Going the Distance

to Assess, Diagnose, and Treat Diabetic Microvascular Complications

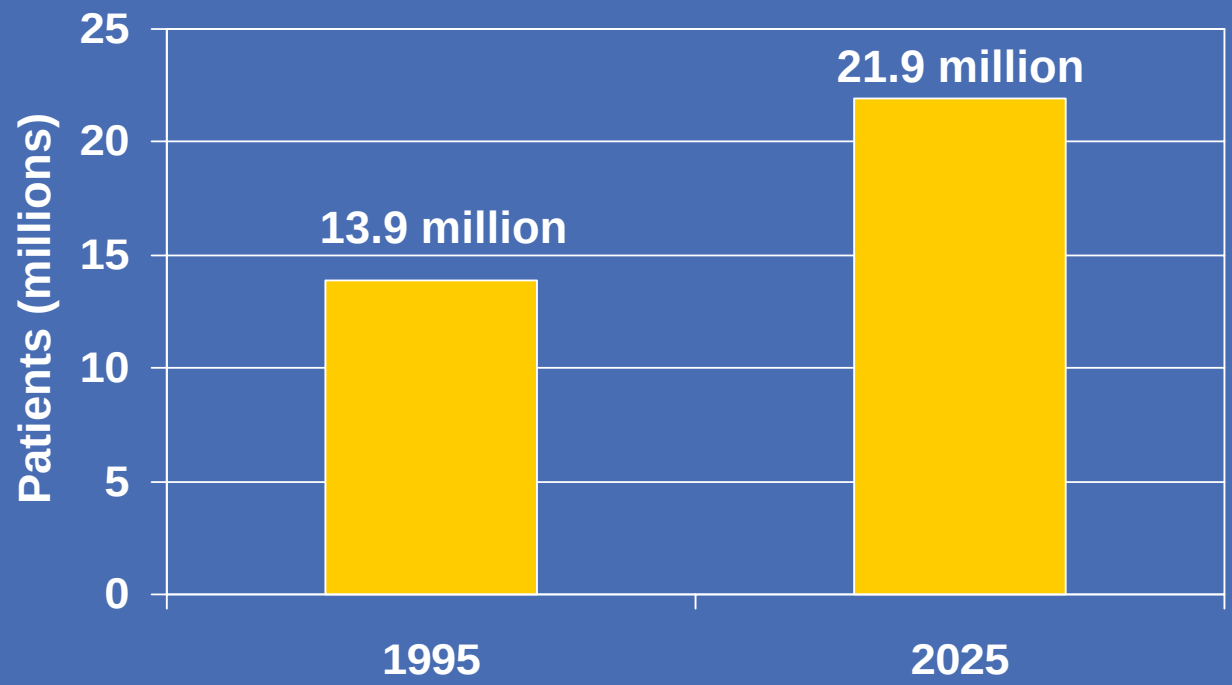
How Far Would You Go To Address Diabetic Microvascular Complications?

Diabetes is a Significant Healthcare Problem in the United States

- Over 18 million Americans have diabetes
- Up to 30% of diabetes cases have not been diagnosed
- 1.3 million new cases are diagnosed each year in the US
- Economic burden of $132 billion per year (2002 healthcare costs)
  - Approximately $7333 per patient

American Diabetes Association. Available at: http://www.diabetes.org/diabetes-statistics/national-diabetes-fact-sheet.jsp.
Hogan P, et al. *Diabetes Care*. 2003;26:917-932.
World Health Organization. Available at: http://www.wpro.who.int/pdf/rcm51/rd/bhcp-4b.pdf. Accessed November 13, 2003.

Diabetes is a Growing Healthcare Epidemic



Hogan P, et al. *Diabetes Care*. 2003;26:917-932.
King H, et al. *Diabetes Care.* 1998;21:1414-1431.

Long-term Diabetic Complications are Devastating

- **Diabetic Macrovascular complications**
  - **Coronary artery disease**
  - **Cerebrovascular disease**
  - **Peripheral vascular disease**

- **Diabetic Microvascular complications**
  - **Diabetic Nephropathy**
  - **Diabetic Neuropathy**
  - **Diabetic Retinopathy (including Diabetic Macular Edema)**

Rousch JEB. *J Clin Invest*. 2003;112:986-988.
Sheetz MJ, King GL. *JAMA*. 2002;288:2579-2588.
Williams R, et al. *Diabetologia*. 2002;45:S13-S17.

Impact of Diabetic Microvascular Complications in the United States

- **Diabetic Nephropathy (DN)**
  - **10 to 21%** of all people with diabetes have nephropathy
  - Leading cause for kidney dialyses or transplants: 129,183/year
    - 50% (dialysis) attributed to Type 2 patients due to greater prevalence
- **Diabetic Peripheral Neuropathy (DPN)**
  - **60 to 70%** of people with diabetes have mild to severe forms of nerve damage
  - Leading cause for lower-limb amputations: 82,000/year
- **Diabetic Retinopathy (DR)**
  - During the first two decades of disease, nearly all Type 1 patients **and >60%** of type 2 patients have retinopathy
  - Leading cause of new cases of blindness: **12,000-24,000/year**

American Diabetes Association. Accessed March 17, 2004, from http://diabetes.org/diabetes-statistics/kidney-disease.jsp
American Diabetes Association. *Diabetes Care*. 2004;27(suppl 1):S79-S83;
Centers for Disease Control and Prevention. Accessed March 17, 2004, from http://www.cdc.gov/diabetes/pubs/estimates.htm#complications
Fong DS, et al. *Diabetes Care*. 2004;27(suppl 1): S84-87.

Diabetic Nephropathy

Progression of Diabetic Nephropathy

	Chronology	Pathology	Diagnosis and Screening
Stage 1	Present at diagnosis of diabetes	Increased kidney and glomerular size	Mean arterial BP normal
Stage 2	Within first 5 years	Basement membrane thickening	Normal BP or slight elevation (1 mm Hg/year)
Stage 3	After 6-15 years (~35% patients)	Further basement membrane thickening, mesangial expansion	UAE = 20-200 µg/day BP >3 mm Hg/year
Stage 4	After 15-25 years (~35% of patients)	Clear, pronounced abnormalities proteinuria	GFR decline ~10 mL/min/year BP >5 mm Hg/year
Stage 5	ESRD after 25-30 years	Glomerular closure, advanced glomerulopathy	GFR <10 mL/min BP >5 mm Hg/year

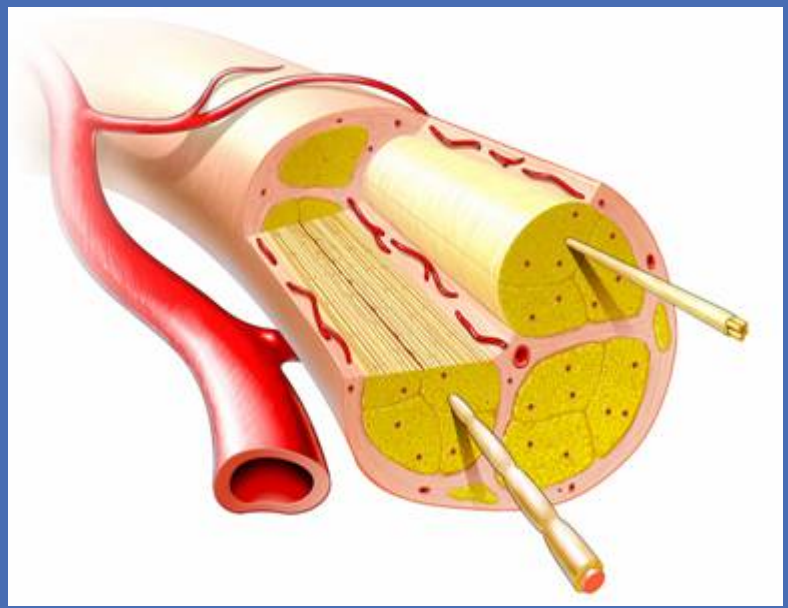
UAE = Urinary albumin excretion

Mogensen CE. *Diabetologia*. 1999;42:263-285.

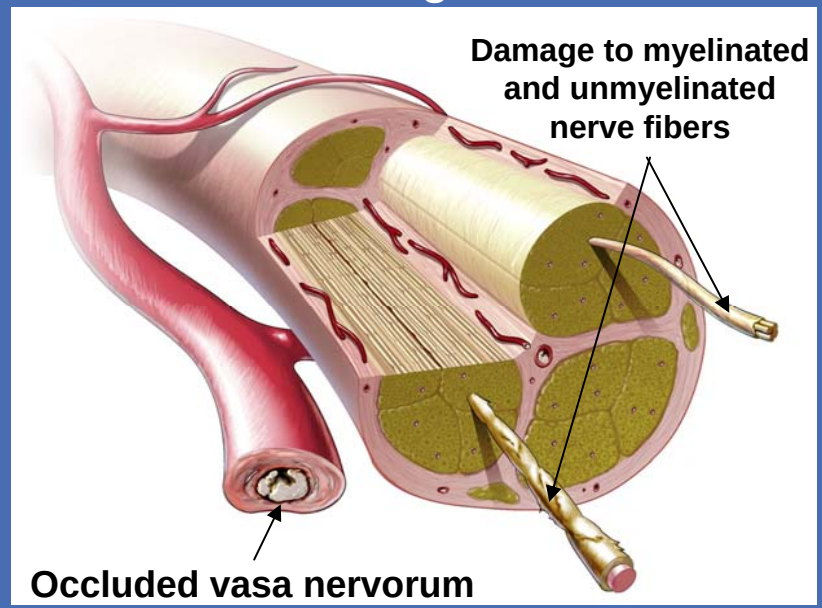
Diabetic Peripheral Neuropathy

Microvascular Damage Leads to Diabetic Peripheral Neuropathy (DPN)

Normal nerve



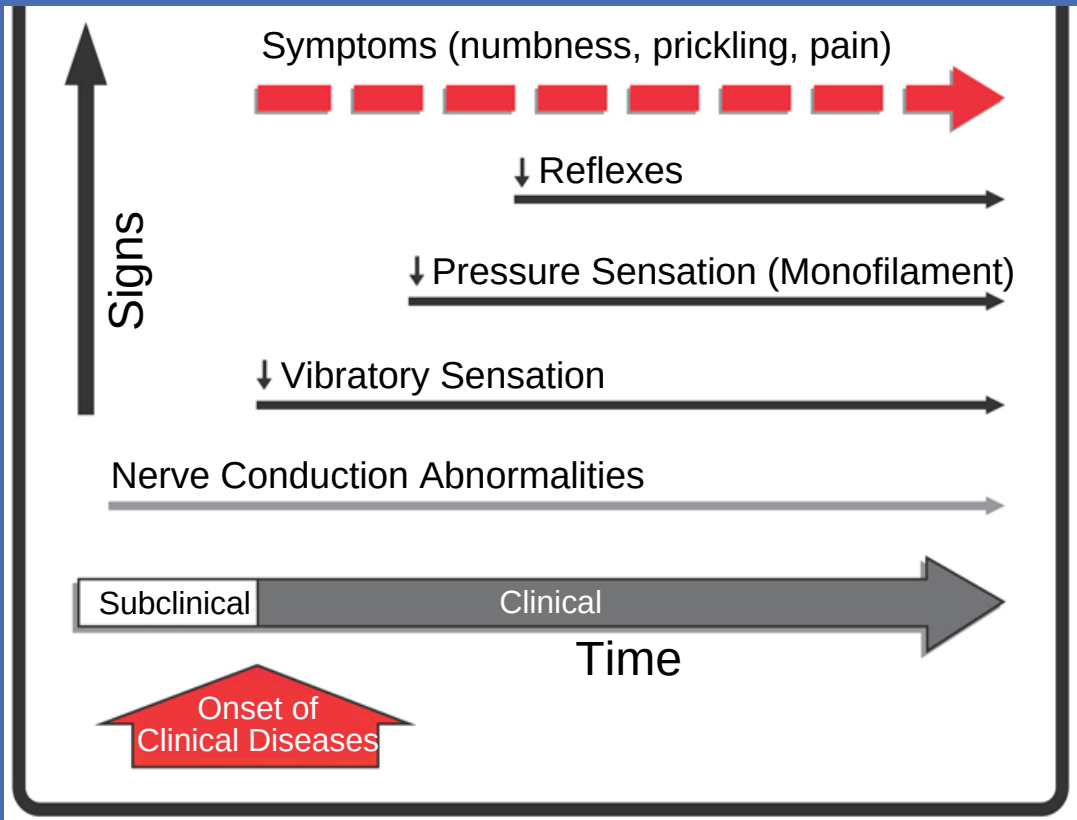
Damaged nerve



- Examination of tissues from patients with diabetes reveals capillary damage, including occlusion in the vasa nervorum
- Reduced blood supply to the neural tissue results in impairments in nerve signaling that affect both sensory and motor function

Dyck PJ, Giannini C. *J Neuropathol Exp Neurol*. 1996;55:1181-1193.
Sheetz MJ, King GL. *JAMA*. 2002;288:2579-2588.

Diabetic Peripheral Neuropathy Can Progress Over Time



- Symptoms may occur any time and intermittently
- Patients may or may not have symptoms of diabetic peripheral neuropathy
- Patients frequently do not report symptoms to their physicians until the symptoms are severe
- The majority of signs of diabetic peripheral neuropathy are not evident at the onset of diabetes

Adapted from ADA. *Diabetes Care*. 2003;26:S33-S50; Abbott CA, et al. *Diabetes Care*. 1998;21:1071-1075; Armstrong DG, et al. *Arch Intern Med*. 1998;158:289-292; Armstrong DG, et al. *Ostomy Wound Manage*. 1998;44:70-76; Carrington AL, et al. *Diabetes Care*. 2002;25:2010-2015; Feldman EL, et al. *Diabetes Care*. 1994;17:1281-1289; Shearer A, et al. *Diabetes Care*. 2003;26:2305-2310; Veves A, et al. *Diabet Med*. 1991;8:917-921.

Symptoms and Signs of Diabetic Peripheral Neuropathy

Symptoms

- Numbness or loss of feeling (asleep or “bunched up sock under toes” sensation)
- Prickling/Tingling
- Aching Pain
- Burning Pain
- Lancinating Pain
- Unusual sensitivity or tenderness when feet are touched (allodynia)

Signs

- Diminished vibratory perception
- Decreased knee and ankle reflexes
- Reduced protective sensation such as pressure, hot and cold, pain
- Diminished ability to sense position of toes and feet

Symptoms and signs progress from distal to proximal over time

Diabetic Peripheral Neuropathy Severity Scale

Rating	Description
0	No neuropathy
1	Subclinical diabetic peripheral neuropathy
2a	Clinical diabetic peripheral neuropathy with symptoms, mild to moderate
2b	Clinical diabetic peripheral neuropathy insensate foot, loss of feeling/negative symptoms
3	Disability/late stage

Adapted from Dyck PJ. Muscle Nerve 1988; 11:21-32.

Effects of Diabetic Peripheral Neuropathy

1

Early tissue damage

2

Clawing toes, callus, superficial ulceration

3

Plantar ulcer, callus

4

Calluses scraped away revealing ulcers

Images: [1,4]Edward J Bastyr, III, MD;
[2,3]Rayaz A Malik, MBChB, PhD, MRCP.

Diabetic Retinopathy
(Including Diabetic Macular Edema)

Diabetic Retinopathy: A Progressive Disease

	Preclinical	Nonproliferative Diabetic Retinopathy	Proliferative Diabetic Retinopathy	Diabetic Macular Edema
Symptoms	None	None, or blurred vision and glare	None, or reduced vision or floaters	None, or blurred vision
Clinical signs indicating need for referral	• Normal appearing retina	• Retinal vasodilation • Microaneurysms • Nerve fiber layer infarcts • Intraretinal hemorrhages • IRMAs • Venous bleeding	• Retinal vasodilation • Beading • IRMAs • Neovascularization of optic disc, retina, and/or iris	• Swelling of retina due to leaky capillaries • Increased capillary leakage • Fluid accumulation in retinal layers

Flynn HW, Smiddy WE, eds. *Diabetes and Ocular Disease: Past, Present, and Future Therapies*. AAO Monograph No. 14. San Francisco: The Foundation of the American Academy of Ophthalmology; 2000.

American Academy of Ophthalmology (AAO): Staging of Diabetic Retinopathy

Disease Severity Level	Observable (Dilated Ophthalmoscope)
No apparent retinopathy	No abnormalities
Mild Non-Proliferative Diabetic Retinopathy	Microaneurysms only
Moderate Non-Proliferative Diabetic Retinopathy	More than just microaneurysms but less than severe nonproliferative diabetic retinopathy
Severe Non-Proliferative Diabetic Retinopathy	Any of the following - More than 20 intraretinal hemorrhages in each of 4 quadrants - Definite venous beading in 2+ quadrants - Prominent IRMA in 1+ quadrant and no signs of proliferative diabetic retinopathy
Proliferative Diabetic Retinopathy	One or more of the following - Neovascularization - Vitreous/peretinal hemorrhage

American Academy of Ophthalmology, October, 2002.

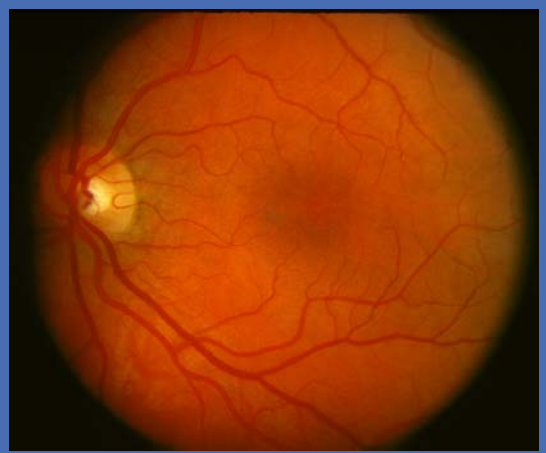
AAO Staging of Diabetic Macular Edema

Disease Severity Level	Observable (Dilated Ophthalmoscope)
No diabetic macular edema present	No retinal thickening or hard exudates in posterior pole
Diabetic macular edema present	**Mild Diabetic Macular Edema** Some retinal thickening or hard exudates in posterior pole but distant from the center of the macula
	Moderate Diabetic Macular Edema Retinal thickening or hard exudates approaching the center of the macula but not involving the center
	Severe Diabetic Macular Edema Retinal thickening or hard exudates involving the center of the macula

American Academy of Ophthalmology, October, 2002.

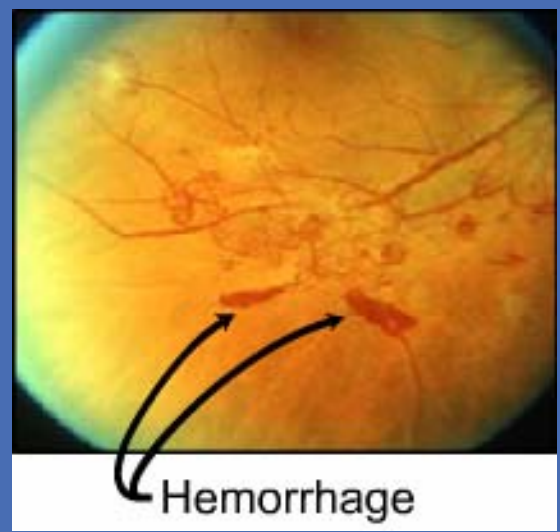
Types of Diabetic Retinopathy

Normal retina



Nonproliferative diabetic retinopathy

Proliferative diabetic retinopathy



Diabetic macular edema

- Diabetic macular edema may coexist with either nonproliferative or proliferative diabetic retinopathy of any severity
- The retina is the one place where the microvasculature can be viewed

Images: [1,2]Diabetic Retinopathy Study Research Group; [3]Phototake.

Treatment

Current Treatment Options for Diabetic Microvascular Complications

Disease	Direct Treatment	Indirect Treatment
Diabetic Nephropathy	None	BP Control
Diabetic Neuropathy	None	Analgesic relief for pain only
Diabetic Retinopathy	Laser (late stage)	BP/GC Control
Any Diabetic Microvascular Complications	None	BP/GC Control

Therapies that target the underlying process are needed

Until new therapies are available, early detection is the only way to predict the development and progression of Diabetic Microvascular Complications (DMCs)

Clinical Guidelines for Early Detection of Diabetic Nephropathy

Test	When	Normal Range
Blood pressure	Each office visit	<130/80 mm Hg
Urinary albumin	Type 2: Annually beginning at diagnosis Type 1: Annually, 5 years post-diagnosis	<30 µg/mg creatinine (random spot collection) Equivalent to: <30 mg/day urinary albumin excretion <20 µg/min urinary albumin excretion (timed specimen)

American Diabetes Association: Nephropathy in Diabetes (Position Statement). *Diabetes Care.* 2004; 27(suppl 1):S79-S83.

Clinical Guidelines for Early Detection of Diabetic Peripheral Neuropathy

Stages	Characteristics
Stages 0/1: No clinical neuropathy	• No symptoms or signs
Stage 2a: Clinical neuropathy	• Positive symptomology (increasing pains at night): burning, shooting, stabbing pains, “pins & needles”; absent sensation to several modalities and reduced or absent reflexes • Less common–diabetes poorly controlled, weight loss; diffuse (trunk); minor sensory signs
Stage 2b: Clinical neuropathy	• No symptoms or numbness of feet; reduced thermal sensitivity; painless injury
Stage 3: Disability/late stage	• Foot lesions (eg, ulcers); neuropathic deformity (eg, Charcot joint); non-traumatic amputation

Adapted from Boulton AJM, et al. Diabet Med. 1998; 15(6):508-514.
Adapted from Dyck PJ. Muscle Nerve 1988; 11:21-32

Clinical Guidelines for Management of Diabetic Peripheral Neuropathy

Stages	Objectives	Referral
Stage 0/1: No clinical neuropathy	Education to reduce risk of progression; glycemic control; annual assessment	As required
Stage 2a: Clinical neuropathy	Stable glycemic control; symptomatic treatment	Diabetologist, neurologist
Stage 2b: Clinical neuropathy	Education, especially foot care; glycemic control according to needs	Foot care team
Stage 3: Disability/late stage	Prevention or new/ recurrent lesions and amputation; emergency referral if lesions present; otherwise referral within 4 weeks	Diabetologist, neurologist, chiropodist, podiatrist, diabetes specialist nurse, diabetic foot clinic if available

Adapted from Boulton AJM, et al. Diabet Med. 1998; 15(6):508-514.
Adapted from Dyck PJ. Muscle Nerve 1988; 11:21-32

Clinical Guidelines for Early Detection of Diabetic Retinopathy and Diabetic Macular Edema

Patient group	Recommended first examination*	Minimum routine follow-up†
Type 1 diabetes	Within 3–5 years after diagnosis of diabetes once patient is age 10 years or older	Yearly
Type 2 diabetes	At time of diagnosis of diabetes	Yearly
Pregnancy in preexisting diabetes	Prior to conception and during first trimester	Physician discretion pending results of first trimester exam

*Eye exam should be performed through dilated pupils by qualified eye specialist

†Abnormal findings necessitate more frequent follow-up

Fong DS et al. *Diabetes Care*. 2004;27 (suppl 1): S84-S87.

Conclusions

- As the incidence and prevalence of diabetes continues to increase globally, more effective risk assessment and diagnostic procedures should be employed to identify patients with DMC
- Tight control of glucose, blood pressure, and lipids can slow progression, but not always prevent DMC
- Additional treatment options could provide further benefits for patients with DMC