A Framework for Screening and Early Multifactorial Interventions for Diabetic Peripheral Neuropathy

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ABSTRACT

Diabetic peripheral neuropathy (DPN) is common complication of both type 1 and 2 diabetes. It is a leading cause of lower limb amputation and disabling neuropathic pain. Amputations have a devastating impact not only on quality of life but also result in an alarmingly low life-expectancy which on average is only two years from the event. It also places a substantial financial burden on healthcare systems and society in general. Whilst the prevalence of blindness in working age adults in the UK is falling, diabetes-related amputations are rising not only in the UK but also globally. This article reviews innovative point-of-care devices that enable the early diagnosis of DPN and assesses the evidence for early multiple risk factor management strategies to improve DPN. Through this review we put forward a framework for screening and early multifactorial interventions as the best prospect for preventing/halting DPN, and it's devastating sequelae. Urgent action is needed to tackle the rising pandemic of lower limb amputations in people with diabetes.

KEYWORDS

Diabetic peripheral neuropathy, limb amputation, multifactorial intervention, diabetes mellitus.

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INTRODUCTION

Diabetic peripheral neuropathy (DPN) is the most common complication of both type 1 and 2 diabetes and occurs in over half of affected individuals [1,2]. It is a predominantly sensory neuropathy with autonomic nervous system involvement although there are often motor features with advancing disease. Diabetic peripheral neuropathy is the key initiating factor for the development of diabetic foot ulceration [3] and the commonest cause of non-traumatic lower limb amputations in the UK [4]. It can also cause impaired balance and gait [5,6] and distressing neuropathic pain that is often unresponsive to therapy [7]. The neuropathy is symmetrical and length-dependent, affecting the longest nerves, hence involves the feet first [8]. Unfortunately, the early manifestations of this insidious disease are often missed until the disease is well established, at which point it appears irreversible.

Each week in England there are around 140 amputations in people with diabetes and virtually all have DPN [9]. Amputation is not only devastating in its impact on the individual and their family but also leads to loss of independence and livelihood. In low-income countries the financial costs can be equivalent to 5.7 years of annual income, potentially resulting in financial ruin for these individuals and their families [10]. Diabetic peripheral neuropathy also places a substantial financial burden on healthcare systems and society in general. In the USA, the total annual cost of managing symptomatic DPN (painful) and its complications (foot ulcerations and lower limb amputations) was estimated to be between $4.6 and $13.7 billion, with up to 27% of the direct medical costs of diabetes attributed to DPN [11]. Urgent action is needed in order to address this growing global health problem. Unfortunately, only 50 per cent of people with diabetes who have an amputation survive for two years [12,13]. The most shocking fact of all, however, is that most of these amputations are preventable. It is estimated that 80% of amputations could be prevented through good multidisiplinary care which not only reduces amputation risk, but also dramatically impacts the rate of hospitalization, and indeed re-ulceration [3]. Moreover, the relative likelihood of death within five years following a lower extremity amputation secondary to a diabetic foot ulcer is greater than for prostate and breast cancer (Figure 1) [14,15]. Recent data from the Scottish Diabetes Register of 17,353 patients with diabetes and high-risk feet showed that those with healed ulcers had a 23% mortality within two years [16]. This shows that DPN patients with or without ulceration have high mortality rates.

This article reviews innovative point-of-care devices that enable the early diagnosis of DPN and assesses the evidence for early multiple risk factor management strategies to reduce the incidence and slow the progression of DPN. Through this review we put forward a framework

for screening and early multifactorial interventions as the best prospect for preventing/halting DPN, and it's devastating sequelae.

DIAGNOSIS OF DPN: CURRENT STATUS

Diabetic peripheral neuropathy is the strongest initiating risk factor for foot ulceration and amputations. Recent data from the UK-wide audit showed that nearly 100% of patients attending foot clinic have DPN. Nerve conduction studies are the current 'gold' standard for the diagnosis of DPN [17]. This robust measure also predicts foot ulceration and mortality [18]. However, they are labour intensive, time consuming and costly and impractical to implement in routine clinical care. Currently, there are no simple markers for early detection in routine clinical practice for DPN. The measures we use are crude and detect the disease very late in its natural history. Even the benefits gained by standardising clinical assessment using scored clinical assessments such as the Michigan Neuropathy Screening Instrument (MNSI) [19], the Toronto Clinical Neuropathy Score (TCNS) [20] and the United Kingdom Screening Test (UKST) [21], remain subjective, heavily reliant on the examiners' interpretations [22]. Bedside tests used to aid diagnosis of DPN such as the 10g monofilament [23,24], the Ipswich Touch Test [25] and vibration perception threshold using the Vibratip [26] or a tuning fork [27] are not only reliant on patients' subjective response but are mainly utilised to identify the loss of protective foot sensation and risk of ulceration [28]. As such, these tests tend to diagnose DPN when it is already well established [29]. Late diagnosis hampers the benefits of intensified multifactorial intervention at an early stage of the disease which could prevent the sequelae of DPN. Conversely, the situation is different for the detection of diabetic retinopathy using digital camera-based retinal photography or diabetic kidney disease using blood and urine tests. These developments led to the institution of a robust annual screening program in many countries that has led to significant reduction in blindness [30], such that retinopathy is no longer the commonest cause of blindness in working age adults [31,32] and reductions in end stage renal failure [33]. Unfortunately, by the time DPN is detected using these crude tests, it is often very well established and consequently impossible to reverse or even to halt the inexorable neuropathic process.

RECENT DEVELOPMENTS IN EARLY DIAGNOSIS OF DPN USING POINT-OF-CARE DEVICES (POCD)

Significant progress has been made to develop point-of-care devices (POCD) that are capable of diagnosing DPN early, before overt clinical signs are apparent. These devices are still predominantly at an experimental stage, although specialist centres are beginning to explore their utility in clinical practice [34]. Papanas et al have recently comprehensively reviewed

these devices [35]. Therefore, we will briefly outline the following devices which are most advanced in terms of their development and hold the most promise for adoption in clinical practice (Table 1): NeuroQuick [36], NeuroPAD [37], DPN-Check [38-40], Corneal Confocal Microscopy (CCM) [41,42] and Sudoscan [43,44].

1. DPN Check

The DPN-Check is a novel, user-friendly, handheld POCD that performs a sural nerve conduction study in three minutes. It is an acceptable proxy for standard nerve conduction studies which are time-consuming, expensive and often require patients to be seen in specialists clinics. The DPN check has been demonstrated to have excellent reliability with inter- and intra-observer intraclass correlation coefficients of between 0.83 and 0.97 for sensory nerve action potentials respectively [38]. It also has good validity with 95% sensitivity and 71% specificity when compared against reference standard nerve conduction study [38,39] for the diagnosis of DPN.

Nerve conduction studies, however, is only an assessment of large nerve fibre function. DPN, on the other hand, usually involves both small and large nerve fibres, with some evidence suggesting small nerve fibre involvement early in its natural history [45,46]. Small nerve fibres constitute 80-91% of peripheral nerve fibres and control pain perception, autonomic and sudomotor function. Although intraepidermal nerve fibre density measurement from lower limb skin biopsy is considered the gold standard for the diagnosis of small fibre neuropathy [47,48] it is invasive and hence not suitable for routine screening. However, a number of POCDs have been developed to assess small fibre dysfunction. These include:

2. NeuroQuick

Thinly myelinated Aδ and unmyelinated C-fibres are small calibre nerves that mediate thermal sensation and nociceptive stimuli. Quantitative sensory testing of thermal discrimination thresholds is a non-invasive test used to examine impaired small nerve fibre function. NeuroQuick is a handheld device for quantitative bedside testing of cold thermal perception threshold. It allows near patient assessment of small fibre dysfunction avoiding the use of time-consuming and expensive quantitative sensory testing equipment in a laboratory. To date, one published clinical validation study has been performed in a diabetic population which suggests it is a valid and reliable screening tool for the assessment of small fibre dysfunction [36]. Use of NeuroQuick was more sensitive in detecting early DPN compared to the traditional bedside screening tests such as the tuning fork or elaborate thermal testing [36]. However, it

is a psychophysical test that relies on the cognition/attention of the patient. Furthermore, the coefficients of variation for repeated NeuroQuick measurements ranged between 8.5% and 20.4% [36]. Further studies are required to demonstrate whether the NeuroQuick is a useful screening tool to detect small fibre dysfunction in DPN.

3. NeuroPad

This is a 10-minute test which measures sweat production on the plantar surface of the foot. It is based on a colour change in a cobalt compound from blue to pink which produces a categorical output with a modest diagnostic performance for DPN compared to electrophysiological assessments. A number of clinical validation studies [49-51] have been conducted which demonstrates low sensitivity for large fibre neuropathy (50-64%) but much higher sensitivity for small fibre neuropathy (80%) [52]. Neuropad has also shown good reproducibility with intra- and inter-observer coefficient of variation between 4.1% and 5.1% [53].. No training is required to administer Neuropad, nor does it require responses from the patient. Hence, some argue that this method of assessment may be more suitable for screening in community settings and those with cognitive or communication difficulties who have to respond to other methods of assessment. However, there is insufficient evidence to support the use of Neuropad in patients in whom 10 g monofilament testing for diabetic peripheral neuropathy is not possible [54].

4. Sudoscan

Sudomotor function has been proposed as a surrogate marker for the small fibre involvement in DPN [43,44,61]. Sudoscan, provides a quantitative measurement of sudomotor function within 3-minutes. Its measurement is based on an electrochemical reaction between electrodes and chloride ions, after stimulation of sweat glands by a low-voltage current (<4volts) [62]. A measurement of electrochemical skin conductance (ESC) for the hands and feet, that are rich in sweat glands, is generated from the derivative current associated with the applied voltage [62]. Sensitivity and specificity of foot ESC for classifying DPN were 87.5% and 76.2%, respectively [44]. The area under the ROC curve (AUC) was 0.85 [44]. The reproducibility was also tested in T2DM with feet and hands ICC 0.95 (0.89–0.98) and 0.88 (0.74–0.96) respectively [63].

In summary, the sensitivity of POCDs are acceptable and a combination of devices assessing both small and large fibre function should be used for detecting DPN. However, there is high heterogeneity and participant selection bias in most of the studies. Further studies are needed to evaluate the performance of each POCDs based on Wilson criteria for screening of

undiagnosed DPN at the population level [64]. Prospective studies of hard endpoints (e.g. foot ulcerations and lower limb amputations) are also necessary to ensure that the benefits of screening are important for patients. The cost-effectiveness of implementing screening using these devices also needs to be carefully appraised. POCDs provide rapid, non-invasive tests that could be used as an objective screening test for DPN in busy diabetic clinics, ensuring adherence to current recommendation of annual assessment for all people with diabetes that remains unfulfilled.

MODIFIABLE RISK FACTORS FOR DPN INCIDENCE AND PROGRESSION

Early detection of DPN can only be advocated if there is robust evidence that early treatment or intervention results in better outcomes than at a later stage. Diabetic peripheral neuropathy is a culmination of a complex interaction of several aetiologically linked pathophysiological processes –many not fully understood. Although hyperglycaemia and duration of diabetes play an important role in DPN, other risk factors have also been identified [65,66]. The EuroDiab Prospective Complications study in type 1 diabetes demonstrated that the incidence of DPN is associated with other potentially modifiable cardiovascular risk factors, including a raised triglyceride level, hypertension, obesity and smoking (Figure 2), [67]. More recently, the ADDITION study also implicated similar cardiovascular risk factors in the pathogenesis of DPN in type 2 diabetes [REF Andersen ST, Witte DR, Dalsgaard EM, Andersen H, Nawroth P, Fleming T, Jensen TM, Finnerup NB, Jensen TS, Lauritzen T, Feldman EL. Risk Factors for Incident Diabetic Polyneuropathy in a Cohort With Screen-Detected Type 2 Diabetes Followed for 13 Years: ADDITION-Denmark. Diabetes care. 2018 Feb 26:dc172062].

Here we discuss potentially modifiable risk factors that affect the incidence or progression of DPN:

1) Hyperglycaemia

Chronic hyperglycaemia plays a key role in the pathogenesis of DPN [68,69]. Through several disturbances in the metabolic pathways, hyperglycaemia leads to abnormalities in nerve polyol, hexosamine and protein kinase C pathways [70]. This triggers the release of proinflammatory cytokines [poly ADP-ribose polymerase (PARP)], the accumulation of advanced glycation end products (AGEs) and generation of reactive oxygen species [70]. Simultaneously, microangiopathic changes of the vasa nervorum result in neuroischaemia [71]. This is further exacerbated by impaired endothelial nitric-oxide mediated vasodilatory mechanisms (nitrosative stress) [72]. Separately and in concert, these glucotoxic metabolic and ischaemic changes lead to DPN by producing nervous system oxidative stress and apoptosis of both neurons and supporting glia.

In the Diabetes Control and Complications Trial (DCCT) intensive insulin treatment in T1DM reduced the risk of DPN (78% relative risk reduction) [73,74]. In the Epidemiology of Diabetic Complications (EDIC) study, at the 14 years after DCCT closeout, although DPN progressed substantially in both treatment groups, its prevalence and incidence remained significantly lower in the former intensively treated group [75]. A recent Cochrane review, however, indicated that the evidence for the benefit of intensive glucose control in T1DM is mainly from studies in younger patients at early stages of the disease and that the effects of tight blood glucose control seem to become weaker once complications are established [76]. On the other hand, in T2DM improving glycaemic control alone does not have the same impact on reducing the incidence of DPN (5-9% relative risk reduction) [76]. Even when trials demonstrate tighter glucose control might have a beneficial impact in preventing progression of DPN in T2DM e.g. the ACCORD study [77], confusion arises when it is reported that a self-reported history of DPN at baseline was associated with a higher risk of mortality with intensive glycaemic treatment [78]. However, in this study, neither MNSI-documented DPN nor history of amputation was associated with a differential effect on mortality between the two treatment arms. This discrepancy suggests the different methods of detecting DPN may identify different populations and merits further investigation. Similar discordance among various indices of DPN in their strength for predicting outcome was also apparent in the DIAD study [79]. Several other long term studies of multi-factorial cardiovascular risk intervention in T2DM [80-83] and pre-diabetes [84] have failed to slow the progression or reduce the incidence of DPN. It must be emphasised that DPN was not a primary outcome in these trials and its inclusion appears to be an afterthought, as inconsistent and insensitive measures to detect and monitor DPN were employed.

In contrast, when appropriate DPN clinical endpoints are used the outcomes appear more promising. The first randomised controlled trial that demonstrated the benefit of intensive management on the incidence of DPN in T2DM was the Kumamoto trial [85]. This study showed significant improvement in nerve conduction parameters, albeit of the median nerve, in the intensively treated group demonstrating the importance of choosing the most appropriate surrogate marker of DPN. Nearly 50 years ago, a smaller study also utilizing nerve conduction studies demonstrated that DPN is reversible in newly diagnosed T2DM patients with appropriate treatment [86]. Moreover, in T2DM the choice agents used to achieve targets may also be as important as the glucose targets themselves. The BARI 2D trial demonstrated that the cumulative incidence of DPN was significantly lower when insulin-sensitizing agents (metformin, thiazolidinediones) were used compared to an insulin-providing (sulphonylureas, insulin) strategy [87].

2) Dyslipidaemia

Observational and cross-sectional studies have demonstrated, to varying degrees, an association between hyperlipidaemia and DPN [88]. The strongest evidence, however, is for the association of elevated levels of triglycerides and DPN [89]. In T2DM there was a graded relationship between triglyceride levels and the risk of lower-limb amputations [89]. Another study demonstrated that hypertriglyceridaemia was an independent risk factor for loss of sural (myelinated) nerve fibre density supporting the concept that hyperlipidaemia is instrumental in the progression of DPN [90]. In addition to hypertriglyceridemia, low-level of HDL cholesterol has been reported as an independent risk factor for DPN [88]. However, clinical studies investigating the effects of statins on the development of DPN are far from conclusive. This is partly because several large statin studies that included participants with diabetes did not report data on the development of microvascular disease [91-93] let alone DPN. The Freemantle Diabetes Study, an observational study with cross-sectional and longitudinal analysis, suggested that statin or fibrate therapy may be associated with a reduced risk of DPN in T2DM [94]. Two subsequent, relatively small, randomised clinical studies have reported improvements in nerve conduction parameters of DPN following 6 to 12 weeks of statin treatment [95,96]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study has since, demonstrated that fibrates are beneficial in preventing microvascular complications (retinopathy and nephropathy) and non-traumatic lower limb amputations but DPN outcomes have not been reported [97]. More recently, a patient registry study from Denmark, found that the use of statins before diagnosis of incident diabetes was protective against the development of DPN. In summary, whether lipid lowering treatment reduces the risk of DPN —a possibility raised by these data—will need to be addressed in other studies preferably in randomised controlled trials.

3) Hypertension

An association between hypertension and DPN has been demonstrated in several observational studies in both T2DM [98,99] and T1DM [100]. There is some preliminary evidence from relatively small randomised control trials of improvements in DPN based on clinical and nerve conduction parameters following antihypertensive treatment with angiotensin converting enzyme (ACE) inhibitors [101] and calcium channel blockers [102].

4) Lifestyle

Several studies have revealed an association between obesity and DPN even in the presence of normoglycaemia [103-106]. Not surprisingly, DPN prevalence increases in obese patients

with prediabetes and diabetes [107]. Subsequent studies appear to demonstrate that adopting a healthy lifestyle incorporating a balanced diet, regular aerobic and weight-resistance physical activities may reverse the process, particularly if they are undertaken at an early stage of DPN [108-110]. A randomised control study of a 2.5-hour, weekly supervised treadmill exercise and dietary intervention programme aimed at normalising body mass index or losing 7% baseline body weight in T2DM demonstrated significant improvement in markers (intraepithelial nerve fibre density and regenerative capacity) of DPN [111]. However, once DPN is established, restoration of normal weight did not show significant improvement [111]. A variety of different dietary interventions have been examined including a low fat, low calorie diet in the DPP study [112] and a Mediterranean diet [113] but presently there is no consensus on a specific regime. Once again, these studies suggest that if the disease is identified early and the appropriate surrogate marker is used, DPN can be reversed by lifestyle intervention.

5) Multiple risk factor lowering interventions

Based on the studies above, there is some evidence to suggest targeting lifestyle and individual risk factors can improve DPN. Disappointingly, however, several large intervention studies targeting multiple risk factors (UKPDS [114], STENO-2 [115], ADDITION [116]) failed to show a reduction in DPN despite clear benefits in renal and retinal complications. The best possible explanation is that the methods used to diagnose/quantify DPN lacked the necessary sensitivity or reliability to diagnose/quantity DPN let alone examine differences between study groups. The heterogeneity in effect size estimates for DPN in these studies supports this view. Furthermore, in the ADDITION study there were only minor differences in CVD risk between the standard and intensive treatment arms throughout the trial. Some would Nevertheless, the STENO-2 study did show that 4 years of intensive multifactorial treatment slowed the progression of autonomic neuropathy (OR, 0.32; 0.12-0.78) [115]. More recently, publication of the 21-year follow-up showed a reduction in the progression to autonomic neuropathy (HR, 0.59; 95% CI, 0.40-0.89) in the intensive treatment arm [117]. This data suggests a long-term benefit of earlier multifactorial intervention i.e. a legacy effect. Further research is needed to re-examine the impact of multifactorial interventions upon DPN using more reliable, reproducible and sensitive measures of DPN. However, some would argue that further efficacy studies of multiple risk factor interventions may not be feasible due to the anticipated improvement risk factors in the standard treatment group as seen in the ADDITION Study. In reality, however, overall standard of care remains extremely poor and these targets are not being achieved in the majority of patients in most countries. In this context, a prospective study comparing standard arm with a more intensive target driven approach using sensitive

measures to detect differences may be justified as this might be a robust rationale for a change in practice.

In summary, although the risk factors for DPN are well recognised, to-date only small-scale intervention studies targeting these risk factors have been conducted which have used DPN measures that are 'fit-for-purpose'. These studies suggest that such interventions are capable of delaying the onset and slowing the progression of DPN. Furthermore, once DPN has reached at a stage detectable by conventional bed-side tools, it might be too advanced for any intervention to reverse/halt the process. Unfortunately, despite several clinical trials [118], there has been relatively little progress in the development of disease-modifying treatments [119-121] despite some advances in the management of symptoms in painful DPN [122-124]. Most of the current evidence points to multifactorial risk reduction strategies, including structured exercise and education on lifestyles, a healthy diet, smoking cessation and obesity management as the best way to prevent the development and progression of DPN, particularly at the stage of pre-diabetes and early diabetes [108,109]

FUTURE PERSPECTIVES

Ultimately, the prevention of DPN will have the greatest impact on reducing amputations dramatically as 90% of patients attending the diabetic foot clinic and virtually all diabetes amputees have DPN [9]. Clearly, in those with established DPN careful foot ulcer risk assessment (including peripheral vascular status, deformity etc.) and appropriate management (education, footwear, podiatry) and risk factor management is warranted.

Currently, a robust system of an annual foot screening, yet alone multifactorial risk factor interventions, for all people with diabetes, as advocated by the American Diabetes Association and Diabetes UK has not been implemented systematically. This was confirmed by the UK National Diabetes Audit (2016) [125] and the US National Health and Nutrition Examination Surveys (NHANES) [126]. These showed that the attainment of recommended vascular risk management targets was alarmingly low between 19-40%. More worryingly, only 30% adults aged 50 years or less achieved these targets. The National Diabetes Foot Care Audit (2014-17) showed a high prevalence of diabetic foot ulcers where 30% of patients self-presented despite an 85% attendance of annual foot surveillance screening. In addition, foot surveillance screening did not identify a third of individuals who subsequently developed diabetic foot ulcers [127]. This suggests that 1) the current process of care is inadequate (involving multiple visits to different members of the clinical team who do not have specialist training to assess the level of risk and provide advice/education and signpost patients to receive the appropriate

interventions/treatment) [128] and 2) the methods used to screen for DPN are insensitive and/or lack reliability to accurately measure risk of developing foot ulceration.

To improve clinical outcomes in DPN as in retinopathy and nephropathy, there is an urgent need to: 1) diagnose DPN early before overt clinical signs are apparent and 2) assess disease progression accurately in order to effectively reduce morbidity and 3) reliably inform patients of their underlying risk of foot ulceration. A 'One-Stop service' is needed to screen for complications in one visit (Figure 3). Foot screening could be performed by a specialist podiatrist to assess the level of foot ulcer risk and manage patients appropriately, in order to prevent foot ulceration and amputation. In addition, DPN screening can be performed using POCDs in patients with normal physical examination (e.g. 10g monofilament, 128hz tuning fork, Ipswich touch test, Vibratip) to identify early sub-clinical disease. One methodology that has attracted significant interest, backed by a large body of evidence and may have future potential is corneal confocal microscopy (CCM). This is a non-invasive ophthalmic application that measures various structural parameters (e.g. branch density and length) of small corneal nerve fibres [55,56]. Currently, CCM is not a POCD and is mainly used in specialist centres. Nevertheless, it would suit widespread application given its easy application for patient follow-up.

A 'One-Stop' service for screening of complications was recently piloted in retinal screening clinics in a hospital and community setting [129]. A trained podiatrist performed detailed assessments of foot ulcer risk and used combined small and large nerve fibre assessments (NC-stat DPN-check and Sudoscan) for the diagnosis of subclinical DPN. This pilot study also examined the feasibility and acceptability of a "one-stop clinic" for combined screening for all microvascular complications. Combined eye, renal, DPN and foot ulcer risk screening was found to have a high uptake, reduced clinic visits, led to an early diagnosis of DPN (93.2% sensitivity for the diagnosis of DPN) and unmasked new painful DPN. This is an effective model for the early diagnosis of DPN and management of foot complications. Future studies should now examine if intensive cardiometabolic risk factor management targeted at patients with incipient/sub-clinical DPN identified using POCDs can prevent clinical DPN or halt disease progression.

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Duality of Interest

KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme.

MJD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and Investigator-initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly

Figures:

Figure 1: Relative 5-year survival (2005-2009) after diabetic foot ulcer post lower extremity amputation (LEA) [14] and the most common cancers. * Cumulative 10-year survival (1995-2005) following diabetic foot ulcer [15]. Cancer survival data from 2008-2014 taken from the Surveillance, Epidemiology and End Results Program (SEER) Cancer Statistics Review https://seer.cancer.gov/statfacts/html].

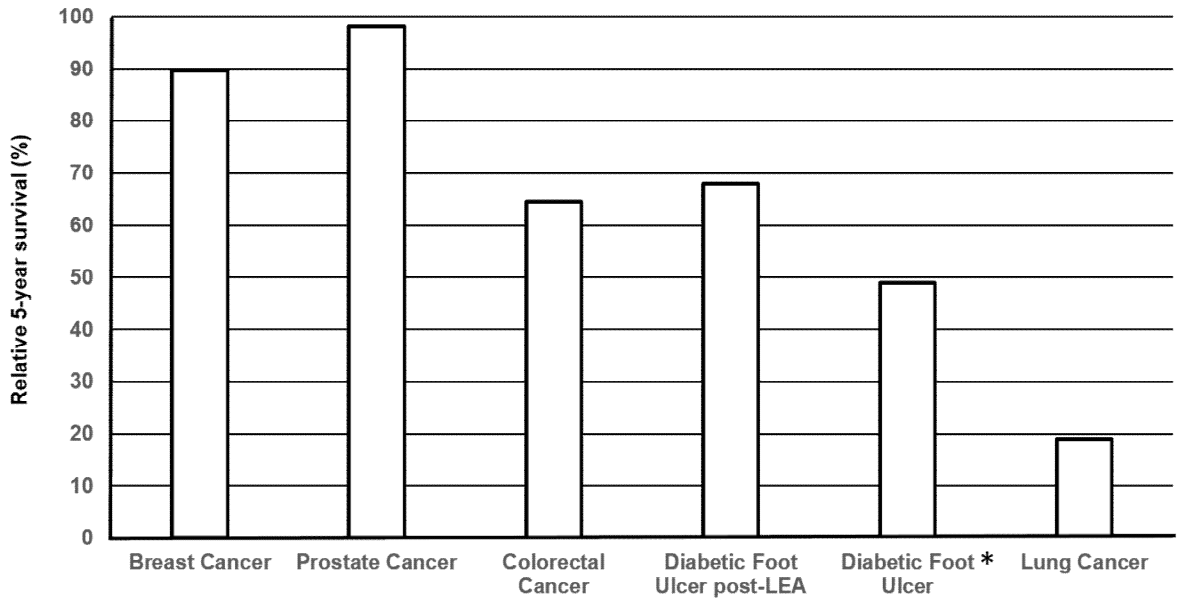


Figure 2: Standardised odds ratios and 95% confidence intervals (CI) for associations between key risk factors and the incidence of diabetic peripheral neuropathy. Adapted from [67].

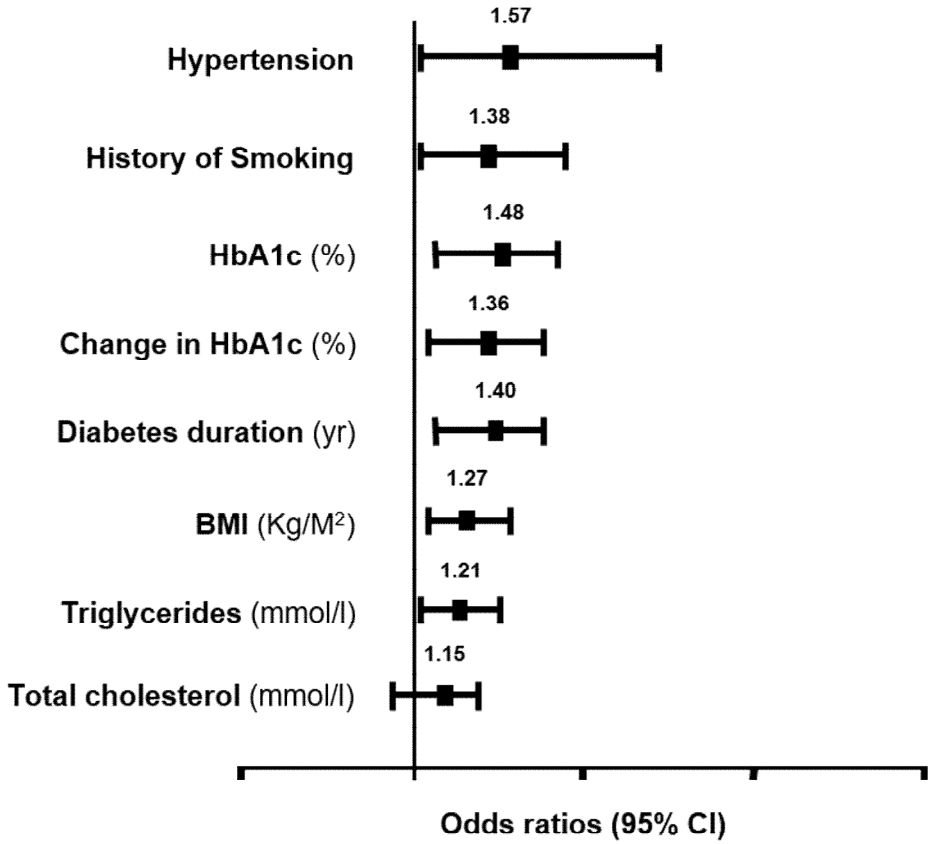
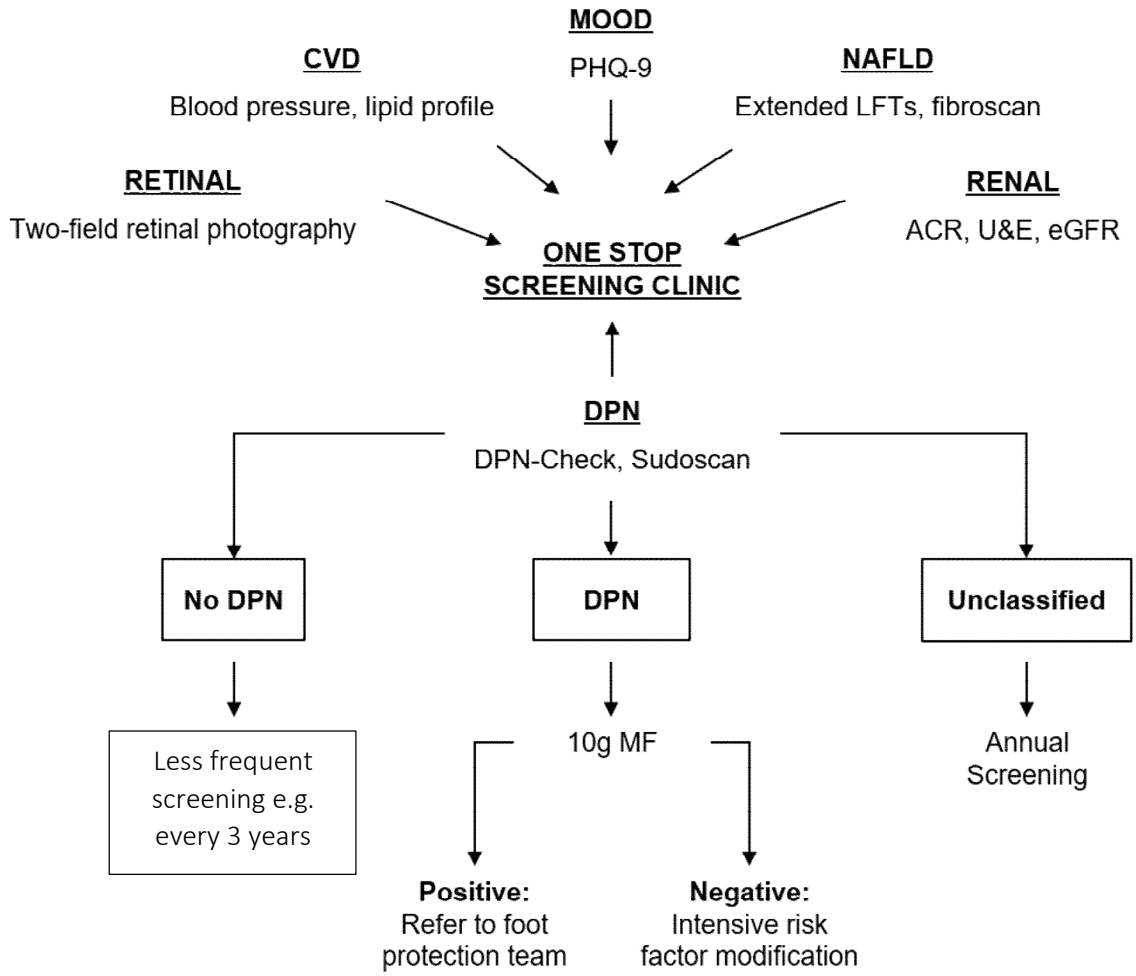


Figure 3: Proposed assessments for One-Stop Screening clinic for diabetic complications including proposed diabetic peripheral neuropathy (DPN) diagnostic algorithm for the clinical application of point of care devices (DPN-Check and Sudoscan). CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease; LFts, liver function tests; ACR, urine albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; PHQ-9, Patient Health Questionnaire- 9; 10g MF, 10 gram monofilament.



Tables:

Table 1: Clinical utility of devices used for the diagnosis of DPN (adapted from Papanas et al) [33]. *Intraclass correlation coefficient using an automated algorithm; N/A not available.

Devices	**Function**	**Fibres Assessed**	**Validated against**	**Sensitivity (%) /Specificity (%)**	**Intra/Inter Observer ICC**	**Early Diagnosis**
DPN Check [39,129,130]	Sural Sensory Nerve function	Large Aα/Ab fibres	Nerve conduction studies, Standardised clinical examination, Laser Doppler LDI flare	84.3-90.5/68.3-86.1	0.94-0.97/0.79-0.83	Yes
NeuroQuick [36]	Thermal Sensory Perception	Small Aδ/C fibres	Nerve conduction studies, Standardised clinical examination, Vibration perception threshold,	N/A	0.75-0.95/N/A	Yes
NeuroPad [53,54]	Sudomotor Function	Small C fibres	Nerve conduction studies, Standardised clinical examination, Vibration perception threshold, Skin biopsy IENFD	65.1-100/32-78.5	4.1/5.1	Yes
CCM [57-60,131]	Corneal Nerve Fibre Morphometry	Small C fibres	Nerve conduction studies, Standardised clinical examination, Vibration perception threshold, Skin biopsy IENFD	82/69	0.66-0.95/0.54-0.93 1.0*	Yes

Sudoscan [43,63]	Sudomotor Function	Small C fibres	Nerve conduction studies, Standardised clinical examination, Thermal Perception Threshold	87.5/76.2	0.88/0.95	Yes

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