Macula Risk: predictive testing for the risk of age-related macular degeneration

Information Monitoring Summary

*Documentary research*
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Summary

Macula Risk® is a test that determines a person’s lifetime risk of developing advanced stage age-related macular degeneration (ARMD), by analyzing a saliva sample for genetic variations strongly associated with ARMD. This test is the result of numerous intensive, rigorous research conducted jointly by many different universities on more than 20,000 subjects. It is apparently able to identify ARMD genes with 100% accuracy and detect 70% of individuals who will develop ARMD. However, the test is less reliable if the subject is non-white.

Macula Risk is intended among others for people showing the first signs of AMD or those who have immediate relatives with the disease. Identifying individuals at risk would allow for closer ophthalmological monitoring and earlier diagnosis and treatment of AMD, which would help to prevent or delay vision loss. Knowing that they are strongly predisposed to ARMD may encourage people to modify their lifestyle to lower their risk, for example by giving up smoking and maintaining a healthier diet.

Before recommending genetic testing, it is important to consider whether the person really wants to know more about their risks, and how they will react to the results. A number of variables should also be contemplated, such as the predictive validity of the test, about which we found no information, the accuracy of the test, the psychological impact of the results, possible consequences in terms of employment and insurability of the person tested, and the availability of genetic counseling and prophylactic treatments to reduce the risk of the illness. We should also think about whether genotyping improves diagnosis of ARMD and whether the test results can impact the management of detected cases, particularly since even if the person is at higher risk due to genetic modifications, they will not necessarily develop the disease. It is also important to decide whether genetic profiling is a better predictor than classic risk factors such as phenotype for soft drusen and pigment changes, smoking and family history.
1. Background

A private Canadian company, ArcticDx Inc, recently launched the Macula Risk® test, which assess the risk of Age-related Macular Degeneration (ARMD) progression from early or intermediate to advanced ARMD. This article seeks to provide as much insight as possible into this new test.

2. What is ARMD?

ARMD is the leading cause of impaired vision in people aged 55 and over in industrialized countries [2]. There are two forms of the illness: dry and wet. It is apparently caused by abnormal vascular and inflammatory reactions in the eye. One of the first signs is the presence of drusen, which are sediments on the retina. Over time, these increase in size and number. An inflammatory reaction occurs and may trigger abnormal growth of blood vessels beneath the macula, a sub-retinal hemorrhage, fluid exudation, and various other types of retinal damage [7]. ARMD is classified in 5 stages; stages 4 and 5 are the advanced form, characterized by geographic atrophy and choroidal neovascularization [3].

3. Risk factors

The risk factors for developing ARMD are [3; 7]:

- Advanced age. Risk increases with age, particularly after 50. Prevalence of early ARMD would increase from 8% in persons 43 to 54 of age to 30% in those aged 75 and over. Prevalence of the advanced form of ARMD is reported to increase from 0.1% to 7.1% in these two age groups [7].
- A history of smoking in the past 20 years. Smokers appear to be 2 to 3 times more likely than non-smokers to develop ARMD [12; 7];
- Obesity (high body mass index);
- High consumption of vegetable fats;
- Low consumption of antioxidants and zinc.
- Genetic factors (known family history of ARMD);
- Presence of specific genetic variants;
- Being Caucasian (white);
- Being female;
Age, smoking and obesity are the three main non-genetic factors [13; 14].

4. What is Macula Risk?
The Macula Risk® test is designed to determine the lifetime risk of developing advanced stage ARMD (category 4 or 5). The calculation is based on the analysis of a saliva sample, to test for genetic variations associated with an increased risk of ARMD. The analysis report sets out risk in percentage terms of being diagnosed with the advanced form of ARMD by 5-year width strata from age 50, as compared to the North American average. The report also states the degree of risk (low, medium, moderate, high or very high) of developing the advanced form of ARMD at age 80.

The Macula Risk test looks at DNA sequences in eight genes strongly associated with ARMD, and examines certain variants of them, known as single-nucleotide polymorphisms (SNPs). The analyses focus on the following genes [3]:

- The complement factor H (CFH) region on chromosome 1. This gene encodes a protein involved in inflammation, which may lead to macular damage. Many sequence variations (haplotypes) may occur in this gene. The Macula Risk test distinguishes eight different CFH haplotypes. Some are highly protective (reduced risk of ARMD) and some are neutral, while others are associated with a significant increase in risk [9]. CFH haplotypes are the chief predictors of risk for ARMD; however, their clinical importance varies according to ethnicity [3].

- Complement factor 3 (C3), which affects the functions of proteins activated in inflammation. People who have inherited the risk allele are twice as likely to develop ARMD [3; 14; 17].

- The ARMS2 gene, located on chromosome 10. This encodes a protein that plays a major role in the response to oxidative stress [3]. ARMS2 is linked to the advanced forms of wet and dry ARMD. A sequence of the variant in ARMS2 is associated with an up to seven times greater risk of developing ARMD [3].

- Mutations in mitochondrial DNA 4917G. A variant in the mitochondrial DNA sequence is associated with double the risk of developing ARMD through deterioration in the response to oxidative stress [3].

The Macula Risk test is the culmination of numerous intensive, rigorous research conducted jointly by various universities (including Cambridge, Harvard, Miami, Duke, Michigan and Vanderbilt) on over 20,000 subjects [3; 9]. The data used to develop the prediction algorithm comes from 26 independent peer-reviewed published articles [1]. All of the Macula Risk markers have been validated in at least two independent peer-reviewed studies.
Macula Risk testing can apparently identify ARMD genes with 100% accuracy and detect 70% of the people who will develop ARMD [16]. According to the Macula Risk website, a wide-ranging independent prospective clinical study, including many (but not all) of the Macula Risk genes, demonstrated a predictive value of 83% when the genes were used in combination with other factors, such as a history of smoking, to predict vision loss in ARMD [15]. Literature produced by ArcticDx indicates that Macula Risk calculates the risk based on an algorithm taking into account the person’s genetic data and their smoking history [1]. It should be noted, however, that at present, smoking history is not recorded and this variable is not therefore considered in calculating the risk (personal communication with Brigitte St-Hilaire, account manager, Eastern Canada, Clarion Medical Technologies, Ophthalmology Division, April 20th, 2009). On the other hand, the report provides general information about the potential impact of non-genetic factors (smoking, obesity, hyperlipidemia, diet high in fats and/or meats, hypertension) on the risks of developing ARMD. It also gives advice about what the person can do to reduce their risks of developing advanced ARMD.

The Macula Risk® test is developed by ArcticDx Inc. It is distributed in Canada by Clarion Medical Technologies (Cambridge, Ontario).

5. Administering the test
A saliva sample is collected in the vision professional’s office. The sample is then sent to a laboratory in Hamilton (Ontario) where it is analyzed to determine the presence or absence of genes associated with ARMD. The $750 analysis fee is payable by the individual being tested. In 2 to 4 weeks, the practitioner receives two copies of the report, one for the patient and the other for their file. They should then meet with the patient to explain the results. It is estimated that vision professionals will require 30 minutes to inform the patient about the test, administer it and explain the results (personal communication with Brigitte St-Hilaire, April 20th, 2009).

6. Potential benefits of the Macula Risk test
According to the promoters of Macula Risk, this test is intended, among others, for adults showing the first signs of ARMD. Individuals who have one or more immediate relatives (father, mother, brother or sister) with ARMD are also part of this target population. Direct descendants of a person with wet ARMD have a 50% risk of acquiring the same condition; of these, 1 in 5 (20%) will apparently lose their sight as they age [1].

The principal advantage of this test is that it identifies persons at risk so that they can be closely monitored as the disease progresses. Early detection can potentially mean significantly better final vision in a person who goes on to develop advanced ARMD [6]. Treatment efficacy is superior in individuals who are diagnosed earlier, have better
basic visual acuity and smaller lesions. When people are aware from the earliest stage of the disease that they are at high risk of losing their sight, they may decide to consult an ophthalmologist sooner. It is expected that the ophthalmologist will then be able to monitor the person more closely in order to diagnose and treat their ARMD earlier, thereby helping to prevent or delay vision loss [1; 6; 11]. In addition, knowing that they are highly predisposed to ARMD may encourage the person to make changes in their lifestyle, for example stop smoking and adopt a healthier diet, in order to lower their risks [6].

7. Potential impact of test results on the individual

In an editorial published in the scientific journal *Ophthalmology* (2006), Dr. Albert O. Edwards does not automatically recommend using genetic testing for predisposition to ARMD, given that this practice may have major consequences for patients [5]. Diverse variables should be considered before recommending a genetic test, such as the test’s predictive validity and its accuracy, the psychological impact of the results, possible consequences affecting the subject’s employment and insurability, and the availability of genetic counseling and prophylactic treatment that could reduce the risk of the illness. It is also important to consider whether the patient really wants to know more about their risks, and how they will react to the results. Some people prefer not to be given this type of information, fearing it will cause them needless anxiety; they should acknowledge this and the practitioner should respect their decision [6]. However, other patients may feel they should find out their risk profile (e.g. if an immediate relative has ARMD) and may want to be tested.

As already mentioned, lifestyle changes such as smoking cessation and a healthier diet can reduce the risk of developing ARMD. In cases where predicting high risk motivates the person to makes positive lifestyle changes and maintain them, the test could deliver substantial benefits for society and the individual alike. On the other hand, the question then arises as to what steps people will take if genetic testing finds their risk of developing ARMD is below average [8].

8. Limitations of the Macula Risk test

The risk calculation used in the Macula Risk test is based on clinical studies involving Caucasian subjects [12]. Very little data is available on the genetic variants associated with ARMD in non-Caucasian individuals, though they are clearly at lower risk. If the person is non-white or has a recent family history of the disease in non-Caucasians, the Macula Risk test results are less reliable.

We also know that the prevalence of ARMD in men is much lower than in women. However, the literature consulted does not indicate whether the “gender” variable is
taken into account in the Macula Risk test. If it is not, then the risk of developing ARMD that is predicted for a man is probably overestimated.

9. Limitations of genetic testing
Genetic identification clearly opens the way to new scientific research. Advances in genetics are providing major insights into the pathogenesis of ARMD and could lead to new therapies, more targeted applications of genotype-based therapies, and improved care [4; 10]. However, there are certain inherent limitations and caution should be exercised when interpreting results and using them in the clinical setting. For example, in most studies assessing the risk of developing ARMD based on certain markers, estimations are based on comparison between extreme phenotypes: a group of subjects with advanced ARMD is contrasted with a control group of individuals with no, or very few, clinical results [8]. For this reason, it is highly likely that the test’s predictive result overestimates the relative risk and discriminating power for individuals with intermediate clinical results [8]. Longitudinal studies are therefore needed to allow for a more accurate assessment of the potential value of genetic data in terms of predicting the lifetime risk of ARMD.

We also need to consider whether or not these genetic discoveries currently enable us to improve our prediction of the end result, i.e. whether they allow us to distinguish between people who will develop the disease and those who will not. For example, the Macula Risk test is based on a risk calculation model. Yet in most models of this kind, predicted or estimated risk does not necessarily correspond with actual risk. A set of markers may be very strongly linked to a risk but not be clinically valid, i.e. not discriminate well between people with the disease and those without it [8]. The data consulted during preparation of this article did not supply any information regarding the discriminant validity of the test.

Another point to consider is whether the test results can influence management of detected cases, particularly since even if the person is at higher risk due to genetic modifications, they will not necessarily develop the disease [5]. According to Despriet, Klaver, van Duijn and Janssens (2007), genetic profiling needs to be a better predictor than classic risk factors such as phenotype for soft drusen and pigment changes, smoking and family history [4].

In his editorial (2006), Dr. Edwards stated that at this time, the diagnosis of ARMD remains based on clinical examination, not genetic testing and that there is no support for basing preventative therapy or management of choroidal neovascularization on genetic testing. He added that no evidence exists that smoking or other reported modifiable risk factors for development or progression of ARMD are more or less important in subjects with specific CFH genotypes, and that genotypes probably do not predict the risk of developing complications of ARMD. Moreover, according to Dr. Alan
Cruess, Head of the Department of Ophthalmology & Visual Sciences at Dalhousie University (Halifax), tests for genetic predisposition to ARMD are only in their initial stages and not yet ready for large-scale use [6]. Further progress is needed before we can select the treatments best suited to the genetic baggage of each individual.

10. Conclusion
The Macula Risk® test represents valuable scientific progress by enabling us to determine the lifetime risk of developing advanced stage ARMD (category 4 or 5). It is hoped that individuals identified as high risk will now consult an ophthalmologist sooner, so that they can be more closely monitored and where applicable, diagnosed and treated for ARMD earlier, so as to prevent or delay vision loss. In preventive terms, people who find out that they are strongly predisposed to ARMD may be encouraged to modify their lifestyle in order to lower their risk, for example by giving up smoking and adopting a healthier diet. However, we do not yet know whether this test improves our capacity to diagnose ARMD, or whether the test results can influence the way detected cases are managed, particularly since a person who is at high risk due to genetic modifications will not necessarily go on to develop the disease.
11. Appendix

The following scientific articles give details about the experimental data supporting the technical and interpretative components of the Macula Risk test. The list comes from Renseignements supplémentaires au sujet du rapport Macula Risk [3].

**Complement factor H haplotypes and risk of ARMD**

Hageman GS et al. (2006). Extended haplotypes in the complement factor H (CFH) and CFH-related (CFHR) family of genes protect against age-related macular degeneration: characterization, ethnic distribution and evolutionary implications. *Annals of Medicine* 38(8): 592-604


Li M et al. (2006). CFH haplotypes without the Y402H coding variant show strong association with susceptibility to age-related macular degeneration. *Nature Genetics* 38: 1049-1054


**CF3 and risk of ARMD**


**ARMS2 and risk of ARMD**


Rivera A et al. (2005). Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. *Human Molecular Genetics* 14: 3227-3236

**Mitochondrial DNA polymorphism and risk of ARMD**

References


3. Bay Area Genetic Laboratory. (n/a). Renseignements supplémentaires au sujet du rapport Macula Risk.


