

Comparison of Staging Systems to Assess Lymphedema Caused by Cancer Therapies, Lymphatic Filariasis, and Podoconiosis

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Abstract

Background: Lymphedema is a disease of the skin and subcutaneous tissue resulting from a disturbance in lymph flow. Anyone can be affected, and causes include cancer therapy when lymph nodes are removed or irradiated, the parasitic disease lymphatic filariasis, and damage caused by exposure to irritant soils known as podoconiosis. Manifest lymphedema is progressive and a major contributor to disability, stigma, and social isolation for affected people. Although the pathogenesis of connective tissue changes in lymphedema will follow a similar course regardless of the disease of causation, several systems are used to stage progression. Disparity in these staging systems leads to inconsistency in reporting of the severity of lymphedema and prevents meta-analysis of research results. In the global health environment, integrated morbidity management for chronic illness is essential to meet the needs of affected people and to be sustainable for health care systems. Clinical descriptors for staging criteria within each system may assist clinicians in assessment and provide a format for consistency in reporting by lymphedema researchers.

Methods and Results: Lymphedema staging systems used in oncology, filariasis, and podoconiosis settings were reviewed and the assessment techniques, diagnostic procedures, and clinical observations used by each system are described. The most commonly used staging systems are compared to identify similarities, and a matrix approach to lymphedema staging is proposed.

Conclusion: A universal staging system would contribute to more consistent reporting of research on and clinical management of lymphedema arising from multiple causes.

Keywords: lymphedema, lymphatic filariasis, podoconiosis, oncology/cancer, staging system

Introduction

LYMPHEDEMA IS A leading cause of disability worldwide, yet it remains underdiagnosed, under-researched, and underfunded in most health systems.¹⁻⁵ It is a connective tissue disease that occurs in the subcutaneous tissues when normal lymphatic clearance is disturbed.⁶ The etiology of lymphedema can be wide ranging, and pathogenesis of the resulting connective tissue disease may also vary.⁷⁻¹⁰ Despite these variations, when lymph flow is impeded for any reason, an accumulation of protein-rich fluid in the loose connective tissue follows. This excess fluid is eventually replaced by fibrotic induration and fat deposition. Regardless of the cause, long-term reduction in lymphatic activity will always lead to chronic inflammation, skin pathologies, and an increased risk

of bacterial and fungal infections.^{11,12} Untreated lymphedema is progressive and beyond the earliest stages management becomes increasingly difficult and resource intensive.^{4,13}

Lymphedema can affect anyone. Male, female, young or old, rich or poor, in every country there will be people living with, or at risk of developing lymphedema. Global prevalence estimates are as many as 250 million people worldwide.¹⁴ The major single cause is lymphatic filariasis (LF), a parasitic disease affecting 17 million people in developing tropical countries where it is closely associated with poverty.¹⁵ At the other end of the spectrum, breast-cancer-related lymphedema affects up to 40% of breast cancer survivors,¹⁶ which probably accounts for less than 1 million people worldwide, mostly women in developed country settings. Despite being such a wide-ranging disease affecting people from every demographic and

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socioeconomic group, adequate provision of health care services is lacking in most countries.¹⁴ Research to provide the evidence basis for better provision of such services is hampered by several issues, including heterogeneity in disease manifestation and difficulty in conducting large-scale, randomized interventions.¹⁷ This is exacerbated by inconsistencies in diagnostic criteria and staging of disease progression. Inconsistencies in staging criteria have been previously described,^{18,19} with authors reporting difficulty in identifying lymphedema stages^{20,21} or the lack of suitable data for meta-analysis of study results.²²

Current criteria to determine lymphedema stage display a historically vertical approach to differential diagnosis and management of lymphedema by disease causation. However, increasing global awareness of disability generally, an increasing focus on rehabilitation and inclusion, and the need to offer management strategies within populations affected by multiple chronic diseases has created the need to approach lymphedema from a more holistic view point. This examination of current staging systems aims at bringing together criteria commonly used in oncology, LF, and podoconiosis settings to highlight similarities and differences in staging descriptors. Combining the defining features of lymphedema into a staging matrix rather than a linear disease-specific scale may enable clinicians and health workers in co-endemic areas, or with clients who present with multiple forms of lymphedema, to more accurately and consistently assess lymphedema progression.

Materials and Methods

Current and historical staging systems used to assess lymphedema occurring from cancer therapies, LF, and podoconiosis were reviewed, as well as any assessment techniques, diagnostic procedures, or clinical observations used. Descriptors that determine each stage were entered into a table, and the Common Terminology Criteria for Adverse Events v5.0 (CTCAE)²³ was used as a template to align the severity of each stage across systems.

Designed for adverse events arising from cancer therapy, the CTCAE offers unique clinical descriptions to determine the severity for each adverse event based on a general guideline, which includes symptoms, clinical presentation, level of intervention required, and activities of daily living (ADLs). ADLs are defined as either instrumental ADL—the ability to prepare meals, shop for groceries or clothes, use the telephone, manage money, etc., or self-care ADL—the ability to manage bathing, dressing and undressing, feeding self, using the toilet, and taking medications, without being bedridden. There are five CTCAE grades; however, only the first three grades are relevant to lymphedema. The five CTCAE grades are:

- Grade 1: Mild, asymptomatic, or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate, minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care (ADL).

- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to the adverse event.

A staging matrix was created by using separate domains for edema (E), skin pathologies (S), and degree of disability (D), and levels within each domain (range 0–3) were aligned to common descriptors across systems. This three-domain, three-level matrix produces a staging system in the format Ex.Sx.Dx.

Results

Several staging criteria are currently in use. The International Society of Lymphology (ISL) publishes a biannual consensus document that initially described a three-stage system.²⁴ Later versions include reference to a latent, or covert, stage of lymphedema,⁶ which is mostly relevant to oncology-related lymphedema. More recently, the International Lymphedema Framework (ILF)²⁵ has described a five-stage system based on the ISL stages which includes a definition for latent (stage 0) lymphedema, and it also splits stage 2 into early and late substages (stages 2A and 2B). In LF-related lymphedema, the World Health Organization (WHO) initially recommended the use of a four-stage system,²⁶ later simplified to three stages⁷ but after publication of a manual on management of LF-related lymphedema by Dreyer et al.,²⁷ a seven-stage system has been adopted. Although the seven-stage system has been shown to have good inter-rater reliability,²⁸ researchers have collapsed these stages into a simpler three-stage format of mild (stages 1 and 2), moderate (stage 3, or stages 3 and 4), and severe (stages 5 and 6, or stages 4–7).^{29,30} A five-stage system, adapted from the Dreyer seven stages, has been developed and field tested for lymphedema caused by podoconiosis.³¹ Although podoconiosis and LF-related lymphedema are frequently co-endemic, the development of a podoconiosis-specific system was driven by recognition of differences in the clinical presentation between the two etiologies. To overcome inconsistencies between staging systems, some researchers have defined their own criteria for staging of disease-specific lymphedema.³²

Assessment techniques and lymphedema staging systems

Various methods can be used to quantify the physiological changes occurring in lymphedema, and in breast cancer-related lymphedema, self-reported symptoms are also frequently acknowledged.^{33,34} No single assessment procedure or diagnostic test is accepted across all forms of lymphedema and each staging system may use several different criteria to determine each stage. The most commonly used assessment tools are described first and then the staging systems are described.

Assessment techniques, diagnostic criteria, and clinical observations.

Reversal on limb elevation. The affected limb is observed over time, usually overnight or after a period of prolonged elevation, and any variation in observable swelling is noted. The change in swelling may be the effect of resorption of fluid into the venous system under low pressure conditions and is an indication of the volume of free fluid accumulating

in the subcutis. Swelling that does not reverse overnight indicates that connective tissue overgrowth has begun, and that accumulated fluid is less “free.”

Comparison in circumference of the collateral limb. A tape measure is used to record circumference measures of both limbs at defined locations, frequently the ankle or wrist. This measure is best used when there is an unaffected contralateral limb. If the measure is taken over a muscle, an accounting for limb dominance should be included in interpretation of the results. Circumference measures are useful to determine the size of unilateral limb enlargement but do contribute to assessment of underlying connective tissue change or skin pathologies.

Pitting test. A firm pressure is applied perpendicular to the skin into the subcutaneous tissue by using a finger or thumb and held until the underlying tissue deforms. The depth and appearance of the pit will change with lymphedema progression. A deep pit with a rounded base that forms easily and resolves slowly indicates that a protein-rich fluid is present without significant fibrotic induration. Prolonged pressure that produces a shallow pit with a flat base indicates that the fluid load has been largely replaced by the growth of fibrotic tissue or fatty deposits.

Stemmer sign. The skin is pinched and lifted away from the underlying tissue, usually at the base of the toes or fingers. Skin that cannot be lifted away from the subcutaneous tissue (positive Stemmer sign) indicates an edema of lymphatic origin, progressed enough to create subcutaneous connective tissue changes. This test is frequently used in differential diagnosis between edema of a lymphatic origin that will produce a positive Stemmer sign and edema of a vascular origin (phlebedema) that will produce a negative Stemmer sign (skin can be lifted away from the underlying tissue).

Bio-impedance spectroscopy. A low-level, multi-frequency electrical current is passed through the skin and subcutaneous tissue via electrodes attached to the skin. Different frequencies detect resistance in fluid contained within the cells (R_i) and free fluid in the extracellular compartment (R_e). The difference between these fluid compartments can then be compared ($R_i:R_e$). This test can be used to detect a visually imperceptible edema as well as to quantify the free fluid load in more pronounced edema. The stage of lymphedema should be considered in the interpretation of results as although early-stage lymphedema is fluid rich, late-stage lymphedema with heavy fibrosis and fat induration may have little or no excess extracellular fluid.

Assessment of changes in the skin. As lymphedema progresses the epidermis becomes thickened (hyperkeratosis). This may be accompanied by projections of fibrous and fatty overgrowth in the underlying connective tissue appearing as raised lesions—commonly called knobs, lumps, or bumps. Papillomata, frequently referred to as mossy lesions, and warty growths (verruccosis) may also form as the barrier function of the skin is reduced. These skin changes are usually assessed visually but hyperkeratosis can also be assessed by using skin callipers.

Staging systems.

Lymphedema stages as described by the ISL and ILF. These are the only systems that include recognition of a stage

0 (latent lymphedema).^{6,25} Bio-impedance spectroscopy is frequently used to monitor people at risk of arm lymphedema after treatment for breast cancer to identify stage 0, and self-reported symptoms may also be a valid assessment of this stage.^{34,35} The criteria for each stage are determined by history, diagnostic investigation, clinical presentation, pitting test, Stemmer sign, and skin changes. Reduction of edema on elevation and the pitting test are used to differentiate stages 1 and 2, and stage 3 is defined by the presence of any skin changes; however, there are no further distinctions as to the degree of skin changes. This system is most commonly used in developed country settings.

Lymphedema stages as described by the WHO. Developed specifically to assess LF-related lymphedema, this system depends solely on clinical examination of affected body parts.^{7,26} Stages 1 and 2 are differentiated by the response to elevation, and stage 3 is defined by skin changes. If stage 4 is used, this is defined by warty or nodular growths. Other diagnostic criteria that may assist clinical decision making such as the pitting test and Stemmer sign are not used.

Lymphedema stages described by Dreyer et al. Developed specifically to assess progression in LF-related lymphedema, this system also depends solely on clinical observation of affected body parts.²⁷ The stages progressively describe changes observed as edema, which is reversible on elevation (stage 1) and becomes irreversible (stage 2). Stage 3 recognizes the combination of thickened skin and the presence of underlying fibrotic induration that creates shallow folds in the skin. In stage 4, knobs or bumps are present; stage 5 involves deep skin folds that must be separated by hand to see the base; and mossy lesions define stage 6. This system is the only one to include any assessment of the level of disability experienced, and stage 7 is defined by an inability to perform daily self-care activities such as bathing and dressing without help. Although this system appears to give a more detailed account of lymphedema progression, neither the pitting test nor Stemmer sign is used to determine the level of free fluid remaining in the extracellular spaces.

Lymphedema stages described for podoconiosis. Developed specifically to determine progression in podoconiosis-related lymphedema.³¹ This is caused by long-term barefoot exposure to volcanic soils and can cause skin changes in the feet earlier than in other forms of lymphedema. Stages 1 and 2 are still defined by the resolution of edema on elevation (or not), but stage 2 is further defined as swelling that is present only below the knee and may include knobs or bumps that, if present, occur only below the ankle or mossy lesions around the rim of the foot. Knobs and bumps above the ankle indicate stage 3. Stage 4 describes swelling above the knee, and stage 5 is defined by joint fixation at the ankle or toes. This system also allows for further descriptors by the addition of a circumference measure and recording of the presence (M+) or absence (M-) of mossy changes. For example, an individual with stage 2, M-, 25 will have swelling below the knee without mossy lesions and an ankle circumference of 25 cm.³¹

Alignment of the staging systems

The CTCAE²³ is organized by anatomical or physiological system, etiology, or purpose, and adverse events are listed

TABLE 1. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS v5.0 CRITERIA FOR LIMB EDEMA DEFINED AS “A DISORDER CHARACTERIZED BY SWELLING DUE TO EXCESSIVE FLUID ACCUMULATION IN THE UPPER OR LOWER EXTREMITIES”

Grade	Descriptor
1	5%–10% inter-limb discrepancy in volume or circumference at point of greatest visible difference, or swelling or obscuration of anatomic architecture on close inspection
2	>10%–30% inter-limb discrepancy in volume or circumference at point of greatest visible difference, or readily apparent obscuration of anatomic architecture, or obliteration of skin folds, or readily apparent deviation from normal anatomic contour, or limiting instrumental ADL
3	>30% inter-limb discrepancy in volume, or gross deviation from normal anatomic contour, or limiting self-care ADL

ADL, activity of daily living.

within each system along with a description of severity (grade). Categories relevant to lymphedema are general disorders and administration site conditions (edema of the limbs), musculoskeletal and connective tissue disorders (fibrosis of the connective tissues), and generalized edema defined as “fluid accumulation in the tissues of the body including the skin.” Not all CTCAE grades are appropriate for staging and management of lymphedema, therefore grades 4 (life-threatening) and 5 (death) were not used to align the staging systems. Tables 1–3 give the CTCAE grades relevant to edema and fibrosis. Table 4 aligns the lymphedema staging systems with CTCAE grades 1–3.

Proposed lymphedema staging matrix

Based on the common descriptors that aligned across all systems, three domains were created. Domains for swelling and skin changes were ranked in terms of mild, moderate, and severe. A scoring system for the disability domain could be developed from a validated quality-of-life tool, linear scale,

TABLE 2 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS v5.0 CRITERIA FOR FIBROSIS DEFINED AS “A DISORDER CHARACTERIZED BY FIBROTIC DEGENERATION OF THE CONNECTIVE TISSUES”

Grade	Descriptor
1	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)
2	Moderate induration, able to slide skin, unable to pinch skin, or limiting instrumental ADL
3	Severe induration, unable to slide or pinch skin, or limiting joint or orifice movement (e.g., mouth, anus), or limiting self-care ADL

TABLE 3. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS v5.0 CRITERIA FOR GENERALIZED EDEMA DEFINED AS “FLUID ACCUMULATION IN THE TISSUES OF THE BODY INCLUDING THE SKIN”

Grade	Descriptor
1	Noted on exam; 1+ pitting edema
2	Interfering with instrumental ADLs; oral therapy initiated
3	Interfering with self-care ADL; intravenous therapy indicated; skin breakdown

or self-reported symptoms.^{36,37} Table 5 shows the proposed staging matrix with descriptors and potential clinical tests.

Discussion

All staging systems differentiated stages 1 and 2 by observation of the edema after a period of elevation. Skin changes were also used to define further stages, the podoconiosis system being the only one that included any skin change at stage 2. Definitions of swelling were mostly limited to whether there was any reversal on elevation or not, and assessments of skin changes relied solely on visual assessment. No system considered self-reported symptoms; however, studies on prevention of lymphedema after breast cancer suggest that this may be a valid way to detect sub-clinical edema.³⁴

Each system presented a linear progression that was disease specific and could, therefore, result in a person with significant skin changes but minimal swelling to be staged “higher” than someone with a grossly enlarged limb and good skin integrity. This is problematic within the Dreyer system, which has a fixed stage (stage 4) for the presence of knobs (bumps lumps and skin protrusions), but these features may begin to appear in some patients at an early stage or remain absent in another patient with more advanced lymphedema. The linear nature of each system also makes it difficult to correlate stages defined by skin changes with the podoconiosis system. The appearance of mossy lesions in the Dreyer system defines stage 6 but can be present at the feet in podoconiosis at a much earlier stage (stage 2). The ISL/ILF systems do not differentiate between the various skin features, but they are the only systems that recognize that lymphedema has a latent or covert stage. Further, no system adequately takes into account the level of disability that lymphedema causes. The Dreyer system defines stage 7 as the inability to perform self-care ADL but subtler degrees of disability are not acknowledged. Podoconiosis stage 5 is characterized by joint fixation but no degree of accompanying disability is assessed. No staging systems account for the frequency, duration, or severity of acute infections, even though for many people with lymphedema these may be the biggest contributors to disability, reduction in quality of life, and dependence on others.

Only the podoconiosis criteria included objective measures of circumference and recording of specific skin changes to further define the individual presentation for each case. The use of such quantifiers in other staging systems could increase their usefulness to clinicians and researchers in tracking the benefits of interventions or progression over time.

TABLE 4. LYMPHEDEMA STAGING SYSTEMS ALIGNED TO COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS v5.0 GRADING CRITERIA

Stage	ISL/ILF	WHO	Dreyer	Podoconiosis
0	A subclinical state where swelling is not evident. May be present for months/years before clinical symptoms.			
1	A visible swelling that subsides with limb elevation. Pitting test may be negative. If positive, will result in deep pits only.	Mostly pitting edema and spontaneously reversible on elevation.	Lymphedema reversible overnight.	Swelling reversible overnight. The swelling is not present when the patient first gets up in the morning.
2	Stage IIa Limb elevation alone rarely reduces swelling. Deep pitting is manifest. <i>Stage IIb</i> <i>No, or only shallow pitting. Tissue fibrosis is more evident. There may be fatty induration.</i>	Mostly nonpitting edema and not spontaneously reversible on elevation. Skin not thickened.	Irreversible lymphedema with normal skin.	Below-knee swelling that is not completely reversible overnight; if present, knobs/bumps are only below the ankle. Mossy changes may be apparent in a “slipper” pattern around the rim of the foot.
3	<i>The tissue is hard (fibrotic) and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop.</i>	<i>Edema not spontaneously reversible on elevation. Skin thickened, marked dermatosclerosis with or without papillomata.</i>	<i>Irreversible lymphedema with thickened skin and permanent shallow folds, the base of which is visible with joint movement.</i>	<i>Below-knee swelling that is not completely reversible overnight; knobs/bumps present above the ankle.</i>
4		<i>Edema not spontaneously reversible on elevation. Skin thickened with warty/nodular or papillomatous growth.</i>	<i>Irreversible lymphedema with knobs (bumps and lumps).</i>	<i>Above-knee swelling that is not completely reversible overnight; knobs/bumps present at any location.</i>
5			<i>Irreversible lymphedema with deep folds, the base of which is visible when separated by hand.</i>	Joint fixation; swelling at any place in the foot or leg. The ankle or toe joints become fixed and difficult to flex or dorsiflex. This may be accompanied by apparent shortening of the toes.
6			<i>Irreversible lymphedema with mossy lesions.</i>	
7			Irreversible lymphedema, inability to do routine activities adequately.	

Bold fields align to CTCAE Grade 1, *Italic* fields align to CTCAE Grade 2, **Bold and Italic** fields align to CTCAE Grade 3.

CTCAE, Common Terminology Criteria for Adverse Events v5.0; ILF, International Lymphedema Framework; ISL, International Society of Lymphology; WHO, World Health Organization.

Few staging systems have undergone the rigorous reliability analysis that was performed during development of the podoconiosis system.³¹ One study reported a high level of consistency in assessors using the Dreyer 7 stages but these were experienced health workers who had 3 days of training,²⁸ which is not representative of many real-life scenarios, particularly in low-income settings. The podoconiosis system was assessed after only a 2-hour training session for health workers and reflects more accurately the level of training

likely to happen in podoconiosis and LF settings. We found no reliability studies on staging systems in use in cancer-related lymphedema.

Despite the availability of specific staging systems, researchers and clinicians frequently find it convenient to identify lymphedema status as mild, moderate, or severe. When this is based on limb size, rather than the nature of any skin or underlying tissue changes, it may be problematic in all settings. A person with a very large limb who does not

TABLE 5. PROPOSED LYMPHEDEMA STAGING MATRIX

<i>Symptom</i>	<i>Level</i>	<i>Descriptor</i>	<i>Prospective clinical tests</i>
Edema	0	Increased excess extracellular fluid without visible swelling	Bio-impedance spectroscopy
	1	Visible swelling that resolves completely after prolonged elevation	Self-reported symptoms Pitting test
	2	Visible swelling that does not resolve completely after prolonged elevation	Circumference or volume measures
Skin	0	Skin appears normal	Observation
	1	Hyperkeratosis, sclerosis, or connective tissue fibrosis with shallow or no skin folds	Skin calliper Ultrasonography
	2	Deep folds, knobs, papillomatosis, or other obvious skin pathology	Laboratory testing for pathogens
	3	Ulceration or nonhealing wounds, significant interdigital lesions	
Disability	0	None	Validated QoL ^a tool relevant to the population tested
	1	Minor interruption to instrumental ADL ^b	
	2	Major interruption to instrumental ADL	
	3	Interruption to self-care ADL ^c	

^aA QoL tool is a survey that assesses how people's experience of their disease or condition affects their life across multiple domains.

^bInstrumental ADL—the ability to prepare meals, shop for groceries or clothes, use the telephone, manage money, etc.

^cSelf-care ADL—the ability to manage bathing, dressing and undressing, feeding self, using the toilet, and taking medications, without being bedridden.

ADL, activities of daily living; QoL, quality of life.

suffer debilitating infections or significant disability may be considered severe, whereas another individual with a relatively small limb but frequently debilitating secondary infections may be rated as mild or moderate. In research settings, whenever stages are grouped into broader clusters, or are based on limb size alone, some sensitivity will be lost in analysis of the outcomes of the intervention. In resource-poor areas, it may also be useful for health care workers to identify analogous disease stages to guide treatment; however, the currently available staging systems are inadequate for this purpose.

Using the proposed matrix, a breast cancer patient presenting with a large arm, significant fat induration but few skin changes may be rated as E2:S0:D1, which tells the reader that there is irreversible edema (underlying tissue change) but the skin is in good order and the person is able to perform most ADLs. A patient in rural Bangladesh with lymphedema of filarial origin with significant swelling around the ankle, deep skin folds, and a few knobs and bumps may be rated as E2:S2:D1, which tells us that the person has irreversible swelling, significant skin changes without wounds, and is able to perform most instrumental ADLs. A person in rural Ethiopia who has an early-stage podoconiosis with “mossy” changes and multiple interdigital lesions but minimal swelling may be rated as E1:S3:D0, which tells us that we should focus first on restoring skin integrity. Whether this matrix method of staging will permit some meta-analysis of previous studies needs investigation. Any acceptable use of such a staging format will require comprehensive development, including clinical, research, and academic testing.

Recommendations

Lymphedema staging systems should capture the true clinical presentation of lymphedema, aid in decision making on appropriate treatment approaches, accurately reflect

lymphedema progression or improvement both within individual cases and among cohorts, and provide meaningful objective data for research purposes. Explanation of the criteria used by differing staging systems offers here a resource for clinicians, health workers, and researchers working in settings where more than one form of lymphedema is present. The aligning of the various staging systems suggests that further work could be done to develop a matrix to enable much needed meta-analysis on the evidence for lymphedema interventions. Such a matrix could also be used by health workers on the ground where diseases of causation may be difficult to differentiate without laboratory testing such as African countries which are co-endemic for LF and podoconiosis.

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