



AlphaID™ At Home  
Genetic Health Risk Service  
Package Insert



: PROGENIKA BIOPHARMA S.A.  
Parque Tecnológico de Bizkaia  
Ibaizabal bidea, Edificio 504  
48160 Derio – Bizkaia - SPAIN

**GRIFOLS**

## Contents:

- [Intended Use](#)
- [Consideration for testing](#)
- [Summary and explanation of the Service](#)
- [Important](#)
- [Warnings and limitations of the Service](#)
- [For healthcare professionals](#)
- [Clinical Performance](#)
- [Analytical Performance](#)
- [User studies](#)
- [References](#)
- [Trademarks](#)
- [Customer Support](#)

## Intended use:

The AlphaID™ At Home Genetic Health Risk Service uses qualitative genotyping to detect clinically relevant genetic variants associated with alpha-1 antitrypsin deficiency (AATD) in genomic DNA isolated from human saliva collected from individuals  $\geq 18$  years with ORAcollect®-Dx (OCD-100.014) for the purpose of reporting and interpreting Genetic Health Risks (GHR).

This Service is indicated for reporting 14 genetic variants in the *SERPINA1* gene: PI\*S; PI\*Z; PI\*I; PI\*M procida; PI\*M malton; PI\*S iiyama; PI\*Q0 granite falls; PI\*Q0 west; PI\*Q0 bellingham; PI\*F; PI\*P lowell; PI\*Q0 mattawa; PI\*Q0 clayton, and PI\*M heerlen. The report describes if a person is at an increased risk of developing either lung and/or liver disease linked to AATD. The Service does not describe a person's overall risk of developing lung and/or liver disease. AATD is more common in persons of European descent.

## Consideration for testing:

- The COPD Foundation, the World Health Organization, the American Thoracic Society, and the GOLD COPD guidelines recommend testing all COPD patients for variants linked to AATD ([1](#), [2](#), [3](#), [4](#)). Testing also extends to people with unexplained liver disease ([1](#), [3](#)).
- Signs and Symptoms Linked to AATD includes:
  - Shortness of breath and wheezing
  - Chronic cough
  - Lung disease, including chronic obstructive pulmonary disease (COPD), emphysema, chronic bronchitis, and bronchiectasis
  - Liver disease, including cirrhosis, jaundice, hepatic enzyme elevations, chronic hepatitis, and liver scarring (fibrosis)
- To find a doctor with experience in AATD from the Alpha-1 Foundation's Clinical Resource Center, visit <http://www.alpha1.org/alphas-friends-family/resources/find-an-alpha-1-specialist>

- To find a healthcare professional near you with experience testing for AATD, please visit <http://www.AlphaFindADoctor.com>
- To find a genetic counselor, visit <https://findageneticcounselor.nsgc.org>

## Summary and explanation of the Service:

The AlphaID™ At Home Genetic Health Risk Service is composed of:

- AlphaID™ At Home Saliva Collection Kit: for human saliva sample collection with ORAcollect®·Dx (OCD-100.014).
- A1AT Genotyping Test: for the genetic analysis and detection of genetic variants associated with AATD.
- AlphaID™ At Home Genetic Health Risk Service website and results portal ([www.AlphaIDAtHome.com](http://www.AlphaIDAtHome.com)): to provide the contents and the procedure to order and use the 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 will receive an email telling them to log onto their secure account to review their results.

## Important:

- Please follow the instructions in the AlphaID™ At Home Saliva Collection Kit for sample collection with ORAcollect®·Dx (OCD-100.014) and use the collection device within the expiration date to ensure your DNA results can be processed and connected to your online account.
- If you have a family history of AATD, talk to a healthcare professional about family testing.

## Warnings and limitations of the Service:

- DTC – Direct-To-Consumer.
- It is intended for users ≥18 years old.
- It is not a substitute for an appointment with a healthcare professional. We strongly recommend you consult with a healthcare professional if you have any questions or concerns about your result or health.
- It does not diagnose any disease or condition. Only a healthcare professional can diagnose a disease or condition.
- It does not determine if you have or will develop lung and/or liver disease linked to AATD during your lifetime.
- It cannot be used to make healthcare decisions. It does not tell you anything about your overall health. Only a healthcare professional can help you with healthcare decisions.
- It detects 14 variants in the *SERPINA1* gene linked to AATD. These 14 variants explain 95% of AATD cases. It does not detect all possible variants linked to AATD.

- There may be other, non-genetic factors that affect your risk. The Service does not determine your overall risk of developing lung and/or liver disease.
- Different companies offering a genetic risk test may be measuring different genetic variants for the same condition, so you may get different results from a different test.
- The test may not be able to determine a result for all variants analyzed.
- Some people feel a little anxious about getting 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 test done by your doctor.
- The laboratory may be unable to process every person's sample. The probability that the laboratory cannot process a sample can be up to 0.8%. If this happens, you will receive an email notification. You will also receive another AlphaID™ At Home Saliva Collection Kit to provide a new sample with ORAcollect®-Dx (OCD-100.014) to the laboratory.
- Share your results report with a healthcare professional. Healthcare professionals can answer questions you may have about your results, risk, and how they may apply to your health. They should know you were tested for AATD. You should also inform a healthcare professional if you:
  - Have symptoms of lung or liver disease
  - Have a personal or family history of lung or liver disease
  - Are feeling anxious, uncertain, or concerned about your genetic result or risk
  - Have questions about any risk factors
- The user's race, ethnicity, age and sex may affect how the genetic results are interpreted.

## For healthcare professionals:

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

## Clinical performance:

Alpha-1 antitrypsin deficiency (AATD) is an under-recognized hereditary disorder. It is passed on from parents to their children through genes and is associated with the premature onset of lung and/or liver disease (5). More than 90% of the estimated 100,000 people in the United States with AATD don't know they have it (6, 7).

AATD occurs in people of all ethnicities worldwide (5). However, it is most common in people of European descent. AATD affects about 1 in 1,500 to 3,500 people of European descent (1, 8)

Many individuals with AATD are likely undiagnosed, particularly people with a lung condition called chronic obstructive pulmonary disease (COPD). COPD can be caused by AATD; however, AATD is rarely diagnosed. Some people with AATD are misdiagnosed with asthma (9). Two to

three percent of patients with COPD in the United States are estimated to have AATD (1). The percentage of patients with liver disease who have AATD is not known.

AATD is caused by certain genetic variants in the *SERPINA1* gene. These variants cause low levels of a protein called alpha-1 antitrypsin (AAT). Low levels of the AAT protein can lead to AATD (1, 2).

A1AT Genotyping Test detects 14 variants in the *SERPINA1* gene linked to AATD: PI\*S; PI\*Z; PI\*I; PI\*M procida; PI\*M malton; PI\*S iiyama; PI\*Q0 granite falls; PI\*Q0 west; PI\*Q0 bellingham; PI\*F; PI\*P lowell; PI\*Q0 mattawa; PI\*Q0 clayton and PI\*M heerlen. These 14 variants explain 95% of AATD cases (5). These variants are mainly found in European population, except for PI\* S iiyama, which was described in the Asian population (10).

The most common variants are PI\*S and PI\*Z. Published studies estimate frequency ranges of 5-10% and 1-3% for PI\*S and PI\*Z, respectively, in the European population (8). An analysis of the prevalence of PI\*S and PI\*Z amongst the five major ethnic subgroups in the United States has demonstrated that the highest risk for AATD is found in Caucasians, followed by Hispanics and Blacks, with the lowest prevalence amongst Mexican Americans and no risk amongst Asian (8). The remaining 12 genetic variants tested are reported with a very low frequency in the population (8).

Detailed description of the 14 variants detected by the AlphaID™ At Home Genetic Health Risk Service in the *SERPINA1* gene and the supported References can be found [here](#).

The Service interpretation provides information about the lung and liver disease risk. Detailed description on the risk categories used by the Service can be found [here](#). The risk categorization is done based on the reported clinical cases for each genetic result. References that support the lung and liver disease risk categorization of each genetic result can be found in [Table 1](#).

## Analytical performance:

Saliva samples are processed using A1AT Genotyping Test. This test is based on a labeled multiplex PCR amplification and hybridization (Thermal Cycler, Thermo Fisher Scientific) and signal detection using Luminex's xMAP® Technology. The results were analyzed using a property software to obtain the result report file. The result report file is processed by AlphaID™ At Home website and results portal to provide the final report to the user.

### **Accuracy**

A method comparison study was performed to assess the accuracy of A1AT Genotyping Test to correctly detect the genetic variants. A total of 227 samples representing all genetic variants interrogated by the assay were analyzed and compared with Bi-Directional-Sequencing (BDS) (reference method). Percent Agreement (PA) between the two methods for the overall variants and samples (14 variants and 227 samples) was 100% (227/227) with a 95% confidence interval 98.3% to 100%. The percentage of overall "Invalid Tests" was 0% (0/227) with 95% confidence interval 0% to 1.7%.

## **Precision/Reproducibility**

A precision study was performed to assess the reproducibility of the test under different conditions. A total of 792 sample replicates were processed across three sites. The study included two operators per site and was conducted over three days. The reproducibility obtained for the test was 100%.

## **Minimum DNA input**

The minimum DNA input was obtained by testing five human cell line samples using two lots of reagents. The lowest limit of detection was determined to be 0.0215 ng/µl.

## **Interfering substances**

Studies were performed to evaluate the potential interference of substances that may be present in saliva samples.

Endogenous substances: Saliva samples collected in ORAcollect®·Dx (OCD-100.014) from five (5) random donors were spiked with substances usually found in saliva samples: salivary α-amylase, hemoglobin, immunoglobulin A and total protein. These substances did not interfere with test performance.

Exogenous substances: Saliva samples from five (5) random donors were collected in ORAcollect®·Dx (OCD-100.014) prior to the activity, immediately after the activity and 30 minutes after the activity. Seven (7) activity groups were tested: eating food without beef, eating food with beef, drinking, smoking, chewing gum, using mouthwash and brushing teeth. The results indicated that saliva samples collected in ORAcollect®·Dx (OCD-100.014) should be collected at least 30 minutes after the activity, which is compatible with the instructions for use of ORAcollect®·Dx (OCD-100.014) included in the AlphaID™ At Home Saliva Collection Kit: “Do not eat, drink, smoke or chew gum for 30 minutes before collecting saliva sample.”

Microbial substances: Five microbial interfering substances usually found in saliva samples were tested: *Staphylococcus epidermis*, *Streptococcus mutans*, *Lactobacillus casei*, *Actinomyces viscosus* and *Candida albicans*. These substances did not interfere with test performance.

## **Interfering variants**

The performance of this test may be affected by the presence of rare variants, such as:

### Not tested interfering variants:

rs149537225 for PI\*S (rs17580); rs201774333, rs551595739, and rs372571769 for PI\*Z (rs28929474); rs199422213 for P\*I (rs28931570), PI\*M procida (rs28931569), PI\*M malton (rs775982338) and PI\*S iiyama (rs55819880); rs544632177 and rs577164283 for PI\*F (rs28929470); rs1049800 for PI\*P lowell (rs121912714); rs61761869 and rs372571769 for PI\*M heerlen (rs199422209); rs148207011 for PI\*Q0 granite falls (rs267606950) and PI\*Q0 west (rs751235320); rs200634040 and rs72552401 for PI\*Q0 bellingham (rs199422211); rs148362959 and rs372571769 for PI\*Q0 mattawa (rs763023697), and rs143329723, rs121912712 and rs372571769 for PI\*Q0 clayton (rs764325655).

### Tested interfering variants:

- When PI\*M malton (c.226\_228delTTC, rs775982338) is delTTC/delTTC, the reported result for PI\*S iiyama (c.230C>T, rs55819880) can be either a homozygous -/-, a heterozygous +/-, or not detected. In any case, the Sample Result PI\*M malton/PI\*M malton will be reported.
- For a sample compound heterozygous for PI\*M malton (c.226\_228delTTC, rs775982338) and PI\*S iiyama (c.230C>T, rs55819880), a homozygous ++ result for both PI\*S iiyama and PI\*M malton will be provided. The Sample Result PI\*M malton/PI\*S iiyama will be reported. Either sample result (PI\*M malton/PI\*S iiyama; or PI\*M malton/PI\*M malton; or PI\*S iiyama/PI\*S iiyama) is phenotypically associated with a severe A1AT deficiency.
- Variant PI\*Q0 amersfoort (c.552C>G, rs19942210) (reference 11) in homozygosis affects to the detection of variant PI\*Q0 granite falls (c.552delC, rs267606950) leading to a false positive detection (++ or +/-) or an Invalid Test sample result. Variant PI\*Q0 amersfoort is described with a global minor frequency (MAF) <0.001%. Both PI\*Q0 amersfoort/PI\*Q0 amersfoort and PI\*Q0 granite falls/PI\*Q0 granite falls allelic variant combinations are phenotypically associated with a severe A1AT deficiency.
- The intronic variant rs375637084 (c.1066-26C>T) affects to the detection of variant PI\*Z (rs28929474), leading to a false ++ homozygous result (PI\*Z/PI\*Z) instead of +/- heterozygous result (PI\*M/PI\*Z). This variant is described with a global minor frequency (MAF) <0.001%.
- The variant PI\*P Donauwoerth (c.1093G>A, rs143370956) (reference 12) affects to the detection of variant PI\*Z, leading to a false -/- homozygous result (PI\*M/PI\*M) instead of +/- heterozygous result (PI\*M/PI\*Z). This variant is described with a global minor frequency (MAF) 0.06%.
- The variant rs1049800 (c.840T>C) affects to the detection of variant PI\*P lowell, leading to a false ++ homozygous result (PI\*P lowell/PI\*P lowell) instead of +/- heterozygous result (PI\*M/PI\*P lowell). This variant is described with a global minor frequency (MAF) 5.7%.
- Variant PI\*Q0 bolton (c.1158delC, rs764325655) (reference 13) in homozygosis affects to the detection of variant PI\*Q0 clayton (c.1158dupC, rs764325655) leading to a false positive detection (++ or +/-) or an Invalid Test sample result. Variant PI\*Q0 bolton is described with a global minor frequency (MAF) <0.001%. Both PI\*Q0 bolton/PI\*Q0 bolton and PI\*Q0 clayton/PI\*Q0 clayton allelic variant combinations are phenotypically associated with a severe A1AT deficiency.
- The intronic variant rs1019260714 (c.917+55T>C) affects to the detection of variant PI\*S, leading to a false ++ homozygous result (PI\*S/PI\*S) instead of +/- heterozygous result (PI\*M/PI\*S). This variant is described with a global minor frequency (MAF) <0.001%.
- The variant c.1178C>G (rs199422209) in homozygosis affects to the detection of the variant PI\*M heerlen (c.1178C>T, rs199422209), leading to a false positive detection (+/-) or an Invalid Test sample result. This variant is described with a global minor frequency (MAF) <0.001%.

For more information of the variants, introduce the rs ID at: <https://www.ncbi.nlm.nih.gov>

## User studies:

### ***AlphaID™ At Home Saliva Collection Kit user study for ORAcollect®-Dx (OCD-100.014)***

Saliva collection kit user study was performed to assess how users understand the saliva collection kit instructions and to assess the ability of naïve users to provide samples adequate for the Service. Study participants represented a demographically diverse US population of naïve users (389 participants). Participants collected and mailed a saliva sample and answered a survey about the collection kit instructions. Saliva samples were processed according to A1AT Genotyping Test package insert. The overall comprehension rate on the collection kit instructions was 98.6%. A1AT Genotyping Test result was obtained for 386 of 389 samples (99.2%) Therefore, the probability that the laboratory cannot process a sample can be up to 0.8%.

### ***AlphaID™ At Home Genetic Health Risk Service report user comprehension study***

The user comprehension study for the AlphaID™ At Home Genetic Health Risk Service showed that a demographically diverse US population of naïve users (525 participants) of the Service reports had excellent comprehension of the service's purpose, limitations, results, relevance of ethnicity, other factors that may impact test results, and appropriate next steps. Comprehension was tested through a two-step process. First, participants' comprehension was tested prior to viewing the educational module and Service reports. Second, participants were shown the educational module and the Service reports. Participants completed a survey after the first and second step. As a result, each comprehension domain achieved a minimum of 90.1% or higher user comprehension score in the first step, and 94.0% or higher user comprehension score in the second step, across all reports. The overall comprehension scores were of 92.7% and 96.8% across all comprehension domains and reports, for the first and second step respectively.

## References:

### ***General references***

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### References that support the lung and liver disease risk categorization

Table 1. References that support the lung and liver disease risk categorization for each possible genetic result of the AlphaID™ At Home Genetic Health Risk Service. The most frequent and/or most studied genetic results (No Variants, PI\*S, PI\*Z, PI\*S and PI\*S, PI\*S and PI\*Z, PI\*Z and PI\*Z) are showed in the first rows of the table. The complete list of bibliographic references can be found at the bottom of the table.

| Genetic Result in the AlphaID™ At Home Genetic Health Risk Service Report | Number of variants | Reported Lung Disease Risk Category       | References that support Lung Disease Risk Category  | Reported Liver Disease Risk Category | References that support Liver Disease Risk Category   |
|---|--------------------|---|---|--------------------------------------|---|
| No Variants   | 0                  | Not likely at risk for AATD               | <a href="#">ATS/ERS 2003</a> ; <a href="#">DeMeo &amp; Silverman 2004</a> ; <a href="#">de Serres &amp; Blanco 2014</a> ; <a href="#">Stoller et al 2006 (updated 2017)</a> ; <a href="#">Stoller et al 2006 (updated 2020)</a> | Not likely at risk for AATD          | <a href="#">ATS/ERS 2003</a> ; <a href="#">de Serres &amp; Blanco 2014</a>  |
| PI*S  | 1                  | Not likely at increased risk <sup>1</sup> | <a href="#">Matzen et al 1977</a> ; <a href="#">Chang-Yeung et al 1978</a> ; <a href="#">Ostrow et al 1978</a> ; <a href="#">Gulsvik et al 1979</a> ; <a href="#">Dahl et al 2002</a>   | Not likely at increased risk         | <a href="#">Eigenbrodt et al 1997</a> ; <a href="#">Graziadei et al 1998</a> ; <a href="#">Arnaud et al 1977</a> ; <a href="#">Bell et al 1990</a> ; <a href="#">Carlson et al 1981</a> |

| Genetic Result in the AlphaID™ At Home Genetic Health Risk Service Report | Number of variants | Reported Lung Disease Risk Category                       | References that support Lung Disease Risk Category  | Reported Liver Disease Risk Category      | References that support Liver Disease Risk Category  |
|---|--------------------|---|---|---|--|
| PI*Z  | 1                  | Not likely at increased risk <sup>1</sup> (never-smokers) | <a href="#">Seersholm et al 2000</a> ; <a href="#">Klayton et al 1975</a> ; <a href="#">Matzen et al 1977</a> ; <a href="#">Chang-Yeung et al 1978</a> ; <a href="#">Gulsvik et al 1979</a> ; <a href="#">Dahl et al 2002</a>   | Slightly increased risk <sup>3</sup>      | <a href="#">Schneider et al 2020</a> ; <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Bell et al 1990</a> ; <a href="#">Eigenbrodt et al 1997</a> ; <a href="#">Graziadei et al 1998</a> ; <a href="#">Blenkinsopp &amp; Haffenden 1977</a> ; <a href="#">Strnad et al 2019</a> ; <a href="#">Schaefer et al 2018</a> ; <a href="#">Propst et al 1992</a> ; <a href="#">Arnaud et al 1977</a> |
|   |                    | Slightly increased risk (ever-smokers)                    | <a href="#">Sørheim et al 2010</a> ; <a href="#">Molloy et al 2014</a>  |   |  |
| PI*S and PI*S   | 2                  | Not likely at increased risk                              | <a href="#">Dahl et al 2002</a> ; <a href="#">Fagerhol et al 1969</a> ; <a href="#">Gulsvik et al 1979</a> ; <a href="#">Kueppers et al 1977</a> ; <a href="#">Lieberman et al 1986</a> ; <a href="#">Lochon et al 1978</a> ; <a href="#">Sandford et al 1999</a> ; <a href="#">Arnaud et al 1977</a> | Not likely at increased risk              | <a href="#">Eigenbrodt et al 1997</a> ; <a href="#">Arnaud et al 1977</a> ; <a href="#">Strnad et al 2019</a> ; <a href="#">Carlson et al 1981</a>   |
| PI*S and PI*Z   | 2                  | Slightly increased risk                                   | <a href="#">McElvaney et al 2020</a> ; <a href="#">Fagerhol &amp; Hauge 1969</a> ; <a href="#">Abboud et al 1979</a> ; <a href="#">Bartmann et al 1985</a> ; <a href="#">Lieberman et al 1986</a> ; <a href="#">Gulsvik et al 1979</a> ; <a href="#">Dahl et al 2002</a>                              | Slightly increased risk <sup>3</sup>      | <a href="#">McElvaney et al 2020</a> ; <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Eigenbrodt et al 1997</a> ; <a href="#">Graziadei et al 1998</a> ; <a href="#">Propst et al 1992</a> ; <a href="#">Strnad et al 2019</a>  |
| PI*Z and PI*Z   | 2                  | Increased risk  | <a href="#">McElvaney et al 2020</a>  | Slightly increased risk <sup>3</sup>      | <a href="#">McElvaney et al 2020</a> ; <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Schneider et al 2020</a> ; <a href="#">Hamesch et al 2019</a> ; <a href="#">Eriksson et al 1986</a> ; <a href="#">Elzouki &amp; Eriksson 1996</a> ; <a href="#">Graziadei et al 1998</a> ; <a href="#">Propst et al 1992</a> ; <a href="#">Bell et al 1990</a>  |
| PI*I  | 1                  | Not likely at increased risk <sup>1</sup>                 | <a href="#">Arnaud et al 1978</a> ; <a href="#">Baur &amp; Bencze 1987</a> ; <a href="#">Duk et al 2016</a> ; <a href="#">Zhumagaliyeva et al 2017</a>  | Not likely at increased risk              | <a href="#">Arnaud et al 1978</a> ; <a href="#">Baur &amp; Bencze 1987</a>   |
| PI*M procida  | 1                  | Not likely at increased risk <sup>1</sup>                 | <a href="#">Montealegre et al 2006</a>  | Not likely at increased risk <sup>4</sup> | <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Balduyck et al 2014</a>  |

| Genetic Result in the AlphaID™ At Home Genetic Health Risk Service Report | Number of variants | Reported Lung Disease Risk Category       | References that support Lung Disease Risk Category  | Reported Liver Disease Risk Category      | References that support Liver Disease Risk Category  |
|---|--------------------|---|---|---|--|
| PI*M malton   | 1                  | Not likely at increased risk <sup>1</sup> | <a href="#">Sproule et al 1983</a> ; <a href="#">Allen et al 1986</a> ; <a href="#">Canva et al 2001</a> ; <a href="#">Orrù et al 2005</a> ; <a href="#">Corda et al 2006</a> ; <a href="#">Joly et al 2015</a> ; <a href="#">Figueira Gonçalves et al 2017</a> | Slightly increased risk <sup>3</sup>      | <a href="#">Canva et al 2001</a> ; <a href="#">Janciauskiene et al 2004</a> ; <a href="#">Orrù et al 2005</a> ; <a href="#">Corda et al 2006</a> ; <a href="#">Joly et al 2015</a> ; <a href="#">Figueira Gonçalves et al 2017</a> ; <a href="#">Callea et al 2018</a> |
| PI*S iiyama   | 1                  | Not likely at increased risk <sup>1</sup> | <a href="#">Takabe et al 1992</a>   | Unknown risk                              | Clinical cases not reported  |
| PI*Q0 granite falls   | 1                  | Not likely at increased risk <sup>1</sup> | <a href="#">Poller et al 1999</a>   | Not likely at increased risk <sup>4</sup> | Clinical cases not reported  |
| PI*Q0 west  | 1                  | Not likely at increased risk <sup>1</sup> | <a href="#">Laubach et al 1993</a>  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported  |
| PI*Q0 bellingham  | 1                  | Not likely at increased risk <sup>1</sup> | <a href="#">Cook et al 1994</a>   | Not likely at increased risk <sup>4</sup> | Clinical cases not reported  |
| PI*F  | 1                  | Not likely at increased risk <sup>1</sup> | <a href="#">Cockcroft et al 1981</a> ; <a href="#">Beckman et al 1984</a> ; <a href="#">Cook et al 1996</a> ; <a href="#">Kwok et al 2004</a> ; <a href="#">Tete-Benissan &amp; Gbeassor 2011</a> ; <a href="#">Duk et al 2016</a>                              | Not likely at increased risk <sup>4</sup> | <a href="#">Kelly et al 1989</a> ; <a href="#">Tete-Benissan &amp; Gbeassor 2011</a>   |
| PI*P lowell   | 1                  | Not likely at increased risk <sup>1</sup> | <a href="#">Seri et al 1992</a> ; <a href="#">Cook et al 1995</a> ; <a href="#">Jardí et al 1997</a> ; <a href="#">Denden et al 2009</a> ; <a href="#">Corda et al 2011</a>   | Not likely at increased risk <sup>4</sup> | <a href="#">Corda et al 2011</a>   |
| PI*Q0 mattawa   | 1                  | Not likely at increased risk <sup>1</sup> | <a href="#">Cox &amp; Levison 1988</a> ; <a href="#">Lara et al 2013</a>  | Not likely at increased risk <sup>4</sup> | <a href="#">Cox &amp; Levison 1988</a> ; <a href="#">Lara et al 2013</a>   |
| PI*Q0 clayton   | 1                  | Not likely at increased risk <sup>1</sup> | <a href="#">Rodriguez-Frias et al 2011</a>  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported  |
| PI*M heerlen  | 1                  | Not likely at increased risk <sup>1</sup> | <a href="#">Kramps et al 1981</a> ; <a href="#">Poller et al 1999</a> ; <a href="#">Kalsheker et al 1992</a> ; <a href="#">Rodriguez et al 2002</a>   | Not likely at increased risk <sup>4</sup> | <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Balduyck et al 2014</a>  |
| PI*Z and PI*I   | 2                  | Slightly increased risk                   | <a href="#">Baur &amp; Bencze 1987</a> ; <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Corda et al 2006</a>   | Slightly increased risk <sup>3</sup>      | <a href="#">Baur &amp; Bencze 1987</a> ; <a href="#">Mahadeva et al 1999</a> ; <a href="#">Ferrarotti et al 2005</a>   |
| PI*Z and PI*M procida   | 2                  | Unknown risk                              | <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Lonardo et al 2002</a>  | Slightly increased risk <sup>3</sup>      | <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Lonardo et al 2002</a>   |
| PI*Z and PI*M malton  | 2                  | Increased risk                            | <a href="#">Sproule et al 1983</a> ; <a href="#">Allen et al 1986</a> ; <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Corda et al 2006</a> ; <a href="#">Suh-Lailam et al 2014</a> ; <a href="#">Joly et al 2015</a> ; <a href="#">Figueira</a>           | Slightly increased risk <sup>3</sup>      | <a href="#">Sproule et al 1983</a> ; <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Joly et al 2015</a> ; <a href="#">Figueira Gonçalves et al 2017</a>   |

| Genetic Result in the AlphaID™ At Home Genetic Health Risk Service Report | Number of variants | Reported Lung Disease Risk Category | References that support Lung Disease Risk Category   | Reported Liver Disease Risk Category | References that support Liver Disease Risk Category  |
|---|--------------------|-------------------------------------|--|--------------------------------------|--|
|   |                    |                                     | <a href="#">Gonçalves et al 2017</a>   |                                      |  |
| PI*Z and PI*S iiyama  | 2                  | Unknown risk                        | Clinical cases not reported  | Slightly increased risk <sup>3</sup> | Clinical cases not reported  |
| PI*Z and PI*Q0 granite falls  | 2                  | Increased risk <sup>2</sup>         | <a href="#">Nukiwa et al 1987</a> ; <a href="#">Balduyck et al 2014</a> ; <a href="#">Pavičić et al 2019</a>   | Slightly increased risk <sup>3</sup> | Clinical cases not reported  |
| PI*Z and PI*Q0 west   | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Slightly increased risk <sup>3</sup> | Clinical cases not reported  |
| PI*Z and PI*Q0 bellingham   | 2                  | Increased risk <sup>2</sup>         | <a href="#">Poller et al 1990</a>  | Slightly increased risk <sup>3</sup> | <a href="#">Poller et al 1990</a>  |
| PI*F and PI*Z   | 2                  | Slightly increased risk             | <a href="#">Cockcroft et al 1981</a> ; <a href="#">Beckman et al 1984</a> ; <a href="#">Kelly et al 1989</a> ; <a href="#">Okayama et al 1991</a> ; <a href="#">Cook et al 1996</a> ; <a href="#">Sinden et al 2014</a> ; <a href="#">Franciosi et al 2019</a> | Slightly increased risk <sup>3</sup> | <a href="#">Kelly et al 1989</a> ; <a href="#">Sinden et al 2014</a> ; <a href="#">Franciosi et al 2019</a>  |
| PI*Z and PI*P lowell  | 2                  | Slightly increased risk             | <a href="#">Holmes et al 1990</a> ; <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Esteves-Brandão et al 2019</a> ; <a href="#">Bamforth &amp; Kalsheker 1988</a>   | Slightly increased risk <sup>3</sup> | <a href="#">Holmes et al 1990</a> ; <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Bornhorst et al 2007</a> ; <a href="#">Bamforth &amp; Kalsheker 1988</a> |
| PI*Z and PI*Q0 mattawa  | 2                  | Increased risk <sup>2</sup>         | <a href="#">Balduyck et al 2014</a>  | Slightly increased risk <sup>3</sup> | Clinical cases not reported  |
| PI*Z and PI*Q0 clayton  | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Slightly increased risk <sup>3</sup> | Clinical cases not reported  |
| PI*Z and PI*M heerlen   | 2                  | Unknown risk                        | <a href="#">Klaassen et al 2001</a>  | Slightly increased risk <sup>3</sup> | Clinical cases not reported  |
| PI*S and PI*I   | 2                  | Unknown risk                        | <a href="#">Seri et al 1992</a> ; <a href="#">Huang et al 2017</a>   | Unknown risk                         | Clinical cases not reported  |
| PI*S and PI*M procida   | 2                  | Unknown risk                        | Clinical cases not reported  | Unknown risk                         | Clinical cases not reported  |
| PI*S and PI*M malton  | 2                  | Unknown risk                        | <a href="#">Figueira Gonçalves et al 2017</a>  | Slightly increased risk <sup>3</sup> | <a href="#">Figueira Gonçalves et al 2017</a>  |
| PI*S and PI*S iiyama  | 2                  | Unknown risk                        | Clinical cases not reported  | Unknown risk                         | Clinical cases not reported  |
| PI*S and PI*Q0 granite falls  | 2                  | Unknown risk                        | Clinical cases not reported  | Unknown risk                         | Clinical cases not reported  |
| PI*S and PI*Q0 west   | 2                  | Unknown risk                        | Clinical cases not reported  | Unknown risk                         | Clinical cases not reported  |
| PI*S and PI*Q0 bellingham   | 2                  | Unknown risk                        | Clinical cases not reported  | Unknown risk                         | Clinical cases not reported  |
| PI*F and PI*S   | 2                  | Unknown risk                        | <a href="#">Cook et al 1996</a>  | Unknown risk                         | Clinical cases not reported  |
| PI*S and PI*P lowell  | 2                  | Unknown risk                        | <a href="#">Jardí et al 1997</a> ; <a href="#">Balbi et al 2019</a>  | Unknown risk                         | Clinical cases not reported  |
| PI*S and PI*Q0 mattawa  | 2                  | Unknown risk                        | Clinical cases not reported  | Unknown risk                         | Clinical cases not reported  |

| Genetic Result in the AlphaID™ At Home Genetic Health Risk Service Report | Number of variants | Reported Lung Disease Risk Category | References that support Lung Disease Risk Category | Reported Liver Disease Risk Category      | References that support Liver Disease Risk Category |
|---|--------------------|-------------------------------------|--|---|---|
| PI*S and PI*Q0 clayton  | 2                  | Unknown risk                        | <a href="#">Rosenbaum et al 2017</a>               | Unknown risk                              | <a href="#">Rosenbaum et al 2017</a>                |
| PI*S and PI*M heerlen   | 2                  | Unknown risk                        | <a href="#">Kramps et al 1981</a>                  | Unknown risk                              | Clinical cases not reported                         |
| PI*I and PI*I   | 2                  | Unknown risk                        | Clinical cases not reported                        | Unknown risk                              | Clinical cases not reported                         |
| PI*I and PI*M procida   | 2                  | Unknown risk                        | Clinical cases not reported                        | Unknown risk                              | Clinical cases not reported                         |
| PI*I and PI*M malton  | 2                  | Unknown risk                        | Clinical cases not reported                        | Slightly increased risk <sup>3</sup>      | Clinical cases not reported                         |
| PI*I and PI*S iiyama  | 2                  | Unknown risk                        | Clinical cases not reported                        | Unknown risk                              | Clinical cases not reported                         |
| PI*I and PI*Q0 granite falls  | 2                  | Unknown risk                        | Clinical cases not reported                        | Unknown risk                              | Clinical cases not reported                         |
| PI*I and PI*Q0 west   | 2                  | Unknown risk                        | Clinical cases not reported                        | Unknown risk                              | Clinical cases not reported                         |
| PI*I and PI*Q0 bellingham   | 2                  | Unknown risk                        | Clinical cases not reported                        | Unknown risk                              | Clinical cases not reported                         |
| PI*F and PI*I   | 2                  | Unknown risk                        | Clinical cases not reported                        | Unknown risk                              | Clinical cases not reported                         |
| PI*I and PI*P lowell  | 2                  | Unknown risk                        | Clinical cases not reported                        | Unknown risk                              | Clinical cases not reported                         |
| PI*I and PI*Q0 mattawa  | 2                  | Unknown risk                        | Clinical cases not reported                        | Unknown risk                              | Clinical cases not reported                         |
| PI*I and PI*Q0 clayton  | 2                  | Unknown risk                        | Clinical cases not reported                        | Unknown risk                              | Clinical cases not reported                         |
| PI*I and PI*M heerlen   | 2                  | Unknown risk                        | Clinical cases not reported                        | Unknown risk                              | Clinical cases not reported                         |
| PI*F and PI*M procida   | 2                  | Unknown risk                        | Clinical cases not reported                        | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*F and PI*M malton  | 2                  | Unknown risk                        | Clinical cases not reported                        | Slightly increased risk <sup>3</sup>      | Clinical cases not reported                         |
| PI*F and PI*S iiyama  | 2                  | Unknown risk                        | Clinical cases not reported                        | Unknown risk                              | Clinical cases not reported                         |
| PI*F and PI*Q0 granite falls  | 2                  | Unknown risk                        | Clinical cases not reported                        | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*F and PI*Q0 west   | 2                  | Unknown risk                        | Clinical cases not reported                        | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*F and PI*Q0 bellingham   | 2                  | Unknown risk                        | Clinical cases not reported                        | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*F and PI*F   | 2                  | Unknown risk                        | <a href="#">Sinden et al 2014</a>                  | Not likely at increased risk <sup>4</sup> | <a href="#">Sinden et al 2014</a>                   |
| PI*F and PI*P lowell  | 2                  | Unknown risk                        | Clinical cases not reported                        | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*F and PI*Q0 mattawa  | 2                  | Unknown risk                        | Clinical cases not reported                        | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*F and PI*Q0 clayton  | 2                  | Unknown risk                        | <a href="#">Ringebach et al 2011</a>               | Not likely at increased risk <sup>4</sup> | <a href="#">Ringebach et al 2011</a>                |
| PI*F and PI*M heerlen   | 2                  | Unknown risk                        | Clinical cases not reported                        | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*M procida and PI*M procida   | 2                  | Unknown risk                        | <a href="#">Ferrarotti et al 2005</a>              | Not likely at increased risk <sup>4</sup> | <a href="#">Ferrarotti et al 2005</a>               |

| Genetic Result in the AlphaID™ At Home Genetic Health Risk Service Report | Number of variants | Reported Lung Disease Risk Category | References that support Lung Disease Risk Category  | Reported Liver Disease Risk Category      | References that support Liver Disease Risk Category   |
|---|--------------------|-------------------------------------|---|---|---|
| PI*M malton and PI*M procida  | 2                  | Unknown risk                        | Clinical cases not reported   | Slightly increased risk <sup>3</sup>      | Clinical cases not reported   |
| PI*M procida and PI*S iiyama  | 2                  | Unknown risk                        | Clinical cases not reported   | Unknown risk                              | Clinical cases not reported   |
| PI*M procida and PI*Q0 granite falls                                      | 2                  | Unknown risk                        | Clinical cases not reported   | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*M procida and PI*Q0 west   | 2                  | Unknown risk                        | Clinical cases not reported   | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*M procida and PI*Q0 bellingham   | 2                  | Unknown risk                        | Clinical cases not reported   | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*M procida and PI*P lowell  | 2                  | Unknown risk                        | Clinical cases not reported   | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*M procida and PI*Q0 mattawa  | 2                  | Unknown risk                        | Clinical cases not reported   | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*M procida and PI*Q0 clayton  | 2                  | Unknown risk                        | Clinical cases not reported   | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*M procida and PI*M heerlen   | 2                  | Unknown risk                        | Clinical cases not reported   | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*M malton and PI*M malton   | 2                  | Slightly increased risk             | <a href="#">Curiel et al 1989b</a> ; <a href="#">Ferrarotti et al 2005</a> ; <a href="#">Orrù et al 2005</a> ; <a href="#">Balduyck et al 2014</a> ; <a href="#">Joly et al 2015</a> ; <a href="#">Figueira Gonçalves et al 2017</a> ; <a href="#">Franciosi et al 2019</a> ; <a href="#">Reid et al 1987</a> | Slightly increased risk <sup>3</sup>      | <a href="#">Curiel et al 1989b</a> ; <a href="#">Janciauskiene et al 2004</a> ; <a href="#">Orrù et al 2005</a> ; <a href="#">Joly et al 2015</a> ; <a href="#">Figueira Gonçalves et al 2017</a> ; <a href="#">Reid et al 1987</a> ; <a href="#">Callea et al 2018</a> |
| PI*M malton and PI*S iiyama   | 2                  | Unknown risk                        | Clinical cases not reported   | Slightly increased risk <sup>3</sup>      | Clinical cases not reported   |
| PI*M malton and PI*Q0 granite falls                                       | 2                  | Unknown risk                        | Clinical cases not reported   | Slightly increased risk <sup>3</sup>      | Clinical cases not reported   |
| PI*M malton and PI*Q0 west  | 2                  | Unknown risk                        | Clinical cases not reported   | Slightly increased risk <sup>3</sup>      | Clinical cases not reported   |
| PI*M malton and PI*Q0 bellingham  | 2                  | Unknown risk                        | Clinical cases not reported   | Slightly increased risk <sup>3</sup>      | Clinical cases not reported   |
| PI*M malton and PI*P lowell   | 2                  | Unknown risk                        | Clinical cases not reported   | Slightly increased risk <sup>3</sup>      | Clinical cases not reported   |
| PI*M malton and PI*Q0 mattawa   | 2                  | Unknown risk                        | <a href="#">Lara et al 2013</a> ; <a href="#">Balduyck et al 2014</a>   | Slightly increased risk <sup>3</sup>      | <a href="#">Lara et al 2013</a> ; <a href="#">Balduyck et al 2014</a>   |
| PI*M malton and PI*Q0 clayton   | 2                  | Unknown risk                        | <a href="#">Rodríguez-Frias et al 2011</a>  | Slightly increased risk <sup>3</sup>      | Clinical cases not reported   |
| PI*M malton and PI*M heerlen  | 2                  | Unknown risk                        | Clinical cases not reported   | Slightly increased risk <sup>3</sup>      | Clinical cases not reported   |
| PI*S iiyama and PI*S iiyama   | 2                  | Slightly increased risk             | <a href="#">Takabe et al 1992</a> ; <a href="#">Lomas et al 1993</a> ; <a href="#">Yuasa et al 1993</a>   | Unknown risk                              | <a href="#">Takabe et al 1992</a> ; <a href="#">Yuasa et al 1993</a>  |
| PI*Q0 granite falls and PI*S iiyama                                       | 2                  | Unknown risk                        | Clinical cases not reported   | Unknown risk                              | Clinical cases not reported   |
| PI*S iiyama and PI*Q0 west  | 2                  | Unknown risk                        | Clinical cases not reported   | Unknown risk                              | Clinical cases not reported   |
| PI*S iiyama and PI*Q0 bellingham  | 2                  | Unknown risk                        | Clinical cases not reported   | Unknown risk                              | Clinical cases not reported   |

| Genetic Result in the AlphaID™ At Home Genetic Health Risk Service Report | Number of variants | Reported Lung Disease Risk Category | References that support Lung Disease Risk Category   | Reported Liver Disease Risk Category      | References that support Liver Disease Risk Category                 |
|---|--------------------|-------------------------------------|--|---|---|
| PI*P lowell and PI*S iiyama   | 2                  | Unknown risk                        | Clinical cases not reported  | Unknown risk                              | Clinical cases not reported   |
| PI*S iiyama and PI*Q0 mattawa   | 2                  | Unknown risk                        | Clinical cases not reported  | Unknown risk                              | Clinical cases not reported   |
| PI*S iiyama and PI*Q0 clayton   | 2                  | Unknown risk                        | <a href="#">Ko et al 2011</a> ; <a href="#">Miyahara et al 2001</a>  | Unknown risk                              | <a href="#">Ko et al 2011</a> ; <a href="#">Miyahara et al 2001</a> |
| PI*M heerlen and PI*S iiyama  | 2                  | Unknown risk                        | Clinical cases not reported  | Unknown risk                              | Clinical cases not reported   |
| PI*Q0 granite falls and PI*Q0 granite falls                               | 2                  | Increased risk <sup>2</sup>         | <a href="#">Holmes et al 1989</a> ; <a href="#">Hubbard et al 1989</a> ; <a href="#">Balbi et al 2019</a>                                    | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*Q0 granite falls and PI*Q0 west  | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*Q0 bellingham and PI*Q0 granite falls                                  | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*P lowell and PI*Q0 granite falls                                       | 2                  | Unknown risk                        | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*Q0 granite falls and PI*Q0 mattawa                                     | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*Q0 clayton and PI*Q0 granite falls                                     | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*M heerlen and PI*Q0 granite falls                                      | 2                  | Unknown risk                        | <a href="#">Poller et al 1999</a>  | Not likely at increased risk <sup>4</sup> | <a href="#">Poller et al 1999</a>                                   |
| PI*Q0 west and PI*Q0 west   | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*Q0 bellingham and PI*Q0 west   | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*P lowell and PI*Q0 west  | 2                  | Unknown risk                        | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*Q0 mattawa and PI*Q0 west  | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*Q0 clayton and PI*Q0 west  | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*M heerlen and PI*Q0 west   | 2                  | Unknown risk                        | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*Q0 bellingham and PI*Q0 bellingham                                     | 2                  | Increased risk <sup>2</sup>         | <a href="#">Sato et al 1988</a> ; <a href="#">Cook et al 1994</a> ; <a href="#">Garver et al 1986</a> ; <a href="#">Fregonese et al 2008</a> | Not likely at increased risk <sup>4</sup> | <a href="#">Cook et al 1994</a> ; <a href="#">Garver et al 1986</a> |
| PI*P lowell and PI*Q0 bellingham  | 2                  | Unknown risk                        | <a href="#">Cook et al 1994</a> ; <a href="#">Cook et al 1995</a>  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*Q0 bellingham and PI*Q0 mattawa  | 2                  | Increased risk <sup>2</sup>         | <a href="#">Curiel et al 1989a</a>   | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*Q0 bellingham and PI*Q0 clayton  | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*M heerlen and PI*Q0 bellingham   | 2                  | Unknown risk                        | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |
| PI*P lowell and PI*P lowell   | 2                  | Unknown risk                        | <a href="#">Faber et al 1989</a>   | Not likely at increased risk <sup>4</sup> | Clinical cases not reported   |

| Genetic Result in the AlphaID™ At Home Genetic Health Risk Service Report | Number of variants | Reported Lung Disease Risk Category | References that support Lung Disease Risk Category                       | Reported Liver Disease Risk Category      | References that support Liver Disease Risk Category |
|---|--------------------|-------------------------------------|--|---|---|
| PI*P lowell and PI*Q0 mattawa   | 2                  | Unknown risk                        | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*P lowell and PI*Q0 clayton   | 2                  | Unknown risk                        | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*P lowell and PI*M heerlen  | 2                  | Unknown risk                        | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*Q0 mattawa and PI*Q0 mattawa   | 2                  | Increased risk <sup>2</sup>         | <a href="#">Cox &amp; Levinson 1988</a>                                  | Not likely at increased risk <sup>4</sup> | <a href="#">Cox &amp; Levinson 1988</a>             |
| PI*Q0 clayton and PI*Q0 mattawa   | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*M heerlen and PI*Q0 mattawa  | 2                  | Unknown risk                        | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*Q0 clayton and PI*Q0 clayton   | 2                  | Increased risk <sup>2</sup>         | Clinical cases not reported  | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*M heerlen and PI*Q0 clayton  | 2                  | Unknown risk                        | <a href="#">Brantly et al 1997</a>                                       | Not likely at increased risk <sup>4</sup> | Clinical cases not reported                         |
| PI*M heerlen and PI*M heerlen   | 2                  | Slightly increased risk             | <a href="#">Kramps et al 1981</a> ; <a href="#">Fregonese et al 2008</a> | Not likely at increased risk <sup>4</sup> | <a href="#">Kramps et al 1981</a>                   |
| Variant not determined  | N/A                | Not determined risk                 | N/A  | Not determined risk                       | N/A   |

<sup>1</sup>All carriers (except ever-smokers PI\*M/PI\*Z) are reported as “Not likely at increased risk” for lung disease risk even if insufficient number of clinical cases have been reported.

<sup>2</sup>PI\*Z/PI\*Null and PI\*Null/PI\*Null combinations are assigned as “Increased risk” for lung disease risk even if insufficient number of clinical cases have been reported. Null variants: PI\*Q0 granite falls, PI\*Q0 west, PI\*Q0 bellingham, PI\*Q0 mattawa and PI\*Q0 clayton.

<sup>3</sup>Individuals with at least one PI\*Z or PI\*M malton severe accumulation variants and their combinations are reported as “Slightly Increased risk” for liver disease risk even if insufficient number of clinical cases have been reported.

<sup>4</sup>All the combinations including two non-accumulation alleles are reported as “Not likely at Increased risk” for liver disease risk even if insufficient number of clinical cases have been reported. Non-accumulation alleles: PI\*M, PI\*M procida, PI\*Q0 granite falls, PI\*Q0 west, PI\*Q0 bellingham, PI\*F, PI\*P lowell, PI\*Q0 mattawa, PI\*Q0 clayton, and PI\*M heerlen.

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## Revision History:

### Version PI\_12923D0000\_02:

- Update of the 12<sup>th</sup> warning in section “Warnings and limitations of the Service”.
- Inclusion of an assay limitation in section “Tested interfering variants” related to the tested interfering variant PI\*P Donauwoerth (c.1093G>A, rs143370956).
- Inclusion of an assay limitation in section “Tested interfering variants” related to the tested interfering variant PI\*Q0 bolton (c.1158delC, rs764325655). Inclusion of the reference 13 in the General References section.
- Update of the summary of the AlphaID™ At Home Saliva Collection Kit user study for ORAcollect®·Dx (OCD-100.014).

### Version PI\_12923D0000\_03:

- Inclusion of an assay limitation in section “Tested interfering variants” related to the tested interfering variant rs1019260714.

### Version PI\_12923D0000\_04:

- Inclusion of an assay limitation in section “Tested interfering variants” related to the tested interfering variant rs199422209.