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RETINA TODAY

DIABETIC EYE CARE

Best Practices for Patient Education and Comanagement

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Diabetes and Retinopathy

BY ANNE PETERS, MD, CDE

For patients with diabetes, becoming blind is at the top of their list of fears, higher than even amputations. In fact, many of my patients tell me that they would rather have a heart attack and die than go blind. An international survey based on experiences with diabetic microvascular complications found that 2 of the 4 top concerns of patients with diabetes are vision-related, the first being blindness and the fourth being other eye problems such as blurriness and cataracts (Figure 1).[1]

There have been many quality-of-life studies that have been conducted, including one by Brown et al[2] that was a time-tradeoff utility value analysis and in which patients were asked to rank the impact of vision loss. These answers were then compared to other systemic conditions regarding the perceived impact on quality of life (Figure 2). In other studies by Brown et al,[3,4] patients were asked how many years of life would they be willing to give up to have good vision. Visually impaired patients from diabetic retinopathy were willing to trade years of remaining life for normal vision, and the worse the vision was, the more time patients said they would be willing to trade (Figure 3).

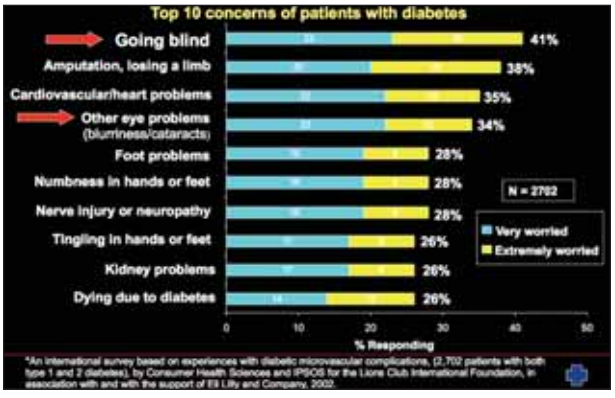

Figure 1. Results from an international survey regarding the top 10 concerns of patients with diabetes in which blindness is ranked number 1.

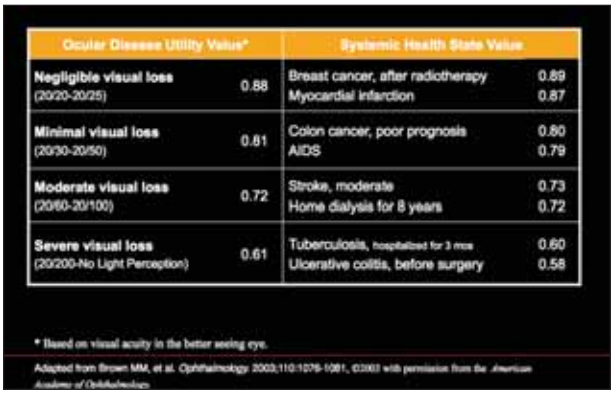

Figure 2. The perceived impact on quality of life from visual loss as compared with other systemic conditions from a utility analysis.

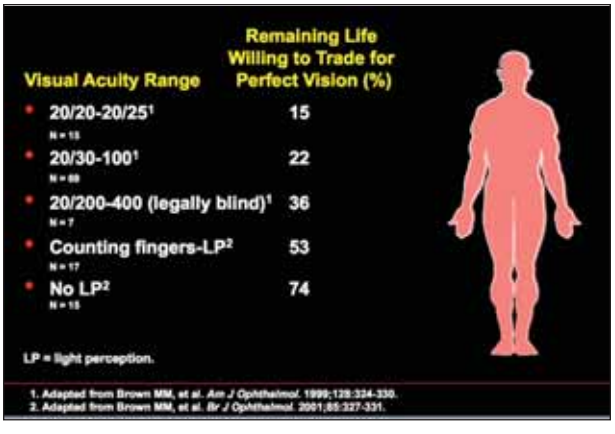

Figure 3. Results from a time-tradeoff study showing the number of years of life patients at decreasing levels of vision would trade for perfect vision.

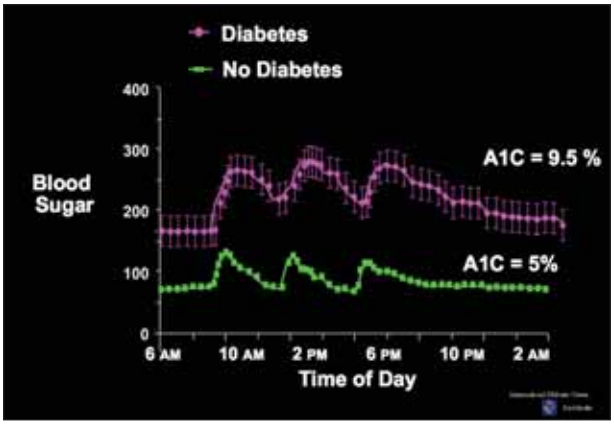

Figure 4. Patients with diabetes begin the day with high levels and continue to have high blood glucose levels all day long as compared to patients with no diabetes.

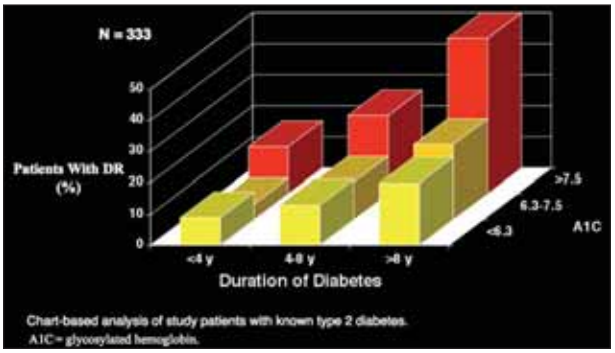

Figure 5. Longer duration of disease and higher A1C levels are directly associated with a higher risk of developing diabetic retinopathy.

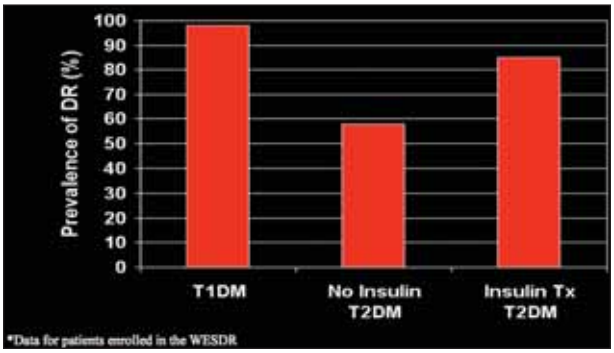

Figure 6. When comparing Type 1 diabetes vs Type 2 vs Type 2 taking insulin, the prevalence of diabetic retinopathy is highest in patients with Type 1 diabetes.

It is not a surprise that patients consider loss of vision as having such a great impact on their quality of life. Vision affects both ambulatory and vehicle mobility, specifically recognition of landmarks and street signs. It also has a direct effect on the ability to read or perform close work, which encompass the activities of daily living such cooking, shopping, and paying bills. Patients with reduced vision have difficulty performing tasks involved with self-care such as reading medicine or food labels and preparing for insulin injections or glucose testing. Finally, patients with vision loss often shy away from social participation or dependence on others, which can result in feelings of vulnerability, depression, and emotional distress.[5,6]

RISKS FOR PROGRESSION TO DIABETIC RETINOPATHY

As an endocrinologist, I spend much of my time tackling issues such as insulin resistance and vascular disease. When considering the elemental issues in diabetes, however, the main goal is to maintain normal glucose levels. Recently, although I do not have diabetes, I chose to start wearing a continuous glucose monitor to gain a better understanding of the technology. I was fairly surprised at how normal "normal" is—my levels stayed within 70-120 mg/dL throughout the day. Our patients with diabetes, however, begin the day with high levels, and continue to have high blood glucose levels all day long (Figure 4). To achieve normal levels is difficult, particularly because insulin use increases hypoglycemia.

Many of our patients will develop some diabetic retinopathy over time. It is estimated that approximately 40% of patients with diabetes aged 40 years or older will develop diabetic retinopathy and that approximately 20% of those patients will have vision-threatening disease.[7]

We know that longer duration of disease and higher

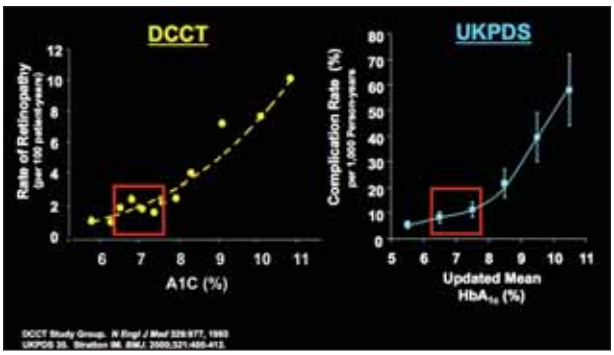

Figure 7. In the DCCT and the UKPDS there was a clear relationship between A1C levels and the risk of developing retinopathy.

A1C levels are directly associated with a higher risk of developing diabetic retinopathy (Figure 5). In a study by Tapp et al,[8] the authors surveyed 11 247 adults older than age 25 in Australia, including 2476 participants with diabetic complications. They found that at all levels of glycemic control, the likelihood of diabetic retinopathy increased with duration of disease. Looking at patients with Type 1 diabetes vs Type 2 vs Type 2 taking insulin, the prevalence of diabetic retinopathy (not necessarily vision threatening) is highest in patients with Type 1 diabetes (Figure 6).[9,10]

In the Diabetes Control and Complication Trial (DCCT)[11] and the United Kingdom Prospective Diabetes Study (UKPDS),[12] there was a clear relationship between A1C levels and the risk of developing retinopathy (Figure 7). The challenge is that as A1C levels go down, the risk for severe hypoglycemia goes up, requiring additional intervention (Figure 8).[13] Thus, it is important to find a balance for our patients to both reduce the risk of diabetic retinopathy and hypoglycemia. Other more recent studies, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[14] show a similar rela-

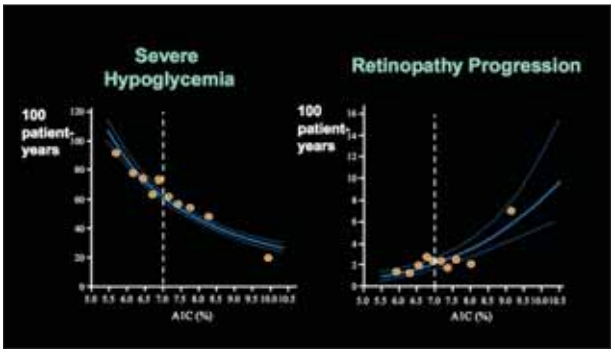

Figure 8. As A1C levels go down, the risk for severe hypoglycemia goes up, requiring additional intervention.

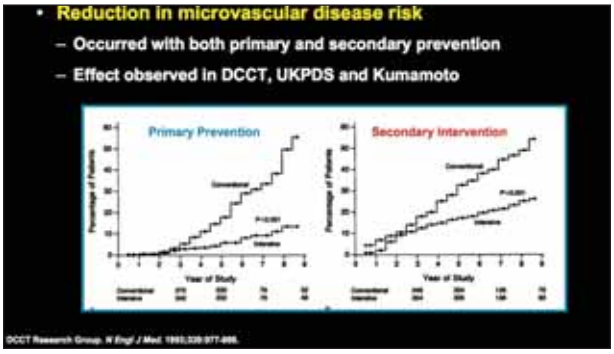

Figure 9. The data from the DCCT shows that a benefit to both primary and secondary early intervention.

tionship between lipids and the progression to diabetic retinopathy.

With regard to intervention, there is a real difference in terms of progression to retinopathy. The data from the DCCT shows that a benefit to both primary and secondary early intervention (Figure 9).[11] The durability of intervention is demonstrated in the UKPDS[15] and the follow-up study to the DCCT, the Epidemiology of Diabetes Interventions and Complications trial,[16] both of which showed that glycemic control over an extended period of time leads to a continued benefit.

I have seen many patients who have been put on an angiotensin-converting enzyme (ACE) inhibitor, not because they have nephropathy or even hypertension, but as a preventive measure. Recently, a study was performed to evaluate the renal and retinal effects of enalapril and losartan in patients with Type 1 diabetes.[17] Some of the patients had some form of retinopathy upon study entry, but none had nephropathy. The progression of nephropathy and the development of microalbuminuria was approximately the same with enalapril and placebo, but was higher in patients using the angiotensin-receptor blocker losartan. The progression of retinopathy was slowed by both the ACE-inhibitor and the angiotensin receptor blocker, suggesting that an ACE-inhibitor may be a good preventive measure against retinopathy, even in the absence of nephropathy.

SUMMARY

Among the current management recommendations for diabetic retinopathy, screening is of utmost importance, as is referral to an ophthalmologist, but it is also important to understand the importance of glycemic and blood pressure control, as well as interventions that can reduce the risk of progression to diabetic retinopathy.

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The Role of Technology in Diabetic Eye Care

BY TIMOTHY BAILEY, MD, FACP, FACE

Diabetes is inherently challenging to treat as it is so complex and data-intensive. As this patient population grows and our offices get busier, the challenge will only become more acute. The field of diabetes has been revolutionized in not only how we treat our patients, but also in the way that we are able to diagnose and monitor them. As an endocrinologist who has embraced technology and its advances over the years, I am impressed by how underutilized that the available tools are. This article will review the evolving role of technology in caring for our patients, specifically in regard to diabetic eye care.

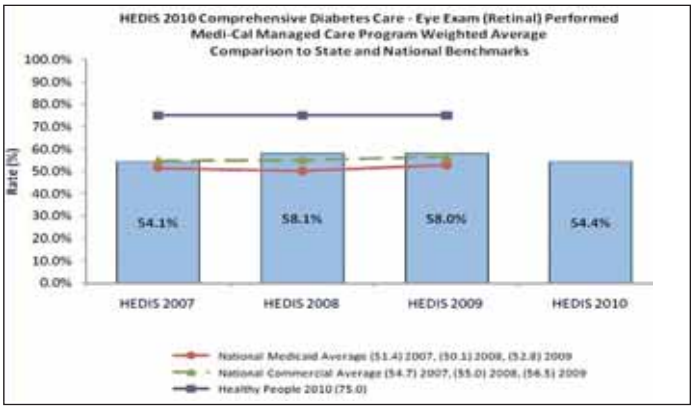

Figure 1. Medi-Cal data for 2010.

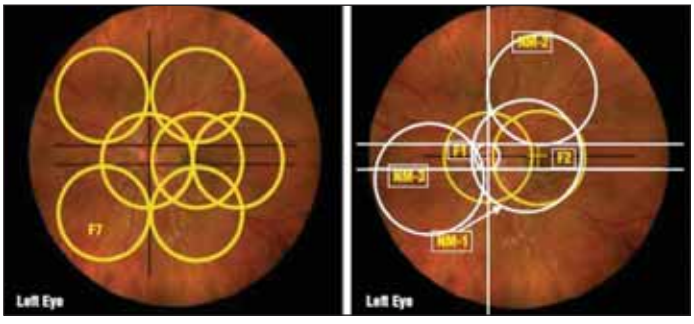

Figure 2. The ETDRS 30º 7-field color reference.

SCREENING FOR DIABETIC RETINOPATHY

Screening for diabetic retinopathy is an essential task for those who manage patients with diabetes. Diabetic retinopathy has been shown to be a prevalent comorbidity and to be the complication that has the greatest impact on quality of life.[1-3] If patients are properly screened for retinopathy they can be referred to the ophthalmologist earlier, potentially preventing vision loss.

Who should be screened? According to the American Diabetes Association, patients with Type 1 diabetes should be screened for diabetic retinopathy after 10 years with the disease within 5 years of diagnosis.[4] Patients with Type 2 diabetes, however, should be screened upon diagnosis and yearly thereafter. It is reasonable to consider screening at 2-3 year intervals for patients who are considered normal after initial or subsequent screening. For our patients who are pregnant, we should be screening them for diabetic retinopathy both before and during pregnancy, as retinopathy can exacerbate during this time.

The gold standard of screening for diabetic retinopathy are the guidelines set forth by the Early Treatment Diabetic Retinopathy Study (ETDRS), which can be seen in the sidebar "American Diabetes Association Guidelines for Screening for Diabetic Retinopathy."

For various reasons, it may be difficult to have all of our patients screened by an ophthalmologist with a full retina exam. Figure 1 shows Medi-Cal data for 2010 on how screening for residents of California compare to the national average, indicating missed opportunities for screening; similar data are available for other states.

The barriers to universal screening for diabetic retinopathy include geography, economic status, social limitations, and lack of education regarding the importance of screening. Another barrier is the magnitude of the task of screening. There are approximately 160 000 ophthalmologists worldwide as of 2010 and an estimated 285 million patients with diabetes. This translates into 1781 patients per ophthalmologist. These numbers are projected to become less favorable in the future, with the number of patients with diabetes expected to balloon to 438 million by 2030 and the number of ophthalmologists to increase only to 224000—1955 patients per every ophthalmologist.

Even if there were enough ophthalmologists to see every patient with diabetes, it is a challenge to persuade patients to see an eye doctor. It may be the required co-pay, or the distance, or simply the inconvenience of having to see another doctor. The first step that we can take as diabetologists is to learn how to the technology that will enable us to screen for this disease more effectively.

TECHNOLOGY FOR SCREENING

When deciding what kind of technology to include in

AMERICAN DIABETES ASSOCIATION GUIDELINES FOR SCREENING FOR DIABETIC RETINOPATHY[1]

1. Patients >10 years of age with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 3–5 years after the onset of diabetes. In general, screening for diabetic eye disease is not necessary before 10 years of age. However, some evidence suggests that the prepubertal duration of diabetes may be important in the development of microvascular complications; therefore, clinical judgment should be used when applying these recommendations to individual patients. Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after the diagnosis of diabetes is made.
2. Subsequent examinations for both type 1 and type 2 diabetic patients should be repeated annually by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing the presence of diabetic retinopathy and is aware of its management. Examinations will be required more frequently if retinopathy is progressing. This follow-up interval is recommended recognizing that there are limited data addressing this issue. As previously discussed, data from WESDR showed that patients with type 2 diabetes who received ETDRS standard seven-field stereoscopic color fundus photographs that revealed no retinopathy when evaluated by a skilled reader did not generally require another retinopathy examination for 4 years because of low risk of disease progression. However, in patients with gross proteinuria or poor glycemic control (>2 SD from the mean of the nondiabetic population), annual examinations were indicated even if the initial review using fundus photography revealed no retinopathy. Despite the WESDR findings, we believe that an annual eye examination is still warranted for the following reasons. First, these data were derived from a study that evaluated white, northern European-extraction patients with diabetes living in southern Wisconsin. The results may not be applicable to African-American, Hispanic-American, Asian-American, or other populations where it is unknown if retinopathy progresses in the same manner. Second, a well-designed quality-control program was used in WESDR to ensure accurate interpretation of fundus photographs. Such quality control efforts have not been standardized or completely described, let alone adopted nationwide. Third, the potential for patient loss to follow-up induced by an extended hiatus between ophthalmic evaluations introduces further uncertainty.
3. When planning pregnancy, women with preexisting diabetes should have a comprehensive eye examination and should be counseled on the risk of development and/or progression of diabetic retinopathy. Women with diabetes who become pregnant should have a comprehensive eye examination in the 1st trimester and close follow-up throughout pregnancy. This guideline does not apply to women who develop gestational diabetes because such individuals are not at increased risk for diabetic retinopathy.
4. Patients with any level of macular edema, severe NPDR, or any PDR require the prompt care of an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. Referral to an ophthalmologist should not be delayed until PDR has developed in patients who are known to have severe nonproliferative or more advanced retinopathy. Early referral to an ophthalmologist is particularly important for patients with type 2 diabetes and severe NPDR, since laser treatment at this stage is associated with a 50% reduction in the risk of severe visual loss and vitrectomy.
5. Patients who experience vision loss from diabetes should be encouraged to pursue visual rehabilitation with an ophthalmologist or optometrist who is trained or experienced in low-vision care.

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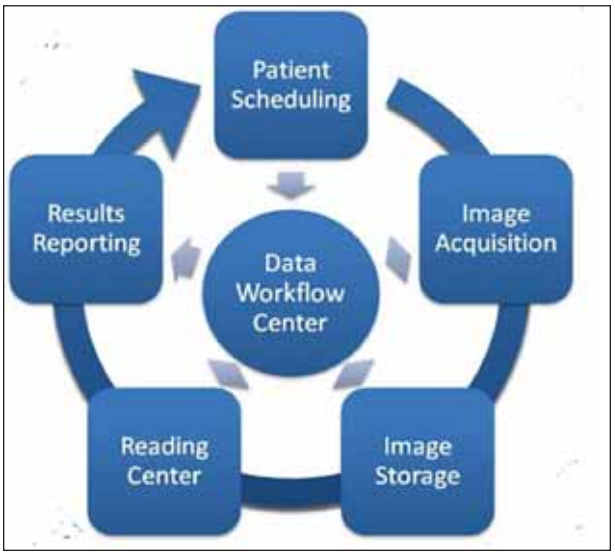

Figure 3. The typical workflow for telescreening.

your practice for screening patients, it is important to consider staffing and training to properly use the equipment. The gold standard to evaluate diabetic retinopathy is the ETDRS 30° 7-field color reference (Figure 2 with color fundus photography. A skilled photographer is necessary for this technology, and in my experience, such an individual can be harder to come by than an ophthalmologist. The most commonly employed technique to evaluate diabetic retinopathy is direct ophthalmoscopy. However, the literature shows that this to be an insensitive and inaccurate methodology, particularly to detect macular edema.[5]

An important advance to image the retina and screen for diabetic retinopathy is the nonmydriatic retina camera. This device does not require the patient to be dilated, making it more convenient for the patient and faster to use for the technician. It is also much lower in cost and is appropriate for a diabetes clinic. A new technology, 200° laser scanning ophthalmoscopy, may prove useful, but in my opinion, it must prove its worth before finding a "prime time" spot in the diabetologist's office, as this is a costly and more complicated device.

TELEMEDICINE

Image acquisition is only the first step in the process of retinal screening. The next step is the processing and interpretation of the images, which is where telemedicine potentially comes in. Because it is crucial to involve an ophthalmologist in the reading of the images to accurately screen for diabetic retinopathy, teleophthalmology may make this more cost-effective. A typical scenario is where the images are captured and then sent to an ophthalmology reading center to determine if the patient is a suspect for diabetic retinopathy.

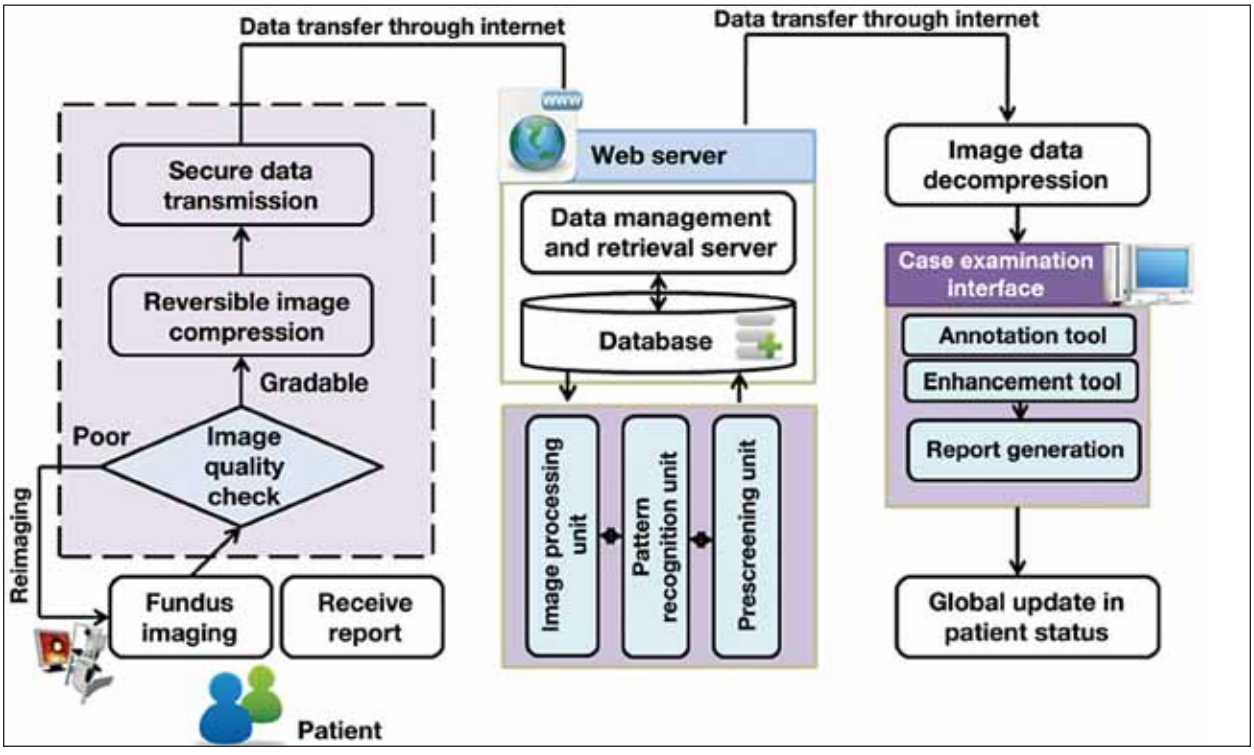

Figure 4. Workflow and analysis diagram for DrishtiCare telescreening program.

The American Telemedicine Association has established categories of clinical validation for diabetic retinal performance in telemedicine[6]:

Category 1. Category 1 validation indicates a system can separate patients into 2 categories: (1) those who have no or very mild nonproliferative diabetic retinopathy (ETDRS level 20 or below), and (2) those with levels of diabetic retinopathy more severe than ETDRS level 20. Functionally, Category 1 validation allows identification of patients who have no or minimal diabetic retinopathy and those who have more than minimal diabetic retinopathy.

Category 2. Category 2 validation indicates a system can accurately determine if sight-threatening diabetic retinopathy is present or not present as evidenced by any level of DME, severe or worse levels of nonproliferative diabetic retinopathy (ETDRS level 53 or worse), or proliferative diabetic retinopathy (ETDRS level 61 or worse). Category 2 validation allows identification of patients who do not have sight-threatening diabetic retinopathy and those who have potentially sight-threatening diabetic retinopathy. Patients with sight-threatening diabetic retinopathy generally require prompt referral for management.

Category 3. Category 3 validation indicates a system can identify ETDRS defined levels of nonproliferative diabetic retinopathy (mild, moderate, or severe), proliferative diabetic retinopathy (early, high-risk), and DME with accuracy sufficient to determine appropriate follow-up and treatment strategies. Category 3 validation allows patient management to match clinical recommendations based on clinical retinal examination through dilated pupils.

Category 4. Category 4 validation indicates a system matches or exceeds the ability of ETDRS photos to identify lesions of diabetic retinopathy to determine levels of diabetic retinopathy and DME. Functionally, Category 4 validation indicates a program can replace ETDRS photos in any clinical or research program.

The Joslin Vision Network is a Category 3 system, which is human-enabled. These types of systems are the most common in the United States and work well with defined populations such as the Veterans Health Administration and the Indian Health Service. Category 3 systems, however, are typically not utilized outside of these large systems or in private practice, due to the enormous startup and maintenance costs.

Figure 3 shows the workflow that has been used by a telemedicine company (Inoveon Corporation, Oklahoma City, OK) that is representative of what might be used by private practices and academic centers. It is a comprehensive system of getting the patients in, acquiring good images, and then moving the images to a reading center.

In my opinion, the future of screening technology will be in having a computerized method with which to identify potential abnormalities and flag them for a screener, making the process faster and less expensive. DrishtiCare, which is a telescreening platform that is in development in India, uses a server-based prescreening system to evaluate fundus images and then refer suspect images to human examiners.[7] The workflow and analysis diagram for this program is seen in Figure 4. Critical to the success of all of these approaches is appropriate reimbursement for the service.

SUMMARY

The technology for point-of-care retinal examination is approaching the point where we will be able efficiently and affordably screen our patients with diabetes for retinopathy. This will allow for interventions that may drastically reduce the numbers of patients who suffer severe vision loss. With a point-of-care system, we would be able to reduce the amount of travel time and lost work hours for patients, ensuring that they are not lost to follow-up because of inconvenience. We could offer expert care in any geographic location using technology, such as nonmydriatic cameras, that are easier for both the technician and the patient. Additionally, we will be able to utilize automated systems that increase efficiency and reduce staffing costs. The drawbacks to telemedicine include a high initial capital cost, reimbursement issues, and the limitations of diagnosis for non-diabetic retinopathy pathologies. Despite the drawbacks and potential challenges, creating a system that will overcome the barriers to screening is a worthwhile task. This has the potential to increase our chances of getting patients screened with appropriate imaging and referred for treatment that has been demonstrated to reduce the overall incidence of vision loss and blindness from diabetes.

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Networking in Clinical Research:
Rapid Breakthroughs in the Management of Diabetic Retinopathy

BY SUSAN B. BRESSLER, MD

There are currently a large number of people, particularly in the United States, who have some level of glucose impairment, if not frank diabetes. The estimated prevalence of diabetes in this country is currently 24 million people with the disease. These numbers are expected to grow as we see an increase in the aging population. Whether patients with diabetes have excellent control of their blood glucose levels or poor control, as longevity increases, many of these patients will develop some kind of retinopathy. It is estimated that 9 million people in the United States alone have diabetic retinopathy, which represents 3% of the entire US population, making eye disease one of the most, if not the most, prevalent comorbidity of diabetes (Figure 1).

Because of the increase in patients who will experience some form of diabetic retinopathy in their lifetimes, it is crucial that the following information on diabetic retinopathy be understood by not only the ophthalmologist, but by all clinicians and health care providers involved in the care of patients with diabetes.

DIABETIC RETINOPATHY: A BRIEF HISTORY

The first documented description of diabetes was in approximately 1500 BC, and was described as a "melting down of flesh into the urine," and it was in the early part of the 20th century with the advent of insulin, that people with diabetes could potentially survive. The increase in survival allowed clinicians to uncover morbidity associated with the disease, and for approximately 40 years from 1930 through 1970, many patients with diabetes became blind as a result. Fortunately, in the late 1970s, the development of ophthalmic lasers allowed for ablation of the peripheral retinal, what is called panretinal photocoagulation (PRP), and a subsequent reduction in the prevalence of blindness from proliferative diabetic retinopathy (PDR). This development led to a collaboration of a large group of vision scientists who put together the first classification of diabetic retinopathy.

The following 20 years witnessed a heyday of clinical research in diabetic retinopathy, beginning with the first clinical trial in retinal diseases, the Diabetic Retinopathy Study, which proved that PRP decreases the prevalence of blindness in the setting of proliferative retinopathy.[1-14] This was followed 10 to 15 years later by the Early Treatment Diabetic Retinopathy Study (ETDRS), which provided further information about the timing of PRP in the setting of proliferative disease and more importantly, introduced the first treatment for diabetic macular edema which also involved laser treatment using a different technique, focal/grid photocoagulation.[15-39]

For the past 25 to 30 years, focal/grid laser photocoagulation has remained the gold standard for treatment for PDR. A few years later, the Diabetic Retinopathy Vitrectomy Study highlighted surgery for eyes with vitreous hemorrhage or tractional retinal detachment.[40-44]

UNDERSTANDING DIABETIC RETINOPATHY

The natural history of diabetic retinopathy can be viewed as an orderly progression from one phase to another. Nonproliferative diabetic retinopathy may not be associated with visual loss unless macula edema is present as part of it. It includes basement membrane thickening, loss of pericytes, and vascular hyperpermeability, and is categorized into mild, moderate, and severe levels. Macular edema, swelling in the retina, can occur at any one of the stages of mild nonproliferative retinopathy through proliferative disease. PDR is an advanced stage that includes retinal ischemia, neovascularization, retinal detachment and may have associated visual impairment. In PDR, abnormal blood vessels grow from the retina into the vitreous cavity.

Patients with diabetes lose vision from proliferative disease through various mechanisms. If the new vessels bleed and fill the vitreous cavity with blood ("vitreous hemorrhage"), vision will be affected but this can be addressed surgically with vitrectomy. They can also lose vision from traction retinal detachment whereby scarring, fibrous bands from neovascular proliferative tissue develop and pull the retina off the eye wall. This can also be corrected surgically; however, visual function will be returned only if the retina has been separated from its underlying blood supply for a brief period of time, and only if the blood supply within the retina is still intact. Unfortunately, most

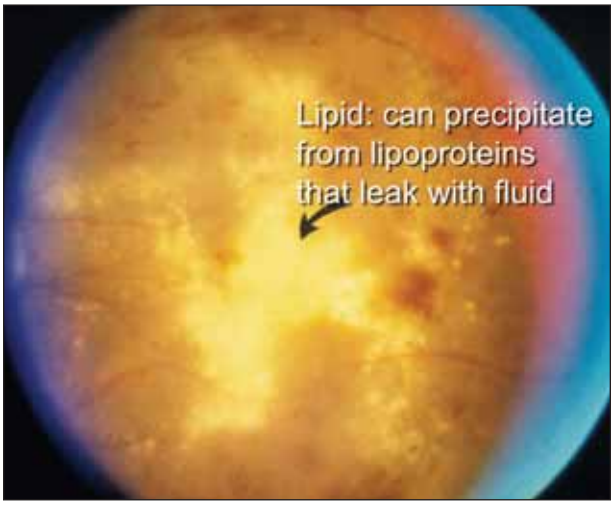

Figure 1. In an eye with severe macular edema, the lipid is a marker indicating leakage from retina vessels.

patients arrive at this point because of ischemia or nonperfusion. The ischemia that occurs in the severe nonproliferative phase of the disease leads to angiogenic factors, which allow proliferation to develop and leads to the end-stage form of PDR. Thus, if the ischemia is profound, even in an attached retina, vision loss may not resolve.

Figure 1 shows an eye with severe macular edema. Lipid is a marker indicating leakage from the retinal vessels, which results from years of hyperglycemia. Hyperpermeability of the vessels can easily be seen with fluorescein angiography (Figure 2). On the left the microaneurysms are clearly visualized. On the right, 10 minutes after that bolus injection of fluorescein, all of the fluorescein is leaking out into the retinal tissue, showing why the retina might be thickened.

In the last 5 years, optical coherence tomography (OCT) has become a standard imaging technology. OCT is similar to ultrasound, but instead of using sound waves, OCT utilizes light to generate images, providing a virtual biopsy of the retina. Figure 3A shows a thickened macula where the fovea bulging forward from interstitial retinal fluid vs Figure 3B, which is a relatively flat macula after successful treatment. OCT is a useful tool for monitoring responsiveness to therapy for macular disorders.

In regard to visual acuity and diabetic retinopathy, ophthalmologists typically use the ETDRS eye chart to test vision. Significant loss of vision correlates to a 3-line loss in visual acuity on ETDRS testing; what a patient actually sees in relation to ETDRS testing can significantly affect his or her quality of life. Thus, it is important to address diabetic retinopathy before patients lose vision to such a degree.

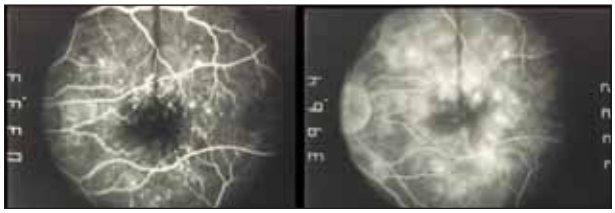

Figure 2. Hyperpermeability can easily be seen with fluorescein angiography.

THE DRCR.NET: OVERVIEW

The Diabetic Retinopathy Clinical Research Network (DRCR.net) was established 8 years ago in 2003 as a collaborative network to facilitate multicenter clinical research on diabetic retinopathy, diabetic macular edema and associated conditions. Funding for the DRCR.net comes from several sources, including a Cooperative Clinical Research Agreement (U10 Award) with National Eye Institute, which is now in its second 5-year cycle (2009 to 2013); the National Institute of Diabetes and Digestive and Kidney Diseases through Type 1 Diabetes Research; other foundations such as the Juvenile Diabetes Research Foundation; and industry collaborations. The DRCR.net priority initiatives include: the opportunity for all retina specialists to be involved at all levels of organization; establishment of community-based and academic-based clinical centers; ownership by investigators at front end (protocol development) and back end (publication and presentation) of clinical research; industry collaboration while maintaining academic integrity; establishment of control of design and operation of trials by the DRCR.net; ownership of data by the DRCR.net; and the ability of the DRCR.net to present and publish data independent of industry (not withstanding protection of intellectual property).

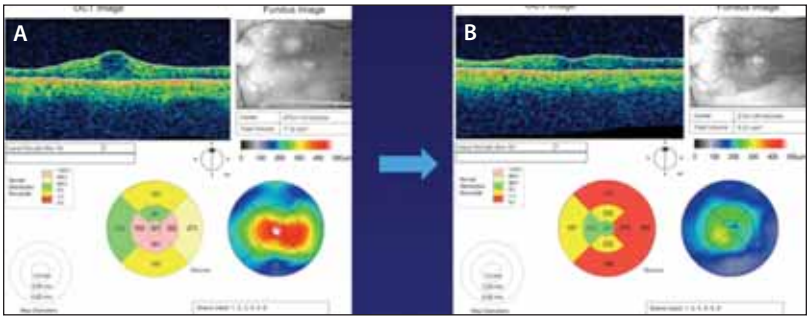

Figure 3. OCT images. The left image shows a thickened macula and the right image shows a flat macula with little to no edema.

As of June 18, 2010, the DRCR.net has 103 active and 203 total research sites (community and academic centers), 66% (68) of which are community-based active centers. There are 300 active investigators (797 total), 862 active personnel (2352 total), and active participation is present in 36 states (47 total) of our country.

NEW PARADIGMS FOR TREATMENT

We are currently in a new era in the treatment of DR, in which we are administering anti-vascular endothelial growth factor (anti-VEGF) agents on a monthly basis into the vitreous. The DRCR.net completed a landmark study, a Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema, the results of which were published in 2010[45] and for which extended follow-up data were published in 2011.[46]

In this DRCR.net trial, Protocol I, 691 patients (854 eyes) were randomly assigned to 1 of 3 experimental treatments for diabetic macular edema (DME), and the results with each were compared to those with the gold standard of focal/grid laser photocoagulation. The 3 experimental arms included 1 using an anti-VEGF agent, ranibizumab (Lucentis, Genentech), injected into the vitreous cavity with prompt laser treatment; 1 using ranibizumab with deferred laser treatment, which was defined as deferring focal/grid laser treatment until such time that the DME may have persisted and was no longer improving; and 1 using intravitreal injection of a corticosteroid, triamcinolone acetonide, in combination with prompt laser treatment. All of these outcomes were compared to a fourth arm, in which sham injection with prompt laser was administered. Laser treatment is associated with a 50% reduction in risk of at least moderate vision loss when compared to no treatment per the results of the ETDRS. In addition, less than 20% of patients will experience moderate gain in visual acuity (improvement of at least 3 lines of acuity) when managed with focal/grid laser as a monotherapy.

In the more recent DRCR.net study the primary outcome was mean change in visual acuity 12 months after initiation of treatment. Figure 10 shows that the standard laser group, after receiving 1 treatment at entry and repeating laser every 3 to 4 months if the edema persisted, gained on average 3 letters (half of 1 line of vision) on the ETDRS eye chart at 12 months. In contrast, patients who were receiving ranibizumab with prompt laser or ranibizumab plus deferred laser gained an average of 9 letters (nearly 2 full lines of vision). In the group assigned to deferred laser two-thirds of these patients did not require any laser through out the 12-month time period. The results for the patients who received corticosteroid plus laser were disappointing in that they did no better than with laser alone.

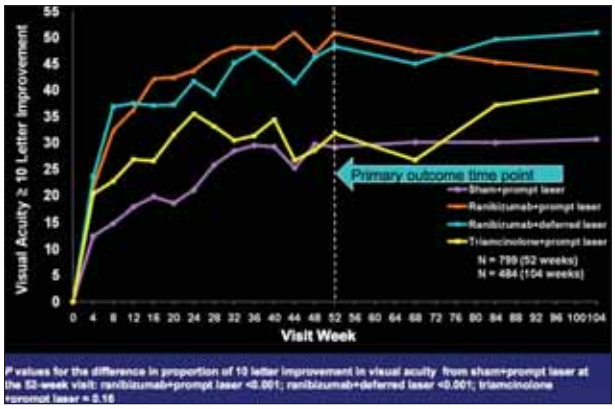

Figure 4. The 12-month results of Protocol I showed that with the use of ranibizumab, 50% achieved this gain in vision, whereas with standard laser, only 25% achieved these gains.

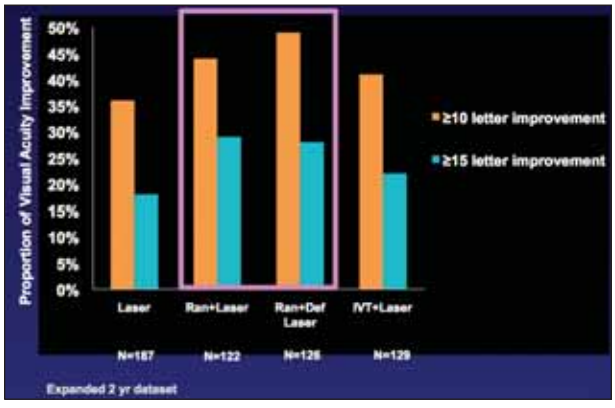

Figure 5. The proportion of patients who continued to improved vision of more that 10 letters with treatment in the ranibizumab plus prompt or deferred laser is higher than the other groups, and is also higher when considering gains of 15 letters or more (3 lines of vision).

What is the importance of monitoring the statistic of or mean change in vision over time? Movement of the mean change in visions tells us that patients on the highest end of the spectrum are increasing in numbers. For example, the proportion of patients who have gained 10 or more letters over a period of time will be greater when the average change in vision, as measured in letters increases in one group vs another. A 10 letter increase (2 lines of acuity) represents a meaningful, or significant change in vision that more likely affects life style: a patient who was 20/50 at baseline has improved to 20/30, and a patient who was 20/100 at baseline has improved to 20/60 or getter. The 12-month results of Protocol I showed that with the use of ranibizumab, 50% achieved this amount of vision increase, whereas with standard laser, only 25% achieved these gains (Figure 4).

Figure 5 shows change in visual acuity at 2 years. The pro-

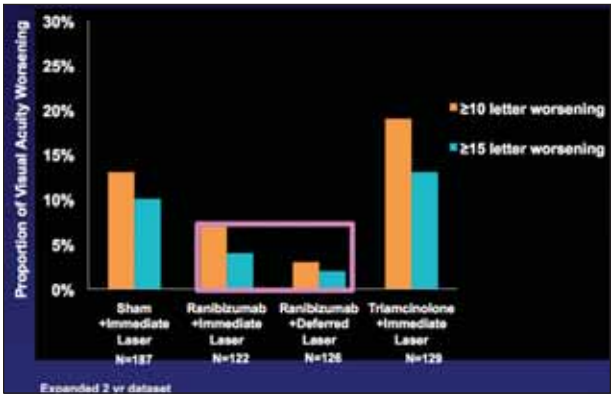

Figure 6. Despite laser treatment, approximately 10%-15% lost vision.

portion of patients who manifest improvement of vision in the ranibizumab plus prompt or deferred laser groups is higher than the other groups, and this is true for improvements of 10 or 15 letters of acuity (3 lines of vision).

It is important to also consider the patients who fared the worst-those who lost vision during the study. Despite laser treatment, approximately 10%-15% lost at least 2 lines of vision (Figure 6). In contrast, less than 5% in either of the ranibizumab groups lost vision, showing that ranibizumab plus prompt or deferred laser is very effective in preventing vision loss from DME.

The hidden pearl in this clinical trial is the possibility that anti-VEGF agents, such as ranibizumab, cannot only address hyperpermeability, but that they may also slow the process of ischemia and angiogenesis. When we looked at the patients treated in the same study, specifically at their general level of retinopathy and assessed progression or regression of that level of retinopathy, we saw a higher proportion of patients that improved their overall retinopathy level, meaning they manifested regression in regard to classification of their precise level of diabetic retinopathy, among the patients in the ranibizumab groups. This behavior was evident across a spectrum of entry levels of DR from mild NPDR thru PDR.

To answer the question of whether anti-VEGF agents can aid in slowing the process of ischemia and angiogenesis, the DRCR.net is embarking on a new trial that will evaluate anti-VEGF agents in the setting of proliferative disease to see if we can avoid using PRP.

CONSIDERATIONS REGARDING INTRAVITREAL INJECTIONS

Is there a downside to administering intravitreal injections of anti-VEGF? Frequent injections are required, often monthly, raising the risk for intraocular infection, or endophthalmitis. In our study, however, the incidence of infection was less than 1%. Retinal detachment is also a risk with intravitreal injection, but again, in our study, the incidence was low. The incidence of elevation in intraocular pressure and cataract was also low in the laser monotherapy and ranibizumab plus laser groups, as compared with the corticosteroids plus laser group, which had higher rates of both of these ocular adverse events. These findings are consistent with what we know about steroids and the increased risk of glaucoma and cataract. We did not see any increased mortality or systemic side effects in this trial, which is always a concern, as we are treating patients who have a larger number of co-morbidities than the general population, particularly with increased cardiovascular issues.

SUMMARY

In summary, intravitreal ranibizumab with prompt or deferred (≥24 weeks) focal/grid laser had superior visual acuity and OCT outcomes compared with focal/grid laser treatment alone for a period of at least 2 years. Approximately 50% of eyes had moderate improvement (≥10 letters) while approximately 30% gained ≥15 letters. Moderate visual acuity loss (≥10 letters) was uncommon, and the results were similar whether focal/grid laser was given starting with the first ranibizumab injection or it was deferred for 24 weeks or more and placed only if DME persisted.

For the first time in 25 years, we have a treatment that supersedes the gold standard of laser, and one with which ophthalmologists are accustomed to because of its widespread use in the neovascular form of age-related macular degeneration. Challenges with this treatment option exist, however. Frequent injections will place a higher burden on retina specialists and their patients, and so research efforts to address this issue are under way.

How can diabetologists and primary care physicians help to improve the eye health of their patients? The obvious answer is to control patients blood glucose levels, blood pressure, and lipid levels, all of which will decrease the number of patients who develop diabetic retinopathy and more severe disease. However, there will be patients who develop eye disease despite the best efforts of their health care providers. For these patients, the most crucial element is appropriate referral to a retinal specialist, who is armed with the highest level of medical training and expertise to treat and follow diabetic retinopathy.

Ophthalmologists can help by investing and participating in the research that is being performed to combat diabetic eye disease, such as the work that is performed by the DRCR.net. The DRCR.net is a success story, with approximately $4.5 million per year contributed by the National Eye Institute and approximately $1 million per year from the NIDDK through at least 2013. Through this

and other generous funding (frequent collaboration with industry groups), the DRCR.net will continue to expand its research efforts to include increasing communication with basic science research to provide a wider platform for translational research; genetic research initiatives; and numerous new protocol ideas and protocols at various stages of development. ■

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