Influence of Risk Factors and Individualized Risk Scores for Age-Related Macular Degeneration through a Variable Influence Analysis Model

Influência dos Fatores de Risco e *Scores* de Risco Individualizados na Degenerescência Macular da Idade através de um Modelo de *Variable Influence Analysis*

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ABSTRACT

INTRODUCTION: To explore the relative influence of different risk factors in age-related macular degeneration (AMD) development and progression in an epidemiologic-based study through the novel variable influence analysis (VIA) model, aiming to compute personalized AMD risk scores.

METHODS: Population-based 2-visit epidemiologic study (Coimbra Eye Study) on AMD prevalence and 6.5-year incidence. Participants were imaged with color fundus photography at both visits and additionally with NIR, FAF, and OCT at the follow-up visit. Data on medical history and risk factors were obtained, including a food frequency questionnaire to calculate adherence to the Mediterranean diet. Blood samples were collected, and 69 SNPs were genotyped with the EYE-RISK genotype assay. A novel VIA model was developed to calculate the influence score of each risk factor in the transition between AMD stages. A global patient 'risk score' for AMD was then computed.

RESULTS: We included 948 subjects, 243 with AMD and 705 controls. The transition from no AMD (Rotterdam stages 0 or 1) to AMD (Rotterdam stages 2, 3 or 4) was mainly predicted by baseline AMD stage, age, risk variants *CFHrs35292876*, *CFHrs10922109* and *ARMS2/HTRA1rs3750846*. To predict the transition to more severe stages (stages 3 and 4), the influence score of smoking almost doubles, and new influential factors that were negligible become more relevant, including diabetes, high blood pressure at baseline, and variant *C3rs2230199*.

For root cause analysis, the most influential variables, explaining what caused these transitions, were variant *C2rs429608*, adherence to Mediterranean diet, physical exercise, body mass index, and arterial hypertension.

Based on the influence scores obtained, global AMD risk scores were computed for each participant.

CONCLUSION: The risk of AMD development was mainly predicted by baseline age, and risk variants in *CFH* and *AMRS2/HTRA1*, while clinical and lifestyle factors, including diet, were influential

in causing such transition from no disease to disease. As the disease progressed to more severe stages, other clinical risk factors such as smoking almost doubled its influence score, and clinical factors like diabetes and high blood pressure became more relevant. This approach enables personalized AMD risk scores, allowing targeted interventions to risk reduction by addressing modifiable risk factors.

KEYWORDS: Macular Degeneration/genetics; Precision Medicine; Risk Factors.

RESUMO

INTRODUÇÃO: Explorar a influência relativa de diferentes fatores de risco no desenvolvimento e progressão da degenerescência macular relacionada com a idade (DMRI) num estudo epidemiológico através do novo modelo *variable influence analysis* (VIA), com o objetivo de calcular *scores* de risco personalizados.

MÉTODOS: Estudo epidemiológico populacional com 2 visitas (*Coimbra Eye Study*) sobre a prevalência de DMRI e incidência a 6,5 anos. Os participantes foram avaliados com retinografia e, adicionalmente, com NIR, FAF e OCT na visita de *follow-up*. Avaliaram-se os antecedentes e fatores de risco, incluindo um questionário de frequência alimentar para calcular a adesão à dieta mediterrânica. Recolheu-se amostras de sangue e genotipou-se 69 *SNPs*, segundo o consórcio *EYE-RISK*. Foi desenvolvido um modelo VIA para calcular o *score* de influência de cada fator de risco na transição entre os estádios da DMRI. Um *score* de risco global para DMRI foi calculado para cada paciente.

RESULTADOS: Incluiu-se 948 participantes, 243 com DMRI e 705 controlos. Os principais fatores preditores da transição "ausência de DMRI" (estádios de Rotterdam 0 ou 1) para "DMRI" (estádios de Rotterdam 2, 3 ou 4) foram: estádio inicial da doença, idade, e as variantes de risco *CFHrs35292876*, *CFHrs10922109* e *ARMS2/HTRA1rs3750846*. Para prever a transição para estádios mais severos (estágios 3 e 4), o *score* de influência do tabagismo quase duplicou, e novos fatores previamente negligenciáveis tornaram-se relevantes: diabetes, hipertensão arterial e a variante *C3rs2230199*.

Na análise *root cause*, as variáveis mais influentes foram a variante *C2rs429608*, adesão à dieta mediterrânea, exercício, índice de massa corporal e hipertensão arterial.

Com base nestes *scores*, calculou-se *scores* globais de risco para cada participante.

CONCLUSÃO: Os principais fatores preditores do risco de desenvolver DMRI foram a idade e variantes de risco nos genes *CFH* e *AMRS2/HTRA1*. Fatores clínicos e de estilo de vida, incluindo a dieta, foram influentes na transição de não-doença para doença. Com a progressão para estádios mais graves, outros fatores clínicos de risco, como o tabagismo, diabetes e hipertensão arterial tornaram-se mais relevantes. Essa abordagem permite a personalização dos scores de risco de DMRI, possibilitando intervenções em fatores de risco modificáveis para a redução de risco.

PALAVRAS-CHAVE: Degenerescência Macular/genética; Fatores de Risco; Medicina de Precisão.

INTRODUCTION

Age-related macular degeneration (AMD) is currently the leading cause of irreversible blindness in older individuals in developed countries.[1–3] AMD is commonly classified into three stages: early, intermediate, and late AMD, which can manifest as either atrophic (dry) or neovascular (wet) macular degeneration.[4] Dry AMD makes up for the majority of diagnosed cases, and currently lacks approved treatment in Europe, while neovascular AMD is responsible for most cases of severe vision loss.[5] Therefore, considerable efforts are focused on creating strategies to predict the individual risk of developing AMD and to prevent disease progression to later stages. However, these goals have been hard to achieve due to the multifactorial nature of the condition, which is influenced by demographic, environmental, and genetic factors.[6,7]

Numerous genetic variants have been associated with AMD. Significant risk effects have consistently been associated with common and rare variants found at the *CFH* and *ARMS2/HTRA1* loci, which have been utilized to calculate genetic risk scores (GRS).[8,9] By estimating the preponderance of these genetic factors, together with previously known AMD-related factors such as smoking, diet, sex, and body mass index (BMI), a global risk score could be computed to help guide interventions that could delay the development and progression of the disease.

Risk prediction models can be used to support decision-making for various medical conditions, yet their adoption in clinical practice remains limited.[10] A complex challenge

with conventional, widely used regression models is their difficulty to incorporate the complex interdependencies between variables. Additionally, they often face limitations when dealing with numerous risk factors that have only minor individual effects, as is the case of AMD.[10] These challenges are addressed by Bayesian networks (BNs), which present as flexible, probabilistic graphical models that represent dependency relationships between selected variables.[10] BNs deal with the probability of a hypothesis given a particular dataset, incorporating prior information into the analysis and updating hypothesis probabilities as more data becomes available.[11]

Our work aims to investigate the relative influence of several risk factors on the development and progression of AMD in an epidemiologic-based study and enable data-driven decisions to reduce a patient´s risk score. To achieve this, the Department of Mathematics of the University of Aveiro utilized a novel variable influence analysis (VIA) model, which is a generalization of Bayesian networks (BN) based on belief propagation (BP).

MATERIAL AND METHODS

STUDY POPULATION AND DATA COLLECTION

The Epidemiological Coimbra Eye Study (NCT01298674) estimated AMD prevalence in two distinct Portuguese populations aged 55 and older – one inland (Lousã) and one coastal (Mira).[12] The AMD Incidence study (NCT02748824),[13] a single-centre population-based study, was conducted 6.5 years later and included only participants from the coastal town. The Rotterdam staging system[14] was used to classify the AMD stage by using color fundus photography (CFP) at baseline and a multimodal evaluation at the follow-up visit (CFP, spectral domain optical coherence tomography (SD-OCT), near infra-red (NIR), and autofluorescence (FAF) imaging). Blood was also collected for genetic analysis in the consenting patients of Mira cohort. The following characteristic variables were collected: age, gender, body mass index (BMI), exercise and smoking habits, history of diabetes or high blood pressure, adherence to the Mediterranean diet, genetic variants and AMD stage.

Signed informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Commission of the Faculty of Association for Innovation and Biomedical Research on Light and Image (AIBILI).

GENETIC SEQUENCING PROCEDURES

Genomic DNA samples from participants in the AMD Incidence Study were genotyped using standard procedures as part of a collaboration with E3-The European Eye Epidemiology Consortium and the EYE-RISK Consortium. Of the 948 genomic DNA samples obtained, 243 corresponded to AMD cases (Rotterdam Classification stages 2 to 4) and 705 to controls (Rotterdam Classification stage 0 and 1).

DATA PREPARATION

From the original AMD dataset, the relevant characteristic variables were grouped into five categories: demographic (age, sex, BMI), clinical (diabetes, arterial hypertension), lifestyle (smoking history, physical activity, adherence to a Mediterranean diet), genetic variants and phenotype variables (AMD stage). Some characteristics were measured at baseline and follow-up visit 6.5 years later and were treated as separate variables. Only subjects with major risk variants genotyped (*CFHrs570618*, *CFHrs10922109*, *C2/CFB/SKIV2Lrs429608*, *ARMS2/HTRA1rs3750846* and *C3rs2230199*) were considered for the Genetic Risk Score (GRS) computation, along with variants previously reported as significantly associated with AMD in our cohort (*CFH rs35292876*, *SLC16A8 rs8135665*, *ARMS2rs10490924*, *TGFBR1rs1626340*),[15] making a total of 9 SNPs.

VARIABLE INFLUENCE ANALYSIS

The Center for Research and Development in Mathematics and Applications (CIDMA) of University of Aveiro developed a Variable Influence Analysis model, a Belief Propagation based generalization of Bayesian networks. Similar to the BN structure, in the VIA model each characteristic value was assumed to directly influence the manifestation of AMD. However, contrary to BNs, the developed VIA model did not require the verification of independence between variables (*ie*, BMI may be dependent on diet and exercise) and was able to deal with any relationships between the characteristics and the disease. These metrics allowed for the computation of risk and protective effects tailored more effectively to our dataset compared to BN-derived results. Some prior knowledge from the literature, regarding AMD risk and protective factors, is required for the VIA algorithm to determine (automatically) which are the suited metrics for each variable. The metrics available are specifically designed to measure the relevance of the variables to be correctly used for root cause analysis or for predictive approaches.

RESULTS

Among the 1617 eligible participants in the AMD incidence study, a total of 948 subjects underwent genotyping, with 243 diagnosed with AMD and 705 serving as controls.

We calculated the influence scores for the transition from no disease (Rotterdam stages 0 or 1) to disease (Rotterdam stages 2, 3, 4), dividing them into predictive metrics or root cause metrics. Root cause metrics are tailored to explain what causes a transition between disease stages, instead of having a predictive value for the disease status. The influence scores ranged from 0 to 1, and the values for each risk characteristic are presented in Figs. 1 and 2.

The predictive characteristics with a higher score for the transition no-disease/disease were: baseline AMD stage, age, and major genetic variants in the *CFH* and *ARMS2*/

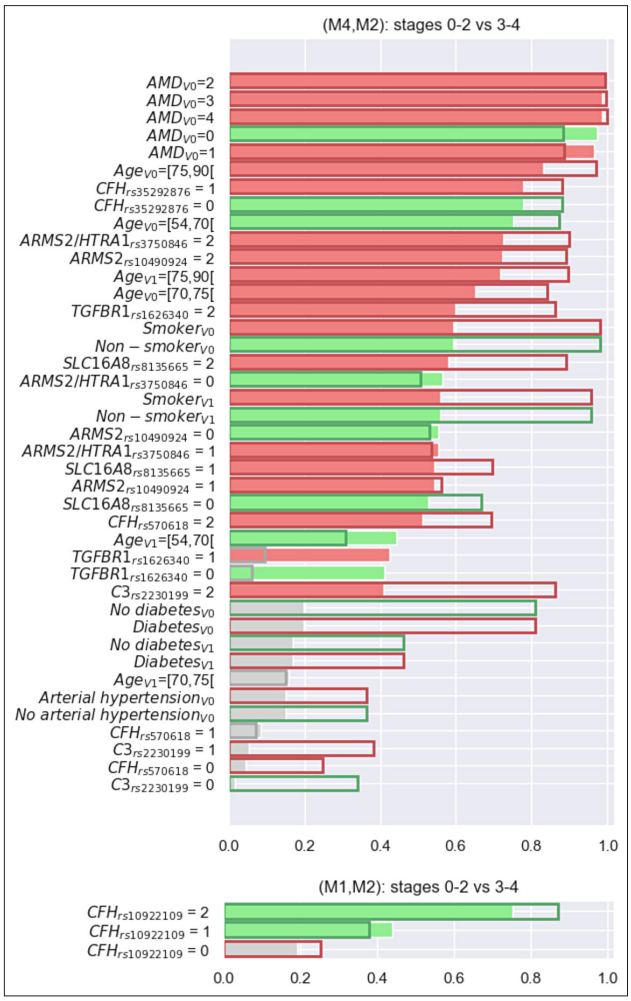

Figure 1. Representation of the most relevant characteristics influence scores for each pair of metrics. Transitions from stage 0-1 *vs* stage 2-4 (no disease/disease) are represented with solid bars and transitions between stage 0-2 *vs* stage 3-4 are represented with non-solid bars. The magnitude of the positive values (for AMD risk factors) is represented in red, while the magnitude of the negative values (for AMD protective factors) is represented in green. Values of 0.2 or lower were considered negligible.

HTRA1 genes (Fig. 1). However, for root cause analysis, the most influential variables were a genetic variant in the *C2* gene, adherence to the Mediterranean diet, physical activity, BMI, and arterial hypertension, representing lifestyle, demographic, and clinical factors (Fig. 2).

When analysing the transition to more severe AMD stages (stages 3 and 4), other risk factors became more relevant in the predictive analysis (Fig. 1). Most characteristics showed an increase in influence, with smoking and comorbidities like diabetes (which was previously negligible) showing the greatest increment. These, together with additional genetic variants, subsequently became the most influential. For the root cause analysis, the scores remained almost unchanged (Fig. 2).

A personalized global AMD risk score was then created for individuals in our population, based on the influence score for each characteristic. Fig. 3 illustrates the example of

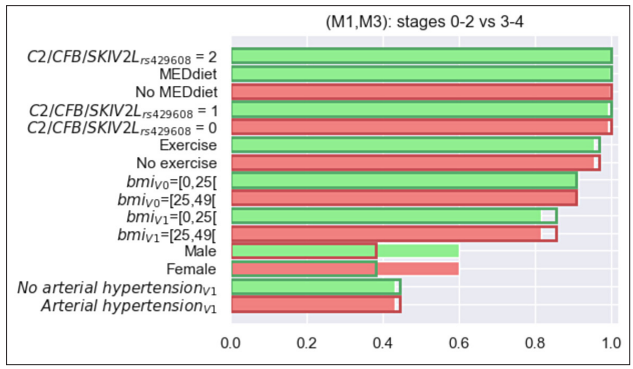

Figure 2. Root cause analysis representation of the characteristics explaining the transition between stage 0-1 *vs* stage 2-4 (no disease/disease) at 6.5 years of follow-up, represented with solid bars. The analysis for the transition from stages 0-2 *vs* stages 3-4 (progression to advanced disease) is represented with non-solid bars. The magnitude of the positive values (for AMD risk factors) is represented in red, while the magnitude of the negative values (for AMD protective factors) is represented in green. Values of 0.2 or lower were considered negligible.

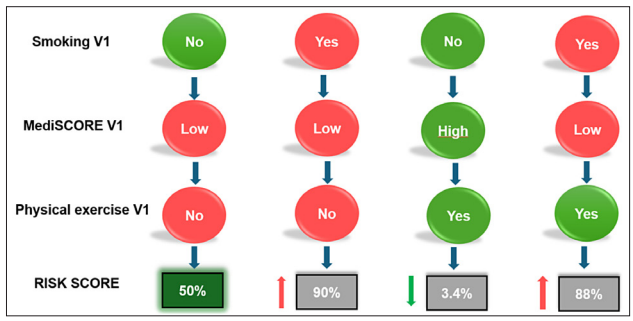

Figure 3. Modifiable characteristics at visit *V1* [smoking, adherence to the Mediterranean diet (MediSCORE), and physical exercise] for a 67-year-old female *CFHrs35292876* carrier, and the respective global risk score for transitioning from stages 0 or 1 to stages 2 to 4.

a 67-year-old female, carrier of the *CFHrs35292876* variant, who progressed from stage 1 to stage 3. At baseline, she did not smoke, had a low adherence to the Mediterranean diet and did not pursue physical exercise. Her global risk was calculated at 50%. Hypothetically, in a different scenario, if she started smoking and pursued physical exercise, her risk would have increased to 88%, but if she had improved the adherence to the Mediterranean diet and pursued physical exercise, her risk would further decrease to 3.4%.

DISCUSSION AND CONCLUSION

This is the first study to investigate, simultaneously, the relative impact of several risk factors on the development and progression of AMD using a VIA model in an epidemiological study, ultimately calculating personalized AMD risk scores. To predict the transition to AMD (disease onset), we found that age and major genetic variants in the *CFH* and *ARMS2* genes had the highest influence scores. However, to predict the progression to intermediate or late AMD stages, smoking, diabetes, high blood pressure, and additional genetic variants gained particular relevance, showing that different risk factors may predict disease on-

set and disease transition to more severe stages. Additionally, the genetic variant in the *C2* gene, adherence to the Mediterranean diet, physical exercise, BMI, and arterial hypertension explained what caused these transitions.

Genome-wide association studies (GWAS) have identified 52 variants across 34 genomic regions strongly associated with AMD.[16] While common variants influence AMD development, rare variants have a significant impact as well.[15] In our previous study by Farinha and colleagues, the rare *CFH* variant *rs35292876*, identified as a low-frequency variant in the population, conferred the highest risk of AMD and the greatest risk of progression during follow-up.[8] However, the etiology of AMD depends not only on the genetic background but is also modified by environmental factors.[9,17] Thus, a score that integrates genetic and lifestyle factors alongside phenotypic characteristics, and weighs the relative impact of each risk factor in an individualized and personalized manner, may provide a more comprehensive assessment of the disease personalized risk rather than relying on GRS alone.[18,19]

Most models for risk prediction of diseases today are based on regression prediction models, which fail to incorporate dependencies among variables and the presence of numerous risk factors with only a small effect.[10] There are several reasons why BNs outperform standard regression models in disease risk assessment: BNs need fewer data to reach their best performance when compared to logistic regression, are easier to interpret due to the graphical representation, can include prior information, and have the flexibility to include both observational and causal inference.[10] Also, even if the naïve assumption of conditional independence between variables is violated, the asymptotic error with BNs is still lower than with logistic regression, even if more data is incorporated.[10,20]

With the interest in predicting the disease risk for a new patient, given what is already known for previous patients, it becomes more appropriate to formulate the problem with the Bayesian paradigm.[10] Root cause analysis refers to various methods designed to understand how and why an incident occurs, with the ultimate goal of identifying measures to prevent similar occurrences in the future.[21,22] One approach to root cause analysis involves learning data-driven methods like machine learning, deep learning, or BNs, which can learn directly from data and require minimal human intervention.[22] Machine learning encompasses a set of methods that enable systems to learn and improve automatically through experience.[23] It is divided into supervised learning (for classification), unsupervised learning (for clustering), and reinforcement learning (for decision-making).[10] An example of supervised learning, which is applied when predicting outcomes from input variables, are BNs.[10,11]

The improved accuracy in machine learning and deep learning models often comes with increased complexity.[21] Even though this complexity, combined with large datasets, increases predictive power, it simultaneously reduces the transparency of the model´s inner workings.[21] Consequently, the rationale behind their decisions becomes hard to understand, and their predictions become hard to interpret. There is a clear trade-off between the performance of machine-learning and deep-learning models and their ability to generate explainable and interpretable predictions, functioning as "black boxes" when actionable insights are needed for decision-making.[22,24,25]

Given these limitations, CIDMA researchers employed a novel VIA model to calculate the influence scores of individual risk factors on AMD development. This model allowed the assessment of how changes in modifiable risk factors could significantly impact the reduction of disease risk. Developing effective treatments for neovascular AMD requires a deeper understanding of who is most at risk of progression and improving tools to accurately track disease progression over time.[18,26] From our results, differences in the influential characteristics were found, depending on whether we were predicting the disease stage at follow-up or investigating the factors that caused this transition through root cause analysis: in the first, AMD stage at baseline, older age, and certain genetic variants of *CFH* and *ARMS2/HTRA* where the most influential, while in the second, a genetic variant in the *C2*, adherence to the Mediterranean diet, exercise, BMI, and arterial hypertension gained notoriety. In the progression to more severe disease stages, other risk factors such as smoking, diabetes and additional genetic variants became more relevant in the predictive analysis. Taken together, the most influential risk factors predictive of the transition to intermediate or late AMD and the risk factors causing the transition from non-disease to disease and the transition from early to intermediate or late AMD are pointing to potentially modifiable risk factors

There are currently no approved targeted interventions to prevent the onset of intermediate or late-stage AMD, however, lifestyle changes and supplements can help lower the risk of progressing from early to late-stage AMD. Smoking, for example, is considered the most consistent modifiable risk factor for AMD, with a 2-4 fold increased risk for all forms of disease.[26,27] On the other hand, adherence to a Mediterranean diet and regular exercise has been found to delay AMD progression.[18] By calculating risk scores based on different possible states of modifiable factors (as opposed to fixed genetic traits), physicians can offer valuable guidance on actions that may help lower a patient´s risk of progressing to more severe stages of AMD (Fig. 3).

Contrary to pre-existing models,[28] our VIA model allows for data-driven decisions to reduce a patient´s AMD risk, by obtaining each characteristic´s (risk factor) influence score, for any transition between AMD stages at two different time points. As such, it calculates a personalized and individualized AMD risk score based on demographic, clinical, and lifestyle characteristics. As an example, we analysed the case of a 67-year-old female with the *CFHrs35292876* variant who progressed from stage 1 to stage 3. At follow-up, as a non-smoker with low adherence to the Mediterranean diet and no exercise, her risk was 50%. If she started smoking, her risk would rise to 88%, but if she improved her diet and exercise, her global risk would lower to 3.4%.

Our study has some limitations that should be considered when interpreting our results. First, the developed model may be overly fitted to our study population and may not be extrapolated to other populations. As such, calculating the risk score for individuals of a different group outside the one of our model may lead to less accurate outcomes. Also, the model assumed that the various characteristics were independent of each other, so future improvements could involve incorporating their interrelationships into the model.

In conclusion, the new VIA model appears to demonstrate great potential to assist healthcare providers in determining the most effective interventions for reducing the risk of AMD. With this model, predictive factors were separated from causal factors, with the latter showing potential for intervention, since most were modifiable risk factors. In addition, risk stratification was possible to compute for each individual in our cohort, along with tailored identification of which risk factors' magnitude of change led to a global decrease in the disease risk in a personalized way. By calculating risk scores based on different possible states of modifiable factors (as opposed to fixed genetic traits), physicians can offer valuable guidance on actions that may help lower a patient's risk of progressing to more severe stages of AMD. In practical terms, this includes smoking cessation, adopting a Mediterranean diet rich in fruits, vegetables, whole grains, fish, and healthy fats, engaging in regular physical activity, maintaining a healthy body mass index, and controlling systemic conditions such as hypertension and diabetes. Future research should focus on externally validating the model across different populations or independent databases to evaluate its generalizability. Such studies could lead to the development of a reliable AMD risk score suitable for routine clinical use, supporting personalized prevention and patient counselling.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

IF: Conceptualization, drafting of the text, sourcing and editing of investigation results.

JM, CF, PB, RC, MLC, ER, RS: critical revision for important intellectual content.

All authors approved the final version to be published.

IF: Conceptualização, redação do texto, obtenção e edição dos resultados da investigação.

JM, CF, PB, RC, MLC, ER, RS: Revisão crítica do conteúdo intelectual relevante.

Todos os autores aprovaram a versão final a ser publicada.

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Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

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Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

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