Sudoscan

Diabetes is the fastest growing chronic condition in Australia. It is increasing at a rate faster than all other chronic diseases including cancer and cardiovascular disease.

Diabetes is the biggest challenge confronting Australia's health system and has become a world-wide epidemic.

- 280 Australians develop diabetes every day.
- Around 1.7 million Australians have diabetes. This includes all types of diagnosed diabetes (1.2 million known and registered) as well as silent, undiagnosed type 2 diabetes (estimated to be 500,000 people).
- More than 100,000 Australians have developed diabetes in 2015.
- For every person diagnosed with diabetes there is usually a family member or carer who also 'lives with diabetes' every day in a support role. This means that an estimated 2.4 million Australians are affected by diabetes every day.
- Total annual cost impact of diabetes in Australia estimated at $14.6 billion.

Type 2 diabetes accounts for 85% of all diabetes cases and gestational diabetes in pregnancy is also increasing and is a common precursor for Type 2 diabetes later in life.

Indigenous Australians are three times more likely to have Type 2 diabetes than non-indigenous Australians; develop it at an earlier age and often die from it at a younger age than non-indigenous Australians.

The Australian Bureau of Statistics (2014) reported 5% of Indigenous people aged 25-34 years had diabetes, and up to 39% of those aged over 55 years had the disease.

Indigenous Australians are also at greater risk of complications than non-indigenous Australians, with a ten-fold higher risk of kidney failure and an eight-fold higher risk of high blood pressure.

Aboriginal and Torre Strait Islander Australians with diabetes are 38 times more likely to undergo a major leg amputation compared to non-Indigenous Australians with diabetes.

They are also 27 times more likely to undergo a minor leg amputation.

Nearly all (98%) of amputations in Aboriginal and Torres Strait Islander people are related to diabetes.

Diabetes is the second leading cause of death for indigenous Australians.

In 2013-2014, there were 900,000 hospitalisations where diabetes was the principle or additional diagnosis.

Common complications affect the feet, eyes, kidneys and cardiovascular health. Nerve damage in the lower limbs affect approximately 13% of Australians with diabetes, diabetic

retinopathy occurs in over 15% of Australians with diabetes and diabetes is now the leading cause of end-stage kidney disease in this country.

Cardiovascular disease is the primary cause of death for Australians with diabetes and pre-diabetes, accounting for as much as 65% of all cardiovascular deaths.

Research by Diabetes Australia has shown anxiety, depression and stress are reported by 41% of Australians suffering from diabetes due to the complications of the condition and the daily management of it; and diabetes is ranked in the top ten causes of death nationally.

Diabetes Australia predicts that if diabetes continues to rise in Australia at it's current rate, it is estimated three million Australians aged 25 years and older will have diabetes by the year 2025 - a mere nine years away. When you consider 85% of all cases of diabetes are Type 2, you can see how serious this issue is.

SUDOSCAN is a unique device that identifies neuropathies not detected by the traditional tools used for large fibre testing; and the early detection of small fibre neuropathiescan predict the future health of a person, as well as improve disease management and the prevention of severe complications associated with some diseases, in particular diabetes mellitus (type 2 diabetes).

As such, Sudoscan an invaluable tool for preventative health and wellness programs.

During the test, a low electrical current stimulates the sweat glands of the hands and feet.

The sweat glands release chloride ions which react with the sensor plates and the generated current quantifies a score called Electrochemical Skin Conductances.

After 3 minutes, quantitative and objective results for both hands and both feet are displayed immediately to help evaluate the small C fibres.

The test is highly reproducible and the technology is backed by over 80 publications in international scientific journals, which show that SUDOSCAN has similar results to reference tests such as skin biopsy and QSART; or clinical scores like NIS-LL.

Sudoscan has been included in the European Network for TTR-FAP Amyloidosis; the Polish guidelines for diabetes management; and by the Latin America Diabetes Association.

SUDOSCAN is being used worldwide by more than 3,000 neurologists and endocrinologists mainly in departments of diabetes, neurology, neurophysiology, oncology, cardiology, pain for early detection of neuropathy and to follow-up with patients.

SUDOSCAN is CE certified and cleared for use by the US FDA and is registered and distributed in 34 countries, including Australia and New Zealand.

Reducing the risk of Diabetic Foot and Cardiovascular complications in people with type 2 diabetes.

Diabetic Autonomic Neuropathy (DAN) is a serious and common complication of diabetes that can involve the entire autonomic nervous system.

In the long run, amputation and foot ulceration are the most common consequences of peripheral diabetic neuropathy and major causes of morbidity and disability.

According to Diabetes Australia:

- There are more than 4,400 amputations every year in Australia as a result of diabetes.
- Every year there are 10,000 hospital admissions in Australia for diabetes-related foot ulcers many of these admissions end with people having a limb, or part of a limb, amputated.
- People with diabetes hospitalised for lower limb amputation have longer stays in hospital than other diabetes-related complications. The average length of stay is around 24 days.
- Diabetic foot disease costs Australia around $875 million every single year.
- 85% of diabetes-related amputations are preventable if problems are detected early and managed appropriately.

Sudoscan is an innovative and proactive device that can test for small nerve fibre neuropathy when there is still the opportunity to reverse the damage, or cease disease progression before irreversible damage is done.

Cardiovascular Autonomic Neuropathy (CAN) is the clinically most critical form of diabetic autonomic neuropathy. It is caused by a loss of autonomous cardiac innervation and results in diminished Heart Rate Variability(HRV) and vascular dynamics.

Detecting Cardiovascular Autonomic Neuropathy early can help prevent sudden cardiac death and myocardial infarction .

Heart Rate Variability has proven to be a predictor for all-cause mortality but is time consuming and requires specific diagnostic equipment.

SUDOSCAN is an innovative device to detect and follow-up cardiac autonomic neuropathy.

Sudoscan and Diabetes -Controlling Disease Progression

Type 2 diabetes often progresses in silence, without developing clinically relevant symptoms. It frequently remains undiagnosed until complications appear and as many as one third of all cases may not be detected at all. There is also epidemiologic evidence that complications are triggered in a much earlier stage of the disease than previously thought.

For a substantial number of diabetic patients, irreversible tissue damage (peripheral vascular disease, nephropathy, retinopathy, neuropathy) have already set in at the time of diagnosis and 60-70% of patients with diabetes have neuropathies which lead to serious medical complications.

Sudoscan has the ability to forecast a persons health and provide them with enough warning to make the lifestyle changes required to prevent diabetes from taking hold.

SUDOSCAN2

EARLY IDENTIFICATION AND FOLLOW-UP OF PERIPHERAL AUTONOMIC NEUROPATHIES

- Establish diagnosis
- Control effectiveness of treatment
- Provide quantitative data to adapt patient care and lifestyle

3 MINUTES

SIMPLE

QUANTITATIVE

NON-INVASIVE

OBJECTIVE

impetomedical

SWEAT GLAND FUNCTION – A RELIABLE INDICATOR FOR PERIPHERAL AUTONOMIC NEUROPATHY

Why test sweat gland function?

Sweat glands are innervated by small sympathetic C-fibers. Sudomotor (sweat) dysfunction can be one of the earliest detectable neurophysiologic abnormalities in distal small fiber neuropathies. Quantitative assessment of sweat response has been proposed as an index of the severity of autonomic failure as well as an early indicator for regeneration of small fibers [1,2,3].

Diabetes has been shown to be the most common identifiable cause of small fiber neuropathy. The American Diabetes Association (ADA) has identified sudomotor (sweat) dysfunction as one of the major clinical manifestations of diabetic autonomic neuropathy. Furthermore, the assessment of autonomic dysfunction may identify patients at high risk for cardiac autonomic neuropathy, which carries a very high rate of morbidity and mortality [4].

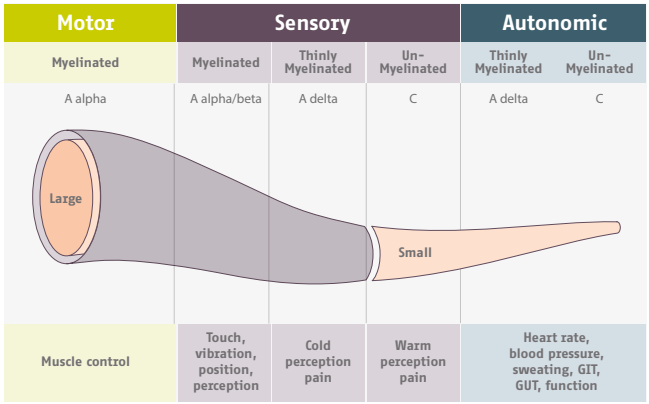


Figure 1: The peripheral nervous system is made of large and small fibers. The small, un-myelinated C-fibres are in charge of autonomic functions such as sweating [5].

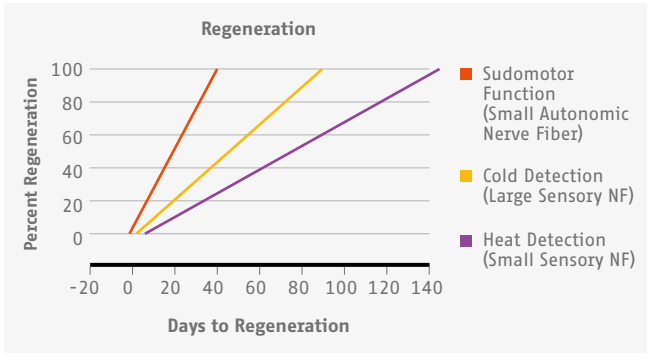


Figure 2: Small fiber autonomic nerves regenerate more quickly than the large fiber nerves upon capsaicin application [adapted from 6].

What are the alternatives ?

The use of skin biopsy to measure Intraepidermal Nerve Fiber Density (IENFD) or Sweat Gland Nerve Fiber Density (SGNFD) is an accepted surrogate measure of small fiber neuropathy. While skin biopsy is well accepted by the medical community, it has certain limitations as: invasiveness, risk of infection, bleeding, and a limited number of labs that can process the sample [7].

The Quantitative Sudomotor Axon Reflex Testing (QSART) measures sweat response under controlled humidity and temperature conditions. It requirs fairly expensive equipment and is available in few centers.

SUDOSCAN MEASURES THE CONCENTRATION OF CHLORIDE IONS PRODUCED BY SWEAT GLAND ACTIVITY

How does it work ?

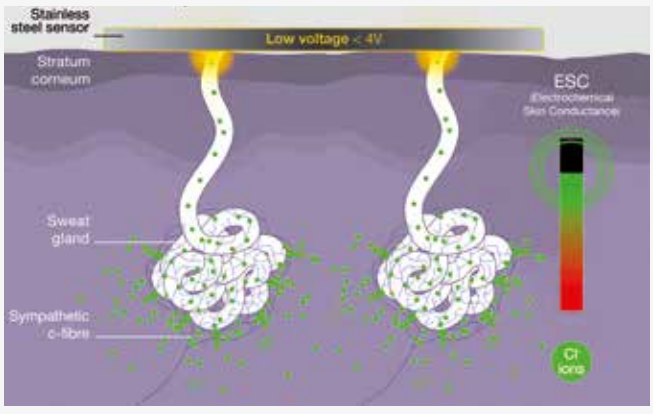
The degeneration of small nerve fibers reduces sweat gland innervation and alters sudomotor function [12]. Sudoscan measures the concentration of chloride ions produced by sweat gland activity.

A low-voltage current (<4V) is applied to the hands and feet through stainless steel sensor electrodes. The applied tension extracts chloride ions from the sweat glands which are densely concentrated on the palms and soles. Since the stratum corneum acts as an isolator, the ions can only pass via the sweat ducts. This ensures that the findings correspond solely to sweat gland function. The chloride ions create a detectable electrochemical reaction with the sensor plates which is measured.

What is measured

SUDOSCAN records the Electrochemical Skin Conductances (ESC) of the hands and feet generated from the current associated with the applied voltage. Loss of sweat glands or loss of their innervations results in reduced ESC [16].

Subject with normal sweat function



Subject with abnormal sweat function

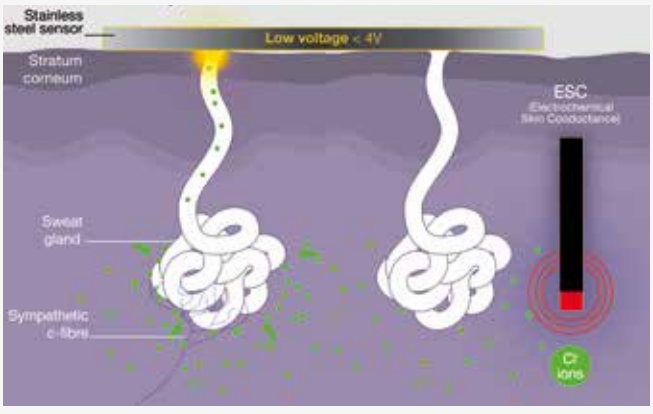


Figure 10: ESC measurement of a subject with normal (left) and abnormal (right) sweat function.

SUDOSCAN ENABLES FAST AND EASY QUANTIFICATION OF SUDOMOTOR FUNCTION

SUDOSCAN at a glance

Fast

- No patient preparation
- Results in 3 minutes
- Automatic reports

Simple

- Non-invasive
- No fasting necessary
- Easy training
- Touch screen operation

Accurate

- Quantitative results
- Proven clinical results
- Operator independent
- Four hands and feet electrodes
- Automatic quality check

Fast testing

SUDOSCAN provides an accurate evaluation of sudomotor function by measuring the ability of sweat glands to release chloride ions in response to an electrochemical activation on the palm of the hands and soles of the feet, areas with the highest sweat gland density [7].

Clear results

1 Simple

Ergonomic touch screen operation and detailed graphics allow for visual representation of the results. An immediate quality check ensures reliable results. Results are easy to interpret: Green suggests no neuropathy, Yellow a moderate neuropathy and Orange a more severe neuropathy.

2 Quantitative

Actual numerical values of the Electrochemical Skin Conductance (ESC) on the hands and feet are displayed. The level of ESC indicates the severity of the neuropathy. This measure can be compared with later test results to assess the patient's response to treatment or other prescribed interventions.

3 Symmetry

Measure of symmetry between right and left sides help identify the type of peripheral neuropathy.

Figure 3: Conductance and asymmetry of hand and feet.

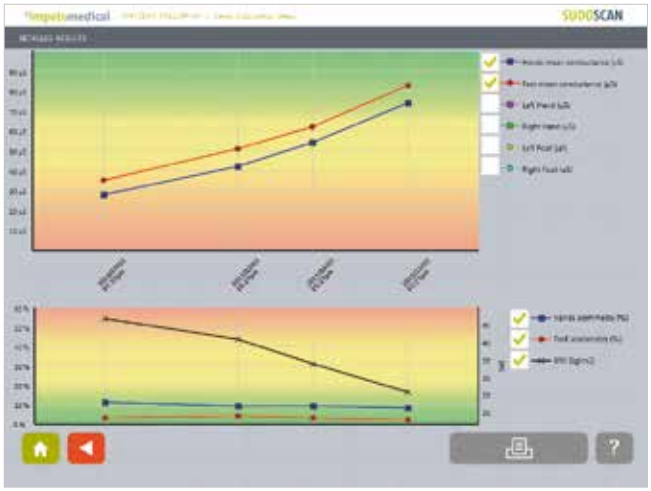


Figure 4: Easy follow-up of the evolution of the neuropathy.

SUDOSCAN FACILITATES PREVENTION, EVALUATION AND FOLLOW-UP OF DIABETES RELATED PERIPHERAL NEUROPATHY

A broad range of diseases

Sudomotor dysfunction is a common finding, and one of the earliest detectable abnormalities in a number of peripheral and autonomic neuropathies.

SUDOSCAN has been tested for small fiber nerve neuropathies in several diseases and compared to guidelines reference tests:

- **Diabetes**
- **Parkinson**
- **Chemotherapy induced polyneuropathy**
- **Familial amyloid polyneuropathy**
- **Fabry disease**

Diabetes

Diagnosing diabetic neuropathy

Diabetes is the primary identifiable cause of small fiber neuropathy. Early identification of small fiber neuropathy, which may be asymptomatic in up to 50% of diabetes patients, can reduce or delay diabetes complications by timely preventative treatment [4]. The sensitivity and specificity of SUDOSCAN scores to detect diabetic neuropathy were 78 and 92% when compared to NIS-LL [8].

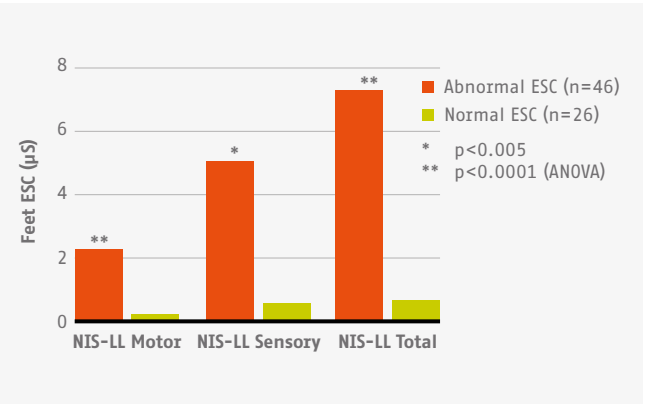


Figure 5: Mean Neuropathy Impairment Score within the Lower Limbs (NIS-LL) in diabetes patients with normal vs abnormal feet Electrochemical Skin Conductance (ESC).

Evaluate cardiac autonomic neuropathy

Cardiovascular Autonomic Neuropathy (CAN) is a common but often overlooked complication of diabetes. Studies have shown that SUDOSCAN may be used for early screening of CAN in everyday clinical practice before resorting to the more sophisticated and specific, but ultimately more time-consuming, Ewing tests [9].

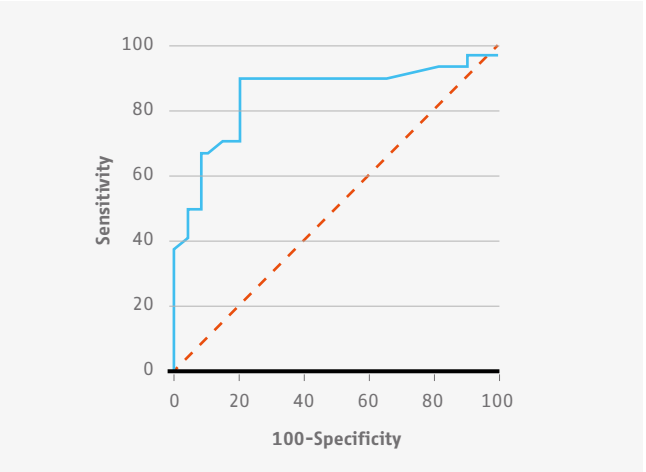


Figure 6: Graphic representation of the diagnostic performance of the SUDOSCAN 2 risk-score, E:I ratio,30:15 ratio and Blood Pressure (BP) change on standing by Receiver Operating Curve (ROC) analysis, using the low-frequency, power component during moderate activity at a threshold of 90 ms² (first quartile).

Follow-up

Diabetes treatment

In type 2 diabetes, sweat function improves with insulin therapy [10]. Improvement is reflected by increasing ESC values.

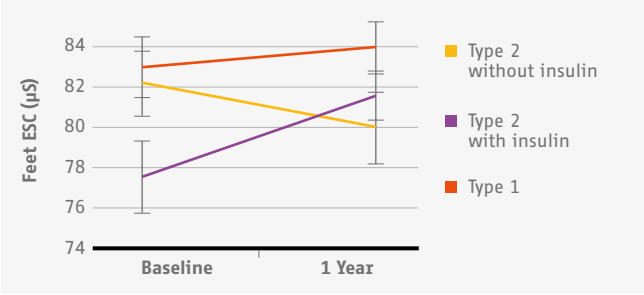


Figure 7: Changes in feet Electrochemical Skin Conductances (ESC) during one-year follow-up in patients with type 2 diabetes receiving insulin or not and patients with type 1 diabetes.

Lifestyle interventions

SUDOSCAN and VO_2-max have parallel evolution in response to lifestyle changes.

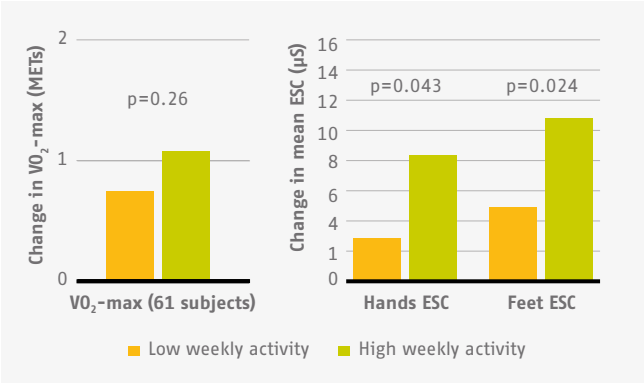


Figure 8: Improvements of VO_2-max and ESC in individuals undergoing a 12 months lifestyle intervention program [11].

Neurology

Positive comparison to IENFD

SUDOSCAN has demonstrated a diagnostic performance similar to Intra Epidermal Nerve Fiber Density (IENFD) [11].

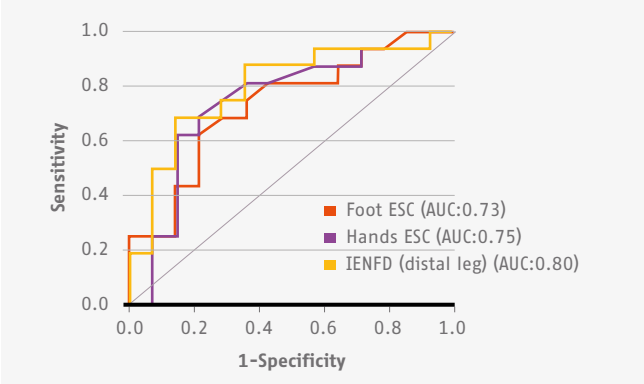


Figure 9: ROC curves for foot and hands ESC and IENFD at the distal leg (using Utah Early Neuropathy Score (UENS) as gold standard).

Oncology

Chemotherapy Induced Polyneuopathy (CIPN)

SUDOSCAN has results parallel to Total Neuropathy Score clinical version (TNSc). SUDOSCAN can easily be performed in the Oncology department, before and after treatment for an optimal follow-up of patients to detect Chemotherapy Induced Polyneuropathy (CIPN) [11].

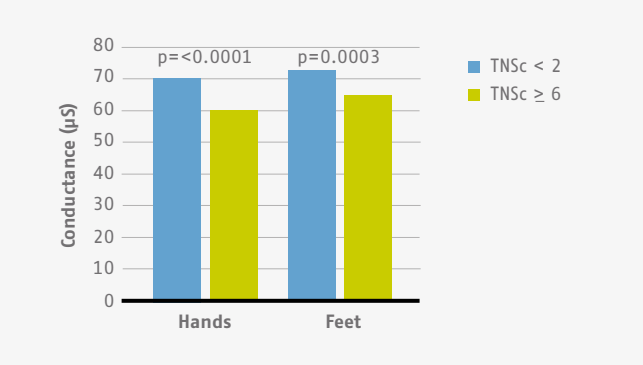


Figure 10: SUDOSCAN scores correlates to TNSc extreme values [11].

Comparison to other technologies

Detection of Small Fiber Polyneuropathy (SFPN)

SUDOSCAN demonstrates to be an easy, rapid and reliable method compared to other tests to detect Small Fiber Polyneuropathy [15].

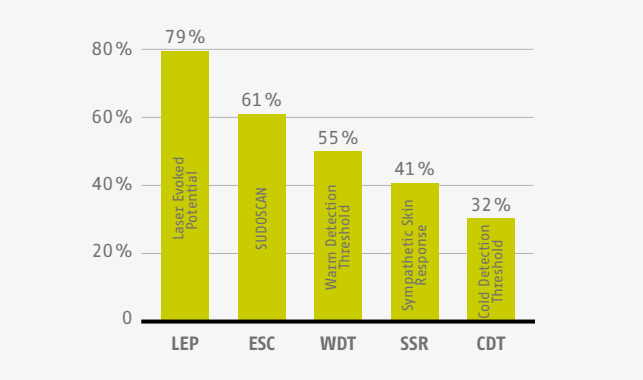


Figure 11: Diagnostic performance of Laser Evoked Potential (LEP), SUDOSCAN, Warm Detection Threshold, Sympathetic Skin Response (SSR) and Cold Detection Threshold for detecting Small Fiber Polyneuropathy (SFPN).

Amyloidosis

Included in the TTR-FAP Guidelines

SUDOSCAN has been included in the testing and management of individual at risk guidelines written by the ATTReuNet Network [17].

SUDOSCAN is a sensitive test to assess early autonomic dysfunction in TTR-FAP subjects and can easily be introduced as a routine assessment in this population [18].