

Genetic Testing for Ophthalmologic Conditions

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I. Policy Description

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.¹ 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.²

II. Related Policies

Policy Number	Policy Title
AHS-M2144	Genetic Testing for Connective Tissue Disorders

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

- 1) For individuals with clinical signs of an inherited retinal degeneration (see Note 1), single gene or multi-gene panel testing **MEETS COVERAGE CRITERIA.**
- 2) For individuals with clinical findings suggestive of other ophthalmologic disorders with a known causative gene(s) where identification of a genetic variant will affect clinical management, testing of the known causative gene(s) **MEETS COVERAGE CRITERIA.**
- 3) For individuals with retinal dystrophy, genetic testing of *RPE65* prior to treatment with Luxturna (voretigene neparvovec-rzyl) **MEETS COVERAGE CRITERIA and is required.**

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual’s illness.

- 4) Genetic testing for age-related macular degeneration **DOES NOT MEET COVERAGE CRITERIA.**

5) For individuals with ophthalmologic conditions, whole exome sequencing (WES) **and/or** whole genome sequencing (WGS) **DOES NOT MEET COVERAGE CRITERIA.**

NOTES:

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 degeneration [choroideremia])
- Inherited dystrophies that involve the macula (e.g., *ABCA4*-associated macular degeneration [Stargardt disease])

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

IV. Table of Terminology

Term	Definition
AAO	American Academy of Ophthalmology
<i>ABC1</i>	<i>ATP binding cassette 1</i>
<i>ABCA4</i>	<i>ATP binding cassette subfamily A member 4</i>
<i>ABCG1</i>	<i>ATP binding cassette subfamily G member 1</i>
AGBL5	<i>AGBL Carboxypeptidase 5 gene</i>
AMD	Age-related macular degeneration
Anti-VEGF	Anti-vascular endothelial growth factor
AOA	American Optometric Association
<i>APE1</i>	<i>Apurinic/aprimidinic endonuclease 1 gene</i>
AREDS	Age-Related Eye Disease Study
<i>ARMS2</i>	<i>Age-related maculopathy susceptibility 2 gene</i>
<i>HTRA1</i>	<i>HtrA Serine Peptidase 1 gene</i>
ASRS	American Society of Retina Specialists
<i>BAP1</i>	<i>BRCA1 associated protein 1 gene</i>
<i>C2</i>	<i>Complement C2 gene</i>
<i>C3</i>	<i>Complement C3 gene</i>
<i>CALM2</i>	<i>Calmodulin 2</i>
CAV1/2	Calcium channel, voltage-dependent, L type, alpha 1C subunit
<i>CBS</i>	<i>Cystathionine beta-synthase</i>
<i>CDKN2A</i>	<i>Cyclin dependent kinase inhibitor 2A gene</i>
<i>CETP</i>	<i>Cholesteryl ester transfer protein gene</i>
CF	Complement factor
CFB	Complement factor B

CFH	Complement factor H
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
C-MET	Tyrosine-protein kinase met
CMS	Centers for Medicare and Medicaid
CNGA1	<i>Cyclic nucleotide gated channel subunit alpha 1 gene</i>
COL8A1	<i>Collagen type VIII alpha 1 chain gene</i>
CRYAA	<i>Crystallin alpha A gene</i>
CRYBB2	<i>Crystallin beta B2 gene</i>
Cx50/GJA3 & 8	Connexin α8 (GJA8 or Cx50) and connexin α3
CYP1B1	<i>Cytochrome P450 family 1 subfamily B member 1 gene</i>
CYP2C19	Cytochrome P450 2C19
CYP51A1	<i>Cytochrome P450 family 51 subfamily a member 1 gene</i>
DDEF1	Development and differentiation enhancing factor 1
DNA	Deoxyribose nucleic acid
EIF1AX	<i>Eukaryotic translation initiation factor 1A X-Linked gene</i>
EPHA2	<i>Ephrin type-A receptor 2 gene</i>
ERN-EYE	European Reference Network for Rare Eye Diseases
EURETINA	European Society of Retina Specialists
FBN1	<i>Fibrillin 1 gene</i>
FDA	Food and Drug Administration
FGD6	<i>FYVE, rhoGEF and ph domain containing 6 gene</i>
FOXC1	<i>Forkhead box C1 gene</i>
GEMIN4	<i>Gem nuclear organelle associated protein 4 gene</i>
GNA11	<i>G protein subunit alpha 11 gene</i>
GNAQ	<i>G protein subunit alpha q gene</i>
HERC2	<i>HECT and RLD domain containing E3 ubiquitin protein ligase 2 gene</i>
HGF	<i>Hepatocyte growth factor gene</i>
HK1	<i>Hexokinase 1 gene</i>
IGF-1	<i>Insulin-like growth factor 1 gene</i>
IL-8	<i>Interleukin 8 gene</i>
IRDs	Inherited retinal degenerations
LCD	Local Coverage Determination
LDT	Laboratory-developed test
LOX1	<i>Lectin-type oxidized LDL receptor 1 gene</i>
LTBP2	<i>Latent transforming growth factor beta binding protein 2 gene</i>
MIP	<i>Major intrinsic protein of lens fiber gene</i>
MMP-1/2	<i>Matrix metalloproteinases 1/2 gene</i>
MMP-9	<i>Matrix metalloproteinase 9 gene</i>
MPP-7	<i>Membrane protein, palmitoylated 7</i>
MTHFR	<i>Methylenetetrahydrofolate reductase gene</i>
MTR	<i>5-Methyltetrahydrofolate-homocysteine methyltransferase</i>

MTRR	<i>5-Methyltetrahydrofolate-homocysteine methyltransferase reductase</i>
MVL	Molecular vision tests
MYOC	<i>Myocilin gene</i>
NAMD	Neovascular age-related macular degeneration
NGS	Next-gene sequencing
NOS2A	<i>Nitric oxide synthase 2A gene</i>
OCA2	<i>Oculocutaneous Albinism type 2 gene</i>
OPA1	<i>Optic atrophy 1 gene</i>
P14arf	ARF tumor suppressor
P4HA2	<i>Prolyl 4-Hydroxylase Subunit Alpha 2 gene</i>
PAX6	<i>Paired box 6 gene</i>
PCV	Polypoidal choroidal vasculopathy
PDE6A	<i>Phosphodiesterase 6A gene</i>
PDE6B	<i>Phosphodiesterase 6B gene</i>
PEDF	<i>Pigment epithelium-derived factor gene</i>
PITX2	<i>Paired like homeodomain 2 gene</i>
POLR3B	<i>Ribonucleic acid polymerase III subunit b gene</i>
PPFIA2	<i>PTPRF interacting protein alpha 2 gene</i>
PRPF3	<i>Pre-mRNA processing factor 3 gene</i>
PRPF31	<i>Pre-mRNA processing factor 31 gene</i>
PRPH2	<i>Peripherin 2</i>
PRX	<i>Periaxin gene</i>
PTEN	<i>Phosphatase and tensin homolog gene</i>
PTPRR	<i>Protein tyrosine phosphatase receptor type r gene</i>
RAD51B	<i>RAD51 paralog b gene</i>
RDH12	<i>Retinol dehydrogenase 12 gene</i>
RED	Rare eye diseases
RHO	<i>Rhodopsin gene</i>
RIC1	<i>RIC1 homolog, RAB6A GEF complex partner 1 gene</i>
RP	Retinitis pigmentosa
RP1	<i>RP1 axonemal microtubule associated gene</i>
RP2	<i>RP2 activator of ARL3 GTPase gene</i>
RPE65	<i>Retinal pigment epithelium-specific 65 gene</i>
RPGR	<i>Retinitis pigmentosa GTPase regulator gene</i>
SERPING1	<i>Serpin family g member 1 gene</i>
SF3B1	<i>Splicing factor 3b subunit 1 gene</i>
SLC16A8	<i>Solute carrier family 16 member 8 gene</i>
Snps	Single nucleotide polymorphisms
STGD	Stargardt Disease
TAF1A	<i>TATA-Box Binding Protein Associated Factor, RNA Polymerase I Subunit A gene</i>
TAPT1	<i>Transmembrane Anterior Posterior Transformation 1 gene</i>

TEK	<i>Tyrosine, kinase, endothelial gene</i>
TGFBR2	<i>Transforming growth factor beta receptor 2 gene</i>
TIE2	<i>TEK receptor tyrosine kinase gene</i>
TIMP3	<i>Tissue inhibitor of metalloproteinase 3 gene</i>
UMODL1	<i>Uromodulin Like 1 gene</i>
USH2A	<i>Usherin gene</i>
VEGF	<i>vascular endothelial growth factor agents</i>
VEGF-A	<i>Vascular endothelial growth factor A gene</i>
VEGFR-2	<i>Vascular endothelial growth factor receptor 2 gene</i>
WDR87	<i>WD Repeat Domain 87 gene</i>
WES	Whole exome sequencing
WGS	Whole genome sequencing
XRCC1	<i>X-ray repair cross complementing 1 gene</i>
ZNF350	<i>Zinc finger protein 350 gene</i>

V. Scientific Background

Approximately 4,000 diseases or syndromes affect humans, and nearly one-third of these diseases are related to the eyes.² Several ophthalmologic disorders may be inherited, including age-related macular degeneration, cataracts, glaucoma, inherited optic neuropathies, retinitis pigmentosa and Stargardt’s disease.² Early diagnoses, knowledge of family history and genetic testing can positively influence outcomes and treatment regimens. Inherited retinal diseases (IRDs) affect one in 1380 individuals; it is estimated 36% of healthy people could be considered carriers of at least one IRD-related mutation.³

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.⁴ To date, genetic tests can identify dozens of ophthalmologic conditions,⁵ and panel tests are already used clinically for early-onset glaucoma, retinal dystrophies, inherited optic neuropathies and more.⁶ 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 is 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.⁷

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.⁸ 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 are not integrated into the host genome. Second, they have low pathogenicity. Lastly, they can transfer genetic material to multiple retinal cell types.⁹

Recent advancements in AAV ocular gene therapy have been effective in treating certain types of ophthalmologic conditions. For example, Luxturna – the first Food and Drug Administration approved ocular therapy – is a prescription gene therapy product used to treat patients with inherited retinal

degenerations (IRDs) 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.¹⁰ 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.⁹

Table 1: Genes/gene variants linked with common human eye diseases/disorders ²

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

Uveal melanoma	<i>PTEN, BAP1, GNAQ, GNA11, DDEF1, SF3B1, EIF1AX, CDKN2A, p14ARF, HERC2/OCA2, etc.</i>	50 to 80
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Age-Related Macular Degeneration (AMD)

Age-Related Macular Degeneration 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.¹¹

Age-Related Macular Degeneration 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.¹² 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.¹³

Proprietary Testing

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.¹⁴ GeneDx has developed a Glaucoma Panel which tests for 38 glaucoma-related genes.¹⁵ Invitae has developed the Inherited Retinal Disorders Panel which tests for 248 genes associated with inherited retinal disorders.¹⁶ Blueprint Genetics has developed 25 different ophthalmology panels which test for over 3,900 genes collectively.¹⁷ Finally, Prevention Genetics has developed the Stargardt Disease and Macular Dystrophies Panel which tests for 28 relevant genes.¹⁸

Clinical Utility and Validity

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.”¹⁹ The diagnostic yield for this study was 64% with testing results leading to altered disease management in 33% of probands.¹⁹

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 VEGF-A rs699947, but results from randomized controlled trials found no such association.²⁰

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.”²¹

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.²²

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*, *VEGF-A* 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.²³

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.²⁴

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.”²⁵

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.²⁶

Sheck, et al. (2021) reported on the performance of a next-generation 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 six and ten 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.²⁷

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. A total of 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.⁷

VI. 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.”⁵ 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.”⁵

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.”²⁸

In 2025, the AAO published the Age-Related Macular Degeneration Preferred Practice Pattern guidelines and state that “Risk factors for the development of advanced AMD include smoking, increasing age, northern European ancestry, and genetic factors. . . The routine use of genetic testing is not supported by the existing literature and is not recommended at this time.”²⁹ The AAO also states, “Early detection and prompt treatment of active neovascular AMD improves visual outcomes. Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents, which may or may not target other factors such as placental growth factor or angiopoietin-2, is the most effective way to manage neovascular AMD and is the first-line treatment.”²⁹

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.³⁰

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.”³¹

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 counselling.”³²

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <http://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

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.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)

CPT	Code Description
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)
81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
81479	Unlisted molecular pathology procedure

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

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X. Review/Revision History

Effective Date	Summary
10/15/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity and consistency: Note 2 edited to change “2” to “two”: “Note 2: For two or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy.” Added CPT code 81415, 81416, 81417, 81425, 81426 Removed CPT code 81599
12/01/2024	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: New CC2: “2) For individuals with clinical findings suggestive of other ophthalmologic disorders with a known causative gene(s) where identification of a genetic variant will affect clinical management, testing of the known causative gene(s) MEETS COVERAGE CRITERIA.” Note 2 was updated to reflect changes to Avalon’s definition of a genetic panel within R2162. Now reads: “Note 2: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy.” Added CPT code 81404
12/01/2024	Initial Policy Implementation