Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/25**
(See policy history boxes for previous effective dates)

Title: GENE ANALYSIS FOR CORNEAL DYSTROPHY

Description/Background

Corneal Dystrophy

Corneal dystrophies are a group of genetic, often progressive, eye disorders in which abnormal material often accumulates in the clear (transparent) outer layer of the eye (cornea). Corneal dystrophies may not cause symptoms (asymptomatic) in some individuals; in others they may cause significant vision impairment. The age of onset and specific symptoms vary among the different forms of corneal dystrophy. The disorders have some similar characteristics; most forms of corneal dystrophy affect both eyes (bilateral), progress slowly, do not affect other areas of the body, and tend to run in families. Most forms are inherited as autosomal dominant traits; a few are inherited as autosomal recessive traits.

An international classification of the corneal dystrophies has been developed that takes into account the chromosomal loci of the various corneal dystrophies as well as the responsible genes and their mutations. Traditionally, these disorders have been classified based upon their clinical findings and the specific layer of the cornea affected. Advances in molecular genetics (e.g., identification of specific disease genes) have led to a greater understanding of these disorders.

Diagnosis

The presence of a corneal dystrophy may be found incidentally during a routine eye examination. A diagnosis may be confirmed by a thorough clinical evaluation, a detailed patient history and a variety of tests, such as a slit lamp examination, in which a special microscope (slit lamp) allows a physician to view the eye through high magnification. Some specific corneal dystrophies can be diagnosed with molecular genetic tests even before symptoms develop.

Treatment

The treatment of corneal dystrophies varies. Individuals who do not have symptoms

(asymptomatic) or only have mild symptoms may not require treatment and may instead be regularly observed to detect potential progression of the disease.

Specific treatments for corneal dystrophies may include eye drops, ointments, lasers and corneal transplant. Recurrent corneal erosions (a common finding in most corneal dystrophies) may be treated with lubricating eye drops, ointments, antibiotics or specialized (bandage soft) contact lenses. If recurrent erosions persist, additional measures such as corneal scraping or the use of excimer laser therapy, which can remove abnormalities from the surface of the cornea (phototherapeutic keratectomy). At this time, there is no known preventive treatment for corneal dystrophies.

In individuals with significant associated symptoms a corneal transplant, known as a keratoplasty, may be necessary. Corneal transplants have been highly successful in treating individuals with advanced symptoms of corneal dystrophies. There is a risk however, in certain corneal dystrophies, that the lesions will eventually develop in the graft (donated) cornea.[1]

Although genetic testing strategies for corneal dystrophies are continuously improving, the potential benefits and harms of such testing have yet to be clearly defined. More research is needed to analyze the significance of results and estimate the probability of the change being pathogenic.

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. The U.S. Food and Drug Administration (FDA) has not regulated these tests to date. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

Medical Policy Statement

The peer reviewed medical literature has not demonstrated the clinical utility of gene analysis for corneal dystrophies. Therefore, this service is experimental/investigational.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

81333

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

CORNEAL DYSTROPHY

Clinical Context and Test Purpose

The purpose of testing for *TGFBI* variants in high-risk individuals is to evaluate whether corneal dystrophy is present and, if it is, to determine the appropriate surveillance and treatment.

The question addressed in this evidence review is: Does testing for *TGFBI* variants improve the net health outcome in individuals with or suspected of having corneal dystrophy?

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is patients with corneal dystrophy, or patients with a personal or family history of corneal dystrophy, or patients who meet certain criteria that might suggest they are at risk of hereditary corneal dystrophy.

Intervention

The intervention of interest is *TGFBI* variant testing.

Comparator

The comparator of interest is the withholding of genetic testing for *TGFBI* variants.

Outcomes

The outcomes of interest are overall survival, test accuracy and validity, and quality of life.

Literature

In 2017, Wang et al examined the clinical features of three Chinese families with autosomal dominant corneal dystrophy specifically transforming growth factor-β-induced (*TGFBI*) gene mutations.[2] The *TGFBI* gene mutations were detected using direct sequencing of the whole coding regions and exon-intron boundaries of the *TGFBI* gene in the affected members from the three families with CD. The phenotypes of all affected individuals in the three families were observed via slit lamp examination. Sections of the cornea were used for biopsy following keratoplasty. Three types of *TGFBI* gene mutations, R124C, H626R and R124H, were detected in the patients from these three families. One family, with the R124C mutation, was diagnosed with lattice corneal dystrophy type 1, and the family with the H626R mutation was diagnosed with lattice corneal dystrophy type IIIB. The family with the R124H mutation was diagnosed with granular corneal dystrophy type 2. The *TGFBI* gene mutations were

considered underlying factors in the molecular mechanism underlying the pathogenesis of corneal dystrophy.

Zhao et al (2019) also studied three Chinese families with Reis-Bucklers corneal dystrophy (RBCD), lattice corneal dystrophy type 1 (LCD1), or Avellino corneal dystrophy (ACD) to identify the types of TGFBI gene mutations.[3] The authors investigated investigate the relationship between the phenotypes and genotypes of corneal dystrophy. Peripheral blood was collected from 24 patients and 76 phenotypically normal members in three Chinese families as well as from 100 healthy controls. Genomic DNA was extracted. All 17 exons of the *TGFBI* gene, and the exon-intron junctions were examined by polymerase chain reaction (PCR) and direct DNA sequencing to identify and analyze gene mutations. In addition, all members of the three families were subjected to detailed clinical examinations. The heterozygous c.371G > T (p.R124L) mutation was detected in exon 4 of the *TGFBI* gene in nine patients from the family with RBCD. In contrast, this mutation was not found in the phenotypically normal members of the family. The heterozygous c.370C > T (p.R124C) mutation was found in exon 4 of the *TGFBI* gene in 11 patients from the family with LCDI. This mutation was not found in the phenotypically normal members of the family. The heterozygous c.371G >A (p.R124H) mutation was detected in exon 4 of the *TGFBI* gene in four patients from the family with ACD. Again, this mutation was not found in the phenotypically normal members of the family. The *TGFBI* gene mutations cosegregated with the disease phenotypes in the three families and exhibited an autosomal dominant mode of inheritance. No *TGFBI* gene mutations were detected in the 100 healthy controls. There is a high degree of correlation between the phenotypes and genotypes of *TGFBI*-linked corneal dystrophies. R124 represents a mutational hotspot in the *TGFBI* gene.

Bouyacoub et al (2019) reported the clinical features and the mutational analysis in a large Tunisian family with granular corneal dystrophy type 1 (GCD1).[4] Thirty-three members of the Tunisian family underwent a complete ophthalmologic examination. DNA extraction and direct Sanger sequencing of the exons 4 and 12 of transforming growth factor β Induced (*TGFBI*) gene was performed for 42 members. For the molecular modeling of *TGFBI* protein, we used pGenTHREADER method to identify templates, 3D-EXPRESSO program to align sequences, MODELLER to get a homology model for the FAS1 (fasciclin-like) domains and finally NOMAD-ref web server for the energy minimization. The diagnosis of GCD1 was clinically and genetically confirmed. Sequencing of exon 4 of *TGFBI* gene revealed the p.[R124S] mutation at heterozygous and homozygous states in patients with different clinical severities. Visual acuity was severely affected in the homozygous patients leading to a first penetrating keratoplasty. Recurrence occurred rapidly, began in the seat of the corneal stitches and remained superficial up to 40 years after the graft. For heterozygous cases, visual acuity ranged from 6/10 to 10/10. Corneal opacities were deeper and predominating in the stromal center. According to bioinformatic analysis, this mutation likely perturbs the protein physicochemical properties and reduces its solubility without structural modification.

Chao-Shem et al (2019) discussed one commercially available test that examines for the five most common of these mutations: R124H, R124C, R124L, R555W, and R555Q.[5] To expand the capability of identifying the causative mutation in the remaining cases, 57 mutations would need to be added. The aim of this study was to obtain a better understanding of the worldwide distribution and population differences of *TGFBI* mutations and to assess which mutations could be included or excluded from any potential assay. A total of 184 published papers in Human Gene Mutation Database (HGMD) from 34 countries worldwide reporting over 1600

corneal dystrophy cases were reviewed. Global data from 600,000 samples using the commercially available test were analyzed. Case studies by University College of London (UCL), Moorfield's Corneal Dystrophy Study data and 19 samples from patients with clinical abnormality or uncertainty for which the current test detected no mutation were used to predict an achievable detection rate. Data from the literature search showed no difference in the spectrum and frequency of each mutation in different populations or geographical locations. According to the authors' analysis, an increase to the worldwide detection rate in all populations from 75 to 90% may be achieved by the addition of six mutations-H626R, A546D, H572R, G623D, R124S, and M502V-to the currently available test and that may be beneficial for LASIK pre-screening worldwide.

Choo et al (2022) provided the initial confirmation of the c.1772C>T (p.Ser591Phe) mutation in the transforming growth factor-ββ-induced (*TGFBI)* gene as being associated with variant lattice corneal dystrophy (LCD).[6] Ophthalmologic examination of the proband was performed with slit lamp biomicroscopy. Saliva was collected as a source of DNA for screening all 17 exons of *TGFBI*, after which three family members were selectively screened for variants in exon 13. Rosetta-based structure prediction was used to calculate changes in TGFBI protein (TGFBIp) stability secondary to the c.1772C>T (p.Ser591Phe) missense mutation. Slit lamp examination of the 38-year-old proband revealed a clear cornea right eye and unilateral, discrete, and branching lattice lines in the anterior and mid-stroma of the central cornea left eye. Screening of *TGFBI* in the proband revealed a heterozygous missense mutation in exon 13 (c.1772C>T (p.Ser591Phe)) that was also identified in her affected mother but not in her brother or maternal grandmother. Calculated energy change in Rosetta (ΔΔG) for the TGFBIp variant p.Ser591Phe was 23.5, indicating a thermodynamic destabilization resulting from energetic frustration.

SUMMARY OF EVIDENCE

Corneal dystrophies are a group of heterogeneous conditions caused by numerous genes, many of which have almost the same clinical picture. Although genetic testing strategies for corneal dystrophies are continuously improving, the potential benefits and harms of such testing have yet to be clearly defined. All tests are not 100% sensitive or 100% specific. More research is needed to analyze the significance of results and estimate the probability of the change being pathogenic. The evidence is insufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

No guidelines or position statements were found specific to gene analysis for corneal dystrophies.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might impact this policy are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02771236	Clinical and molecular studies in families with inherited eye disease.	5000	Jan 2032

NCT: national clinical trial

Government Regulations

National:

There is no national coverage determination for *TGFBI* variant testing.

Local:

here is no local coverage determination for *TGFBI* variant testing.

There is a fee for code 81333 in the 2019 Clinical Diagnostic Lab Fee Schedule.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing for Retinal Dystrophy
- Genetic Testing and Counseling

References

1. The Corneal Dystrophy Foundation. What is corneal dystrophy? Available at: https://www.cornealdystrophyfoundation.org/what-is-corneal-dystrophy. Accessed December 2019. Located in supplemental documents.
2. Wang X, Ying M, Fu C. et al. TGFBI gene mutations analysis in Chinese families with corneal dystrophies. Mol Med Reports. 2017;15:3198-3202.
3. Zhao F, Liu Y, and Guan T. Analysis of TGFBI gene mutations in three Chinese families with corneal dystrophy. J Ophthal. 2019; Article ID 6769013: 9 pages.
4. Bouyacoub Y, Falfoul Y, Ouederni M, et al. Granular type I corneal dystrophy in a large consanguineous Tunisian family with homozygous p.R124S mutation in the TGFBI gene. Ophthal Genet. July 2019; [Epub ahead of print].
5. Chao-Shern C, DeDionisio LA, Jang JH, et al. Evaluation of TGFBI corneal dystrophy and molecular diagnostic testing. Eye (Lond). June 2019;33(6):874-881.
6. Nithianandan H, Chao-Shern C, DeDionisio L, et al. Trauma-induced exacerbation of epithelial-stromal TGFBI lattice corneal dystrophy. Can J Ophthal. Feb 2019;54(1):e47-e49.

7. Choo CH, Chung DD, Ledwitch KV, et al. Confirmation of association of TGFBI p.Ser591Phe mutation with variant lattice corneal dystrophy. Opthalmic Genet. Aug 2022; 43(4): 530-533.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/20	2/18/20		Joint policy established
5/1/21	2/16/21		Routine policy maintenance, no change in policy status.
5/1/22	2/15/22		Routine policy maintenance, no change in policy status.
5/1/23	2/21/23		Routine policy maintenance, no change in policy status. (ds)
5/1/24	2/20/24		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)
5/1/25	2/18/25		Rationale updated added reference #6. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 1st Qtr. 2026

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENE ANALYSIS FOR CORNEAL DYSTROPHY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.