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Corporate Medical Policy

Genetic Testing for Ophthalmologic Conditions AHS-M2083

File Name: genetic_testing_for_ophthalmologic_conditions_
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Description of Procedure or Service

Genetic eye diseases involve every part of the eye, including the visual system and ocular adnexa (accessory structures attached to the eye, such as the eyelids, extraocular muscles and orbits); conditions within this group of disorders may be rare or common, and they may exhibit a significant impact on vision or may not affect eyesight at all (Lee & Couser, 2016). Many genes involved in ophthalmologic disorders are now mapped and, due to this, scientists have developed a greater understanding of how these genes influence vision and eye health (Singh & Tyagi, 2018).

Related Policies:
Genetic Testing for Connective Tissue Disorders AHS-M2144
Genetic Testing, Somatic Disorders AHS-M2146

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for genetic testing for ophthalmologic conditions when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Ophthalmologic Conditions is covered

1. For individuals with clinical signs of an inherited retinal degeneration (see Note 1), single gene or multi-gene panel testing is considered medically necessary.
2. For individuals with retinal dystrophy, genetic testing of *RPE65* prior to treatment with Luxturna (voretigene neparvovec-rzyl) is considered medically necessary and **is required.**

When Genetic Testing for Ophthalmologic Conditions is not covered

1. Genetic testing for age-related macular degeneration is considered investigational for all applications.

2. For individuals with ophthalmologic conditions, whole exome sequencing (WES) and/or whole genome sequencing (WGS) is considered investigational for all applications.

Note 1: The American Academy of Ophthalmology recommends genetic diagnostic testing for the four major types of inherited retinal degenerations (IRDs):

- Rod-cone degenerations (e.g., retinitis pigmentosa)
- Cone-rod degenerations (e.g., achromatopsia)
- Chorioretinal degenerations (e.g., CHM-associated retinal degenerations [choroideremia])
- Inherited dystrophies that involve the macula (e.g., ABCA4-associated macular degeneration [Stargardt disease]).

Note 2: For 5 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

Policy Guidelines

Approximately 4,000 diseases or syndromes affect humans, and nearly one-third of these diseases are related to the eyes (Singh & Tyagi, 2018). Several ophthalmologic disorders may be inherited, including age-related macular degeneration, cataracts, glaucoma, inherited optic neuropathies, retinitis pigmentosa and Stargardt's disease (Singh & Tyagi, 2018). Early diagnoses, knowledge of family history and genetic testing can positively influence outcomes and treatment regimens. Inherited retinal diseases (IRDs) affect 1 in 1380 individuals; it is estimated 36% of healthy people could be considered carriers of at least one IRD-related mutation (Hanany et al., 2020).

Genetic testing for eye disorders is growing in popularity. Further, there is considerable overlap between the clinical phenotypes of many eye disorders, highlighting the importance of genetic testing to determine the cause and most effective treatment avenue (Sangermanoa et al., 2020). To date, genetic tests can identify dozens of ophthalmologic conditions (Stone et al., 2014), and panel tests are already used clinically for early-onset glaucoma, retinal dystrophies, inherited optic neuropathies and more (Wiggs, 2017). Further, many genes have been linked to various human eye diseases and disorders. Table 1 below, adapted from Singh and Tyagi (2018), lists genes and gene variants associated with ten different ophthalmologic conditions. However, it's also important to recognize that there is a broad clinical spectrum of disorders and many involved genes in IRD-related disorders. Over 270 genes have currently been associated with IRD and the number of genes and heterogeneity of disease is compounded by variations in familial inheritance patterns (García Bohórquez et al., 2021).

Ocular gene therapy shows promise for both inherited and acquired retinal pathologies. Adeno-associated viruses (AAVs) are the most common and leading platform used in retinal gene therapy. These vectors deliver gene-specific approaches to promote expression of a healthy copy of a disease-causing gene (Michalakis et al., 2021). A combination of factors has led to the adeno-associated virus method as the primary vector option for IRDs. First, AAVs have smaller risks of mutagenesis because they aren't integrated into the host genome. Second, they have low pathogenicity. Lastly, they can transfer genetic material to multiple retinal cell types (Avalyon, 2021).

Recent advancements in AAV ocular gene therapy have been effective in treating certain types of ophthalmologic conditions as well. For example, Luxturna (the first FDA approved ocular therapy) is a prescription gene therapy product used to treat patients with inherited retinal diseases due to mutations in the *RPE65* (retinal pigment epithelium-specific 65) gene; however, genetic testing must first be used to determine a potential mutation in this gene (Luxturna, 2019). Therefore, accurate genetic diagnoses have become imperative for some ophthalmologic treatments.

Other retinal conditions such as choroideremia, achromatopsia, X-linked retinitis pigmentosa, X-linked retinoschisis and AMD are among those being investigated as potential targets for gene therapies using AAVs. In addition, additional viral vectors and non-viral platforms are in the process of consideration

because AAVs are limited in the amount of genetic information they can carry, that is, they cannot carry large therapeutic gene sets. For example, larger gene targets (such as the gene associated with Stargardt disease) present a barrier to AAV-specific gene therapy (Avalyon, 2021).

Table 1: Genes/gene variants linked with common human eye diseases/disorders (Singh & Tyagi, 2018)

Disease	Gene/variant	Age of disease or disorder onset
AMD (age-related macular degeneration)	*NOS2A, CFH, CF, C2, C3, CFB, HTRA1/LOC, MMP-9, TIMP-3, SLC16A8*, etc.	Old
Cataract	*GEMIN4, CYP51A1, RIC1, TAPT1, TAF1A, WDR87, APE1, MIP, Cx50/GJA3 & 8, CRYAA, CRYBB2, PRX, POLR3B, XRCC1, ZNF350, EPHA2,* etc.	Old
Glaucoma	*CALM2, MPP-7, Optineurin, LOX1, CYP1B1, CAV1/2, MYOC, PITX2, FOXC1, PAX6, CYP1B1, LTBP2*, etc.	Over 40 except congenital form that can affect an infant
Inherited optic neuropathies	*Complex I* or *ND* genes, *OPA1, RPE65*, etc.	Young males
Marfan syndrome	*FBN1, TGFBR2, MTHFR, MTR, MTRR*, etc.	Born with disorder but may not be diagnosed until later in life
Myopia	*HGF, C-MET, UMODL1, MMP-1/2, PAX6, CBS, MTHFR, IGF-1, UHRF1BP1L, PTPRR, PPFIA2, P4HA2,* etc.	Typically progresses until about age 20
Polypoidal choroidal vasculopathies	*C2, C3, CFH, SERPING1, PEDF, ARMS2-HTRA1, FGD6, ABCG1, LOC387715, CETP,* etc.	Between ages 50 and 65
Retinitis pigmentosa	*RPGR, PRPF3, HK1, AGBL5,* etc.	Between 10 and 30
Stargardt's disease	*ABC1, ABCA4, CRB1,* etc.	Signs may appear in early childhood to middle age
Uveal melanoma	*PTEN, BAP1, GNAQ, GNA11, DDEF1, SF3B1, EIF1AX, CDKN2A, p14ARF, HERC2/OCA2,* etc.	50 to 80

Several genetic tests have been developed to identify ophthalmologic conditions. The MVL Vision Panel (v2) by Molecular Vision tests for 581 genes associated with vision-related inherited conditions (MolecularVision, 2020). GeneDx has developed a Glaucoma Panel which tests for 38 glaucoma-related genes (GeneDx, 2023). Invitae has developed the Inherited Retinal Disorders Panel which tests for 248 genes associated with inherited retinal disorders (Invitae, 2020). Blueprint genetics has developed 25 different ophthalmology panels which test for over 3,900 genes collectively (Blueprint, 2020). Finally, Prevention Genetics has developed the Stargardt Disease and Macular Dystrophies Panel which tests for 28 relevant genes (PreventionGenetics, 2020).

Age-Related Macular Degeneration (AMD)

AMD is caused by pathologic changes to the deeper retinal layers of the macula and surrounding vasculature,

which can result in central vision loss. There are two main types of AMD: neovascular ("dry" AMD) and nonneovascular ("wet" AMD). Nonneovascular AMD accounts for 80-85% of all cases and generally carries a more favorable visual prognosis, whereas Neovascular AMD affects the remaining 15% to 20% and accounts for approximately 80% of severe vision loss. (Thomas et al., 2021)

AMD is caused by a combination of genetic and environmental factors. The strongest genetic association is due to genes involved in complement pathways. For instance, a major polymorphism of complement factor H (CFH) and CFH related genes (*CFHR1*-5) may predispose an individual to AMD (Cipriani et al., 2020). This polymorphism (histidine in place of tyrosine on position 402, CFH Y402H) on chromosome 1 has been associated with higher risk of AMD. One copy of the polymorphism has been associated with a 2.4-4.6 times higher risk of developing AMD whereas both copies of the allele have been associated with a 3.3-7.4 times higher risk. Single nucleotide polymorphisms (SNPs) such as CYP2C19 (G681A) Rs4244285 and CYP1A2 (-163C>A) Rs762551 may also confer added risk for AMD (Stasiukonyte et al., 2017).

Clinical Validity and Utility

Lenassi et al. (2019) studied the clinical utility of genetic testing in children with inherited eye disorders. A total of 201 children in preschool (aged 0-5) participated in this study; all participants underwent panel testing. This cohort included "74 children with bilateral cataracts, 8 with bilateral ectopia lentis, 28 with bilateral anterior segment dysgenesis, 32 with albinism, and 59 with inherited retinal disorders (Lenassi et al., 2019)." The diagnostic yield for this study was 64% with testing results leading to altered disease management in 33% of probands (Lenassi et al., 2019).

Fauser and Lambrou (2015) analyzed potential biomarker candidates that could be used in a clinical setting to predict response to anti-vascular endothelial growth factor (anti-VEGF) treatment of neovascular AMD (nAMD). SNPs from 39 publications were evaluated and divided into two categories; those associated with AMD pathogenesis and those targeted by anti-VEGF therapies. The authors found that several studies supported an association between anti-VEGF treatment response and two SNPs, CFH rs1061170 and VEGFA rs699947, but results from randomized controlled trials found no such association (Fauser & Lambrou, 2015).

Chew et al. (2014) determined whether genotypes at two major loci associated with late AMD, complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2), influenced the relative benefits of Age-Related Eye Disease Study (AREDS) supplements; the original AREDs formulation contained vitamins C and E, zinc, copper and beta-carotene. A total of 1237 AREDS participants, 385 with late AMD, were genotyped. Both *CFH* and *ARMS2* genotypes were noted to individually associate with progression to late AMD. However, the investigators found that the genotypes at the *CFH* and *ARMS2* loci did not significantly alter the benefits of AREDS supplements. The investigators concluded that "genetic testing remains a valuable research tool, but these analyses suggest it provides no benefits in managing nutritional supplementation for patients at risk of late AMD (Chew et al., 2014)."

Hagstrom et al. (2015) evaluated the pharmacogenetic relationship between genotypes of SNPs in the VEGF signaling pathway and response to treatment with ranibizumab or bevacizumab for nAMD. For each of the measures of visual equity evaluated, there was no association with any of the genotypes or with the number of risk alleles. The investigators concluded that there are no pharmacogenetic associations between the studied *VEGF-A* and *VEGFR-2* SNPs and response to anti-VEGF therapy (Hagstrom et al., 2015).

Cascella et al. (2018) aimed to characterize exudative AMD in the Italian population and to identify the susceptibility/protective factors (genetic variants, age, sex, smoking, and dietary habits) that are specific for the onset of disease. The study involved a cohort of 1976 subjects, including 976 patients affected with exudative AMD and 1000 control subjects who underwent genotyping analysis of 20 genetic variants known to be associated with AMD. This analysis revealed that eight genetic variants (*CFH, ARMS2, IL-8, TIMP3, SLC16A8, RAD51B, VEGFA* and *COL8A1*) were significantly associated with AMD susceptibility. Following a multivariate analysis, considering both genetic and non-genetic data available, age, smoking,

dietary habits, and sex, together with the genetic variants, were significantly associated with AMD (Cascella et al., 2018).

Chen et al. (2020) completed a study of 2,343 Chinese and Japanese individuals including patients with neovascular age-related macular degeneration (nAMD), polypoidal choroidal vasculopathy (PCV) and healthy controls. PCV is a disease of the choroidal vasculature in the eye. The *TIE2* (tyrosine kinase, endothelial, *TEK*) gene was the main focus in this study. In the analysis of all participants, a SNP of the *TIE2* gene (rs625767) was significantly associated with nAMD and PCV (Chen et al., 2020).

Strunz et al. (2020) completed a transcriptome-wide association study that included data from 6,144 late-stage AMD cases and 17,832 healthy controls. A total of 10 genes were significantly associated with AMD variants in at least one tissue in this study (27 different human tissues were analyzed). The authors conclude by stating that "our study highlights the fact that expression of genes associated with AMD is not restricted to retinal tissue as could be expected for an eye disease of the posterior pole, but instead is rather ubiquitous suggesting processes underlying AMD pathology to be of systemic nature" (Strunz et al. 2020).

Pontikos et al. (2020) conducted a retrospective study of electronic records in families with molecularly characterized IRD, to investigate proportions with disease attributable to gene variants. It was found that depending on the inheritance pattern, different genes were more likely to be implicated; among all the genes encountered, *ABCA4* was most frequent, but when accounting for types of retinitis pigmentosa (RP), the autosomal recessive type was most frequently caused by *USH2A* whereas autosomal dominant RP was most linked with *RHO, RP1, and PRPF31*. Additionally, many X-linked retinopathies were the result of variants in *RPGR* (about 40%). More families in the study's pediatric cohort were affected by variants in X-linked genes, likely a result of earlier onset and severity of X-linked pathologies and likelihood of earlier diagnoses. The researchers also noted a weak but statistically significant positive correlation with transcription lengths and number of families affected by eye conditions, as longer transcripts are more likely to contain loss of function or premature termination mutations (Pontikos et al. 2020).

Sheck et al. (2021) reported on the performance of a next-gene sequencing (NGS) panel of 176 retinal genes (NGS 176) in patients with IRD. Among 488 patients, a diagnostic yield of 59.4% was recorded, with younger children being more likely to receive a molecular diagnosis than older adults. The clinical diagnoses were also statistically significantly associated with the diagnostic yield after multivariate analyses. Homogeneous IRD phenotypes of achromatopsia and congenital stationary night blindness, which were associated with 6 and 10 genes, respectively, had diagnostic yields of 100% and 94%, respectively. This study demonstrated the effectiveness of using a new sequencing panel in the UK, and other factors, like age and clinical diagnoses that could correlate with a higher diagnostic yield (Sheck et al. 2021).

García Bohórquez et al. (2021) investigated the genetic basis for IRD in 92 patients using two custom NGS panels. At the time of the study, there were 270 genes associated with IRD. Using NGS, the authors found: among 92 patients, 53 had known gene variants, in 12 patients there was just one mutation in a gene found with a known autosomal recessive pattern of inheritance, and 27 patients (29.3%) had zero specified or identified genes, representing "unsolved" cases. 120 pathogenic or likely pathogenic instances were identified. The most common gene variant was *ABCA4*. The *USH2A* gene was the most frequently found gene amongst patients diagnosed with retinitis pigmentosa. Lastly, a total of 10 families had pathogenic variants in more than one IRD-related gene (García Bohórquez et al., 2021).

Guidelines and Recommendations

American Academy of Ophthalmology (AAO)

In 2014, the American Academy of Ophthalmology (AAO) Task Force on Genetic Testing published recommendations for genetic testing of inherited eye diseases. The Task Force stated that standard clinical diagnostic methods like biomicroscopy, ophthalmoscopy, tonography, and perimetry will be more accurate for assessing a patient's risk of vision loss from a complex disease than the assessment of a small number

of genetic loci. The authors also state that "skilled counseling should be provided to all individuals who undergo genetic testing to maximize the benefits and minimize the risks associated with each test (Stone et al., 2014)." The recommendations include:

- "Offer genetic testing to patients with clinical findings suggestive of a Mendelian disorder whose causative gene(s) have been identified. If unfamiliar with such testing, refer the patient to a physician or counselor who is. In all cases, ensure that the patient receives counseling from a physician with expertise in inherited disease or a certified genetic counselor.

- Use Clinical Laboratories Improvement Amendments– approved laboratories for all clinical testing. When possible, use laboratories that include in their reports estimates of the pathogenicity of observed genetic variants that are based on a review of the medical literature and databases of disease-causing and non–disease-causing variants.

- Provide a copy of each genetic test report to the patient so that she or he will be able independently to seek mechanism-specific information, such as the availability of gene-specific clinical trials, should the patient wish to do so.

- Avoid direct-to-consumer genetic testing and discourage patients from obtaining such tests themselves. Encourage the involvement of a trained physician, genetic counselor, or both for all genetic tests so that appropriate interpretation and counseling can be provided.

- Avoid unnecessary parallel testing— order the most specific test(s) available given the patient's clinical findings. Restrict massively parallel strategies like whole-exome sequencing and whole-genome sequencing to research studies conducted at tertiary care facilities.

- Avoid routine genetic testing for genetically complex disorders like age-related macular degeneration and late-onset primary open-angle glaucoma until specific treatment or surveillance strategies have been shown in 1 or more published prospective clinical trials to be of benefit to individuals with specific disease-associated genotypes. In the meantime, confine the genotyping of such patients to research studies.

- Avoid testing asymptomatic minors for untreatable disorders except in extraordinary circumstances. For the few cases in which such testing is believed to be warranted, the following steps should be taken before the test is performed: (1) the parents and child should undergo formal genetic counseling, (2) the certified counselor or physician performing the counseling should state his or her opinion in writing that the test is in the family's best interest, and (3) all parents with custodial responsibility for the child should agree in writing with the decision to perform the test" (Stone et al., 2014).

In 2019, the AAO published the Age-Related Macular Degeneration Preferred Practice Pattern guidelines and state that "The primary risk factors for the development of advanced AMD include increasing age, northern European ancestry, and genetic factors… The routine use of genetic testing is not recommended at this time" (AAO, 2019). In 2023, they reaffirmed that the AAO "does not currently recommend genetic testing for AMD" (Mukamal, 2023).

In 2022, the AAO published recommendations on clinical assessment of patients with inherited retinal degenerations (IRDs). These clinical guidelines state that "Genetic testing and genetic counseling are essential components of the management of patients with IRDs as genetic testing may confirm the diagnosis, provide information to optimize management of the patient and family members, and potentially confirm eligibility to participate in clinical trials." They also note that "genetic testing for patients with IRDs can take multiple forms, including single gene analyses, panel-based tests that include many IRD

disease genes, or more expansive testing such as whole exome and whole genome sequencing. Because of the genetic heterogeneity of the other phenotypes (>80), next generation sequencing testing using a retinal dystrophy panel provides an efficient first step for genetic testing. Whether the patient has syndromic features or not, testing should include genes known to be associated with syndromic forms of retinal disease, since some patients may only show the syndromic features later. Some 'syndromic genes' can be associated with a non-syndromic retinal degeneration." AAO also reiterates the importance of genetic testing for gene therapy: "patients would need to have genetic testing to determine if they are eligible for the FDA-approved voretigene neparvovec or be considered for any of the numerous clinical trials of gene-based therapies" (AAO, 2022).

European Reference Network for Rare Eye Diseases (ERN-EYE)
The ERN-EYE released a position statement on the need for eliminating gaps in genetic testing, as collectively, rare eye diseases (RED) are the "leading cause of visual impairment and blindness for children and young adults in Europe." There are still critical gaps in the administration of genomic testing that need to be addressed, especially in Europe's smaller countries where no formal genomic testing pathways exist. However, the ERN-EYE emphasizes promoting access to genetic testing to RED and the clinical need and relevance of it with increasing evidence for clinical utility (Black et al., 2021).

American Society of Retina Specialists (ASRS)
The ASRS states that there is no clinical evidence that changing treatment based on genetic risk is beneficial to the patient. At present there is "insufficient data to support the use of genetic testing in patients with AMD prior to recommendation of current Age-Related Eye Disease Study (AREDS) nutritional supplement use" (Csaky et al., 2017).

Italian IRD Working Group

An interdisciplinary panel of IRD experts convened to discuss IRD. They established parameters surrounding eligibility for *RPE65*-associated IRD gene therapy. The working group published "a strong consensus" recommendation for the use of "a targeted multi-gene NGS approach, including all the genes known to be responsible for IRDs, both isolated and syndromic forms." The authors also specify that larger panels such as clinical exome or whole-exome sequencing may also be used. They write, "The use of a larger panel (i.e. either a clinical exome or a whole-exome sequencing) is not excluded but, due to the issue of possible incidental findings, requires a more careful pre-test counseling" (Sodi et al., 2021).

State and Federal Regulations, as applicable

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81401, 81405, 81406, 81408, 81434, 81479, 81599

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy Titled: Genetic Testing for Macular Degeneration

For Policy Re-Titled: Genetic Testing for Ophthalmologic Conditions

AAO. (2019). Age-Related Macular Degeneration PPP 2019. Retrieved from https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp

AAO. (2022). *Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations - 2022*. https://www.aao.org/education/clinical-statement/guidelines-on-clinical-assessment-of-patients-with#top

Avalyon, J. Y., Glenn. (2021). Ocular gene therapy: The next generation. *Retina Specialist*. https://www.retina-specialist.com/article/ocular-gene-therapy-the-next-generation

Black, G. C., Sergouniotis, P., Sodi, A., Leroy, B. P., Van Cauwenbergh, C., Liskova, P., . . . group, E.-E. s. (2021). The need for widely available genomic testing in rare eye diseases: an ERN-EYE position statement. *Orphanet journal of rare diseases, 16*(1), 142-142. doi:10.1186/s13023-021-01756-x

Blueprint. (2020). Ophthalmology. Retrieved from https://blueprintgenetics.com/tests/panels/ophthalmology/

Cascella, R., Strafella, C., Longo, G., Ragazzo, M., Manzo, L., De Felici, C., . . . Giardina, E. (2018). Uncovering genetic and non-genetic biomarkers specific for exudative age-related macular degeneration: significant association of twelve variants. *Oncotarget, 9*(8), 7812-7821. doi:10.18632/oncotarget.23241

Chen, Z. J., Ma, L., Brelen, M. E., Chen, H., Tsujikawa, M., Lai, T. Y., . . . Chen, L. J. (2020). Identification of TIE2 as a susceptibility gene for neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. *Br J Ophthalmol*. doi:10.1136/bjophthalmol-2019-315746

Chew, E. Y., Klein, M. L., Clemons, T. E., Agron, E., Ratnapriya, R., Edwards, A. O., Abecasis, G. R. (2014). No clinically significant association between CFH and ARMS2 genotypes and response to nutritional supplements: AREDS report number 38. *Ophthalmology, 121*(11), 2173-2180. doi:10.1016/j.ophtha.2014.05.008

Cipriani, V., Lores-Motta, L., He, F., Fathalla, D., Tilakaratna, V., McHarg, S., . . . Clark, S. J. (2020). Increased circulating levels of Factor H-Related Protein 4 are strongly associated with age-related macular degeneration. *Nat Commun, 11*(1), 778. doi:10.1038/s41467-020-14499-3

Csaky, K. G., Schachat, A. P., Kaiser, P. K., Small, K. W., & Heier, J. S. (2017). The Use of Genetic Testing in the Management of Patients With Age-Related Macular Degeneration: American Society of Retina Specialists Genetics Task Force Special Report. *Journal of VitreoRetinal Diseases, 1*(1), 75-78. doi:10.1177/2474126416680671

Fauser, S., & Lambrou, G. N. (2015). Genetic predictive biomarkers of anti-VEGF treatment response in patients with neovascular age-related macular degeneration. *Surv Ophthalmol, 60*(2), 138-152.

https://doi.org/10.1016/j.survophthal.2014.11.002

García Bohórquez, B., Aller, E., Rodríguez Muñoz, A., Jaijo, T., García García, G., & Millán, J. M. (2021). Updating the Genetic Landscape of Inherited Retinal Dystrophies [Original Research]. *Frontiers in Cell and Developmental Biology*, *9*. https://doi.org/10.3389/fcell.2021.645600

GeneDx. (2023). *Glaucoma Panel*. https://www.genedx.com/tests/detail/glaucoma-panel-940

Hagstrom, S. A., Ying, G. S., Maguire, M. G., Martin, D. F., Gibson, J., Lotery, A., & Chakravarthy, U. (2015). VEGFR2 Gene Polymorphisms and Response to Anti-Vascular Endothelial Growth Factor Therapy in Age-Related Macular Degeneration. *Ophthalmology, 122*(8), 1563-1568. doi:10.1016/j.ophtha.2015.04.024

Hanany, M., Rivolta, C., & Sharon, D. (2020). Worldwide carrier frequency and genetic prevalence of autosomal recessive inherited retinal diseases. *Proceedings of the National Academy of Sciences*, *117*(5), 2710-2716. https://doi.org/doi:10.1073/pnas.1913179117

Invitae. (2020). Invitae Inherited Retinal Disorders Panel. Retrieved from https://www.invitae.com/en/inherited-retinal-disorders-panel/

Lee, K., & Couser, N. (2016). Genetic Testing for Eye Diseases: A Comprehensive Guide and Review of Ocular Genetic Manifestations from Anterior Segment Malformation to Retinal Dystrophy. *Genetic Counseling and Clinical Testing 4*, 41-48. Retrieved from https://link.springer.com/article/10.1007/s40142-016-0087-0

Lenassi, E., Clayton-Smith, J., Douzgou, S., Ramsden, S. C., Ingram, S., Hall, G., . . . Sergouniotis, P. I. (2019). Clinical utility of genetic testing in 201 preschool children with inherited eye disorders. *Genet Med*. doi:10.1038/s41436-019-0722-8

Luxturna. (2019). *Could LUXTURNA® be right for you?* Retrieved from https://luxturna.com/about-luxturna/

Michalakis, S., Gerhardt, M., Rudolph, G., Priglinger, S., & Priglinger, C. (2021). Gene Therapy for Inherited Retinal Disorders: Update on Clinical Trials. *Klin Monbl Augenheilkd*, *238*(3), 272-281. https://doi.org/10.1055/a-1384-0818 (Gentherapie für erbliche Netzhauterkrankungen: Übersicht zu aktuellen klinischen Studien.)

MolecularVision. (2020). Browse Our Test Menu. Retrieved from https://www.molecularvisionlab.com/mvl-vision-panel/

Mukamal, R. (2023, 01/19/2023). *Genetics and Age-Related Macular Degeneration*. https://www.aao.org/eye-health/diseases/age-related-macular-degeneration-amd-genetic

Pontikos, N., Arno, G., Jurkute, N., Schiff, E., Ba-Abbad, R., Malka, S., . . . Mahroo, O. A. (2020). Genetic Basis of Inherited Retinal Disease in a Molecularly Characterized Cohort of More Than 3000 Families from the United Kingdom. *Ophthalmology, 127*(10), 1384-1394. doi:10.1016/j.ophtha.2020.04.008

PreventionGenetics. (2020). Stargardt Disease (STGD) and Macular Dystrophies Panel. Retrieved from https://www.preventiongenetics.com/testInfo.php?sel=test&val=Stargardt+Disease+%28STGD%29+and+Macular+Dystrophies+Panel

Sangermanoa, R., Scotta, H., Wagner, N., Place, E., & Bujakowska, K. M. (2020). *Genetics and Genomics of Eye Diseases: Chapter 14 - Genetic testing of various eye disorders*.

Sheck, L. H. N., Esposti, S. D., Mahroo, O. A., Arno, G., Pontikos, N., Wright, G., . . . Michaelides, M. (2021). Panel-based genetic testing for inherited retinal disease screening 176 genes. *Mol Genet Genomic Med*, e1663. doi:10.1002/mgg3.1163

Singh, M., & Tyagi, S. C. (2018). Genes and genetics in eye diseases: a genomic medicine approach for investigating hereditary and inflammatory ocular disorders. *Int J Ophthalmol, 11*(1), 117-134. doi:10.18240/ijo.2018.01.20

Sodi, A., Banfi, S., Testa, F., Della Corte, M., Passerini, I., Pelo, E., Rossi, S., Simonelli, F., & Italian, I. R. D. W. G. (2021). RPE65-associated inherited retinal diseases: consensus recommendations for eligibility to gene therapy. *Orphanet journal of rare diseases*, *16*(1), 257. https://doi.org/10.1186/s13023-021-01868-4

Stasiukonyte, N., Liutkeviciene, R., Vilkeviciute, A., Banevicius, M., & Kriauciuniene, L. (2017). Associations between Rs4244285 and Rs762551 gene polymorphisms and age-related macular degeneration. *Ophthalmic Genet, 38*(4), 357-364. doi:10.1080/13816810.2016.1242018

Stone, E. M., Aldave, A. J., Drack, A. V., Maccumber, M. W., Sheffield, V. C., Traboulsi, E., & Weleber, R. G. (2014). Recommendations for Genetic Testing of Inherited Eye Diseases - 2014. Retrieved 1/29/2015, from https://www.aao.org/clinical-statement/recommendations-genetic-testing-of-inherited-eye-d

Strunz, T., Lauwen, S., Kiel, C., Hollander, A. D., & Weber, B. H. F. (2020). A transcriptome-wide association study based on 27 tissues identifies 106 genes potentially relevant for disease pathology in age-related macular degeneration. *Sci Rep, 10*(1), 1584. doi:10.1038/s41598-020-58510-9

Thomas, C. J., Mirza, R. G., & Gill, M. K. (2021). Age-Related Macular Degeneration. *Medical Clinics of North America*, *105*(3), 473-491. https://doi.org/https://doi.org/10.1016/j.mcna.2021.01.003

Wiggs, J. L. (2017). Progress in Diagnostic Genetic Testing for Inherited Eye Disease. *JAMA Ophthalmol, 135*(12), 1385-1386. doi:10.1001/jamaophthalmol.2017.4957

Specialty Matched Consultant Advisory Panel review 6/2019

Medical Director review 9/2019

Specialty Matched Consultant Advisory Panel review 6/2020

Medical Director review 6/2020

For Policy Re-Titled: Genetic Testing for Ophthalmologic Conditions

Medical Director review 7/2020

Specialty Matched Consultant Advisory Panel review 6/2021

Medical Director review 6/2021

Medical Director review 8/2022

Medical Director review 7/2023

Policy Implementation/Update Information

For Policy Titled: Genetic Testing for Macular Degeneration

1/1/2019 New policy developed. Genetic testing for macular degeneration is considered investigational for all applications. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

7/16/19 Specialty Matched Consultant Advisory Panel review 6/19/2019. No change to policy statement. (lpr)

10/1/19 Reviewed by Avalon 2nd Quarter 2019 CAB. Deleted coding table from Billing/Coding section. Medical Director review 9/2019. (lpr)

6/30/20 Specialty Matched Consultant Advisory Panel review 6/17/2020. No change to policy statement. Medical Director review 6/2020. (lpr)

For Policy Titled: Genetic Testing for Ophthalmologic Conditions

7/28/20 Reviewed by Avalon 2nd Quarter 2020 CAB. Added medical necessity coverage for RPE65 testing for retinal dystrophy prior to treatment with Luxturna in "When Covered" section. Added whole exome and whole genome sequencing for ophthalmologic conditions is investigational in "When Not Covered" section. Extensive updates to Description and Policy Guidelines sections. Added CPT codes 81434 and 81406 to "Billing/Coding" section. **Title changed from: "Genetic Testing for Macular Degeneration" to: "Genetic Testing for Ophthalmologic Conditions."** References updated. Medical Director review 7/2020. (lpr)

7/27/21 Specialty Matched Consultant Advisory Panel review 6/16/2021. Medical Director review 6/2021. Reviewed by Avalon 2nd Quarter 2021 CAB. Updated Policy Guidelines, guidelines/recommendations and added references. Added Note 1. No change to policy statement. (lpr)

9/13/22 Reviewed by Avalon 2nd Quarter 2022 CAB. Updated policy guidelines and references. Medical Director review 8/2022. (lpr)

8/15/23 Reviewed by Avalon Q2 2023 CAB. Medical Director review 7/2023. Removed AHS-G2138 Evaluation of Dry Eyes from related policies section. Edited and expanded "when covered" section for new medical necessity criteria for individuals with clinical signs of an inherited retinal degeneration, single gene or multi-gene panel testing. Added new Note 1. Updated policy guidelines and references. (lpr)