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# I-Maculaweb: A Tool to Support Data Reuse in Ophthalmology

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**ABSTRACT** This paper intends to present a Web-based application to collect and manage clinical data and clinical trials together in a unique tool. I-maculaweb is a user-friendly Web-application designed to manage, share, and analyze clinical data from patients affected by degenerative and vascular diseases of the macula. The unique and innovative scientific and technological elements of this project are the integration with individual and population data, relevant for degenerative and vascular diseases of the macula. Clinical records can also be extracted for statistical purposes and used for clinical decision support systems. I-maculaweb is based on an existing multilevel and multiscale data management model, which includes general principles that are suitable for several different clinical domains. The database structure has been specifically built to respect laterality, a key aspect in ophthalmology. Users can add and manage patient records, follow-up visits, treatment, diagnoses, and clinical history. There are two different modalities to extract records: one for the patient's own center, in which personal details are shown and the other for statistical purposes, where all center's anonymized data are visible. The Web-platform allows effective management, sharing, and reuse of information within primary care and clinical research. Clear and precise clinical data will improve understanding of real-life management of degenerative and vascular diseases of the macula as well as increasing precise epidemiologic and statistical data. Furthermore, this Web-based application can be easily employed as an electronic clinical research file in clinical studies.

**INDEX TERMS** Macula diseases, Web based clinical data collection for reuse, multi-level and multi-scale data management model.

## I. INTRODUCTION

Electronic Health Records (EHR) play an important role in the improvement of data collection and healthcare efficiency [1]. Some papers on Evidence-Based Medicine recognize the value of a data set to guide clinical decision-making [1], [2].

EHRs offer significant advantages to patients as well. By facilitating storage, retrieval and communication between different healthcare providers, patients do not need to look after their own information and possible mistakes can be avoided when receiving care from different physicians [3]. However, due to the large amounts of heterogeneous information stored (i.e. laboratory values, text-based documents, demographics, and medications), EHRs can be difficult to search and relevant patient information hard to retrieve [4]. Finding a solution to overcome this issue is complex, particularly since it is difficult to obtain the right balance between easy access and the amount of information stored [4].

Degenerative and vascular diseases of the retina are the main causes of legal blindness in industrialized countries (Europe, US, Asia). The incidence in the population has increased steadily over the years as a consequence of ageing and the increased prevalence of systemic diseases

(e.g. diabetes and hypertension). For example: an estimated 20 – 25 million people worldwide currently have Age-related Macular Degeneration (AMD) and this number is expected to increase as a result of aging of the population and increased life expectancy [5]. Diabetes mellitus is the most common endocrine disease in developed countries, with prevalence estimates ranging between 2% to 5% of the world's population [6]. Diabetic Macular Edema (DME) is another important cause of severe deterioration of visual acuity. It has been estimated that in the US in 2010, about 740.000 people had DME [7].

The recent introduction of new treatment modalities, i.e. anti-vegf drugs, has significantly decreased the rate of legal blindness due to macular pathologies [8]. However due to the transient effect of these new drugs, patients need to be monitored on a monthly-basis and treated as needed through complex longitudinal follow-up programs. It has been previously reported that the level of benefit of such treatment seen in randomized trials has not been achieved using either a monthly-based follow-up or a treat-and-extend strategy [9]. Within this complicated scenario, systems and software applications are needed to correctly store, manage, and analyze the large amount of heterogeneous data. Moreover, routinely collected data about treatments could provide new evidence about the efficiency of clinical trial results and real-life clinical outcomes. Such systems and software applications should: allow easy access to complete patient information to help the ophthalmologist in the decision-making process; implement a user-friendly interface, which intuitively allows performing complex tasks such as data extraction and statistical analysis. Furthermore, these applications should involve end-users in all phases of the software life cycle; permit data sharing and integration between different levels of medical care as well as national and international institutions, to stimulate collaborations and favor public health policies on macular diseases.

The benefits of the integration between different levels of medical care and clinical research have already been shown [10] and many workgroups are focusing their strengths on achieving this objective [11]. However, vendors of electronic medical/health record systems are so far, still not working in the same direction. Consequently, a wide integration of administration and routine care information systems with those used for clinical research is not yet possible.

Bibliographic research reveals that the more frequently used EHR tools in ophthalmology do not offer the possibility for a fine-tuned interface and for smart data extraction in external statistical studies [12]–[15].

Therefore, particularly in the academic community where financial resources are lacking, physicians have to adopt craft-made or open source solutions (eg, OpenClinica [16], OpenCDMS [17], REDCap [18]) to manage data in clinical trials. Furthermore, to fulfil clinical trial protocol requirements, repetitive and time consuming manual data copy operations are generated, with increased possibilities of introducing errors [19]–[21]. In clinical trials the use of longitudinal follow-up is increasing [22], with new and more advanced statistical methodologies needed.

Furthermore, in ophthalmology, the inclusion of paired-eye data in prospective studies complicates multilevel structuring of data and its analysis; this complexity should be identified and considered before the study [22].

One of the main issues in implementing an EHR system in ophthalmology is the representation of medical concepts [3]. Often, customised solutions are used that refer to inconsistent terminologies, which make it difficult to compare data coming from different sites and for physicians to interpret stored data [3]. Therefore, the use of standard terminologies to describe the different events is an essential component of an efficient and coherent system. The International Classification of Diseases 9$^{th}$ Revision [23] and Logical Observation Identifiers, Names and Codes [24], which provides universal names and codes for laboratory and clinical observations, can be used to achieve this goal [3].

Concerning the means of delivering the system, web-based solutions are increasingly used [25], [26]. In fact, once in possession of the view rights and credentials, it allows quick access to information from anywhere only requiring an internet connection and a computer; moreover, it is not necessary to install any software only a web browser to go online [10], [27].

This paper intends to present I-maculaweb, a web-based platform to collect and manage data in a routine clinical practice as well as integrating it with data from clinical research in an Ophthalmology domain. In particular, it focuses on patients affected by degenerative and vascular diseases of the macula. The platform, via state-of-the-art technological methods, brings a novel perspective to ophthalmology by combining individual patients and population data relevant for degenerative and vascular diseases of the macula. Furthermore, stored data can be extracted for statistical purposes and used for clinical decision support systems. The platform is available for different simultaneous multicenter Clinical Trials. The proposed system takes into account personal medical data accumulated over time in order to develop a Clinical Decision Support System. Moreover, the inclusion of standardization procedures offers a stable quality of data over time.

## II. CLINICAL DATA

Most of the clinical data, collected during ophthalmological visits, comprised phenotypic characterization of the patients (signs and symptoms), including records of in vivo images, or data concerning administration of therapeutics and nutrition/exposure to environmental factors. Data were also linked to computer models of personalized algorithms for drug administration, physiology, functional disorders and other diseases.

Numerical values are used to quantify visual acuity as well as the thickness of the retina. Early Treatment Diabetic Retinopathy Study (ETDRS) charts have been employed in many clinical trials and is accepted worldwide as the

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gold Standard for accurate and standardized methodology to measure visual acuity [28]. Optical Coherence Tomography (OCT) is used to obtain detailed B-scan images and to quantify the thickness of the central part of the retina (macula). OCT is considered a mandatory step in the evaluation and follow-up of degenerative and vascular diseases of the macula. In addition to OCT, ophthalmoscopy and retinal angiography were also employed to obtain images of the retina, so that objective values could be observed and changes over time, evaluated.

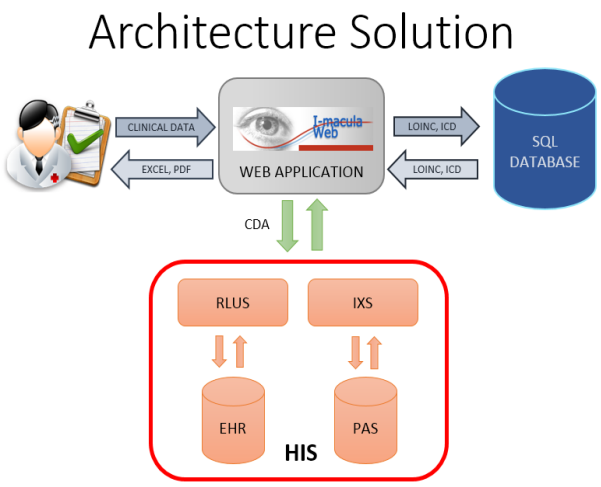


**FIGURE 1.** **Architecture solution.**

## III. METHODS

### A. ARCHITECTURE SOLUTION

Many aspects were considered for the choice of the architecture solution. After continuous interaction with the users and considering the positive features described above [10], a web based Database interaction system was used. In "Fig. 1", the architecture solution, the web-application relies on a SQL database where data are stored and retrieved through standard terminologies and users (i.e. ophthalmologist) can enter, access and retrieve information on the web as well as saving reports in Microsoft Excel and PDF formats. The figure also shows the way in which the proposed solution was integrated with the Hospital Information System (HIS), in particular with the Electronic Health Record (EHR) and the Patient Administration System (PAS). Some authors were involved in the design and implementation of a standardized infrastructure that was able to completely support interoperability for the HIS of the care facility involved in the proposed solution. The standardized infrastructure was based on the Service Oriented Architecture (SOA) paradigm to support technical interoperability and it exchanged HL7 Version 3 (v3) Clinical Document Architecture (CDA) Release 2 (R2) [29] objects combined with standardized vocabularies to ensure semantic interoperability. Finally, its web service interfaces were compliant to Healthcare Services Specification Project (HSSP) [30] standards (Retrieve, Locate and Update Services (RLUS) Release 1 [31], [32] and Identification and Cross-Reference Service (IXS) Release 1 [33], [34]) to provide process interoperability [35]–[37]. This infrastructure provided access to the content of the EHR and PAS of the same hospital for other similar research purposes [38]. As shown in "Fig. 1", the proposed solution was connected with the HIS, adopting the same strategy reported by Gazzarata *et al.* [38]. In detail, the web application described in this manuscript represents a client agent of the EHR web service that adopts the *put*() functionality of RLUS standard to feed the EHR with a clinical document [35].

In this project, we used a Microsoft SQL Server 2014 as the Database Management System [39] and a .NET framework [40] to develop the web application respectively [40].

### B. MULTI-LEVEL AND MULTI-SCALE MODEL

The I-maculaweb database is based on an existing multi-level and multi-scale data management model based on some general principles, which are suitable for several different clinical domains. Previous implementation of such a template originated a specific tool for data reuse in Infective Diseases [19].

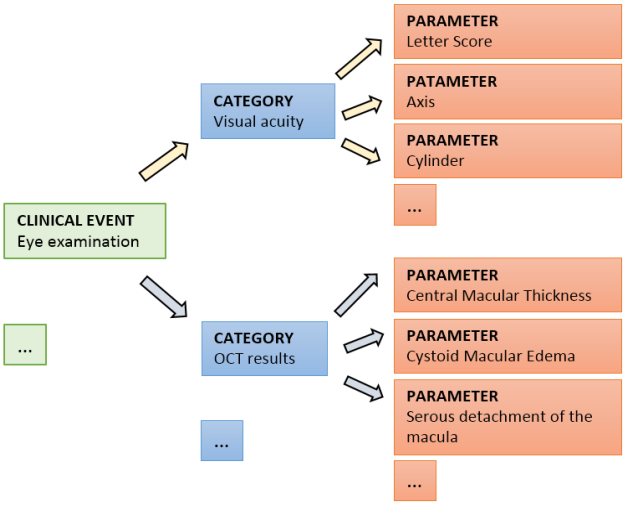


**FIGURE 2.** **Example of the multi-level structure.**

"Fig. 2" shows the conceptual framework developed. In detail, it is structured on a three-level hierarchical structure: Clinical Events, Categories, Parameters (with Unit of measure). Results are appropriately contextualized for the patient and for the time of measurement. For example, information concerning the "Letters score" and "Axis" are parameters that are grouped into the "Visual acuity" Category that belongs to the "Eye examination" Event.

Clinical results, obtained during the visit, are automatically saved in several tables according to the type of parameter and format to save.

Centers often utilize different instruments such as OCT, so numeric parameters, in particular the integer and float value may have different characteristics, like normal

ranges or units. These differences are central to the data extraction phase, therefore relevant information is specifically recorded for each center (''Unit_Conversion'' and ''Conversion_Coefficients'' tables in the database). In detail, all possible conversion coefficients between different units are stored. Finally, once converted to the same unit, data are harmonized using the z-score methodology, which allows the comparison of data collected with different normal ranges.

Patients and operators are both saved in the table ''Person'' where encrypted name, date of birth, address, telephone number and other mainly general demographic information are saved. The patient's tax code is generated automatically, using the demographic information, and then compared with the actual code stated by the patient, in order to ensure reliable patient identification.

The operator role and affiliate center are stored in a separate table. In this way, a physician can also assume different roles in different hospitals. Access to the database is strictly limited to authorized physicians with credentials checked for their security level and with a strict change policy. Furthermore, each user can be authorized, with different levels of permission, to access various studies; this information is stored in ''Operator_Studies''. All actions are recorded and linked to the specific operator, through the concept of sessions, which include the date and time of the user login.

### C. LATERALITY

The database structure was designed specifically to respect laterality, a key aspect in ophthalmology. As the template used to develop this database was mainly focused on general clinical concepts, it does not consider the concept of laterality. For this reason, a new table was added to identify the eye responsible for a specific parameter. In this way, each result is associated with the correct eye. Laterality was also added to the table of ''Patients in Studies'' because, in many cases, only one or both eyes could be enrolled in the study.

### D. STANDARD INTERACTIONS

In order to manage semantics, LOINC and ICD9 were used in this application, which translated the local vocabularies into sharable information. In particular, in the table ''Parameters'' the associated LOINC codes are specified and diagnosis can be chosen from a table where the corresponding IDC9 codes are saved.

As previously mentioned, all data recorded in a clinical event, ''eye examination'', were mapped within a CDA R2 document to feed the EHR. In order to constrain the CDA R2 specification for this specific use case, the Italian CDA R2 Implementation Guide (CDA R2 IG) for Discharge Summarization Note [41] was adopted.

### E. MODULARITY

The modular nature of both the database and web interface could allow a moderately easy definition of similar approach in other medical fields. The key aspect of the system is a relational database which, by using high data structuring through a meta description approach, permits archiving of various types of clinical information in multiple formats.

The modular design of the database allows the quick addition of new parameters without any required modification to the database structure, even if the strong relational structure of the database is maintained, ensuring a data set of high quality. In particular, this aspect is essential within the macular disease context because, management and treatment criteria are constantly evolving; therefore, the inclusion of new criteria is often necessary.

The database is managed through a web-platform, which dynamically builds the required web pages [20]. One relevant characteristic is that once the data has been collected into the database the first time, it is then available, without any further copy operations, during routine clinical care and for clinical studies according to specific research purposes.

All web page contents, in terms of components through ASP.NET's ASCX controls [42], [43], were dynamically loaded by using the archived information in the database.

The web application was built starting from basic bricks, which give access to specific portions of the database (even at the level of a single parameter / categories). These portions are frequently present in different pages whose content and order are defined according to the specific study.

Both the modularity and multi-level features of the present tool makes the creation of new studies, which can be considered the fifth and most external level of the system, very easy. In fact, all features present can be imported into a study without data replication and registered people can be indicated by automatic routines starting from a formal description of the study protocol. To enhance the potentiality of these modular features, a maintenance layer was developed to provide administrators with quick access and enable modification to all structural aspects of the platform as well as rapid addition of new clinical features.

### F. SECURITY

Confidentiality is a main factor in the platform. To respect patients' privacy, all sensitive data are stored using a hash cryptography algorithm during the registration process and a strict viewing rights policy. Although, each patient is enrolled in the database by a physician operating in the center where he/she receives healthcare services, patients' anonymized data are accessible by other center users if needed, only in aggregate format. As the whole system is based on web, Hypertext Transfer Protocol Secure [44], a protocol for safe communication, was employed to encrypt data flow between the client and server. During the login process, the connection switches from an unprotected connection to a safe one in order to safely exchange credentials and all clinical data during each session. Crucial memory segment isolation was used to assure transaction independency, in order to avoid interaction problems in multiple user access, mainly during simultaneously access to the database. A medium level isolation approach was chosen, allowing multiple simultaneous connections to databases from different procedures

but, within the same procedure, no simultaneous connections were allowed.

### G. USABILITY

The development of the interface was performed using the AGILE [45] methodology with strict interaction with end users in order to get indications to obtain an extremely user-friendly tool that would cover all their needs in this field. This is the main reason for its good acceptance and integration into a routine workflow.

Since one of the main objectives was to allow physicians to extract data for research and epidemiological purposes, a specific extraction tool was developed. Such instruments permit physicians to access normalized and comparable information according to their criteria and to extract these data in a portable format. Moreover, the search rationale can be saved for future needs and integration with the same modularity philosophy present in the whole tool.

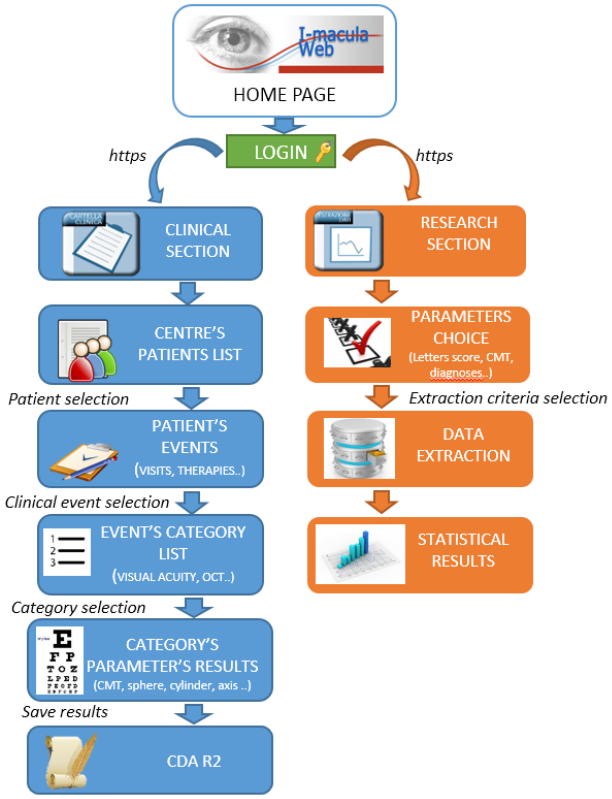


**FIGURE 3.** **Web interface sections and functionality.**

## IV. RESULTS

The Web Platform architecture (shown in Fig.3) is structured in two different sections: Clinical section and Research section. By using the Clinical section, with a user friendly and intuitive interface, physicians are able to record, modify and view patients' results. On the other hand, the research section is used to extract and export information according to the requirements. Referring to the first activities, the process is structured in a few passages and almost all web page contents are dynamically loaded. Physicians are able to access the Centre's Patients list, from which a patient can be selected to display further details. The Clinical section main menu shows patient details and it is organized as follow: unique identification number of the patient, last and first name, date of birth, gender, date of the last visit, center Id, and three buttons linked to demographic data, clinical chart and delete function pages. The web page "Patient's Clinical chart homepage" shows a summary of specified patient activity (visits, diagnoses, Intravitreal/laser/surgery treatments, clinical studies) that the system automatically loads from the list of the Clinical Events associated with the selected patient. As soon as there are more than two visits, ETDRS score letters and mean Central Macular Thickness (CMT) are plotted onto two separate graphs in the clinical homepage.

If a patient participates in a specific study, the relative information is highlighted in an ad hoc panel. For example, indications for Intravitreal treatments, according to the "Two Eyes" study, are inserted in a red rectangle. If the patient is not yet enrolled in a study, but he/she has the feature to be inserted, an study-specific alert button is visible on the page.

After choosing the particular Clinical Event, the platform shows the related list of available Categories. After selecting a specific Category, physicians can access a Parameter list and record or view results; the web page is dynamically loaded in relation to the Parameters format, Centre's units and ranges. Lastly, the physician can save the results in a report that the web application encapsulates within a CDA R2 document and sends to the hospital EHR calling the *put*() capability of the RLUS interface.

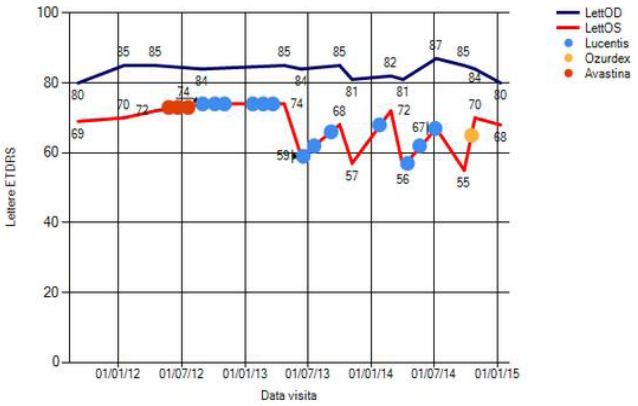


**FIGURE 4.** **ETRDS chart shows the trend of visual acuity during the follow-up.**

In order to improve the visualization and contextualization of the data, each graph can be enlarged to full-screen size. In this case, temporary sequences of ETDRS score letters and CMT values are automatically put in relation to the patient's recorded therapies. Therapies are identified (with simple color and form differentiation) according to the method and/or drug used ("Fig. 4"). The "Visit" menu is

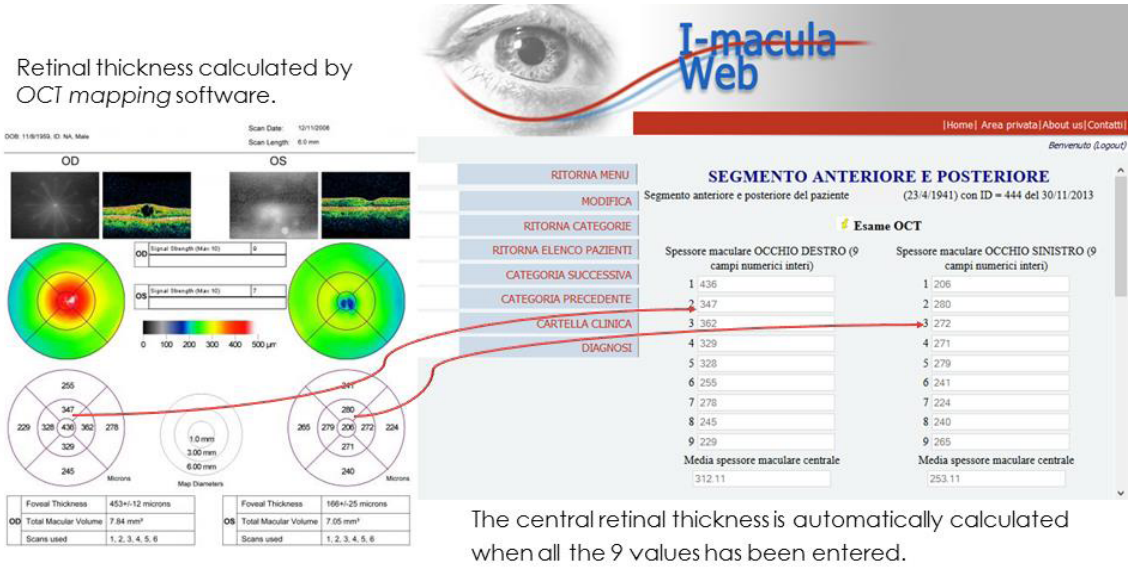


**FIGURE 5.** **OCT results are automatically imported in the application.**

divided in four sections: visus and symptoms, anterior and posterior segment, topical therapies ongoing and report. The main characteristic of the visus and symptoms section is the automatic calculation of the ETDRS score letter and Snellen equivalent. To simplify this operation an electronic image of the ETDRS chart pops out. The operator only needs to digit the number of letters correctly read at each line and the system automatically calculates the ETDRS score and Snellen equivalent [46]. In the posterior and anterior segment section, there are four different menus regarding OCT, ophthalmoscopic, angiographic and anterior segment signs. In some cases, such as subretinal fluid or cystoid macular edema, it is possible to compare the signs with the same signs recorded at the previous visit, specifying if it has increased, decreased, disappeared or remained unchanged. As well as the ETDRS letter score, it is possible to digit the thickness values for the nine ETDRS thickness field maps available in every OCT machine and one of the main points to improve in the system is the automation of data input from clinical instruments to the database. An application connected to a web service allows the export of OCT results to the web application, in this way data will be automatically stored in the database. The system will automatically calculate the mean value of the CMT (''Fig. 5''). Using the same application, direct recording of patient's demographics will also be possible.

The treatment menu is divided in injection, laser and surgical treatments. In the injection treatment section, there is a list of Intravitreal drugs that can be selected for each eye with the corresponding injection data. In the laser treatment section, there is the possibility to select the available retinal laser treatments, panretinal or scatter photocoagulation, grid/focal laser, micropulse or subthreshold laser and photodynamic therapy. It is also possible to save and print a pdf document as a visit report containing all relevant information collected during the examination as well as free text comments added by the physicians.

I-maculaweb has been in use at the Medical Retinal Center of the Clinical Ophthalmology, San Martino Hospital in Genoa, Italy, for about 2 years. In January 2015, the demographic and clinical information of 1105 patients, affected by degenerative and vascular disease of the retina, were entered and managed by I-maculaweb for a total of 3706 visits. The most frequent diagnoses were: AMD (490 cases), Diabetic Retinopathy (231 cases) and Central Serous Chorioretinopathy (155 cases). Furthermore, data related to 13 other diagnoses are present in the database. When needed other diagnostic sub-classifications are memorized. In the database, 1582 injective therapies and 257 laser therapies are also recorded. Some normal macula cases (199) were also inserted for statistical comparisons.

In addition, I-maculaweb was further implemented with automatic algorithms to assist ophthalmologists in the decision-making process related to starting treatment or re-treatment. These algorithms were developed in order to help physicians to follow, the Diabetic Retinopathy Clinical Research Network retreatment guidelines [22] and other international protocols, often expressed in an informal graphic design. Specifically, using patient diagnoses, visual acuity, CMT, and follow-up data, the system displayed a hint to start or stop treatment.

The platform can also be used as an electronic Clinical Research File, which is now mandatory in clinical studies. In April 2014, a 12-month prospective, multicenter, open-label, single arm interventional study (protocol CRFB002AIT02) took place. The study had the aim of assessing the safety and tolerability of 0.5 mg ranibizumab in wet AMD patients in eyes with visual acuity below 2/10 and/or fellow affected eye. The literal indications of this

Change from baseline visual-acuity score

| Visual-acuity score | n paz | % |
|---|---|---|
| Increase >= 15 letters | 28 | 24% |
| Increase 5-14 letters | 30 | 26% |
| Stable -4 to 4 letters | 28 | 24% |
| Decrease 5-14 letters | 14 | 12% |
| Decrease >= 15 letters | 15 | 13% |

Visual-acuity score and Snellen equivalent

| Visual-acuity score and Snellen equivalent | bsl | bsl % | 1 yr | 1 yr % |
|---|---|---|---|---|
| | | | | |
| 68-85 letters, 20/25-40 | 23 | 20% | 35 | 30% |
| 53-67 letters, 20/50-80 | 45 | 39% | 38 | 33% |
| 38-52 letters, 20/100-160 | 17 | 15% | 15 | 13% |
| <= 37 letters, 20/200-320 | 30 | 26% | 26 | 23% |

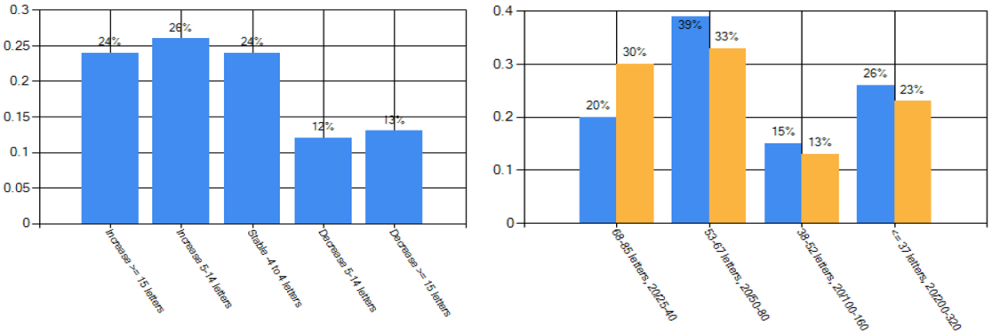


**FIGURE 6.** **Example of statistical extraction.**

interventional study were also coded in a specific page of the I-maculaweb, so that it automatically notifies physicians if a particular patient has the main inclusion criteria to be eligible for the study. The system was also implemented with the retreatment criteria based on visual acuity stability. Therefore, once the patient was recruited, the system suggested if treatment should be continued or discontinued according to the protocol study.

Thanks to previous study results produced using the described solution, the involved hospital has been selected to participate in a randomized multicenter double-blind phase III study of *Lampalizumab*, using I-maculaweb, to evaluate its safety and efficacy in patients with geographic atrophy secondary to AMD. This registrative study is important for the commercialisation of *Lampalizumab*, the only known drug to cure this type of AMD.

Another objective was to allow physicians to extract data according to their needs, independently from technical administration of the tool. We planned two different modalities to extract records: one for the patient's own center, in which personal details are shown and the other, used for statistical purposes, where all the center's anonymized data are visible. Physicians can enter specific extraction criteria to obtain information by selecting which parameters are required. Criteria can be set in order to select which parameter values will be visible in the results table. Records can be exploited with the possibility of defining particular thresholds, both inclusive and exclusive, for numeric parameters. For all other formats, there is the opportunity to indicate specific requirements: for example positivity or negativity for Boolean and equality or inequality to a certain value for categorical parameters. All the criteria can be added, modified or deleted as required. There is also the possibility to save extractions and reuse thereafter. Queries are built dynamically by interpreting the operators' demands, and once the extraction is completed, it is possible to view and save Z score normalized data in an Excel format. In order to avoid patients being individually recognizable, if the number of patients involved in the results obtained is less than five, the system will not show the search outcome. Fig. 6 shows an example of statistical extraction that may be useful for evaluating treatment efficacy in patients affected by selected diagnosis.

## V. DISCUSSION AND CONCLUSION

The application described in this paper fulfils the requirements specified by Chiang *et al.* [47] for Electronic Health Record Systems in Ophthalmology.

The web-platform allows effective management, sharing and reuse of information within primary care and clinical research. The system results as highly user-friendly by operators and it can be effectively integrated into the physician workflow.

Clear and precise clinical data will improve understanding of real-life management of degenerative and vascular diseases of the macula as well as increasing precise epidemiologic and statistical data. Furthermore, this web-based application can be easily employed as an electronic clinical research file in clinical studies.

The achievement of this web tool attests that it can be considered a valuable tool for ophthalmology EHRs and clinical studies as it overcomes the problems of other available EHR systems.

It is planned, in the near future, to share the system with other Italian hospitals not only for clinical research but also for use in routine clinical practice. To encourage international collaborations, the application will also be translated into a multilingual website.

Specific aspects of the platform and implementation methods and techniques have already been presented to an

international conference [48]. Moreover a journal paper (entitled "Combining macula clinical signs and patient characteristics for age-related macular degeneration diagnosis: a machine learning approach") has been published by the BMC Ophthalmology Journal [49]. This study exploited the high data quality of stored information and the ease of extracting data according to specific clinical criteria.

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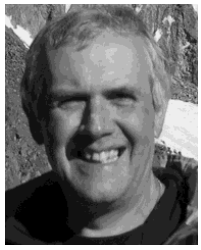

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