological, socio-economic, other environmental factors).

4.3 Understand progression to develop disease-modifying therapies that reduce the likelihood that a person will develop severe disease.

4.3.1 Understand how specific adipose depots change in response to time or potential triggers of progression.

4.3.2 Better characterize and explore dynamics of cellular contributions to affected tissue.

4.3.3 Characterize the adipose microenvironment in affected areas, with attention to lobule organization and fibrosis.

4.3.4 Characterize crosstalk between affected tissues via paracrine and endocrine signaling.

4.3.5 Consider and investigate the basic biological implications of "successful" therapies. Examine tissue following liposuction, or left in situ following liposuction, for evidence of change.

4.4 Understand symptom triggers and flares and investigate underlying biological causes.

- Patients report periodic flaring of symptoms, defined as patterns of symptomatic quiescence and exacerbation.
- Examples of symptoms reported to flare include feelings of swelling, discomfort, pain, and brain fog.
- Examples of commonly reported triggers include diet (e.g., dietary changes, salty foods), changes in temperature and weather (e.g., heat, atmospheric pressure), clothing and textiles (e.g., rough/heavy material such as denim), and stress.

4.5 Because Lipedema is unlikely to involve single tissue systems, develop hypotheses that account for both primary and secondary interactions that contribute to pathogenesis and impaired QOL.

4.6 Support the development of animal, *in vitro*, *in- silico*, and clinical models.

Characterize by Affected System

Genetics

4.7 Conduct functional validation of results from recently published Genome-Wide Association Studies (GWAS) with attention to differences in participant demographics, diagnostic criteria, inclusion criteria, and exclusion criteria used between studies.

4.8 Design and perform GWAS analysis on new patient cohorts with attention to differences in participant demographics, diagnostic criteria, inclusion criteria, and exclusion criteria used between studies.

4.9 Collect families' DNA and bank samples for future genetic studies, genome-wide genotyping, and whole-exome or whole-genome sequencing (WES or WGS). Although Lipedema is likely to be polygenic, there may be monogenic forms of disease because there are examples of families with mother-to-daughter transmission.

4.10 Build genetic resources available for future association studies by identifying larger numbers of clinically characterized Lipedema populations representing broadened demographic diversity. Although these resources may be considered as specific repositories of biospecimens representing unique cohorts, standard procedures and infrastructure for data sharing to ensure efficient interrogation of collected data must be developed. This resource should consider the value of different sequencing approaches (e.g., WES versus WGS approaches).

4.11 Focus on specific cohorts:

4.11.1 Women whose signs and symptoms began prior to puberty and may therefore represent a strong genetic contribution to risk.

4.11.2 Women whose signs and symptoms began with an unknown relationship to hormonal change, and thereby may represent a subset of women with distinct, and possibly non-hormone related, initiation events.

4.11.3 "Non affected" female and male family members of women with Lipedema, who may exhibit subtle Lipedema-like signs and symptoms.

4.12 In the long term, consider epigenetic studies on new patient cohorts because there is a wide array of phenotypic and temporal signs and symptoms. (This type of analysis may need to wait until more is understood about potential subtypes.)

Cardiovascular System

4.13 Continue investigation to understand prevalence of increased cerebral blood flow. Cerebral blood flow has been reported to be increased in Lipedema patients relative to age- and sex-matched controls.[38]

4.14 Seek independent confirmation of Szolnoky and Nemes' aortic stiffening and dilation phenotype.[39]

4.15 Follow up on studies investigating abnormal left ventricular rotation and mitral annulus.[40,41]

4.16 Follow up on vacuum-based angiosterometry and vascular fragility hypothesis.

- **4.16.1** Determine whether leaky vessels contribute to microedema as imaged by magnetic resonance imaging angiography (MRA), nailfold capillaroscopy, Rumpel Leede, or similar techniques.
- **4.16.2** Confirm reports of varicose veins and telangiectasia, and determine prevalence (Figure 10).
- **4.16.3** Confirm reports of easy bruising and its prevalence.
- **4.16.4** Evaluate molecular drivers of thrombotic outcomes with respect to published reports of PF4 and similar molecules.
- **4.16.5** Confirm skin hypothermia and livedo reticularis/acrocyanosis as clinical signs.

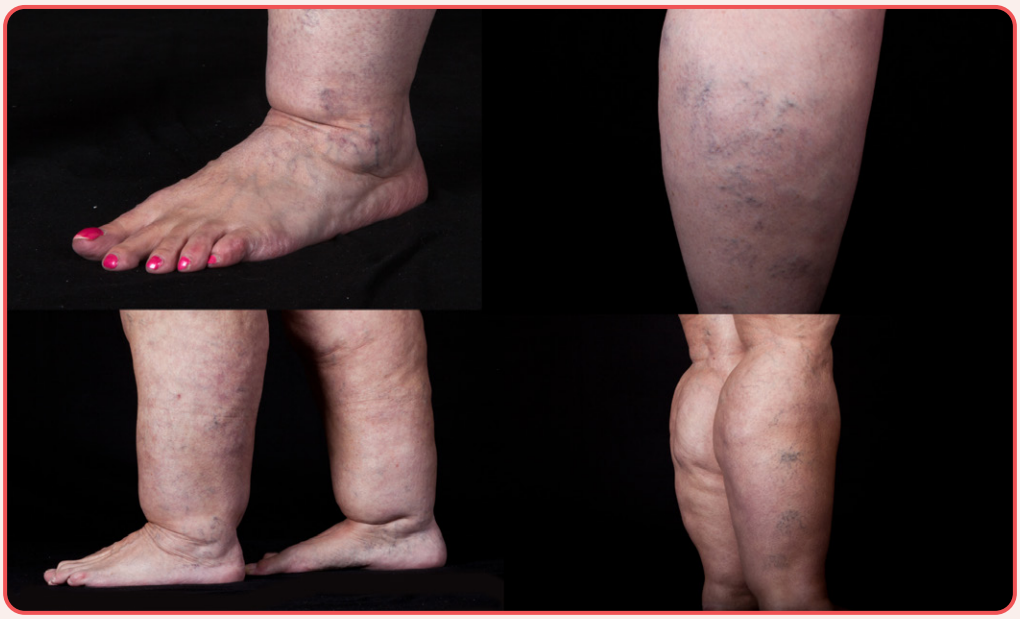

Figure 10. Manifestations of venous insufficiency in women with Lipedema. (Top Left) foot, (Top Right) right calf, (Bottom Left) feet, calves, and ankles, and (Bottom Right) bilateral calves.

Lymphatics and Edema

4.17 Explore the prevalence and origin of any lymphatic deficits that may exist in women with Lipedema.

- **4.17.1** Study the prevalence of any edema or subclinical micro-edema regardless of whether the phenotype is comorbid, secondary, or directly related to Lipedema. This investigation should also explore differences in these phenomena by stage.
- **4.17.2** Examine both structure and function of lymphatics with a focus on documenting anatomic sites and compartments being studied.

- Most common reports (e.g., indocyanine green lymphangiography) may exhibit blind spots with respect to posterior and deeper lymphatic networks, and forthcoming reports should include these considerations if possible. Current near-infrared fluorescence lymphatic imaging (NIRFLI) and tracerless magnetic resonance lymphangiography (MRL) offer benefits beyond these traditional clinical techniques but face limitations in their ability to assess the fine points of lymphatic function.

4.17.3 Explore whether measures of pump strength, frequency, synchrony, efficiency, excess interstitial fluid, or other measures of lymphatic function might reveal distinct Lipedema-associated patterns—potentially by stage—and if so understand their impact.

4.17.4 Confirm whether compensatory changes such as tertiary lymphoid organs (suggested by Ketterings, Rasmussen and colleagues,[42,43] and others) are evident in larger cohorts and can provide a model to account for findings of both slower and more rapid lymphatic transport.

Endocrine and Adipose

SEX HORMONE REGULATION

4.18 Study hormonal connection to initiation events, which is strongly suggested, from pre-pubescent to post-menopausal stages.

4.19 Explore the menstrual cycle's relationship to signs and symptoms. Analyze in particular circulating sex hormones.

4.20 Explore differences in pre- and post-menopausal women.

4.21 Perform simple tests such as urinalysis, which may reveal readily accessible markers of metabolism, salt homeostasis, or hormonal phenotypes. Although unreported in the medical literature, such data may be available in EHRs or through healthcare systems.

4.22 Explore incidence cohorts that would be predicted from long-term surveillance of hormone replacement, contraception, or gender affirming hormone therapy studies in all genders.

4.23 Investigate whether environmental estrogens (e.g., phytoestrogens, microplastics, gut microbiota metabolites) contribute to Lipedema; although isolating the impact of any individual stressor is challenging, similar investigations have been done in obesity research.

ADIPOSE

4.24 Understand to what degree dysfunctional adipose is a sign of underlying disorder or the primary driver of disease.

- There is a parallel debate about the role of adipose in other diseases, including the ischemia and no obstructive coronary artery disease (INOCA) space. In this condition, ectopic fat accumulation in the heart muscle is hypothesized to be a clinical sign rather than the driver of disease.
- There is a need to understand how and in what ways Lipedema fat may differ from "typical" types of fat and how they relate. For example, is Lipedema fat created de novo? Can healthy fat be "texturized" and become Lipedema fat? Could multiple processes be occurring at the same time?

4.25 Characterize body composition of patients by correlating MRI findings to bioimpedance spectroscopy, ultrasound, dual-energy x-ray absorptiometry (DXA/DEXA), or composite measures to better understand the adipose depots affected in patients.

4.26 Understand the histological, morphological, and molecular differences between adipose depots in the superficial SAT, deep SAT, and visceral adipose tissue, and by region of the body. Also investigate and compare these histological, morphological, and molecular differences of various fat depots among Lipedema, healthy lean, obesity, and other lipid disorders.

4.27 Understand the developmental plasticity of the adipose environment and role of adipose stem cells and progenitors in development—that is, conduct lineage tracing of Lipedema adipocytes.

4.27.1 Investigate whether any chromosomal abnormalities prevalent in conventional lipomas are associated with Lipedema-affected adipose. Although more than half of non-Lipedema lipomas may have chromosome aberrations, particularly at 12q13-15,[44] no examination of chromosomal structure has been reported for Lipedema adipose.

4.27.2 Compare the adipose environment to that of lipoma-related conditions, including comparison to fascial tails, encapsulation, and angiolipomas seen in disorders such as Dercum's disease.

4.28 Understand relative contributions of Lipohypertrophy versus lipohyperplasia and the mechanisms involved.

4.29 Analyze Lipedema-affected adipose, which might represent benign tumors, by examining cell cycle regulation. Notable progress in adipose-derived stromal/stem cells demonstrating cell cycle-related phenotypes and molecules should be explored (e.g., Bub1, CD34, ZIC1).

4.30 Investigate potential causes and biology of unusual, nodular, firm, and lobular textures and structures in adipose. In addition to fibrosis and benign tumors, other hypotheses include tertiary lymphoid organs, cysts, and clumps of adipose (Figure 11).

4.31 Characterize the adipose environment with respect to descriptions of key cellular and extracellular players that contribute to Lipedema-affected and non-affected adipose.

4.31.1 Pay specific attention to 3D structure of the adipose environment, including the organization of adipose lobules, using advanced imaging platforms capable of subcellular resolution and multiple marker imaging.

4.31.2 Pay specific attention to fibrosis, adipose inflammation, and ECM composition (including C-Jun, trichrome and picrosirius staining) and any evidence of textural changes between Lipedema and control tissue. This exploration might include examining both skin ligaments and superficial fascia, and small collagen fibers around fat lobules.

4.31.3 Consider consequences of tissue overgrowth and apoptosis with respect to hypoxia and local nutrient supply.[28,45,46]

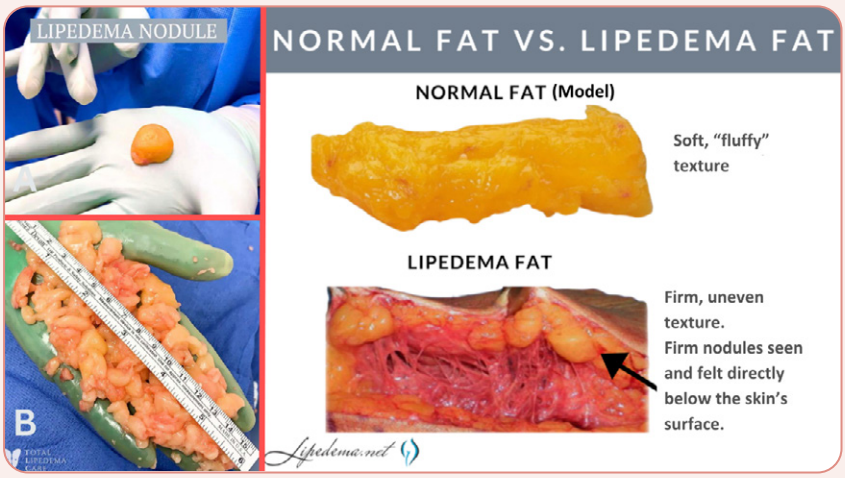

Figure 11. Visual examples of Lipedema fat samples. (A, B) Lipedema fat nodules extracted by Dr. Jaime Schwartz, TotalLipedemaCare.com; (C) Normal fat compared to a Lipedema fat sample from Dr. Jaime Schwartz. Publication credit to Dr. Thomas Wright, Lipedema.net.

METABOLIC CHANGES

4.32 Characterize subcellular architecture of Lipedema-affected adipose, including thermogenic and energy expenditure properties such as beiging, lipid storage, lipolysis, mitochondrial function (including the role of UCP-1).

4.33 Investigate the secretion of molecules from adipose tissue, including adipokines, to understand how they are affected in individuals with Lipedema versus lean and obese individuals.

4.34 Examine the crosstalk between the adipose tissue and liver via the FGF21 metabolic pathway.

4.35 Prioritize systematic study of thyroid function to understand whether higher incidence of hypothyroidism exists outside of patient/clinician reporting.

4.36 Investigate whether hypothyroidism is a causal mechanism and the degree to which hypothyroidism associates with the condition independent of adiposity, because neither have been reported.

4.37 Understand the dynamics of metabolic changes throughout progression.

- **4.37.1** Perform additional studies to confirm reports of overall preserved metabolic health in people with Lipedema (e.g., low rates of diabetes). Previous reports have largely been upheld but have recently been challenged and therefore warrant replication in structured studies with attention to metabolic stability and any changes to metabolic status with progression. Controls are a challenge because BMI and age are not sufficient to match control versus Lipedema; additional data are required.
- **4.37.2** Investigate patient reports of general resistance to dietary and exercise interventions to understand specific body composition effects and cellular and molecular changes across the body following weight loss.
- **4.37.3** Consider Lipedema as a metabolically healthy obesity (MHO) state. Patients should be compared to MHO individuals without Lipedema to understand whether Lipedema constitutes a type of MHO.

4.38 Investigate whether patient and clinician reports of continued weight loss in the months following liposuction in Lipedema patients differ from similar reports for post-surgical weight loss in other conditions. Some clinicians note this phenomenon particularly in larger patients. If true, investigate potential factors driving this phenomenon, such as an improved adipose and/or inflammatory environment.

- **4.38.1** Also monitor the re-acquisition of Lipedema tissue post-surgery.

4.39 Explore the molecular mechanisms underlying fat resistance by challenging Lipedema participants with acute and/or chronic exercise, aerobic exercise, diet, spontaneous exposure to colder temperatures, and other potential stressors and by investigating fat depots prior to, after, and at various stages of the selected challenge.

4.40 Validate the correlation of hypovitaminosis D in Lipedema.[47]

RENAL AND HEPATIC FUNCTION

4.41 Conduct kidney functional analysis of Lipedema patients. No study of kidney functional analysis has been reported, although tissue sodium changes suggest the need for evaluation to understand quality of sodium homeostatic mechanisms. One potential approach could be retrospective analysis of EHRs, specifically investigating estimated glomerular filtration rate (eGFR).

4.42 Explore tissue sodium accumulation to understand whether it results from clearance failures or enhanced deposition of sodium in tissue.

4.43 Formally evaluate clinical reports of adipose accumulation in the liver.[48]

IMMUNE

4.44 Employ unbiased approaches to profiling the immune cell and cytokine profiles relative to unaffected control tissue in the peripheral blood and adipose tissue, including any potential correlation between immune function and disease stage.

4.45 Conduct follow-up studies on specific questions related to known immune contributors, such as the following:

4.45.1 Average activation status/polarization of macrophages relative to unaffected tissue and unaffected individuals.

4.45.2 Whether macrophage M2 polarization drives adipogenesis and angiogenesis in vivo.

4.45.3 Distribution and activation status of mast cells relative to unaffected tissue and unaffected individuals.

4.45.4 Whether mast cells are recruited to Lipedema-affected adipose relative to obesity matched controls. Mast cell involvement has been suggested by histological observation of CD117, although RNA sequencing of CD11b+ cells has been more equivocating.[49] In addition, mast cell interactions with fibrotic environments and the SAT should be explored based on suggestions that mast cell activation is associated with the release of inflammatory cytokines and histamine.

4.45.5 The recent hypothesis that bacteria-derived lipopolysaccharides in gluteofemoral white adipose tissue might stimulate a range of features consistent with Lipedema, including fibrosis and adipogenesis, which would also be consistent with mast cell recruitment to the same area.

4.45.6 Observations of lower progesterone receptors on tissue-resident mast cells in Lipedema, which have prompted a hypothesis that histamine release could affect local vascular permeability. This topic, and progesterone concentration itself, should be considered further in future research.

4.46 Study the effects of immune-modulating drugs, allergy rates, or antihistamines on women with Lipedema. Review of EHRs could potentially suggest differing outcomes for women on specific medications.

Nervous System and Pain

GENERAL NEURONAL PHENOTYPES

4.47 Conduct systematic studies to understand the characterization of the electrical parameters of neurons. Although not suggested by case reports, a deficit in conduction or latency may be predicted by recent studies reporting allodynia.[50]

4.48 Integrate more precise understanding of clinical presentations to suggest hypotheses regarding specific molecular mechanisms beyond what has been provided through discovery science approaches to neuroscience thus far.

4.49 Understand whether innervation of the superficial fascia or deep fascia and, more generally, of the subcutaneous tissue is altered. Inflamed fascia is known to increase the amount of free nerve endings.

PAIN

4.50 Consider and propose whether pain should be required for diagnosis and, if so, by what measurement. Questions worth consideration include the following:

- If pain is to be used as a diagnostic criterion, what duration (i.e., chronic, acute), type (i.e., nociceptive, neuropathic, central sensitization), or method of assessment (i.e., palpation, scales, threshold testing) should be considered, given that pain is highly variable across individuals and pain assessment is currently subjective? How should pain diagnosis account for the extensive list of ~30

diverse descriptions of pain reported by Schmeller and Meier-Vollrath[51] and other descriptors such as "shearing"?

- Is there a pain-free early/prodromal stage (e.g., Lipohypertrophy), as some propose, that sometimes progresses to have pain?
- Which patients develop pain and might there be subtype(s) that do not present with pain but do present other signs and symptoms (e.g., canonical adipose distribution, cuff sign at the wrists or ankles)?

4.51 Characterize domains of pain—such as type (i.e., nociceptive, neuropathic, central sensitization), description,[51] duration (i.e., chronic, acute), frequency, intensity, interference, location (deep versus skin-associated—that are most typically involved in Lipedema.

- Pain in Lipedema patients may be primary as reported in recent literature but may also be secondary because of joint destabilization or discomfort from clothing or compression garments. The potential for multiple types of pain should be considered in studies that use pain as a measurement.

4.52 Investigate the crosstalk between adipose tissue and the nervous system. Szél and colleagues[52] hypothesized that inflammation of sympathetic sensory nerves may also contribute to neuropathy in Lipedema.

4.53 Develop tests for Lipedema-specific qualities of pain relative to other chronic pain conditions. Consider whether specific characteristics of pain can be used to differentiate Lipedema from other conditions.

4.54 Validate pain measurements in the Lipedema population if pain is to be used to inform basic biology questions, or as a therapeutic target or endpoint in clinical trials.

Mental health and Cognition

4.55 Conduct studies that confirm the prevalence of different mental health symptoms and investigate potential biological causes (e.g., immune or metabolism changes manifesting as mental health symptoms including depression and anxiety). Investigate whether a clear mechanism exists to connect mental health–related symptoms to the underlying etiology of Lipedema, although some limited evidence points to the relatedness of specific symptoms.[39] In addition, research suggests a potential correlation between Ehlers-Danlos Syndrome and psychiatric conditions.[40,41]

4.56 Consider whether to include analysis of signs and symptoms without a biologically plausible mechanism of action, because they are likely to be managed symptomatically without respect to the underlying Lipedema. They may be better addressed in other fields of study (e.g., lupus, long COVID, chronic fatigue syndrome) and may benefit from a consideration of mental health as a component of a more holistic concept of health.

4.57 Conduct studies that confirm the prevalence of different cognitive symptoms and investigate potential biological causes (e.g., brain fog).

Dermal

4.58 Investigate reports of visible differences in the skin in historic literature for prevalence in structured studies, including translucency.[53] The presence of erythrocyanosis has been suggested as indicative of a subtype of Lipedema.[54,55]

4.59 Follow up on studies that have suggested that skin thickness may be increased in Lipedema relative to controls by performing a histological examination of this phenomenon, as well as the degree to which it differentiates Lipedema from lymphedema and obesity; this could potentially be done using images and tissue samples from existing studies.

4.60 Test for a functional role of skin sodium and any interplay with immune, adipose, and microvascular regulation.

4.61 Consider and document any effect on other skin structures including hair and sweat glands (that may be responsive to sex hormones), including patient reports of post-liposuction hair growth and tanning.

4.62 Confirm tissue elasticity changes over time that may account for skin thickness or "peau d'orange" appearance.[53]

4.63 Confirm the observation of reduced density of structures such as dermal lymphatics[56] and dermal neurons.[50]

4.64 Examine the frequency and stage association with perniosis follicularis and other cold cutaneous signs and symptoms.

Pelvic

4.65 Perform exploratory research to understand patient pelvic health issues. Validate findings from a retrospective analysis of EHRs of an association between abnormal uterine bleeding and urinary tract infection and Lipedema.[57] A single case study reported a uterine abnormality.[55]

4.66 Study pelvic congestion and pelvic floor dysfunction, which are noted to be common comorbid conditions experienced by people with Lipedema (e.g., hypermobility spectrum disorder, pelvic venous insufficiency). These conditions have been reported by patients and healthcare providers but remain unaddressed in research literature.

4.67 Study impacts of sexuality and intimacy. These components of health-related QOL (HRQOL) have received little attention in research.

Fascia

4.67.1 Understand to what degree different fascia systems are disrupted or disorganized, and the implications for diagnosis or therapy.

4.67.2 Evaluate whether the superficial fascia and related skin ligaments (also called retinacula cutis) are involved and what types of alterations are present in collagen components, sensitive and autonomic innervation, hyaluronan, and cell types including fibroblasts, myofibroblasts, immune cells.

4.67.3 Evaluate whether the 3D organization of the subcutaneous tissue is maintained or disrupted, as has been shown in other pathologies, such as lymphedema.

4.68 Investigate whether any structural change implies a consequent functional change to the fascia's typical roles in the body including tissue support, blood and lymph flow, fluid movement, gliding functions, and wound repair.

Extracellular Environment and Related

4.69 Understand to what degree other extracellular features such as skin ligament networks or adipose lobule septa are affected by Lipedema or comorbid conditions. Although some single-cell and full-tissue sequencing has been performed to surface alterations in the extracellular environment, more study and validation are needed.

4.70 Perform testing of GAG hypothesis and relation to sodium dynamics in affected tissues. This could include the quantification and molecular weight of hyaluronan, the most common GAG in the fasciae.

4.71 Investigate hypotheses related to ECM deposition and remodeling processes, including molecular characterization of the matrix metalloprotease and caveolin axis.[58]

4.72 Using Lipedematous tissue, explore specific molecules suggested in *in vitro* models (e.g., collagen VI) or possible clinical models (e.g., elastin).[59,60]

4.73 Characterize collagen types at different stages.

Musculoskeletal System

4.74 Explore mechanisms that might contribute to any demonstrable muscle weakness phenotype, including the roles of excess tissue sodium in muscle and crosstalk between muscle and adipose tissue.

4.74.1 Examine three existing reports of muscle strength, endurance, and volume loss with respect to whether the severity of these features is progressive.[61–63]

4.75 Investigate the potential for a systemic joint laxity phenotype, which may enable testing of the hypothesis that Lipedema represents a generalized disorder of connective tissue and may provide a connection to non-canonical signs and symptoms such as back pain, fallen arches, knee instability, and ankle pronation (Figure 12). Hypermobility of joints has been frequently reported in the literature at a prevalence of 17-58%.[64–67]

- Characterization of collagen types in superficial fascia, as well as percentages of various collagen types at different stages, could be instructive.

4.76 Investigate the effect of Lipedema on range of motion. At advanced stages, range of motion impairment has been suggested, but so far mechanistic insight is lacking into whether contributory factors beyond tissue bulk are present.[68,69]

4.77 Explore the potential for mast cell interactions with muscle via histamine release and whether this process could contribute a hypothetical mechanism by which mast cells might contribute to pathogenesis.

Digestive System

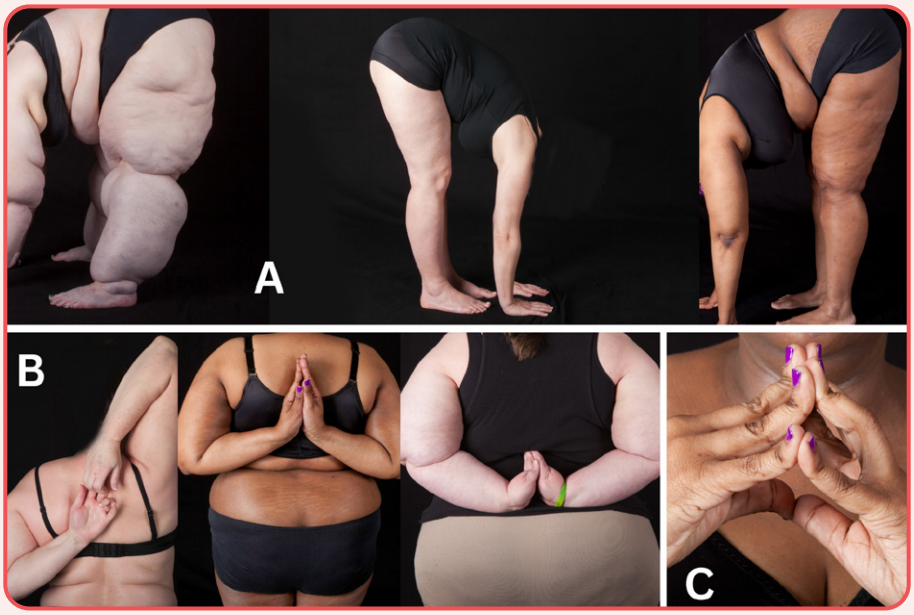

Figure 12. Hypermobility in women with Lipedema. Examples of hypermobility of (A) hip joints, (B) shoulder, elbow, and wrist joints, and (C) finger joints.

4.78 Employ a systematic approach to understanding potential gut phenotypes. No studies on the microbiome or gut lacteals exist in Lipedema research. In lymphatic conditions, microbiome or gut lacteals may be disrupted. Gut dysregulation may be impacted by diets focusing on medium chain triglycerides versus long chain triglycerides. Identification and understanding of common mechanisms shared with these conditions may explain the apparent comorbid associations of these conditions.

4.79 Sequence fecal flora and perform mass spectroscopy profiling of organic acids.

Characterize by Body Segment

4.80 Investigate potential systemic effects of Lipedema affecting multiple tissues systems and regions of the body.

4.81 Consider the possibility that Lipedema-associated changes are found across the body, albeit at a lower prevalence or to a lesser degree. Multiple efforts have suggested that pain, swelling and fibrosis, textural changes, and nodularity are found outside of the limbs of women with Lipedema. Particular attention should be paid to adipose tissue irregularity in the abdomen, face, hands, and feet.

- **4.81.1** Conduct detailed clinical phenotyping in different patient groups and across stages. Progress in this area will likely require a Lipedema-specific working group to consider what an effective approach would entail because of the complexities of Lipedema's genetic and phenotypic heterogeneity and a relative scarcity of relevant data. Current EHR-based approaches such as Human Phenotype Ontology or SNOMED offer a consistent nomenclature for describing phenotypes. However, the necessity for case matching and longitudinal collection makes meaningful progress nontrivial relative to available resources. Inclusion of other complex disease communities such as diabetes or Parkinson's disease may help develop guidance appropriate for advancement.
- **4.81.2** For the systems referenced above, leverage the different contributions or functions of different segments to query basic relationships between Lipedema and lymphatics. This work might inform development of diagnostic approaches.
- **4.81.3** Collect longitudinal data. With respect to body segment, whether segment-specific parameters might influence progression in that segment is unknown.
- **4.81.4** Study the degree to which affected depots influence the rate of incidence or progression in other segments.

4.82 Investigate the scattered, informal clinical reports of potentially four groups of Lipedema body types: shorter, muscular, tall, and arm involvement significantly delayed behind leg involvement.

4.83 Support phenotyping through cadaver studies.

4.84 Conduct studies to explore why hands and feet are "spared."

- **4.84.1** Investigate reports of nodular structures in hands and feet.

4.85 Develop a consistent description of the biology of cuffing to support consistent and replicable research. This description should expand beyond speculation that the lymphatic drainage pathways are different.

4.86 Investigate why not all women have cuffing signs.

Develop Models

There is a vast need for experimental models as a component of the infrastructure of the research community. Any given model will not fully recapitulate the entirety of the condition but may nevertheless have tremendous importance in creating testing environments in which specific questions can be addressed rapidly, at low cost, and often with reduced concerns for human welfare. Some suggestions for future model exploration are vascular permeability (rather than primary vascular defect as in the Notch4 model), immunological aberrations (macrophages), and adipose tissue defects.

Mouse Models

There are significant physiological differences between mice and humans in the organization of both adipose and lymphatics. Humans differ from standard animal models with respect to intrinsic factors such as distinctions in lymphatic and adipose anatomy, as well as physiological responses to extrinsic factors such as gravity. Thus, the likelihood that any model will completely recapitulate the human phenotypes is low. However, modeling of specific features is very likely to be transformative in its ability to probe relevant molecular pathways and test future therapeutics under controlled genetic, dietary, and environmental backgrounds.

4.87 Evaluate the potential of proposed mouse models, including the "Notch4" mouse.

- Recent demonstration of enhanced SAT deposition and reduced dermal lymphatics in Notch4 deficient female mice may offer an opportunity to model sex-dependent adipose and lymphatic crosstalk in a manner that may have relevance to mechanisms at play in Lipedema.[56] However, it should be noted that Notch4 impacts multiple cell functions and may not adequately recapitulate key features of the condition, particularly because it has not appeared in recent GWAS study results.[64]

4.88 Validate all prior genetics hits in an *in vivo* or *in vitro* system. Although priority should be placed on data arising from unbiased -omic approaches, there is value in examining specific candidate genes with plausible mechanisms (e.g., Akr1c1) as well.

- CRISPR gene editing could be used to research any molecular regulators or switches known to be implicated in Lipedema.

4.89 Explore surgically induced models of Lipedema (e.g., xenograft or ligation or ablation experiments). Hypotheses such as the Kruglikov endotoxin hypothesis would be amenable to testing in this kind of mouse model.

4.90 Consider other potential mouse models such as humanized immunodeficient mice grafted with Lipedema tissue or fat organoids.

Other Models

4.91 Develop *in vitro* models (including "on-chip" and organoid engineered systems).

4.91.1 Understand the degree to which adipose stem cells or progenitor populations recapitulate Lipedema phenotypes seen *in vivo*.

- Adipose stem cell lines have been important for characterizing adipose-specific phenotypes including proliferation and differences in developmental potential. Cell lines exist for both Lipedema and control populations, as do a limited diversity of fat depots from Lipedema-affected women.
- Although proliferation phenotypes have been consistently reported, effects on mechanosensation, lipid metabolism, and energetics are underreported for this model.

4.91.2 Pursue development of fluid dynamics models.

- Microcultures of lymphatics, adipose, or ECM environments have roles in describing fluid transport and generating hypotheses regarding testing of fluid accumulation and transport defects. No models have thus far been published, though some are known to be in development.

4.92 Develop clinical models.

- Explore clinical models for Williams Syndrome (WS). Mechanisms linking WS phenotype to therapeutic and WS-related pathologic hormonal changes are of interest, although likely difficult to study directly in the WS population because of challenges in recruiting to WS clinical studies.
- Progression models are needed for identification of rapidly or slowly progressing cohorts for both basic biology understanding and as a potential cohort for consideration in future clinical studies. A rapidly progressing cohort would require less time to observe changes in a multi-year study than a cohort that progresses at the population average.

OBJECTIVE 5.
Develop Treatments

Introduction

Although research into the basic biological questions about Lipedema prioritized in this Roadmap can help lead to effective therapies for the disease, several other principles of therapeutic development are also critical. First, effectively managing the condition's impact on patients will require developing high-quality outcome measures that reflect patient and clinical needs—which requires the identification of appropriate controls. Second, treatment development should respect the need for a broad array of options for patients, acknowledging differences in signs and symptoms and individual therapeutic goals. Finally, interventions should be evaluated for cost-effectiveness.

Recommendations to efficiently create opportunities to improve existing therapies or discover new interventions are summarized below.

Challenges to Progress

- A lack of mechanistic understanding of the disease limits the ability to efficiently target and investigate repurposed and new potential therapeutics.
- Little is known about disease progression and which treatments may or may not slow or even stop progression.
- Evidence on efficacy and safety of existing treatments is minimal.
  - Some preliminary evidence based on small sample studies indicates that physical therapy (including multimodal mnual therapy, exercise, and education[70]) and complete decongestive therapy plus exercise and compression[71] can improve inflammation, function, and QOL, although these preliminary conclusions warrant further research.
  - Therapeutic reduction of pain has been reported following conservative treatments including manual lymphatic drainage and compression/pneumatic pumps,[67,69–75] liposuction,[76–81] and dietary interventions.[82–85]
  - Patient and clinician reports indicate a prevailing view that Lipedema tissue is inadequately responsive to caloric restriction and exercise, although published research confirming this view is still nascent.
  - Liposuction is often characterized by retrospective studies examining effectiveness and safety. Despite the accumulation of knowledge reflecting favorably on this intervention, many questions remain regarding variations in the technique, choice of endpoints and outcome measurements, and the impact of surgery on younger or earlier-stage patients.
  - Questions also remain about feasibility, cost-effectiveness, and access and equity implications of liposuction, an expensive procedure for which

there is likely to be insufficient supply of well-trained surgeons and limited reimbursement by insurance companies. For reference, in 2020 in the United States, approximately 211,067 total liposuction procedures (including cosmetic procedures) were performed—a small number compared to an adult patient population believed to be in the millions.[86] Anecdotally, there is a particular shortage of surgeons both familiar with Lipedema and qualified to do high-volume lipectomy.

- High-quality peer-reviewed research on safety and efficacy of other treatments in Lipedema patient populations (e.g., nutritional foods, many devices and garments, pharmaceuticals such as GLP-1 receptor agonist drugs) is of variable quality and currently lacking.

- In many cases, patients may not have received a formal diagnosis or may have an uncertain diagnosis. Nonetheless, they are using many treatments without a clear sense of which ones are likely to be beneficial and safe in the short and long term (Figure 13). Thus, risk-benefit analyses must include the potential that some individuals may derive no Lipedema-specific benefit but may still be exposed to risk.
- The field lacks a clear sense of which outcomes matter most to patients and therefore which should be prioritized. As awareness and availability of research data grow, expectations regarding treatment outcomes may also change. The field is currently not configured to monitor longitudinal changes in patient perceptions or prioritizations, much less able to perform such evaluations with respect to regional or cultural differences.
- No HRQOL domain or instrument has been validated in a Lipedema patient population, although some instruments may be of value (e.g., the NIH's Patient Reported Medical Outcome Measurement Information System

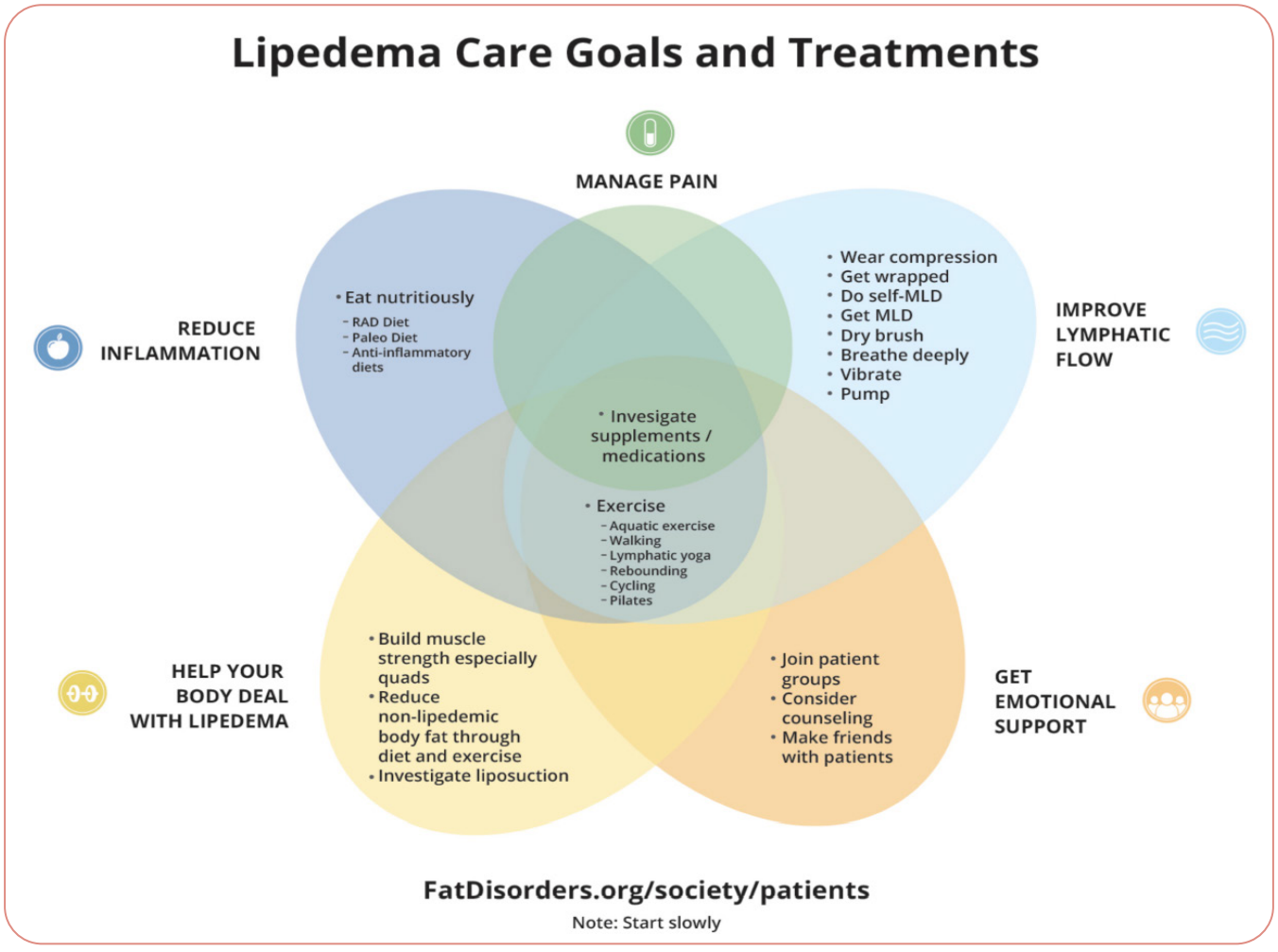

Figure 13. Many treatments are already in use by patients; most lack data about safety and efficacy.
Source: Fat Disorders Resource Society. fatdisorders.org/treatments-summary

[PROMIS], which is validated in U.S. populations, and the Lymphedema Quality of Life Questionnaire [LYMQOL], which is validated in lymphedema). A lack of defined canonical signs and symptoms further limits the relative value of using specific signs and symptoms as endpoints in clinical studies.

- Anecdotal reports suggest many clinicians may be administering multiple therapies simultaneously and patients may also be trying other approaches through self-management. In the context of research, if treatment application is not carefully controlled, this simultaneity of therapy makes it difficult to isolate the independent effect of individual therapies.
- Many studies on treatments focus on endpoints that are biological (e.g., tissue sodium) or anatomical (e.g., limb volume or circumference, BMI) whereas few focus on functional outcomes and impact on daily life and physical activity (e.g., 6-minute walking test). In addition, there is potential for more studies to focus on more varied and holistic measures of functioning, as proposed in the World Health Organization's ICF.[8]

Busy clinical schedules, limited opportunities to participate in research, and low levels of familiarity with research methodologies, standards, and practices limit the ability of clinicians to contribute meaningfully to applied and basic research—even though they are invaluable sources of practical knowledge.

Strategic Recommendations

Objective 5. Top Recommendations

- Investigate the canonical belief that Lipedema tissue is resistant to caloric restriction.
- Conduct rigorous, sufficiently powered research on the contribution of diet, exercise, and other modifiable behavioral approaches to stopping or slowing disease progression, reversing disease, and improving QOL.
- Leverage and validate patient-reported outcome measures (PROMs), clinician-reported outcomes measures (CROMs), integrative measurements of HRQOL in Lipedema populations, and measures of physical function and daily life.
- Conduct studies that disaggregate the effects of individual elements of therapy, and build upon existing small studies on conservative therapy.
- Understand patient prioritization of outcomes.
- Investigate the potential of GLP-1 receptor agonists (e.g., semaglutide) and future related drugs and drug classes in Lipedema patients.
- Further develop the research base around safety and efficacy of liposuction.

Conduct More and Higher-Quality Research on Treatments

5.1 Develop and provide a routine assessment of the therapeutic pipeline and the relative maturity of different therapeutic approaches, including recommendations for funding support by private and public entities.

5.2 In the absence of clinical trials and other high-quality prospective research on treatment efficacy and safety, explore near-term opportunities to improve the rigor of existing treatment research.

5.2.1 Conduct observational studies that evaluate the impact of treatments (e.g., compare pre- and post-QOL for patients undergoing a particular treatment regimen).

5.2.2 Investigate "n of 1 trials," "Quantified Self"-style experiments via apps or websites, and other single case designs as potential approaches to aggregating single-patient experience with treatments.

5.2.3 Investigate infrastructure conducive to inclusion of meaningful Real-World Data in future clinical studies.

5.2.4 Encourage and adhere to standards of rigor around clinical study design and contextualization of results.

- Published studies should adhere to best practices around diagnosis and disclosure (see "Develop a Standard Lexicon" chapter for more detail).
- Small pilot studies should be explicitly acknowledged as part of reporting standards. The degree to which such small studies are generalized to broader claims of effectiveness is a concern that needs to be navigated in a manner that still permits documentation of preliminary findings.
- Specific attention should be paid to "where and when" descriptions of any procedures being reported, including a detailed description of the severity of the area of analysis and the severity of the Lipedema involved in the analysis.

5.3 Leverage and validate PROMs, CROMs, integrative measurements of HRQOL in Lipedema populations, and measures of physical function and daily life.

- Specific areas of interest include symptoms such as pain, fatigue, depression, and anxiety, as well as composite measurements relating to mobility and physical function.

5.3.1 Emphasize established testing measures where possible, rather than creating "Lipedema-specific" measures and analysis across many demographic variables.

- Some potential measures are PROMIS, which has been validated in the U.S. population and enables comparison across diseases; WHO's Disability Assessment Schedule; and specific function measures (e.g., Timed Up and Go [TUG] test).

5.3.2 Include a rigorous definition of controls and follow validation best practices to limit bias. In clinical research studies, emphasis should be placed on determining minimal clinically important differences (MCID) due to the relationship to sample size calculations.

5.3.3 Validate HRQOL domains or instruments in a Lipedema patient population.

- Lipedema-specific supplement instruments could be developed for use in conjunction with available valid HRQOL instruments. One instrument that could potentially be adapted in the future and that is currently validated for use in lymphedema populations is the Lymphoedema Patient Reported Outcome Measure (LYMPROM).
- Leverage existing patient surveys and registries (e.g., LFR, Lipoedema UK International Survey on Psychological Well-being In Women With Lipoedema, and existing survey data from Lipoedema UK's The Big Survey 2014, and QOL surveys of Polish women with lipedema[87]) to guide future

hypotheses for validation of future HRQOL domain or instrument. Consider comparing results across countries. Although patient surveys may not always be validated measures, there is still vital information to be gained.

- In the context of clinical research, in addition to focusing on biological and anatomical endpoints, consider incorporating measures of function and impact on daily life. For additional context on this topic and potential functional endpoints, see Kloosterman.[8]

5.4 Understand patient prioritization of outcomes and evaluate patient risk-benefit tradeoff for treatment approaches.

5.4.1 Conduct patient prioritization studies to identify generalizable goals of potential therapies and expectations of successful interventions. Such expectations may not be limited to the endpoints of future studies but may include expectations surrounding issues such as recovery times, financial expense, or aesthetic considerations.

- Attention should be paid to the following:
  - Patient values relative to disease modification or symptom management, including ranking of factors that inform patient therapeutic decisions.
  - Priority assigned to specific measures used as clinical endpoints (e.g., pain versus mobility).
  - Generalizability of conclusions to patient subgroups.
  - Risk tolerance relative to specific adverse events.

5.5 Conduct studies that disaggregate the effects of individual elements of therapy. Simultaneous administration of multiple modes of physician and manual therapies (e.g., manual lymphatic drainage, exercise, compression, fascia work, and functional manual therapy) complicates understanding of the contribution of each individual therapy.

5.5.1 Eventually, conduct high-quality prospective studies (especially clinical trials) to evaluate the safety and efficacy of existing treatments, understanding where possible how these differ across patient subgroups.

5.5.2 Investigate opportunities to integrate CROMs with PROMs for a more holistic picture of outcomes.

5.5.3 Review prospective and retrospective evaluations to assess likelihood of potential risks of specific therapies to assure safety for users. As better characterization of the underlying biology of the disease matures, clinical studies performed in larger populations may prompt awareness of adverse events specific to Lipedema-related mechanisms.

Develop Physical Approaches to Treatment (Physical, Occupational, and Lymphatic Therapy)

5.6 Replicate and build upon existing small pilot and case report–based studies on conservative therapy.

- Of particular interest is further evidence and recommendations about compression, including different types of compression and containment garments.

5.7 Understand the relative contributions of physically manipulable phenomena such as edema or fascial perturbation, and the degree to which manipulation of these elements might positively or negatively impact the Lipedema-affected areas, by performing pre- and post-treatment studies.

5.8 Explore Lipedema-associated changes to tissue texture and their potential association with patient complaints.

5.9 Explore whether systemic changes to muscle or joints may indicate exploration of strengthening or tissue mobilization therapies.

5.10 Study impact on joints and muscle.

5.11 Study the potential of self-care and self-management for at-home treatment as well as "hands-off" approaches to physical therapy.

Develop Metabolic Interventions

5.12 Investigate the canonical belief that Lipedema tissue is resistant to caloric restriction.

5.13 Conduct rigorous, prospective, sufficiently powered research on the contribution of diet, exercise, and other modifiable behavioral approaches to prevent occurrence in susceptible individuals, stop, slow, or reverse progression and improve QOL.

- There is a relative lack of knowledge regarding differential effects of different diets on Lipedema. For example, do hypocaloric diets have different outcomes than Mediterranean or ketogenic approaches?
- In the exercise domain, investigate the potential of graded exercise paradigms.[88] Readers should note recent revisions to the British National Institute for Health and Care Excellence (NICE) guidelines recommending advising against graded exercise in myalgic encephalomyelitis/chronic fatigue syndrome patients.

Develop Pharmaceutical Approaches to Treatment

5.14 Repurpose existing pharmacological therapies as a more efficient near-term approach than the pursuit of novel therapies, given the absence of validated and clear druggable targets.

- Candidate drugs may be informed by review of EHRs for any relationship to Lipedema-related outcomes.
- Studies that include "non-affected" female family members may also illuminate medications that could have potential protective effects.
- Raising awareness about Lipedema patients among pharmaceutical studies and major research centers, to ensure that patients participating in studies are correctly identified and monitored, may be worthwhile.

5.15 Develop a better understanding of the natural history of Lipedema to reveal new targets amenable to pharmacological medication. Some of these targets will already have pharmacological agents known to modify them or their pathways in a manner supportive of consideration of drug repurposing/repositioning strategies.

5.16 Further explore drug repurposing opportunities in therapeutic areas with large and potentially relevant pharmacological armamentaria, such as rheumatology and obesity medicine. Currently available genomic and transcriptomic leads, if validated, may suggest candidate targets for further exploration. Examples include immunomodulatory drugs (such as macrophage modulators or drugs for mast cell depletion in tissue explant or xenotransplant models) and venotonic drugs.

5.16.1 Parallel effort should be made to identify Lipedema patients in existing studies of immunomodulators and weight management interventions.

5.17 Investigate the potential of GLP-1 receptor agonists (e.g., semaglutide) and future related drugs and drug classes in people with Lipedema. As with bariatric surgery and other weight-targeting therapies, understand the impact on overall metabolism and weight management goals as well as therapeutic potential specific to Lipedema signs and symptoms (e.g., pain).

Develop Surgical Approaches to Treatment

5.18 Study the metabolic state of the remaining tissue following liposuction, which may inform future refinements of existing surgical interventions. Lipedema-affected tissue has been hypothesized to be fibrotic and some stakeholders have observed it to be more resistant to removal by liposuction than healthy adipose, though opinions on this subject differ.

5.19 Further develop the research base around safety and efficacy of liposuction. Once further investigated and consensus is reached, recommendations to the field should be developed and disseminated.

- This effort should consider variations in techniques and approaches (e.g., surgical, pre/post-op, in-patient versus out-patient) with respect to differences in proposed therapeutic mechanisms, as well as differential outcomes for different patient subgroups.
- Surgical specifics should be identified in published research and case reports. Proposals for information to include are pre-op procedures and recommendations, post-op procedures and recommendations, equipment utilized, removal versus lift of excess skin, identification of the surgeon, patient differences (e.g., menstrual cycle, menstrual phase of life), medications, and products used before, during and after surgery, and surgeon changes over time.

5.20 Develop an understanding of how guidance for cosmetic surgery might apply to Lipedema. Are there population differences that might provide more clear recommendations for issues such as anesthesia or threshold values for definition of high-volume liposuction?

5.21 Outcomes of bariatric surgery should be further explored, both prospectively and retrospectively, to understand its therapeutic potential relative to signs and symptoms versus its more generalized metabolism and weight management goals.

5.22 Understand short- and long-term musculoskeletal outcomes (e.g., impact on joints, overall function, positive and negative impacts) of surgical intervention.

OBJECTIVE 6.

Cultivate Greater Epidemiology Understanding

Introduction

Epidemiological evidence is lacking for Lipedema—often limited to estimates of population prevalence and widely inclusive of self-assessment data and patients who are self-diagnosed. These data, however, are fundamentally important to estimating both the burden of disease to patients and costs to healthcare systems. Better epidemiological data and understanding would increase research interest, strengthen applications for public and private funding, better articulate the aggregate burden of the disease on the patient population and society at large, and inform further development of healthcare coverage. In the absence of strong diagnostic strategies or consistent medical coding, novel approaches to epidemiology will be required to estimate impacts.

Challenges to Progress

- Conducting prevalence research is clinically intensive, expensive, and often requires larger-scale recruitment tactics.
- Estimations of epidemiological data in both treated and untreated populations are not rigorous enough to
  - create a broader awareness of the disease.
  - demonstrate Lipedema as a serious public health concern.
  - motivate further research.
  - persuade private and public funders to provide substantial support for research.
  - estimate direct and indirect costs of care and treatment. Estimates should consider not only direct medical costs but also lost workplace productivity due to signs and symptoms or time spent seeking and receiving treatment.
  - characterize factors influencing disease severity and access to care.
- Lipedema is often described as rarely diagnosed but not rare. However, available epidemiological data are scarce and of limited quality.
  - Major methodological issues complicate interpretation of most studies performed to date. The frequently cited report that Lipedema may affect as much as 11% of European women has in recent years been questioned.[29,89,90] Despite the lack of data to support estimates in European populations, recent estimates among adult Brazilian women suggest a 12% prevalence in this population.[91]
- Lack of coding and consistent diagnostic criteria complicates epidemiological estimates.
- Inconsistent definitions and applications of diagnostic criteria make it difficult to rely on existing public health databases and datasets (e.g., patient EHRs). (See chapter on "Develop Diagnostic and Biomarker Tools" for recommended strategies.)

- In the United States, a lack of adoption of dedicated medical diagnostic (e.g., ICD and Current Procedural Terminology (CPT) codes related specifically to Lipedema complicates analysis of EHRs.

• There is insufficient diversity represented in currently published epidemiology estimates, including around race, geography, culture, and ethnicity.

• Most of the epidemiology studies have been performed in European populations, with the exception of a recent estimate calculated from a Brazilian population.[91]

- Dutch Guidelines[9] report physician consensus that the condition is exceptionally rare in Asian populations. Some anecdotal evidence suggests that prevalence among women of Asian ancestry is low in Asia, but lifestyle differences with Western countries make direct comparisons difficult.
- The degree to which existing diagnostic criteria apply to non-White populations has not been studied. The absence of a thorough examination of Lipedema in the context of race and ethnicity represents a significant gap in the research.

• The burden of illness is not well understood.

- General HRQOL data are emerging but have not been extrapolated to epidemiological estimates. Uncertainty remains about which instruments most reliably capture HRQOL for Lipedema populations.
- Mental health impact has not been studied from an epidemiological perspective but when reported, anxiety and depression affect 10-25% of various study populations.[87]

• The cost of illness and treatment are not well understood.

- Cost of illness calculations typically require reliable prevalence data in order to make population estimates.
- No systematic survey of individual patient costs to the healthcare system and out-of-pocket costs have been conducted.
- No value framework for evaluation of the cost-effectiveness of therapies has been proposed to date for the patient community.
- Because Lipedema is a chronic condition, common valuations such as the quality-adjusted life-year (QALY) are unlikely to adequately account for long-term gains in health. Therefore, the value of therapy to patients is likely underestimated. Because pricing models for therapies consider QALY estimates, undervaluation can reduce the incentive to innovate new therapies, or provide appropriate reimbursement for existing therapies.
- Other costs to consider include loss of wages (individual cost) and morbidity costs (community and population-level costs).

• It is believed that Lipedema is not itself fatal; no study of all-cause mortality has been reported. Because the condition may lead to complications in receiving care it is conceivable that it may indirectly contribute to premature death in some patients. In addition, some common comorbidities, such as obesity and lymphedema, themselves are associated with serious medical complications. These comorbidities may affect wellbeing by reducing mobility, sleep, or other quality-of-life concerns associated with poorer health.

• Weight biases affect the quality of care.

- Weight and size biases associated with obesity, and overreliance on and flawed interpretations of BMI measures, can negatively affect medical care. Therefore, other conditions may go unrecognized or be inappropriately attributed to weight, leading to delayed or inadequate care.
- Relatively common tools of medicine (e.g., simple blood pressure cuffs and magnetic resonance imaging machines) may be unable to accommodate larger and heavier patients. Such biases may contribute to the avoidance of clinical care or other behaviors associated with negative health outcomes.
- Weight bias can also lead to inadequate or incorrect diagnosis, which in turn, impacts prevalence data.

Strategic Recommendations

Objective 6. Top Recommendations

- Convene stakeholders, including subject matter experts, to develop a rational approach to advancing understanding of epidemiology.
- Consider opportunities to leverage existing studies and resources to make prevalence estimates for Lipedema.
- Gain a better understanding of prevalence across demographic subpopulations, the cost burden of disease, impact on QOL, and mental health burden.

Develop a Strategy for Estimating Prevalence

6.1 Convene stakeholders, including subject matter experts, to develop a rational approach to advancing understanding of epidemiology that

- takes inventory of what efforts are currently under way.
- grades potential approaches by feasibility, cost, speed, effort, and accuracy.
- considers opportunities to better understand epidemiology in specific subpopulations that may advance the goals of well-resourced funding constituencies/agencies (e.g., U.S. military and Department of Defense, cancer and heart disease research funders).

6.2 Consider various potential epidemiology approaches, especially opportunities to leverage existing studies and resources to make estimates for Lipedema.

6.2.1 Cross-sectional resources to leverage include the following:

- Large survey-based studies (e.g., the CDC's National Health and Nutrition Examination Study [NHANES] and *Behavioral Risk Factor Surveillance System* [BRFSS] telephone survey).
- Monitoring of consecutive cases at specialty medical practices.
- Because patients are likely to present to a range of general and specialty practices, awareness of their frequency in those populations is valuable. Specific attention to obstetrics/gynecology, bariatric surgery, or primary care clinics may be helpful in estimating population prevalence in a geographical area because of the likelihood that these practices see a more representative sample of the broader population than may be available in more specialized care scenarios. However, it is important to note that this approach is still biased toward a population with access to and seeking healthcare.
- Imaging data collected as part of national health databases or through novel resources such as millimeter wave imaging data examined as part of airport security. People with Lipedema note difficulties with security screening and air travel.

6.2.2 Case control studies to leverage include those that

- utilize existing EHR systems or genetics databases to identify patients at high risk for or known to have Lipedema as compared to matched controls.
- use EHR databases.
- use large dataset assessments of body shape/morphometry (e.g., German National Cohort [NAKO], UK Biobank, or NHANES, which contain medical imaging datasets that may prove useful for estimating risk of Lipedema in study populations).

6.2.3 Longitudinal studies to develop include

- those that partner with existing obesity or long-term surveillance studies to identify Lipedema incidence in those cohorts. Opportunities for exploration include long-term surveillance of hormone-based contraceptives or follow-up to gender-affirming care.
- Potential examples include Norway HUNT Trøndelag Health Study, the NIH All of Us study, and obesity-specific surveys and databases.
- those that are novel and Lipedema-specific, such that they might be structured to follow progression of disease and impact on HRQOL over time (Box 4). Specific consideration might be given to following women entering periods of hormonal change (e.g., pregnancy, menopause) or children of diagnosed women.

6.3 Generate better understanding of prevalence across demographic subpopulations. Such studies should ideally incorporate demographic parameters such as race, ethnicity, age, gender, sex, and socioeconomic status to support accurate estimations of population prevalence and burden.

Better Understand Burden of Disease

6.4 Better understand impact on QOL. Work with patient groups to prioritize and emphasize QOL domains that matter most to patients and consider disparate impact on groups with high risk for severe QOL impact. QOL impacts include the following:

- Impaired mobility
- Pain
- Gait impairment
- Venous disorders
- Cognitive impacts (e.g., brain fog)
- Fatigue
- Potential development of secondary lymphedema, Dercum's Disease, and obesity
- Mental health issues (see next recommendation for more detail)
- Sexual dysfunction and negative impact on intimacy

6.5 Better understand mental health burden for individuals and the general population. Mental health burdens include the following:

- Comorbid mental disorders (e.g., anxiety, depression) over time (e.g., longitudinal mental health study)
- Self-perception and self-worth
- Impact on socialization and social life, including sexual health
- Eating disorders, for example, simultaneous anorexia nervosa and Lipedema-induced obesity

- Self-harm
- Suicide

6.6 Understand the cost burden of disease. Incorporate, as feasible, common metrics such as QALY and disability-adjusted life years. Components of the cost burden of disease include the following:

- Cost of care (direct and indirect)
- Patient out-of-pocket expenses
- Presenteeism
- Absenteeism
- Leaving the workforce
- Financial toxicity
- Mental health impacts
- Mental health burden on patients
- Psychosocial impacts on family members and caretakers

Box 6. Considerations for Longitudinal Burden of Illness Studies

Given patient report of disease initiation and progression around periods of hormonal change, future cost burden of disease analysis might consider how impact varies during different phases of life demarcated by periods of hormonal change, such as

- Youth to puberty
- Puberty to pregnancy
- Pregnancy through pregnancy loss or birth
- Giving birth to 12 months after cessation of breastfeeding
- Fertility to perimenopause
- Perimenopause to menopause
- Post-menopause

Other subpopulations/segments/life events that may be of interest to analyze include

- Children of people with Lipedema
- Recipients of abdominal surgery or Caesarean sections
- Recipients of sex change or gender-affirming care (male to female or female to male)
- Initiation and termination of birth control (e.g., pill, IUD)

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APPENDIX C: REFERENCES

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APPENDIX D: LIST OF ABBREVIATIONS

AUC	area under the curve
BEST	Biomarkers, EndpointS, and other Tools
BRFSS	Behavioral Risk Factor Surveillance System
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence Interval
CME	continuing medical education
CoE	center of excellence
CPT	Current Procedural Terminology
CRF	case report form
CRISPR	clustered regularly interspersed short palindromic repeats
CROMs	clinician reported outcomes measures
CTA	computed tomography angiography
CVI	chronic venous insufficiency
DEXA	dual-energy X-ray absorptiometry
DXA	dual-energy X-ray absorptiometry
ECM	extracellular matrix
eGFR	estimated glomerular filtration rate
EHR	electronic health record
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FM	fat mass
GAG	glycosaminoglycan
GWAS	Genome-Wide Association Study
HRQOL	health-related quality of life
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability, and Health
INOCA	ischemia with no obstructive arteries
L-Dex	Lymphedema Index
LC-MS	Liquid Chromatography mass spectrometry
LF	Lipedema Foundation
LFR	Lipedema Foundation Registry
LYMPROM	Lymphoedema Patient Reported Outcome Measure
LYMQOL	Lymphoedema Quality of Life tool
MCAS	mast cell activation syndrome
MCID	minimal clinically important difference
MDA	malondialdehyde
MHO	metabolically healthy obesity
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MRL	magnetic resonance lymphangiography
MS	mass spectrometry
NGS	Next-generation sequencing
NHANES	National Health and Nutrition Examination Study
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIRFLI	near-infrared fluorescence lymphatic imaging
PC	Phosphatidylcholine
PCOS	polycystic ovarian syndrome
POTS	postural orthostatic tachycardia syndrome

PROMs	patient reported outcome measures
PROMIS	Patient-Reported Outcomes Measurement Information System
QALY	quality-adjusted life year
qPCR	quantitative polymerase chain reaction
QOL	quality of life
ROC	receiver operating characteristic curve
RNA	ribonucleic acid
SAT	subcutaneous adipose tissue
scRNA-seq	single-cell RNA sequencing
SNOMED	Systemized Nomenclature of Medicine
snRNA-seq	Small Nuclear RNA Sequencing
TUG	Timed Up and Go
VIPAR	volume information-based histopathological analysis by 3D reconstruction and data extraction
WES	whole-exome sequencing
WGS	whole-genome sequencing
WHO	World Health Organization
WHtR	waist-to-height ratio
WS	Williams Syndrome