AvaGen™
THE GENETIC EYE TEST

PATIENT INFORMATION

Patient ID:
DOB (MM/DD/YYYY):
Sex:

SAMPLE INFORMATION

Sample ID:
Sample Type:
Date Collected:
Date Received:
Date Reported:

ORDERING PROVIDER

Physician Name:
Clinic Name:
Test Indication: Copy Clin.diag. from TRF

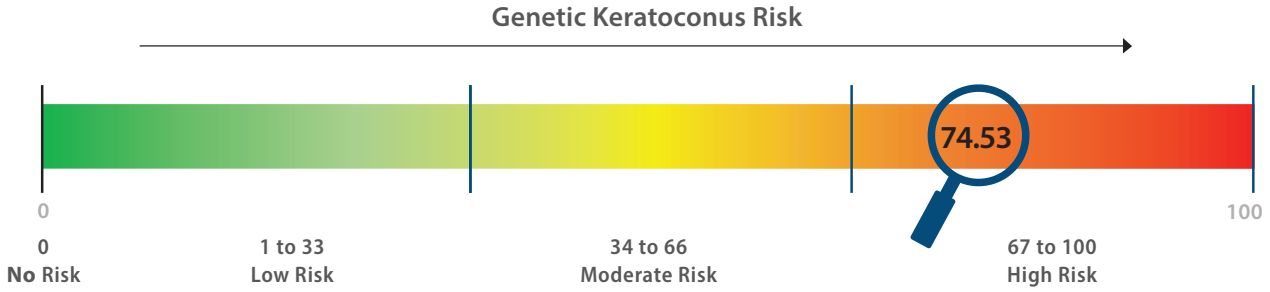
FINAL RESULTS SUMMARY:

CONDITION TESTED	RESULT	DETAIL	EXPLANATION
Keratoconus (KC)	Genetic high risk	74.53 polygenic risk score	Tested for 75 covered genes and thousands of variants associated with KC
TGFBI Corneal Dystrophies (CD)	Positive for Reis-Bucklers	c.337G>A variant	Tested positive for 1 out of 70 known variants associated with TGFBI corneal dystrophies

This AvaGen Genetic Test result should be considered with other clinical criteria, the patient's family history and communicated in a setting that includes appropriate genetic counseling.

Keratoconus (KC) Risk Assessment

Based on the polygenic genetic risk score of **74.53**, this patient's risk for **KC** is **high**.



THE POLYGENIC KC RISK SCORE: The AvaGen Genetic Eye Test provides a polygenic risk score for individuals interested in their genetic risk for KC. It is based on thousands of variants in 75 genes that are known to be associated with this disease. Genetics is an important indicator in KC risk. Factors such as an individual's medical exam findings, their family's medical history, and environment may also play a role in determining a person's risk of developing this condition.

UNDERSTANDING THE RISK SCORE: The AvaGen Genetic Eye Test polygenic risk scores are shown on a scale of 0 to 100.

A PRS below 0 indicates that there is no genetic risk detected by the AvaGen Genetic Eye Test.

A PRS above 0 is divided into three risk segments (low, moderate, and high). Each risk segment represents the relative risk a patient has of developing KC, based on their genetic profile, when compared to known KC patients. A higher polygenic risk score indicates a greater genetic risk of developing KC.

Avellino Lab USA, Inc. 1505 Adams Drive, Suite B2, Menlo Park, CA 94025 650-396-3741 www.avellino.com
CLIA ID: 05D2048075 CA ID: CLF-00343311* Laboratory Director: Mir Noorbash, PhD

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Keratoconus Polygenic Test Details

Genes with Keratoconus associated variants for this patient:

ABCA4, ABCC6, ADAMTS18, ADGRV1, COL17A1, COL4A3, COL4A4, CYP4V2, FOXE3, GJA8, KRT3, LTBP2, PIKFYVE, TACSTD2, VSK1, ZNF469

Keratoconus-Related Genes Tested:

ABCA4, ABCB5, ABCC6, ADAMTS18, ADGRV1, AGBL1, ANGPTL7, BEST1, CHST6, COL2A1, COL4A1, COL4A2, COL4A3, COL4A4, COL5A1, COL5A2, COL6A1, COL8A2, COL12A1, COL17A1, CYP4V2, DIAPH1, DOCK9, FOXE3, FYN, GJA8, GSN, HGF, IL1A, IL1RN, IL6, IL10, ITGB1, KERA, KRT3, KRT12, KRT13, KRT15, KRT16, KRT23, KRT24, LCAT, LOX, LRRN1, LTBP2, MAP2K1, MAP3K19, MTOR, MYLK, NLRP1, OVOL2, PAX6, PIK3CG, PIKFYVE, PIK3R1, PRDM5, PTK2, PXDN, PXN, RAF1, RHOA, SFTPD, SHC1, SIX5, SLC4A11, TACSTD2, TCF4, TGFBI, TLN1, UBIAD1, VSX1, WNT9A, WNT9B, ZEB1, ZNF469

Corneal Dystrophy (CD) Test Result

This patient has 1 out of 70 known variants associated with TGFBI corneal dystrophies.

Variants with TGFBI Corneal Dystrophy associated gene for this patient:

POSITIVE for a disease-causing variant, c.673T>C (p.Cys225Arg) in TGFBI gene. Heterozygous TGFBI p.Cys225Arg is a disease-causing variant for Lattice Corneal Dystrophy type I.

AvaGen Detects The Following TGFBI Associated Corneal Dystrophies

- Epithelial Basement Membrane
- Granular Type 1
- Granular Type 2 (Avellino)
- Lattice Type 1
- Lattice Type IIIA
- Reis-Bucklers
- Schnyder
- Theil-Behnke

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Methodology and Limitations:

After extracting the patient's genomic DNA from a buccal swab sample, a next-generation sequencing (NGS) analysis is carried out. Avellino utilizes a custom panel that primarily targets the coding regions of 75 genes identified to be involved in the structure and function of the eye. Sequence results are aligned with the Genome Reference Consortium Human Genome Build 37 (GRCH37.p13) and a risk score is calculated. The test also screens for 70 known disease-causing TGFBI variants.

TGFBI Corneal Dystrophy Variants Tested: c.337G>A, c.367G>C, c.370C>T, c.371G>A, c.371G>T, c.370C>A, c.393G>T, c.535C>T, c.1209T>G, c.1486C>T, c.1501C>A, c.1504A>G, c.1514T>A, c.1526T>G, c.1526T>C, c.1541G>C, c.1545T>A, c.1548C>G, c.1553T>G, c.1553T>C, c.1565T>A, c.1580T>G, c.1603G>T, c.1613C>G, c.1612A>C, c.1616T>A, c.1619T>C, c.1625C>G, c.1631A>G, c.1637C>A, c.1636G>A, c.1640T>G, c.1640T>C, c.1643G>C, c.1649T>C, c.1652C>A, c.1664G>A, c.1663C>T, c.1673T>G, c.1673T>C, c.1675T>G, c.1694T>C, c.1706T>G, c.1706T>A, c.1715A>G, c.1781G>T, c.1838T>G, c.1856T>A, c.1859C>A, c.1858G>C, c.1861A>C, c.1864A>C, c.1866T>A, c.1866T>G, c.1867G>C, c.1868G>A, c.1870G>A, c.1874T>A, c.1877A>G, c.1877A>C, c.1892T>A, c.1998G>C, c.310_311delTC, c.1618_1620delTTT, c.1714_1716delCAC, c.1838_1849del12, c.1870_1875delGTGGTC, c.1879delG, c.1886_1894dupCCAATGTTC, c.371_378delGCACGGAGinsTC

A patient cohort consisting of 739 cases and 368 controls was used to calculate an Odds Ratio (OR) for each of the 2,335 variants found in the 75 genes tested. A Polygenic Risk Score (PRS) was calculated from the sum of the log for these ORs to determine a risk for developing keratoconus. The PRS is specific to the patient's genome and every individual has a unique PRS.

The availability of an individual's unique genomic information can contribute to preventative health strategies and allows therapy to begin at an earlier stage.

Furthermore, including genomic information into the patient's family's health history (FHH) may be valuable in determining personal health risk factors. NGS has the power to detect very rare variants that often are integral to understanding the etiology of complex, multifactorial diseases, such as keratoconus, related corneal diseases, and TGFBI corneal dystrophy. Design Studio Software (Illumina Inc.; San Diego, CA) found our targeted panel design to be 97% accurate for calling variants within the test's targeted regions of the genome.

As knowledge of genetic information improves over time, new data may become available in the future that could potentially impact the interpretation of your test results. However, Interpretation of the test results is limited by the information that is currently available. More comprehensive interpretation of test results may be possible in the future as more data and knowledge about the molecular mechanism of keratoconus and TGFBI corneal dystrophies is accumulated.

The laboratory sequences all coding exons for each given transcript. Any variants that do not meet internal quality standards are not reported. This test may not provide detection of certain variants or portions of certain genes due to local sequence characteristics, high/low genomic complexity, or the presence of closely related pseudogenes. Analytically difficult features of the genome, such as deletions and duplications >20bp may not be detected in this assay. Rarely, novel sequence variants may interfere with NGS read creation, sequence alignment, and variant calling. Large deletion and/or mosaic variants may not be detected with this technology. Gross deletions, duplications, and changes from repetitive sequences may not be accurately identified by this methodology.

The laboratory has confidence in the test's ability to track a specimen once it has been received. However, the laboratory takes no responsibility for any specimen labeling errors that occur before the sample arrives at Avellino. Genetic counseling to help to explain test results to the patients and to discuss treatment options is recommended.

Literature References

1. Wang, J. *Nucleic Acids Research* 2018, 46 (8), e47-e47. **2.** Chan, I. S. *Annual Review of Genomics and Human Genetics* 2011, 12, 217-244. **3.** Shendure, *J. Nat Rev Genet* 2004, 5 (5), 335-44. **4.** Lu, Y. *Nat Genet* 2013, 45 (2), 155-63. **5.** Bisceglia, L. *Invest Ophthalmol Vis Sci* 2009, 50 (3), 1081-6. **6.** Hughes, A. E. *Investigative Opthalmology & Visual Science* 2003, 44 (12). **7.** Czugala, M. *Eur J Hum Genet* 2012, 20 (4), 389-97. **8.** Gajecka, M. *Invest Ophthalmol Vis Sci* 2009, 50 (4), 1531-9. **9.** Tyynismaa, H. *Investigative Ophthalmology & Visual Science* 2002, 43 (10), 3160-3164. **10.** Brancati, F. *Journal of Medical Genetics* 2004, 41 (3), 188-192. **11.** Tang, Y. G. *Genetics in Medicine* 2005, 7 (6), 397-405. **12.** Burdon, K. P. *Human Genetics* 2008, 124 (4), 379-386. **13.** Li, X.; Rabinowitz *Invest Ophthalmol Vis Sci* 2006, 47 (9), 3791-5. **14.** Liskova, P. *Archives of Ophthalmology* (Chicago, Ill. : 1960) 2010, 128 (9), 1191-5. **15.** Klintworth, G. K., Corneal dystrophies. *Orphanet J Rare Dis* 2009, 4, 7. **16.** Lakshminarayanan, R. *The Ocular Surface* 2014, 12 (4), 234-251. **17.** Weiss, J. S. IC3D classification of corneal dystrophies--edition 2. *Cornea* 2015, 34 (2), 117-59. **18.** Copeland, R. A. *JP Medical Ltd*: 2013; Vol. 1. **19.** Chao-Shern, C. Eye 2019, 1. **20.** Avellino Lab USA, Inc. White paper on file.

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