

Woundchek Protease Status for assessing elevated protease status in chronic wounds

Medtech innovation briefing

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Summary

- The **technology** described in this briefing is the Woundchek Protease Status point-of-care diagnostic test. It is designed to qualitatively assess protease activity (the presence of which may impair healing) in chronic wounds.
- The potential **innovative aspect** is that it is currently the only commercially available test that can detect whether a wound has an elevated protease status.
- The intended **place in therapy** would be for use by clinical staff treating chronic wounds, to aid decision-making on wound dressings. Protease modulating dressings could be chosen for wounds where elevated protease status is detected. The test could be used in any care setting.

- The **key points from the evidence** summarised in this briefing are from 4 studies involving 412 people. One published prospective, non-comparative study showed that elevated protease activity (EPA), detected with the Woundchek Protease Status test, was significantly associated with dermal graft failure in diabetic foot ulcers. The Woundchek Protease Status test had a high positive predictive value (80%) for non-healing status in chronic wounds in a further study. A randomised controlled trial in people with diabetic foot ulcers found that more wounds healed or improved in a group tested for EPA and treated with protease modulating dressings where appropriate, compared with standard care.
- **Key uncertainties** around the evidence are that it is limited in quality and quantity. The published prospective study was small (n=35) and the other publications lacked detail because 2 were conference presentations on small studies and 1 was a research poster.
- The Woundchek Protease Status test **costs** £30 per test and does not need maintenance or calibration. Kits with control samples and additional reagent are also available.
- NICE has also published a medtech innovation briefing on the [UrgoStart](#) dressing for treating chronic wounds.

The technology

The Woundchek Protease Status test (Woundchek Laboratories) is an in-vitro diagnostic test for the qualitative assessment of human neutrophil-derived inflammatory protease activity in chronic wounds, including matrix metalloproteases (MMPs) and human neutrophil-derived elastase.

This information is intended to guide treatment, for example using protease modulating therapies or dressings. In the same way, the test is also intended to identify wounds for which more advanced treatments (such as protease modulating therapy) are not necessary. A review by [Lazaro et al.](#) (2016) found that chronic wounds have higher levels of protease activity than acute wounds, and that there is a correlation between high MMP levels and delayed wound healing in chronic wounds.

The main components of the Woundchek Protease Status test are a test card and reagent. Reagent is added to the test card and then a fluid swab collected from the chronic wound is inserted into a slot in the test card, rotated and left for 10 minutes. After this incubation

period, the test card is folded over and closed. Test results must be viewed exactly 5 minutes after this.

The results are shown by the intensity of the coloured test line (labelled T) on the card compared to a separate printed reference strip provided in the kit. The test is only valid if a second line, a control (labelled C on the card) becomes visible during the test. If proteases are present in the collected wound fluid, they degrade the synthetic peptide in the test card. High levels of protease activity are indicated when the colour of the test line is less intense than the line on the reference strip, or the test line is not visible at all. Low levels of protease activity are indicated when the intensity of the test line is more than or equal to the reference strip line.

A control kit can be used as a further reference for testing. This kit contains 3 low and 3 high protease activity control swabs that can be used to establish that the test is reporting the expected results. The manufacturer recommends using the kit once with each shipment of Woundchek tests, or in accordance with local laboratory protocols.

The innovation

The Woundchek Protease Status test is the only point-of-care in-vitro diagnostic test for the detection of elevated protease activity (EPA) in chronic wounds currently available.

Current NHS pathway

NICE has published guidelines on the [prevention and management of foot problems in people with diabetes, pressure ulcers, and surgical site infections](#). Although these guidelines give important recommendations about wound care, they do not make recommendations on specific products. NICE advice on [wound care products and advanced and antimicrobial dressings for chronic wounds](#) states that dressing selection should be made after careful clinical assessment of the person's wound, their clinical condition, and their personal experience and preferences. The NICE advice also states that the least costly dressings that meet the required clinical performance characteristics should be used, as there is insufficient evidence to determine whether modern or advanced dressings (such as hydrocolloids, alginates and hydrofibre dressings) are more clinically effective than conventional dressings for treating wounds. Additionally, [NICE advice](#) states that there is currently no robust evidence supporting the use of antimicrobial dressings (such as silver, iodine or honey) over non-medicated dressings for treating

chronic wounds. The Scottish Intercollegiate Guideline Network (SIGN) guideline on the [management of venous leg ulcers](#) recommends simple non-adherent dressings and compression therapy.

If the Woundchek Protease Status test was widely adopted in the NHS, it would be used in addition to current wound care practices. If EPA is detected, protease modulating therapies or dressings may be chosen to treat wounds instead of more basic dressings. Where EPA is not detected, the more basic, cheaper dressings may be used instead. Also, assessments of infection and microbial colonisation can be done, to determine whether an anti-microbial dressing may be of more benefit to the patient.

Population, setting and intended user

Chronic wounds are often treated by wound care nurses in hospital or attending people in their homes. The Woundchek Protease Status test can be used in any setting, including in a patient's home, by clinical staff with the appropriate experience and training.

Costs

Device costs

Prices (excluding VAT) for Woundchek Protease Status tests, control kits and reagent accessory packs are presented in table 1. There are no other costs associated with maintenance or calibration because neither are needed. Initial product training is offered by the company at no extra cost.

Table 1: Woundchek Protease Status test costs

Description	Cost	Additional information
Woundchek Protease Status test	£30	Per single-use test
Control test kit	£15	Contains 3 low and 3 high protease activity result control swabs for visual reference of possible test results

Reagent accessory pack	£18	Contains 3 reagent bottles
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The Woundchek Protease Status test and reagent accessory packs have a shelf-life of 21 months from the date of manufacture, and the control kits have a shelf-life of 12 months.

Costs of standard care

Currently, protease activity testing is not done in standard care. Predictions of complete wound healing are often based on visual assessments of wounds and the rate of wound healing. Protease modulating dressings are sometimes used without testing for EPA.

Resource consequences

The Woundchek Protease Status test is not currently used routinely in any NHS trusts but evaluation studies are planned in 3 centres.

The test would present an additional cost to standard care.

Testing for EPA may be used in the clinical decision about which wound dressings to use. Protease-modulating dressings are generally more expensive than standard dressings. If a negative EPA test was used to change treatment to a cheaper, standard dressing then this may lead to some cost savings. It is not clear whether this would happen in practice because protease modulating dressings are often used without previous testing for EPA. Protease modulating dressings may also be used in patients without EPA, as they are often highly absorbent. The costs of some protease modulating dressings and other dressings are shown in table 2.

Table 2: Costs of protease modulating dressings and other dressings

Description	Cost (NHS Supply Chain)	Additional information
Protease modulating dressings		
Promogran	£5.80	28 cm ²

Promogran Prisma	£7.07	28 cm ²
UrgoStart Contact	£2.94 to £9.88	5 x 7 cm to 15 x 20 cm
UrgoStart	£4.69 to £11.70	6 x 6 cm to 15 x 20 cm
UrgoStart Border	£5.43 to £15.54	8 x 8 cm to 20 x 20 cm (sacrum)
Other dressings		
UrgoTul contact	£3.20	10 x 10 cm
Aquacell foam dressing	£2.65	10 x 10 cm
UrgoTul Absorb	£2.78	10 x 10 cm
Kendall non-adhesive foam dressing	£1.00	10 x 10 cm
Tegaderm hydrocolloid dressing	£2.33	10 x 10 cm
Hydrosorb hydrogel dressing	£1.51	10 x 10 cm

A study by [Frenthoff et al. \(2015\)](#) presented as a poster reported that identifying EPA in wounds using the Woundchek Protease Status test could save €2,044 (£1,748.95) on materials per wound identified because of a reduction in materials needed to treat the wound. [Nherera et al. \(2013\)](#) estimated a potential saving of £1,906 per wound identified as having EPA with the Woundchek Protease Status. However, this UK-based study, also presented as a poster, reported the cost of each Woundchek Protease Status test to be £21.50 compared with the current £30 list price.

Regulatory information

The Woundchek Protease Status test was CE-marked as a class II in-vitro diagnostic device (98/79/EC) in January 2012.

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).

Older people, people with diabetes and those with restricted mobility are more likely to have chronic or non-healing wounds. Age and disability are protected characteristics under the 2010 Equality Act.

Clinical and technical evidence

A literature search was done for this briefing in accordance with the published 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.

Published evidence

Four publications on the Woundchek Protease Status test to assess chronic wounds are summarised in this briefing. The studies included 1 prospective, non-comparative study ([Izzo et al. 2014](#)); 1 poster presentation ([Gibson et al. 2013](#)), which included the results of 2 prospective non-comparative studies; 1 oral presentation ([Duteille et al. 2013](#)) on a prospective, non-comparative study and 1 oral presentation on a non-blinded randomised controlled trial ([Anichini et al. 2013](#)). There were a total of 412 patients in the 4 included studies.

The prospective, non-comparative study by Izzo et al. (2014) screened for elevated protease activity (EPA), with the Woundchek Protease Status test, in 35 patients who needed a dermal graft for their diabetic foot ulcers. Duteille et al. (2013) gave the results from a prospective, non-comparative study of 30 chronic wounds in an oral presentation.

Chronic wounds were assessed for EPA using the Woundchek Protease Status test before a dermal graft was done.

Gibson et al. (2013) presented the results from 2 studies in a poster. Both studies were prospective and non-comparative. The first study (Study A) investigated the prevalence of EPA in a range of chronic wounds as well as the duration of wounds with EPA and disagreements between clinician opinion and wound area reduction. The second study (Study B) aimed to determine how frequently clinicians would choose to use the Woundchek Protease Status test to assess a chronic wound. If the clinician chose not to use the Woundchek Protease Status test, they noted their reasons for this decision.

The oral presentation by Anichini et al. (2013) gave the results from a non-blinded randomised controlled trial of 20 diabetic foot ulcers. Patients (n=20) were randomised to either have testing for EPA with the Woundchek Protease Status test (n=10) or standard care (n=10). Table 3 summarises the clinical evidence as well as its strengths and limitations.

Table 3: Summary of clinical evidence

Study	Details of intervention and comparator	Outcomes	Strengths and limitations
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<p><u>Izzo et al.</u> 2014. 35 patients with diabetic foot ulcers needing dermal graft. Prospective, non-comparative. Single-centre. Italy.</p>	<p>Patients with Texas Wound Classification A2 diabetic foot ulcers (n=35) were tested with the Woundchek Protease Status test.</p>	<p>Monovariate analysis showed high MMP levels were significantly associated with graft failure. In multivariate analysis, high MMP levels were the only predictor of graft failure. Dermal graft integration was seen in all patients with low protease activity, but in significantly fewer patients with EPA.</p>	<p>Inclusion criteria were reported but exclusion criteria were not. Monovariate and multivariate analysis was done. The study was small.</p>
<p><u>Duteille et al.</u> 2013. 30 chronic wounds. Prospective, non-comparative. Single-centre. France.</p>	<p>Woundchek Protease Status (n=30 chronic wounds) Used to identify chronic wounds with an increased risk of graft failure.</p>	<p>Wounds were tested for EPA. Wounds were grouped according to high or low EPA activity. Graft success rate in the EPA group was lower than in the low protease activity group.</p>	<p>Patient numbers were not clearly stated, only the number of wounds was presented. The study was small. There were no inclusion or exclusion criteria reported and no statistical analysis was done.</p>

<p><u>Gibson et al.</u> 2013. Study A. 215 patients with chronic wounds of varying aetiology. Prospective, non-comparative. Multi-centre. US. Study B 112 patients with chronic wounds. Prospective, non-comparative. Multi-centre. UK.</p>	<p>Study A: Woundchek Protease Status (n=215). Study B: Chronic wounds (n=112).</p>	<p>Study A: The prevalence of EPA in all chronic wounds was assessed using the Woundchek Protease Status test. The Woundchek Protease Status test had a PPV of 80% for non-healing status in chronic wounds. Study B: A study of UK sites using the Woundchek Protease Status test. Most wounds were not tested with Woundchek Protease Status. The most common reason for this was that clinicians assessed the wound as healing.</p>	<p>The studies had high patient numbers relative to the other identified studies. There were no inclusion or exclusion criteria reported for either study. In study A, PPV was calculated but no other statistical analyses were done.</p>
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<p><u>Anichini et al.</u> 2013. 20 patients with diabetic foot ulcers. Non-blinded RCT. Single-centre. Italy.</p>	<p>Woundchek Protease Status (n=10) Standard care (n=10) Patients were assessed before treatment and after 12 weeks of treatment. Patients tested with the Woundchek Protease Status test were treated with protease-modulating dressings if the test showed they had EPA. Patients having standard care were not tested for EPA with the Woundchek Protease Status test.</p>	<p>A significantly higher number of wounds were completely healed at week 12 in the Woundchek Protease Status test group compared with the standard care group. All wounds with EPA in the Woundchek Protease Status test group had healed or improved by week 12.</p>	<p>The study had low patient numbers and no sample size calculation was reported. Inclusion criteria were reported, but exclusion criteria were not. Statistical analysis was done but the statistical methods used were not noted. Although randomised, the study was not blinded.</p>
<p>Abbreviations: MMP, metalloproteinases; EPA, elevated protease activity; PPV, positive-predictive value; RCT, randomised controlled trial.</p>			

Strengths and limitations of the evidence

Overall there was limited evidence on using the Woundchek Protease Status test for chronic wounds and only 1 study used the test to determine the choice of dressing. Two studies (Izzo et al. 2014 and Duteille et al. 2013) assessed whether the test could predict graft failure and this may not be generalisable to non-healing wound prediction.

The paper by Izzo et al. (2014) was a full text journal article and therefore included more detailed reporting of the study than the poster presentation by [Gibson et al. \(2013\)](#) and the oral presentations by [Duteille et al. \(2013\)](#) and [Anichini et al. \(2013\)](#). The studies by Izzo et al. (2014) and Anichini et al. (2013) received no funding from Woundchek and no employees were involved with the studies. The study by Duteille et al. (2013) was supported by a grant from Systagenix, owned by Acelyty, who also own Woundchek. Six out of seven named authors on the poster by Gibson et al. (2013) work for Woundchek or Systagenix.

The study by Anichini et al. (2013) compared the use of the Woundchek Protease Status test with standard care in a prospective, randomised manner. It is unclear if allocation concealment was done and the study was not blinded. Therefore, selection bias, performance bias and detection bias may have been introduced. The remaining studies were non-comparative.

The studies had variable levels of reporting on the statistical techniques used to analyse results. The study by Izzo et al. (2014) used the Woundchek Protease Status test in patients with chronic wounds having a dermal graft, and analysed the data using inferential statistics. The study by Anichini et al. (2013) included p values but the methods of statistical analysis were not presented. Gibson et al. (2013) also did some statistical analysis (positive-predictive value), whereas Duteille et al. (2013) analysed graft success rates but did not include confidence intervals or ranges.

The studies by Izzo et al. (2014), Duteille et al. (2013) and Anichini et al. (2013) had relatively small sample sizes of between 20 and 35 people compared with Gibson et al. (2013) which included 215 people. The studies by Izzo et al. (2014) and Anichini et al. (2013) presented some inclusion criteria but no exclusion criteria. Neither Gibson et al. (2013) or Duteille et al. (2013) presented inclusion or exclusion criteria.

The studies by Izzo et al. (2014), Anichini et al. (2013) and Duteille et al. (2013) were single-centre studies, which may decrease selection bias. But they did not report whether patients were recruited consecutively or not. The 2 studies presented by Gibson et al. (2013) were multi-centre. This could mean that each centre had a low number of patients, and each centre would have had different clinicians, treatments and assessment procedures. Conversely, multi-centre studies evaluate the use of the technology in different centres increasing the generalisability of the results. The studies by Izzo et al. (2014), Anichini et al. (2013) and Duteille et al. (2013), as well as 1 of the studies presented by Gibson et al. (2013), were done outside of the UK and therefore treatment and

assessment procedures may differ from UK standard care. One of the studies presented by Gibson et al. (2013) was done in the UK and so its results may be more generalisable to the NHS. However this study presented results on clinical decision making and not patient outcomes.

Recent and ongoing studies

Two trials on this technology were identified:

- [NCT01537003](#) – Woundchek Protease Status Point of Care (POC) Diagnostic Test in venous leg ulcers. This study's status is listed as unknown.
- [NCT01537016](#) – Woundchek Protease Status Point of Care (POC) Diagnostic Test on diabetic DFU (diabetic foot ulcers). This study's status is listed as unknown.

The manufacturer provided the following information on these studies: NCT01537003 and NCT01537016 started but were cancelled when the technology was divested in 2013, following acquisition of Systagenix by Acelity (formerly KCI). Woundchek is currently auditing the data collected up to the point of termination, with the intention to analyse and publish the results.

Specialist commentator comments

Two specialist commentators were concerned about the length of time it takes for the Woundchek Protease Status test to give results. At 15 minutes this is longer than the 10 minute appointment time that practice nurses have to see patients. It was also noted that precision is needed in timing the tests to avoid false positive results, and that this precision is not always feasible in a clinic setting.

One specialist said that this test could be beneficial to wound care nurses who have the expertise to assess wounds and use the results of the elevated protease activity (EPA) test to develop a care plan. Two of the specialist commentators had been asked to do evaluations of the Woundchek protease status kit. One had concluded that the test was too costly because each wound care nurse would need to have the test kit and control kit, at a total cost of £45, although it should be noted that the control kit would be used for local quality control purposes and would not need to be used at each Woundchek test. The other specialist tried the test on around 20 patients, but found the kit complex to use and the need for precise timings made it impractical. One commentator noted that multiple

matrix metalloproteases (MMPs) are involved in wound healing and it is unclear if the test is specific to certain MMPs or a broader range.

It was noted by one specialist that protease modulating dressings may still be used in the event of a negative EPA result, because some of these dressings tend to be highly absorbent. They felt that further guidance would be needed around which patients should be tested and whether testing should be repeated for non-healing wounds.

One specialist concluded that experienced wound care nurses use their clinical knowledge and experience to assess wounds and provide the best dressings, and that in their experience, most wounds heal regardless of EPA testing. They noted that many chronic wounds are seen by general nurses in primary care, who might not understand the role of proteases in chronic wounds so may still prescribe inappropriate dressings regardless of this test.

Specialist commentators

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.

The following clinicians contributed to this briefing:

- Professor Michael Clark, Professor in Tissue Viability – Birmingham City University; Director of the Welsh Wound Network, Commercial Director Welsh Wound Innovation Centre. Professor Clark consults for the Welsh Wound Innovation Centre, which does commercially funded research, and for several wound care companies. The Welsh Wound Innovation Centre has done research on behalf of Woundchek.
- Mrs Caryn Carr, Lead Clinical Nurse Specialist in Tissue Viability – Southern Health NHS Foundation Trust. No conflicts of interest declared.
- Mrs Fania Pagnamenta, Nurse Consultant (Tissue Viability) – The Newcastle upon Tyne Hospitals NHS Foundation Trust. No conflicts of interest declared.

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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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