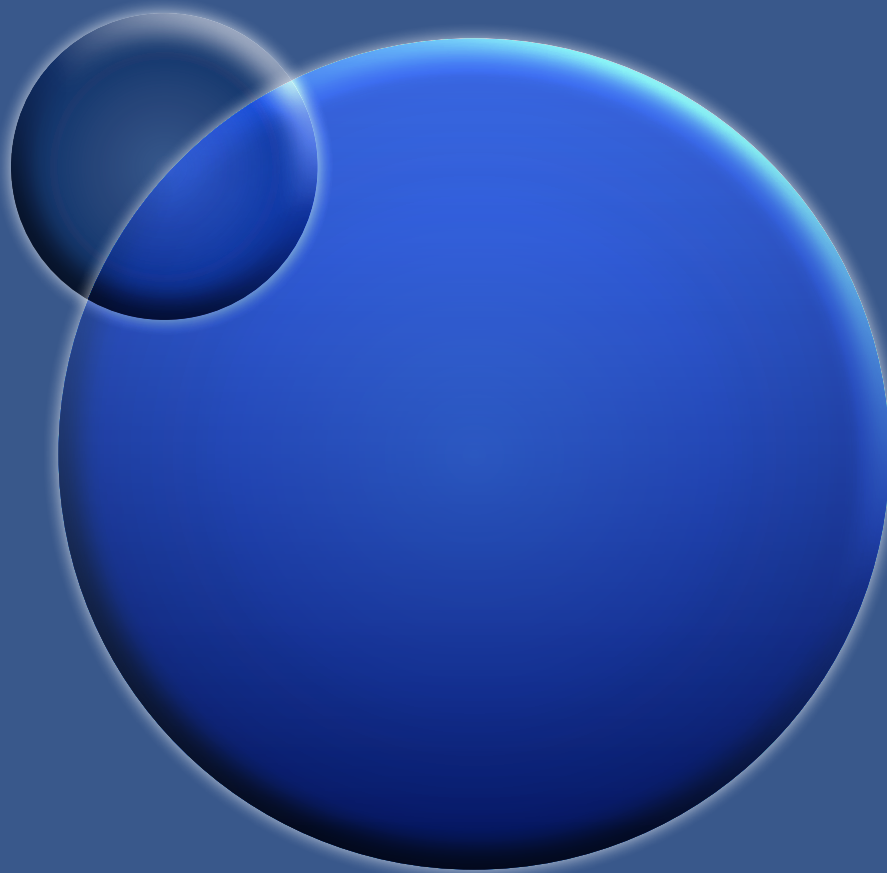


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# Protease diagnostic in wound care: round-table meeting



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# Diagnostics: round-table meeting

## Foreword

The National Health Service (NHS) has undergone significant changes in recent years with clinicians constantly encouraged to work in 'leaner' ways, reducing costs and increasing productivity without compromising the quality of care delivered (Department of Health [DH], 2011). Meeting this challenge is about achieving the highest possible value from the resources available. The Quality, Innovation, Productivity and Prevention (QIPP) programme is all about ensuring that each pound spent is used to bring maximum benefit and quality of care to patients (DH, 2010a).

In order to do this, clinicians need to ensure that patients are seen by the right person at the right point in time, and that they have a full assessment before instigation of treatment. This round table meeting focused on key issues in introducing a new point of care (PoC) diagnostic test, which tie in with the stated objectives of the 2010 White Paper, 'Equity and Excellence Liberating the NHS' (DH, 2010b) of putting the patient at the heart of care, delivering improved healthcare outcomes and empowering healthcare professionals to improve quality.

Throughout the text it is evident that the clinicians involved are used to working in a broad range of circumstances with healthcare professionals whose knowledge and experience vary. They are striving to ensure that any innovation is introduced in the best way for all concerned. The algorithm that they have produced shows how the patient drives care, and the frequent review points guide the clinician to focus on whether or not they are achieving the expected outcome. Crucial within this system is the need to ensure appropriate use of the test to guide delivery of what may appear to be 'expensive' care based on the unit cost of the product, but which, in reality, has the potential to produce not only cost-savings, but also improved patient outcomes.

This document poses almost as many questions as it answers, but serves to provide clinicians with a framework from which to work when introducing this exciting new piece of technology.

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October, 2011

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Department of Health (2011) *Maintaining and improving quality during the transition: safety, effectiveness, experience (Part One — 2011–2012)*. DH, London. Available online at: [www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/documents/digitalasset/dh\\_125497.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_125497.pdf)

A round-table meeting, supported by Systagenix and attended by a group of clinicians, was held in Birmingham on 22 February 2011. The focus of the meeting was to explore the introduction and adoption of a point-of-care (PoC) protease activity test that helps clinicians assess when to start treatment with a protease modulating therapy, such as collagen/oxidised regenerated cellulose (ORC), or when to stop treatment. At times, there are no visual clues as to why a therapy is not working. Diagnostic tools give the clinician the ability to see what is happening in the underlying chemistry of wounds.

As proteases are involved and central to the wound healing process (Agren et al, 2001; Gibson et al, 2009), it is crucial that clinicians are aware of their impact and how a test would influence practice, treatment and care pathways both in primary and acute care settings, while also offering greater control over costs.

While more is known about proteases than other biochemical markers involved in wound healing, the working group identified that nurses have a paucity of knowledge and that more education was needed.

Previous documents have been published which recognise that without the right diagnosis, the right treatment cannot be identified. The first document to try and get people to think about diagnostics was the Wound Union of Wound Healing Societies (WUWHS) Consensus Document on diagnostics and wounds (WUWHS, 2008). Statements included in that document emphasise current thinking about diagnostic tools at that time (Table 1).

While there is a potential with diagnostics, there is also a significant challenge. The use of new technologies should not be regarded as an alternative to thorough clinical assessment and monitoring of the patient and the wound by an experienced clinician. This

should be done first, with the diagnostic test adding on to the value of managing the patient (WUWHS, 2008).

If a structured approach is to be adopted on patients, diagnostic tests should be considered.

### **The use of new technologies should not be regarded as an alternative to thorough clinical assessment and monitoring of the patient and the wound by an experienced clinician.**

Clinicians (surgeons, clinicians, podiatrists and scientists) then came together at a meeting, supported by Systagenix, at the Wounds International Conference in South Africa at the end of January 2011, to develop an international consensus document on wound diagnostics and proteases.

The international consensus was introduced to the working group by Keith Harding (International Consensus, 2011). The purpose of this UK round-table meeting was to create a UK consensus, and to define an initial algorithm for the appropriate introduction of a protease test. The group also identified areas where further evidence and guidance were needed.

### **The effect of proteases**

Seventy plus years ago the first wave of traditional, passive dressings, i.e. gauzes and sponges were introduced. However, with the work of Winter in 1960, the second wave of moist wound healing (MWH) dressings started to be developed, incorporating different materials, e.g. hydropolymers, hydrocolloids, collagen dressings, gels, saline and wet gauze. These passive dressings were designed to deal with the symptoms of the wound, the exudate, and were therefore applicable for a wide range of wounds.

More recently, people have looked at developing dressings that interact with the wound, thus doing more than just managing the local wound environment. This third wave of dressings are designed to target non-healing or 'hard-to-heal' wounds, i.e. those that do not heal within an expected time-frame despite optimum care (Marjolis et al, 2004; Harding et al, 2006). However, due to their complexity, these new interactive dressings are more expensive than passive products and less well accepted as first-line treatment as, in many instances, clinicians are unable to identify the potential reason for the delay in healing. This can be due to:

- ▶▶ Damaged matrix
- ▶▶ Growth factor receptors
- ▶▶ Oxygen deficiency
- ▶▶ Infection
- ▶▶ High levels of proteases
- ▶▶ Deficient growth factors
- ▶▶ Biofilms
- ▶▶ Inflammatory environment
- ▶▶ Non-migratory hyperproliferative edge
- ▶▶ Senescent cells.

The round-table meeting concentrated on proteases (protein degrading enzymes) in wounds. Some wounds have elevated levels of protease activity which can be detrimental to the healing process. Studies have shown high levels of proteases in non-healing wounds, which decrease as the wounds begin to heal (Tren Grove, 1997; Ladwig et al, 2002).

The body has four different types of proteases. However, two large categories are of concern:

1. Matrix metalloproteases, e.g. MMPs
2. Serine proteases, e.g. trypsin and elastase (a much larger group of enzymes, but less well known in the field of wound healing than MMPs).

Both these categories of enzymes are needed for wound healing to occur, as they function optimally under physiological conditions and can collectively degrade all components of

# round-table meeting

the extracellular matrix (ECM). They are normally controlled at the tissue level by natural inhibitors, e.g. tissue inhibitors of metalloproteinases (TIMPs), alpha-1 antitrypsin (AAT) and synthesised and stored as inactive pro-enzymes.

However, when the control system breaks down you end up in a disease state. Thus, in many cases, be it cancer or an inflammatory state, there is a misregulation of proteases. In wound care, when protease activity is too high, the balance between tissue breakdown and repair is disturbed.

## Role of proteases in wound healing

Without proteases, wound healing would not be achieved (Figure 1). They are the body's natural way of debriding the wound (Gibson et al, 2009).

Literature (Trengrrove et al, 1997; Harding et al, 2002) shows that in chronic, non-healing wounds, the level is not only elevated above expected, but persists throughout the lifetime of the non-healing wound, and only when the wound starts to progress to healing does the level drop (Figure 2). This lack of control of proteases in non-healing wounds has been accepted for the past 20 years.

Cullen et al (2002) looked at venous leg, diabetic foot and pressure ulcers and found that the level of activity varies dramatically. In all these cases, the wounds had been present for longer than four weeks, and some for years. Figure 3 shows that the level of protease activity is in excess of what would be expected to be present during the inflammatory phase of healing, which should be in the region of 3–5 days. Thus, when enzymes, such as MMPs and elastase, are found to be elevated a month, two months or a year later, the wound is probably still in the inflammatory state and has not progressed to the next phase of healing.

MMPS are a large family of enzymes (more than 20 MMPs have

## Table 1

### Comments on the use of diagnostics (WUWH, 2008)

- ▶▶ Clinicians use a wide range of tests to determine wound aetiology, comorbidities and current wound status, and to guide management.
- ▶▶ Re-evaluation of the patient and the wound may include or indicate the need for repetition of certain tests or new tests.
- ▶▶ Diagnostic tests vary in the degree to which they indicate a diagnosis and guide treatment.
- ▶▶ Current tests are not always able to determine the reason for non-healing in an optimally managed wound.
- ▶▶ The development of specific diagnostic tests for use in wounds has the potential to revolutionise their treatment.
- ▶▶ For maximum benefit, these tests need to provide objective support for treatment decisions. This will help to improve standards of wound care and aid the cost-effective use of limited resources.

been identified). Cullen et al (2002) investigated which ones were important in the wound healing process. By looking at which assay systems were available to measure the different MMPs, MMP-9 (gelatinase), MMP-8 (neutrophil collagenase) and MMP-2 (elastase) come out as predominant (Figure 3). Thus indicating that the wound is still in an initial inflammatory stage, and to progress, the wound needs to be encouraged to move on to the next stage of healing.

## The potential impact a test might have

Given the thousands of molecules that play a role in healing, it is unlikely that a 'magic' bullet will be found that heals all wounds. Therefore, treatments have and will become more targeted, thus:

- ▶▶ If proteases are elevated, use a protease modulator
- ▶▶ If a wound is infected, use an antimicrobial agent
- ▶▶ If no granulation tissue, use growth factors or tissue replacements.

As more is learnt about wound biochemistry, better and more intelligent treatments and therapies will be developed in the future. There are a number of different types of diagnostics that could potentially be used, such as

an indicator, a diagnostic marker, or a theranostic.

## Could a protease point of care (PoC) test help?

There are modulating therapies available that can help to rebalance protease activity levels. By monitoring these proteases with diagnostic guides, the clinician can detect when certain therapies are appropriate, or otherwise, thereby targeting therapy.

While it is important to realise that proteases are needed and what they do at different stages of wound healing, it is crucial that the tool does not change people's attitude so that the focus is only on proteases, ignoring anything else that might be contributing to a non-healing wound. Holistic assessment is key before dealing with the more complex issues.

It is crucial to identify when this tool is needed and take this forward with guidelines and flowcharts. It should just be part of the overall treatment plan, not the only tool. In addition, there are not tissue viability nurse specialists/experts in every area. Guidelines therefore need to be precise, as otherwise they might be open to abuse and misinterpretation.

The feeling of the working group was that many general clinicians lack an in depth knowledge of proteases and their role in wound healing. Thus, to start talking about modulating proteases without any additional education would be inappropriate. It may be for now that the average nurse working today would not be able to use the test in a productive way. In addition, the terminology of MMPs and elastase is not used in general practice, or in specialist units. In the last few years, biofilms have become part of the language of wounds, but proteases are yet to be fully adopted.

If a product has a good effect, it becomes a panacea and is used on every wound. Thus, a test would be helpful in the hands of the right clinician. There is also a lack of understanding of when an acute wound becomes a chronic wound, and when it is appropriate to start thinking that the treatments being used are not working. There is no fixed protocol that if progress is not being seen at this point, stop the treatment. Patients are frequently referred late, after having had numerous dressings applied.

However, if a holistic assessment has been undertaken and all the underlying issues have been addressed with appropriate wound bed preparation and treatments, i.e. everything to stimulate wound healing has been done, but still nothing has happened, then proteases should be considered, as something is occurring on a molecular level. If wound healing is subsequently promoted, confidence will be gained that they work in practice, reinforcing the message that the dressing has addressed the molecular protease within the wound bed, as this is the only factor that differs from previous treatments. This will also give justification to use higher priced dressings, as we know cost of care can be reduced with advanced dressings. In today's economic climate, specialist clinicians need justification and evidence that these dressings work. Thus, being able to show that the dressings are being

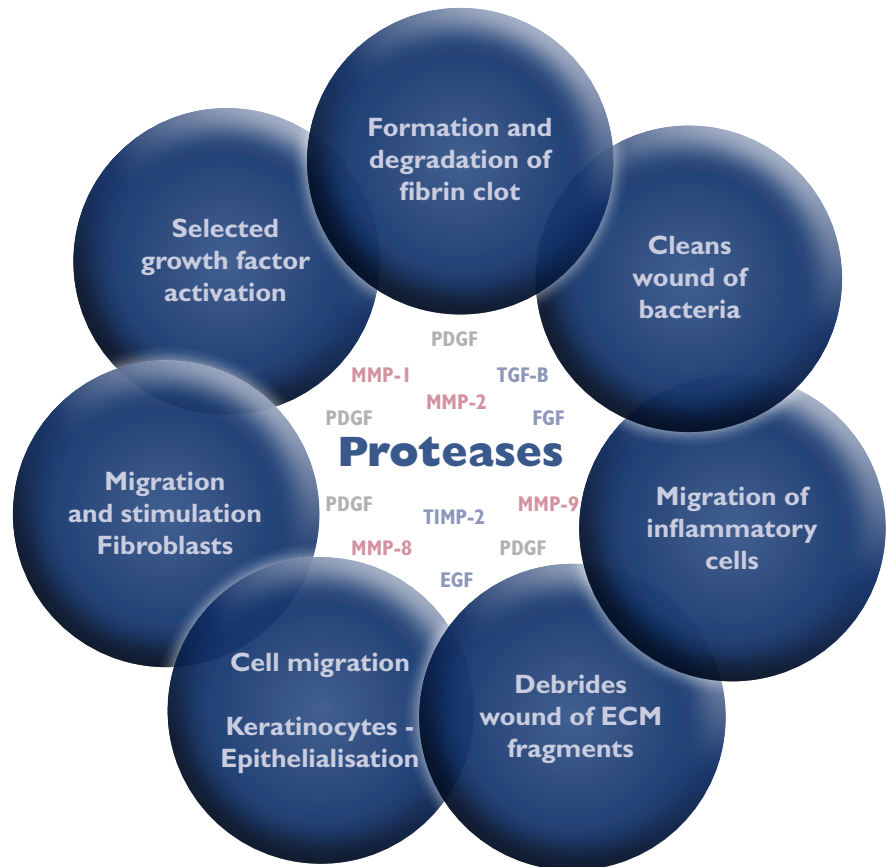


Figure 1. Role of proteases in wound healing.

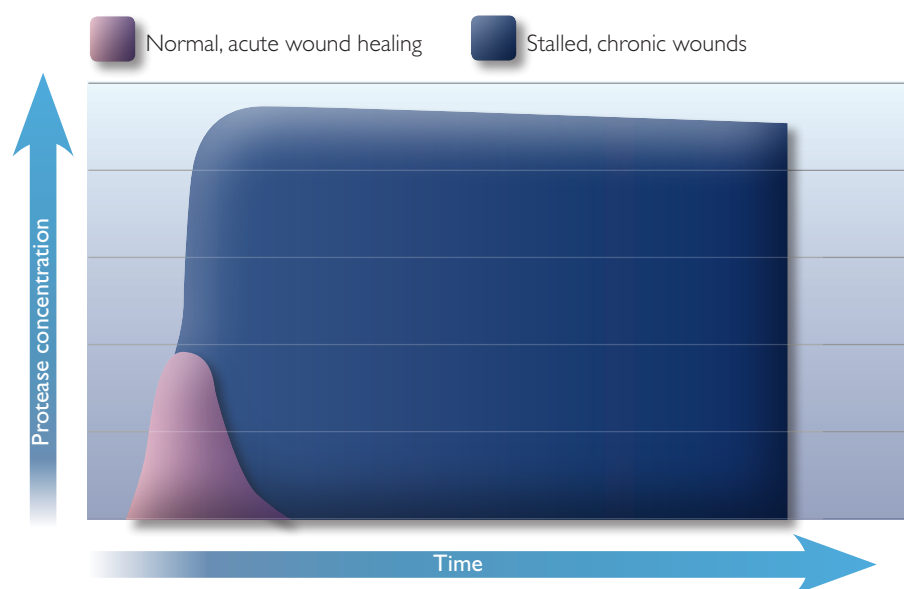


Figure 2. Proteases in chronic wounds.

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used on the right patients at the right time would be useful.

If you have an indicator for the level of protease activity, you potentially might start using that dressing earlier in the treatment process, which again could lead to cost-savings. The ability of knowing when to start and stop using a product would also ensure cost-effectiveness. Traditionally, this has been done by guesswork, but now there is the potential not to guess. Thus, it is not just about looking, listening and touch, but thinking as well.

There are many ways of modulating proteases, with the marketing literature of various companies claiming protease modulation from everything from dry gauze through to products that have a biological interaction. An alternative approach to protease modulation could be one specific group of dressings or a range of strategies, such as debridement or topical negative pressure (TNP) therapy.

## Education

In health care today, no one is taught to challenge. Education is also being cut, hence the popularity of practical workshops. It is only when litigation occurs that something is done, with everyone blaming the dressing, not the inappropriate assessment. Often the only education is from companies who may be biased about their products. Furthermore, although keen while attending a training day, nurses are often unable to translate what they have learnt into practice. Training needs to be more competency-based, although that could become more task-orientated.

The group all agreed that there is a paucity of tissue viability education, despite tissue viability being a considerable part of a registered nurse's role.

## Current treatment pathway, patterns of referral

There is currently a great deal of frustration around referral patterns.

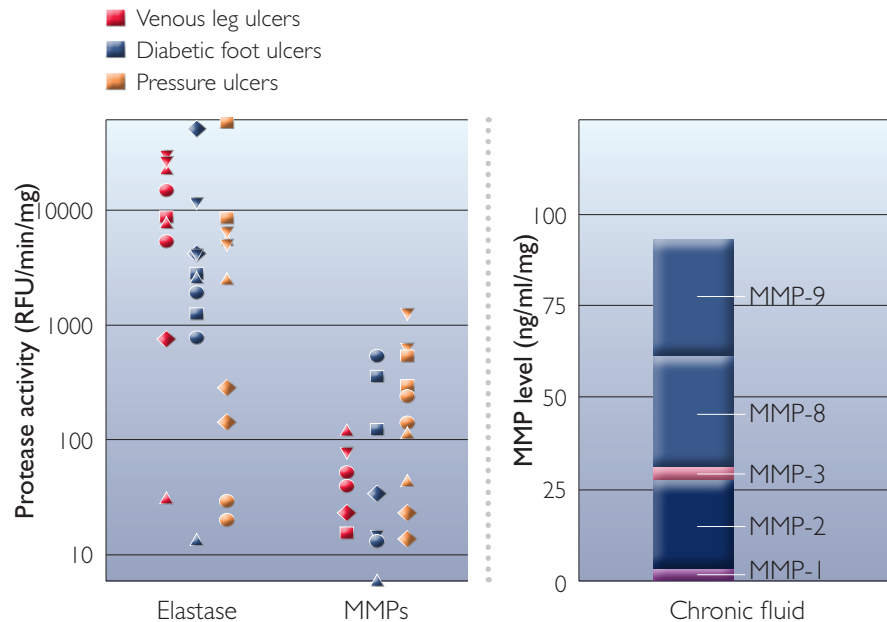


Figure 3. Proteases in excess in chronic wounds (Cullen et al, 2002).

Often it is not until the wound is non-healing that patients are referred. Pathways in and out are not as fluid as they should be, with multiple points of entry into the service and where you can be referred.

There are few criteria regarding referrals. Points of entry into healthcare include: GPs, practice nurses, community nurses, minor injury clinics, A&E, planned or emergency admissions, or patients may self-refer and go directly to clinics such as Leg Clubs. Once in those services, there is a system of initiating treatment. Many podiatry services have a flowchart, but for other wounds there are few criteria on how you manage care.

The people who may send patients to those services are:

- ▶▶ Patients themselves
- ▶▶ Continence services
- ▶▶ Social services
- ▶▶ Homeless healthcare service
- ▶▶ Learning disability
- ▶▶ Mental health
- ▶▶ Prison services
- ▶▶ Out of area referrals.

However, within all of these points, whether it is entry into health care or

the referral service, there is an element of 'keep and treat'.

The working group agreed that healthcare providers are faced with a lack of cohesion and that a triage system is missing.

## Where would you fit a test into a treatment pathway?

The test should possibly be used only after conventional treatment and full holistic assessment. It would depend on when the patient presented and their condition, and be individual for each patient. It is important to ensure that as many other complications as possible, such as infection, have been eliminated. Tissue viability nurses and other specialist practitioners should first do the test before it is rolled out to anyone else — and flow chart protocol would be needed so that there was clear guidance.

If, for example, a patient with a leg ulcer was referred who had not followed the guidelines, they should be referred back so that the basics could be completed. If they had followed guidelines but their wound had still not healed, their protease status should be considered. Patients who deteriorate

tend to get referred quickly because there is an element of panic as to what is happening. However, patients in the middle, who are not deteriorating but not necessarily improving, tend to be the ones who people 'keep and treat'. Thus, in terms of timing, it might be variable when they are referred. It would be good, therefore, to do the test once in specialist services.

Other factors also influence when the test should be performed, namely:

- ▶▶ Aetiology-based
- ▶▶ Time-based
- ▶▶ Assessment criteria
- ▶▶ Wound healing curve
- ▶▶ Process driven (if you have a good flowchart for how patients are treated).

It is important that practical considerations of putting together a diagnostic algorithm should be looked at.

Any patient referred should be thoroughly assessed again, i.e. go back to a blank canvas without making any assumptions and being accountable. The test would be considered only when there was a clean, healthy wound that was not progressing. If a patient was static and started deteriorating, more than one element needs to be looked at. The test would therefore be done at specialist level unless there was a good algorithm, as a test is only as good as the person who utilises it. Specialists also need to have knowledge of what to do after taking the test.

Benefits of diagnostic tests are tangible, but it is important to be mindful about not adding complication with a test which may be taken away if it is inappropriately used. Planned, appropriate usage of this test needs to be ensured, while also identifying the complex process involved.

### Practical application of putting together a diagnostic algorithm

A seamless service needs to be developed between acute and

primary care facilities. Pooling people's experiences and collecting the same data in the same way would produce useful information on how and when the diagnostic tool might be used.

#### Acute care

A detailed holistic assessment would first be taken before considering whether to do the diagnostic test. Before taking the test, all corrective measures should have been put in place. If the patient's condition could not be improved, the whole process of assessment would need to begin again before surgery. If the decision was taken to use one of the new diagnostic tools, this would need to be authorised and ordered by key personnel.

If the result of the test was low, the patient would need to be reassessed. If it were elevated, the patient would be treated with a protease modulator with ongoing assessment. After four weeks of treatment, the wound would be assessed to see if protease activity had reduced. If low, treatment would be stopped, if still elevated, holistic assessment would be undertaken again to see what had been missed. Elevated results, history of wound, costs involved, cost of nursing time, wound dimensions, and wound parameters would all be recorded in a database to build up a complete picture of the patient before they were referred, and what was happening while they were being treated.

The acute sector would not use the test as much as primary care, because if the tool was available in primary care it might prevent referral into the acute sector.

#### Primary care

Primary care would also start with holistic assessment. The wound would be reviewed and, if static, referral to the appropriate person would be considered, i.e. designated TVN, who would review and consider whether or not to do the test. The results would

be generated to determine treatment. Clinically, it was thought that there would be no reason to retest (unless the protease modulating dressing had been used for a period of time and stopped at an appropriate point, when another dressing was introduced with the wound becoming static once more), other than for data collection and audit with a view to getting the product onto a formulary.

#### How long would you use the protease modulating dressing?

Currently, there is some good data but the optimum use is not known. MMPs drop at week 2 and then level, but the wound size does not reduce until week 4 with continued use of the dressing. This raises the question of if the dressing was used until week 2 and then stopped, would the wound still reduce at week 4. This test has not been done and so the evidence is not there.

The working group said that they would stop treatment at four weeks, based on clinical view and not the test. Four to six weeks is the recommended length of time to use protease modulating dressings.

#### Adopting the test in clinical practice?

Proteases are a problem for which both acute and primary would like to modulate and have a test. However, various factors need to be considered:

- ▶▶ Education facilities
- ▶▶ Getting the test into practice
- ▶▶ Securing funding.

#### Primary care

A two-pronged approach would be needed: national and local. The task of the national approach would be to:

- ▶▶ Raise profile
- ▶▶ Raise awareness
- ▶▶ Tie in with NHS innovations.

From a local point of view clinicians would need:

- ▶▶ To know how many patients needed to be treated



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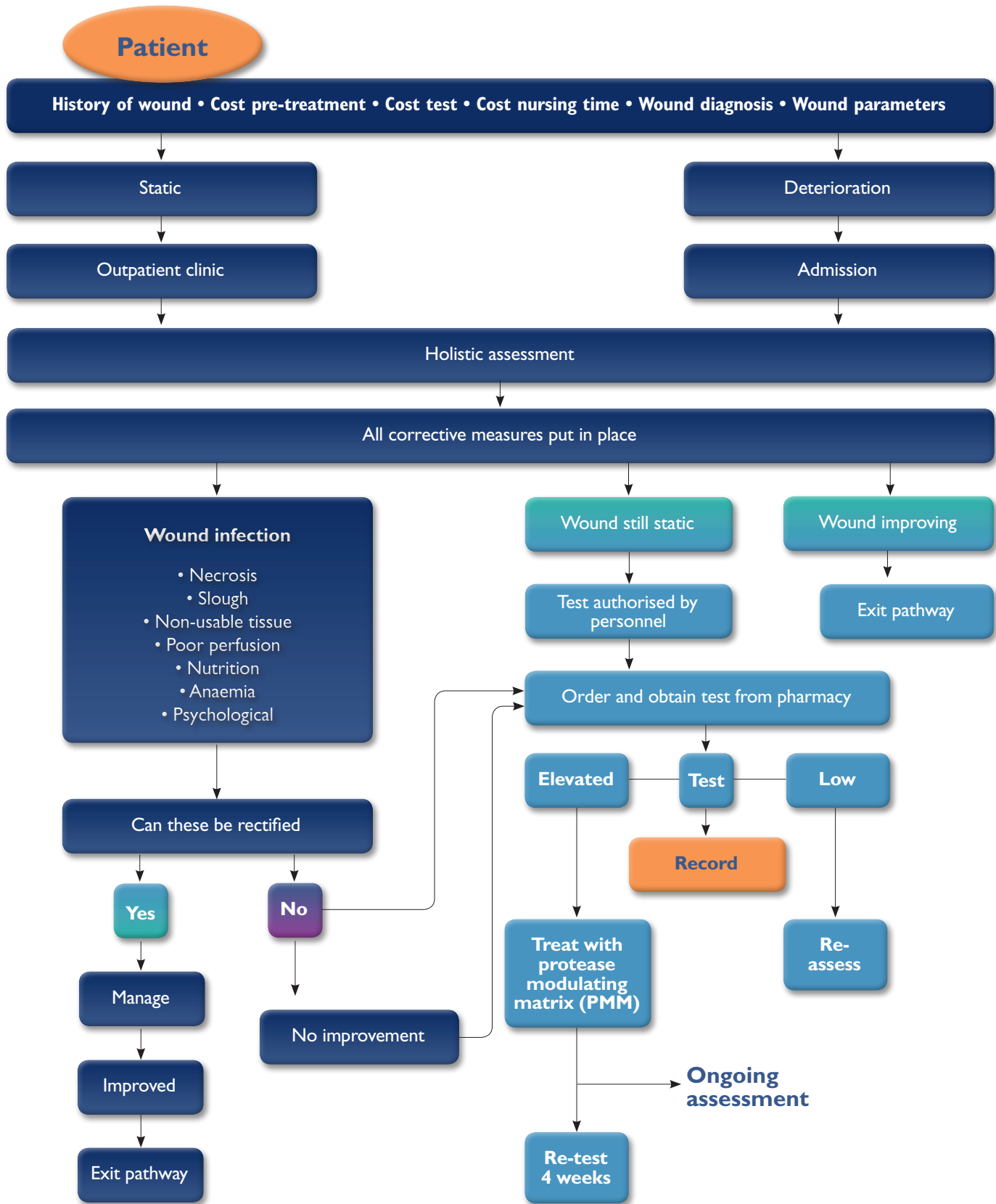


Figure 4. Potential pathway for use of test.

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- ▶ To get a pooled dataset with a standardised data tool so that everyone has access to how many patients are being treated and how effective the test is
- ▶ To provide information to demonstrate cost-savings
- ▶ New, clear guidelines as to when to use the test and how long to use protease modulators.

Access to that information and some analysis on a national scale would be useful. While there may be pockets where there is local data, that data is not freely available everywhere. Industry could help to correlate and collect some of the data.

Data protection should also be considered, with all data being stripped and cleared, i.e. a secure registry.

## Acute care

Clinical and market evaluation would be needed as data entry is always a problem. Printed conditional randomised fields (CRFs) with tick boxes anonymised by number would be helpful. These would need to be divided by specialties and be specialist specific.

By collecting information in an easy way, data could be pooled as well as looking at other aspects, such as:

- ▶ What does it mean to patients?
- ▶ Can we demonstrate a reduction in costs?
- ▶ Can we stop treatment with protease modulators at two weeks.

Confidence in this would help to offset the cost both pre- and post-treatment. More information as to what is going on in the wound itself is needed, as well as cost-savings.

## Clinical adoption

Training needs to be given to those using the test. Techniques to collect wound fluid should also be addressed.

Again, how the patient's quality of life is going to improve should be taken into

account. Financial costs are a small part of forecasts, with reduced bed days and complications being more significant.

## **Nurses need to be educated about the basics of care and develop their knowledge of factors that delay wound healing, as the hard-to-heal wound not only has a negative impact on the patient and carer, but also on healthcare economy.**

A standardised business plan is needed, that tissue viability nurses could take to commissioners to show that this is something that would benefit patients.

Use of the diagnostic tool should be carefully considered and, in the first instance, it should only be used by more experienced or specialist clinicians. In order to ensure equity of service provision for patients a management algorithm was proposed (*Figure 4*). This would ensure that patients receive a full holistic assessment and appropriate gold standard care as part of usual management before the test was implemented. The algorithm also builds in balances and checks to ensure that when the test is used, appropriate management pathways are both followed and reviewed.

## Conclusion

From the discussion of the round-table about the role of proteases in wound healing and how they can be used as a diagnostic marker, it is clear that further research is needed to identify the link between proteases and infection, as well as the effect of protease modulating dressings and their length of usage.

Nurses need to be educated about the basics of care and develop their knowledge of factors that delay wound healing, as the hard-to-heal wound not only has a negative impact on the patient and carer, but also on healthcare economy.

It is important to ensure that all the basics have been covered and that the underlying comorbidities have been addressed, and only when the wound still continues not to progress to healing should a point of care test for protease activity be considered. Not all advanced dressings work on every wound, rather a subsection of that population. Diagnostics would help the clinician to select appropriate therapies for particular wounds and to decide when a therapy should be stopped, i.e. it has performed its function and it is time to move on to something else. Establishing a registry that collects data on protease activities in different wound types at different states of healing would provide useful data on wound healing prognosis. **WUK**

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