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# Andalusian program for early detection of diabetic retinopathy: implementation and 15-year follow-up of a populationbased screening program in Andalusia, Southern Spain

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ABSTRACT

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Dr Maria Asuncion Martinez-Brocca; masuncion.martinez.sspa@ juntadeandalucia.es **Introduction** Diabetic retinopathy (DR) is a preventable cause of vision loss and blindness worldwide. We aim at analyzing the impact of a population-based screening program of DR using retinal photography with remote reading in terms of population coverage, diagnosis of asymptomatic DR and impact on visual disability, in the region of Andalusia, Spain, in the period 2005–2019. **Research design and methods** Descriptive study. Sociodemographic and clinical features included in the Andalusian program for early detection of diabetic retinopathy (APDR) were analyzed. Population coverage, annual incidence of DR, and DR severity gradation were analyzed. Estimated data on prevalence and incidence of legal blindness due to DR were included.

**Results** 407 762 patients with at least one successful DR examination during the study period were included. Most of the performed retinographies (784 584, 84.3%) were 'non-pathological.' Asymptomatic DR was detected in 52 748 (5.9%) retinographies, most of them (94.2%) being classified as 'mild to moderate non-proliferative DR.' DR was detected in 44 815 patients, while sight-threatening DR (STDR) in 6256 patients; cumulative incidence of DR was 11.0% and STDR was 1.5%, as DR and STDR was detected in 44 815 and 6256 patients, respectively. Annual incidence risk per patient recruitment year progressively decreased from 22.0% by January 2005 to 3.2% by June 2019.

**Conclusions** Implementation of a long-term populationbased screening program for early detection of DR is technically feasible and clinically viable. Thus, after 15 years of existence, the program has enabled the screening of the vast majority of the target population allowing the optimization of healthcare resources and the identification of asymptomatic DR.

# **INTRODUCTION**

The region of Andalusia, which covers an area of  $87597 \text{ km}^2$  in the south of Spain, has a population of 8.4 million (18% of the country's population). The prevalence of diabetes is higher (15.3%) than in the rest of Spain (12.5%), in

# Significance of this study

#### What is already known about this subject?

Diabetic retinopathy (DR) is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. There is strong support for screening to detect DR, as severe forms are asymptomatic and an effective therapy to prevent blindness is available.

#### What are the new findings?

- In a public health system covering a large area of Southern Spain, a population-based screening program using retinal photography with remote reading by experts is technically feasible and clinically viable.
- As a population-based screening program develops, annual incidence risk of DR significantly declines.
- After 15-year follow-up, a robust contribution of a population-based screening program in retinopathyrelated health outcomes is shown.

# How might these results change the focus of research or clinical practice?

The higher incidence rates of asymptomatic DR that are found at the beginning of a population-based screening program within the context of a public healthcare system, should be considered in order to plan human and technological resources and warrant ophthalmological assistance.

close relation to lifestyle and socioeconomic factors.<sup>1</sup> Thus, Andalusia, as well as the rest of Europe, faces a rapid increase in their population with chronic conditions (specifically with diabetes), which puts a high pressure on their public health systems.

The Andalusian Public Health System (APHS) is responsible for the provision of universal healthcare in the region and it comprises a wide network, with two levels of

#### Epidemiology/Health services research

care (1500 primary healthcare and 49 hospitals) based on accessible, high-quality, patient-centered care, in a system with universal coverage and funded by taxes.

Within the Andalusian health policy competences, the 'Comprehensive Healthcare Plan for Diabetes' (CHPD), was developed in 2003 to improve the care provided and to reduce the incidence and impact in the region.<sup>2</sup> It was focused on preventive activities and promoted changes for a healthy lifestyle, organization of healthcare delivery, training of professionals and research. Since then, the CHPD has been updated twice.<sup>34</sup>

Diabetic retinopathy (DR) is the most frequent microvascular complication in people with diabetes, and its prevalence increases with the duration of the disease (overall rate,  $\leq 30\%$ ), with a high risk of severe visual impairment (10% of patients).<sup>5</sup> Thus, 20 years after diagnosis, most patients will have some degree of DR. Diabetes affected an estimated 422 million adults worldwide, with the number expected to rise to 642 million by 2040. Thus, the number of people with DR is expected to be increased.<sup>5-9</sup>

DR meets all required criteria to implement a systematic screening,<sup>10</sup> so early detection and treatment has been claimed as the best strategy for preventing (or delaying) loss of vision.<sup>5 7</sup> However, although detailed examination of the retina by an ophthalmologist is required for an accurate DR diagnosis, this highly resource and timeconsuming process hinders the long-term sustainability of systematic screening programs. To overcome this problem, digital retinography was introduced as a first sorting-level in DR screening programs, achieving high levels of sensitivity, specificity and a positive benefit-cost ratio.<sup>5 8 11</sup> Unfortunately, there are only few examples of population-based early detection screening programs with data assessment coming from long-term follow-up.<sup>6 9 12–19</sup>

Based on all these evidences and recommendations, a program for early detection of DR was incorporated in 2005 into the APHS and within the framework of the CHPD. This paper shows how the Andalusian program for early detection of diabetic retinopathy (APDR) was implemented and its long-term impact between 2005 and 2019. Thus, the aims of this study, based on a long-term follow-up data of the Andalusian population diagnosed with diabetes, were:

- i. to show how the population-based screening program was deployed,
- ii. to study the incidence of DR diagnosed within the framework of the screening program,
- iii. to describe how incidence has changed over time,
- iv. to show the potential of a population-based screening program to lower the burden of visual impairment of the Andalusian population diagnosed with diabetes.

# RESEARCH DESIGN AND METHODS Program description

The APDR targets the entire Andalusian population diagnosed with diabetes susceptible to being screened for DR according to clinical practice guidelines and without a previously known DR.<sup>4–6 20</sup> There were no

additional restrictions on participants' demographics or characteristics.

The screening program is based on two stages: in the first one, digital retinographies are performed to the target population while, in the second one, retinographies that show positive or inconclusive results are transferred through a telematics platform to ophthalmology services for reassessment and patient referral to the ophthalmologist when necessary.

Patients eligible for screening were identified following the diabetes definition and the screening criteria established by the American Diabetes Association.<sup>20</sup> All target population is invited for periodic screening.

To assess the APDR feasibility, mainly in terms of healthcare professionals training, devices provision and outcomes assessment, a pilot project was launched in 2004; it included 360 patients with diabetes, 11 primary care centers, and 6 hospitals centers. After a successful assessment, the program was extended progressively throughout the region.

Currently, the APDR works as follows:

- Patients with diabetes are invited to undergo retinal screening according to national clinical practice guidelines.<sup>21</sup>
- In primary care centers and endocrinology services in hospitals, trained nurses perform retinography, and the results are stored in the patient's electronic health record within the corporate system (Diraya).
- DR screening is performed by assessment of the first retinography by a trained family physician in a primary care center for type 2 diabetes or an endocrinologist in a hospital, usually for type 1 diabetes.
- Patients for whom the results are negative are scheduled for the next examination cycle according to national clinical practice guidelines.<sup>21</sup>
- Retinographies that show positive or inconclusive results are reviewed by an ophthalmologist for reassessment.
- Patients with DR (or any other pathological finding) are referred to an ophthalmology services through the digital platform for examination, confirmation of diagnosis, follow-up, and treatment if necessary.

The screening procedure is carried out by using digital retinographs after pupils are dilated with 1% tropicamide drops (unless contraindication). Three photographs of each fundus are taken, centered on the macula, nasal, and upper temporal fields, respectively.<sup>7 22</sup> Each retinography is transferred and stored in a central served once performed, so healthcare professionals in charge of retinographies grading can access for screening.

# **Quality control**

Blind and randomized samples of retinographies classified as 'normal' were periodically assessed by ophthalmologists specialized in DR as internal auditors. This quality control procedure aims of detecting false negatives and, therefore, to improve overall APDR performance.

# **Technological resources**

Technological resources have increased progressively and distributed through the whole region, since the beginning of the program. Thus, 203 retinographers (including 44 mobile retinography units for covering certain rural areas) are available nowadays.

# **Data sources**

Data on patient population (age, sex, years from diagnosis, type of diabetes, treatment, screening date, and screening result) were obtained from the APDR registry. These data were complemented with those included in the Health Population Data Base (HPDB) of Andalusia (which includes personal and health-related data). For each patient, data from APDR and HPDB are linked thanks to the existence of a unique citizen/patient identifier system within the APHS, that ensures that everyone is correctly identified, treated, and followed up within the system.

Data on Andalusian population were obtained from the Spanish National Statistics Institute (INE) website.<sup>23</sup>

Neither Andalusia nor Spain has implemented corporate registries of disability or legal blindness due to DR. However, the vast majority of Spanish blind people or suffering serious visual impairment are members of the Organización Nacional de Ciegos Españoles (the Spanish National Association for the Blind, ONCE) since they have access to benefits and specialized social services.<sup>24</sup> To be a member, at least one of the following visual requirements must be met: (i) visual acuity ≤0.1 (obtained with the best possible optical correction) and (ii) Visual field reduced to 10 degrees (or less).<sup>25</sup> Thus, ONCE provided the number of its Andalusian members, as well as those members (new and total) diagnosed with diabetes and DR in the region per year.

#### **Study population**

The study includes all patients with diabetes registered in the APDR from January 2005 to June 2019. This group of patients constitutes a dynamic cohort, where individuals can enter (due to diabetes diagnosis) or leave the cohort (eg, when DR is confirmed, abandonment of the program or death of patient). These data come from of a continuous-time process of observations at screening visits. Only data coming from people without DR that had at least one successful DR examination were included.

Given the aim of the program and an overall prevalence of DR  $\leq$ 30%, the target population was estimated in the 70% of the entire diabetic population registered in electronic corporate database. Main characteristics of the studied population are shown in table 1.

#### **Data analysis**

Retinographies with DR signs were graded according to the International Clinical Diabetic Retinopathy Severity Scale.<sup>26</sup> DR was graded in no DR, mild, moderate, or severe non-proliferative DR, and proliferative DR. When 
 Table 1
 Sociodemographic and clinical characteristics of included population

	Mean	SD
Age (years)	62.8	12.8
Years from diagnosis	6.4	6.9
Gender	n	%
Male	222 574	54.6%
Female	185 188	45.4%
Age (years)		
<35	9950	2.4%
35–64	202 032	49.6%
>65	195 780	48.0%
Diabetes type		
Type 1 diabetes	18 250	4.5%
Type 2 diabetes	386 895	94.9%
Others	2617	0.6%
Years from diagnosis		
<5	205 577	50.4%
5–9	101 537	24.9%
10–19	78 934	19.4%
≥20	21 714	5.3%
Drug treatment		
Insulin (only)	26 108	6.4%
Non-insulin treatments	231 674	56.8%
Combination of treatments	38 705	9.5%

severity differences were found in each patient eye, the most severe one was selected.

The finding of any DR grade was considered as positive screening result. Any DR grade equal to or greater than severe non-proliferative DR was classified as sightthreatening diabetic retinopathy (STDR).

Descriptive statistic was used to depict main characteristic of the cohort. Mean value, SD, and CI were used as descriptors.

Incidence was calculated as cumulative incidence by dividing the number of new DR cases by the respective number of people at risk (patients included without a previously known DR). Therefore, these assessments were performed to the cohort as a whole and per cohort subgroups and per year of patient recruitment within the program. In addition, 95% CIs for cumulative incidence rates were also calculated.

All statistical analyses were carried out using the RStudio software V.1.2.1335 (RStudio, Boston, USA).

# RESULTS

# Program coverage

There were 429 791 patients included within the APDR with, at least, one performed test, of which, 16 531

patients without results fully assessed and 413 260 with results: from them, 5498 patients had a previously known and treated DR, and 407 762 people without previously known DR between January 2005 and June 2019. This means a total follow-up of 1 182 211 persons-year and an average of 2.9 years per screening cycle. Main sociodemographic and clinical characteristics of the studied population at the entrance of the APDR are shown in table 1.

The estimated program coverage shows a practically linear growth since the beginning of the program. Assuming that target population would be 70% of Andalusian diabetic population, in 2011, nearly half of the target population of the program (48.9%) was reached. After 3 years, it quickly rose until reaching around 75% and, by the end of 2018, almost 90% of the target population was reached (online supplementary figure S1).

#### Main program results

Within the study period, 888 318 retinographies were performed, so  $2.22\pm1.47$  (mean $\pm$ SD) retinographies per patient were performed. 84.3% retinographies (784 584) were classified as 'non-pathological', 52 315 (5.9%) were not evaluable, and 28 913 (3.3%) showed other findings. Asymptomatic DR (any DR grade) was detected in 52 748 (5.9%) retinographies, the majority of them (94.2%)

To date, none of the quality control samples have been classified as false negative that requires immediate/ urgent treatment were found.

# **Diabetic retinopathy incidence**

DR was detected in 44 815 patients, while STDR in 6256 patients, so cumulative incidence of DR and STDR was 11.0% (95% CI 10.8 to 11.1) and 1.5% (95% CI 1.5 to 1.6), respectively.

DR incidence was slightly higher in men and at younger ages. Moreover, it prevailed in patients with type 1 diabetes. However, it seems that the most important factor is the time from diabetes diagnosis. Thus, DR incidence is four times higher in patients with a known diabetes progression exceed 20 years than in those with less than 5 years of evolution (table 2).

Regardless of the date of inclusion, most DR cases (92%) were detected in the first three examination cycles and, more specifically, 64% of total cases were detected in the first one. Regarding the sequence of retinographies performed in each patient, DR and STDR incidence in the first screening cycle was, at least, twice that in the second one and decreased progressively in subsequent cycles (online supplementary figure S2).

	DR	DR		STDR	
	Incidence	95% CI	Incidence	95% CI	
Gender					
Male	11.39	11.26 to 11.52	1.60	1.55 to 1.65	
Female	10.51	10.37 to 10.65	1.45	1.40 to 1.51	
Age (years)					
<35	12.87	12.22 to 13.55	1.60	1.36 to 1.86	
35–64	11.57	11.43 to 11.71	1.77	1.71 to 1.82	
>65	10.30	10.16 to 10.43	1.29	1.24 to 1.34	
Diabetes type					
Type 1 diabetes	15.04	14.52 to 15.56	2.12	1.91 to 2.33	
Type 2 diabetes	10.82	10.73 to 10.92	1.51	1.47 to 1.55	
Years from diagnosis					
<5	6.47	6.36 to 6.58	0.82	0.78 to 0.86	
5–9	12.14	11.94 to 12.34	1.60	1.52 to 1.68	
10–19	16.94	16.68 to 17.21	2.48	2.38 to 2.60	
≥20	26.79	26.20 to 27.39	4.50	4.23 to 4.78	
Drug treatment of diabetes					
No treatment	9.49	9.32 to 9.67	1.22	1.15 to 1.28	
Insulin (only)	23.84	23.33 to 24.36	3.85	3.62 to 4.09	
Non-insulin treatments	8.14	8.03 to 8.25	1.06	1.02 to 1.10	
Combination of treatments	23.68	23.26 to 24.11	3.73	3.55 to 3.93	

DR, diabetic retinopathy; STDR, Sight-threatening diabetic retinopathy.

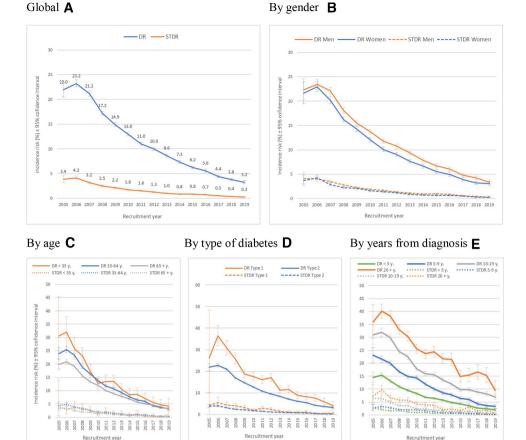


Figure 1 Annual incidence risk of DR and STDR per patient recruitment year in the APDR. Results are expressed as % of total number of patients with diabetes enrolled within APDR. Vertical bars represent the 95% CI. APDR, Andalusian Program for early detection of diabetic retinopathy; DR, diabetic retinopathy; STDR, sight-threatening diabetic retinopathy.

Annual incidence risk per APDR recruitment year also progressively decreased from 22.0% by December 2005 to 3.2% by June 2019 (figure 1A). Slight differences were also found in annual incidence risk of DR by gender, age, type of diabetes and per years from diagnosis (figure 1B–E).

# **Diabetic retinopathy-related legal blindness**

The percentage of new annual ONCE registrations in Andalusia due to DR decreased regarding new annual registrations, from 12.8% in 2004 to 6.1% in 2018. In the same way, the incidence and prevalence of DR among ONCE members per 1000 people with diabetes fell dramatically over the last decade from 20.1 to 4.6 and from 2.5 to 1.5, respectively (figure 2).

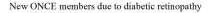
# **CONCLUSION**

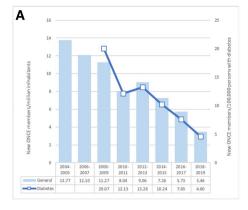
Our work provides the main population-based screening program of Spain in terms of people with diabetes covered (407 762 people with at least one successful DR examination), and the second one in the world, as far as we know, just after NHS Diabetic Eye Screening Program in England.<sup>13</sup> Despite being a regional screening program, the number of people covered and screened in this study is

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far ahead of those shown in other publications that tackle country and regional screening programs.<sup>6</sup> <sup>12</sup> <sup>14</sup> <sup>16–18</sup> <sup>27</sup> <sup>28</sup>

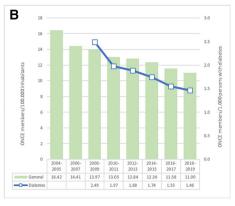
Identification of new cases of DR was concentrated just following the launch of the APDR and in the first screening cycles of each patient; a dramatic lower annual incidence risk of DR was detected at the end of follow-up. This striking pattern could be due to different reasons. First, the main justification for implementing a population-based DR screening program in our region was the evidence of low adherence to periodic retinopathy screening related to insufficient access to ophthalmology services.<sup>2</sup> Thus, implementation of a new DR screening program would make a relevant initial pool of undiagnosed DR emerge. As extension of the program was progressive, this downward trend was maintained along the analyzed period. Second, when years from diagnosis were analyzed, earlier recruitment was progressively achieved and accordingly, less risk of developing DR. Thus, the average elapsed time from diabetes diagnosis to inclusion in APDR was 3 years lower among patients included at the end of the analyzed period in comparison with the ones included at the launch of the program. Finally, better access to medical care and improved educational, pharmacological, and technological resources for diabetic population could also contribute



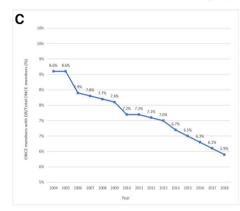


Accumulated ONCE members due to diabetic retinopathy





Andalusian ONCE members due to diabetic retinopathy



**Figure 2** New and accumulated ONCE affiliations cases due to DR in Andalusia (2004–2019). Frequency is calculated according to Andalusian population (general) and to Andalusian diabetic population (Diabetes), respectively. DR, diabetic retinopathy; ONCE, Organización Nacional de Ciegos Españoles, Spanish National Association for the Blind.

to decreased rates of DR in last years. In any case, the higher incidence rates that are found at the beginning of this kind of programs should always be considered when a population-based screening program is implemented within the context of a public healthcare system, in order to plan human and technological resources and warrant ophthalmological assistance.

After 15 years of data collection in Andalusia, main variables associated with the DR incidence were years from diagnosis of diabetes and patient age. This result is consistent with other publications.<sup>14</sup> <sup>15</sup> <sup>17</sup> <sup>29</sup> Most RD cases (95% of screened population) were identified in people with type 2 diabetes, although the probability of RD among type 1 diabetes population is higher than in type 2 diabetes.

DR screening programs worldwide have varied in terms of sample size, demographic of patients, inclusion criteria, follow-up period, type of diabetes and even grading protocols employed, limiting the comparison of results in terms of DR detection.<sup>917</sup> Among the European studies, the main one (in terms of people screened) was carried out by Scanlon. He assessed the results of the English NHS Diabetic Eye Screening Program for DR; in 2015–2016, this program reached a coverage of 82.8%, when 2.14 million people were screened, and a rate of retinopathy was 2807 per 100 000 screened patients was

found.<sup>13</sup> In Italy, a decade of telemedicine program for screening DR in a large metropolitan area of North East of Italy (where 9347 patients with type 1 diabetes and type 2 diabetes were followed from 2005 to 2015) was assessed by Vujosevic et al. In this study, the overall incidence of STDR was 3.1% during the 10-year follow-up.<sup>14</sup> In Portugal, within the context of the 5-year retrospective analysis of the RETINODIAB study (55 496 patients with type 2 diabetes were studied between 2009 and 2014), showed a cumulative incidence of 16.3%; on the other hand, in a study carried out by Ribeiro et al in the Central Region of Portugal following 45 148 patients with type 1 diabetes and type 2 diabetes from 2011 to 2014, higher rates of DR (25.0%) were found.<sup>6</sup><sup>17</sup> These cumulative incidence differences might be mainly due to disparities in the inclusion criteria in each screening programs. Thus, in the work of Ribeiro et al only treatment for 'STDR' was considered exclusion criteria, so other cases of DR would be included.

In Spain, most studies report data from a very limited area and sample size.<sup>16</sup> <sup>29</sup> <sup>30</sup> The cumulative incidence of DR found in the MADIABETES Study (a prospective cohort study where 3443 outpatients with type 2 diabetes, followed up from 2008 to 2011) was 8.1%.<sup>29</sup> On the other hand, the study published by Romero-Aroca *et al* in 2016 (a prospective population-based study carried

out in the north-east of Spain, where 15 396 patients with diabetes, were screened between 2007 and 2014) found a yearly mean incidence value of 8.4% (increasing from 8.1% in 2007 to 8.9% in 2014).<sup>15</sup> They also observed that, although incidence remained stable between 2007 and 2011 (8.1%), it rose to 8.8% in 2012, and remained after that more or less stable (8.9% in 2013 and 8.9% in 2014).<sup>15</sup> These differences might be due to the methods used to detect DR and data analysis and to the regional inequalities in the prevalence of visual impairment and blindness (correlated with concomitant diseases, regional level of economic development, rural environment, ultraviolet light exposure, or gender inequalities, among others).<sup>15</sup> 16 29 30

As well as most screening programs, APDR is not designed to assess neither DR severity nor its progression. Nevertheless, in line with other publications, a first approximation of data comparison can be performed. Thus, most of the performed retinographies (84.3%) were classified as 'non-pathological', reducing the workload of the ophthalmology services. Asymptomatic DR was only detected in 5.9% of retinographies, 94.2% of them being classified as 'mild to moderate non-proliferative DR.' On the other hand, one in seven patients with DR detected (14%) has STDR. These patients are susceptible to immediate treatment, and their referral to ophthalmology services should be prioritized. This issue needs to be considered in the design phase of a population-based screening program to ensure the availability of resources.

In comparison with other studies assessing DR severity within screening DR programs at European level, in the study carried out by Vujosevic in Italy, most patients (86.3%) showed 'mild' or 'moderate' DR.<sup>14</sup> In Portugal, in the RETINODIAB study, only 71.5% of the results were non-pathological, in contrast with the 83.7% obtained in the study performed by Dutra Medeiros et al.<sup>6</sup><sup>17</sup> The MADIABETES study showed that 49.5% of cases were classified as 'non-proliferative DR' and 35.1% as 'proliferative DR'; of those cases classified as 'nonproliferative DR', 88.5% were classified as 'mild' and 11.5% as 'moderate' or 'severe.'<sup>29</sup> In the study published by Romero-Aroca, although most cases were classified as 'mild' or 'moderate' DR, a progressive increase of most severe cases ('severe' and 'proliferative' DR) from 2010 to 2014 was observed.<sup>15</sup> These slight discrepancies might also be due to the aforementioned differences in methods used, as well as the intra/interterritorial differences in the disease pattern.

On the other hand, a positive tendency on ONCE data were also observed. Thus, the reduction on the incidence and prevalence of DR per 1000 ONCE's members with diabetes fell 15.5 and 1 points, respectively, so it can be inferred that the implementation of the APDR has shown clinical effectiveness due to its real impact on the complications in people with diabetes.

The quality and performance of the program has been recognized as good practice by two independent organisms, the Spanish Ministry of Health and the WHO.<sup>31–33</sup>

These recognitions mean that the APDR fulfills all requirements for and is ready to provide the needed information to any healthcare systems that would be interested to implement it. Moreover, new technologies could improve our DR screening strategy and their cost-effectiveness. In addition, emerging evidence suggests that retinal imaging could add the role of DR to other diseases beyond the prevention of sight-threatening disease.<sup>34</sup>

The strengths of our study include the progressive program implementation after an initial feasibility assessment based on a pilot project. Furthermore, the large sample size is one of the main strengths of this study. Moreover, it is the main national population-based screening program in terms of population coverage and the second one worldwide. Therefore, the analyzed sample would be representative of the Andalusian diabetic population. Outcome assessment is based on long-term monitoring, where disease criteria have not been altered.

Conversely, only DR incidence estimations can be calculated, as our results come from clinical practice observation and could lack the robustness of epidemiological studies. As there is a lack of an official database of visual disability due to DR, the real impact of the APDR on prevalence and incidence of visual impairment in diabetic Andalusian population cannot be accurately calculated.

The results of the APDR demonstrate the success of the implementation of a long-term population-base screening program for DR, since the program coverage rose rapidly while incidence of asymptomatic DR progressively decreased. After 15 years of activity, the APDR has enabled the screening of the vast majority of target population, the rapid identification of asymptomatic DR cases in Andalusia, and the optimization of healthcare resources of the Andalusian Public Healthcare System. These results reinforce the need and feasibility of programs focused on early detection of DR in public health systems.

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**Contributors** RR-A and EM undertook the analysis and drafted the manuscript. MA-D, RR, BO, CL and AC worked with MAM-B to process and provide relevant datasets. All authors were involved in scientific discussions and cowriting and editing the final manuscript. MAM-B is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Patient consent for publication Not required.

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Data availability statement Data are available on reasonable request. Deindentified participant data are available on reasonable request at ORCID identifier: https://orcid.org/0000-0001-9740-122X.

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