Package Insert
GlutenID Celiac Genetic Health Risk (GHR) Test

Manufactured by:

TARGETED GENOMICS™

711 Navarro, Suite 235
San Antonio, TX 78205

Date of last revision: 6-30-2022

IVD

For *in-vitro* diagnostic use

Table of Contents

1. Summary and Intended Use

General Description: The GlutenID Celiac Genetic Health Risk (GHR) Test is an OTC and direct-to-consumer (DTC) DNA genetic testing service. The test creates a report that identifies one HLA-DFQ2.5 haplotype variant, one HLA-DQ8 haplotype variant, one HLA-DQ7 haplotype variant, and three HLA-DQ2.2 haplotype variants that associated with the risk of developing Celiac disease. The tests are conducted with genomic DNA isolated from human buccal (cheek) cells collected in the Class I FLOQSwabs manufactured by COPAN Italia.

The user self-collects the sample using FLOQSwabs. The collected sample is shipped to CAP accredited and Clinical Laboratory Improvement Amendments (CLIA) certified laboratory for processing, testing and analysis. Genomic DNA isolated from the buccal cells are processed and sequenced using next generation sequencing (NGS) reagents and instrumentation, FDA cleared Illumina MiSeqDx (K123989/ DEN130011) manufactured by Illumina. After the genotype sequencing run, the raw data is analyzed with MiSeq integrated system software and the final report for each sample is generated using the laboratory developed GlutenID Reporting Software

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. 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.

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 human buccal (cheek) cells collected by 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. This report is most relevant for people of European descent.

Intended User(s): The GlutenID Celiac GHR Test is intended for use by laypersons and healthcare professionals. The test is intended for Users aged >=18 years old. Users must be 18 years or older to self-test. The device is for over-the counter use only.

Kit Component	Description	Count
FLOQSwabs (GlutenID Kit swabs)	Copan Swabs in Active Drying System Tubes	2
Kit Booklet IFU	Instructions for sample collection and kit registration	1
USPS mailing label	Label for returning Human buccal cell samples to the laboratory	1

2. Important Limitations and Warnings

WARNING:

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 two COPAN single-use dry flock swabs inside active drying system tubes 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 buccal cell 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.

Special Conditions of Use Statements

- For over-the-counter use.
- 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 two COPAN single-use dry flock swabs inside active drying system tubes 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 buccal cell 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.

Contra-indications: 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. Rinsing the mouth with water prior to sample collection is recommended.

Do Not Reuse this Product: Risks of re-use include microbial exposures and swab breakage.

Providing the DNA Sample Buccal cell collection is different from saliva collection since there is no shortage of buccal cells in the mouth, and they are easy to collect. Be sure to review the instructions included with your kit about providing your buccal cell sample.

WARNING: Biting or scraping your cheeks is not recommended; gentle rubbing of the cheeks is all that is required for adequate sample collection. The full buccal cheek cell sample should be collected within 30 minutes of opening the swab kit

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.

3. Test Performance

Relevant ethnicities

The variants included in this test are common in many ethnicities 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.

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 likelihood that your newborn will develop a disease later in life. Our reports include only information related to genetic health risk.


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.

- 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.
- Result not determined the results of your test could not be determined. It can be due to a random test error or to other factors that interfere with the test.


WARNING:

- If you have other risk factors for the condition, you should discuss the condition with a doctor.
- This test [does not/may not, as appropriate] detect all genetic variants related to a given 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 genetic counselor. 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.

Speak to a genetic counselor

There are also certain limitations to genetic testing that need to be understood. Several factors, including your medical history, your goals, and your family's history, should be considered when deciding whether to test.

You can get answers to your questions and make an informed decision by talking with a genetic counselor, a healthcare professional who is specially trained in genetic conditions. To help you understand your results and what steps to take, we recommend you speak with a genetic counselor before and after testing. If the condition is preventable or treatable, this is especially important.

FAQ

The FAQ section for the genetic health report 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 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?

Test Performance Studies

Samples for the GlutenID test were collected using COPAN 4N6 FLOQSwabs 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 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. 48 swab samples self-collected by four individuals with known DQ2 and DQ8 status (previously established by GlutenID testing) were sent to PacificDx laboratory for re-testing. The samples were collected following exposure to common endogenous, exogenous, and microbial interfering substances **before and after** rinsing the mouth with water as directed in the GlutenID instructions for use (IFU.) One sample collected before rinsing mouth yielded insufficient DNA. All other samples produced accurate DQ2/DQ8 results.

The following interferents were tested:

- Alcohol
- Protein
- Wheat
- Dairy
- Toothpaste

- Gum base
- Sugar
- Blood
- Bacteria (S. Thermophilus, L. Bulgaricus, L. Acidophilus, L. Casel, Bifidus)

Gluten ID Cheek Swab Collection (CSC) Kit contains COPAN FLOQSwabs and include instructions for Use (IFU) recommending the user rinse their mouth with water prior to swab collection of buccal cells thus minimizing the presence of interferents in the sample.

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

4. User Studies

Cheek swab collection kit user study

User studies were performed to assess the ability of naive users to provide samples adequate for testing from home based on the kit instructions alone.

A total of 100 participants across a range of age and educational backgrounds collected and mailed swab samples from their home to the laboratory using the collection kit instructions. Cheek cell samples were processed according to standard laboratory procedures. DNA quantity and quality was assessed as evidence of successful collection.

All (100%) of samples in the study yielded adequate DNA for testing. All results were reported successfully to the users demonstrating that users from diverse backgrounds can understand the collection kit instructions and provide adequate cheek swab samples.

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 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 form 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.

5. Selected References

Nellikkai S et al. (2019) “High prevalence of celiac disease among screened first-degree relatives.” Mayo Clin Proc.94(9):1807-1813. pubmed.ncbi.nlm.nih.gov/31447136/

Singh P et al. (2018). “Global prevalence of celiac disease: systematic review and meta-analysis.” Clin Gastroenterol and Hepatol. 16:823-836. pubmed.ncbi.nlm.nih.gov/29551598/

Singh P et al. (2015). "Risk of celiac disease in the First- and Second-Degree Relatives of Patients with celiac disease: A Systematic Review and Meta-Analysis." Am J Gastroenterol. 110(11):1539-48. ncbi.nlm.nih.gov/pubmed/26416192

Taylor AK et al. (2008). "Celiac disease." [Updated 2015 Sep 17. ncbi.nlm.nih.gov/pubmed/20301720

Additional references can be found in the GlutenID Celiac GHR Test Report.

TARGETED GENOMICS™

711 Navarro, Suite 235
San Antonio, TX 78205