510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K221420

B Applicant

Progenika Biopharma S.A.

C Proprietary and Established Names

AlphaID At Home Genetic Health Risk Service

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
PTA	Class II	21 CFR 866.5950 - Genetic Health Risk Assessment System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

New device

B Measurand:

14 SERPINA1 gene variants in genomic DNA obtained from a human saliva sample

C Type of Test:

The AlphaID At Home Genetic Health Risk Service determines if a person has variants associated with a higher risk of developing alpha-1 antitrypsin deficiency (AATD) associated lung or liver disease. The Service is intended to provide the AATD risk report. The report is based on a qualitative genetic test for detecting 14 genetic variants in the serpin peptidase

inhibitor class A member 1 (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 AlphaID At Home Genetic Health Risk Service is for over-the-counter use.

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for 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 ≥ 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 or decreased risk of developing either lung and/or liver disease linked to AATD. The report does not describe a person´s overall risk of developing lung and/or liver disease. AATD is more common in persons of European descent.

C Special Conditions for Use Statement(s):

- For over-the-counter (OTC) use.
- The test is intended for users ≥18 years old.
- The test is not a substitute for an appointment with a healthcare professional. It is recommended that the user consults with a healthcare professional if the user has any questions or concerns about his/her results.
- The test does not diagnose a disease or condition, determine medical treatment or other medical intervention, or tell the user anything about their current state of health. Only a healthcare professional can diagnose a disease or condition.
- Any diagnostic or treatment decisions must be based on confirmatory prescription testing and/or other information that a healthcare professional determines to be appropriate for the patient, such as additional clinical testing and other risk factors that may affect individual risk and health care.
- The test detects 14 variants in the SERPINA1 gene linked to AATD. These 14 variants explain 95% of AATD cases. The absence of a variant tested does not rule out the presence of other genetic variants that may be disease-related.
- The test does not describe a person's overall risk of developing AATD. In addition, other genetic and all non-genetic factors should be considered
- The laboratory may be unable to process every user’s sample. The probability that the laboratory cannot process a sample can be up to 0.5%. If this happens, the user will receive an

email notification. The user will also receive another AlphaID At Home Saliva Collection Kit to provide a new sample to the laboratory.
- The user´s race, ethnicity, age, and sex may affect how the genetic results are interpreted.
- Subject to meeting limitations contained in the special controls under the regulation 21 CFR 866.5950.

D Special Instrument Requirements:

The AlphaID At Home Genetic Health Risk Service is to be performed using 384-well Veriti Dx and 96-well Veriti Dx thermal cyclers, and the Luminex 200 instrument.

IV Device/System Characteristics:

A Device Description:

The AlphaID At Home Genetic Health Risk Service uses qualitative genotyping to detect clinically relevant genetic variants associated with alpha1-antitrypsin deficiency (AATD) in genomic DNA isolated from human saliva and provides a report describing if a person is at risk of developing either lung and/or liver disease linked to AATD. This Service is direct-to-consumer and intended for an over-the-counter (OTC) use.

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

(i) ORAcollect·Dx OCD-100.014 (cleared under K212745) is intended for use in the non-invasive collection of saliva samples.
(ii) A1AT Genotyping Test (cleared under K192858) is intended for the genetic analysis and detection of genetic variants associated with alpha-1 antitrypsin deficiency (AATD) using the A1AT Genotyping Test ANALYSIS SOFTWARE, and
(iii) AlphaID At Home Genetic Health Risk Service website and result portal software are intended to provide the contents and the procedure to order and use the OTC Service.

A consumer's saliva is self-collected using ORAcollect·Dx OCD-100.014 manufactured by DNA Genotek, Inc which consists of a collection tube containing a stabilizing buffer solution. Once the sample is collected, it is shipped to a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory for processing.

Human DNA from the saliva sample is isolated, processed and analyzed with the A1AT Genotyping Test that 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. Briefly, genomic DNA extracted from human saliva is amplified and biotinylated by multiplex polymerase chain reaction (PCR) and the resulting labeled PCR products are denatured and hybridized to allele-specific oligonucleotide probes coupled to color-coded microspheres. Hybridized DNA is labeled with a fluorescent conjugate and the resulting signal is detected with a Luminex 200 system. Raw fluorescence data is processed with the A1AT Genotyping Test ANALYSIS SOFTWARE to provide allelic variant genotypes, which are subsequently converted into associated alleles. Additionally, the software application also provides the type of

Genetic Health Risk Report associated with the identified alleles, which is subsequently used as the basis for the generation of personalized reports by the AlphaID At Home Genetic Health Risk Service website and result portal.

Depending on the specific variant combination detected, the AlphaID At Home Genetic Health Risk Service provides the individuals' genetic health risk for developing lung and liver disease linked to AATD. Personalized reports, in an easy-to-understand format, are generated for each consumer that help to understand the meaning of their results and any appropriate actions that may be taken based on their results. In addition, every user before receiving report must undergo the educational module that helps to understand the AlphaID At Home Genetic Health Risk Service results report and explain how genetics can impact a person's health risk for lung disease and/or liver disease linked to AATD. The AlphaID At Home Genetic Health Risk Service uses four (4) categories summarized in the table below to define risk. One of these risk categories has been assigned to each genetic result based on the information gathered from reported clinical cases for each genetic result. If any of the 14 variants tested by this Service is detected, one of the following four risk categories will be reported:

Risk Categories	
Increased risk	Above 80% of people with this genetic result develop lung or liver disease during their lifetime.
Slightly increased risk	20-80% of people with this genetic result develop lung or liver disease during their lifetime.
Not likely at increased risk	Below 20% of people with this genetic result develop lung or liver disease during their lifetime.
Unknown risk	More clinical studies are needed to determine the risk level associated with this genetic result

When no variants are detected, the report shows '*Not Likely at Risk'* for AATD. When the service is not able to provide a genetic result, the associated lung and liver disease risk categories cannot be determined, and another type of report will be generated: '*Variant not determined*'.

Based on the number of variants detected (0, 1, 2, or variant not determined) and specific lung and liver disease risk categorization reported, a total of 15 types of reports can be generated by the AlphaID At Home Genetic Health Risk Service, which are shown in the table below:

Type of Report	**Number of variants**	**Reported Lung Disease Risk Category**	**Reported Liver Disease Risk Category**	**Number of genetic results**	**Frequency of genetic results, %**
1	0	Not likely at risk for AATD	Not likely at risk for AATD	1	94.95
2	1	Not likely at increased risk	Not likely at increased risk	11	4.23
3	1	Not likely at increased risk	Slightly increased risk	1	0.002
4	1	Not likely at increased risk	Unknown risk	1	0.002
5	1	Not likely at increased risk (never-smokers) Slightly increased risk (ever-smokers)	Slightly increased risk	1	0.780
6	2	Not likely at increased risk	Not likely at increased risk	1	0.40
7	2	Slightly increased risk	Not likely at increased risk	1	<0.00001
8	2	Slightly increased risk	Slightly increased risk	5	0.017

Type of Report	Number of variants	Reported Lung Disease Risk Category	Reported Liver Disease Risk Category	Number of genetic results	Frequency of genetic results, %
9	2	Slightly increased risk	Unknown risk	1	<0.00001
10	2	Increased risk	Not likely at increased risk	15	<0.00001
11	2	Increased risk	Slightly increased risk	7	0.0016
12	2	Unknown risk	Slightly increased risk	15	0.0001
13	2	Unknown risk	Not likely at increased risk	29	0.0001
14	2	Unknown risk	Unknown risk	31	0.0069
15	Variant not determined	Not determined risk	Not determined risk	N/A	N/A

B Principle of Operation:

The AlphaID At Home Genetic Health Risk Service is performed by a CLIA-certified laboratory using the Alpha-1 antitrypsin (A1AT) Genotyping Test.

The A1AT Genotyping Test utilizes Luminex xMAP technology. Genomic DNA is extracted from human saliva samples collected as buccal swabs using ORAcollect·Dx OCD-100.014. Extracted DNA is amplified and biotinylated by multiplex PCR and the PCR products are denatured and hybridized to oligonucleotide probes coupled to color-coded beads. Hybridized DNA is labeled with fluorescent conjugate and the resulting signal is detected with a Luminex 200 system (with xPONENT software). Raw data obtained is processed with the A1AT Genotyping Test Analysis Software.

The A1AT Genotyping Test Analysis Software algorithm converts the allelic variant genotypes into associated alleles. Additionally, this software application also provides an associated template number for each sample, this is, a code that defines the type of Genetic Health Risk Report that is to be generated for each individual, depending on its combination of variants. This template number will be subsequently used as the basis for the generation of personalized reports by the AlphaID System.

V Substantial Equivalence Information:

A Predicate Device Name(s):

23andMe Personal Genome Service (PGS) Genetic Health Risk Report for Alpha-1 Antitrypsin Deficiency

B Predicate 510(k) Number(s):

DEN160026

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device K221420	Predicate DEN160026
Device Trade Name	AlphaID At Home Genetic Health Risk Service	23andMe Personal Genome Service (PGS) for A1AT
General Device Characteristic Similarities		
Intended Use/ Indications For 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 ≥ 18 years with ORAcollect·Dx OCD-100.014 for the purpose of reporting and interpreting Genetic Health Risks (GHR). The AlphaID At Home Genetic Health Risk 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 or decreased risk of developing either lung and/or liver disease linked to AATD. The report does not describe a person´s overall risk of developing lung and/or liver disease. AATD is more common in persons of European descent.	The 23andMe Personal Genome Service (PGS) Test uses qualitative genotyping to detect the following clinically relevant variants in genomic DNA isolated from human saliva collected from individuals ≥18 years with the Oragene Dx model OGD-500.001 for the purpose of reporting and interpreting Genetic Health Risks (GHR). The 23andMe PGS Genetic Health Risk Report for Alpha-1 Antitrypsin Deficiency is indicated for reporting of the PI*Z and PI*S variants in the SERPINA1 gene. This report describes if a person has variants associated with AAT deficiency and a higher risk for lung or liver disease, but it does not describe a person's overall risk of developing lung or liver disease. This test is most relevant for people of European descent.
Special Conditions for Use Statements	a. For over-the-counter (OTC) use. b. The test is intended for users ≥18 years old. c. The test is not a substitute for an appointment with a healthcare professional. It is recommended that the user consult with a healthcare professional if the user have any questions or concerns about his/her results. d. The test does not diagnose a disease or condition, determine medical treatment or other medical intervention, or tell the user anything	a. For over-the-counter (OTC) use. b. 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. c. The 23andMe PGS Genetic Health Risk Tests for Hereditary Thrombophilia, Alpha-1 Antitrypsin Deficiency, Alzheimer's disease, Parkinson's disease, Gaucher Disease, Factor XI Deficiency, Celiac disease, and

	about their current state of health. Only a healthcare professional can diagnose a disease or condition. e. Any diagnostic or treatment decisions must be based on confirmatory prescription testing and/or other information that a healthcare professional determines to be appropriate for the patient, such as additional clinical testing and other risk factors that may affect individual risk and health care. f. The test detects 14 variants in the SERPINA1 gene linked to AATD. These 14 variants explain 95% of AATD cases. The absence of a variant tested does not rule out the presence of other genetic variants that may be disease-related. g. The test does not describe a person's overall risk of developing AATD. In addition, other genetic and all non-genetic factors should be considered h. The laboratory may be unable to process every user's sample. The probability that the laboratory cannot process a sample can be up to 0.5%. If this happens, the user will receive an email notification. The user will also receive another AlphaID At Home Saliva Collection Kit to provide a new sample to the laboratory. i. The user´s race, ethnicity, age, and sex may affect how the genetic results are interpreted. j. Subject to meeting limitations contained in the special controls under the regulation 21 CFR 866.5950	Glucose-6- Phosphate-Dehydrogenase Deficiency, Early-Onset Primary Dystonia and Hereditary Hemochromatosis do not detect all genetic variants associated with the aforementioned diseases. The absence of a variant tested does not rule out the presence of other genetic variants that may be disease related. d. The test is intended for users ≥ 18 years old. e. The test does not diagnose any specific health conditions. Results should not be used to make medical decisions. f. The laboratory may not be able to process a user's sample. The probability that the laboratory cannot process a sample can be up to 7.6%. g. A user's race, ethnicity, age, and sex may affect how the genetic test results are interpreted. h. Subject to meeting the limitations contained in the special controls under regulation 21 CFR 866.5950.
Type of Test	Qualitative genotyping for allelic variant determination through single nucleotide polymorphism detection	Same
Design	Software application that includes product information page, e-commerce (registration and order DNA kit), secure login, download genetic report	Same

Interpretation of results	For over-the-counter use (OTC). Specialized interpretation by a physician not required	Same
Specimen Type	Saliva	Same
Measurand	Genomic DNA	Same
Comparison with Sanger Bidirectional Sequencing	Overall agreement for the 14 variants was 100%.	Overall agreement for the two variants was 100%.
Human factors	User Comprehension Study	Same
General Device Characteristic Differences		
Specimen Collection Kit	DNA Genotek Inc., ORAcollect Dx OCD-100.014	DNA Genotek Inc., Oragene Dx model OGD-500.001
Technology	Polymerase Chain Reaction (PCR) amplification and hybridization based Luminex technology	Multiplex customized genotyping chip (BeadChip v4 assay)
Method and Sequencing Platform	Multiplex polymerase chain reaction (PCR) and multiplex Allele Specific Primer Extension (ASPE) with Luminex's Universal Tag sorting system on the Luminex 200 xMAP platform with xPONENT software and A1AT Genotyping Test Analysis software for the simultaneous detection and identification of allelic variants and their associated alleles.	Magnetic bead DNA extraction is performed using Tecan Evo. Genotyping and PCR analysis is conducted using a chip-based method with Illumina Infinium's BeadChip v4 assay, the Illumina iScan System for detection and analysis is facilitated with the use of GenomeStudio and Coregen software.
Special Instrument Requirements	Luminex 200 instrument (with xPONENT® software) The A1AT Genotyping Test ANALYSIS SOFTWARE processes raw data from the Luminex System (csv. files containing the MFI value for each bead type) to provide allelic variant genotypes which are subsequently converted into associated alleles, and the type of Genetic Health Risk Report associated with the identified alleles	Tecan Evo and Illumina iScan instruments GenomeStudio is a modular software application that is used to view and analyze genotypic data obtained from the iScan. Coregen software conducts a variety of control checks on the file, resulting in a final genotype profile for each sample. These data are used to generate test reports on a user's genotype and associated risk of disease.
Allelic Variants Detected	14 allelic variants in the SERPINA1 gene: 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;	Two allelic variants in the SERPINA1 gene: P*Z and P*S

	PI*Q0 clayton, PI*M heerlen).	
Analytical Sensitivity	The performance requirement for the A1AT Genotyping Test has been set at a minimum of 0.0215 ng/µL DNA.	The performance requirement for the PGS has been set at a minimum of 15 ng/µL DNA and maximum of 50 ng/µL DNA.

VI Standards/Guidance Documents Referenced:

- CLSI guideline EP07-A2, "Interference Testing in Clinical Chemistry; Approved Guideline–Second Edition"
- Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (2005)
- General Principles of Software Validation Guidance for Industry and FDA Staff (2002)
- Off-The-Shelf Software Use in Medical Devices Guidance for Industry and Food and Drug Administration Staff (2019)
- Content of Premarket Submissions for Management of Cybersecurity in Medical Devices (2014)
- ISO 14971 Third Edition 2019-12 Medical devices - Application of risk management to medical devices

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

All results presented below met the sponsor's pre-defined acceptance criteria outlined in the Special Controls of 21 CFR 866.5950. Information regarding samples that failed quality control (FQC) was also evaluated and presented in each study below.

1. Precision/Reproducibility:

   Refer to K171868 for results of the reproducibility study that was conducted with a total of 17 samples. The reproducibility of the assay was evaluated at three sites, with two operators at each site performing one run per day across three non-consecutive days (three runs per operator or six runs per site). Within a given run, the sample panel was tested in duplicate. Concordance with the expected results was 100% at the three sites.

   Refer to K192858 for DNA extraction variability in saliva samples that was conducted using three different extraction methods: QIAamp DNA Blood Mini Kit (Qiagen), Commercial lysis and neutralization solutions (Sigma) and QIAsymphony DNA Mini Kit (Qiagen).

   Refer to K171868 and K211115 for results of the lot-to-lot imprecision study.

2. Linearity:

   Not applicable

3. Analytical Specificity/Interference:

i. Interference

Refer to K192858 for results of studies conducted to evaluate the potential interference of substances usually found in saliva samples.

ii. Cross-reactivity

Refer to K171868. An *In Silico* DNA sequence analysis of A1AT Genotyping Test primers and probes confirmed sequence specificity and the absence of cross-reactivity.

iii. Cross-contamination

Refer to K171868

4. Assay Reportable Range:

Not applicable

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

i. Reagent stability:

Refer to K192858. The claimed reagent stability is 24 months when stored at 2−8ºC and up to 9 months after the kit vials were first opened.

ii. Stability of collection device and specimens:

Saliva samples for testing are collected with the ORAcollect·Dx OCD-100.014 (customized version of ORAcollect·Dx OCD-100). Refer to K152464 for pre-collection shelf-life stability of the collection device, stability of samples post-saliva collection, and freeze-thaw stability of samples stored in the Oragene Dx collection device.

6. Detection Limit:

Refer to K211115 for results of the Lower Limit of Detection (LLoD) study that evaluated the impact of different levels of DNA input on test performance.

7. Assay Cut-Off:

Not applicable

B Comparison Studies:

1. Comparison with Sanger Bidirectional Sequencing:

A method comparison study was performed with saliva samples collected in ORAcollect·Dx OCD-100.014 (customized version of ORAcollect·Dx OCD-100) to assess the accuracy of the AlphaID At Home Genetic Health Risk Service 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 Sanger sequencing (reference method).

The percent agreements (PAs) per allelic variant from clinical samples and contrived samples (8 synthetic DNAs samples) were calculated separately. The PA per allelic variant between the two methods was 100% for both clinical samples and contrived samples. The percentage of "No call' or "Invalid test" per allelic variant was also calculated and was 0% for both clinical samples and contrived samples.

The PAs of AlphaID At Home Genetic Health Risk Service genotype results with comparator results are summarized in the tables below.

PI*I (c.187C>T) variant of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	203	0	0
	C/T (heterozygous)	0	15	0
	T/T (homozygous rare)	0	0	1
	'No call' or 'Invalid test'	0	0	0
Total=219		203	15	1
PA (C/C | C/C) = 100% (203/203) with 95% CI: 98.1%−100% PA (C/T |C/T) = 100% (15/15) with 95% CI: 79.6%−100% PA (T/T | T/T) = 100% (1/1) with 95% CI: 20.7%−100% Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%				
Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	4	0	0
	C/T (heterozygous)	0	1	0
	T/T (homozygous rare)	0	0	3
	'No call' or 'Invalid test'	0	0	0
Total=8		4	1	3
PA (C/C | C/C) = 100% (4/4) with 95% CI: 51.0%−100% PA (C/T | C/T) = 100% (1/1) with 95% CI: 20.7%−100% PA (T/T | T/T) = 100% (3/3) with 95% CI: 43.9%−100% Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%− 2.4%				
All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	207	0	0
	C/T (heterozygous)	0	16	0
	T/T (homozygous rare)	0	0	4
	'No call' or 'Invalid test'	0	0	0
Total=227		207	16	4
PA (C/C | C/C) = 100% (207/207) with 95% CI: 98.2%−100% PA (C/T | C/T) = 100% (16/16) with 95% CI: 80.6%−100% PA (T/T | T/T) = 100% (4/4) with 95% CI: 51.0%−100% Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7%.				

Minor allele frequency for PI*I SERPINA1 in the 1000 Genomes Project was 0.06%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of C/T and T/T are 99.128% and 99.997% correspondingly

PI*M procida variant (c.194T>C) of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		T/T	T/C	C/C
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	211	0	0
	C/T (heterozygous)	0	5	0
	T/T (homozygous rare)	0	0	3
	'No call' or 'Invalid test'	0	0	0
Total=219		211	5	3

PA (C/C | C/C) = 100% (211/211) with 95% CI: 98.2%−100%
PA (C/T | C/T) = 100% (5/5) with 95% CI: 56.6%−100%
PA (T/T | T/T) = 100% (3/3) with 95% CI: 43.9%−100%
Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%

Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	4	0	0
	C/T (heterozygous)	0	1	0
	T/T (homozygous rare)	0	0	3
	'No call' or 'Invalid test'	0	0	0
Total=8		4	1	3

PA (C/C | C/C) = 100% (4/4) with 95% CI: 51.0%−100%
PA (C/T | C/T) = 100% (1/1) with 95% CI: 20.7%−100%
PA (T/T | T/T) =100% (3/3) with 95% CI: 43.9%−100%
Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%

All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	215	0	0
	C/T (heterozygous)	0	6	0
	T/T (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=227		215	6	6

PA (C/C | C/C) = 100% (215/215) with 95% CI: 98.2%−100%
PA (C/T | C/T) = 100% (6/6) with 95% CI: 61.0%−100%
PA (T/T | T/T) = 100% (6/6) with 95% CI: 43.9%−100%
Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7%
Minor allele frequency for PI*M procida SERPINA1 in the 1000 Genomes Project was <0.001%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of C/T and T/T are 97.603% and 99.999% correspondingly

PI* M malton variant (c.226_228delTTC) of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		TTC/ TTC	TTC/ delTTC	delTTC/ delTTC
AlphaID At Home Genetic Health Risk Service	TTC/TTC (homozygous common)	195	0	0
	TTC/ delTTC (heterozygous)	0	21	0
	delTTC/ delTTC (homozygous rare)	0	0	3
	'No call' or 'Invalid test'	0	0	0
Total=219		195	21	3
PA (TTC/TTC | TTC/TTC) = 100% (195/195) with 95% CI: 98.1%−100% PA (TTC/delTTC | TTC/delTTC) = 100% (21/21) with 95% CI: 84.5%−100% PA (delTTC/delTTC | delTTC/delTTC) = 100% (3/3) with 95% CI: 43.9%−100% Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%				
Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		TTC/ TTC	TTC/ delTTC	delTTC/ delTTC
AlphaID At Home Genetic Health Risk Service	TTC/TTC (homozygous common)	4	0	0
	TTC/delTTC (heterozygous)	0	1	0
	delTTC/delTTC (homozygous rare)	0	0	3
	'No call' or 'Invalid test'	0	0	0
Total=8		4	1	3
PA (TTC/TTC | TTC/TTC) = 100% (4/4) with 95% CI: 51.0%−100% PA (TTC/delTTC | TTC/delTTC) = 100% (1/1) with 95% CI: 20.7%−100% PA (delTTC/delTTC | delTTC/delTTC) =100% (3/3) with 95% CI: 43.9%−100% Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%				
All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		TTC/ TTC	TTC/ delTTC	delTTC/ delTTC
AlphaID At Home Genetic Health Risk Service	TTC/TTC (homozygous common)	199	0	0
	TTC/ delTTC (heterozygous)	0	22	0
	delTTC/ delTTC (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=227		199	22	6
PA (TTC/TTC | TTC/TTC) = 100% (199/199) with 95% CI: 98.1%−100% PA (TTC/delTTC | TTC/delTTC) = 100% (22/22) with 95% CI: 85.1%−100% PA (delTTC/delTTC | delTTC/delTTC) = 100% (6/6) with 95% CI: 61.0%−100% Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7% Minor allele frequency for PI*M malton SERPINA1 in the 1000 Genomes Project was <0.001%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of TTC/delTTC and delTTC/delTTC are 99.382% and 99.996% correspondingly.				

PI* S iiyama variant (c.230C>T) of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	217	0	0
	C/T (heterozygous)	0	2	0
	T/T (homozygous rare)	0	0	0
	'No call' or 'Invalid test'	0	0	0
Total=219		217	2	0
PA (C/C | C/C) = 100% (217/217) with 95% CI: 98.3%−100% PA (C/T | C/T) = 100% (2/2) with 95% CI: 34.2%−100% PA (T/T | T/T) = N/A Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%				
Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	4	0	0
	C/T (heterozygous)	0	1	0
	T/T (homozygous rare)	0	0	3
	'No call' or 'Invalid test'	0	0	0
Total=8		4	1	3
PA (C/C | C/C) = 100% (4/4) with 95% CI: 51.0%−100% PA (C/T | C/T) = 100% (1/1) with 95% CI: 20.7%−100% PA (T/T | T/T) = 100% (3/3) with 95% CI: 43.9%−100% Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%				
All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	221	0	0
	C/T (heterozygous)	0	3	0
	T/T (homozygous rare)	0	0	3
	'No call' or 'Invalid test'	0	0	0
Total=227		221	3	3
PA (C/C | C/C) = 100% (221/221) with 95% CI: 98.3%−100% PA (C/T | C/T) = 100% (3/3) with 95% CI: 43.9%−100% PA (T/T | T/T) = 100% (3/3) with 95% CI: 43.9%−100% Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7% Minor allele frequency for PI*S iiyama SERPINA1 in the 1000 Genomes Project was <0.001%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of C/T and T/T are 95.257% and 99.9995% correspondingly.				

PI*Q0 granite falls (c.552delC) variant of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/delC	delC/delC
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	216	0	0
	C/ delC (heterozygous)	0	3	0
	delC/delC (homozygous rare)	0	0	0
	'No call' or 'Invalid test'	0	0	0
Total=219		216	3	0
PA (C/C | C/C) = 100% (216/216) with 95% CI: 98.3%−100% PA (C/delC | C/delC) = 100% (3/3) with 95% CI: 43.9%−100% PA (delC/delC | delC/delC) = N/A Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%				
Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/delC	delC/delC
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	0	0	0
	C/delC (heterozygous)	0	2	0
	delC/delC (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=8		0	2	6
PA (C/C | C/C) = N/A PA (C/delC | C/delC) = 100% (2/2) with 95% CI: 34.2%−100% PA (delC/delC | delC/delC) =100% (6/6) with 95% CI: 61.0%−100% Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%				
All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/delC	delC/delC
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	216	0	0
	C/ delC (heterozygous)	0	5	0
	delC/delC (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=227		216	5	6
PA (C/C | C/C) = 100% (216/216) with 95% CI: 98.3%−100% PA (C/delC | C/delC) = 100% (5/5) with 95% CI: 56.6%−100% PA (delC/delC | delC/delC) = 100% (6/6) with 95% CI: 61.0%−100% Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7% Minor allele frequency for PI*Q0 granite falls SERPINA1 in the 1000 Genomes Project was <0.001%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of C/delC and delC/delC are 97.124 and 99.999% correspondingly.				

PI*Q0 west (646+1G>T) variant of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		G/G	G/T	T/T
AlphaID At Home Genetic Health Risk Service	G/G (homozygous common)	215	0	0
	G/T (heterozygous)	0	4	0
	T/T (homozygous rare)	0	0	0
	'No call' or 'Invalid test'	0	0	0
Total=219		215	4	0
PA (G/G | G/G) = 100% (215/215) with 95% CI: 98.2%−100% PA (G/T | G/T) = 100% (4/4) with 95% CI: 51.0%−100% PA (T/T | T/T) = N/A Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%				
Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		G/G	G/T	T/T
AlphaID At Home Genetic Health Risk Service	G/G (homozygous common)	0	0	0
	G/T (heterozygous)	0	2	0
	T/T (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=8		0	2	6
PA (G/G | G/G) = N/A PA (G/T | G/T) = 100% (2/2) with 95% CI: 34.2%−100% PA (T/T | T/T) =100% (6/6) with 95% CI: 61.0%−100% Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%				
All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		G/G	G/T	T/T
AlphaID At Home Genetic Health Risk Service	G/G (homozygous common)	215	0	0
	G/T (heterozygous)	0	6	0
	T/T (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=227		215	6	6
PA (G/G | G/G) = 100% (215/215) with 95% CI: 98.2%−100% PA (G/T | G/T) = 100% (6/6) with 95% CI: 61.0%−100% PA (T/T | T/T) = 100% (6/6) with 95% CI: 61.0% − 100%. Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7%. Minor allele frequency for PI*Q0 west SERPINA1 in the 1000 Genomes Project was <0.001%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of G/T and T/T are 97.603% and 99.999% correspondingly.				

PI*Q0 bellingham (c.721A>T) variant of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		A/A	A/T	T/T
AlphaID At Home Genetic Health Risk Service	A/A (homozygous common)	213	0	0
	A/T (heterozygous)	0	5	0
	TT (homozygous rare)	0	0	1
	'No call' or 'Invalid test'	0	0	0
Total=219		213	5	1

PA (A/A | A/A) = 100% (213/213) with 95% CI: 98.2%−100%
PA (A/T | A/T) = 100% (5/5) with 95% CI: 56.6%−100%
PA (T/T | T/T) = 100% (1/1) with 95% CI: 94.7%−100%
Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%

Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		A/A	A/T	T/T
AlphaID At Home Genetic Health Risk Service	A/A (homozygous common)	0	0	0
	A/T (heterozygous)	0	2	0
	TT (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=8		0	2	6

PA (A/A | A/A) = N/A
PA (A/T | A/T) = 100% (2/2) with 95% CI: 34.2%−100%
PA (T/T | T/T) = 100% (6/6) with 95% CI: 61.0%−100%
Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%

All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		A/A	A/T	T/T
AlphaID At Home Genetic Health Risk Service	A/A (homozygous common)	213	0	0
	A/T (heterozygous)	0	7	0
	TT (homozygous rare)	0	0	7
	'No call' or 'Invalid test'"	0	0	0
Total=227		213	7	7

PA (A/A | A/A) = 100% (213/213) with 95% CI: 98.2%−100%
PA (A/T | A/T) = 100% (7/7) with 95% CI: 64.6%−100%
PA (T/T | T/T) = 100% (7/7) with 95% CI: 64.6%−100%
Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7%.
Minor allele frequency for PI*Q0 bellingham SERPINA1 in the 1000 Genomes Project was <0.001%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of A/T and T/T are 97.947% and 99.999% correspondingly.

PI*F (c.739C>T) variant of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	194	0	0
	C/T (heterozygous)	0	23	0
	T/T (homozygous rare)	0	0	2
	'No call' or 'Invalid test'	0	0	0
Total=219		194	23	2
PA (C/C | C/C) = 100% (194/194) with 95% CI: 98.1%−100% PA (C/T | C/T) = 100% (23/23) with 95% CI: 85.7%−100% PA (T/T | T/T) = 100% (2/2) with 95% CI: 34.2%−100% Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%				
Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	0	0	0
	C/T (heterozygous)	0	2	0
	T/T (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=8		0	2	6
PA (C/C | C/C) = N/A PA (C/T | C/T) = 100% (2/2) with 95% CI: 34.2%−100% PA (T/T | T/T) = 100% (6/6) with 95% CI: 61.0%−100% Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%				
All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	194	0	0
	C/T (heterozygous)	0	25	0
	T/T (homozygous rare)	0	0	8
	'No call' or 'Invalid test'	0	0	0
Total=227		194	25	8
PA (C/C | C/C) = 100% (194/194) with 95% CI: 98.1%−100% PA (C/T | C/T) = 100% (25/25) with 95% CI: 86.7%−100% PA (T/T | T/T) = 100% (8/8) with 95% CI: 67.6%−100% Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7% Minor allele frequency for PI*F SERPINA1 in the 1000 Genomes Project was 0.1%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of C/T and T/T are 99.464% and 99.996% correspondingly.				

PI*P lowell (c.839A>T) variant of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		A/A	A/T	T/T
AlphaID At Home Genetic Health Risk Service	A/A (homozygous common)	201	0	0
	A/T (heterozygous)	0	14	0
	TT (homozygous rare)	0	0	4
	'No call' or 'Invalid test'	0	0	0
Total=219		201	14	4

PA (A/A | A/A) = 100% (201/201) with 95% CI: 98.1%−100%
PA (A/T | A/T) = 100% (14/14) with 95% CI: 78.5%−100%
PA (T/T | T/T) = 100% (4/4) with 95% CI: 51.0%−100%
Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%

Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		A/A	A/T	T/T
AlphaID At Home Genetic Health Risk Service	A/A (homozygous common)	0	0	0
	A/T (heterozygous)	0	2	0
	TT (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=8		0	2	6

PA (A/A | A/A) = N/A
PA (A/T | A/T) = 100% (2/2) with 95% CI: 34.2%−100%
PA (T/T | T/T) =100% (6/6) with 95% CI: 61.0%−100%
Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%.

All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		A/A	A/T	T/T
AlphaID At Home Genetic Health Risk Service	A/A (homozygous common)	201	0	0
	A/T (heterozygous)	0	16	0
	TT (homozygous rare)	0	0	10
	'No call' or 'Invalid test'	0	0	0
Total=227		201	16	10

PA (A/A | A/A) = 100% (201/201) with 95% CI: 98.1%−100%
PA (A/T | A/T) = 100% (16/16) with 95% CI: 80.6%−100%
PA (T/T | T/T) = 100% (10/10) with 95% CI: 72.2%−100%
Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7%
Minor allele frequency for PI*P lowell SERPINA1 in the 1000 Genomes Project was <0.001%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of A/T and T/T are 99.464% and 99.996% correspondingly.

PI*S (c.863A>T) variant of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		A/A	A/T	T/T
AlphaID At Home Genetic Health Risk Service	A/A (homozygous common)	163	0	0
	A/T (heterozygous)	0	36	0
	T/T (homozygous rare)	0	0	20
	'No call' or 'Invalid test'	0	0	0
Total=219		163	36	20
PA (A/A | A/A) = 100% (163/163) with 95% CI: 97.7%−100% PA (A/T | A/T) = 100% (36/36) with 95% CI: 90.4%−100% PA (T/T | T/T) = 100% (20/20) with 95% CI: 83.9%−100% Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%				
Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		A/A	A/T	T/T
AlphaID At Home Genetic Health Risk Service	A/A (homozygous common)	0	0	0
	A/T (heterozygous)	0	2	0
	T/T (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=8		0	2	6
PA (A/A | A/A) = N/A PA (A/T | A/T) = 100% (2/2) with 95% CI: 34.2%−100% PA (T/T | T/T) = 100% (6/6) with 95% CI: 61.0%−100% Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%				
All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		A/A	A/T	T/T
AlphaID At Home Genetic Health Risk Service	A/A (homozygous common)	163	0	0
	A/T (heterozygous)	0	38	0
	T/T (homozygous rare)	0	0	26
	'No call' or 'Invalid test'	0	0	0
Total=227		163	38	26
PA (A/A | A/A) = 100% (163/163) with 95% CI: 97.7%−100% PA (A/T | A/T) = 100% (38/38) with 95% CI: 90.8%−100% PA (T/T | T/T) = 100% (26/26) with 95% CI: 87.1%−100% Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7%. Minor allele frequency for PI*S SERPINA1 in the 1000 Genomes Project was 2%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of A/T and T/T are 99.669% and 99.992% correspondingly.				

PI*Z (c.1096G>A) variant of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		G/G	G/A	A/A
AlphaID At Home Genetic Health Risk Service	G/G (homozygous common)	167	0	0
	G/A (heterozygous)	0	37	0
	A/A (homozygous rare)	0	0	15
	'No call' or 'Invalid test'	0	0	0
Total=219		167	37	15
PA (G/G | GG) = 100% (167/167) with 95% CI: 97.8%−100% PA (G/A | G/A) = 100% (37/37) with 95% CI: 90.6%−100% PA (A/A | A/A) = 100% (15/15) with 95% CI: 79.6%−100% Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%				
Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		G/G	G/A	A/A
AlphaID At Home Genetic Health Risk Service	G/G (homozygous common)	0	0	0
	G/A (heterozygous)	0	2	0
	A/A (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=8		0	2	6
PA (G/G | G/G) = N/A PA (G/A | G/A) = 100% (2/2) with 95% CI: 34.2%−100% PA (A/A | A/A) = 100% (6/6) with 95% CI: 61.0%−100% Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%.				
All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		G/G	G/A	A/A
AlphaID At Home Genetic Health Risk Service	G/G (homozygous common)	167	0	0
	G/A (heterozygous)	0	39	0
	A/A (homozygous rare)	0	0	21
	'No call' or 'Invalid test'	0	0	0
Total=227		167	39	21
PA(G/G | GG) = 100% (167/167) with 95% CI: 97.8%−100% PA (G/A | G/A) = 100% (39/39) with 95% CI: 91.0%−100% PA (A/A | A/A) = 100% (21/21) with 95% CI: 84.5%−100% Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7%. Minor allele frequency for PI*Z SERPINA1 in the 1000 Genomes Project was 0.4%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of G/A and A/A are 99.680% and 99.992% correspondingly				

PI*Q0 mattawa (c.1130dupT) variant of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		T/T	T/dupT	dupT/dupT
AlphaID At Home Genetic Health Risk Service	T/T (homozygous common)	212	0	0
	T/dupT (heterozygous)	0	5	0
	dupT/dupT (homozygous rare)	0	0	2
	'No call' or 'Invalid test'	0	0	0
Total=219		212	5	2
PA (T/T | T/T) = 100% (212/212) with 95% CI: 98.2%−100% PA (T/dupT | T/dupT) = 100% (5/5) with 95% CI: 56.6%−100% PA (dupT/dupT | dupT/dupT) = 100% (2/2) with 95% CI: 34.2%−100% Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%				
Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		T/T	T/dupT	dupT/dupT
AlphaID At Home Genetic Health Risk Service	T/T (homozygous common)	0	0	0
	T/dupT (heterozygous)	0	2	0
	dupT/dupT (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=8		0	2	6
PA (T/T | T/T) = N/A PA (T/dupT | T/dupT) = 100% (2/2) with 95% CI: 34.2%−100% PA (dupT/dupT | dupT/dupT) = 100% (6/6) with 95% CI: 61.0%−100% Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%				
All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		T/T	T/dupT	dupT/dupT
AlphaID At Home Genetic Health Risk Service	T/T (homozygous common)	212	0	0
	T/dupT (heterozygous)	0	7	0
	dupT/dupT (homozygous rare)	0	0	8
	'No call' or 'Invalid test'	0	0	0
Total=227		212	7	8
PA (T/T | T/T) = 100% (212/212) with 95% CI: 98.2%−100% PA (T/dupT | T/dupT) = 100% (7/7) with 95% CI: 64.6%−100% PA (dupT/dupT | dupT/dupT) = 100% (8/8) with 95% CI: 67.6%−100% Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7% Minor allele frequency for PI*Q0 mattawa SERPINA1 in the 1000 Genomes Project was <0.001%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of T/dupT and dupT/dupT are 97.947% and 99.999% correspondingly.				

PI*Q0 clayton (c.1158dupC) variant of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		CC	C/dupC	dupC/dupC
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	217	0	0
	C/dupC (heterozygous)	0	2	0
	dupC/dupC (homozygous rare)	0	0	0
	'No call' or 'Invalid test'	0	0	0
Total=219		217	2	0
PA (C/C | C/C) = 100% (217/217) with 95% CI: 98.3%−100% PA (C/dupC | C/dupC) = 100% (2/2) with 95% CI: 34.2%−100% PA (dupC/dupC | dupC/dupC) = N/A Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%				
Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		CC	C/dupC	dupC/dupC
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	0	0	0
	C/dupC (heterozygous)	0	2	0
	dupC/dupC (homozygous rare)	0	0	6
	'No call' or 'Invalid test'"	0	0	0
Total=8		0	2	6
PA (C/C | C/C) = N/A PA (C/dupC | C/dupC) = 100% (2/2) with 95% CI: 34.2%−100% PA (dupC/dupC | dupC/dupC) =100% (6/6) with 95% CI: 61.0%−100% Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%				
All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		CC	C/dupC	dupC/dupC
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	217	0	0
	C/dupC (heterozygous)	0	4	0
	dupC/dupC (homozygous rare)	0	0	6
	'No call' or 'Invalid test'	0	0	0
Total=227		217	4	6
PA (C/C | C/C) = 100% (217/217) with 95% CI: 98.3%−100% PA (C/dupC | C/dupC) = 100% (4/4) with 95% CI: 51.0%−100% PA (dupC/dupC | dupC/dupC) = 100% (6/6) with 95% CI: 61.0%−100% Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7% Minor allele frequency for PI*Q0 clayton SERPINA1 in the 1000 Genomes Project was <0.001%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of C/dupC and dupC/dupC are 96.415% and 99.999% correspondingly.				

PI*M heerlen (c.1178C>T) variant of the SERPINA1 gene				
Clinical Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	210	0	0
	C/T (heterozygous)	0	5	0
	T/T (homozygous rare)	0	0	4
	'No call' or 'Invalid test'	0	0	0
Total=219		210	5	4
PA (C/C | C/C) = 100% (210/210) with 95% CI: 98.2%−100% PA (C/T | C/T) = 100% (5/5) with 95% CI: 56.6%−100% PA (T/T | T/T) = 100% (4/4) with 95% CI: 51.0%−100% Percent of no calls or invalid is 0.0% (0/219) with 95% CI: 0.0%−1.7%				
Contrived Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	0	0	0
	C/T (heterozygous)	0	2	0
	T/T (homozygous rare)	0	0	6
	'no calls' or 'invalid"	0	0	0
Total=8		0	2	6
PA (C/C | C/C) = N/A PA (C/T | C/T) = 100% (2/2) with 95% CI: 34.2%−100% PA (T/T | T/T) = 100% (6/6) with 95% CI: 61.0%−100% Percent of no calls or invalid is 0.0% (0/8) with 95% CI: 0.0%−32.4%				
All Samples	**Genotype**	**Sanger Bidirectional Sequencing**		
		C/C	C/T	T/T
AlphaID At Home Genetic Health Risk Service	C/C (homozygous common)	210	0	0
	C/T (heterozygous)	0	7	0
	T/T (homozygous rare)	0	0	10
	'No call' or 'Invalid test'	0	0	0
Total=227		210	7	10
PA (C/C | C/C) = 100% (210/210) with 95% CI: 98.2%−100% PA (C/T | C/T) = 100% (7/7) with 95% CI: 64.6%−100% PA (T/T | T/T) = 100% (10/10) with 95% CI: 72.2%−100% Percent of no calls or invalid is 0.0% (0/227) with 95% CI: 0.0%−1.7% Minor allele frequency for PI*M heerlen SERPINA1 in the 1000 Genomes Project was <0.001%; technical (analytical) positive predictive values for AlphaID At Home Genetic Health Risk Service test result of C/T and T/T are 97.947% and 99.999% correspondingly.				

2. Matrix Comparison:

Not applicable

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable

2. Clinical Specificity:

Not applicable

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

a) Risk of developing lung and liver disease associated with AATD depends on specific variant combination detected

AATD is a genetic autosomal recessive disease with codominant expression (i.e., each of the two alleles present in each person contributes 50% on the total generated AAT protein), characterized by low levels of the AAT protein in the blood, that may lead to various health conditions. The most common diseases are lung and/or liver disease. AATD occurs in people of all ethnicities worldwide.[1] However, it is most common in people of European descent. AATD affects about 1 in 1,500 to 3,500 people of European descent.[2,3] 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.[4] Two to three percent of patients with COPD in the United States are estimated to have AATD.[2] The percentage of patients with liver disease who have AATD is not known.

AATD is caused by modifications in the genetic sequence of the SERPINA1 gene, which give rise to different variants. More than 120 variants in the SERPINA1 gene have been identified. Some of these variants do not affect the production of AAT protein, but some others may differently affect the levels or functionality of the AAT protein and, therefore, each specific variant may be associated with different probabilities for the development of lung disease and/or liver disease.

The AlphaID At Home Genetic Health Risk Service is indicated for the detection of

[1] Stoller JK, Hupertz V, Aboussouan LS. Alpha-1 Antitrypsin Deficiency. Deficiency. 2006 Oct 27 [Updated 2020 May 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020

[2] American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003 Oct 1;168(7):818-900

[3] de Serres F, Blanco I. Role of alpha-1 antitrypsin in human health and disease. J Intern Med.2014 Oct;276(4):311-35.

[4] Genetics Home Reference-NIH (https://ghr.nlm.nih.gov/condition/alpha-1-antitrypsindeficiency# statistics)

14 variants in the SERPINA1 gene associated with AATD. These 14 variants explain 95% of AATD cases[1] and are mainly found in European population, except for PI*S iiyama, which was described in the Asian population.[5] 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.[3] 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.[3] The remaining 12 genetic variants tested are reported with a very low frequency in the population.[3]

Considering that a given person can have a genetic result of zero, one or two copies of the variants detected, a total of 120 possible genotype combinations of these 14 variants can be reported by the AlphaID At Home Genetic Health Risk Service:

- 1 genetic result with 0 variants detected (wild-type homozygous),
- 14 genetic results with 1 variant detected (heterozygous), and
- 105 genetic results with 2 variants detected (rare homozygous or compound heterozygous).

In some rare circumstances, a "variant not determined" result could be reported, which means that the Service cannot determine if the user has any of the 14 tested variants in the SERPINA1 gene linked to AATD. This is an inconclusive genetic result. The presence of any other rare genetic variant in the DNA sequence can interfere with the genetic analysis, leading to the inability to determine the genetic result. In this case, the risk of developing lung and liver disease cannot be determined, and a different test/Service is recommended to the user (DNA sequencing of the SERPINA1 gene).

Depending on the specific variant combination detected, the AlphaID At Home Genetic Health Risk Service provides the individuals' genetic health risk for developing lung and/or liver disease linked to AATD. These variants can cause mild, severe, or very severe plasma deficiency and can cause no accumulation or mild or severe accumulation of protein in the liver. Normal AAT levels (80−120%) are defined by serum AAT levels above 20 µmol/L (measured by nephelometry).[3] It is considered that severe AATD is defined by serum AAT levels below the lung protective threshold of 35% of the mean expected value (50 mg/dl or 11 µmol/L measured by nephelometry, or 80 mg/dL measured by radial immunodiffusion).[2,3] Very severe AATD is defined by no active AAT or AAT levels below 1%. AAT levels for the most frequent and most studies studied genetic results are reported in Stoller et al. 2017[1] and provided in the table below.

[5] Seyama K. State of alpha1-antitrypsin deficiency in Japan. Respirology. 2001 Jun;6 Suppl:S35-8.

AAT Protein Variants	Serum AAT Levels		AAT Protein Reduction
	True Level Mean, µmol/L (5^{th}–95^{th} percentile)	Commercial Standard Median, mg/dL (5^{th}–95^{th} percentile)	
PI*M/PI*M	33 (20−53)	147 (102−254)	Normal-Mild
PI*M/PI*S	33 (18−52)	125 (86−218)	
PI*M/PI*Z	25.4 (15−42)	90 (62−151)	
PI*S/PI*S	28 (20−48)	95 (43−154)	
PI*S/PI*Z	16.5 (10−23)	62 (233−108)	Mild severe
PI*Z/PI*Z	5.3 (3.4−7)	≤29 (≤29−52)	Severe
Null-Null*	0	0	Very severe
*Null variants include PI*Q0 granite falls, PI*Q0 west, PI*Q0 bellingham, PI*Q0 mattawa and PI*Q0 clayton			

The risk categorization is based on the reported clinical cases (published references) for each genetic result. If any of the 14 variants tested is detected, one of the four following risk categories will be reported:

1) *Increased risk:* There is an increased risk of developing lung or liver disease linked to AATD compared to the general population. The chance of developing lung or liver disease linked to AATD is higher than that of the general population. Above 80% of people with this genetic result develop lung or liver disease during their lifetime.

2) *Slightly at Increased risk:* There is a slightly increased risk of developing lung or liver disease linked to AATD compared to the general population. The chance of developing lung or liver disease linked to AATD is slightly higher than that of the general population. 20−80% of people with this genetic result develop lung or liver disease during their lifetime.

3) *Not likely at increased risk:* There is average risk of developing lung or liver disease linked to AATD compared to the general population. The chance of developing lung or liver disease linked to AATD is similar to that of the general population. Below 20% of people with this genetic result develop lung or liver disease during their lifetime.

4) *Unknown risk:* The risk of developing lung or liver disease linked to AATD is not known due to the lack of reported clinical cases or inconclusive data. The chance of developing lung or liver disease linked to AATD is unknown. More clinical studies are needed to determine the risk level.

When No Variants are detected by this Service, the result will show '*Not Likely at Risk for AATD*'. It cannot rule out the possibility of having an extremely rare variant linked to AATD not tested by this Service. It is still possible to have a higher risk category of developing lung and/or liver disease linked to AATD.

These reported risk categories are based on the evidence in the scientific literature and are summarized below separately for lung disease and liver disease:

a. Lung disease risk categorization

The AAT protein is made in the liver, released into the bloodstream, and enters the lungs, where it inactivates neutrophil elastase, thereby protecting the lung tissue from protease mediated damage. As such, the plasma levels of this protein have widely been described to be directly related to the amount that is reaching the lungs, and consequently, with its lung protection capability. 2% to 3% of patients with COPD in the United States are estimated to have AATD.[2] Symptomatic obstructive lung disease in AATD usually presents in patients in their 30s and 40s. Considerable variability in the time of onset of symptoms has been described. Although severe symptoms are most often seen in current or previous cigarette smokers, some smokers and many nonsmokers develop no symptoms at all.[2,3,6,7]

The classic pulmonary presentation of AATD is a severe, early onset panacinar emphysema with a basilar predominance in adults. However, emphysema may also occur in a diffuse distribution or predominantly in the upper lobes.[2,3,6,7] In addition to emphysema, AATD is also characterized by chronic, progressive fatigue and other nonspecific respiratory symptoms.[3] Shortness of breath, medically known as dyspnea, is generally the prominent symptom, but chronic cough or wheezing may also occur, as early as age 18 years.[2,6] Pulmonary function testing show findings consistent with COPD; however, bronchodilator responsiveness may be seen and may be labelled as asthma.[7] The presence of episodic wheezing and dyspnea consistent with a diagnosis of asthma has been noted in AATD.[2] Recurring lung infections are also shown in subjects with AATD.[2] Bronchiectasis, with or without concomitant emphysema, is less common.[6,7] Although it is likely that AATD can promote the development of bronchial asthma and bronchiectasis, there is no reliable evidence as to whether AATD influences the frequency or gravity of these diseases.[3]

The reported lung disease risk category has been determined based on the clinical outcome which includes chronic obstructive pulmonary disease (COPD), emphysema, chronic bronchitis, and bronchiectasis of the reported cases for each genetic result. The following general criteria summarized in the table below has been followed for the assignment of a risk category for each genetic result. The "*Unknown risk*" category is assigned to genotypes with <3 reported clinical cases, as well those with ≥3 reported clinical cases but with a calculated risk confidence interval overlapping with the other two risk categories.

[6] Silverman EK, Sandhaus RA. Clinical practice. Alpha1-antitrypsin deficiency. N Engl J Med. 2009 Jun 25;360(26):2749-57. doi: 10.1056/NEJMcp0900449. Review. PubMed PMID: 19553648.

[7] Brode SK, Ling SC, Chapman KR. Alpha-1 antitrypsin deficiency: a commonly overlooked cause of lung disease. CMAJ. 2012 Sep 4;184(12):1365-71. doi: 10.1503/cmaj.111749.

General Criteria for Lung Disease Risk Categorization			
Number of reported clinical cases	**%Reported clinical cases with lung disease**	**95% CI**	**Reported lung disease risk category***
n<3	Any	Any	Unknown risk
n≥3	<20%	0−80%	Not Likely at increased risk
		0−100%	Unknown risk
	20-80%	0−80%	Not Likely at increased risk
		20−100%	Slightly increased risk
		0−100%	Unknown risk
	>80%	0−100%	Unknown risk
		20−100%	Slightly increased risk
		>80%	Increased risk
NOTE: Exceptions to this general classification are: • All carriers with at least one PI*M allele (except PI*M/PI*Z ever-smokers) will be reported as '*Not likely at increased risk*' • PI*Z/PI*Null and PI*Null/PI*Null combinations will be assigned as '*Increased risk'*. Null variants: PI*Q0 granite falls, PI*Q0 west, PI*Q0 bellingham, PI*Q0 mattawa and PI*Q0 clayton * The reported risk category may be updated if there is enough data to provide confidence intervals that do not overlap between two consecutive risk categories			

The lung disease risk categorization along with the 95% confidence intervals (CIs) of the risk estimates for the 119 genetic results with one or two variants detected are presented in the table below based on the number of reported clinical cases extracted from the referenced scientific literature and meta-analyses that analyze clinical cases with and without lung disease. Pending new clinical cases being published, the risk category is to be updated if there is enough data to provide confidence intervals that do not overlap between two consecutive risk categories. Since the intended population of the Service is ≥18 years of age, only cases (≥18 years old) have been included in the analysis to estimate the risk, when the age date was described in the study. The exceptions to the general criteria for liver disease risk categorization are shaded in grey in the table below.

#	**Lung Disease Risk Categorization**					
	Genetic Results	Reported Clinical Cases with Lung Disease	Reported Clinical Cases without Lung Disease	%Reported Clinical Cases with Lung Disease[1]	95% CI[1]	**Reported Lung Disease Risk Category**
Most frequent[2] genetic results (#1− #6)						
1	**PI*M/ PI*M**	N/A	N/A	N/A	N/A	**Not Likely at increased risk**
	None of the 14 allelic variants interrogated by the A1AT Genotyping test are detected in the SERPINA1 gene, but other variants could be present					
	PI*M/					

2	**PI*Z**					
	Never-smokers	155	1967	7.3	6.4 − 8.3	**Not Likely at increased risk**
		Dahl *et al.,* 2002: 86 individuals with lung disease and 364 individuals without lung disease; Seersholm *et al.,* 2000: 47 individuals with lung disease and 1504 without lung disease; Klayton *et al.,* 1975: 13 individuals with lung disease and 14 without lung disease; Matzen *et al*., 1977: 2 individuals with lung disease and 10 without lung disease; Gulsvik *et al.,* 1979: 7 individuals with lung disease and 44 without lung disease; Chang-Yeung *et al.,* 1978: 0 individuals with lung disease and 31 without lung disease.				
	Ever-smokers	113	142	44.3	39.3 − 49.5	**Slightly increased risk**
		Sørheim *et al.,* 2010: 43 individuals with lung disease and 72 without lung disease Molloy *et al.,* 2014: 64 individuals with lung disease and 78 without lung disease				
3	**PI*M/ PI*S**	101	590	14.6	12.5 − 17.0	**Not Likely at increased risk**
		Dahl *et al.,* 2002: 73 individuals with lung disease and 383 without lung disease Gulsvik *et al.,* 1979: 14 individuals with lung disease and 46 without lung disease Chang-Yeung *et al.,* 1978: 7 individuals with lung disease and 82 without lung disease Matzen *et al.,* 1977: 6 individuals with lung disease and 54 without lung disease Ostrow *et al*., 1978: 1 individual with lung disease and 25 without lung disease				
4	**PI*S/ PI*S**	4	42	8.7	4.0 − 18.0	**Not Likely at increased risk**
		Sandford *et al.,* 1999 2 individuals with lung disease and 0 without lung disease; Gulsvik *et al.,* 1979 1 individual with lung disease and 0 without lung disease; Lieberman *et al.,* 1986 1 individual with lung disease and 2 without lung disease; Arnaud *et al.,* 1977 23 Individuals without lung disease; Dahl *et al.,* 2002 0 individuals with lung disease and 12 without lung disease; Fagerhol *et al.,* 1969 0 individuals with lung disease and 3 s without lung disease; Kueppers *et al.,* 1977 0 individuals with lung disease and 1 without lung disease; Lochon *et al.,* 1978 0 individuals with lung disease and 1 without lung disease				
5	**PI*S/ PI*Z**	269	228	54.1	50.1 − 57.8	**Slightly increased risk**
		McElvaney *et al.,* 2020: 269 individuals with lung disease and 181 without lung disease Bartmann *et al.,* 1985: 18 individuals with lung disease and 1 without lung disease Dahl *et al.,* 2002: 4 individuals with lung disease and 10 without lung disease Lieberman *et al.,* 1986: 2 individuals with lung disease and 5 without lung disease Abboud *et al.,* 1979: 1 individual with lung disease; Fagerhol *et al.,* 1969: 1 individual with lung disease and 1 individual without lung disease; Gulsvik *et al.,* 1979: 1 individual with lung disease and 3 individuals without lung disease				
6	**PI*Z /PI*Z**	2775	630	81.5	80.4 − 82.6	**Increased risk**
		McElvaney *et al.,* 2020: 2775 individuals with lung disease and 630 without lung disease				
Less common genetic results (#7–#120)						
7	**PI*S/ PI*I**	0	2	0.0	0.0 − 57.5	**Unknown risk**
	Seri *et al.,* 1992 1 individual without lung disease; Huang *et al.,* 2017 1 individual without lung disease					
8	**PI*F/ PI*S**	0	1	0.0	0.0 − 73.0	**Unknown risk**
	Cook *et al.,* 1996 1 individual without lung disease					

9	**PI*I/ PI*I**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
10	**PI*F/ PI*I**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
11	**PI*F/ PI*F**	1	0	100.0	27.0 − 100.0	**Unknown risk**
	Sinden *et al.,* 2014: 1 individual with lung disease					
12	**PI*Z/ PI*I**	4	0	100.0	59.6 − 95.5	**Unknown risk**
	Ferrarotti *et al.,* 2005: 2 individuals with lung disease Baur & Bencze 1987: 1 individual with lung disease Corda *et al.,* 2006: 1 individual with lung disease					
13	**PI*F/ PI*Z**	13	2	86.7	27.0 − 100.0	**Slightly at increased risk**
	Sinden *et al.,* 2014: 5 individuals with lung disease and 1 without lung disease; Cockcroft *et al.,* 1981: 3 individuals with lung disease; Cook *et al.,* 1996: 2 individuals with lung disease; Beckman *et al.,* 1984: 1 individual with lung disease; Franciosi *et al.,* 2019: 1 individual with lung disease; Kelly *et al.,* 1989: 1 individual with lung disease					
14	**PI*S/ PI*M procida**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
15	**PI*S/ PI*M malton**	1	0	100	27.0 − 100.0	**Unknown risk**
	Figueira Gonçalves *et al.,* 2017: 1 individual with lung disease					
16	**PI*S/ PI*iiyama**	0	0	0	N/A	**Unknown risk**
	Clinical cases not reported					
17	**PI*S/ PI*P lowell**	1	1	50.0	12.1 − 87.9	**Unknown risk**
	Jardí *et al.,* 1997: 1 individual without lung disease; Balbi *et al.,* 2019 :1 individual with lung disease					
18	**PI*S/ PI*M heerlen**	1	1	50.0	12.1 − 87.9	**Unknown risk**
	Kramps et al., 1981: 1 individual with lung disease and 1 without lung disease					
19	**PI*I/ PI*M procida**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
20	**PI*I/ PI*M malton**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
21	**PI*I/ PI*iiyama**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
22	**PI*M/ PI*P lowell**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
23	**PI*I/ PI*M heerlen**	0	0	0.0	N/A	**Unknown risk**

	Clinical cases not reported					
24	**PI*F/ PI*M procida**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
25	**PI*F/ PI*M malton**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
26	**PI*F/ PI*iiyama**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
27	**PI*F/ PI*P lowell**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
28	**PI*F/ PI*M heerlen**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
29	**PI*S/ PI*Q0 granite falls**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
30	**PI*S/ PI*Q0 west**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
31	**PI*S/ PI*Q0 bellingham**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
32	**PI*S/ PI*Q0 mattawa**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
33	**PI*S/ PI*Q0 clayton**	1	1	50.0	12.1 − 87.9	**Unknown risk**
	Rosenbaum *et al.,* 2017: 1 individual with lung disease and 1 without lung disease					
34	**PI*I/ PI*Q0 granite falls**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
35	**PI*I/ PI*Q0 west**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
36	**PI*I/ PI*Q0 bellingham**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
37	**PI*I/ PI*Q0 mattawa**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
38	**PI*I/ PI*Q0 clayton**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
39	**PI*F/ PI*Q0 granite falls**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					

40	**PI*F/ PI*Q0 west**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
41	**PI*F/ PI*Q0 bellingham**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
42	**PI*F/ PI*Q0 mattawa**	0	0	0.0	N/A	**Unknown risk**
	Cases not reported					
43	**PI*F/ PI*Q0 clayton**	1	0	100.0	27.0−100.0	**Unknown risk**
	Ringenbach *et al.,* 2011: 1 individual with lung disease					
44	**PI*Z/ PI*M procida**	2	0	100.0	42.5−100.0	**Unknown risk**
	Ferrarotti *et al.,* 2005: 1 individual with lung disease Lonardo *et al.,* 2002: 1 individual with lung disease					
45	**PI*Z/ PI*M malton**	13	0	100.0	82.5 − 100.0	**Increased risk**
	Sproule *et al.,* 1983: 4 individuals with lung disease; Ferrarotti *et al.,* 2005: 3 individuals with lung disease; Joly *et al.,* 2015: 2 individuals with lung disease; Allen *et al.,* 1986: 1 individual with lung disease; Corda *et al.,* 2006: 1 individual with lung disease; Suh-Lailam *et al.,* 2014: 1 individual with lung disease; Figueira Gonçalves *et al.,* 2017: 1 individual with lung disease					
46	**PI*Z/ PI*iiyama**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
47	**PI*Z/ PI*P lowell**	7	0	100.0	72.1 − 100.0	**Slightly at increased risk**
	Bamforth & Kalsheker 1988: 4 individuals with lung disease; Esteves-Brandão *et al.,* 2019: 1 individual with lung disease; Holmes *et al.,* 1990: 1 individual with lung disease; Ferrarotti *et al.,* 2005: 1 with lung disease					
48	**PI*Z/ PI*M heerlen**	2	0	100.0	42.5 − 100.0	**Unknown risk**
	Klaassen *et al*., 2001: 2 individuals with lung disease					
49	**PI*M procida/ PI*M procida**	2	0	100.0	42.5 − 100.0	**Unknown risk**
	Ferrarotti *et al.,* 2005: 2 individuals with lung disease					
50	**PI*M malton/ PI*M procida**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
51	**PI*M procida/ PI*iiyama**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
52	**PI*M procida/ PI*P lowell**	0	0	0.0	N/A	**Unknown risk**
	Cases not reported					
53	**PI*M procida/ PI*M heerlen**	0	0	0.0	N/A	**Unknown risk**
	Cases not reported					
54	**PI*M malton/ PI*M malton**	19	5	79.2	63.0 − 89.5	**Slightly at increased risk**

	Orrù *et al.,* 2005: 7 individuals with lung disease and 3 without lung disease; Ferrarotti *et al.,* 2005: 5 individuals with lung disease; Reid *et al.,* 1987: 2 individuals with lung disease and 1 without lung disease; Figueira Gonçalves *et al.,* 2017: 1 individual with lung disease and 1 without lung disease; Curiel *et al.,* 1989: 1 individual with lung disease; Balduyck *et al*., 2014: 1 individual with lung disease; Franciosi *et al.,* 2019: 1 individual with lung disease; Joly *et al.,* 2015: 1 individual with lung disease					
55	**PI*M malton/ PI*iiyama**	0	0	0.0	N/A	**Unknown risk**
	Cases not reported					
56	**PI*M malton/ PI*P lowell**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
57	**PI*M malton/ PI*M heerlen**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
58	**PI*iiyama/ PI*iiyama**	3	0	100.0	52.6−100.0	**Slightly at increased risk**
	Takabe *et al.,* 1992: 1 individual with lung disease; Lomas *et al.,* 1993: 1 individual with lung disease; Yuasa *et al.,* 1993: 1 individual with lung disease					
59	**PI*P lowell/ PI*iiyama**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
60	**PI*M heerlen/ PI*S iiyama**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
61	**PI*P lowell/ PI*P lowell**	1	0	100.0	27.0 − 100.0	**Unknown risk**
	Faber *et al.,* 1989: 1 individual with lung disease					
62	**PI*P lowell/ PI*M heerlen**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
63	**PI*M heerlen/ PI*M heerlen**	5	0	100.0	64.9 − 100.0	**Slightly at increased risk**
	Fregonese *et al.,* 2008: 4 individuals with lung disease; Kramps *et al.,* 1981: 1 individual with lung disease					
64	**PI*M procida/ PI*Q0 granite falls**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
65	**PI*M procida/ PI*Q0 west**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
66	**PI*I/ PI*Q0 bellingham**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
67	PI*M procida/ PI*Q0 mattawa	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
68	**PI*M procida/ PI*Q0 clayton**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
69	**PI*M malton/**	0	0	0.0	N/A	**Unknown risk**

	PI*Q0 granite falls					
	Clinical cases not reported					
70	**PI*M malton/ PI*Q0 west**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
71	**PI*M malton/ PI*Q0 bellingham**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
72	**PI*M malton/ PI*Q0 mattawa**	1	1	50.0	12.1 − 87.9	**Unknown risk**
	Lara *et al.,* 2013: 1 individual with lung disease; Balduyck *et al.,* 2014: 1 individual without lung disease					
73	**PI*M malton/ PI*Q0 clayton**	1	0	100.0	27.0 – 100.0	**Unknown risk**
	Rodríguez-Frias *et al.,* 2011: 1 individual with lung disease					
74	**PI*iiyama/ PI*Q0 granite falls**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
75	**PI*iiyama/ PI*Q0 west**	0	0	0.0	N/A	**Unknown risk**
	Cases not reported					
76	**PI*iiyama/ PI*Q0 bellingham**	0	0	0.0	N/A	**Unknown risk**
	Cases not reported					
77	**PI*iiyama/ PI*Q0 mattawa**	0	0	0.0	N/A	**Unknown risk**
	Cases not reported					
78	**PI*iiyama/ PI*Q0 clayton**	2	0	100.0	42.5 − 100.0	**Unknown risk**
	Ko *et al.,* 2011: 1 individual with lung disease; Miyahara *et al.,* 2001: 1 individual with lung disease					
79	**PI*P lowell/ PI*Q0 granite falls**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
80	**PI*M heerlen/ PI*Q0 granite falls**	1	0	100.0	27.0 − 100.0	**Unknown risk**
	Poller *et al.,* 1999: 1 individual with lung disease					
81	**PI*P lowell/ PI*Q0 west**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
82	**PI*M heerlen/ PI*Q0 west**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
83	**PI*P lowell/ PI*Q0 bellingham**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
84	**PI*M heerlen/ PI*Q0 bellingham**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
85	**PI*P lowell/ PI*Q0 mattawa**	0	0	0.0	N/A	**Unknown risk**

	Clinical cases not reported					
86	**PI*P lowell/ PI*Q0 clayton**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
87	**PI*M heerlen/ PI*Q0 mattawa**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
88	**PI*M heerlen/ PI*Q0 clayton**	1	0	100.0	27.0 − 100.0	**Unknown risk**
	Brantly *et al.,* 1997 1 individual with lung disease					
	Assignment of **'Not likely at Increased risk'** to all carriers with **at least one PI*M allele** (Exceptions to the general criteria for lung disease risk categorization are shaded)					
89	**PI*M/ PI*I**	4	24	14.3	6.6 – 28.3	**Not Likely at Increased risk**
	Zhumagaliyeva *et al.,* 2017: 2 individuals with lung disease; Duk *et al.,* 2016: 2 individuals with lung disease and 2 without clinical data; Arnaud *et al.,* 1978: 23 individuals without lung disease and 20 without clinical data Baur & Bencze 1987: 1 individual without lung disease					
91	**PI*M/ PI*F**	17	87	16.3	11.2 − 23.1	**Not Likely at Increased risk**
	Beckman *et al.,* 1984: 5 individuals without lung disease and 7 with lung disease; Duk *et al.,* 2016: 5 individuals with lung disease; Kwok *et al.,* 2004: 5 individuals with lung disease; Tete-Benissan & Gbeassor 2011: 74 individuals without lung disease; Cockcroft *et al.,* 1981: 3 individuals without lung disease; Cook *et al.,* 1996: 1 individual without lung disease					
94	**PI*M/ PI*M malton**	3	47	6.0	2.4 − 14.1	**Not Likely at Increased risk**
	Corda *et al.,* 2006: 2 individuals with lung disease and 4 without lung disease Figueira Gonçalves *et al.,* 2017: 1 individual with lung disease and 11 without lung disease; Sproule *et al.,* 1983: 14 individuals without lung disease; Orrù *et al.,* 2005: 10 individuals without lung disease; Allen *et al.,* 1986: 6 individuals without lung disease; Joly *et al.,* 2015: 1 individual without lung disease; Canva *et al.,* 2001: 1 individual without lung disease					
90	**PI*M/ PI*M heerlen**	3	8	27.3	11.5 − 52.1	**Not Likely at Increased risk**
	Kalsheker *et al.,* 1992: 2 individuals with lung disease and 1 without lung disease; Rodriguez *et al.,* 2002: 1 individual with lung disease; Kramps *et al.,* 1981: 4 individuals without lung disease; Poller *et al.,* 1999: 3 individuals without lung disease					
92	**PI*M/ PI*M procida**	0	2	0	0.0 − 57.5	**Not Likely at Increased risk**
	Montealegre *et al.,* 2006: 2 individuals without lung disease					
93	**PI*M/ PI*S iiyama**	0	4	0.0	0.0 − 40.4	**Not Likely at Increased risk**
	Takabe *et al.,* 1992: 4 individuals without lung disease					
95	**PI*M/ PI*P lowell**	2	16	11.1	3.7 − 28.6	**Not Likely at Increased risk**
	Seri *et al.,* 1992: 1 individual with lung disease; Denden *et al.,* 2009: 1 individual with lung disease; Jardí *et al.,* 1997: 12 individuals without lung disease; Cook *et al.,* 1995: 3 individuals without lung disease; Corda *et al.,* 2011: 1 individual without lung disease					
96	**PI*M/ PI*Q0 granite falls**	0	3	0.0	0.0 − 47.3	**Not Likely at Increased risk**
	Poller *et al.,* 1999: 3 individuals without lung disease					

97	**PI*M/ PI*Q0 west**	1	0	100	27.0 − 100.0	**Not Likely at Increased risk**
	Laubach *et al.,* 1993: 1 individual with lung disease					
98	**PI*M/ PI*Q0 bellingham**	0	3	0.0	0.0 − 47.3	**Not Likely at Increased risk**
	Cook *et al.,* 1994: 3 individuals without lung disease					
99	**PI*M/ PI*Q0 mattawa**	1	0	100	27.0 − 100.0	**Not Likely at Increased risk**
	Cox & Levison 1988: 2 individuals with lung disease and 11 without lung disease Lara *et al.,* 2013: 1 individual with lung disease					
100	**PI*M/ PI*Q0 clayton**	0	1	0.0	0.0 − 73.0	**Not Likely at Increased risk**
	Rodriguez-Frias *et al.,* 2011:1 individual without lung disease					
	Assignment of **'Increased risk'** category to all carriers with **PI*Z/PI*Null or PI*Null/PI*Null** (Exceptions to the general criteria for lung disease risk categorization are shaded)					
101	**PI*Z/ PI*Q0 granite falls**	3	0	100.0	52.6 − 100.0	**Increased risk**
	Nukiwa *et al.,* 1987: 1 individual with lung disease Balduyck *et al.,* 2014: 1 individual with lung disease Pavičić *et al.,* 2019: 1 individual with lung disease					
102	**PI*Q0 mattawa/ PI*Q0 mattawa**	3	0	100.0	52.6 − 100.0	**Increased risk**
	Cox & Levinson 1988 3 individuals with lung disease					
103	**PI*Q0 granite falls/ PI*Q0 granite falls**	4	0	100.0	59.6 − 100.0	**Increased risk**
	Hubbard *et al.,* 1989: 2 individuals with lung disease Balbi *et al.,* 2019: 1 individual with lung disease Holmes *et al.,* 1989: 1 individual with lung disease.					
104	**PI*Q0 bellingham/ PI*Q0 bellingham**	6	0	100.0	68.9 − 100.0	**Increased risk**
	Fregonese *et al.,* 2008 3 individuals with lung disease. Satoh *et al.,* 1988 1 individual with lung disease Cook *et al.,* 1994 1 individual with lung disease Garver *et al*., 1986 1 individual with lung disease					
105	**PI*Z/ PI*Q0 west**	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					
106	**PI*Z/ PI*Q0 bellingham**	1	0	100.0	27.0 − 100.0	**Increased risk**
	Poller *et al.,* 1990: 1 individual with lung disease					
107	**PI*Z/ PI*Q0 mattawa**	1	0	100.0	27.0 − 100.0	**Increased risk**
	Balduyck *et al.,* 2014: 1 individual with lung disease					
108	**PI*Z/ PI*Q0 clayton**	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					
109	**PI*Q0 granite falls/ PI*Q0 west**	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					

110	**PI*Q0 bellingham/ PI*Q0 granite falls**	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					
111	PI*Q0 granite falls/ PI*Q0 mattawa	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					
112	**PI*Q0 clayton/ PI*Q0 granite falls**	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					
113	**PI*Q0 west/ PI*Q0 west**	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					
114	**PI*Q0 bellingham/ PI*Q0 west**	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					
115	**PI*Q0 mattawa/ PI*Q0 west**	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					
116	**PI*Q0 clayton/ PI*Q0 west**	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					
117	**PI*Q0 bellingham/ PI*Q0 mattawa**	2	0	100.0	42.5 – 100.0	**Increased risk**
	Curiel *et al.,* 1989 2 individuals with lung disease					
118	**PI*Q0 bellingham/ PI*Q0 clayton**	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					
119	**PI*Q0 clayton/ PI*Q0 mattawa**	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					
120	**PI*Q0 clayton/ PI*Q0 clayton**	0	0	0.0	N/A	**Increased risk**
	Clinical cases not reported					

[1] The percentage (%) and 95% confidence interval (CI95%) of the reported clinical cases have been calculated following the score method described by Altman *et al.,* 2000.

[2] The different combinations of the PI*S and PI*Z alleles (PI*M/PI*S, PI*M/PI*Z, PI*S/PI*Z, PI*S/PI*S and PI*Z/PI*Z) cover more than 95% of variant alleles identified in the SERPINA1 gene worldwide.

Among the most frequent genetic combinations, the PI*M/PI*S and PI*S/PI*S genetic results do not appear to be associated with an increased risk for lung disease.[1-3] Individuals (especially never-smokers) with PI*M/PI*Z are not considered to be at risk for lung disease.[1] However, a subset of individuals with the PI*M/PI*Z genotype may experience accelerated lung destruction, especially if they are smokers.[2,8] Smokers with this genetic result have a slightly increased risk of developing lung disease linked to AATD. PI*M/PI*Z heterozygotes have a clear predisposition to chronic obstructive pulmonary disease (COPD), at least among smokers.[8] All the

[8] Strnad P, McElvaney NG, Lomas DA. Alpha1-Antitrypsin Deficiency. N Engl J Med. 2020 Apr9; 382(15):1443-1455.

AlphaID At Home Genetic Health Risk Service reports describe smoking as a non-genetic risk factor that can increase the risk of developing lung disease. Except for the PI*M PI*/Z genotype, a differential classification for ever-smokers (Slightly at increased risk) and non-smokers (Not likely at increased risk) has not been possible for other genotypes because information about the smoking history of every specific subject included in the studies was not available.

There is a 20% of individuals with PI*S/PI*Z with AAT levels below the lung protective threshold (<11 μM/L), who are at risk for AATD related lung diseases.[1] Studies demonstrated that the odds ratio for COPD in individuals with this genetic result, compared with normal PI*M/PI*M individuals, was significantly increased at 3.3 (95% CI: 1.2–8.6 %), showing that the PI*S/PI*Z genotype is a significant risk factor for COPD.[9] Although individuals with this genetic result who do not smoke are considered at slightly at increased risk of developing lung disease, existing scientific evidence confirms that the effect of smoking in this specific variant combination is profound and will produce reduction in pulmonary function. It is generally accepted that individuals with PI*S/PI*Z and serum AAT levels below the protective threshold value, have an increased risk of developing lung disease, especially if they smoke.[10] However, available data from ever-smokers indicate that smokers with PI*S/PI*Z may be also assigned to the '*Slightly at increased ris*k' category, the same as the general risk category assigned for this genotype. Hutchinson *et al.,* 1983 described that eight PI*S/PI*Z index cases smokers developed emphysema out of the 12 total index cases smokers (66.7% with 95%CI: 43.1−84.1%).[10] Thus, even considering only smoker and index cases, there is no evidence supporting an "*Increased risk*" classification (>80% reported cases with lung disease) for this subgroup of PI*S/PI*Z individuals.

The PI*Z variant in homozygosis is associated with an increased risk of lung disease.[2,3] Greater than 80% of people with this genetic result develop lung disease during their lifetime.[1]

Exceptions to the criteria for lung disease risk categorization are applied to the following genetic results:

(i) carriers with at least one PI*M (normal) allele due to the limited information available up to date. Based on the clinical data from the carriers of the most common variants, as well as on the expected protein levels above the protective threshold for the subjects presenting at least one PI*M allele, it is more adequate to report all the carriers except for ever-smokers PI*M/PI*Z as "*Not likely at increased risk*" (refer to #88−99 in the 'Lung Disease Risk Categorization' table). Consistent with this risk categorization, for individuals who possess only one deficiency allele, the risk of developing any clinically significant symptoms is

[9] Dahl M, Hersh CP, Ly NP, Berkey CS, Silverman EK, Nordestgaard BG. The protease inhibitor PI*S allele and COPD: a meta-analysis. Eur Respir J. 2005 Jul;26(1):67-76.

[10] Hutchison DC, Tobin MJ, Cook PJ. Alpha 1 antitrypsin deficiency: clinical and physiological features in heterozygotes of Pi type SZ. A survey by the British Thoracic Association. Br J Dis Chest. 1983 Jan;77(1):28-34. doi: 10.1016/0007-0971(83)90003-7. PMID: 6602622

either slight or negligible.[11] Data from carriers with enough clinical cases (refer to #88−94) also support this "*Not likely at increased risk*" classification.

(ii) carriers with the PI*Z/PI*Null and PI*Null/PI*Null combinations that cause severe and very severe plasma deficiency, respectively. The AAT protein levels for the PI*Z/PI*Null and PI*Null/PI*Null individuals are expected to be below the protective threshold. Both the PI*Z/PI*Null and PI*Null/PI*Null combinations are assigned as "*Increased risk*". Data from combinations with enough clinical cases also support this "*Increased risk*" classification because 100% individuals with these genetic results develop lung disease, although the number of cases is not high enough (refer to #100−103 in the 'Lung Disease Risk Categorization' table).

b. Liver disease risk categorization

In addition to pulmonary complications, AATD is also a risk factor for other serious illnesses, most commonly for liver disease. Liver disease associated with AATD is mainly caused by an impaired process of releasing the AAT protein into the bloodstream, which gives rise to its accumulation in the liver. The accumulation of inclusions of the mutant AAT protein triggers cycles of hepatocyte injury, cell death and compensatory proliferation.[2,3]

The severity of the disease correlates with the magnitude of accumulation of the mutant AAT protein. It is known that the prevalence of chronic liver disease in AATD increases with age and that chronic liver disease may be asymptomatic for years. Liver disease linked to AATD may present clinically in a variety of ways: liver enzyme elevations, jaundice, hepatic fibrosis, chronic hepatitis, liver failure or liver cirrhosis, and in a low percentage of subject's hepatocellular carcinoma.[2,3]

The PI*Z, PI*M malton and PI*S iiyama variants (i.e., severe accumulation alleles) cause severe accumulation of the mutant AAT protein in the liver whereas the 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 variants (i.e., non-accumulation variants) are not associated with the accumulation of the mutant AAT protein in the liver. The mild accumulation alleles are PI*I and PI*S.

The PI*Z allele encodes an AAT protein that is able to bind to other AAT proteins, leading to AAT polymers formation, which form inclusion bodies inside the liver and are not secreted into the circulation.[2,3] Clinical studies with these affected individuals have consistently associated this variant with a slightly increased risk of developing liver disease.[2,3] Similarly, the PI*M malton variant is known to be significantly associated with hepatic disease due to intracellular accumulation of the mutant AAT protein.[13] PI*M malton homozygous individuals have also shown a tendency to form

[11] Bornhorst JA, Greene DN, Ashwood ER, Grenache DG. a1-Antitrypsin phenotypes and associated serum protein concentrations in a large clinical population. Chest. 2013 Apr;143(4):1000-1008. doi: 10.1378/chest.12-0564. PubMed PMID: 23632999

polymeric intrahepatic inclusions[12] and available scientific data confirm association with liver disease in these individuals.[2,3]

The liver disease risk category reported by the AlphaID At Home Genetic Health Risk Service was determined based on the probability of each tested variant to be accumulated in the liver and clinical outcome of the reported cases for each genetic result. The following general criteria summarized in the table were followed for the assignment of a liver disease risk category for each genetic result. Pending new clinical cases being published, the risk category may be updated if there is enough data to provide confidence intervals that do not overlap between two consecutive risk categories.

Number of reported clinical cases	%Reported clinical cases with liver disease	95% CI	Reported liver disease risk category*
n<3	Any	Any	Unknown risk
n≥3	<20%	0−80%	Not Likely at Increased risk
		0−100%	Unknown risk
	20−80%	0−80%	Not Likely at Increased risk
		20−100%	Slightly increased risk
		0−100%	Unknown risk
	>80%	0−100%	Unknown risk
		20−100%	Slightly increased risk
		>80%	Increased risk

NOTE: Exceptions to this general liver disease risk classification are:

- Individuals with at least one PI*Z or PI*M malton severe accumulation allele and their combinations will be reported as "*Slightly Increased risk"*
- All the combinations including two non-accumulation alleles will be reported as "*Not likely at Increased risk*". 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

* The reported risk category may be updated if there is enough published data to provide confidence intervals that do not overlap between two consecutive risk categories

The liver disease risk categorization for the 119 genetic results with one or two variants detected is presented in the table below along with the 95% CIs of the risk estimates based on the number of reported clinical cases with and without liver disease in the referenced scientific literature. Considering that the intended population is ≥18 years old and the phenotype of the liver disease in adults is different from that in children, all pediatric cases (<18 years old) have been removed from the analysis performed to estimate the risk of liver disease when the patient age was included in the study.

[12] Rodriguez-Frias F, Miravitlles M, Vidal R, Camos S, Jardi R. Rare alpha-1-antitrypsin variants: are they really so rare? Ther Adv Respir Dis. 2012 Apr;6(2):79-85. doi: 10.1177/1753465811434320. PubMed PMID: 22291048.

#	Liver Disease Risk Categorization					
	Genetic Results	Reported Clinical Cases with Liver Disease	Reported Clinical Cases without Liver Disease	%Reported Clinical Cases with Liver Disease[1]	95% CI[1]	**Reported Liver Disease Risk Category**
Most frequent genetic[2] results (#1–#6)						
1	**PI*M/ PI*M**	N/A	N/A	N/A	N/A	**Not Likely at increased risk**
	None of the 14 allelic variants interrogated by the A1AT Genotyping test are detected in the SERPINA1 gene, but other variants could be present					
2	**PI*M/ PI*S**	122	1124	9.8	8.5 − 11.3	**Not likely at increased risk**
	Eigenbrodt *et al.,* 1997: 56 individuals with liver disease and 37 individuals without liver disease; Graziadei *et al*., 1998: 41 individuals with liver disease and 670 without liver disease; Arnaud *et al*., 1977: 185 individuals without liver disease; Bell *et al.,* 1990: 13 individuals with liver disease and 116 without liver disease; Carlson *et al.,* 1981: 12 individuals with liver disease and 116 without liver disease					
3	**PI*M/ PI*Z**	431	948	31.3	29.2 − 33.3	**Slightly at increased risk**
	Propst *et al.,* 1992: 114 individuals with liver disease and 14 without liver disease; Strnad *et al.,* 2019: 90 individuals with liver disease and 42 without liver disease; Schaefer et al., 2018: 52 individuals with liver disease and 7 without liver disease; Eigenbrodt *et al.,* 1997: 50 individuals with liver disease and 25 without liver disease; Graziadei *et al*., 1998: 49 individuals with liver disease and 292 without liver disease Blenkinsopp & Haffenden 1977: 15 individuals with liver disease and 4 without liver disease; Arnaud *et al.,* 1977: 43 individuals without liver disease					
4	**PI*S/ PI*S**	3	31	8.8	3.6 − 20.1	**Not likely at increased risk**
	Strnad *et al.,* 2019: 3 individuals with liver disease and 2 individuals without liver; Arnaud *et al.,* 1977: 23 individuals without liver disease; Carlson *et al.,* 1981: 4 individuals without liver disease; Eigenbrodt *et al.,* 1997: 2 individuals without liver disease					
5	**PI*S/ PI*Z**	139	359	27.9	24.7 − 31.3	**Slightly at increased risk**
	McElvaney *et al.,* 2020: 113 individuals with liver disease and 337 without liver disease; Strnad *et al.,* 2019: 8 individuals, 7 with liver disease and 1 without liver disease; Ferrarotti *et al.,* 2005: 4 individuals with liver disease and 17 without liver disease; Eigenbrodt *et al.,* 1997: 3 individuals with liver disease; Graziadei *et al.,* 1998: 2 individuals with liver disease; Propst *et al.,* 1992: 2 individuals with liver disease					
6	**PI*Z/ PI*Z**	1199	3238	27	25.9 − 28.1	**Slightly at increased risk**
	McElvaney *et al.,* 2020: 868 individuals with liver disease and 2537 individuals without; Hamesch *et al.,* 2019:197 individuals with liver disease and 357 individuals without liver disease; Schneider *et al.,* 2020: 77 individuals with liver disease and 232 individuals without liver disease; Graziadei *et al.,* 1998: 14 individuals with liver disease; Ferrarotti *et al.,* 2005: 13 individuals with liver disease and 83 without liver disease; Elzouki & Eriksson 1996: 13 individuals with liver disease and 18 individuals without liver disease; Eriksson *et al.,* 1986: 7 individuals with liver disease and 9 individuals without liver disease; Propst *et al.,* 1992: 7 individuals with liver disease and 2 individuals without liver disease; Bell *et al.,* 1990; 3 individuals with liver disease					
Less common genetic results (#7–#120)						
(i) Non-accumulation allele[3] combinations						
7	**PI*I/ PI*M**	0	24	0.0	0.0− 10.1	**Not likely at increased risk**
	Arnaud *et al.,* 1978: 23 individuals without liver disease; Baur & Bencze 1987: 1 individual without liver disease					

8	**PI*M/ PI*M procida**	1	3	25	5.8 – 64.4	**Not likely at increased risk**
	Ferrarotti *et al*., 2005: 3 individuals without liver disease; Balduyck *et al*., 2014:1 individual with cirrhosis					
9	**PI*M/ PI*Q0 granite falls**	0	0	N/A	N/A	**Not likely at increased risk**
	Clinical cases not reported					
10	**PI*M/ PI*Q0 west**	0	0	N/A	N/A	**Not likely at increased risk**
	Clinical cases not reported					
11	**PI*M/ PI*Q0 bellingham**	0	0	N/A	N/A	**Not likely at increased risk**
	Clinical cases not reported					
12	**PI*M/ PI*F**	0	78	0	0.0 – 3.4	**Not likely at increased risk**
	Kelly *et al.,* 1989: 4 individuals without liver disease; Tete-Benissan & Gbeassor 2011: 74 individuals without liver disease					
13	**PI*M/ PI*P lowell**	0	1	0.0	0.0 – 73.0	**Not likely at increased risk**
	Corda *et al.,* 2011: 1 individual without liver disease					
14	**PI*M/ PI*Q0 mattawa**	0	14	0.0	0.0 – 16.2	**Not likely at increased risk**
	Cox & Levison 1988: 13 individuals without liver disease; Lara *et al.,* 2013: 1 individual without liver disease					
15	**PI*M/ PI*Q0 clayton**	0	0	N/A	N/A	**Not likely at increased risk**
	Clinical cases not reported					
16	**PI*M/ PI*M heerlen**	1	1	50	12.1 – 87.9	**Not likely at increased risk**
	Balduyck *et al.,* 2014: 1 individual with liver disease (cholestasis); Ferrarotti *et al.,* 2005: 1 individual without liver disease					
17	**PI*Q0 bellingham/ PI*Q0 bellingham**	0	2	0.0	0.0 – 57.5	**Not likely at increased risk**
	Cook *et al.,* 1994: 1 individual without liver disease; Garver *et al.,* 1986: 1 individual without liver disease					
18	**PI*Q0 granite falls/ PI*Q0 granite falls**	0	0	N/A	N/A	**Not likely at increased risk**
	Clinical cases not reported					
19	**PI*M heerlen/ PI*M heerlen**	0	1	0.0	0.0 – 73.0	**Not likely at increased risk**
	Kramps *et al.,* 1981: 1 individual without liver disease					
20	**PI*P lowell/ PI*P lowell**	0	0	N/A	N/A	**Not likely at increased risk**
	Clinical cases not reported					
21	**PI*Q0 mattawa/ PI*Q0 mattawa**	0	2	0.0	0.0 – 57.2	**Not likely at increased risk**
	Cox & Levinson 1988: 2 individuals without liver disease					
22	**PI*M heerlen/ PI*Q0 clayton**	0	2	0.0	0.0 – 57.2	**Not likely at increased risk**
	Clinical cases not reported					
23	**PI*M procida/ PI*M procida**	1	1	50	12.1 – 87.9	**Not likely at increased risk**

	Ferrarotti *et al.,* 2005: 2 individuals, 1 with liver disease and 1 without liver disease					
24	**PI*Q0 bellingham/ PI*Q0 mattawa**	0	0	N/A	N/A	**Not likely at increased risk**
	Clinical cases not reported					
25	**PI*F/ PI*F**	0	1	0.0	0.0 – 73.0	**Not likely at increased risk**
	Sinden *et al.,* 2014: 1 individual without liver disease					
26	**PI*F/ PI*M heerlen**	0	0	N/A	N/A	**Not likely at increased risk**
	Clinical cases not reported					
27	**PI*F/ PI*Q0 clayton**	0	1	0.0	0.0 – 73.0	**Not likely at increased risk**
	Ringenbach et al., 2011: 1 individual without liver disease					
28	**PI*M heerlen/ PI*Q0 granite falls**	0	1	0.0	0.0 – 73.0	**Not likely at increased risk**
	Poller *et al.,* 1999: 1 individual without liver disease					
29	**PI*P lowell/ PI*Q0 bellingham**	0	0	N/A	N/A	**Not likely at increased risk**
	Clinical cases not reported					
30	**PI*F/ PI*M procida**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
31	**PI*F/ PI*P lowell**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
32	**PI*F/ PI*Q0 bellingham**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
33	**PI*F/ PI*Q0 granite falls**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
34	**PI*F/ PI*Q0 mattawa**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
35	**PI*F/ PI*Q0 west**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
36	**PI*M heerlen/ PI*Q0 bellingham**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
37	**PI*M heerlen/ PI*Q0 mattawa**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
38	**PI*M heerlen/ PI*Q0 west**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
39	**PI*M procida/ PI*M heerlen**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					

40	**PI*M procida/ PI*P lowell**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
41	**PI*M procida/ PI*Q0 bellingham**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
42	**PI*M procida/ PI*Q0 clayton**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
43	**PI*M procida/ PI*Q0 granite falls**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
44	**PI*M procida/ PI*Q0 mattawa**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
45	**PI*M procida/ PI*Q0 west**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
46	**PI*P lowell/ PI*M heerlen**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
47	**PI*P lowell/ PI*Q0 clayton**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
48	**PI*P lowell/ PI*Q0 granite falls**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
49	**PI*P lowell/ PI*Q0 mattawa**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
50	**PI*P lowell/ PI*Q0 west**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
51	**PI*Q0 bellingham/ PI*Q0 clayton**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
52	**PI*Q0 bellingham/ PI*Q0 granite falls**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
53	**PI*Q0 bellingham/ PI*Q0 west**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
54	**PI*Q0 clayton/ PI*Q0 clayton**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
55	**PI*Q0 clayton/ PI*Q0 granite falls**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					

56	**PI*Q0 clayton/ PI*Q0 mattawa**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
57	**PI*Q0 clayton/ PI*Q0 west**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
58	**PI*Q0 granite falls/ PI*Q0 mattawa**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
59	**PI*Q0 granite falls/ PI*Q0 west**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
60	**PI*Q0 mattawa/ PI*Q0 west**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
61	**PI*Q0 west/ PI*Q0 west**	0	0	0.0	N/A	**Not Likely at Increased risk**
	Clinical cases not reported					
	(ii) Mild accumulation allele[4] combinations					
62	**PI*S/ PI*M heerlen**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
63	**PI*S/ PI*P lowell**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
64	**PI*S/ PI*Q0 bellingham**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
65	**PI*S/ PI*Q0 clayton**	1	1	50	12.1–87.09	**Unknown risk**
	Rosenbaum *et al.,* 2017:1 individual with and 1 without liver disease					
66	**PI*S/ PI*F**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
67	**PI*S/ PI*M procida**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
68	**PI*S/ PI*Q0 granite falls**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
69	**PI*S/ PI*Q0 mattawa**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
70	**PI*S/ PI*Q0 west**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
71	**PI*I/ PI*F**	0	0	0.0	N/A	**Unknown risk**

	Clinical cases not reported					
72	**PI*I/ PI*I**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
73	**PI*I/ PI*S**	0	0	N/A	N/A	**Unknown risk**
	Clinical cases not reported					
74	**PI*I/ PI*M heerlen**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
75	**PI*I/ PI*M procida**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
76	**PI*I/ PI*P lowell**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
77	**PI*I/ PI*Q0 bellingham**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
78	**PI*I/ PI*Q0 clayton**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
79	**PI*I/ PI*Q0 granite falls**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
80	**PI*I/ PI*Q0 mattawa**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
81	**PI*I/ PI*Q0 west**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
	(iii) Severe accumulation allele[5] combinations					
82	**PI*S iiyama/ PI*M**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
83	**PI*S iiyama/ PI*Q0 clayton**	0	2	0.0	0.0 − 57.5	**Unknown risk**
	Ko *et al.,* 2011: 1 individual without liver disease; Miyahara *et al.,* 2001: 1 individual without liver disease					
84	**PI*S iiyama/ PI*F**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
85	**PI*S iiyama/ PI*M heerlen**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not repor					
86	**PI*S iiyama/ PI*M procida**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
87	**PI*S iiyama/**	0	0	0.0	N/A	**Unknown risk**

	PI*P lowell					
	Clinical cases not reported					
88	**PI*S iiyama/ PI*Q0 granite falls**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
89	**PI*S iiyama /PI*Q0 bellingham**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
90	**PI*S iiyama/ PI*Q0 mattawa**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
91	**PI*S iiyama/ PI*Q0 west**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
92	**PI*S iiyama/ PI*S**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
93	**PI*S iiyama/ PI*I**	0	0	0.0	N/A	**Unknown risk**
	Clinical cases not reported					
94	**PI*S iiyama/ PI*S iiyama**	0	2	0.0	0.0 − 57.5	**Unknown risk**
	Takabe *et al.,* 1992: 1 individual without liver disease; Yuasa *et al.,* 1993: 1 individual without liver disease					
95	**PI*M/ PI*M malton**	12	14	46.2	31.2 − 61.8	**Slightly at increased risk**
	Orrù *et al.,* 2005: 5 individuals with liver disease and 1 without liver disease; Corda *et al.,* 2006: 3 with liver disease and 3 without liver disease; Callea *et al.,* 2018: 2 individuals with liver disease; Canva *et al.,* 2001: 1 individual with liver disease; Janciauskiene *et al.,* 2004: 1 individual with liver disease (hepatitis and AAT accumulation); Figueira Gonçalves *et al.,* 2017: 9 individuals without liver disease; Joly *et al.,* 2015: 1 individual without liver disease					
96	**PI*M malton/ PI*M malton**	8	8	50	31.0 − 69.0	**Slightly at increased risk**
	Orrù *et al.,* 2005: 2 individuals with liver disease and 6 without liver disease; Callea *et al.,* 2018: 2 individuals with liver disease; Curiel *et al.,* 1989b: 1 individual with liver disease; Joly *et al.,* 2015: 1 individual with liver disease; Janciauskiene *et al.,* 2004: 1 individual with liver disease; Reid *et al.,* 1987: 1 with liver disease; Figueira Gonçalves *et al.,* 2017: 2 individuals without liver disease					
97	**PI*M malton/ PI*Z**	1	9	10	2.3 − 34.8	**Slightly at increased risk**
	Ferrarotti *et al.,* 2005: 3 individuals, 1 with liver disease and 2 without liver disease; Sproule *et al*., 1983: 4 individuals without liver disease; Joly *et al.,* 2015: 2 individuals without liver disease; Figueira Gonçalves *et al.,* 2017: 1 individual without liver disease					
98	**PI*M malton/ PI*I**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
99	**PI*M malton/ PI*S iiyama**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
100	**PI*M malton/ PI*S**	0	1	0.0	0.0 − 73.0	**Slightly at increased risk**
	Figueira Gonçalves *et al.,* 2017: 1 individual without liver disease					

101	**PI*M malton/ PI*Q0 mattawa**	0	2	0.0	0.0 − 57.5	**Slightly at increased risk**
	Lara *et al*., 2013: 1 individual without liver disease; Balduyck *et al.,* 2014: 1 individual without liver disease					
102	**PI*M malton/ PI*Q0 clayton**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
103	**PI*M malton/ PI*F**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
104	**PI*M malton/ PI*M heerlen**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
105	**PI*M malton/ PI*M procida**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
106	**PI*M malton/ PI*P lowell**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
107	**PI*M malton/ PI*Q0 bellingham**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
108	**PI*M malton/ PI*Q0 granite falls**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
109	**PI*M malton/ PI*Q0 west**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
110	**PI*Z/ PI*M heerlen**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
111	**PI*Z/ PI*P lowell**	2	3	40	14.3 − 72.8	**Slightly at increased risk**
	Ferrarotti *et al.,* 2005: 1 individual with liver disease and 1 without liver disease; Bornhorst *et al.,* 2007: 1 individual with liver disease; Holmes *et al.,* 1990: 1 individual without liver disease; Bamforth & Kalsheker 1988: 1 individual without liver disease					
112	**PI*Z/ PI*I**	2	2	50	18.2 − 81.8	**Slightly at increased risk**
	Baur & Bencze 1987: 1 individual with liver disease; Mahadeva *et al.,* 1999: 1 individual with liver disease; Ferrarotti *et al.,* 2005: 2 individuals without liver disease					
113	**PI*Z/ PI*S iiyama**	0	0	N/A	N/A	**Slightly at increased risk**
	Clinical cases not reported					
114	**PI*Z/ PI*Q0 granite falls**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
115	**PI*Z/ PI*F**	2	6	25	8.7 − 54.0	**Slightly at increased risk**
	Franciosi *et al.,* 2019: 1 individual with liver disease; Kelly *et al.,* 1989: 1 individual with liver disease; Sinden *et al.,* 2014: 6 individuals without liver disease					

116	**PI*Z/ PI*Q0 clayton**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
117	**PI*Z/ PI*Q0 bellingham**	0	1	0.0	0.0 − 73.0	**Slightly at increased risk**
	Poller *et al.,* 1990: 1 individual without liver disease					
118	**PI*Z/ PI*Q0 mattawa**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
119	**PI*Z/ PI*Q0 west**	0	0	0.0	N/A	**Slightly at increased risk**
	Clinical cases not reported					
120	**PI*Z/ PI*M procida**	1	1	50	12.1 − 87.9	**Slightly at increased risk**
	Lonardo *et al.,* 2002: 1 individual with liver disease; Ferrarotti *et al.,* 2005: 1 individual without liver disease					

[1] The percentage (%) and 95% confidence interval (CI95%) of the reported clinical cases have been calculated following the score method described by Altman *et al*., 2000.
[2] The different combinations of the PI*S and PI*Z alleles (PI*M/PI*S, PI*M/PI*Z, PI*S/PI*Z, PI*S/PI*S and PI*Z/PI*Z) cover more than 95% of variant alleles identified in the SERPINA1 gene worldwide.
[3] Non-accumulation variants: PI*M, PI*M procida, PI*F, PI*P lowell, PI*M heerlen, PI*Q0 granite falls, PI*Q0 west, PI*Q0 bellingham, PI*Q0 mattawa, and PI*Q0 clayton.
[4] Mild accumulation variants: PI*I and PI*S.
[5] Severe accumulation variants: PI*S iiyama, PI*M malton, and PI*Z.

Exceptions to this general liver disease risk classification are shaded in grey in the table above and are applied to the following genetic results:

i) Any combinations of a non-accumulation allele:

It is well-established that 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 variants do not cause AAT protein accumulation in the liver. Therefore, all the combinations including two non-accumulation alleles **(**refer to #6 to 59 in the 'Liver Disease Risk Categorization' table) will be reported with as '*Not likely at increased risk*' result for liver disease.

*ii) Any combination with the severe accumulation alleles PI*Z and PI*M malton:*

Due to the high amount of scientific evidence showing the severe accumulation of the mutant AAT protein in the liver triggered by the PI*Z and PI*M malton variants, as well as on the clinical data obtained from the high number of *(i)* homozygous individuals (i.e., PI*Z/PI*Z and PI*M malton/PI*M malton; refer to #5 and #95 in the 'Liver Disease Risk Categorization' table) and *(ii)* carrier individuals of these two variants that have been studied (PI*M/PI*Z and PI*M/PI*M malton; refer to #2 and #94 in the same table), there is enough scientific evidence supporting the classification of the compound heterozygous (PI*Z/PI*M malton) and the genetic results with at least one severe accumulation allele, PI*Z or PI*M malton (refer to #96−#119 in the same table), to the '*Slightly at Increased risk*' category even though the available clinical data up to date does

not show the same calculated risk e.g., '*Unknown risk*' for PI*Z/PI*I with 50% reported clinical cases of lung disease and 95% CI: 18.2%−81.8% (refer to #111) and '*Not likely at increased risk'* for PI*Z/PI*F with 25% reported clinical cases of lung disease and 95% CI: 8.7−54% (refer to #114).

Although the PI*S iiyama variant has also been widely described as a severe accumulation variant, different combinations of this variant are reported as '*Unknown risk'* (following the general criteria), since no enough clinical data have been published for its combinations except for PI*Z/PI*S iiyama compound heterozygous (refer to #112 in the 'Liver Disease Risk Categorization' table), which is reported as '*Slightly at increased risk*' based on the established evidence of the PI*Z variant.

The risk classification of lung disease and liver disease for each of the 121 possible genetic results of the AlphaID At Home Genetic Health Risk Service including '*Variants not Determined'* is summarized in the table below. The most frequent genetic results are shaded in the table below.

#	Genetic Result in the AlphaID At Home Genetic Health Risk Service Report	Number of variants	Reported Lung Disease Risk Category	Reported Liver Disease Risk Category
1	PI*M/PI*M	0	Not likely at risk for AATD	Not likely at risk for AATD
2	PI*S/PI*M	1	Not likely at increased risk[1]	Not likely at increased risk
3	PI*Z/PI*M	1	Not likely at increased risk[1] (never-smokers) Slightly increased risk (ever-smokers)	Slightly at increased risk[3]
4	PI*S/PI*S	2	Not likely at increased risk	Not likely at increased risk
5	PI*S/ PI*Z	2	Slightly at increased risk	Slightly at increased risk[3]
6	PI*Z/PI*Z	2	Increased risk	Slightly at increased risk[3]
7	PI*I/PI*M	1	Not likely at increased risk[1]	Not likely at increased risk
8	PI*M procida/PI*M	1	Not likely at increased risk[1]	Not likely at increased risk[4]
9	PI*M malton/PI*M	1	Not likely at increased risk[1]	Slightly at increased risk[3]
10	PI*S iiyama/PI*M	1	Not likely at increased risk[1]	Unknown risk
11	PI*Q0 granite falls/PI*M	1	Not likely at increased risk[1]	Not likely at increased risk[4]
12	PI*Q0 west/PI*M	1	Not likely at increased risk[1]	Not likely at increased risk[4]
13	PI*Q0 bellingham/PI*M	1	Not likely at increased risk[1]	Not likely at increased risk[4]
14	PI*F/PI*M	1	Not likely at increased risk[1]	Not likely at increased risk[4]
15	PI*P lowell/PI*M	1	Not likely at increased risk[1]	Not likely at increased risk[4]
16	PI*Q0 mattawa/PI*M	1	Not likely at increased risk[1]	Not likely at increased risk[4]
17	PI*Q0 clayton/PI*M	1	Not likely at increased risk[1]	Not likely at increased risk[4]
18	PI*M heerlen/PI*M	1	Not likely at increased risk[1]	Not likely at increased risk[4]
19	PI*Z/PI*I	2	Slightly increased risk	Slightly at increased risk[3]
20	PI*Z/PI*M procida	2	Unknown risk	Slightly at increased risk[3]
21	PI*Z/ PI*M malton	2	Increased risk	Slightly at increased risk[3]
22	PI*Z/PI*S iiyama	2	Unknown risk	Slightly at increased risk[3]
23	PI*Z/PI*Q0 granite falls	2	Increased risk[2]	Slightly at increased risk[3]
24	PI*Z/PI*Q0 west	2	Increased risk[2]	Slightly at increased risk[3]
25	PI*Z/PI*Q0 bellingham	2	Increased risk[2]	Slightly at increased risk[3]
26	PI*F/PI*Z	2	Slightly at increased risk	Slightly at increased risk[3]
27	PI*Z/PI*P lowell	2	Slightly at increased risk	Slightly at increased risk[3]

#	Genetic Result in the AlphaID At Home Genetic Health Risk Service Report	Number of variants	Reported Lung Disease Risk Category	Reported Liver Disease Risk Category
28	PI*Z/PI*Q0 mattawa	2	Increased risk[2]	Slightly at increased risk[3]
29	PI*Z/PI*Q0 clayton	2	Increased risk[2]	Slightly at increased risk[3]
30	PI*Z /PI*M heerlen	2	Unknown risk	Slightly at increased risk[3]
31	PI*S/PI*I	2	Unknown risk	Unknown risk
32	PI*S/PI*M procida	2	Unknown risk	Unknown risk
33	PI*S/PI*M malton	2	Unknown risk	Slightly at increased risk[3]
34	PI*S/ PI*S iiyama	2	Unknown risk	Unknown risk
35	PI*S/PI*Q0 granite falls	2	Unknown risk	Unknown risk
36	PI*S/PI*Q0 west	2	Unknown risk	Unknown risk
37	PI*S/PI*Q0 bellingham	2	Unknown risk	Unknown risk
38	PI*F/PI*S	2	Unknown risk	Unknown risk
39	PI*S/PI*P lowell	2	Unknown risk	Unknown risk
40	PI*S/PI*Q0 mattawa	2	Unknown risk	Unknown risk
41	PI*S/PI*Q0 clayton	2	Unknown risk	Unknown risk
42	PI*S/PI*M heerlen	2	Unknown risk	Unknown risk
43	PI*I/PI*I	2	Unknown risk	Unknown risk
44	PI*I/PI*M procida	2	Unknown risk	Unknown risk
45	PI*I/PI*M malton	2	Unknown risk	Slightly at increased risk[3]
46	PI*I/PI*S iiyama	2	Unknown risk	Unknown risk
47	PI*I/PI*Q0 granite falls	2	Unknown risk	Unknown risk
48	PI*I/PI*Q0 west	2	Unknown risk	Unknown risk
49	PI*I/PI*Q0 bellingham	2	Unknown risk	Unknown risk
50	PI*F/PI*I	2	Unknown risk	Unknown risk
51	PI*I/PI*P lowell	2	Unknown risk	Unknown risk
52	PI*I/PI*Q0 mattawa	2	Unknown risk	Unknown risk
53	PI*I/ PI*Q0 clayton	2	Unknown risk	Unknown risk
54	PI*I/PI*M heerlen	2	Unknown risk	Unknown risk
55	PI*F/PI*M procida	2	Unknown risk	Not likely at increased risk[4]
56	PI*F/PI*M malton	2	Unknown risk	Slightly at increased risk[3]
57	PI*F/ PI*S iiyama	2	Unknown risk	Unknown risk
58	PI*F/PI*Q0 granite falls	2	Unknown risk	Not likely at increased risk[4]
59	PI*F/ PI*Q0 west	2	Unknown risk	Not likely at increased risk[4]
60	PI*F/PI*Q0 bellingham	2	Unknown risk	Not likely at increased risk[4]
61	PI*F/PI*F	2	Unknown risk	Not likely at increased risk[4]
62	PI*F/PI*P lowell	2	Unknown risk	Not likely at increased risk[4]
63	PI*F/PI*Q0 mattawa	2	Unknown risk	Not likely at increased risk[4]
64	PI*F/PI*Q0 clayton	2	Unknown risk	Not likely at increased risk[4]
65	PI*F/PI*M heerlen	2	Unknown risk	Not likely at increased risk[4]
66	PI*M procida/PI*M procida	2	Unknown risk	Not likely at increased risk[4]
67	PI*M malton/PI*M procida	2	Unknown risk	Slightly increased risk[3]
68	PI*M procida/PI*S iiyama	2	Unknown risk	Unknown risk
69	PI*M procida/PI*Q0 granite falls	2	Unknown risk	Not likely at increased risk[4]
70	PI*M procida/PI*Q0 west	2	Unknown risk	Not likely at increased risk[4]
71	PI*M procida/PI*Q0 bellingham	2	Unknown risk	Not likely at increased risk[4]
72	PI*M procida/PI*P lowell	2	Unknown risk	Not likely at increased risk[4]
73	PI*M procida/PI*Q0 mattawa	2	Unknown risk	Not likely at increased risk[4]
74	PI*M procida/PI*Q0 clayton	2	Unknown risk	Not likely at increased risk[4]
75	PI*M procida/PI*M heerlen	2	Unknown risk	Not likely at increased risk[4]

#	Genetic Result in the AlphaID At Home Genetic Health Risk Service Report	Number of variants	Reported Lung Disease Risk Category	Reported Liver Disease Risk Category
76	PI*M malton/PI*M malton	2	Slightly at increased risk	Slightly at increased risk[3]
77	PI*M malton/PI*S iiyama	2	Unknown risk	Slightly at increased risk[3]
78	PI*M malton/ PI*Q0 granite falls	2	Unknown risk	Slightly at increased risk[3]
79	PI*M malton/PI*Q0 west	2	Unknown risk	Slightly at increased risk[3]
80	PI*M malton/PI*Q0 bellingham	2	Unknown risk	Slightly at increased risk[3]
81	PI*M malton/ PI*P lowell	2	Unknown risk	Slightly at increased risk[3]
82	PI*M malton/ PI*Q0 mattawa	2	Unknown risk	Slightly at increased risk[3]
83	PI*M malton/PI*Q0 clayton	2	Unknown risk	Slightly at increased risk[3]
84	PI*M malton/PI*M heerlen	2	Unknown risk	Slightly at increased risk[3]
85	PI*S iiyama/PI*S iiyama	2	Slightly at increased risk	Unknown risk
86	PI*Q0 granite falls/PI*S iiyama	2	Unknown risk	Unknown risk
87	PI*S iiyama/PI*Q0 west	2	Unknown risk	Unknown risk
88	PI*S iiyama/PI*Q0 bellingham	2	Unknown risk	Unknown risk
89	PI*P lowell/ PI*S iiyama	2	Unknown risk	Unknown risk
90	PI*S iiyama/PI*Q0 mattawa	2	Unknown risk	Unknown risk
91	PI*S iiyama/PI*Q0 clayton	2	Unknown risk	Unknown risk
92	PI*M Heerlen/PI*S iiyama	2	Unknown risk	Unknown risk
93	PI*Q0 granite falls/PI*Q0 granite falls	2	Increased risk[2]	Not likely at increased risk[4]
94	PI*Q0 granite falls/PI*Q0 west	2	Increased risk[2]	Not likely at increased risk[4]
95	"PI*Q0 bellingham/PI*Q0 granite falls"	2	Increased risk[2]	Not likely at increased risk[4]
96	PI*P lowell/PI*Q0 granite falls	2	Unknown risk	Not likely at increased risk[4]
97	PI*Q0 granite falls/PI*Q0 mattawa	2	Increased risk[2]	Not likely at increased risk[4]
98	PI*Q0 clayton/PI*Q0 granite falls	2	Increased risk[2]	Not likely at increased risk[4]
99	PI*M heerlen/PI*Q0 granite falls	2	Unknown risk	Not likely at increased risk[4]
100	PI*Q0 west/PI*Q0 west	2	Increased risk[2]	Not likely at increased risk[4]
101	PI*Q0 bellingham/PI*Q0 west	2	Increased risk[2]	Not likely at increased risk[4]
102	PI*P Lowell/PI*Q0 west	2	Unknown risk	Not likely at increased risk[4]
103	PI*Q0 mattawa/PI*Q0 west	2	Increased risk[2]	Not likely at increased risk[4]
104	PI*Q0 clayton/PI*Q0 west	2	Increased risk[2]	Not likely at increased risk[4]
105	PI*M heerlen/PI*Q0 west	2	Unknown risk	Not likely at increased risk[4]
106	PI*Q0 bellingham/PI*Q0 bellingham	2	Increased risk[2]	Not likely at increased risk[4]
107	PI*P lowell/PI*Q0 bellingham	2	Unknown risk	Not likely at increased risk[4]
108	PI*Q0 bellingham/PI*Q0 mattawa	2	Increased risk[2]	Not likely at increased risk[4]
109	PI*Q0 bellingham/PI*Q0 clayton	2	Increased risk[2]	Not likely at increased risk[4]
110	PI*M heerlen/PI*Q0 bellingham	2	Unknown risk	Not likely at increased risk[4]
111	PI*P lowell/PI*P lowell	2	Unknown risk	Not likely at increased risk[4]
112	PI*P lowell/PI*Q0 mattawa	2	Unknown risk	Not likely at increased risk[4]
113	PI*P lowell/PI*Q0 clayton	2	Unknown risk	Not likely at increased risk[4]
114	PI*P lowell/PI*M heerlen	2	Unknown risk	Not likely at increased risk[4]
115	PI*Q0 mattawa/PI*Q0 mattawa	2	Increased risk[2]	Not likely at increased risk[4]
116	PI*Q0 clayton/PI*Q0 mattawa	2	Increased risk[2]	Not likely at increased risk[4]
117	PI*M heerlen/PI*Q0 mattawa	2	Unknown risk	Not likely at increased risk[4]
118	PI*Q0 clayton/ PI*Q0 clayton	2	Increased risk[2]	Not likely at increased risk[4]
119	PI*M heerlen/PI*Q0 clayton	2	Unknown risk	Not likely at increased risk[4]
120	PI*M heerlen/PI*M heerlen	2	Slightly at increased risk	Not likely at increased risk[4]
121	Variant not determined	N/A	Not determined risk	Not determined risk

[1]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.

[2]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.
[3]Individuals with at least one PI*Z or PI*M malton severe accumulation variants and their combinations are reported as 'Slightly at Increased risk' for liver disease risk even if insufficient number of clinical cases have been reported.
[4]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.

i. User Comprehension Study

a. Saliva collection kit user study:

Refer to K212745 for the saliva collection device (ORAcollect®·Dx OCD-100.014) instructions for use and to assess the ability of lay users to provide samples adequate for testing.

b. AlphaID At Home GHR Service user comprehension study:

Objectives:

The user comprehension study for the AlphaID At Home GHR Service was conducted in a demographically diverse U.S. population of naïve users (e.g., age, gender, ethnicity, and education level) to assess comprehension of the GHR reports through a survey that covers the six comprehension domains (purpose of the test, other risk factors, limitations of the test, relevance of ethnicity, results of the test, and appropriate next steps) in a controlled online setting.

Study Methods:

The study was implemented as described below:

Step 1: Quota-based sampling per U.S. Census was employed to recruit a diverse set of study participants from urban and rural settings across a wide geography based on their demographic variables in age, gender, ethnicity, and education level. Each of the four U.S. Census geographic regions are adequately represented by participants: Northeast, Midwest, South and West.

Step 2: Study participants were asked to review and confirm their agreement to an informed consent form.

Step 3: Eligible study participants who had consented were passed to a Pre-Interview web-based survey which was self-administered and took approximately 10 minutes to complete a Pre-Test user comprehension questionnaire. At this stage, participants were randomly assigned into study arms which determined which type of report participants received.

The substantive exclusion criteria and operational exclusion criteria listed in the table below were applied at each step when necessary and detailed reasons were documented.

Substantive Exclusion Criteria (criteria identified about potential users' background)	
1	Indicated that they are not naive to the test subject of the study, in that they:

	• Have had direct to consumer genetic testing themselves
	• Have had research or healthcare-based genetic testing themselves (including
	• genetic testing for AATD)
	• Have a personal diagnosis of AATD
	• Have significant medical and/or genetic education
	• Have had experience working:
	  o as a healthcare provider where, genetic testing could have been involved (i.e., as a nurse, physician, physician's assistant, or genetic counselor)
	  o in the field of human genetics.
	• Have been a customer, employee, or study participant of Progenika, Grifols, or SoundRocket

2	Indicated they would never be interested in using a direct-to-consumer genetic test
Operational Exclusion Criteria (criteria identified before or during study implementation)	

	• Failure to consent to participate.
	• Failure to follow study instructions
	• Failure to review GHR test report
	• Failure to complete the PRE survey (including scheduling Live Televideo Interview)
	• Failure to complete the Live Televideo Interview (LTI) which includes the POST survey within a 60-minute session
	• Failure to commit to, schedule, or show up for a one-time effort to participate in the LTI
	• Failure to follow verbal and/or written instructions during the study protocol
	• Communicated that they will not take, are not taking, or did not take the study tasks seriously
	• Failure of facilities (i.e., technological issue, power outage, Internet down for moderator or participant, etc.)
	• Lacking abilities (self-reported or observed by moderator):
	  o to read the report (i.e., forgot glasses, are legally blind, etc.)
	  o to use a computer to complete the basic tasks of viewing a browser window, navigating a mouse to click survey responses, etc.
	• Demonstrated or described cognitive impairment, either self-reported or observed by
	• moderator and corroborated with score on the Six-Item Cognitive Impairment Test (6CIT)
	• Other failures not related to comprehension

An individual was considered a refusal if they did not consent or withdrew consent to participate in the study.	

Step 4: Study participants who completed the last step were invited to participate in a live televideo interview (LTI). The LTI was administered via a video conferencing platform at a time scheduled individually between the participant and a study

moderator. The interview was scheduled for no more than 60 minutes total. Each participant was required to review the Education Module for approximately 5−10 minutes).and then the GHR Service Report (Your Result section) for approximately 15−20 minutes. Each participant was informed regarding accessibility to Supplemental Materials consisting of the “Table of Risk Categories”, “Table of Variants”, “Package Insert”, and “References”.

User comprehension was tested through a two-step process. First, participants’ comprehension was tested prior to viewing the Educational Module and GHR Reports. The Pre-Test questionnaire included basic demographics (for inclusion/ exclusion criteria) and baseline comprehension questions that covered the following comprehension domains: test purpose [PURPOSE], test limitations [LIMITATIONS], race/ethnicity [ETHNICITY], and other factors that may have an impact on the test results [OTHER FACTORS]. Second, on completion of reviewing a representative sample of all the material that is included in these documents, participants were provided with the Post-Test questionnaire to complete (approximately 20 minutes). The Post-Test questionnaire included comprehension questions designed to measure all six comprehension domains: test results [RESULTS] and appropriate action [NEXT STEPS] in addition to PURPOSE, LIMITATIONS, ETHNICITY, OTHER FACTORS. The RESULTS and NEXT STEPS domains were only included in the Post-Test questionnaire because they represented specific results that participants could not know prior to viewing the GHR reports and related materials. Each comprehension domain included at least two comprehension questions.

Throughout the completion of the study tasks, the Moderator was able to help the participant navigate between tabs or with technical difficulties as needed but did not give any instructions or answer any questions about how to interpret the report or answer questions. Both the participant's face and screen actions were recorded during this interview. Time on-task (length of time to complete questionnaire) was also recorded for each participant. Operational exclusion criteria were applied at this step when necessary and detailed reasons were documented.

Of the 15 total possible GHR Reports that can be generated by the AlphaID At Home GHR Service, five were selected for the User Comprehension Study. The selected Reports summarized in the table below cover all the possibilities for number of variants and risk categories associated with both lung disease and liver disease that can be reported by the AlphaID At Home GHR Service:

- *Number of variants detected in the SERPINA1 gene*: a total of four different reports can be obtained: 0, 1, or 2 variants detected, and ‘Variant not determined’.

- *Risk category:* four different risk categories (‘Not likely at increased risk’, ‘Slightly increased risk’, ‘Increased risk', and ‘Unknown risk) can be provided by the test, which represent the risk for developing lung and /or liver disease. Additionally, a ‘Not determined risk’ result can also be provided under certain circumstances (Variant not determined).

	GHR Report	Number of Variant Detected	Risk Category for	
			Lung Disease	Liver Disease*
1	PI*M/PI*M	0	Not likely at risk	Not likely at risk
2	PI*M/PI*Z	1	Not likely at increased risk (non-smokers)	Slightly increased risk
			Slightly increased risk (ever smokers)	
3	PI*Z/PI*Z	2	Increased risk	Slightly increased risk
4	PI*S/PI*I	2	Unknown risk	Unknown risk
5	Variant not determined	Variant not determined	Risk not determined	Risk not determined

* None of the genetic results currently provided by the Service yield an "increased risk" for liver disease. The Sponsor indicated that there is no evidence that users think of the risk of liver vs. lung disease to be substantially differently in the context of the GHR report and, therefore, testing user comprehension of the "increased risk" concept with lung disease would be sufficient to extrapolate these results to the comprehension of the concept of "increased risk" of liver disease.

The study was set up to randomly assign each eligible study participant (refer to Step 3) to one of five study arms identified by the five pre-selected test report types, with the following number of participants included per study arm as summarized in the table below.

Study Arm	GHR Report	Total Participants
1	PI*M/PI*M	105
2	PI*M/PI*Z	105
3	PI*Z/PI*Z	105
4	PI*S/PI*I	105
5	Variant not determined	104
	Total	**525**

Each GHR Report includes the following sections: 'Your Result' (Result Report), 'Scientific Details', 'Frequently Asked Questions' (FAQs), and 'Glossary of Terms'. The GHR Reports and Supplemental Materials were reviewed by a Certified Genetic Counselor (GC) to ensure that the materials sufficiently cover the relevant general and variant-specific concepts [comprehension domains]. Prior to recruitment for the user comprehension study, the test report materials (GHR Report, Education Module, and Supplemental Materials) with content targeted no more difficult than 8th grade reading level were evaluated for readability. The Educational Module and Supplemental Materials generated to support the test result report were also evaluated for readability. The Education Module, as well as all Results Reports, Scientific Details, FAQs, and Glossary reached the 8th grade readability target. The Supplemental Information section (which includes Table of Risk Categories, Table of Variants, and Package Insert) achieved a 10th grade readability score overall which

was within the targeted readability maximum for the level of technical detail and language required in this document.

Of the 768 study participants engaged (consented) in this study, 57 were determined to be ineligible during the Pre-Interview web-based survey administration. Of those 711 eligible participants in the study, 186 were ultimately excluded after the Pre-Interview web-based survey for a variety of reasons. This includes 18 cases that failed to complete the pre-survey in full. Of the 693 respondents who completed the pre-survey and scheduled a live televideo interview (LTI), 133 either failed to show up or cancelled their scheduled LTI. Of the 560 cases that were present at their scheduled LTI, 35 cases were excluded due to operational exclusion criteria applied with moderator judgment during the LTI. The most common operational exclusion criterion applied (in 26 of these 35 cases) was "failed to complete LTI due to inadequate technological capabilities". The other reasons for exclusion include: *(i)* lacking abilities to read the report (i.e., forgot glasses, are legally blind, etc.), *(ii)* lacking abilities to use a computer or tablet to complete the basic tasks of viewing a browser window, navigating a mouse to click survey responses, etc., *(iii)* failure to follow verbal and/or written instructions during the study protocol, *(iv)* failure to review test report; *(v)* failure to follow study instructions, and *(vi)* failure to complete the live televideo interview (LTI) which includes the POST survey within a 60-minute session, *(vii)* Failure of facilities outside of control of moderator or participant (i.e., power outage, Internet down for moderator or participant, etc.).

Results:

Comprehension scores were calculated using the total number of responses received that were correct over the total number of eligible responses received. The calculated proportion for each domain serves as the comprehension score for that domain. The target score for each comprehension domain was 90% across all reports. A mean comprehension rate was calculated across all comprehension question domains and all reports. To evaluate whether the comprehension scores had significantly improved statistically, the pre- and post-test scores in each domain, and overall, were compared by using paired sample t-test. Results summarized in the table below show that each comprehension domain achieved a minimum of 90.1% or higher user comprehension score in the pre-test questionnaire, and 94.0% or higher user comprehension score in the post-test questionnaire, across all reports. The overall comprehension scores were of 92.7% and 96.8% across all comprehension domains and reports, for the pre-test and post-test questionnaire, respectively, exceeding the study goals of 90% comprehension overall. Results of the pre- to post-test comparison by paired sample t-tests showed a statistically significant improvement in the user comprehension scores ($p < 0.0001$) between the pre-and post-test questionnaire for the Education Module, and the domains of 'Purpose', 'Limitations', and 'Ethnicity' as well as overall (all report domains). Statistical significance demonstrates that the increase in user comprehension score was a result of the labeling. The 'Other Factors' domain which was the highest Pre-Test score of all the domains showed no significant difference ($p = 0.662$) because the score remained effectively the same from pre-test (98.0%) to post-test (97.7%). The results showed that the GHR 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.

User Comprehension Pre- to Post-Test Scores for all GHR Reports by Domain				
Domain Name	**n**	**Pre-Test (%)***	**Post-Test (%)***	**%Improvement**
All Report Domains	525	92.7	96.8	4.1
Purpose Domain	525	90.1	97.2	7.1
Other Factors Domain	525	98.0	97.7	-0.3
Limitations Domain	525	90.6	97.2	6.6
Ethnicity Domain	525	93.3	97.8	4.5
Results Domain	525	N/A	94.0	N/A
Next Steps Domain	525	N/A	99.1	N/A

* The calculation (for each domain) is based on: Sum of all correct responses for all domain items for all individuals / Total count of all questions asked for all domain items for all individuals

When analyzed individually for each of the five GHR reports, the post-test comprehension scores for each domain are 91.7% or higher, result domain in the PI*M/PI*Z report has a post-test score of 91.7.

Comprehension Rates (%) by GHR Report Type						
Domain Name	**PI*M/PI*M**	**PI*M/PI*Z**	**PI*Z/PI*Z**	**PI*S/PI*I**	**Result Not Determined**	**Overall Comprehension Rates (%)**
Purpose Domain	98.1	98.4	98.4	96.8	97.1	97.2
Other Factors Domain	99.0	97.6	97.6	97.6	97.6	97.7
Limitations Domain	97.1	98.1	98.1	98.1	99.0	97.2
Ethnicity Domain	97.6	99.0	99.0	97.6	98.6	97.8
Results Domain	94.3	91.7	91.7	95.6	95.7	94.0
Next Steps Domain	100.0	99.0	99.0	99.5	99.5	99.1

The user comprehension scores were also analyzed by demographic category and results for the overall study (all five GHR reports combined) are presented in the table below. All demographic categories (including age, sex, race/ethnicity, education, and geographic region) scored 95.3% or higher on the post-test questionnaire overall.

User Comprehension Pre- and Post-Test Scores for all Reports by Demographic				
	Pre-Test		**Post-Test**	
	Mean (%)	n	Mean (%)	n
Overall n				
	92.7	525	96.8	525
Demographics				
Age				
18–39	92.7	203	98.3	203
40–59	92.1	172	96.2	172
60+	93.4	150	95.5	150
Sex				
Female	92.0	266	96.3	266
Male	93.4	259	97.4	259
Race/Ethnicity				
White	94.0	377	97.1	377
Other	89.5	148	96.1	148
Education				
HS* or Less	89.0	181	95.3	181
Some College	93.2	168	97.2	168
Bachelor and Higher	96.1	176	98.0	176
Geographic Region				
Midwest	90.8	116	96.6	116
Northeast	92.3	127	96.9	127
South	93.7	159	96.8	159
West	93.8	120	97.1	120
*HS: High School				

The following table summarizes the user comprehension scores (post-test only) broken out by demographic category (age, sex, race/ethnicity, education level, and geographic region) per domain for the overall study (all five GHR reports combined). Every demographic category scored 91.5% or higher in every domain across all report types. Results showed that participant demographics were unrelated to user comprehension.

User Comprehension Post-Test Scores for all Reports by Demographic												
	Purpose Domain		**Factors Domain**		**Limitations Domain**		**Ethnicity Domain**		**Results Domain**		**Next Steps Domain**	
	Mean (%)	n	Mean (%)	n	Mean (%)	n	Mean (%)	n	Mean (%)	n	Mean (%)	n
Overall n												
	97.2	525	97.7	525	97.2	525	97.8	525	94.0	525	99.5	525
Demographics												
Age (group)												
18-39	98.4	203	98.8	203	98.8	203	98.8	203	96.7	203	100.0	203
40-59	96.3	172	97.7	172	95.6	172	98.0	172	93.2	172	99.7	172
60+	96.7	150	96.3	150	97.0	150	96.3	150	91.5	150	98.7	150
Sex												
Female	97.0	266	97.4	266	96.6	266	97.4	266	93.0	266	99.4	266
Male	97.4	259	98.1	259	97.9	98.3	98.3	259	95.1	259	99.6	259
Race												
White	97.6	377	98.1	377	97.2	377	98.5	377	94.3	377	99.3	377
Black	95.8	71	95.1	71	96.5	71	94.4	71	91.9	71	100.0	71
All Other	96.5	77	98.1	77	98.1	77	97.4	77	94.8	77	100.0	77
Ethnicity												
Hispanic	96.5	38	97.4	38	96.1	38	94.7	38	94.1	38	100.0	38
Education												
High School or Less	94.8	181	97.0	181	94.2	181	95.0	181	93.4	181	99.7	181
Some College	98.2	168	97.0	168	98.5	168	99.1	168	93.6	168	99.7	168
Bachelors (4-year)	98.3	100	99.0	100	98.5	100.0	100.0	100.0	96.0	100.0	99.0	100.0
Graduate/ Professional Degree	99.1	76	99.3	76	100.0	76	98.7	76	94.1	76	99.3	76
Geographic Region												
Midwest	96.0	116	98.3	116	97.4	116	98.7	116	93.1	116	99.6	116
Northeast	96.3	127	96.1	127	96.9	127	98.4	127	95.7	127	99.2	127
South	98.4	159	97.2	159	97.2	159	97.2	159	93.7	159	99.4	159
West	98.6	120	97.9	120	97.5	120	97.5	120	93.8	120	100.0	120

In evaluating potential bias due to study participant nonresponse and exclusion based on eligibility in the Pre-Interview web-based survey or based on exclusion criteria applied after participants were in the study, the demographic make-up of the Completed (Total Participants) group was not different from that of the Target Population suggesting that the desired goal of reaching a diverse population of study participants that reflect the diversity of the U.S. on gender, race/ethnicity, education, and age was met. Even though 'Education' showed the largest difference between the Target Population and the final set of study participants, each education category (including high school or less) individually scored well above the 90% comprehension threshold both overall and on each domain. No significant differences between the categories of the Study Engaged (consented)

participants on 'Age', 'Race/Ethnicity', and 'Geographic Region' ($p<0.001$) were noted. Though the impact of differential exclusion on 'Sex' ($p=0.002$) and 'Education' ($p<0.001$) was statistically significant, the final set of study participants matched the target demographics. The differences in 'Sex' between the categories of Study Engaged participants did not impact user comprehension in this study as both males and females scored well above the 90% user comprehension threshold, both overall and in each domain. With 'Education', no statistical differences were found in user comprehension scores between participants with some college and those with a bachelor's degree or higher. While the differences between those with high school/GED or less and those with a bachelor's degree or higher ($p<0.001$) and those with high school/GED or less and those with some college ($p=0.018$) are significant, the span of 2.7% difference from the lowest to highest education category, all above the 95% threshold, is not meaningful. In sum, the demographic make-up of the potential bias in this study relating to nonresponse/exclusion is negligible and did not have a substantive impact on these study results.

Study Participants by Demographics

	***Target Population**	**Study Engaged (Consented)**		**Excluded for Eligibility in Pre-Interview**		**Excluded for Eligibility after Pre-Interview**		**Completed (Total Participants)**	
	%	n	%	n	%	n	%	n	%
Overall n									
	100	768	100	57	100	186	100	525	100
Demographics									
Age									
18-39**	38	304	40	20	35	81	44	203	39
40-59	32	255	33	17	30	66	36	172	33
60+	29	209	27	20	25	39	21	150	28
Sex									
Female	51	422	51	35	61	121	65	266	51
Male	49	346	49	22	39	65	35	259	49
Race/Ethnicity									
White	72	538	70	41	72	120	65	377	72
Other	28	230	30	16	28	66	36	148	28
Education									
High School or Less	39	329	43	24	42	124	67	181	35
Some College	30	219	29	12	21	39	21	168	32
Bachelor and Higher	31	220	29	21	37	23	12	176	34
Geographic Region* **									
Midwest	NA	172	22	14	25	40	22	118	23
Northeast	NA	182	24	14	25	40	22	128	24
South	NA	238	31	14	25	65	35	159	30
West	NA	176	23	15	26	41	22	120	23

* Based on 2019 Estimates from Census Factfinder

** U.S. Census data is categorized using a lower limit of age 19. Inclusion criteria in this study allowed any individual aged 18 or older to participate.

*** Geographic region was not sampled to match the U.S. population. Rather, it was monitored to ensure that we obtained approximately equal groups of participants from a wide geography within the United States. As such, there are no target population figures for this category.

c. Frequently Asked Questions (FAQ) Material.

A FAQ section was developed and included in each GHR Service Report. The FAQ section was to provide users information to adequately understand the purpose of the test, limitations of the test, meaning of the results of the test, relevance of race and ethnicity on test results, how the results of the test may affect the user's family and children, other risks factors that contribute to disease and appropriate follow-up procedures. Each GHR Report has answers to the FAQs that are specific to the variant(s) of the SERPINA1 gene where applicable. The questions included in the FAQ section for the test include, but are not limit to:

• What is alpha-1 antitrypsin deficiency (AATD)?
• What is the Service for?
• How accurate is the Service?
• My report says l have "2 variants" in the SERPINA1 gene linked to AATD. How did I get these variants?*
• My report says I have "2 variants, Pl*Z and Pl*Z". What are some next steps I can take?*
• What does “at increased risk of developing lung disease linked to AATD” compared to the general population" mean?*
• What does "at slightly increased risk of developing liver disease linked to AATD compared to the general population" mean?*
• Can AATD be treated?
• What are the limitations of the Service?
• How can your genetic result affect your family?*
• My report says AATD is most common in people of European descent. What if • I'm not of European descent?
• Where can I learn more about AATD?
*These FAQs depend on the GHR report type

d. User Opt-In page:

Not applicable

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

Not applicable

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.