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Horizon Scanning Technology Prioritising Summary

Skin biopsy diagnosis of peripheral neuropathy

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AHTA

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PRIORITISING SUMMARY

REGISTER ID: **000340**

NAME OF TECHNOLOGY: **SKIN BIOPSY DIAGNOSIS OF PERIPHERAL NEUROPATHY**

PURPOSE AND TARGET GROUP: **PERIPHERAL NEUROPATHY**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☐	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☒	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number
☐	No	
☒	Not applicable	

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
USA		✓	
UK		✓	

IMPACT SUMMARY:

Using a skin biopsy to diagnose peripheral neuropathy (PN) in the form of small fibre neuropathy (SFN) may be applicable to several illnesses including viral infections such as HIV; autoimmune diseases e.g. Sjögren's syndrome; drug toxicity; genetic conditions e.g. hereditary sensory and autonomic neuropathies (HSANs); and the most prevalent disease associated with PN, diabetes. The diagnosis of PN may allow the underlying cause to be determined and an appropriate therapy to be administered.

BACKGROUND

Peripheral nerves transmit signals from the environment to the central nervous system (CNS) and also from the CNS back to the body. Axons may extend from the brain to the tips of the extremities, and are supplied from a cell body that may be far from a particular section of axon. Due to their extreme length, axons are susceptible to damage which then affects their distal part. Axons are categorised as either myelinated (A fibres) or unmyelinated (C fibres). Only axons wider than 1μm are

myelinated and they conduct signals faster than unmyelinated axons. Epidermal nerve fibres (ENF) are small, unmyelinated, present in the epidermis and are involved in pain perception and involuntary autonomic functions. SFN is the damage to these small fibres and is a subset of PN which may also result from damage to large, myelinated fibres (Fink & Oaklander 2006). PN is the major predisposing factor that leads to amputation of the lower limb either above or below the knee and of the toes or feet (ADS 2000). SFN symptoms usually begin in the feet and may progress to more proximal regions. Symptoms include pain or burning sensations, loss of pain and temperature sensation, the failure of autonomic functions such sweating, blood pressure regulation, or problems with continence, and sexual function. The development of SFN may be an early sign of many polyneuropathies. Thus diagnosis of SFN may lead to an earlier diagnosis of the underlying cause which then may be treated with the appropriate therapy. Symptoms may be treated via pain management utilising surgery, drug treatment, physical or psychological therapy. The ability to accurately diagnose SFN will become increasingly important with the rising incidence of diabetes in Australia and as improved therapies are introduced to treat the symptoms of SFN (Fink & Oaklander 2006).

Skin punch biopsy is becoming the standard method of diagnosing SFN due to its ability to directly visualise the enervation of the epidermis. A 3mm punch is used to take a skin sample at the site of interest under local anaesthetic. Small sections (50μm) of these skin samples are immunostained with antibodies against PGP 9.5[1], which is a non-specific axonal marker. Other more specific markers may also be used. The stained section can be visualised with bright field microscopy or confocal immunofluorescence. The fibre density can be compared to normative values determined for bodily location and the visualisation method used. Morphological and histological information gained from these sections may give further information about disease pathology (Sommer & Lauria 2007).

CLINICAL NEED AND BURDEN OF DISEASE

No direct data were found on the incidence of SFN in Australia. While a wide variety of diseases and modalities can result in SFN, the majority of SFN cases in Australia result from diabetes complications. It is estimated that half of patients with diabetes for more than 25 years have SFN (Lauria & Lombardi 2007). An estimate of diabetes prevalence in Australia, based on blood glucose levels, puts the number of people aged >25 years with diabetes at 950,000 during the period 1999-2000. An alternative figure, based on self-reported glucose levels, estimates the prevalence at 699,600 (AIHW 2006). PN prevalence among diabetes patients has been estimated to be 30 per cent[2] (ADS 2000). Based on these figures the number of diabetes patients with PN in Australia may range from 209,880 to 285,000 cases. Other patient groups that may

[1] PGP 9.5 is a form of ubiquitin carboxyl-terminal hydrolase (removes ubiquitin)
[2] This estimate did not mention constraining factors and is taken to be 30 per cent of the whole diabetic population.

have SFN include people with viral infections e.g. HIV; autoimmune diseases e.g. Sjögren's syndrome; people affected by drug toxicity; people with genetic causes e.g. hereditary sensory and autonomic neuropathies (HSANs). The prevalence of SFN in these patient groups is unknown.

DIFFUSION

From web based searches the diffusion of this technology into Australia seems to be confined to medical research.

COMPARATORS

Most standard diagnostic tests for neuropathy do not work for SFN as they trigger functions that are mediated by large, myelinated axon fibres. One exception is that patients with SFN exhibit higher warm and heat-pain thresholds (Lauria et al 2005). This diagnostic technique, while appearing effective, was conducted on a small patient group and is not widespread as yet, making the assessment of its comparative utility difficult.

SAFETY AND EFFECTIVENESS ISSUES

Skin biopsy is proposed to have two main uses for patients suspected of having SFN. The first is the diagnosis of the immediate cause of symptoms of patients presenting with pain or burning sensations, loss of pain and temperature sensation or the failure of autonomic functions, where PN may be suspected. The second is assessment of the prognosis of patients with a known aetiology that predisposes them to SFN such as. diabetes. In addition, skin biopsy may be used to assess the effect of therapies, either positive or negative, on the underlying cause of SFN.

A study of 69 subjects, 54 with diabetes and 15 normal controls, investigated the correlation between skin biopsy (and corneal confocal microscopy) and other markers in patients with diabetes (Quattrini et al 2007) (level IV prognostic evidence). The patients with diabetes were clinically graded according to neurological function, neurophysiology, and quantitative sensory testing. This was used as the reference to judge the success of the skin biopsy results. It was found that intraepidermal nerve fibre density, branch density and branch length significantly correlated with the severity of neuropathy in diabetic patients. There was a progressive reduction in intra-epidermal nerve fibre *density* in diabetic patients with increasing neuropathy symptoms. The density in diabetic patients with severe (2.54 ± 0.76/mm), moderate (5.84 ± 0.94/mm) and mild neuropathy (5.56 ± 0.86/mm) differed significantly (p <0.01, p <0.05, p <0.05 respectively) when compared to control subjects (11.21 ± 0.84/mm). Although a reduction in intra-epidermal nerve fibre *length* was noted in diabetic patients with no (38.0 ± 3.32), mild (31.47 ± 2.46) and moderate (29.59 ± 5.53) neuropathy compared to control patients (42.10 ± 4.31), only diabetic patients with severe neuropathy were found to have significantly shortened intra-epidermal

nerve fibres (22.61 ± 7.12, p <0.05). This study reported that the assessment of intra-epidermal nerve fibres by skin biopsy *and* corneal confocal microscopy (data not shown) were both good surrogate markers of diabetic neuropathy.

A longitudinal study of 58 HIV-1 infected patients investigated the prognostic factors linked to progression of SFN. The general health of the subjects was assessed using a variety of methods including clinical, virologic, imunnologic, quantitative sensory thresholds, and skin biopsy of the leg for SFN. Patients were assessed serially over a period of up to 4.5 years (median 2.9 years). At study commencement, 26 of the subjects showed no symptomatic SFN. However, by the end of follow up, 19 of these subjects had progressed to symptomatic SFN. Epidermal nerve fibre density correlated with progression to symptomatic SFN. Epidermal nerve fibre density of less than 10 fibres per mm conferred a 14-fold increase in the risk of developing symptomatic SFN (Herrmann et al 2006) (level IV prognostic evidence).

Another prognostic study investigated the progression of SFN. Diabetic patients (n=29) who were clinically free from PN at the beginning of the study and normal controls (n=84) were included. Intra-epidermal nerve fibre density was assessed at the thigh and ankle. There was a significant difference in ankle intra-epidermal nerve fibre density between diabetics and normal patients. Using an intra-epidermal nerve fibre density cut-off less than 10 fibres per mm, a sensitivity and specificity of 72 and 76 per cent, respectively, for diagnosing SFN was reported. Thus the authors concluded skin biopsy is a useful technique for the early diagnosis of diabetes-induced neuropathy (Umapathi et al 2007)(level IV prognostic evidence).

One of the problems with SFN is the damage that can occur to autonomic functions. This was assessed by a small study on 17 patients with symptoms consistent with SFN and 15 normal controls. Skin biopsy showed that there was a significant difference in several parameters measured: the innervation of sweat glands, erector pili and arterioles. This demonstrated that biopsy is useful to diagnose the damage to autonomic systems that may occur in SFN (Dabby et al 2007) (level III-3 diagnostic evidence).

Overall, skin biopsy appears to be a useful technique that allows both the diagnosis of patients suspected to have SFN and the assessment of patients known to have SFN. There is currently no standard method for the diagnosis of SFN, therefore the studies reviewed in this summary were not measured against a relevant reference standard.

COST IMPACT

No cost data were found during the preparation of this prioritising summary.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

No issues were identified/raised in the sources examined.

SUMMARY OF FINDINGS

Although the evidence for the use of skin biopsy to diagnose SFN was mainly from small scale studies, the technique appears to perform well. As yet there are no studies reporting on long term outcomes of patients diagnosed with SFN. In addition, no economic data were found. Although some studies mention the possibility of treatments/therapies for patients diagnosed with SFN, none were identified where the therapies were administered to the patients diagnosed with SFN. Therefore it is unknown whether patients benefit from being diagnosed with SFN.

HEALTHPACT ACTION:

Based on the currently available evidence, skin biopsy appears to be a potentially useful technique for the diagnosis of SFN but as yet there is limited evidence to its efficacy. Therefore HealthPACT has recommended that further assessment of this technology is no longer warranted.

NUMBER OF INCLUDED STUDIES

Level III-3 diagnostic evidence	1
Level IV prognostic evidence	3

REFERENCES:

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SEARCH CRITERIA TO BE USED:

Ankle/innervation
Diabetic Neuropathies/ diagnosis
Early Diagnosis
Epidermis/ innervation/ pathology
Humans
Nerve Fibers/ pathology
Peripheral Nervous System Diseases/ pathology
Skin/ pathology
Biopsy/methods/ standards