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ORIGINAL RESEARCH

Knowledge and Current Practices in Monogenic Uveitis: An International Survey by IUSG and AIDA Network

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ABSTRACT

Introduction: This study aims to explore awareness, knowledge, and diagnostic/therapeutic practices in monogenic uveitis (mU) among uveitis experts.
Methods: This is an explorative, cross-sectional survey study. An anonymous, semi-structured, electronic survey was delivered to uveitis experts from the Autoinflammatory Diseases Alliance (AIDA) Network and International Uveitis Study Group (IUSG). We included respondents answering ≥ 50% of the survey.
Results: Seventy-seven participants rated their knowledge of mU as proficient (3.9%), adequate (15.6%), sufficient (16.9%), or poor (63.6%). When asked about the first mU gene they thought of, 60.4% mentioned *NOD2*, 3.9% mentioned *NLRP3* or *MEFV*, and 49.4% provided incorrect or no answers. Success rates in clinical scenarios varied from 15.6% to 55.8% and were higher for ophthalmologists working

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in multidisciplinary teams ($p < 0.01$). Genetic testing was ordered for suspected mU by 41.6% of physicians. The availability of molecular techniques did not significantly differ based on geography ($p > 0.05$). The public healthcare system ensured a higher percentage of tests prescribed were obtained by patients compared to private insurances ($p < 0.00$). In terms of disease-modifying anti-rheumatic drugs (DMARDs), tumor necrosis factor-α inhibitors were the most familiar to uveitis experts. The difficulties with off-label therapy procedures were the primary barrier to DMARDs prescription for patients with mU and correlated inversely with the obtained/prescribed drug ratio for interleukin-1 ($p < 0.01$) and interleukin-6 ($p < 0.01$) inhibitors.

Conclusions: This survey identifies proficiency areas, gaps, and opportunities for targeted improvements in patients care. The comprehensive outputs may inform evidence-based guidelines, empowering clinicians with standardized approaches, and drive an AIDA Network—IUSG unified effort to advance scientific knowledge and clinical practice.

Keywords: Autoinflammatory diseases; Differential diagnosis; Genetic uveitis; Pathogenesis; Rare diseases

Key Summary Points

Why carry out this study?

The relationship between genetics and uveitis is widely recognized and advances in genetic techniques continue to reveal new insights into monogenic uveitis.

A collaborative effort on monogenic uveitis between the Autoinflammatory Diseases Alliance (AIDA) Network and International Uveitis Study Group (IUSG) is underway.

What was learned from the study?

Conducted among uveitis experts, this survey study identified diagnostic and therapeutic gaps, stressing the necessity for standardized approaches and education.

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Despite the improvement of advanced genetic techniques, multidisciplinary collaboration and an increased familiarity with rare genetic causes remain crucial for advancements in diagnosis.

The newly established "Genetics in Uveitis" group of IUSG is expected to operate as a specialized hub for cross-disciplinary teamwork, learning, and research, with the overarching objective of enhancing the well-being of individuals affected by monogenic uveitis on a global scale.

INTRODUCTION

While the exact pathogenesis of non-infectious uveitis remains incompletely understood, it is recognized to involve intricate interactions between genetic predisposition and environmental factors. The association between human leukocyte antigens and diverse uveitis phenotypes has been observed since the early 1970s [1]; however, the subsequent advancements in sequencing and genotyping techniques have especially contributed to unraveling the genetic foundations of the disease, particularly in the context of monogenic uveitis [2]. This was the case of autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV), whose candidate gene was localized to chromosome 11q13 by chromosomal linkage analysis of the originally identified families [3]. Nevertheless, beyond ADNIV and a limited number of other clinical entities, monogenic uveitis has been mostly described in association with monogenic autoinflammatory diseases (mAID) [4, 5]. The development of uveitis was observed in subjects affected by familial Mediterranean fever and tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), the oldest diseases identified in this nosologic group [6–10]. However, as new mAIDs were characterized over time, uveitis became one of the driving clinical features of the most severe forms of cryopyrinopathies (Muckle-

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Wells syndrome and Chronic, Infantile, Neurologic, Cutaneous, and Articular syndrome) and Blau syndrome, while further monogenic causes of uveitis were identified in pediatric and adult population [11–13]. Among those, VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome deserves to be mentioned, as it represents the prototype of mAIDs with onset in adulthood: this syndrome is associated with eye involvement in up to 40.5% of cases and specifically with uveitis in 9.5% [14, 15]. In this context, the ophthalmologist might play a strategic role screening those who deserve multidisciplinary evaluation in the suspicion of mAID-associated uveitis. Table 1 provides a non-exhaustive list of monogenic forms of uveitis.

At the end of 2022, a scientific partnership was established between the AIDA (Autoinflammatory Diseases Alliance) Network and IUSG (International Uveitis Study Group) with the purpose of defining a common research agenda on monogenic forms of uveitis. A IUSG *"Genetics in Uveitis"* group of interest has been founded and members of both scientific societies were involved to work together on this topic with a multidisciplinary approach. Among the activities carried out in the scoping phase, a survey directed to uveitis experts was designed with the aim of getting a snapshot of the familiarity with monogenic uveitis, mainly associated to mAIDs (referred to later in the manuscript as "monogenic uveitis") and describing current practices in diagnosis and treatment worldwide.

METHODS

An explorative, semi-structured, cross-sectional survey was developed by a team of researchers skilled in monogenic uveitis, members of IUSG (https://www.iusg.net/) and/or AIDA Network (https://aidanetwork.org/en/), including ophthalmologists, rheumatologists, and pediatric rheumatologists. The core domains addressed by the survey included awareness and knowledge of monogenic uveitis, and referral patterns and barriers to monogenic uveitis diagnosis and treatment at the local level. To assess awareness, participants were asked to rate their familiarity with monogenic uveitis from poor to proficient and to indicate the first gene name and all the monogenic diseases coming to their mind in association with uveitis; also, the awareness of any registries collecting data on monogenic uveitis was investigated. To assess the participants' knowledge, the survey included six theoretical multiple-choice questions and clinical scenarios about different forms of monogenic uveitis. The last section of the survey was meant to explore hospital referral practices regarding genetic diagnosis (frequency of genetic test prescription, potential barriers to the prescription and interpretation of the result, types of analysis and genetic platforms available, multidisciplinary approach, and funding covering genetic tests at the local level) and disease-modifying anti-rheumatic drugs (DMARDs) prescription (frequency of DMARDs prescription, potential barriers to the prescription of DMARDs, familiarity with different classes of DMARDs and multidisciplinary approach) in patients with monogenic uveitis. The questionnaire also investigated the participant's country, working experience, type of workplace, focus of clinical practice, familiarity with pediatric ophthalmology, uveitis, and specifically monogenic uveitis. In the survey closure, the respondent's interest in participating in educational programs on genetic forms of uveitis and mAIDs was elicited as well. The survey consisted of 38 questions in all (available in the Supplementary Materials) and took approximately 10 min to complete.

The questionnaire was developed through the survey instrument provided by REDCap (Research Electronic Data Capture, https://projectredcap.org), a secure web application designed to support data capture for research studies. Participants were recruited via the IUSG and AIDA Network mailing lists. Both networks are well established institutions at the international level—with 201 AIDA Network partner centers in 42 countries and hundreds of IUSG uveitis experts from all over the world—coordinating research on uveitis, including the development of international clinical registries such as OASIS (Ocular Autoimmune Systemic Inflammatory Infectious Study) and the AIDA

Table 1 A non-exhaustive list of monogenic causes of uveitis

Gene	Disease	Ocular manifestations	Refs.
CAPN5	Autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV)	Retinal and iris neovascularization, anterior and intermediate uveitis, macular edema, vitreous hemorrhage, traction retinal detachment	[3]
MEFV	Familial Mediterranean fever (FMF)	Uveitis, conjunctivitis, retinal vasculitis	[6–8]
TNFRSF1A	Tumor necrosis factor receptor associated periodic syndrome (TRAPS)	Periorbital edema, episcleritis, panuveitis, optic neuritis	[9, 10]
NLRP3	Familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and chronic, infantile, neurologic, cutaneous, and articular syndrome (CINCA)	Conjunctivitis, papilledema, episcleritis, uveitis	[11, 12]
NOD2	Blau syndrome	Granulomatous uveitis	[13]
UBA1	Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome (VEXAS)	Episcleritis, scleritis, uveitis, blepharitis, orbital mass	[14, 15, 28]
IKBKG	X-linked systemic autoinflammatory disease (SAIDX)	Chorioretinitis, granulomatous uveitis, optic neuritis	[17]
NLRP1	NLRP1-associated autoinflammation with arthritis and dyskeratosis (NAIAD)	Uveitis	[16]
TNFAIP3	Haploinsufficiency of A20	Anterior and posterior uveitis, retinal vasculitis	[18–22]
MVK	Mevalonate kinase deficiency syndrome (MKD)	Anterior uveitis, retinal vasculitis, retinitis pigmentosa, cataract	[23, 24]
PSMB8, POMP, PSMB4, PSMA3, PSMB9	Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)	Uveitis, retinal vasculitis	[25, 26]
PLCG2	Autoinflammation, PLCγ2-associated, antibody deficiency, immune dysregulation syndrome (APLAID)	Posterior uveitis, conjunctivitis	[27]
ALPK1	Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and headache syndrome (ROSAH)	Optic disc and peripapillary elevation, low-grade uveitis, retinal vasculitis, and retinal degeneration	[29]

Ref references

Network registries [30–34]. After careful screening for possible incomplete or inconsistent records, we included in the final dataset respondents defining themselves as ophthalmologists experienced with uveitis and providing answers to at least 50% of the questions included in the survey.

The study protocol was notified to the Ethics Committee of Azienda Ospedaliero-Universitaria Senese on January 10, 2023 (Ref. 14951). Informed consent for using data resulting from the survey for research purposes was obtained electronically via the following statement "By clicking this button, you are expressing your willing to participate in this survey study and voluntarily give your consent." Participants were informed through the accompanying email of invitation that their answers to the questionnaire would be separated from their personal information by using a pseudonym. The researcher who performed the statistical analysis had no access to the mailing list of the candidates invited by the IUSG and AIDA Network nor to any personal information potentially capable of identifying the participants. On the other hand, the representatives from the IUSG and AIDA Network who invited the candidates had no access to the data entered by the participants. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Statistical analysis was performed by using JASP open-source statistics package version 0.16.3. Descriptive statistics included sample sizes, mean and standard deviation or median and interquartile range (IQR), as appropriate. Shapiro–Wilk test was used to assess the normality distribution of data. Associations between categorical variables were analyzed using contingency tables with chi-square test with Yates' continuity correction. Correlations between ordinal variables or continuous variables violating the assumptions required for parametric testing were analyzed by Spearman's rho test Kendall's tau B correlation. Statistical difference between the medians of two independent groups was determined by Mann–Whitney test. Statistical difference between the medians of ≥ 3 independent groups was determined by ANOVA Kruskal–Wallis test with Dunn's post hoc. Multinomial test was applied to test whether a sample frequency was statistically different from a known population frequency (chi-square 'goodness-of-fit' test). The threshold for statistical significance was set to $p < 0.05$ and all p values were two-sided.

RESULTS

Of 123 participants accessing the survey, 77 fulfilled the entry criteria and were included in the study. The general characterization of the participants' group is depicted in Table 2.

Awareness of Monogenic Uveitis

The participants rated their knowledge of monogenic uveitis as proficient in three cases (3.9%), adequate in 12 (15.6%), sufficient in 13 (16.9%), and poor in 49 (63.6%).

When asked to list all monogenic diseases possibly associated with uveitis that they could think of, five physicians (6.5%) listed more than three diseases, 15 (19.5%) listed two or three diseases, 32 (41.6%) listed only one disease, while 25 (32.5%) gave incorrect or no answers. The knowledge self-evaluation grade directly correlated with the number of mAIDs associated with uveitis cited by the participant (Kendall's tau B 0.27, 95% CI (0.14; 0.40), $p = 0.01$). The number of mAIDs associated to uveitis cited by the participants was higher in the group who ever attended courses or seminars on mAIDs than in the group who did not ($p < 0.01$).

When asked to indicate the first gene coming to their mind in association with monogenic forms of uveitis, 29 out of 77 physicians (37.7%) mentioned the *NOD2* gene, three (3.9%) mentioned *NLRP3*, three (3.9%) mentioned *MEFV; ADA2, NLRP4, TNFAIP3* and *UBA1* were each cited once (1.3% each), 38 physicians (49.4%) gave an incorrect or no answer. Thirteen out of 77 respondents (16.9%) were aware of the existence of national and international registries collecting data on genetic forms of uveitis.

Table 2 General characteristics of the respondents to the survey

Country	Spain n = 29 (37.6%)	Colombia *n* = 1 (1.3%)
	India *n* = 14 (18.2%)	Cuba *n* = 1 (1.3%)
	Italy *n* = 6 (7.9%)	Lebanon *n* = 1 (1.3%)
	United Kingdom *n* = 4 (5.2%)	Nepal *n* = 1 (1.3%)
	Netherlands *n* = 3 (4.0%)	Oman *n* = 1 (1.3%)
	Egypt *n* = 2 (2.6%)	Russia *n* = 1 (1.3%)
	Israel *n* = 2 (2.6%)	Slovenia *n* = 1 (1.3%)
	Mexico *n* = 2 (2.6%)	Switzerland *n* = 1 (1.3%)
	United States *n* = 2 (2.6%)	Turkey *n* = 1 (1.3%)
	Belgium *n* = 1 (1.3%)	Yemen *n* = 1 (1.3%)
	Brazil *n* = 1 (1.3%)	Missing *n* = 1 (1.3%)
Years of uveitis practice	< 5 *n* = 16 (20.8%)	10–20 *n* = 27 (35.1%)
	5–10 *n* = 16 (20.8%)	> 20 *n* = 18 (23.4%)
Primary focus of ophthalmology practice	Uveitis	*n* = 69 (89.6%)
	Vitreoretinal surgery	*n* = 16 (20.8%)
	Inherited retinal disease	*n* = 1 (1.3%)
	Pediatric ophthalmology	*n* = 4 (5.2%)
	Medical retina	*n* = 25 (32.5%)
	Other	*n* = 14 (18.2%)
Pediatric practice	0% *n* = 14 (18.2%)	50–75% *n* = 1 (1.3%)
	1–10% *n* = 30 (39.0%)	75–100% *n* = 2 (2.6%)
	10–25% *n* = 23 (29.9%)	100% *n* = 3 (3.4%)
	25–50% *n* = 4 (5.2%)	
Type of workplace	Academic	*n* = 69 (89.6%)
	Non-academic	*n* = 8 (10.4%)
	Solo	*n* = 5 (6.5%)
	Group	*n* = 6 (7.8%)
New patients with uveitis per month	Median 10 (IQR 15), range 1–100	
Total patients with uveitis per month	Median 60 (IQR 90), range 4–800	

Table 2 continued

Availability of a multidisciplinary team for mAIDs	Not at all	$n = 24$ (35.8%)
	Not sure	$n = 15$ (22.4%)
	Yes, but not involving the ophthalmologist	$n = 8$ (11.9%)
	Yes, also involving the ophthalmologist	$n = 20$ (29.9%)
Previous participation in seminars on mAIDs	Yes	$n = 26$ (38.8%)
	No	$n = 41$ (61.2%)

IQR interquartile range, *mAIDs* monogenic autoinflammatory diseases

Knowledge of Monogenic Uveitis

The number of participants giving correct answers to the six theoretical questions and clinical scenarios about monogenic uveitis is shown in Fig. 1a. The frequency of correct answers ranged from 15.6 to 55.8% according to the different topics of the questions (Fig. 1b). The median percentage of correct answers was different according to the geographic areas (Fig. 1c): it was higher in Europe than the Middle East [median 50.0% (IQR 10.1%) vs. 0.0% (IQR 8.3%), $p < 0.01$] and Asia [median 16.6% (IQR 33.3%), $p < 0.01$].

The level of knowledge of monogenic uveitis—expressed as number of correct answers from 0 to 6—directly correlated with the knowledge self-evaluation grade of the participants [Kendall's Tau B 0.37, 95% Confidence Interval (CI) (0.24; 0.45), $p < 0.00$]. The percentage of correct answers was higher in the group of respondents working in an academic hospital than those working in a non-academic one [median 33.3% (IQR 33.4%) vs. 0% (IQR 16.6%), $p < 0.01$] and in those who ever attended courses or seminars on mAIDs compared with those who did not [median 50.0% (IQR 30.9%) vs. 16.6% (IQR 50.0%), $p = 0.01$]. Also, it was higher in the group that had the opportunity to work in a multidisciplinary team [median 50.0% (IQR 33.4%) vs. 25.0% (IQR 33.3%), $p < 0.01$]. Physicians who diagnosed monogenic uveitis at least once in their career gave more correct answers than those who did not [median 50.0% (IQR 31.1%) vs. 16.6% (IQR 50.0%), $p = 0.01$].

Hospital Referral Patterns and Barriers to mAID-U Diagnosis and Treatment

Genetic Testing Availability

Genetic testing was ordered in suspected cases of monogenic uveitis by 32 out of 77 physicians (41.6%). In eight cases (10.4%), the ophthalmologist autonomously interpreted genetic test results by consulting online databases like *Infevers* and scientific publications [35]. Hospital referral patterns for genetic testing and interpretation are represented in Fig. 2a.

The analysis was performed in-house in 29 cases (35.7%)—in the participant's departments in eight (8.4%) or through a medical genetics' platform in 21 (27.3%)—while blood samples were sent to another hospital—domestic in 23 (29.9%) cases or abroad in three (3.9%)—in 26 cases (33.8%). The practice of sending blood samples abroad for genetic testing was more common in the United States (33% of respondents), Central and South America (25%) and the Middle East (25%) than in Europe (0%) and Asia (0%). As for the genetic techniques available (Sanger sequencing, next-generation sequencing, mosaicism analysis, whole exome sequencing, whole genome sequencing), we did not identify any statistically significant differences on a geographic basis nor according to the type of workplace.

Genetic testing for monogenic uveitis was covered by multiple funding sources, namely by the public healthcare system, public insurance, private insurance companies, directly by the patient or combinations of the previous options. Funding quotas from the different

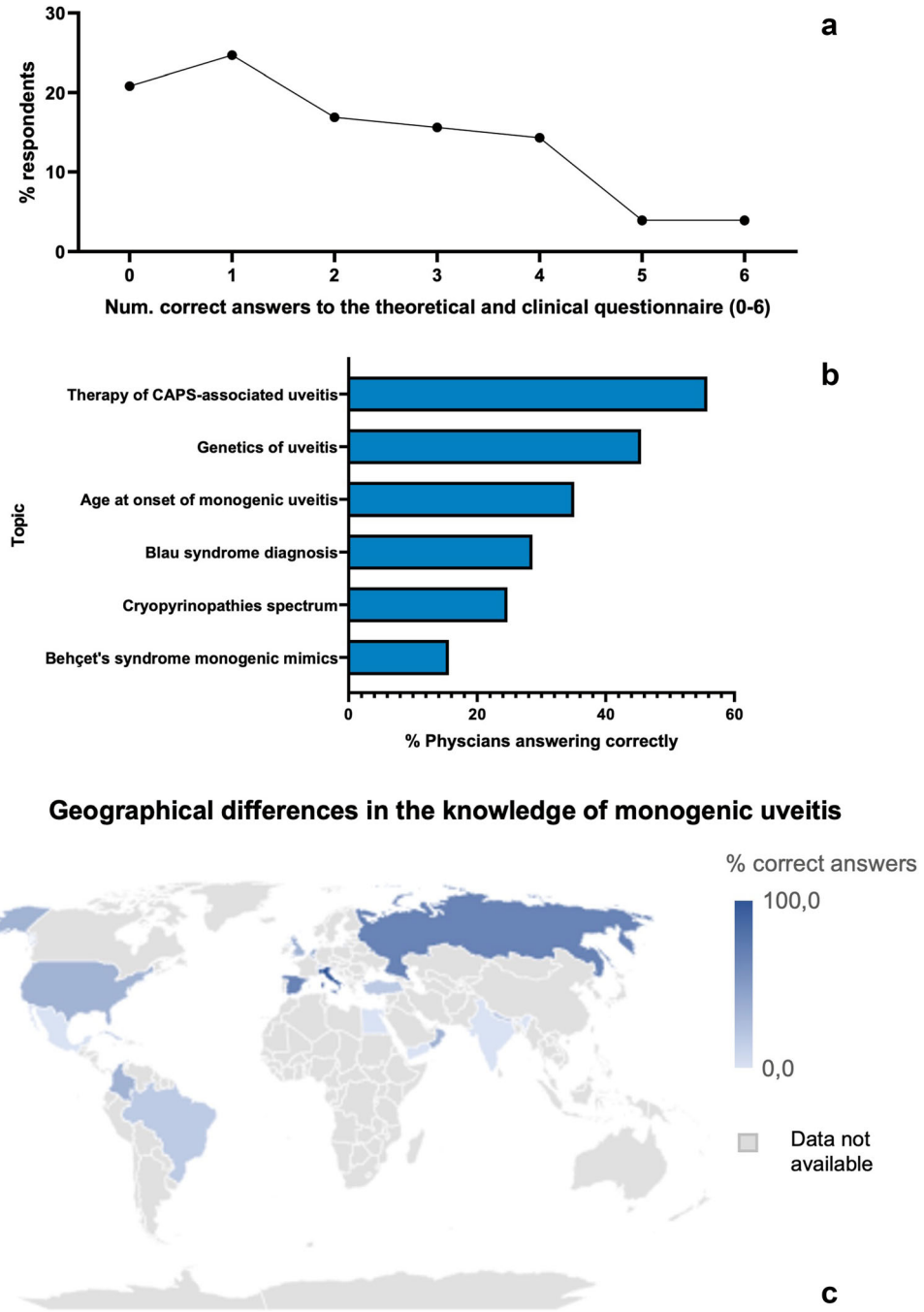
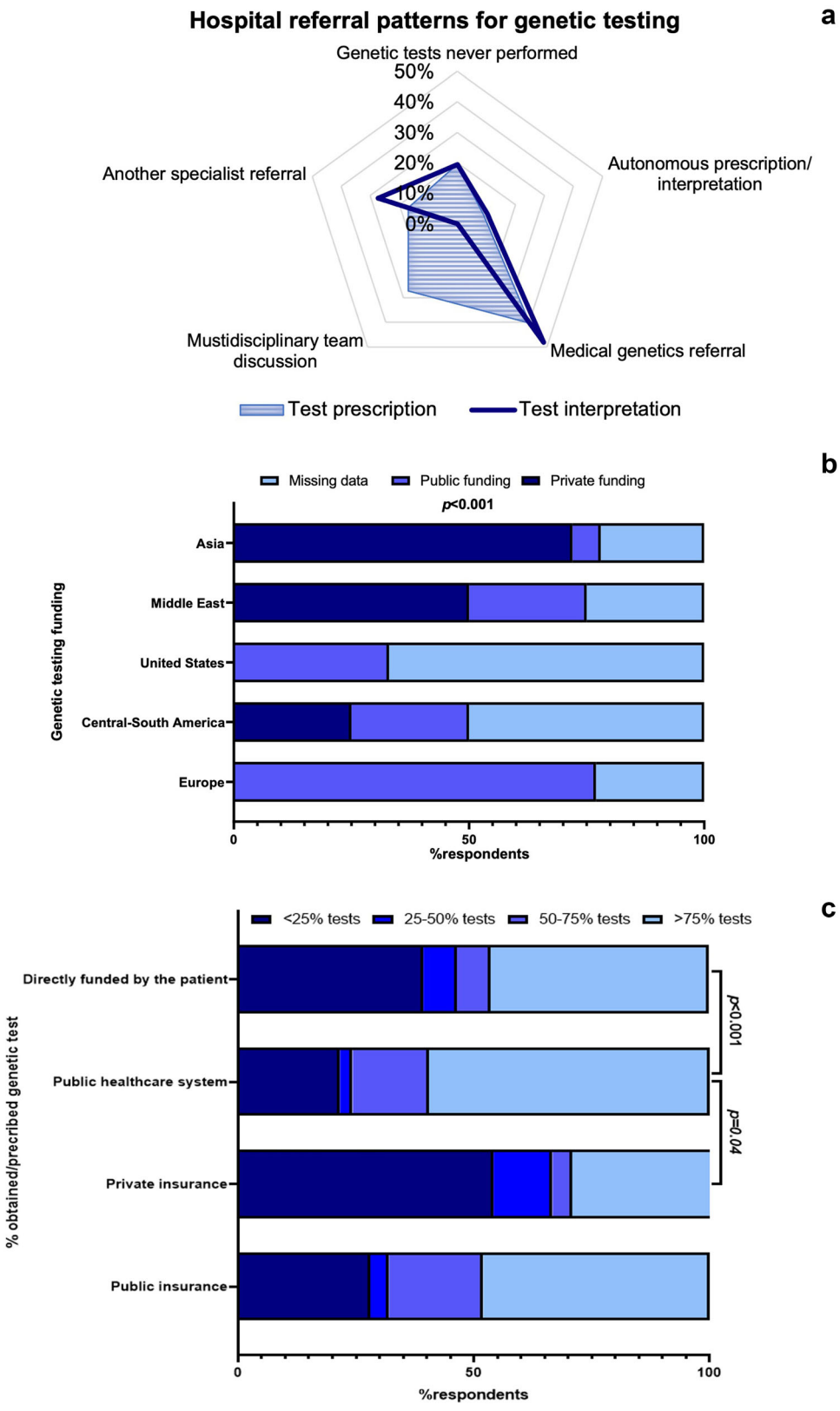


Fig. 1 Percentage of respondents who gave correct answers to 1, 2, 3, 4, 5 or all the 6 theoretical questions and clinical scenarios about monogenic uveitis (**a**). Percentage of correct answers to the theoretical and clinical questions stratified by topics (**b**) and (**c**) countries. *CAPS* cryopyrin-associated periodic syndromes

sources were unequally distributed among the participants' countries ($p < 0.00$), as represented in Fig. 2b. Where genetic testing was covered by public funds, a higher percentage of tests prescribed were effectively obtained by patients: multinomial test for direct funding by patients


a
Hospital referral patterns for genetic testing
Genetic tests never performed
50%
40%
30%
20%
10%
0%
Autonomous prescription/ interpretation
Medical genetics referral
Mustidisciplinary team discussion
Another specialist referral
Test prescription
Test interpretation
b
Missing data
Public funding
Private funding
p<0.001
Asia
Middle East
United States
Central-South America
Europe
Genetic testing funding
0
50
100
%respondents
c
<25% tests
25-50% tests
50-75% tests
>75% tests
Directly funded by the patient
Public healthcare system
Private insurance
Public insurance
% obtained/precribed genetic test
p<0.001
p=0.04
0
50
100
%respondents

◀**Fig. 2** Hospital referral patterns for genetic testing (*striped area*) and interpretation of results (*solid line*) in cases of suspected monogenic uveitis (**a**). Differences in the distribution of public and private funding covering monogenic uveitis genetic testing according to geographic regions (**b**). Percentage of respondents estimating an obtained/prescribed genetic test ratio of < 25%, 25–50%, 50–75% or > 75% according to the different funding sources (**c**)

$p = 0.04$ (reference group: public healthcare system), multinomial test for funding by private insurance $p < 0.00$ (reference group: public healthcare system) (Fig. 2c).

The following barriers would prevent the participants from ordering genetic testing to their patients with suspected monogenic uveitis: logistical challenges to ordering the test (rated 2.5 ± 1.9 on a 0–5 relevance scale), uncertainty about which test to order (rated 2.9 ± 1.7), how to interpret the result (rated 2.7 ± 1.8), how the result would affect management/treatment (rated 2.2 ± 1.8), concerns about additional costs for the patient (rated 2.4 ± 2.0) and the patient's or family's refusal (rated 2.1 ± 1.8). Factors impacting to a statistically significant degree on the subjective relevance of the main barriers identified are listed in Table 3. There was an inverse correlation between the number of correct answers to the theoretical questions/clinical scenarios about monogenic uveitis and the subjective uncertainty about which genetic test to order ($p < 0.00$) and about how the test result would affect management and treatment ($p = 0.03$).

Systemic Therapy Availability

Fifty out of 77 ophthalmologists (64.9%) stated that they prescribe DMARDs to their patients affected by uveitis. Hospital referral patterns for DMARDs prescription and the median familiarity 0–50 rating for the different drug classes employed in monogenic uveitis are represented in Fig. 3a. The group of physicians prescribing DMARDs declared a higher median degree of familiarity with conventional DMARDs ($p < 0.01$), Tumor Necrosis Factor (TNF)α inhibitors ($p < 0.01$) and Interleukin (IL)-1 inhibitors ($p = 0.03$) compared to the non-prescribers group.

The following barriers would prevent the ophthalmologists from prescribing personally DMARDs to their patients with monogenic uveitis: logistical challenges to the prescription (i.e., lack of time, support, or authorization) (rated 1.0 ± 1.9 on a 0–5 relevance scale), challenges in obtaining off-label therapies (rated 3.0 ± 1.8), uncertainty about the therapeutic choice (rated 2.0 ± 1.9) or the clinical management of patients with mAIDs (rated 2.0 ± 1.9), concerns about additional costs for the patient (rated 2.0 ± 1.7), and patients/families declining systemic therapy (rated 1.0 ± 1.7). Factors impacting to a statistically significant degree the subjective relevance of the main barriers identified are listed in Table 4. The lower the score in theoretical questions/clinical scenarios, the more significant the subjective impact of uncertainty becomes in the choice of therapy ($p = 0.01$) and in the clinical management of patients with monogenic uveitis ($p = 0.01$).

The distribution of obtained/prescribed rates (< 25%, 25–50%, 50–75% or > 75%) for TNFα inhibitors, IL-1 inhibitors, IL-6 inhibitors, Janus kinase (JAK) inhibitors and cDMARDs is shown in Fig. 3b. There was an inverse correlation between the logistical challenges to the prescription experienced by the uveitis expert and the obtained/prescribed drug ratio for IL-1 inhibitors ($p < 0.00$), IL-6 inhibitors ($p = 0.04$) and cDMARDs ($p = 0.01$). The same was observed when considering challenges experienced with the off-label prescription procedures (IL-1 inhibitors $p < 0.01$; IL-6 inhibitors $p < 0.01$) and the ophthalmologist's concerns about additional costs for the patient (TNFα inhibitors $p < 0.00$; IL-6 inhibitors $p < 0.00$; IL-1 inhibitors $p < 0.00$; cDMARDs $p = 0.01$). Also, the distribution of obtained/prescribed therapy rates (< 25%, 25–50%, 50–75% or > 75%) was different according to the geographic area, with higher rates in Europe than Asia for cDMARDs ($p = 0.01$), TNFα-inhibitors ($p < 0.00$) and IL-6 inhibitors ($p < 0.00$); with higher rates in Europe than the Middle East for TNFα-inhibitors ($p < 0.00$) and IL-6 inhibitors ($p = 0.00$); and

Table 3 Differences in the ophthalmologists' perception of the importance of different barriers to genetic testing in potential cases of monogenic uveitis (0 = the described barrier has no impact on the responder's behavior; 5 = the described barrier has a profound impact on the responder's behavior)

	Median (IQR)[range]		Median (IQR)[range]	*p*
"Logistical barriers" 0–5 rating				
Europe	2.0 (3.0) [0–5] versus	Central and Southern America	4.5(1.5) [2–5]	0.02
	2.0 (3.0) [0–5] versus	Asia	3.0 (2.0) [0–5]	0.03
	2.0 (3.0) [0–5] versus	Middle East	5.0 (1.0) [1–5]	0.02
Public funding	2.0 (3.0) [0–5] versus	Private funding	3.5(3.0) [0–5]	< 0.01
Multidisciplinary team involving the ophthalmologist	1.0 (2.3) [0–5] versus	Multidisciplinary team not available	3.0 (3.0) [0–5]	< 0.01
"Uncertainty about which test to order" 0–5 rating				
Europe	3.0 (3.0) [0–5] versus	Central-South America	4.5(1.0) [4–5]	< 0.01
	3.0 (3.0) [0–5] versus	Asia	4.0 (3.0) [0–5]	< 0.01
	3.0 (3.0) [0–5] versus	Middle East	5.0 (0.3) [4–5]	< 0.01
Multidisciplinary team involving the ophthalmologist	2.0 (4.0) [0–5] versus	Multidisciplinary team not available	4.0 (2.0) [0–5]	< 0.01
Participation in seminars on mAIDs	2.0 (2.0) [0–5] versus	Seminars on mAIDs never attended	4.0 (2.0) [0–5]	< 0.01
"Uncertainty about how to interpret the result" 0–5 rating				
Europe	2.0 (2.0) [0–5] versus	Central-South America	4.5(1.0) [4–5]	0.01
	2.0 (2.0) [0–5] versus	Middle East	5.0 (0.3) [4–5]	< 0.01
Familiarity with genetic databases and scientific literature on mAIDs	1.5(1.3) [0–3] versus	No familiarity with genetic databases and scientific literature on mAIDs	3.0 (3.0) [0–5]	0.03

Table 3 continued

	Median (IQR)[range]		Median (IQR)[range]	*p*
Participation in seminars on mAIDs	2.0 (2.7) [0–5] versus	Seminars on mAIDs never attended	4.0 (3.0) [0–5]	< 0.01
"Concerns about additional costs for the patient" 0–5 rating				
Europe	1.0 (2.0) [0–5] versus	Central-South America	5.0 (0.0) [5–5]	< 0.001
	1.0 (2.0) [0–5] versus	Asia	5.0 (1.0) [1–5]	< 0.001
	1.0 (2.0) [0–5] versus	Middle East	3.5(1.5) [2–5]	0.03
Public funding	1.0 (2.3) [0–5] versus	Private funding	5.0 (1.3) [0–5]	< 0.001

IQR interquartile range, *mAIDs* monogenic autoinflammatory diseases

with higher rates in Europe than Central-South America for TNFα-inhibitors ($p = 0.01$).

DISCUSSION

This survey was directed to the uveitis experts affiliated to two major scientific institutions in the field of uveitis research and autoinflammatory diseases, respectively the IUSG and the AIDA Network. Around two-thirds of the respondents completed most of the questionnaire, allowing a proper evaluation of their response profile. The geographical distribution of the sample was representative of the international academic panorama, but entirely missed Australia and Africa (except for Egypt, which we counted in the Middle East group). Most respondents were experienced professionals who have been working in the uveitis field for more than 10–20 years in academic hospitals and visit a median of 60 patients with uveitis per month. A few physicians declared themselves as pediatric ophthalmologists, but the pediatric practice accounted for less than one-fourth of the total clinical practice for most participants. Monogenic AIDs have been historically confined to the pediatric setting, but it is now acknowledged that they may occur (and be diagnosed) at any age, depending on genetic and environmental factors [5, 36–38]. Also, subjects whose disease started in childhood decades ago, when mAIDs were almost unknown, may be still seeking a diagnosis from the adult medical services, so adult ophthalmologists are still required to suspect, diagnose, and manage these diseases.

When asked to self-evaluate their knowledge of the topic, most of the participants considered it inadequate (64%), which sounds reasonable given that around 60% were never trained in uveitis associated with mAIDs and that only 30% of the respondents were personally involved in a multidisciplinary group working on mAIDs at their institute. The knowledge self-assessment was a fairly reliable parameter since it correlated both with the number of mAIDs associated to uveitis cited and with the performance of the respondent at the theoretical and clinical questionnaire. The knowledge

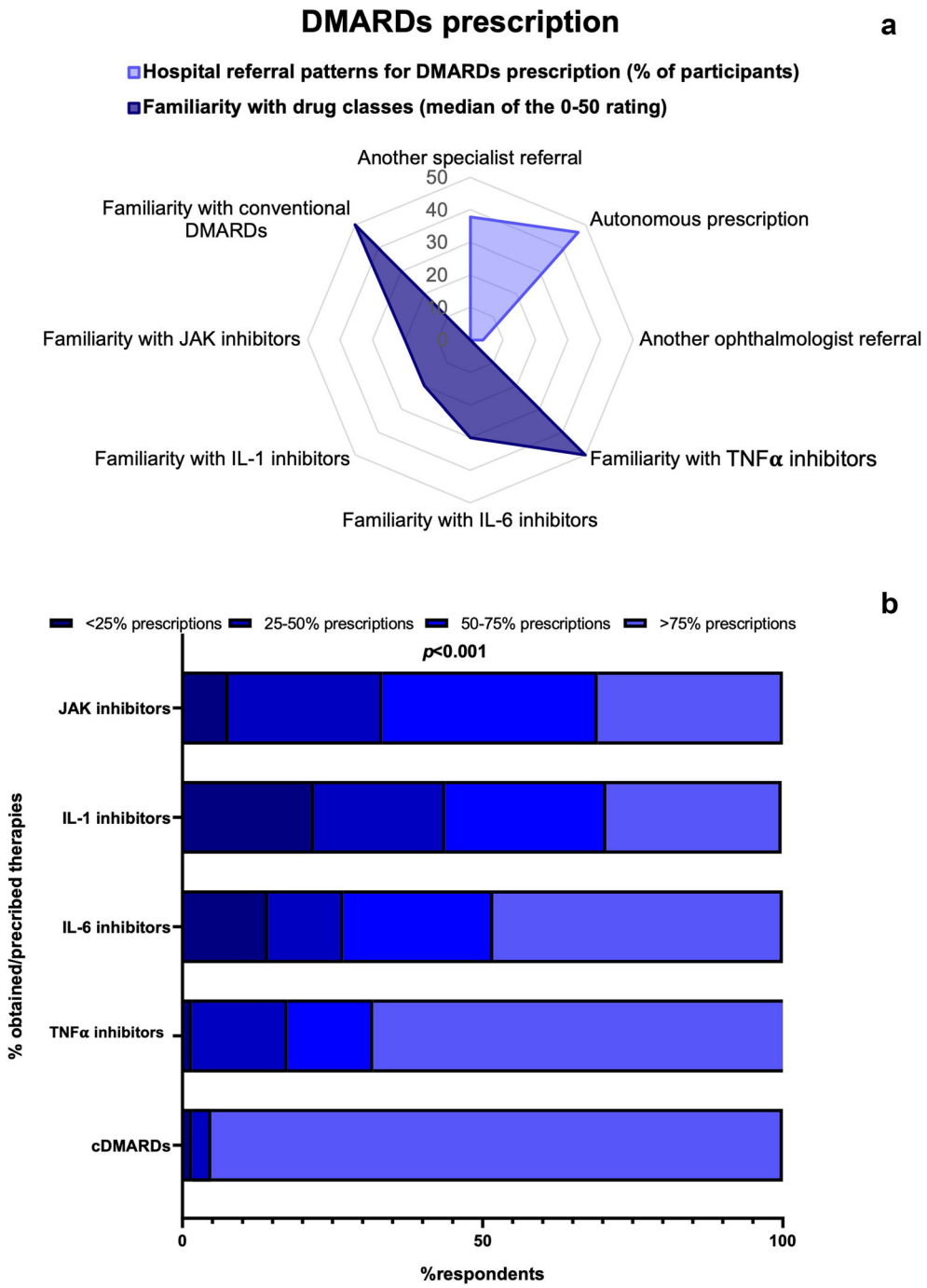


Fig. 3 Hospital referral patterns for systemic immunosuppressive therapy prescription in patients affected by monogenic uveitis (*light blue*) and median values of the familiarity rating (from 0 to 50) according to different classes of systemic immunosuppressive drugs (*blue*) (**a**). Percentage of respondents estimating an obtained/prescribed drug ratio of < 25%, 25–50%, 50–75% or > 75% according to the different classes of systemic immunosuppressive drugs (**b**). c*DMARDs* conventional disease-modifying anti-rheumatic drugs, *IL* interleukin, *JAK* Janus kinase, *TNF*α tumor necrosis factor alpha

Table 4 Differences in the ophthalmologists' perception of the importance of different barriers to systemic immunosuppressive therapy prescription in potential cases of monogenic uveitis (0 = the described barrier has no impact on the responder's behavior; 5 = the described barrier has a profound impact on the responder's behavior)

	Median(IQR)[range]		Median(IQR)[range]	*p*
"Challenges in obtaining off-label therapies" 0–5 rating				
Multidisciplinary team involving the ophthalmologist	1.5 (3.3) [0–5] versus	Multidisciplinary team not involving the ophthalmologist	5.0 (1.0) [2–5]	< 0.001
"Uncertainty about the therapeutic choice" 0–5 rating				
Having ever diagnosed mAID-associated uveitis	1.0 (3.0) [0–5] versus	mAID-associated uveitis never diagnosed	3.0 (3.5) [0–5]	0.012
Multidisciplinary team involving the ophthalmologist	0.0 (2.3) [0–5] versus	Multidisciplinary team not available	3.0 (4.0) [0–5]	< 0.001
Participation in seminars on mAIDs	1.0 (3.0) [0–5] versus	Seminars on mAIDs never attended	3.0 (4.0) [0–5]	0.014
"Concerns about additional costs for the patient" 0–5 rating				
Europe	0.0 (2.0) [0–4] versus	Central-South America	3.5 (3.5) [0–5]	0.025
	0.0 (2.0) [0–4] versus	Asia	4.0 (2.0) [0–5]	< 0.001
	0.0 (2.0) [0–4] versus	Middle East	2.5 (1.5) [2–5]	0.012
Public funding	0.5(2.0) [0–5] versus	Private funding	3.5 (3.0) [0–5]	< 0.001

IQR interquartile range, *mAIDs* monogenic autoinflammatory diseases

assessment focused on general concepts on monogenic uveitis, Blau syndrome, cryopyrinopathies, and mimics of Behçet's disease, assumed to be the most familiar topics among uveitis specialists due to historical reasons. However, around 60% of the respondents scored 2 or less than 2 points out of 6, with more difficulties in the diagnostic scenarios and in the question about the spectrum of CAPS and, on the contrary, better performance in questions about general aspects of mAIDs and therapeutic choices. Respondents with an academic background, previous participation in mAIDs seminars and/or involvement in multidisciplinary teams obtained higher scores. In addition, a geographical gradient in familiarity with mAIDs has been observed favoring Europe over Asia and the Middle East; however, this result may be distorted by the uneven distribution of participants, which makes the sample not sufficiently representative of each geographical area.

When asked to cite the first gene coming to their mind in association with monogenic uveitis, excluding those who gave a wrong answer or no answer, 74% of the ophthalmologists cited Blau syndrome, while CAPS and FMF were both cited in 7% of cases and few other diseases only once. Given the broad spectrum of possible monogenic causes of uveitis, we concluded that awareness of monogenic uveitis and autoinflammatory disorders should be promoted among ophthalmologists, especially regarding less common or newly identified clinical entities.

Except for FMF, which relies on both a clinical and a genetic diagnosis, all mAIDs require molecular detection of a genotype consistent with the patient's clinical picture. Although pure clinical and combined clinical/genetic criteria have been proposed for the classification of patients with FMF, MKD, TRAPS and CAPS, there is no consensus on their applicability for diagnostic purposes when molecular analysis is not accessible [39–41]. Therefore, the availability of genetic testing should be guaranteed for all patients with a consistent clinical suspicion of mAIDs, and a dedicated hospital referral pathway should be in place to avoid diagnostic delay. According to the results of this survey, genetic tests are available for all the participating countries, including the most efficient techniques, such as next-generation sequencing, whole exome sequencing and whole genome sequencing. Despite that, one out of five subjects with potential monogenic uveitis evaluated by an ophthalmologist at first medical consultation may not be referred for genetic testing (neither directly by the ophthalmologist nor through the consultation of another specialist, including the geneticist). Uncertainty about which genetic test to order and how to interpret the result seem to be the main reasons preventing ophthalmologists from ordering genetic testing for potential patients with monogenic uveitis. Those obstacles are perceived as more impactful where the ophthalmologists are not involved in a multidisciplinary group at the local level, have no familiarity with genetic databases such as Infevers and received no specific training in mAIDs [35]. At the same time, concerns about logistical issues and possible additional costs for the patient are reasonably more relevant in countries where genetic testing is not covered by public funds. Indeed, compared to the public healthcare system, private insurance and patient direct funding ensure a lower probability of effectively obtaining the prescribed analysis.

In regard to systemic therapies, almost two-thirds of respondents reported prescribing and managing DMARDs themselves, while the remaining respondents refer to another specialist for these treatments, including the rheumatologist or another ophthalmologist. With specific regard to the management of real or potential patients with monogenic uveitis, the most relevant obstacle perceived by the uveitis experts is the authorization needed in some countries when prescribing "off-label" interleukin inhibitors or small molecules for uveitis. To date, the TNFα inhibitor adalimumab is the only biologic drug authorized by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of pediatric chronic anterior uveitis in patients 2 years of age and older and non-infectious intermediate, posterior, and panuveitis in adults [42, 43]. In fact, even if national

and local regulatory authorities make authorization and market access patchy within and outside the EMA and FDA competence fields, TNFα inhibitors are the biologic drugs uveitis experts are more familiar with, and they show the highest obtained/prescribed drug ratio in this survey. As for the other drug classes, namely IL-1, IL-6, and JAK inhibitors, indication for uveitis treatment is still lacking and, according to our results, both the uveitis experts' familiarity and the actual availability of the drug upon prescription are noticeably lower. Most periodic inflammatory manifestations in patients affected by IL-1-driven diseases such as CAPS, MKD, TRAPS, and FMF are known to benefit from IL-1 inhibitor administration and these indications are currently authorized for canakinumab both in Europe and in the US, while anakinra is approved only for CAPS and FMF in Europe and for the most severe form of CAPS, the neonatal-onset multisystem inflammatory disease (NOMID), in the US [43, 44]. However, in some countries, the formal prescription of these molecules may be a prerogative of the rheumatology, pediatrics, or internal medicine services, where the diagnosis of mAIDs is usually made. Ophthalmologists personally involved in a multidisciplinary group working on mAIDs at their hospital feel indeed less troubled not only by the therapeutic decision per se, but also the bureaucratic procedure related to the prescription.

The AIDA-IUSG survey was meant to sensitize uveitis experts worldwide on monogenic uveitis, mostly associated to mAIDs, which are rare for sure, but underdiagnosed as well, especially outside the rheumatology and pediatric rheumatology settings. The outputs of this comprehensive survey provide invaluable insights into the current state of awareness, knowledge, and diagnostic/therapeutic practices among a cohort of international uveitis experts. The findings reveal both areas of proficiency and significant gaps in understanding, which can serve as the basis for targeted improvements in patient care and treatment outcomes. Thanks to the collaboration among specialized and non-specialized healthcare providers at both national and international levels, the most sophisticated molecular techniques are now more widely accessible than ever before, indicating the potential for global standardization in diagnostic approaches. The result is highly promising, as it suggests that the goal of achieving early diagnosis for all patients with monogenic diseases is becoming increasingly attainable worldwide. Nevertheless, it is important to acknowledge certain limitations, such as that this specific finding might have been influenced by the inclusion of a highly selected cohort of ophthalmologists, primarily from academic centers. This may be potentially due either to a greater presence of academic physicians within the AIDA Network and IUSG subscripts or to a higher response rate from the academic community. On the other hand, the relatively low percentage of physicians ordering genetic testing for suspected monogenic uveitis calls for wider adoption of molecular techniques as part of the diagnostic process. Acknowledgment is warranted by the fact that all participants held a minimum of ten years' experience as uveologists; as a result, the data's relevance to emerging specialists, who might be more inclined to incorporating genetics into their clinical approach, could be somewhat restricted. However, it is important to mention that our survey did not yield any specific findings directly supporting this hypothesis.

CONCLUSIONS

This survey disclosed major gaps in diagnosis and treatment of monogenic uveitis, which are at least in part dependent on socioeconomic inequality and weaknesses in the different healthcare systems. Besides that, the familiarity of ophthalmologists with mAIDs appears limited, as expected given the rapid evolution of this clinical field with new monogenic diseases identified every year. The identification of *NOD2* as the most commonly mentioned monogenic uveitis gene, alongside the substantial percentage of incorrect or no answers, highlights the need for enhanced education and training in this specialized field. The varying success rates in clinical scenarios underscore the importance of collaboration among multidisciplinary teams, demonstrating the potential

benefits of a more holistic approach to patient management. To enable these connections, establishing multidisciplinary groups caring for people with suspected mAIDs at the local level appears to be a crucial strategy not only to share knowledge and complementary views, but also to overcome logistical and regulatory barriers to diagnosis and treatment of these rare diseases. The establishment of the IUSG *"Genetics in Uveitis"* group of interest marks a significant milestone in the field of ophthalmology and immunogenetics. The group will serve as a dedicated platform for multidisciplinary collaboration, education, and research, with the ultimate goal of making transformative advancements in the diagnosis and treatment of monogenic uveitis and improving the quality of life for affected individuals worldwide.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Seven of the authors of this publication [Dr Carla Gaggiano, Prof Bruno Frediani, Prof Gian Marco Tosi, Dr Maria Pia Paroli, Prof Uwe Pleyer, Prof Luca Cantarini and Dr Claudia Fabiani] belong to institutes that are members of the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) [Azienda Ospedaliero-Universitaria Senese; AOU Policlinico Umberto I di Roma; Berlin Charite Universitätsmedizin]. Carla Gaggiano, Vishali Gupta, Rupesh Agrawal, Marc De Smet, Bruno Frediani, Gian Marco Tosi, Maria Pia Paroli, Sudharshan Sridharan, Carlos Pavesio, Uwe Pleyer, Ekaterina Denisova, Kalpana Babu, Alejandra de-la-Torre, Peizeng Yang, Janet Davis, Emmett Cunningham, Ester Carreño, Debra Goldstein, Alex Fonollosa, Luca Cantarini, Lucia Sobrin, and Claudia Fabiani declare that they have no competing interests.

Ethical Approval. The study protocol was notified to the Ethics Committee of Azienda Ospedaliero-Universitaria Senese on January 10, 2023 (Ref. 14951). Informed consent for using data resulting from the survey for research purposes was obtained electronically. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

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