BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Genetic Testing for Ophthalmologic Conditions AHS-M2083

File Name:	genetic_testing_for_ophthalmologic_conditions
Origination:	1/1/2019
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Last Review:	7/2020

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:
Evaluation of Dry Eyes AHS-G2138
Genetic Testing for Connective Tissue Disorders AHS-M2144
General 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

Genetic testing of *RPE65* for individuals with retinal dystrophy is considered medically necessary prior to treatment with Luxturna (voretigene neparvovec-rzyl).

When Genetic Testing for Ophthalmologic Conditions is not covered

Genetic testing for macular degeneration and any other ophthalmologic condition is considered **investigational** for all applications.

Whole exome sequencing (WES) or whole genome sequencing (WGS) for ophthalmologic conditions is

considered **investigational** for all applications.

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.

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, Scotta, Wagner, Place, & Bujakowska, 2020). To date, genetic tests can identify dozens of ophthalmologic conditions (AAO, 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.

Recent advancements in gene therapy have been effective in treating certain types of ophthalmologic conditions as well. For example, Luxturna, a prescription gene therapy product, may be 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.

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 many tests including a Glaucoma Panel which tests for 38 glaucoma-related genes (GeneDx, 2018a) and an optic atrophy with or without deafness, ophthalmoplegia, myopathy, ataxia, and neuropathy test which examines 150 genes (GeneDx, 2018b). 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 an eye condition that causes damage to the central portion of the retina (the macula), impacting the ability to see objects straight ahead. It can lead to complete vision loss and is the leading cause of blindness in industrialized countries (Arroyo, 2018). The two major types of AMD are dry form (atrophic) and wet form (neovascular or exudative). The dry form accounts for 85 to 90 percent of all cases of age-related macular degeneration and typically has a slower progression. Dry AMD is characterized by deposits of drusen under the retina, atrophy of the retinal pigment epithelium, and detachments or clumping of the pigment epithelium. Drusen refers to localized deposits of extracellular material and appears as bright, yellow objects on ophthalmoscopy. The larger and softer variant of drusen is the type seen in AMD. Dry AMD may progress to wet AMD; the risk of dry AMD progressing to wet has been estimated at up to 18% in three years (Arroyo, 2018).

Although accounting for only 10 percent of cases, the wet form results in 80% of legal blindness. Wet AMD, also referred to as choroidal neovascularization, is characterized by growth of abnormal blood vessels into the subretinal space. These vessels leak, which leads to pools of blood or subretinal fluid beneath the retina. This version of AMD often results in rapid loss of central vision (Arroyo, 2018).

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. Other polymorphisms of CFH and other components of the complement pathway (such as *CFB* and *SERPING1*) have also been associated with higher risk of AMD (Arroyo, 2018). Single nucleotide polymorphisms (SNPs) such as CYP2C19 (G681A) Rs4244285 and CYP1A2 (-163C>A) Rs762551 may also confer added risk for AMD (Stasiukonyte, Liutkeviciene, Vilkeviciute, Banevicius, & Kriauciuniene, 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, Lauwen, Kiel, Hollander, and Weber (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."

Guidelines and Recommendations

American Academy of Ophthalmology (AAO) (AAO, 2014, 2015, 2019)

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. Until the benefit of genetic testing can be demonstrated, the AAO task force stated that "the routine genetic testing of patients with complex eye diseases, or unaffected patients with a family history of such diseases, is not warranted." Further, 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 (AAO, 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 (AAO, 2014)."

In 2016, 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 important components of the assessment of patients with IRDs as genetic testing may be valuable to confirm the diagnosis, provide accurate information to the patient and family members and potentially to confirm eligibility to participate in clinical trials (AAO, 2016)."

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)."

American Society of Retina Specialists (ASRS) (Csaky, Schachat, Kaiser, Small, & Heier, 2017)
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).

European Society of Retina Specialists (EURETINA) (Schmidt-Erfurth et al., 2014)
The EURETINA published guidelines for the management of neovascular AMD. These guidelines state that "Doctors should initially ask patients who present with an onset of decreased vision or metamorphopsia, if they have a family history of AMD"; however, genetic testing is not mentioned.

American Optometric Association (AOA) Consensus Panel [(Cavallerano et al., 1999) reviewed 2004]
Last reviewed in 2004, the AOA consensus panel published guidelines on the care of a patient with AMD. These guidelines were reviewed by the AOA clinical guidelines coordinating committee. These guidelines do not mention genetic testing for AMD.

State and Federal Regulations, as applicable

No FDA-approved tests for genetic testing of AMD were found. Additionally, 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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; 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

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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 Titled: Genetic Testing for Ophthalmologic Conditions

Medical Director review 7/2020

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)

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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)