

# L-Dex U400 for lymphoedema after breast cancer treatment

Medtech innovation briefing

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## Summary

- The **technology** described in this briefing is the L-Dex U400. It is used for early detection of unilateral lymphoedema in the limbs after treatment for breast cancer.
- The **innovative aspects** are that it uses bioimpedance spectroscopy to measure fluid status, aiming to detect lymphoedema earlier.
- The intended **place in therapy** would be in diagnosing or monitoring lymphoedema related to breast cancer treatment. It could be used as an alternative to current detection or measurement techniques, such as simple tape measurement of limb circumference.
- The **main points from the evidence** summarised in this briefing are from 3 studies in the UK and the US using prospective observational data, as well as a budget impact analysis, in a total of 978 patients (female adults) in secondary care. They show that the L-Dex U400 is less effective than comparators in diagnosing lymphoedema, but potentially helps detect subclinical lymphoedema, in people who have had treatment for breast cancer.

- **Key uncertainties** around the evidence and technology are that the evidence base is still developing. So far, it shows that the L-Dex U400 is not as effective as current tests for diagnosing lymphoedema. Further complications are that, in NHS practice, there is no current surveillance for subclinical lymphoedema, and no consensus on the diagnostic gold standard for lymphoedema. A further study is ongoing. Once diagnosed, lymphoedema is a chronic condition and treatment involves physical methods to reduce swelling. Surgery is an option in a small number of cases.
- The **cost** of the L-Dex U400 is £7,500 per unit (exclusive of VAT). The **resource impact** for the NHS is unclear because of a lack of evidence.

## The technology

The L-Dex U400 (Impedimed Ltd.) uses bioimpedance spectroscopy to detect unilateral lymphoedema in the limbs (particularly the arms) after treatment for breast cancer that has removed or damaged the lymph nodes. It may also be used to detect leg lymphoedema in men, but this is beyond the scope of this briefing. In bioimpedance spectroscopy, a small electrical current is passed through the affected limb and the resistance to the current is compared with the unaffected limb. The resistance is used to calculate the total water content in the body, which can be used to detect lymphoedema ([Bundred et al. 2015](#)).

Lymphoedema is the build-up of lymphatic fluid in the body, particularly in the limbs, which causes swelling and enlargement. Although it is a chronic condition, detecting lymphoedema earlier may allow more conservative management and better clinical outcomes ([Stout et al. 2012](#); [International Society of Lymphology 2013](#)).

The L-Dex U400 is a small, portable desktop system with a built-in display screen. To use it, the patient lies on their back and a nurse or physiotherapist places 1 electrode on the back of each hand and 1 on the right foot. Colour-coded leads are attached to the electrodes to connect them to the L-Dex U400, and measurements are taken following the on-screen instructions. The results appear on the screen, given as an L-Dex ratio. The accumulation of extracellular fluid in the limb causes the L-Dex ratio value to increase.

The L-Dex ratio is calculated by dividing the bioimpedance reading from the affected arm by that from the unaffected arm. The normal range of the L-Dex ratio is -10 to +10. L-Dex ratio values above the normal range, or values that have changed by at least 10 L-Dex units from the baseline, may suggest early signs of lymphoedema.

Results can be analysed on the L-Dex U400, which can store over 1,000 records and includes analysis software. Results can also be uploaded through the network port onto a Windows computer for storage and additional analysis using the Impsoft Unilateral Lymphedema Analysis Software. The software on the L-Dex U400 device allows readings to be tracked over time to detect increases in fluid accumulation.

## Innovations

Other methods for diagnosing lymphoedema, such as water displacement and tape measurement, are not able to distinguish between lymphatic fluid and the healthy tissues of the body. These methods can therefore be inaccurate, especially if there are changes to the body tissues, such as weight loss or gain. The L-Dex U400 uses bioimpedance spectroscopy, which can specifically measure extracellular fluid. This is designed to enable earlier detection of lymphoedema.

## Current care pathway

Lymphoedema of the arm happens in around 1 in 5 people who have had treatment for breast cancer, involving removal of the lymph nodes or radiotherapy. Lymphoedema is considered to be a chronic condition. Most patients with lymphoedema (around 90%) will not need surgery, but around 10% need invasive treatment such as surgery ([Lymphoedema Support Network](#)). Some patients (10%) will develop serious complications, such as cellulitis ([Asdourian et al. 2016](#)).

The most commonly used method of lymphoedema detection in current NHS practice is periodic measurement of limb circumference using a tape measure, combined with a clinical assessment of the patient's skin and their mobility. The limb circumference measurements are compared to measurements taken before treatment, or compared with the unaffected limb.

Limb volume measurement may also be done, depending on clinical preference. Methods include:

- Water displacement – where the affected limb is placed in a tank of water and the amount of water that is displaced is measured.
- Perometry – where infrared light is used to measure the outline of an affected limb and calculate its volume.

Treatment options for people with lymphoedema include skin care, exercises, use of compression garments and lymphatic drainage massage, which are designed to reduce swelling. In a small number of cases surgical techniques, such as liposuction to remove excess fat from the affected limb, may also be used ([NHS Choices 2016](#)).

The 2002 NICE cancer service guideline on [improving outcomes in breast cancer](#) recommended that networks should agree guidelines for identification and management of lymphoedema and that a lymphoedema service, staffed by trained nurses and physiotherapists, should be available for all patients who have symptoms of lymphoedema. Current provision of lymphoedema services is variable.

## Population, setting and intended user

The L-Dex U400 would be used in secondary care to detect and monitor lymphoedema in people who have had chemotherapy, radiotherapy or surgery for breast cancer. The L-Dex U400 is typically used by an appropriately trained nurse or physiotherapist, as a part of routine screening.

## Costs

### Technology costs

The capital cost of the L-Dex U400 is £7,500 per unit and it has a 5-year lifespan with no maintenance costs, and no calibration is needed. For each patient, 3 single-use electrodes are used at a total cost of £3.75 per patient (£75 per pack of 60 electrodes). Training for staff using the L-Dex U400 is provided by the manufacturer at no additional cost and includes a video and online training materials. The L-Dex U400 could be used during routine follow-up after breast cancer treatment. Currently, the cost of a breast cancer specialty clinic visit is £168 for a first visit and £96 for each subsequent visit.

### Costs of standard care

Clinical practice for lymphoedema diagnosis varies across the NHS. However, lymphoedema is generally diagnosed through arm circumference measurements. These can be completed during routine clinic visits after breast cancer treatment and are not expected to incur additional costs. Perometry or water displacement tests can also be done in specialist centres.

Resources used in the treatment of lymphoedema can include compression bandages (£3.56 each), sleeves (£8.92 each) and physiotherapist-led exercise (£34 per hour). If the condition becomes more serious, then surgical procedures (such as liposuction) may be needed. The cost of liposuction is expected to be at least £2,000 per procedure ([NHS Choices 2015](#)). Lymphoedema can be associated with secondary conditions, such as cellulitis, needing further treatment.

A US study estimated that the medical costs associated with lymphoedema in women with breast cancer were \$8,290 over 2 years ([Shih et al. 2009](#)). A second study done in the US has reported that early detection of lymphoedema can lead to cost savings of \$2,489 per person, per year, because early intervention reduces the need for extensive rehabilitation ([Stout et al. 2012](#)).

## Resource consequences

The L-Dex U400 is currently being used by 21 NHS trusts.

Use of the L-Dex U400 is expected to add about 15 minutes to each clinic appointment, which may increase the cost of each appointment by about £42. Assuming the L-Dex U400 is used on average 5 times per day, over a 5 year period this gives a cost per use of £1.15, plus £3.75 per assessment for the single-use electrodes. Each patient would have 17 assessments with the L-Dex U400 over the course of 5 years.

A US study comparing the budget impact of the L-Dex U400 with standard care for lymphoedema detection showed that use of the L-Dex U400 led to cost savings of \$315,711 for a hypothetical cohort of 627 people with breast cancer in a total population of 1 million people ([Bilir et al. 2012](#)). If the L-Dex U400 leads to early detection of lymphoedema as part of routine screening, then cost savings may be realised in reduced treatment costs for later-stage lymphoedema. However, the US care pathway may be different to the UK and there is currently no evidence showing similar savings in an NHS setting.

## Regulatory information

The L-Dex U400 received its latest CE mark as a class 2a device in September 2016.

A search of the Medicines and Healthcare products Regulatory Agency website revealed

that no manufacturer field safety notices or medical device alerts have been issued for this technology.

## Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Breast cancer occurs mainly in women, and the risk of breast cancer increases with older age. People with cancer are protected under the Act from the point of diagnosis. Sex and age are also protected characteristics. The device is contraindicated in people with existing cardiac implants such as cardiac resynchronisation therapy or pacemaker devices.

## Clinical and technical evidence

A literature search was done for this briefing in accordance with the [interim process and methods statement](#). This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting [mibs@nice.org.uk](mailto:mibs@nice.org.uk).

## Published evidence

Three studies are summarised in this briefing. These are a prospective observational study ([Barrio et al. 2015](#)) done in the US with 186 patients; a prospective observational study done in the UK with 612 patients ([Bundred et al. 2015](#)); and a prospective observational study done in the US with 180 patients ([Soran et al. 2014](#)).

## Overall assessment of the evidence

There are few available studies comparing the diagnostic accuracy of the L-Dex U400 to other ways of diagnosing lymphoedema. There are no published randomised controlled studies to help further inform the clinical utility of the L-Dex U400.

The 2 large comparative studies ([Barrio et al. 2015](#); [Bundred et al. 2015](#)) suggest that the L-Dex U400 has a lower diagnostic accuracy than volume displacement and perometry, respectively. However, it should be noted that in these studies, the comparators were assumed by the authors to be the gold standard, but there is no consensus in the literature on the gold standard for diagnosing lymphoedema. One of these studies ([Bundred et al. 2015](#)) has been shown to have limitations in terms of the methodology and calculations used in the detection of lymphoedema with the L-Dex U400 ([Ward et al. 2015](#)).

A third study ([Soran et al. 2014](#)) examined whether the L-Dex U400 can be used to detect subclinical lymphoedema, which is difficult to detect with standard methods such as measurement of limb circumference. However, the sample size was relatively small and because the control group was not prospectively monitored for preclinical lymphoedema, there was no measurement of the diagnostic accuracy of the L-Dex U400.

A prospective study on the L-Dex U400 and other methods of diagnosing lymphoedema is currently being done in the NHS ([Bundred et al. 2013](#)). This and future randomised controlled trials should add to the evidence base for the diagnostic accuracy of the L-Dex U400 for lymphoedema associated with breast cancer treatments.

Table 1 summarises the clinical evidence as well as its strengths and limitations.

**Table 1. Summary of included studies**

<a href="#">Barrio et al. (2015)</a>	
Study size, design and location	A prospective observational study based in US of 186 women (>18 years) with early-stage breast carcinoma who had planned breast and axillary surgery (SLNB or ALND).
Intervention and comparator(s)	Intervention: L-Dex U400 Comparator: volume displacement.

Key outcomes	<p><b>For all patients (n=13) who developed lymphoedema:</b></p> <p>13 women developed lymphoedema during the study period (as measured by volume displacement). Only 4 were measured as having an abnormality by the L-Dex before diagnosis with volume displacement (sensitivity=31%; specificity=88%). The L-Dex ratio was abnormal in 12 of the 13 patients at the point of diagnosis with volume displacement (sensitivity=92%).</p> <p><b>For all patients (n=186):</b></p> <p>Of 28 abnormal volume displacement measurements, 7 were normal according to the L-Dex (sensitivity=75%; false-negative rate=25%).</p> <p>Of 801 normal volume displacement measurements, 56 were abnormal by L-Dex (specificity=93%, false-positive rate=7%). Overall the NPV=99% and PPV=27% for L-Dex. There was also poor correlation between change in volume displacement and change in L-Dex measurements (correlation coefficient=0.31 at 3 months and 0.21 at 6 months).</p> <p><b>For subgroup of patients undergoing SLNB (n=151):</b></p> <p>Of 2 abnormal volume displacement measurements (occurring in 1 patient), the L-Dex result was normal in both, corresponding to a sensitivity of 0%. Specificity was 96% with a false-positive rate of 4% (28 false-positive measurements). NPV=99.7% and PPV=0%.</p>
Strengths and limitations	<p>Prospective study design; direct comparison against a current standard diagnostic.</p> <p>Low incidence of lymphoedema, particularly for SLNB patients (n=1) leading to large variance in estimates of sensitivity.</p>
<u>Bundred et al. (2015)</u>	
Study size, design and location	A prospective observational study based in UK of 612 women having surgery for breast cancer with follow-up measurements of at least 6 months.
Intervention and comparator(s)	<p>Intervention: L-Dex U400</p> <p>Comparator: 350S Perometer (Pero-System, Germany).</p>

Key outcomes	<p>52 women had developed lymphoedema (detected by perometer) at 6 months. L-Dex detected 91 false positives, 38 true positives, 14 false negatives and 469 true negatives.</p> <p>Sensitivity=73% (95% CI 59 to 84)</p> <p>Specificity=84% (95% CI 80 to 87)</p> <p>There was moderate correlation between changes in perometer and L-Dex measurements both at 3 months (r=0.4) and 6 months (r=0.6).</p> <p>At 18 months post-surgery 71 women had developed lymphoedema detected by perometer, whereas 126 cases were identified by L-Dex.</p>
Strengths and limitations	<p>Prospective study design; large sample size; direct comparison against a current standard diagnostic.</p> <p>Low incidence of lymphoedema; short follow-up time.</p>
<u>Soran et al. (2014)</u>	
Study size, design and location	A prospective observational study based in US of 180 women with breast cancer who had surgery (ALND).
Intervention and comparator(s)	<p>Intervention: L-Dex U400 used to monitor lymphoedema status every 3 to 6 months for first year post-surgery and annually thereafter.</p> <p>Patients with diagnosed subclinical lymphoedema were proactively treated to avoid progression.</p> <p>Comparator: no monitoring. Circumferential arm measurements used to detect clinical lymphoedema at 12 months post-surgery.</p>
Key outcomes	<p>Subclinical lymphoedema was diagnosed in 28 patients (38.9%) monitored with L-Dex and 2 of these patients (2.8%) progressed to clinical lymphoedema. In the control group 16 patients (36.4%) developed clinical lymphoedema. Therefore, incidence of clinical lymphoedema was 8 times higher in the control group (p&lt;0.001), indicating that early detection with L-Dex, and subsequent treatment, may reduce progression to clinical lymphoedema.</p>
Strengths and limitations	<p>Prospective study design.</p> <p>No direct comparison of L-Dex with comparator for diagnosis of clinical lymphoedema.</p>

Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; SLNB, sentinel lymph node biopsy.

## Recent and ongoing studies

A search on [clinicaltrials.gov](https://clinicaltrials.gov) revealed 1 ongoing trial investigating the diagnostic accuracy of the L-Dex U400:

- A 5-year, multi-site randomised clinical trial in the US and Australia involving 1,100 patients. There will be a 3-year follow-up to assess the impact of the L-Dex U400 in the prevention of lymphoedema. (<https://clinicaltrials.gov/ct2/show/NCT02167659>).

There is also a large ongoing NIHR clinical trial of bioimpedance using the L-Dex U400 and other methods for the early detection of lymphoedema. Preliminary results have been reported in an abstract ([Bundred et al. 2013](#)).

## Specialist commentator comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Comments were received from 3 specialists, all of whom had used this technology before. One had used it as part of a research trial.

## Level of innovation

All commentators agreed that the technology is innovative, with 2 noting it represents a novel concept or design.

One commentator felt that while it is innovative, the L-Dex U400 is not the only product that allows early detection of subclinical lymphoedema. This is because there is no consensus on the definition of subclinical lymphoedema and it could be argued that early changes can be detected with a tape measure or perometry.

## Potential patient impact

One commentator stated the L-Dex U400 may be of particular benefit for people with a significant risk of developing lymphoedema, such as people who have had axillary clearance. This is needed for fewer than 20% of women with breast cancer.

One commentator felt that using the L-Dex U400 could lead to earlier and more effective treatment of lymphoedema. However, another commentator stated that there is currently no evidence that early treatment of subclinical lymphoedema has any impact on its development.

Another commentator added that if shown to be effective, the device could improve lymphoedema services and lead to fewer hospital visits for patients. However, another commentator suggested that it would lead to significantly more hospital visits for patients who were at risk of lymphoedema, and would only benefit a small number of patients at risk of arm swelling.

## Potential system impact

Commentators agreed that training would be needed to use this technology; 2 stated that this would be minimal. One commentator clarified that a healthcare assistant or nurse would be able to use the device after around 60 to 90 minutes of training and observation.

One commentator noted that the L-Dex U400 is a portable device and so it could be used in any clinic in primary or secondary care. A second commentator noted that use of the device adds around 15 minutes to each clinic appointment, but all commentators agreed that no changes to infrastructure would be needed.

One commentator suggested that the device would lead to cost savings in the NHS; however, another stated that the technology would only produce cost savings if it was used in a very select group of patients at higher risk of lymphoedema. They felt that if it was used for all patients with breast cancer then cost savings would not be generated. The third commentator was unsure whether the device would lead to cost savings.

## General comments

One commentator noted that the device might be of benefit to patients at high risk of

developing lymphoedema, but that even in these patients, the lymphoedema rate is low. They also commented that the time frame for developing lymphoedema varies, with some patients developing the condition many years after primary surgery or radiotherapy. Because of this, a surveillance programme would need to run for many years to identify patients with early-stage lymphoedema. Patients would need to return for regular clinical assessment which is at odds with the current NHS practice of early discharge to general practitioner care after breast cancer treatment. Additionally, the commentator reported that they had stopped using the device in their clinic because of low rates of detection of lymphoedema.

Another commentator added that bioimpedance currently lacks evidence for widespread introduction on the NHS, particularly in terms of the costs involved and whether it could result in cost savings, but that studies to address this are ongoing.

## **Patient organisation comments**

The Lymphoedema Support Network and Breast Cancer Care provided the following comments on the L-Dex U400.

The commentator from the Lymphoedema Support Network noted that early detection of lymphoedema would potentially prevent skin changes and increased swelling, which may reduce the need for more intensive care. However, despite early detection, current evidence does not support the idea that lymphoedema is reversible at any stage of development. Early diagnosis could delay development of the condition or maintain symptoms at a subclinical level.

They felt that bioimpedance could be a very valuable technology in patients with mid-line, head and neck or breast swelling (although these are not currently indicated for the L-Dex U400), because there are currently no effective technologies for taking measurements in these groups. It was also noted that lymphoedema is now less common in breast cancer since sentinel node biopsy was introduced.

One commentator used more traditional limb volume measurements with a tape measure in their work as a lymphoedema specialist, and had not used the L-Dex U400. They felt that the current evidence on this device was not sufficient to show that the device would be an accurate method to replace existing procedures.

## Specialist commentators

The following clinicians contributed to this briefing:

- Mr Nathan J Combs, Consultant Breast, General and Endocrine Surgeon, Great Western Hospitals NHS Foundation Trust, Great Western Hospital, Swindon. No conflicts of interest declared.
- Prof Nigel J Bundred, Professor in Surgical Oncology, University Hospital of South Manchester NHS Foundation Trust, Manchester. Professor Bundred is the Chief Investigator of an NIHR study on L-Dex U400.
- Prof Peter Mortimer, Professor of Dermatological Medicine, St George's Hospital and The Royal Marsden Hospital, London. No conflicts of interest declared.

Representatives from the following patient organisations contributed to this briefing:

- Breast Cancer Care
- Lymphoedema Support Network

## Development of this briefing

This briefing was developed for NICE by Newcastle and York External Assessment Centre. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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