



American Academy of Ophthalmology Intelligent Research in Sight (IRIS®) Registry and the IRIS Registry Analytic Center Consortium

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The American Academy of Ophthalmology (AAO) Intelligent Research in Sight (IRIS®) Registry is the nation's first centralized and the world's largest medical specialty registry.¹ The IRIS Registry database was established in 2014 and currently includes selected de-identified electronic health record data from thousands of participating ophthalmologists and allied eye care providers across the United States. The data are automatically uploaded to the IRIS Registry, in most cases via systems integration software, and include patient demographics, patient medical and ocular history, clinical examination findings, diagnoses, procedures, and medications.²

The origin of the IRIS Registry is based on previous AAO data collection initiatives that were part of a broader effort to provide routine clinical practice, evidence-based guidance for clinicians. With advances in electronic health record data collection and the development of other specialty-based clinical data registries, the AAO launched a task force in 2012 to explore the creation of an ophthalmic disease data registry.³ At its initial launch in 2014, the registry collected data from 3000 clinicians throughout the United States, but the project has since expanded rapidly. As of October 2021, the IRIS Registry includes data on more than 412 million patient visits from more than 70.8 million unique patients, with nearly 16000 eye clinicians reporting.⁴ Although estimates differ, approximately 70% of all 18000 active practicing ophthalmologists in the United States are currently contributing to the IRIS Registry (Flora Lum, MD, personal communication, 2021).

The goals for the IRIS Registry include creating both national and interpractice benchmark reports on best practices for improving patient care; assisting practices with meeting federal reporting requirements; enabling data analysis for population health, rare disease research, and new scientific discovery; and identifying safety signals in new drugs and devices. The IRIS Registry has already had a significant impact on clinical practice. For example,

providers who use the IRIS Registry to demonstrate their compliance with required quality measures avoid penalties (an average of \$36 156 per ophthalmologist for 2020) and can receive small bonuses (the top was \$7191 per ophthalmologist in 2019) from the Centers for Medicare and Medicaid Services.³ In addition, the IRIS Registry allows physicians to compare their performance with that of other clinicians (both in their own practice and nationally) and to improve patient outcomes.⁵ Clinician performance measures such as cataract surgery visual acuity outcomes were shown to have improved since the IRIS Registry began.⁵

Advancing scientific discovery has been another major goal of the IRIS Registry. In 2017, the AAO selected several academic centers with the capacity for big data analytics for the IRIS Registry Analytic Center Consortium through an application process. Researchers at these selected centers were allowed to develop research questions for consideration and were granted access to the IRIS Registry data in late 2019 that would allow in-house analytics instead of relying on the AAO or its affiliated team. After an application process, the University of Washington, Stanford University, Wills Eye Hospital/Thomas Jefferson University, and Massachusetts Eye and Ear/Harvard Ophthalmology were selected. Over several years, principal investigators in the IRIS Registry Analytic Center Consortium have worked together with the AAO leadership, the AAO Committee on IRIS Registry Analytics, and technology partners such as Verana Health to develop data abstraction methods for big data research approaches using the IRIS Registry data. To date, the Analytic Center Consortium has published more than 10 major studies in addition to numerous meeting abstracts and paper presentations.^{4,6-12} The AAO is currently executing the second phase of the IRIS Registry Analytic Center Consortium and has selected additional centers to join the consortium during this phase.

Scientific discovery via IRIS Registry projects is not unique to the IRIS Registry Analytic Center Consortium because individual research projects are supported by foundations and subspecialty societies through available grants, such as the Research to Prevent Blindness and the AAO Award for IRIS Registry Research, the Hoskins Center IRIS Registry Research Fund, the Knights Templar Eye Foundation Pediatric Ophthalmology Fund, and the American Glaucoma Society IRIS Registry Grant Program.^{13–15} The Hoskins Center and Knights Templar Eye Foundation grants are earmarked for private practice ophthalmologists only.

Several important analyses of IRIS Registry data have been published, covering a wide variety of topics such as usage patterns of minimally invasive glaucoma surgery,¹¹ long-term clinical outcomes in glaucoma,¹³ age-related macular degeneration¹⁶ or diabetic retinopathy,¹⁷ and ocular complications associated with immune checkpoint inhibitors.¹⁸ A recent study from the IRIS Registry Analytic Center Consortium, “Endophthalmitis Rate in Immediate Sequential versus Delayed Sequential Bilateral Cataract Surgery within the IRIS Registry Data,” also highlights the strength of the IRIS Registry, in that an enormous dataset can be available for a rapid, timely analysis.⁷ Lacy et al⁷ analyzed the extensive cataract surgery data in the IRIS Registry to compare rates of postoperative endophthalmitis after immediate sequential bilateral cataract surgery versus delayed sequential bilateral cataract surgery. This was in response to the editorial in *Ophthalmology* that discussed COVID-19–related challenges in managing surgical patients in ophthalmology just a few months earlier that year.¹⁹ Endophthalmitis after cataract surgery is a rare event, and previous studies have relied on much smaller sample sizes, potentially too small to determine accurate endophthalmitis rates after bilateral cataract surgery. The size of the IRIS Registry allowed this study to include 3.5 times more patients undergoing immediate sequential bilateral cataract surgery than previous similar studies.^{8,20} Based on data from more than 5 million patients undergoing cataract surgery, the study found no statistically significant difference in the rates of postoperative endophthalmitis between the immediate sequential bilateral cataract surgery group and the group that underwent delayed sequential bilateral cataract surgery or unilateral cataract surgery.

Despite these successes, several challenges continue to exist in using the IRIS Registry data. Although the data collected from the clinicians who report to the IRIS Registry are quite extensive, to ensure patient confidentiality, strict criteria were implemented to limit the data variables that are accessible to researchers. Although clinicians own their individual practice data, the AAO owns the de-identified, aggregated data after it is uploaded to the IRIS Registry.³ Although the goal is for the Analytic Center Consortium to receive a comprehensive version of the aggregated data that can be used for multiple studies, many important variables such as detailed medication data and practice geographic information were not accessible in the initial IRIS Registry versions made

available to the analytic centers (codenamed Rome 1 and Rome 2). This was because of the imposition of patient privacy protections that were even stricter than the safeguards established by the Health Insurance Portability and Accountability Act. This is in contrast to what has traditionally been available to researchers outside the Analytic Center Consortium through the foundation, subspecialty society funded grants, or industry-sponsored mechanisms mentioned above. For such projects, the AAO provides a dataset that is specific to the study question or even performs the analyses to ensure Health Insurance Portability and Accountability Act compliance, and these datasets often include data fields that are not part of the Rome 1 or 2 versions. Multiple studies have been published through this route, all based on specially selected datasets and analyses that were tailored to the specific research question.^{13,16–18,21–23}

Significant strengths of the IRIS Registry data include not only the pure number of data points that allow observation of rare events, but also the potential to analyze clinical variables beyond the standard diagnosis and procedure codes. The recently updated version of de-identified IRIS Registry data, Chicago, contains many additional variables, such as medication, cup-to-disc ratio, and refraction data, compared with those provided in earlier versions. Additionally, it provides a single standardized resource for all analyses, including the Analytic Center Consortium and the other supported programs, which should decrease discrepancies in available data quality. As the number of important clinical variables become available, the IRIS Registry will allow more sophisticated analyses such as feature-based analyses, where researchers identify biomarkers of a disease or its progression or generate new avenues of investigation using a purely data-driven, hypothesis-agnostic approach.²⁴ In addition, findings from IRIS Registry studies that are consistent with other study results from smaller populations with limited geographic representation would support the validity of those findings in a national sample.

However, the inherent limitations of a large, clinical practice-based dataset, including missing data and coding errors, must be considered at all times.²⁵ Undoubtedly, the completeness of clinical notes depends on factors including clinicians’ documentation habits or examination settings within the IRIS Registry. Even in the updated version, the de-identified dataset still lacks important variables such as refractive target, axial length, and imaging results. Also, the dataset is ophthalmology centric, and therefore, the potential to investigate any correlations between ophthalmic findings and systemic diagnoses or medications is limited. Any free-written text in the electronic health record will remain unavailable for the foreseeable future. Future goals include automatic abstractions of free-written text and numeric data from diagnostic instruments such as visual fields and retinal imaging. Despite these limitations, immeasurable value exists in being able to assess the routine clinical practice patterns and clinical outcomes that often differ from the results of randomized clinical trials. Still, novel findings from big data may not be possible to validate because of the lack of other independent datasets of similar size or quality. Thus, researchers must be

cautious in understanding the scope and limitations of the available dataset and must perform careful sensitivity analyses to explain the plausibility of any results that deviate from previous literature.²⁶

The IRIS Registry is an exceptional, evolving, and ever-expanding resource that will enable great progress in ophthalmology research. The long-term vision for the IRIS Registry, to become a multidimensional dataset that incorporates multimodal and nonophthalmic medical data, is truly exciting. As it currently stands, the IRIS Registry Analytic Center Consortium is uniquely positioned to address relevant research questions because their investigators were instrumental in developing the data abstraction and analysis methods, are aware of the limitations in the datasets available to them, and are capable of

adjusting their analyses to accommodate these limitations. Additional centers have been accepted to join the IRIS Registry Analytic Center Consortium, and this process will continue on a regular basis. The experience gained by the 4 analytic centers from the early challenges will be instrumental in expediting the onboarding and success of new centers. Journal editors, reviewers, and the general readership should be aware of current strengths and limitations of the IRIS Registry Analytic Center Consortium projects. Further collaborations with additional centers and investigators and newer, more inclusive versions of the IRIS Registry dataset will enable the investigation of even more powerful study questions and will help to realize the potential and accomplish the scientific discovery goals of the IRIS Registry.

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