Quest Diagnostics White Paper

Improving diabetes care with digital retinal exams

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Diabetes Prevalence

In the United States, 30.2 million adults aged 18 years or older (12.2% of all U.S. adults) have diabetes – a figure that has almost quadrupled from 7.6 million since 1997 and is expected to continue to rise by more than 50% by 2030.[1, 2] Of the 30.2 million, 23 million are diagnosed and 7.2 million (23.8%) are not aware of having diabetes.[1, 2] In addition, approximately one-third of the U.S. adult population – 84 million Americans – are on the cusp of developing diabetes with having prediabetes or impaired fasting glucose.[2] Most individuals (90% and 95%) with diabetes have Type 2 diabetes, characterized by the development and progression of insulin resistance as an adult.[3] Type 1 diabetes, on the other hand, characterized by insulin deficiency due to beta-cell destruction in the pancreas is associated with more frequent and more severe ocular complications.[4, 5]

Increases in prevalence of diabetes are associated with considerable healthcare expenditures as annual per capita expenditures for persons with diabetes average 2.3x higher than those without diabetes[6] and diabetes with complications averages $30k per person in healthcare spending per year.[7] When inadequately managed, diabetes can lead to microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (ischemic heart, peripheral vascular, cerebrovascular) complications resulting in significant organ damage including blindness, renal failure, and limb amputation.[8-11] The risk of developing complications is often dependent upon the duration and severity of the hyperglycemia (persistently elevated blood sugar) and can be attenuated with appropriate monitoring and care.

Diabetes-related retinopathy

Diabetic retinopathy is the leading cause of vision loss in adults aged 20–74 years.[12] Diabetic retinopathy is a prevalent and often preventable diabetes-related complication which damages the small blood vessels in the retina. Its prevalence is related to both the duration of diabetes and level of glycemic control.[13] Globally, the prevalence of diabetic retinopathy is 35.4%.[14] In the United States, about 28.5% of US adults with diabetes also had diabetic retinopathy (4.4% of which was vision-threatening).[15] At the time of first diagnosis of diabetes, as many as one-fifth of individuals with type 2 diabetes already have retinopathy.[16, 17] Within 5 years, 54.0% of individuals with type 1 diabetes and 24.4% with type 2 diabetes will develop retinopathy.[18] Within 20 years, more than 80% of individuals using insulin to manage diabetes will develop retinopathy.[19]

Stages of diabetes-related retinopathy

Non-proliferative Diabetic Retinopathy / Macular Edema

Non-proliferative diabetic retinopathy is an early stage of the disease. In non-proliferative diabetic retinopathy, blood vessels of the retina may leak causing blood to accumulate in the retina blocking the macula (a central part of the retina required for clear vision). Non-proliferative diabetic retinopathy ranges in severity from mild to moderate and severe. Increasing severity leads to macular edema - a common manifestation of diabetic retinopathy and a leading cause of legal blindness in individuals with type 2 diabetes. Approximately 2.7% of adults with diabetes have clinically significant macular edema,

representing 4 out of every 1,000 (0.4%) adults aged 40 years or older.[15] Over a 10-year period, 10% of Americans with known diabetes will develop clinically significant* macular edema (14% will develop non-clinically significant).[20] Approximately half of patients with macular edema will lose two or more lines of vision within 2 years,[21] a personal catastrophe resulting decline in quality of life.[22]

Treatment

Management of non-proliferative diabetic retinopathy / macular edema requires early detection and optimal glycemic control to slow the progression of disease. In advanced stages* of the disease, laser photocoagulation, may be used to seal or destroy leaking blood vessels in the retina.[23] Photocoagulation treatment of "clinically significant" diabetic macular edema substantially reduces the risk of visual loss and increases the chance of visual improvement.[24] Yet, clinical outcomes are better if individuals are screened and treated early.[25]

> ***Clinically significant** "macular edema occurs if there is thickening of the retina involving the center of the retina (macula) or the area within 500 µm of it, if there are hard exudates at or within 500 µm of the center of the retina with thickening of the adjacent retina, or if there is a zone of retinal thickening one disk area or larger in size, any part of which is within one disk diameter of the center of the retina."

Proliferative diabetic retinopathy

Proliferative diabetic retinopathy is a more advanced stage of the disease when new blood vessels grow and may leak blood, blocking vision. Globally, the prevalence of proliferative diabetic retinopathy is 7.5% in individuals with diabetes.[14] In the United States, approximately 1.5% of adults with diabetes have proliferative diabetic retinopathy which represents 2 of every 1,000 (0.2%) adults aged 40 years or older.[15]

Figure 1. Stages of Diabetic Retinopathy (4)[19]

Stage	Description
Non-proliferative Diabetic Retinopathy	
Mild	Earliest stage of the disease. At least one microaneurysm (small area of balloon-like swelling in the retina's tiny blood vessels) present and may leak fluid into the retina.
Moderate	Hemorrhages and/or microaneurysms increase as retinal blood vessels swell and distort leading to characteristic changes to the appearance of the retina and may contribute to **macular edema**.
Severe	Further blood vessel damage blocks blood supply to the retina. Areas deprived of blood flow secrete growth factors that signal the retina to grow new blood vessels.
Proliferative Diabetic Retinopathy	

	Advanced stage of the disease. Growth factors secreted by the retina trigger the proliferation of new blood vessels. New blood vessels are fragile and susceptible to leaking causing scar tissue and retinal detachment leading to permanent vision loss.

Importance of Screening

Progression of diabetic retinopathy can be mitigated by effective control of serum glucose and blood pressure and by its early detection and timely treatment.[26, 27] The efficacy and cost-effectiveness of early detection and treatment of diabetic retinopathy is well established.[28, 29] Because it is often asymptomatic in its early stages, best practice guidelines recommend that people with diabetes have regular eye exams to screen for retinopathy.[30] American Diabetes Association screening recommendations for diabetic eye care are shown in **figure 2.**[13] Regular screening and early treatment can potentially save years of vision and reduce societal costs.[31] Early identification and treatment for patients with diabetes can prevent over 50% of vision loss in patients with diabetic retinopathy.[19, 32, 33]

Figure 2. Screening recommendations for diabetic eye care from the American Diabetes Association [13]

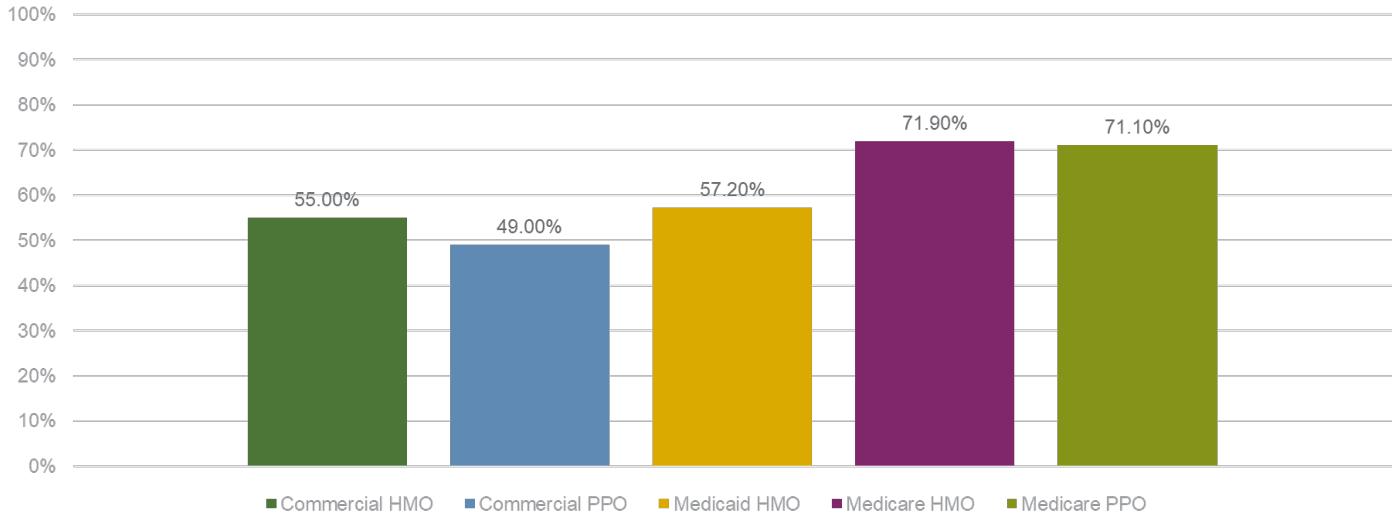
Population	Recommendation
Adults with type 1 diabetes	• Should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes
Patients with type 2 diabetes	• Should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis

No evidence of retinopathy for one or more annual eye exams	• Exams every 2 years may be considered
Any level of diabetic retinopathy	• Subsequent dilated retinal examinations for patients with type 1 or type 2 diabetes should be repeated at least annually by an ophthalmologist or optometrist • If retinopathy is progressing or sight-threatening, then examinations will be required more frequently

Barriers to Screening / Social Determinants of Health

Despite clinical guidelines for comprehensive dilated exams for diabetic retinopathy, only 15.3% of insured patients with type 2 diabetes and no diagnosed diabetic retinopathy meet the American Diabetes Association (ADA) recommendations for annual or biennial eye exams and almost half had no eye exam visits over a 5-year period.[18] In addition, health plans show opportunity for improvements in clinical performance measures (HEDIS®) for comprehensive diabetes care for adults 18–75 years of age with diabetes (type 1 and type 2) who had eye exam (retinal) performed or negative exam in the year prior [34] (**figure 3**), where only ~1/2 of commercial health plans met the criteria. Higher screening compliance by Medicare may be attributed to value-based design which rewards health care providers with incentive payments for the quality of care they provide.[35]

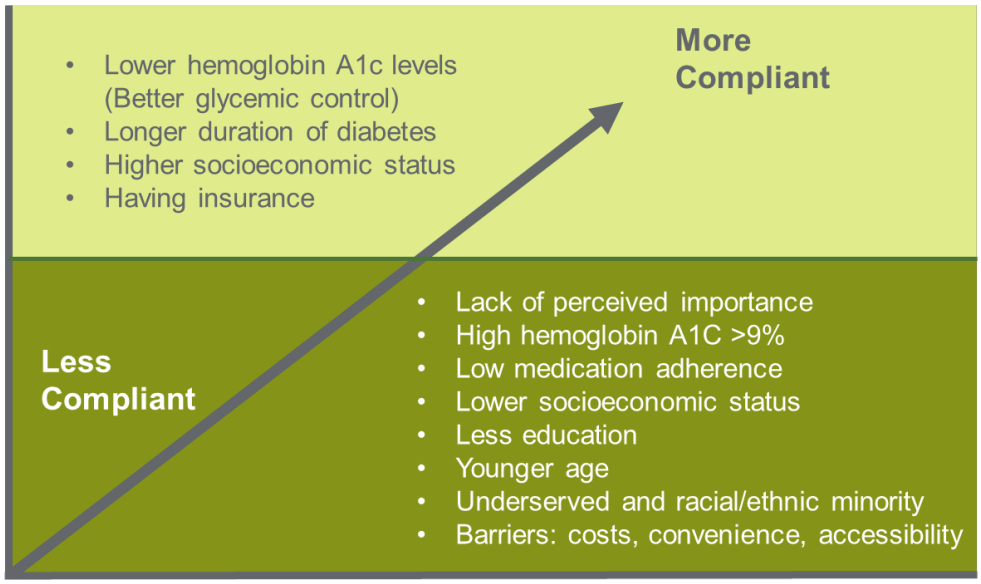
Figure 3. Comprehensive Diabetes Care for adults 18–75 years of age with diabetes (type 1 and type 2) who had Eye exam (retinal) performed (NCAQA / HEDIS 2017)



Criteria: A retinal or dilated eye exam by an eye care professional in the measurement year (regardless of results) or - A retinal or dilated eye exam by an eye care professional in the year prior to the measurement year that was negative for retinopathy.

Adherence to guidelines are associated with better glycemic control (lower hemoglobin A1c levels), having insurance, and a longer duration of diabetes [36] (**figure 4**). In addition, several previous studies have found higher socioeconomic status (SES) to be associated with having retinal exams.[37-40] In a national representative sample of 84,572 people with insulin-dependent diabetes, 72.9% with higher annual income *vs.* only 32.4% with lower annual income had exams in the last year.[37] In addition, rates for annual diabetic retinal exams are lower in underserved and racial/ethnic minority populations.[37, 39-41] Moreover, nonadherence to routine eye screening exams has also been associated with less comorbidity, insulin use, higher specialist copayment plans, and proxies for poor patient behavior (lower adherence to the oral hypoglycemic agents, less diabetes education, hemoglobin A1C >9%).[40] In addition to social and demographic factors, non-adherence is also related to costs, convenience, accessibility, and lack of perceived importance.[36, 42] Thus, delivery of cost-effective, accessible screening to rural, remote, and hard-to-reach populations may increase screenings.[43]

Figure 4. Factors associated with higher and lower compliance to diabetic eye exam recommendations



Improving diabetes care with diabetic retinal exams

There is clear opportunity for improved compliance with diabetic retinopathy screening and treatment. Evidence has shown that clinical outcomes for retinal disease can be improved with retinal imaging performed in accessible locations in the community.[44-46] Bringing retinopathy screening to the community has been previously effective in screening those who had not received a recent eye exam and identifying those with retinopathy.[47] In addition, examination by retinal imaging offers an accessible, efficient, low-cost, high-quality means of improving screening compliance and identifying retinal diseases.[44-46] Remote diagnosis imaging and a standard examination by a retinal specialist appeared equivalent in identifying referable macular degeneration in patients with high disease prevalence;[44] these results may assist in delivering timely treatment and seem to warrant future research into additional metrics.[44]

In 2019, Quest Diagnostics MedXM offered digital retinal examinations to hard-to-engage health plan members. By expanding diabetic retinal exam services to patients' homes and health fair events across 48 states, the solution enabled screening by improving accessibility and convenience – previously identified barriers to testing.[42] In addition, home visits and patient service center services offered punctuality, flexibility, and the ability to combine services (retinal exam during a1c check) – further improving convenience.[42] Remote screening may also lower cost of screening.[48]

Impact: Retinopathy detection and vision saved

Retinal exams were performed on 31,325 individuals (**figure 5**). Screening identified, 8,340 people with pathology (27% of those screened). Of those screened, 10.6% (n=3,309) had non-proliferative diabetic retinopathy and 4.6% (n=1,437) macula edema (**figure 6**). Prevalence of macula edema in the current screened health plan population was higher than population estimates. Previous population estimates showed approximately 2.7% of adults with diabetes had clinically significant macular edema, representing 4 out of every 1,000 (0.4%) adults aged 40 years or older.[15] Screening detected proliferative diabetic retinopathy in 1.4% (n=432) of those screened. Rates of proliferative diabetic retinopathy were similar to population estimates of 1.5% of adults with diabetes having proliferative diabetic retinopathy.[15] In addition, 12.3% (n= 3,836) of those screened showed other pathologies (including vein occlusion, wet AMD, cataract, Dry AMD, HTN retinopathy).

Figure 5. Impact of digital retinal exams for hard-to-engage health plan members with diabetes

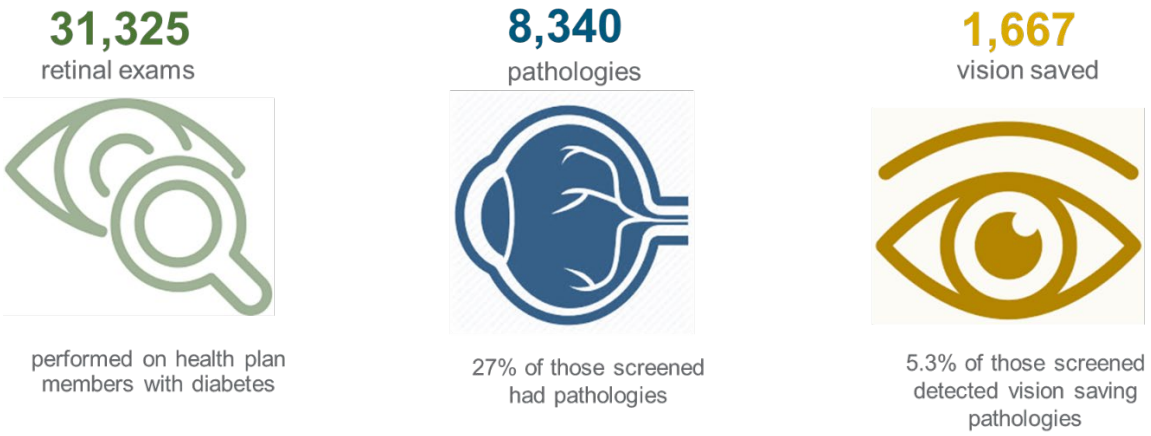
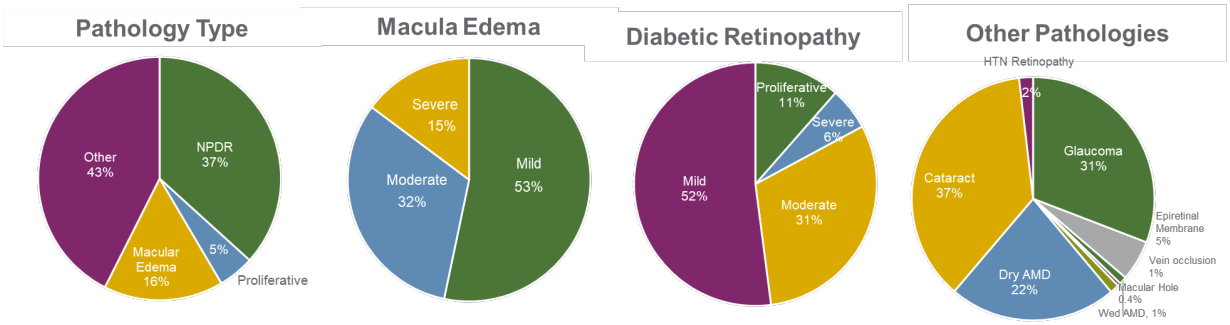


Figure 6. Profile of pathologies detected in digital retinal exams of health plan members with diabetes



Vision saved

Without detection and treatment, nearly all individuals with diabetes will experience vision loss from retinopathy.[19] Over time, early detection and treatment of may prevent as much 98% of visual loss due to diabetic retinopathy for individuals with diabetes.[32, 33] In this evaluation of screenings in non-adherent health plan members, 1,667 cases (5.3% of those screened) saved vision due to the detection of vision-threatening pathologies (glaucoma, macular hole, epiretinal membrane).

Without intervention, individuals may lose vision if the following are present:

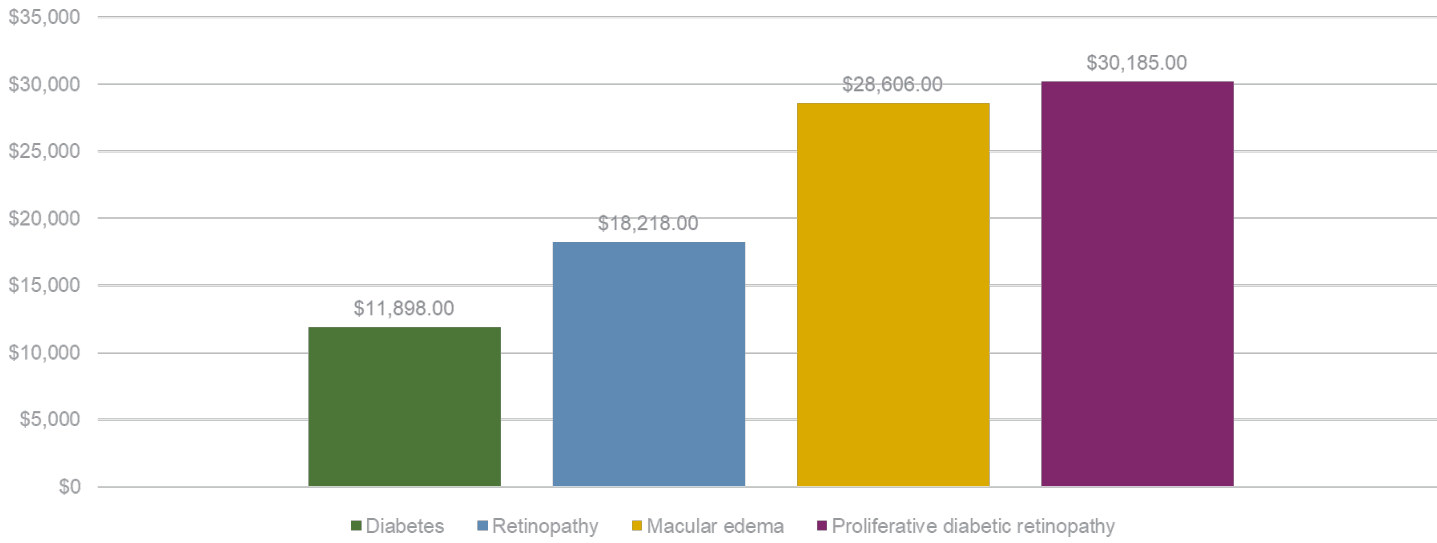
- Moderate diabetic retinopathy
- Severe diabetic retinopathy
- Proliferative diabetic retinopathy
- Moderate macular edema
- Severe macular edema
- Wet AMD
- Macular holes
- Epiretinal membranes if in central macula
- Advanced glaucoma

Value of screening

Nonproliferative retinopathy may progress to more advanced stages of the disease. Among those with nonproliferative retinopathy at baseline, after 5 years 23% may progress in severity, 5.2% to macular edema, and 6.1% to proliferative retinopathy.[49] After 10 years, 53% may develop more severe retinopathy, 9.6% macular edema, and 11% proliferative retinopathy.[49]

There are substantial expenditures associated with diabetic retinopathy related to both ophthalmic care and other care, especially for proliferative diabetic retinopathy.[50] Claims analysis of 17 companies from 1999 to 2004 show that medical costs of diabetics with retinopathy ($18,218) were $6,000 more per year than those without ($11,898) (**figure 7**).[51] Costs associated with macular edema were $28,606 and proliferative diabetic retinopathy were $30,185.[51] (Recent analyses could not be located, but inflation may add 30%-50% to these annual costs or ~$42, 259 for proliferative diabetic retinopathy). In sum, diabetic-related vision loss costs the United States approximately $500 million annually.[28] Detection and treatment of diabetic retinopathy in individuals with Type 1 and Type 2 diabetes has been modeled to reduce the prevalence of blindness by 52%.[52] Detection and treatment is cost effective as direct costs of care are less than costs of lost productivity and disability.[52]

Figure 7. Annual Medical Costs of Diabetic Retinopathy [51]



Diabetic retinopathy is associated with both direct and indirect costs of medical, disability, and quality of life. In the United States, the total financial burden of major visual disorders was $35.4 billion comprised of $16.2 billion in direct medical costs, $11.1 billion in other direct costs, and $8 billion in productivity losses, in 2004.[53] In regards to medical costs, macular edema in individuals with diabetes is associated with 31% higher 1-year costs and 29% higher 3-year costs.[54]

Improved delivery of ophthalmic care to patients with diabetes yields substantial financial and visual savings.[55, 56] In fact, in the United States, screening for and treating diabetic retinopathy were more cost-effective than most commonly provided medical interventions.[28] Annual screening and treatment programs save thousands of years of vision and reduce medical expenditures over the lifetime of a cohort of diabetic patients.[57] Models show that savings may exceed $167.0 million and 79,236 person-years-sight, if all patients received appropriate eye care.[55] Most savings (~2/3) results from treatment of proliferative diabetic retinopathy, while nearly one-third arises from treatment of clinically significant macular edema.[55] Additional savings of $9,571 are realized with each recruitment of a newly diagnosed patient with diabetes.[55]

Screening and treatment costs $966 per person-year of vision saved from proliferative retinopathy and $1,118 per person-year of central acuity saved from macular edema.[56] Costs are only one-seventh of the $6,900 average cost of 1 year of Social Security Disability (in 1989) for those disabled by vision loss,[56] with even higher indirect costs of human suffering and lost productivity. Retinal screening in individuals with type 2 diabetes is cost-effective in terms of sight years preserved, particularly for younger individuals with poorer glucose control.[29, 43] In 1990 dollars, the cost of screening and treating diabetic retinopathy was $1,757 per person-year of sight saved.[28] For all individuals with diabetes mellitus, the cost per QALY was $3,190 [28] (ranging from $1,996 for patients with insulin-dependent diabetes mellitus to $3,530 for patients with non-insulin-dependent diabetes mellitus who do not require insulin).[28] Cost-effectiveness of screening is higher in those taking insulin.[28, 58] In addition, variation in compliance rates,

age of onset of diabetes, glycemic control and screening sensitivities influence the cost-effectiveness of screening programs and are important sources of uncertainty in relation to the issue of optimal screening intervals.[43]

Conclusions

Bringing diabetic retinopathy screening services to hard-to-engage health plan members in their homes or neighborhood patient service centers may improve adherence to screening guidelines, save vision and save costs. As shown, of 31,325 retinal exams performed, 8,340 people with pathology (27% of those screened) were identified. Based on published data,[51] medical costs **(figure 7)** associated with detected retinopathies in this population may total $52.8 M more per year than diabetes without retinopathy broken down as follows:

- $20.9M for n=3,309 with non-proliferative diabetic retinopathy at $18,218 ($6,320 more per year than those without retinopathy at $11,898)
- $24.0M for n=1,437 with macula edema at $28,606 ($16,708 more per year than those without retinopathy at $11,898)
- $7.9M for n=432 with proliferative diabetic retinopathy at $30,185 ($18,287 more per year than those without retinopathy at $11,898)

Preventing progression of non-proliferative diabetic retinopathy to macular edema and proliferative diabetic retinopathy may save $10,388 and $11,967, respectively per person per year. Improved adherence to guidelines for retinal examinations for individuals with diabetes may save vision and related medical- and disability- related costs. Improved adherence to screening guidelines may be achieved by addressing the social barriers to health including accessibility and convenience.

Through screening, we have identified 5,178 (3,309+1,437+432) patients with non-proliferative diabetic retinopathy, macular edema and proliferative diabetic retinopathy. Left unaddressed, diabetic retinopathy progression for those 5,178 patients would likely result in an annual incremental cost of **$52.8 million**. The screening program may provide for a more targeted approach to active patient management, improve the quality of care and potentially avoid or delay costs associated with cost progression.

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