GlutenID Celiac Genetic Health Risk (GHR) Test

Package Insert

IVD

Manufactured by:

TARGETED GENOMICS™

5 Mason
Irvine, CA 92618

For *in-vitro* diagnostic use

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Summary and Intended Use

Summary:

The GlutenID Celiac Genetic Health Risk (GHR) Test is an over the counter (OTC) and direct-to-consumer (DTC) DNA genetic testing service. The test creates a report that identifies the presence or absence of four HLA-DQ haplotype variants associated with the risk of developing Celiac disease. The GlutenID Celiac GHR Test is indicated for reporting of one variant associated with the HLA- DQ2.5 haplotype, one variant associated with the HLA-DQ8 haplotype, one variant associated with the HLA-DQ7 haplotype, and three variants associated with the HLA-DQ2.2 haplotype.

The tests are conducted with genomic DNA isolated from human saliva samples collected in the FDA cleared Class II (K212745) ORAcollect®.Dx (OCD-100) device manufactured by DNA Genotek Inc. https://dnagenotek.com/US/pdf/PD-MSDS-00021.pdf The GlutenID GHR Test website (https://targeted-genomics.com) provides the contents and the procedure to order and use the test service. The consumers order a kit and collect their sample at home. After registering the kit in a HIPAA compliant website portal, they mail their sample to a third-party laboratory in the pre-paid shipping box. When their result is ready, they use a secure portal to receive their test report.

The results of the testing are provided in customized reports for each user. These reports inform the user of the variant(s) detected in their sample as well as the risk of disease associated with the variants. Risk is assigned to three categories: Increased, Low, Not Likely at Risk. If no variants were detected, this information is also provided. The reports are designed to present scientific concepts to users in an easy-to- understand format. Reports provide scientific information about the possible risks associated with each variant.

GlutenID Risk Gradient for 15 GlutenID Markers

GlutenID Marker	Estimated Risk	Risk Category
DQ2+DQ2	1 in 9 (8%)	Increased
DQ2+half-DQ-DQ2	1 in 9 (8%)	
DQ2+DQ8	1 in 12 (6%)	
DQ8+half-DQ2	1 in 25 (4%)	
DQ2+DQ7	1 in 35 (3%)	
DQ2.2+DQ7 [DQ2 trans]	1 in 35 (3%)	
DQ2 (cis)	1 in 35 (3%)	
DQ8+DQ8	1 in 100 (1%)	Low
DQ8	1 in 100 (1%)	
DQ8+DQ7	1 in 100 (1%)	
half-DQ2+half-DQ2 (DQ2.2+DQ2.2)	1 in 210 (0.5%)	Not Likely at Risk
half-DQ2 (DQ2.2)	1 in 210 (0.5%)	
DQ7+DQ7	1 in 1842 (0.05%)	
DQ7	1 in 1842 (0.05%)	
Non-celiac genetics (NCG)	1 in 2518 (0.05%)	

Intended Use

Intended Use/Indications for Use: The GlutenID Celiac Genetic Health Risk (GHR) Test uses qualitative genotyping to detect clinically relevant variants in genomic DNA isolated from saliva collected from Users 18 years of age or older for the purpose of reporting and interpreting celiac GHR.

The GlutenID Celiac GHR Test is indicated for reporting of one variant associated with the HLA-DQ2.5 haplotype, one variant associated with the HLA-DQ8 haplotype, one variant associated with the HLA-DQ7 haplotype, and three variants associated with the HLA-DQ2.2 haplotype. The GlutenID report describes if a person has variants linked to a haplotype associated with an increased risk for developing celiac disease, but it does not describe a person's overall risk of developing celiac disease.

Intended User(s): The GlutenID Celiac GHR Test is intended for use by laypersons and healthcare professionals. DNA is isolated from saliva collected from Users 18 years or older.

Kit Component	Description	Count
ORAcollect®.Dx (OCD-100)	to collect, stabilize and protect DNA saliva samples	1
Kit Booklet IFU	Instructions for sample collection and kit registration	1
USPS mailing label	Label for returning Saliva samples to the laboratory	1

Special Considerations of Use and Risk Mitigation

Kit components

- The lab will only accept samples delivered via postal service or carrier. Do not attempt to drop off your sample directly at the lab.

- We will provide you with free replacement shipping materials if you have misplaced or discarded your return shipping supplies. If you have discarded your return shipping supplies, please contact Customer Care. The only mailed samples accepted are those returned with the pre-paid shipping materials provided by Targeted Genomics.

Intended Patient Population: The GlutenID Celiac GHR Test is intended for use by individuals and families to determine risk for development of celiac disease.

Principles of Operation of the Device:
The Gluten ID device has three components:

1. GlutenID Test Kit
2. GlutenID laboratory developed test (LDT)
3. GlutenID Final Report

Conditions of Use (i.e., Environment of Use): Sample collection for the GlutenID Celiac GHR Test is performed at home or in a healthcare provider's office. Patient/device interaction occurs through ORAcollect swabs contained in the GlutenID test kit. Patients can obtain GlutenID kits fr0m their healthcare provider or order GlutenID kits from the Targeted Genomics website. Following Saliva collection, swab samples are returned to the laboratory in the same kit box using a pre-paid mailing label affixed to the kit box.

Relevant ethnicities

The variants included in this test are common in many ethnicities including White, African American, Asian, and Others but are best studied in people of European descent. The relevance of each report

and how your genetic health risk results are interpreted may differ depending on your ethnicity. Each genetic health report indicates if a person has variants associated with an increased risk of developing a disease, but it does not indicate their overall risk.

Other Limitations, Precautions, and Warnings

- For over-the-counter use.

- This test provides genetic risk information based on the specific genetic risk variants tested. It does not report on a user's entire genetic profile.
- Sample collection for the GlutenID Celiac GHR Test is performed at home or in a healthcare provider's office.
- The minimum age threshold to self-collect a sample is >= 18 years of age
- The test does not diagnose any specific health conditions. Results should not be used to make medical decisions.
- The celiac GHR must be reported and interpreted by users 18 years of age or older.
- Patient/device interaction occurs through ORAcollect swabs contained inside the GlutenID test kit.
- Patients can obtain GlutenID kits from their healthcare provider or order GlutenID kits from the Targeted Genomics website.
- Following saliva sample collection, swab samples are returned to the laboratory in the same tubes and kit box using a pre-paid mailing label affixed to the kit box.
- This test is not a substitute for visits to a healthcare provider. It is recommended that you consult with a healthcare provider if you have any questions or concerns about your results.
- The test does not diagnose any specific health conditions. Results should not be used to make medical decisions.
- A user's race, ethnicity, age, and other lifestyle factors may affect how the genetic test results are interpreted.
- Subject to meeting the limitations contained in the special controls under regulation 21 CFR 866.5950.
- The GlutenID test does not detect all genetic variants related to celiac disease. The absence of a variant tested does not rule out the presence of other variants.
- 24 potentially interfering mutations were identified for HLA-DQ2.5, HLA-DQ8, HLA-2.2, HLA-DQ7. Interference due to these mutations on the performance of the assay has not been evaluated.
- The GlutenID test is not a substitute for visits to a healthcare professional. You should consult with a healthcare professional if you have questions or concerns about your results.
- Different companies offering genetic testing for celiac disease may be analyzing different variants so you may get different results from a different test.
- Some people may feel anxious about receiving genetic health results. This is

normal. If you feel very anxious, you should speak to your doctor or a genetic counselor prior to collecting your sample for testing. You may also consider getting your celiac GHR testing done by your doctor.

The Targeted Genomics Gluten ID test includes GHR reports. The report that meets FDA requirements for genetic health risks as outlined in 866.5950.

Contrandications: No Contraindications

Precautions:

Do not eat, drink, smoke, chew gum, brush your teeth, or use mouthwash for at least 30 minutes prior to providing your sample.

prior to providing your sample.

Do Not Reuse this Product: Risks of re-use include microbial exposures and swab breakage. Providing the DNA Sample ORAcollect®.Dx (OCD-100) instructions included with your kit about providing your Saliva sample.

(live link) https://dnagenotek.com/US/pdf/PD-MSDS-00021.pdf

WARNING: Do NOT ingest DNA stabilizing liquid in the swab tube.

For Healthcare Professionals

- The GlutenID test is not intended to diagnose celiac disease, determine medical treatment, or tell the user anything about their current state of health.
- The GlutenID test is intended to provide users with their genetic information, which may inform health-related lifestyle decisions and conversations with their doctor or other healthcare professional.
- Healthcare professionals should base diagnostic or treatment decisions on testing and/or other information determined to be appropriate for each patient.

Professional Guidelines

- Genetic testing for celiac disease is recommended by health professional organizations including the American College of Gastroenterology. Refer to the American College of Gastroenterology

guidelines for specific recommendations and indications for celiac genetic testing.

WARNING:

Special Conditions and Limitations

- Genetic Health Risk reports will tell you about genetic variations that may increase your risk of certain health problems. These genetic tests are not intended to diagnose health conditions or to determine medical treatment.
- Having a risk variant does not guarantee that you will develop a health condition. Furthermore, it is still possible that you may develop the condition without a variant being identified. These reports may not contain all genetic risk variants.
- Factors like lifestyle and environment affect a person's genetics and can also affect the development of most health conditions. Our reports cannot tell you how likely you are to develop these conditions, nor can they determine if you are likely to develop them.
- These reports do not replace visits to a healthcare professional. To interpret genetic test results and use them effectively, speak with a healthcare professional. Don't base your medical decisions on genetic results.
- In less than 1% of cases, test failure occurs due to low DNA quantity/quality. In this case the laboratory may not be able to process your sample. Targeted Genomics will send a new collection kit free of charge.

- Variant(s) not detected: You do not have the variant(s) we tested. Since these tests do not include all variants that may impact your risk of developing a condition, you may still have another variant that could affect your risk. Non-genetic factors may also affect your risk.
- Variant(s) detected It is possible that you have one or more of the variants we tested. Your risk of developing the condition may be higher. However, this does not mean you will develop it. There are other factors that may also influence your risk.
- Neither the report nor the test is intended to tell you anything about the likelihood that you will develop a disease in the future, the health of your fetus, or the likelihoos that your newborn will develop a disease later in like. GlutenID reports only include information related to your genetic health risk.
- If you have other risk factors for the condition, you should discuss the condition with a doctor.
- This test may not detect all genetic variants related to celiac disease, and the absence of a variant tested does not rule out the presence of other genetic variants

that may be related to the disease

- You can also discuss your results with a genetics counselor https://findageneticcounselor.nsgc.org/?reload=timezone
- Genetic Health Risk reports are intended to provide you with genetic information to inform conversations with a healthcare professional. These reports should not be used to make medical decisions. Always consult with a healthcare professional before taking any medical action.

Analytical Performance

Samples for the GlutenID test were collected using ORAcollect device and sequenced on the Illumina MiSeqDx. Results were analyzed using GlutenID Analysis Software supported by the Galaxy Platform. Variant calls from the technical data were translated into a final GlutenID genotype for each sample.

The variants covered by the GlutenID GHR test are supported by the highest level (Level 1) of peer-reviewed scientific literature. The tested variants are common in many ethnicities. These variants are most often identified in people of European descent. Published medical literature estimate that 30% of people of European descent have at least one copy of the HLA-DQ2 haplotype and 5% have at least one copy of the HLA-DQ8 haplotype. The HLA-DQ2 and HLA-DQ8 haplotypes are present in > 95% of patients diagnosed with celiac disease. The presence of one or more of the Celiac GHR risk alleles is necessary, but not sufficient for development of celiac disease. Ruling out the presence of HLA-DQ2 and HLA-DQ8 has negative predictive value (NPV) of >99% for ruling out celiac disease.

Accuracy

Targeted Genomics performed a method comparison study to assess accuracy of the GlutenID Celiac GHR Test. Results of the GlutenID test were compared with bi-directional Sanger sequencing results for 20 unique samples representing wild-type genotypes and 40 unique samples positive for the four celiac risk haplotypes collectively representing 150 total variants:

- HLA-DQ2.5 wildtype (CC), heterozygous (CT), homozygous (TT)
- HLA-DQ8 wildtype (TT), heterozygous (TC), homozygous (CC)
- HLA-DQ7 wildtype (AA), heterozygous (AG), homozygous (GG)
- HLA-DQ2.2 wildtype (TT), heterozygous (TG), homozygous (GG)

Agreement between the two methods and technical positive predictive value (TPPV) was 100% for all samples analyzed.

Precision/Reproducibility

Precision studies were performed to determine the consistency between independently measured test results for the GlutenID Celiac GHR Test under the following changed conditions: assay run, critical reagent lot, instrument, operator, and day. A total of 322 study replicates were analyzed across these different testing conditions. The precision study yielded repeatability and reproducibility of 100%.

Minimum DNA Input

DNA samples with concentrations in the range of [3.9 ng/ul-250ng/ul] are eligible for further processing by the laboratory.

Interferences with other Substances

Studies were performed to assess whether foreign substances that may be present in the mouth affect the results of GlutenID testing. 90 swab samples self-collected by four individuals with known DQ2,DQ8, DQ2.2, DQ7 status were sent to a CLIA certified laboratory for re-testing. The samples were collected following exposure to common endogenous, exogenous, and microbial interfering substances. Interfering substances did not affect test performance.

The following interferents were tested:

- Eating
- Drinking
- Chewing gum
- Smoking
- Mouthwash
- Brushing Teeth
- Microbial
- Amylase
- IgA
- Hemoglobin
- Total protein

Gluten ID Kit contains ORAcollect swabs and includes instructions for Use (IFU) recommending the user NOT eat, drink, smoke, or chew gum 30 minutes before sample collection. For more information refer to the Material Safety Data sheet at Oracollect.com. https://dnagenotek.com/US/pdf/PD-MSDS-00021.pdf.

Interfering Mutations

Performance of the GlutenID Celiac GHR test may be affected by the presence of the following rare mutations:

Haplotype	Tag SNP(s)	Potentially Interfering Mutations
DQ2.5	rs2187668	rs769029321, rs1189841207, rs1490317600, rs1466681194, rs1379617295

DQ8	rs7454108	rs1398151255, rs1037255898, rs564828053, rs776920125
DQ7	rs4639334	rs1227184065, rs114929610, rs1296659658
DQ2.2	rs2395182 rs7775228 rs4713586	rs1562307508, rs1027315826, rs375347825, rs1022268175, rs1036852583, rs73405373, rs1042832287, rs4713587, rs72844311, rs112931959, rs1475416138, rs1259286745

Clinical Performance

Clinical Summary

The HLA-DQ2.5 haplotype is present in 95% of patients diagnosed with celiac disease and the HLA-DQ8 haplotype is detected in < 5%. (Taylor 2015) Rarely HLA-DQ2 is inherited in the form of two separate haplotypes HLA-DQ7 and HLA-DQ2.2 (one half from each parent) encoding alpha and beta chains differing by only two amino acids from DQ2.5 and conferring similar celiac disease risk. (Pisapia 2020) The DQ2.5 haplotype is commonly referred to as DQ2(*cis*) while the DQ7+DQ2.2 haplotype is called DQ2(*trans*). Although a hetero or homozygous DQ7 haplotype inherited without DQ2.2 confers only slightly increased risk above non celiac genetics (NCG), laboratory testing for celiac genetic risk must include all four haplotypes (DQ2.5, DQ8, DQ2.2, and DQ7) to identify presence or absence of DQ2 (trans).

Celiac GHR test report user comprehension study

User comprehension studies were performed to assess how well people understand the Celiac Genetic Health Risk Test Reports. A diverse group of over 300 people answered questions about the test via an online survey. Comprehension was tested through a two-step process. First, participants' understanding of celiac genetics was tested prior to viewing the educational module. Second, participants were shown the educational module with examples from the GlutenID test reports. Participants then completed the test report comprehension survey.

Overall comprehension rates per test report concept were greater than 90% across all concepts.

FAQs and Definitions

The frequently asked questions (FAQ) section for the genetic health report can be accessed via the Test Info page of the company website: https://targeted-genomics.com/test-info/ The FAQs addresses the purpose, limitations and meaning of the results of the test. The questions included in the FAQ section for each of the tests in this submission include, but are not limited to:

- What does my specific variant variant/disease pair [ex. DQ2(cis)] mean for my genetic risk?

- What does this test do?
- What does this test not do?
- Slightly increased risk: what does it mean?
- What does an increased risk mean?
- What might my result mean for my family and children??
- Reports say that detailed risk estimates for the variant are best studied in people with European ancestry. What if I'm not of European descent?
- How can I find out more about [disease], support groups, and other resources?
- What does it mean when my report says [#] variants detected

For definitions of commonly used scientific terms, visit the Targeted Genomics website https://targeted-genomics.com/test-info/. Terms explained include the following:

- Autoimmune Condition
- Celiac Disease
- Celiac Risk Variant
- DNA
- Gene
- Dietary Gluten
- Gluten Free Diet
- Gluten Sensitivity
- Haplotype
- Immune System

Selected References

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