Definition of indicators of appropriateness in the management of neovascular age-related macular degeneration: An expert opinion

Teresio Avitabile¹, Francesco Boscia², Alessandro Dell’Erba³, Ugo Introini⁴, Paolo Lanzetta⁵, Paolo Locatelli⁶, Federico Ricci⁷, Giovanni Staurenghi⁸, Monica Varano⁹ and Fiorenza Zotti³

Abstract
Wet age-related macular degeneration is a chronic condition culminating, in most cases, in blindness. The introduction of anti-angiogenic agents in 2006 has represented a major breakthrough in the treatment of the disease, but timely and effective treatment with regular follow-up and monitoring is mandatory to stabilize and preserve visual acuity. In clinical practice, however, appropriate therapy provision is frequently challenged by economic and organizational issues that result in suboptimal visual outcomes and increased incidence of legal blindness. International Guidelines have defined a diagnostic and therapeutic pathway to ensure the best practice in wet age-related macular degeneration management, but reference parameters to evaluate and compare the performance of Retina Centers are lacking. To address the appropriateness of wet age-related macular degeneration management in Italy, a multidisciplinary panel of ten experts gathered in three meetings. They defined three sets of indicators and relative benchmark values that each Center should comply with to ensure patients optimal care already from the first access: (a) clinical intervention indicators, to determine the possible Center’s deviation from the diagnostic and therapeutic pathway; (b) outcome indicator, to evaluate the socioeconomic impact of the healthcare systems’ performance; (c) management indicators, to test the size of the gap between the Center’s supply and demand. Once the indicators have been analyzed, healthcare systems can plan actions to improve appropriateness and monitor their effects. However, to put this in practice, a concerted effort by all parts involved in healthcare provision is required, together with adequate systems to analyze clinical and administrative documentation.

Keywords
Appropriateness, clinical practice, indicator, wet age-related macular degeneration, diagnostic-therapeutic pathway, vascular endothelial growth factor inhibitors

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¹G. Rodolico Eye Clinic, University of Catania, Catania, Italy
²Department of Surgical, Microsurgical and Medical Sciences, University of Sassari, Sassari, Italy
³Interdisciplinary Department of Medicine, Section of Legal Medicine, University of Bari, Bari, Italy
⁴Department of Ophthalmology, San Raffaele Scientific Institute, Vita-Salute University, Milan, Italy
⁵Department of Medicine—Ophthalmology, University of Udine, Udine, Italy
⁶Department of Management, Economics and Industrial Engineering, Politecnico di Milano, Milan, Italy
⁷UNIT Retinal Diseases, Policlinico Tor Vergata, University Tor Vergata, Rome, Italy
⁸Ophthalmology Clinic, Department of Biomedical and Clinical Sciences “Luigi Sacco,” Luigi Sacco Hospital, University of Milan, Milan, Italy
⁹IRCCS G.B. Bietti Foundation, Rome, Italy

Corresponding author:
Monica Varano, IRCCS G.B. Bietti Foundation, via Livenza, 3, 00198 Rome, Italy.
Email: monica.varano@fondazionebietti.it
**Introduction**

Age-related macular degeneration (AMD), a chronic and progressive condition that leads to vision loss, represents one of the main causes of legal blindness among the elderly worldwide. As blindness is associated with a considerable socioeconomic burden in terms of morbidity, poor quality of life, and high costs sustained by patients, caregivers, and healthcare systems, provision of high-quality care for subjects affected by AMD is of paramount importance.

In Europe, Italy displays the highest pooled prevalence of AMD in subjects over the age of 60 (52.2% vs 26.3%), and a pooled prevalence of wet age-related macular degeneration (wAMD) equal to 1.3%. Albeit the numbers of people suffering from AMD are expected to rise in the next two decades due to population aging, a decreasing prevalence of AMD has been recorded in Europe over the past 20 years, with an improvement in visual acuity (VA) in subjects affected by choroidal neovascularization after 2006. The main reasons for this likely rely on healthier lifestyles and on the implementation of anti–vascular endothelial growth factor (VEGF) agents in the treatment of patients with wAMD, which accounts for the majority of macular degeneration–related blindness. Indeed, landmark clinical trials showed that, following intravitreal injections (IVIs) of anti-angiogenic drugs, VA (defined as loss of less than 15 ETDRS letters from baseline to 24 months) was preserved in more than 90% of patients and improved (defined as gain ≥15 ETDRS letters) in 30%–40%. Based on these data, anti-VEGF therapy has become the mainstay of wAMD treatment, and the disease is now considered a chronic condition with a better prognosis.

In clinical practice, however, the initial improvement in visual outcomes induced by anti-VEGF therapy is not maintained over time. Although patient characteristics contribute to the discrepancy between data from randomized clinical trials (RCTs) and real-world studies, the main determinants are economic and organizational issues. In fact, the increasing number of subjects affected by wAMD, together with the therapeutic burden imposed by the use of anti-angiogenic drugs, have to face limited resources in terms, for instance, of diagnostic instrumentalations, spaces where to perform monitoring visits and injections, healthcare personnel, and allocated budgets. These barriers hamper appropriate treatment provision that results in suboptimal visual outcomes and increased incidence of legal blindness.

In this complex setting, implementing the diagnostic and therapeutic pathway (DTP) established by International Guidelines sets the basis to attain the best practice in wAMD management. Still, to fully accomplish this goal, it is crucial to carefully measure and compare the performance of Retina Centers administering anti-VEGF therapy. Such evaluation needs reference parameters that, altogether, would represent the benchmark of an efficient therapeutic performance. Prerequisite for this type of monitoring is the identification of adequate outcome measures: although efforts have been made to define and evaluate indicators different from VA measures to assess the quality of services, more work is needed.

Between July and November 2018, ten Italian experts from different disciplines gathered in three meetings to thoroughly discuss the available evidence on the clinical-organizational-economical aspects of anti-VEGF therapy and share their experience. Aim of the venture was to address appropriateness in the management of wAMD in Italy, and to define a minimum set of indicators, covering the key areas of disease management, that each Center should comply with to ensure patients optimal care already from the time of the first access.

The Panel was composed of seven ophthalmologists from seven Italian Centers, who defined the clinical indicators of appropriateness of the DTP, their benchmark values, and treatment outcome indicator, through both clinical trials and real-world evidence; two experts in risk management and legal medicine, who supervised the work and provided the applicability of the indicators in the DTP for patients with wAMD; one expert in health innovation management, who provided indications about management indicators useful to payors. The present document reports the points for which the experts reached full agreement.

**Anti-VEGF therapy regimens**

Currently, the anti-VEGF therapies available in Italy for wAMD are bevacizumab, ranibizumab, and aflibercept. All anti-VEGF treatments start with a loading dose of three consecutive injections (one every 4/5 weeks), followed by a maintenance phase during which IVIs are administered according to one of the following regimens: Pro Re Nata (PRN), Treat and Extend (T&E), or fixed retreatment regimen. Supplemental Appendix A summarizes the Standard Operating Procedure of each regimen, and Table 1 summarizes their main features, advantages, and disadvantages. PRN is the only reactive regimen, meaning that the ophthalmologist performs IVI only during active disease and decides whether to proceed with treatment at each visit. In contrast, IVIs are administered on the same day of the monitoring visit independent of disease activity in the T&E regimen, and at regular intervals (monthly or bimonthly) in the fixed retreatment regimen. Notably, in the first year, personalized and bimonthly regimens applied in clinical trials demonstrated their effectiveness on VA and its maintenance as per the monthly regimen.

**Expert opinion**

Starting from the DTP of wAMD patients, the expert panel defined three sets of indicators deemed as useful, in the discussion between ophthalmologists, healthcare
institutions and payors, to evaluate the quality of services supplied by Retina Centers in daily practice, to objectively compare Centers’ performance, and to plan actions of appropriateness improvement. The modalities (in terms of deadlines and datasets) for measuring the indicators are also provided.

**Definition of three sets of indicators of appropriateness**

**Clinical intervention indicators.** The clinical indicators and relative benchmark values proposed to assess whether Retina Centers are delivering appropriate healthcare services in the setting of wAMD are listed in Table 2.

- **Time to diagnosis**
- **Time from diagnosis to treatment**

According to the Panel, patients with wAMD should receive a diagnosis by the ophthalmologist on the same day of the first access to the Retina Center and anti-VEGF therapy should begin on the same day of diagnosis. A total of 15 days are the maximum accepted tolerance delay from diagnosis to the first treatment.

The time from symptom onset to diagnosis determines whether an early diagnosis is made. Early diagnosis is the most important prognostic factor of therapeutic success, as demonstrated by both post hoc analyses of clinical trials and retrospective observational studies. Notably, a recent multinational survey–based study unveiled a common lack of awareness on eye health and the impact of a delayed diagnosis among patients and caregivers, which may hinder prompt symptom recognition and, therefore, early diagnosis formulation.

The time elapsed between diagnosis and the first injection is a further determinant of vision preservation or improvement, as early treatment protects the neurosensory structures that are not yet irreversibly compromised. Accordingly, delaying the start of anti-angiogenic therapy results in poorer outcomes. The choice of the Panel to recommend a maximum of 15-day delay as the maximum accepted tolerance delay from diagnosis to the first treatment (i.e. the interval usually reported in clinical trials) derives from practical considerations linked to the importance of ensuring prompt treatment start.

Albeit ophthalmologists cannot be considered responsible for the time elapsed between symptom onset and the first visit to the Center, except in terms of informing patients on symptoms, they are responsible for guaranteeing the prompt start of appropriate treatment for patients diagnosed with wAMD. To speed the access of patients

### Table 1. Comparison of the three regimens most frequently employed for the administration of intravitreal anti-VEGF therapy.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Regimen</th>
<th>Treat and Extend (T&amp;E)</th>
<th>Fixed retreatment schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of approach</td>
<td>Pro Re Nata (PRN)</td>
<td>Proactive</td>
<td>Proactive</td>
</tr>
<tr>
<td>Monitoring visit</td>
<td>Reactive</td>
<td>The intervals between visits depend on the visit result and progressively increase</td>
<td>At regular intervals</td>
</tr>
<tr>
<td></td>
<td>Monthly</td>
<td>(up to 12 weeks); a delay is not allowed</td>
<td>(monthly or bimonthly)</td>
</tr>
<tr>
<td>Injection administration</td>
<td>Only during active</td>
<td>On the same day of the monitoring visit; independent of disease activity</td>
<td>At regular intervals</td>
</tr>
<tr>
<td></td>
<td>disease, decided every</td>
<td>Establish an individual patient’s optimal treatment interval to avoid recurrence</td>
<td>(monthly or bimonthly)</td>
</tr>
<tr>
<td></td>
<td>time by the ophthalmologist</td>
<td>of disease activity</td>
<td>Possibility to plan visits and IVIs</td>
</tr>
<tr>
<td>Advantages</td>
<td>Lowest number of IVIs</td>
<td>Reduced number of visits and injections versus the monthly regimen</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower burden for the patient</td>
<td></td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Not to miss recurrence, monthly visits are still required; a delay may affect visual outcomes</td>
<td>Requires a one-stop clinic allowing for the same day visits and injections</td>
<td>Does not account for the high inter-variability of treatment need (frequent undertreatment in those with high need and overtreatment in those with low need)</td>
</tr>
</tbody>
</table>

**VEGF:** vascular endothelial growth factor; **IVIs:** intravitreal injections.
to visits, diagnostic tests, and therapy, physicians should deal also with organizational appropriateness.38

c) Time between injections during the loading phase
d) Average number of injections/treatment-naive eye/first year

The Panel agreed that a loading dose of three consecutive injections every 4 weeks (q4w) should be adopted. One week per injection (5 weeks) is the maximum accepted tolerance delay during this phase. An average of total seven injections during the first year is the benchmark agreed by the Panel.

It is crucial to achieve VA improvement, as demonstrated by the significant difference in VA outcomes reported between patients with wAMD who received a correct loading phase and those who did not.39–43 Real-life data have shown that also the timing between injections during the initial treating phase is critical. Unfortunately, in this setting, IVIs are frequently delayed because of the therapeutic burden imposed on physicians, healthcare systems, patients, and caregivers.

In daily practice, visual outcomes are often suboptimal, and this may depend on the average number of injections given in the first year and in subsequent years.44–47 Indeed, while the mean number of anti-VEGF injections administered in clinical trials in the first year is seven to eight depending on the treatment regimen,21,22,27 it is lower in the real-world setting (mean=5.0).39 Importantly, when the number of injections performed is comparable with those reported in clinical trials, VA gains improve and are maintained over time.48–51 A retrospective study following eyes for 2 years showed that those starting treatment between 2007 and 2012 received an increasing number of injections (from 9.7 in 2007 to 14.2 in 2012), and this was paralleled by improved VA gains.48 In the multinational, retrospective study AURA, the number of injections emerged as a significant prognostic factor for vision maintenance or gain: patients receiving >7 injections in year 1 or >14 injections over 2 years gained more letters and obtained a better stability of VA (loss of <15 letters) than patients who received <5 or 5–7 injections in year 1 or <10 or 10–14 injections over 2 years.45 Moreover, a recent meta-analysis of ~26,360 patients from 42 real-world observational studies employing different treatment regimens demonstrated that the frequency of injections may determine the extent to which visual gains are maintained in the long term.46

Overall, available evidence points at undertreatment as the main reason for poor therapeutic success both in the loading and in the maintenance phase.15,16 In the experts’ opinion, seven injections represent the pragmatic limit for a visual outcome comparable with that reported in the landmark clinical trials; in case of off-label bevacizumab, it was non-inferior to monthly ranibizumab in inducing VA change at 1 year only when administered monthly.21

e) Time between monitoring visits and injections in individualized treatment regimens

The Panel strongly advised to perform visits and injections on the same day regardless of the treatment regimen. A 1-week delay between monitoring visit and injection is the maximum accepted tolerance.

The Panel has thoroughly revised the treatment regimens described in the literature (Supplemental Appendix A and Table 1)10,21–27 In the reactive PRN regimen, as therapy is discontinued in case of inactive disease and restarted only if recurrence occurs,21,22 any delay between detection and retreatment may affect the visual outcome. Although several authors believe that only a monthly monitoring can adequately identify recurrence, especially during the first year,15,18,52,53 in the Panel’s opinion, based on the findings from the SUSTAIN study,54 this type of regimen implies an intrinsic delay in the identification of disease activity, for example, if during a monitoring visit disease is inactive but recurrence occurs during the following week, it will be detected only after three more weeks.

In contrast, in the proactive T&E and fixed retreatment regimens, despite a different approach, a delay may not be allowed.17,55 In the T&E regimen, the ophthalmologist establishes the interval between each injection rather than

<table>
<thead>
<tr>
<th>Clinical indicator</th>
<th>Reference value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to diagnosis</td>
<td>Diagnosis should be made on the same day of the first visit at the Retina Center</td>
</tr>
<tr>
<td>Time from diagnosis to treatment</td>
<td>Treatment should start on the same day of diagnosis and in any case within 15 days</td>
</tr>
<tr>
<td>Average number of injections/treatment-naive eye/first year</td>
<td>7</td>
</tr>
<tr>
<td>Time between monitoring visits and injections in individualized treatment regimensa</td>
<td>Same day/1 week</td>
</tr>
</tbody>
</table>

**wAMD:** wet age-related macular degeneration.

aSee the standard operation procedure of each regimen (Supplemental Appendix A).
deciding whether to inject or not. The goal of the T&E regimen is to plan an individual patient’s optimal treatment interval to avoid disease recurrence. Although IVI should be administered on the same day of the monitoring visit independent of disease activity, the strict application of T&E scheme in clinical practice is challenged by poor patient compliance (in terms of possible missed visit) and by the decision not to administer therapy. 

In order to ensure the best visual outcome, the Panel strongly advised to administer anti-VEGF therapy on the same day of the visit.

As wAMD requires a chronic treatment, the long-term impact of the time between monitoring visits and injections on visual outcomes must be carefully evaluated at the time of therapy choice based on the organizational capacity of the Retina Center.

**Outcome indicator.** The Panel advised to assess the mean variation in VA impairment based on the International Classification of Diseases, 11th Revision (ICD-11) of patients on treatment once a year (Table 3). The lack of variation or the improvement of VA class are considered the result of an appropriate DTP.

This indicator provides information on the outcome of treatment and is considered critical by clinicians, health institutions, and payors to measure the socioeconomic impact of the healthcare systems’ performance.

Besides justifying the investments made to optimize disease management, the outcome indicator determines the value (following a value-based approach) in terms of a lower socioeconomical burden for wAMD patients and for society.

It is not possible to provide a benchmark value for this indicator: achieving even only stable visual impairment can be considered useful not to increase the related economic and social burden. This may depend on the fact that the outcome indicator is less reliable than clinical intervention indicators, as it is influenced by other factors external to healthcare, such as genetics, environment, and the socioeconomic status.

In the setting of wAMD, the variability of anti-VEGF treatment response is related to the neovascular lesion features at diagnosis; moreover, the characteristics of the patients referred to Retina Centers may significantly differ from those of subjects included in RCTs. Still, assessment of some validated prognostic factors, including VA, age, and the size of lesion, may help physicians to establish the treatment benefit for each single patient.

**Management indicators.** According to the Panel, the operational capacity of each Retina Center to take over the management of patients for a DTP can be defined using the following indicators:

(a) Number of visits per patient (and per caregiver);
(b) Total time spent by the patient and his or her caregiver in the healthcare facility at each visit and/or treatment;

### Table 3. Stages of visual acuity impairment based on the ICD-11 classification.

<table>
<thead>
<tr>
<th>20ft</th>
<th>VA impairment stage based on the ICD-11 classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decimal</td>
</tr>
<tr>
<td>NPL</td>
<td></td>
</tr>
<tr>
<td>20/630</td>
<td>1/30</td>
</tr>
<tr>
<td>20/500</td>
<td>1/25</td>
</tr>
<tr>
<td>20/400</td>
<td>1/20</td>
</tr>
<tr>
<td>20/320</td>
<td>0.6/10</td>
</tr>
<tr>
<td>20/250</td>
<td>0.8/10</td>
</tr>
<tr>
<td>20/200</td>
<td>1/10</td>
</tr>
<tr>
<td>20/160</td>
<td>1.25/10</td>
</tr>
<tr>
<td>20/125</td>
<td>1.60/10</td>
</tr>
<tr>
<td>20/100</td>
<td>2/10</td>
</tr>
<tr>
<td>20/80</td>
<td>2.5/10</td>
</tr>
<tr>
<td>20/63</td>
<td>3/10</td>
</tr>
<tr>
<td>20/50</td>
<td>4/10</td>
</tr>
<tr>
<td>20/40</td>
<td>5/10</td>
</tr>
<tr>
<td>20/32</td>
<td>6/10</td>
</tr>
<tr>
<td>20/25</td>
<td>8/10</td>
</tr>
<tr>
<td>20/20</td>
<td>10/10</td>
</tr>
</tbody>
</table>

ICD-11: International Classification of Diseases, 11th Revision; VA: visual acuity; NPL: no perception of light; LogMAR: logarithm of the minimum angle of resolution.
See also http://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment.
(c) Number and type of available diagnostic tools, including imaging tools and charts for the assessment of VA;

(d) Time spent to perform each visual examination (also called “machine time”);

(e) Waiting time for the first visit (diagnosis);

(f) Waiting time to receive the first treatment;

(g) Waiting time for monitoring visit;

(h) Waiting time for treatments during maintenance therapy;

(i) Number of total injections delivered per year.

The increase in health needs and organizational problems related to the DTP has caused a gap between healthcare supply and demand: assessing the management indicators helps to determine the size of this gap. To reduce it, the organization where the DTP is applied has to be measured to possibly increase the Center’s capacity in terms of improvement in management processes, organization, and healthcare supply. From the payors’ point of view, it is important to clarify whether the costs sustained for wAMD management are adequate to ensure appropriate execution of the DTP and optimal patients’ outcome. A careful analysis of indirect costs associated with the time spent in non-value-added activities, such as double imputation of data, research for missing information, and periodic opening/closing of medical records, is necessary to provide dedicated personnel to adapt each Center’s administrative system.

The indicators of management may affect the indicators of clinical appropriateness: for instance, if a Center is asked to improve its performance to reduce the waiting time, it can increase the number of services supplied. In case this exceeds the operative capacity of the Center, and without a corrective action, the clinical appropriateness decreases. Therefore, when focusing on these indicators, the impact of each intervention must be considered, keeping in mind that the main goal is to preserve the therapeutic appropriateness.

Finally, management indicators can help reduce the time spent by patients and caregivers in the Retina Center, thus affecting indirect costs such as the loss of the caregiver’s productivity.

**Measuring the indicators: definition of deadlines and datasets**

The Panel recommends assessing all indicators annually and carrying out the analyses using health and administrative documentation through the collaboration among clinicians, healthcare providers, and payors (Figure 1).

Electronic medical records should be regularly updated, as they are fundamental to measure all the clinical indicators and the outcome indicator as well. As for the management indicators, data may be extrapolated from administrative documentation either already existing or to be arranged, to define the specific resources necessary to implement the DTP.

**Discussion**

Although the DTP for wAMD patients is well established, understanding if and how Retina Centers are able to provide adequate care remains an urgent unmet need in clinical practice. To objectively measure the quality of the services supplied, a panel of experts in ophthalmology, risk management, legal medicine, and health management identified three sets of measurable indicators (i.e. of clinical interventions, outcome, and management). To the best of our knowledge, this is the first attempt of providing a minimum set of appropriateness measures in Italy.

Clinical intervention indicators are required to determine the possible Center’s deviation from the DTP, the outcome indicator to evaluate the socioeconomic impact of the healthcare systems’ performance and the management indicators to test the size of the gap between the Center’s supply and demand. Once the indicators have been analyzed, healthcare systems can plan actions to improve appropriateness and monitor their effects. In fact, when a considerable socioeconomic burden comes to play, as in the case of wAMD, healthcare systems have to continuously work on clinical appropriateness and organizational models. In wAMD, similar to other chronic diseases, treatment has to guarantee patients the best possible quality of life and independence in daily activities: when this happens, both healthcare and socioeconomic costs (e.g. productivity loss, direct and indirect medical costs, and disability insurance awards) decrease.

Besides measuring the quality of services, the proposed indicators will allow to collect epidemiological data from each Retina Center that, in turn, will help to precisely define the health demand; alternatively, this information
may be obtained using the waiting lists for treatments (where available), after filtering the effects related to the re-direction of patients to other Centers. Given the expected increase in wAMD incidence, obtaining epidemiological data from each Center may help to adapt each organizational model to the structure, size, attending patient population, and specific limitations of the service. It is unlikely that one single model will be suitable for every Retina Center, but a number of possible approaches to patient processing have been proposed to improve quality, effectiveness, and productivity. In a linear clinic model, patients are moved sequentially on a pre-set order among rooms dedicated to a single purpose, with tasks carried out by a specific staff member. This conventional model presents some limitations: in particular, when patients are moved in series, a backlog at any single area causes throughput jam at other steps in the chain. Alternatively, wAMD patients can be moved through clinic processes in parallel, with each other using multifunctional rooms (for examination, testing, and IVI) and teams of professionals dedicated to each step of the patient’s pathway. Non-consultant staff, such as nurse practitioners and optometrists, exert key roles, contributing to maximize the Center’s capacity and maintain adequate patients’ follow-up. A one-stop clinic service with expanded roles for non-consultant clinical staff has been tested in South England, Gloucestershire. This clinic allows new patients to be triaged to the appropriate service based on initial assessments, thus optimizing the ophthalmologist’s time. In addition, the involvement of nurses in the photographic review clinic evaluation for patients in follow-up helps to relieve the substantial clinical workload associated with large numbers of returning patients.

This study has some limitations: first, no systematic literature review was performed; second, no new therapies have been considered that may change the indicators of clinical appropriateness and require leaner organizational models and less resources to achieve similar health outcomes. On the other hand, the Panel revised the most recent evidence on appropriate wAMD treatment in clinical practice, and panelists participating in this venture had distinct expertise, to cover all the main aspects of healthcare provision in wAMD.

**Conclusion**

The present document, with the proposed indicators and related benchmark values, is intended to be a practical tool to measure the performance of Retina Centers. Evaluating appropriateness is useful to identify the barriers limiting patients’ access to treatment, compare the performance of Retina Centers, and optimize the utilization of resources, such as instrumentation and personnel, allocated by payors. However, for this to happen, each Center has to make efforts to regularly monitor both clinical and organizational appropriateness. Importantly, the complexity of the interventions required to improve the organizational model where the DTP is executed cannot overlook the collaborations of all the parts involved in healthcare provision, nor the development of adequate systems to analyze patient data (collected in electronic medical records) and administrative documentation.

**Authors’ note**

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**ORCID iDs**

Paolo Lanzetta https://orcid.org/0000-0003-3746-141X

Paolo Locatelli https://orcid.org/0000-0002-8742-5698

Monica Varano https://orcid.org/0000-0002-6530-1563

**Supplemental Material**

Supplemental material for this article is available online.

**References**


