Original Research

Gene Therapy: Knowledge, Attitudes, and Preferences Among Individuals with Alpha-1 Antitrypsin Deficiency

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***Running Head*: AATD Gene Therapy Knowledge and Perspectives**

***Keywords*:** alpha-1 antitrypsin deficiency; gene therapy; clinical trial; knowledge; attitudes;

***Abbreviations*:** AATD = Alpha-1 antitrypsin deficiency**;** SERPINA1 = Serpin peptidase inhibitor, clade A, member 1**;** AAT = Alpha-1 antitrypsin; COPD = Chronic obstructive pulmonary disease**;** ADMAP = Alpha-1 Disease Management and Prevention**;** REACH = Risk Evaluation to Achieve Continued Health; GED = General Education Development**;** FDA = Food

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

and Drug Administration**;** NIH = National Institutes of Health**;** CDC = Centers for Disease Control

Funding Support: This is an unfunded study with questionnaire and administrative support provided by AlphaNet, Inc.

Date of Acceptance: May 21, 2026 | ***Published Online Date***: June 1, 2026

Citation: Foil KE, Stern MM, Strange C, et al. Gene therapy: knowledge, attitudes, and preferences among individuals with alpha-1 antitrypsin deficiency. *Chronic Obstr Pulm Dis*. 2026; Published online June 1, 2026.

This article has an online supplement.

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.0784

ABSTRACT

Background: Gene therapy is a promising approach to treating alpha-1 antitrypsin deficiency (AATD). This study is the first to assess knowledge, attitudes, and preferences of the Alpha-1 patient community regarding gene therapies and gene therapy clinical trials.

Methods: An electronic survey collected demographic and health characteristics among the AlphaNet population and assessed knowledge, attitudes, and preferences related to gene therapy using multiple-choice, Likert-scale, and open-ended questions.

Results: Data were provided by 1,112 participants (98% on augmentation therapy and 18% with liver disease). The number of correct responses to knowledge-based questions varied (range: 0-12; mean: 5.8/12 ± 3.1; median = 6). While participants had generally positive perceptions of AATD gene therapy, attitudes and preferences differed between those at or above the knowledge median and those below. Those with higher knowledge were somewhat/very supportive of gene therapy research and development (56% vs. 43%), somewhat/very willing to participate in a gene therapy clinical trial (70% vs. 64%), and somewhat/very willing to receive an FDA-approved gene therapy (87% vs. 74%) (all $p < 0.001$). A gene therapy capable of targeting both liver and lung disease was preferred, along with therapies that require the least frequent re-dosing.

Conclusions: This study identifies knowledge, attitudes, and opportunities to correct misconceptions related to gene therapy in the Alpha-1 community. Participants indicated desire for additional education, and increased knowledge was associated with more positive attitudes towards gene therapy. Thus, the benefit of educational efforts and materials may extend beyond the individual learner and also facilitate trial enrollment and therapy uptake.

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD. Alpha-1) is caused by pathogenic variants of the *SERPINA1* gene that encodes the circulating serine protease inhibitor alpha-1 antitrypsin (AAT).[1] When insufficient levels of AAT reach the lungs, unchecked protease activity leads to progressive lung damage and the eventual onset of chronic obstructive pulmonary disease (COPD).[2,3] The liver is the main site of AAT production, and liver disease can result when the accumulation of a misfolded form of AAT in hepatocytes triggers an exaggerated inflammatory response.[4-6]

AATD affects at least 1 in 2,500 individuals in the U.S. and follows an autosomal co-dominant pattern of inheritance.[6] *SERPINA1* alleles that code for normal AAT are generally designated "M". Allelic combinations that include one or two non-M alleles may result in low AAT levels and cause increased risk for COPD and liver cirrhosis. The most common AATD-associated alleles are known as "Z" (c.1096G>A; p.Glu366Lys; ClinVar Variation ID 17967) and "S" (c.863A>T; p.Glu288Val; ClinVar Variation ID 17969), and the Z allele encodes a misfolded form of AAT that forms polymers that accumulate in hepatocytes. Individuals who are homozygous for this variant (ZZ) typically have severely deficient AAT serum concentrations.[7,8] The S variant typically results in a moderate AAT deficiency without polymerization and associated risk for liver disease, and numerous other pathogenic variants affect AAT quantity, function, or both.

The management of AATD lung disease includes standard COPD therapies, as well as, for many, the use of augmentation therapy, which is an AATD-specific treatment requiring regular intravenous infusions of plasma-derived AAT.[9-12] While augmentation therapy does not reverse lung damage, it does delay emphysema progression.[13] There is currently no approved,

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.0784

specific treatment for AATD-associated liver disease other than liver transplantation, which is typically reserved for those with the most severe cirrhosis.[14] While liver transplantation is generally successful in relieving both the liver and future lung phenotypes of AATD, its complexity, limited organ availability, and issues related to immune suppression limit the feasibility of wider implementation.

Given the limitations of available treatments, gene therapy holds great promise for the treatment of AATD. A therapy capable of driving the delivery of sufficient levels of AAT to the lungs could prevent the onset or progression of lung disease, and one capable of preventing the accumulation of misfolded AAT in hepatocytes could prevent the onset or progression of liver disease. Such gene therapies are already under development and in clinical trials and many are discussed in a recent review.[15] These treatments include some that target either the lung or liver problem independently and others that target both simultaneously. Such variety is useful given the different pathogeneses of lung and liver disease in AATD.

Patient knowledge and perceptions of gene therapies are likely to inform attitudes and preferences towards gene therapies and ultimately influence the likelihood of choosing to receive a particular gene therapy or participate in a particular gene therapy clinical trial.[18,19,21,25-28] Research across populations of patients with different genetic conditions has demonstrated that patients have limited knowledge of how gene therapies work, including frequent misunderstanding of benefits, limitations, risks, and implications of receiving a gene therapy or participating in a gene therapy clinical trial.[16-24] Understanding patient knowledge, attitudes, and preferences regarding gene therapies is essential for ensuring therapies are aligned with patient preferences and meet patient expectations. Improved understanding of patient preferences can also inform components of adequate education and improve the informed consent process.

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

No prior studies have investigated the knowledge, attitudes, and preferences of individuals with AATD regarding gene therapies or gene therapy clinical trials. The purpose of this study was to fill this gap using a research instrument designed to assess 1) knowledge related to gene therapy for AATD, 2) attitudes towards gene therapy and gene therapy clinical trials, and 3) the impact of different characteristics of a hypothetical gene therapy clinical trial on the likelihood of participating. The results of our study can be used to inform clinical trial design, identify potential misconceptions, and fill knowledge gaps so that patients are appropriately informed and empowered when making gene therapy decisions.

METHODS

Study Design

An electronic invitation to participate in this survey-based study was sent to 4,552 individuals enrolled in AlphaNet, a not-for-profit disease management organization. Study inclusion criteria were age >18 years, AATD, consent to use the data for research, and access to the AlphaNet portal with email. Data were collected between September 24 and November 15, 2024. The study was approved by the Western Institutional Review Board-Copernicus Group (WCG IRB Study Number 1349750).

Individuals with AATD provided input into development and refinement of the data collection instrument; these individuals were ineligible to participate in the study to minimize the potential for bias. Knowledge related to AATD gene therapy was assessed using twelve multiple-choice questions representing four different gene-related knowledge domains. Attitudes and preferences towards gene therapy were assessed using Likert-scale items. Open-ended short response questions were also included. Demographic information collected included self-

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.0784

reported age, sex, race, and highest level of education completed. Health information collected included time since AATD diagnosis, AATD genotype, presence of lung and/or liver disease and number of hospitalizations for each, number of pulmonary exacerbations in the past year, current supplemental oxygen use status, and number of AATD-related conferences or learning days attended. The complete research instrument and details of its development are included in the online supplement.

Data Analysis

Surveys were included if participants completed a predefined minimum set of key variables (demographics and at least one primary outcome domain related to knowledge, attitudes, or preferences). Partial responses were retained to maximize data use, and analyses were conducted using available data for each item (i.e., pairwise deletion). Quantitative data were analyzed using JMP® Pro 18.0.2 (Cary, NC). Interactions between specific demographic or health characteristics and knowledge were analyzed by identifying clinically or demographically relevant groups and then comparing the average number of correct responses between groups using either one-way ANOVA with Tukey-Kramer HSD post-hoc analysis or t-test. The number of knowledge assessment questions answered correctly was used to divide the population at the median for comparative analyses of differences in mean numerically-converted Likert-scale responses to attitude and preference items using t-tests. P values < 0.05 were accepted as significant for all quantitative analyses. Responses to open-ended questions were analyzed using thematic analysis, following an iterative coding process by two researchers. Additional methodological detail is described in the online supplement.

RESULTS

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

Characteristics of the study population

Of the 4,452 individuals invited, 1,112 (25% response rate) completed all or part of the survey. The demographic and health characteristics of participants are summarized in Table 1. Over half of participants (55%) were age 65 or older, 56% were female, and 98% were white, non-Hispanic. Approximately 40% of participants had attended at least one AATD conference or learning day, with 29% having attended two or more.

Nearly half of the participants (48%) received their diagnosis of AATD ten or more years ago, and less than 23% reported their diagnosis for less than five years. The most common genotypes reported were ZZ (64%), MZ (16%), and SZ (10%) with no other genotype surpassing 3% of the study population. Over two-thirds (68%) of participants reported having a genotype associated with severe AAT deficiency. Nearly 90% of participants had been diagnosed with lung disease, and 55% were using supplemental oxygen. Among the 69% who had at least one pulmonary exacerbation in the past year, 12% required hospitalization. Less than 20% of participants had been diagnosed with liver disease with only 1% requiring hospitalization for their liver disease within the past year.

Participant knowledge related to gene therapy for AATD

Twelve knowledge questions assessed four knowledge domains: 1) genes and gene expression, 2) gene therapies, 3) clinical trials, and 4) AATD etiology and genetics. Each question had answers characterized as correct or incorrect, and participants could select an answer option of "unsure". A summary of the percentage of correct, unsure, and incorrect responses for each knowledge domain and each question is provided in Figure 1A. A brief and simplified representation of the specific knowledge being assessed for each question is included.

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.0784

The correct response rate was highest for the domain of AATD etiology and genetics (67%) followed by the domains of clinical trials (52%), genes and gene expression (43%), and gene therapies (30%). The unsure response rate was highest for the domain of gene therapies (52%), followed by clinical trials (39%), genes and gene expression (34%), and AATD etiology and genetics (20%). The incorrect response rate was highest for the domain of genes and gene expression (23%), followed by gene therapies (18%), AATD etiology and genetics (12%) and clinical trials (9%).

On average, participants answered 5.8/12 (48%) questions correctly, answered unsure for 4.3/12 (36%) questions, and answered 1.9/12 (16%) questions incorrectly (Figure 1B). The median number of correct responses was 6/12 (range 0-12). Figure 1C shows the distribution of the number of correct responses across the study population. For subsequent analyses of the interaction between knowledge and attitudes or preferences, participants who answered all questions were divided into two groups: 1) those who answered six or more questions correctly (median or above, 56% of participants), and 2) those who answered five or fewer questions correctly (below median, 44% of participants).

We also evaluated whether differences in demographic and health characteristics were associated with differences in knowledge. Higher level of education, attendance of AATD educational event(s), age <65, increased time since diagnosis, and high genetic risk for lung disease correlated with higher knowledge scores (Table 2).

Responses to open-ended questions asking about gene therapy information needs and potential sources are summarized in supplemental tables 1 and 2. The five most common response themes for desired additional information were: 1) general desire for more information (included in 24% of responses), 2) safety, risks, side effects and/or limitations (23%), 3) efficacy

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

and expected benefits (17%), 4) the results of gene therapy research and clinical trials (13%), and 5) details of how gene therapy is administered and the logistics associated with receiving a gene therapy or participating in a clinical trial (13%). Notably, 4% of responses indicated that no additional information was desired. The five most commonly listed trusted information sources were: 1) The Alpha-1 Foundation, AlphaNet, and/or the Alpha-1 Community (included in 63% of responses), 2) doctor(s) or other healthcare providers involved in participants' AATD care (28%), 3) the internet (10%), 4) scientific literature/research (7%), and 5) government agencies (including the NIH, FDA, CDC, and ClinicalTrials.gov) and the non-profit National Organization for Rare Disorders (NORD) (5%). Notably, 9% of the responses indicated uncertainty in where to seek information about gene therapy.

Participant attitudes towards gene therapy

Figure 2 includes a brief and simplified representation of each item used to assess participant attitudes related to gene therapy along with the distribution of responses. The percentage of respondents who replied "somewhat high" or "very high" increased when moving from willingness to participate in a non-gene therapy clinical trial (40%) to a gene therapy clinical trial (48%) and further increased for an FDA-approved gene therapy (65%). Similarly, concern for safety of gene therapy clinical trials (44% somewhat/very high) was greater than concern for safety of FDA-approved gene therapies (39% somewhat/very high).

Participants expressed high levels of interest in learning more about AATD gene therapies (80% somewhat/very high) and support of gene therapy research and development (79% somewhat/very high) as well as high levels of interest in learning more about gene therapy risks (84% somewhat/very high) and limitations (79% somewhat/very high). Participants

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.0784

expressed the highest levels of trust in the Alpha-1 Foundation/AlphaNet (91%) followed by their AATD healthcare providers (82%), the scientific research community (77%), the healthcare system (50%), the FDA (45%), and pharmaceutical/biotech companies (35%).

To determine if participant knowledge is associated with differences in attitudes towards gene therapy, mean numerical Likert scale responses were compared between respondents who answered six or more knowledge questions correctly (those at or above the median) and those who answered five questions or fewer correctly (those below the median) (Table 3). Higher knowledge correlated with more favorable attitudes for all but three items: there was no difference in concern for safety of gene therapy clinical trials or level of trust in the healthcare system between groups, and the below median knowledge score group had higher concern for the safety of FDA-approved gene therapies.

Participant preferences in gene therapy clinical trial characteristics

To assess preferences, participants were asked whether several characteristics of a hypothetical gene therapy clinical trial would discourage or encourage their likelihood of participating. Figure 3 includes a brief and simplified representation of each characteristic and shows the distribution of responses for each item. Based on percentage of encourage/strongly encourage responses, characteristics that most encouraged participation were: use of a single dose of gene therapy expected to maintain benefits (64%), and a therapy targeting both lung and liver problems (64%). Based on percentage of discourage/strongly discourage responses, characteristics that most discouraged participation were: participant's care team member expressing concerns about participation (51%), not being confident in understanding the risks associated with the gene therapy (46%), chance of receiving a placebo (42%), expectation of

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

weekly re-dosing to maintain benefits of the gene therapy (35%), and possibility of being excluded from future gene therapy clinical trials (31%).

To determine if participant knowledge is associated with differences in clinical trial preferences, mean numerical Likert scale responses were compared between respondents at or above median knowledge to those below (Table 4). The mean numerical Likert scale response was higher (characteristics were more encouraging or less discouraging) in the higher knowledge score group for 10/16 items. In addition, the at or higher knowledge group was more discouraged if not confident in understanding of risks.

Participant responses to open-ended questions asking about factors that would most increase or decrease the likelihood of participating in an AATD gene therapy clinical trial are summarized in supplemental tables 3 and 4. The five most common factors found to increase the likelihood of trial participation were: 1) a low burden of participation (included in 30% of responses), 2) having additional information/knowledge about gene therapy (20%), 3) evidence of efficacy (14%), 4) the ability to continue augmentation therapy and other treatments during the trial (8%), and 5) evidence of safety (8%). The five most common factors found to decrease likelihood of trial participation were: 1) a high burden of participation (included in 33% of responses), 2) safety concerns (25%), 3) having to pause augmentation therapy or other treatments during the trial (12%), 4) current age or health status (9%), and 5) insufficient evidence of efficacy (7%). Notably, a response of none/nothing was given by 8% of respondents.

DISCUSSION

This study is the first to assess knowledge, attitudes, and preferences related to gene therapy in individuals with AATD. Our results indicate a wide range of AATD gene therapy

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.0784

knowledge among our study population, and that, generally, knowledge is highest regarding AATD-specific etiology and genetics, moderate regarding clinical trials, and low regarding genes, gene expression, and genetic therapies. Even for AATD-specific knowledge, the average participant answered only 67% of questions correctly, highlighting gaps in understanding and areas for enhanced and continued educational initiatives. Knowledge gaps were more pronounced in other areas, yet participants were aware of gaps (the unsure response rate was more than double the incorrect response rate). Participants reported high interest in learning more about gene therapies and clinical trials and expressed support of ongoing gene therapy development. Interestingly, the most frequently endorsed desire was for general/non-specific information, suggesting uncertainty of what types of information exist and could be helpful.

The participant characteristic most associated with higher knowledge was having attended an AATD-specific conference or educational event, reflective of the educational value of these events. Other factors associated with greater knowledge included a higher level of education, a longer time since diagnosis, having a genotype associated with high risk for lung disease, and being younger than 65. A high disease risk may intrinsically motivate individuals to learn about their condition and may contribute to more frequent or robust medical attention, serving as learning opportunities. Additionally, those who have been diagnosed longer have had more time, and likely more exposure, to acquire and internalize complex information that extends beyond general knowledge. Therefore, efforts to educate individuals with AATD on gene therapies should be highly visible and accessible, start with basics, provide continuous opportunities for reinforcement and new learning, and be re-evaluated over time.

Given the high level of trust endorsed in organizations like the Alpha-1 Foundation and AlphaNet, as well as healthcare providers who care for individuals with AATD, it is important

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

that these organizations and providers are prepared to serve as a source of information and guidance on gene therapies. Findings of this study also mirror results of previous studies in other genetic conditions, including sickle cell disease, inherited retinal diseases, Friedreich ataxia, and phenylketonuria, which similarly found a relative lack of knowledge about gene therapies[17-21,24] , with awareness of the knowledge deficit and desire for additional information and learning opportunities.[23] Synergy between rare disease communities might also be an avenue to amplify educational efforts.[28]

Understanding patient attitudes and preferences regarding gene therapies is an important aspect to ensure therapies are acceptable to the population. Gene therapy trial characteristics that would increase or decrease the likelihood of participation largely corresponded with AATD clinical features and patient experiences. For example, a therapy capable of targeting both liver and lung disease is preferred over one that only targets lung disease (the most common problem in AATD), which was preferred over one that only targets liver disease. As expected, there was a clear preference for gene therapies that require the least frequent re-dosing, with highest preference for one not requiring re-dosing and decreased preference as re-dosing frequency increased. While this relationship seems logical for any population, it is particularly meaningful to the Alpha-1 community given its familiarity with the burden associated with regular augmentation therapy infusions. The preferences displayed by our study population are aligned with those displayed by populations with other genetic conditions in previous studies. This demonstrates consistent preference for gene therapies (or gene therapy trials) that are efficacious in addressing the most relevant health concerns, have a good safety profile, maintain eligibility for future trial participation, minimize the burden of treatment or trial participation, do not include a chance of receiving placebo, and are well-explained and understood.[18,20-22,24-27]

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Previous studies have found conflicting results regarding the relationship between knowledge related to gene therapy and attitudes and/or preferences regarding gene therapy. In some cases, increased knowledge is associated with more concerns and/or less positive attitudes towards gene therapy. In others, greater knowledge is associated with more positive attitudes about gene therapy.[18,19,21,22] Our study examined the relationship between participant knowledge related to AATD gene therapy and 1) attitudes towards gene therapies and 2) preferences regarding potential characteristics of a gene therapy for AATD. In this Alpha-1 cohort, individuals with greater gene therapy knowledge reported more positive attitudes towards gene therapy and were more willing to participate in a gene therapy clinical trial or receive an approved gene therapy. Thus, the benefit of educational efforts and materials may extend beyond the individual learner and facilitate trial enrollment and therapy uptake.

While results of this study offer insights for gene therapy development, trial design, and patient education, there are several limitations. Individuals who participated represent 25% of the invited AlphaNet population and may differ from the larger AlphaNet cohort and/or the larger community of individuals with AATD. Respondents may represent a more informed and engaged subset of the Alpha-1 community, which could overestimate knowledge levels and favorable attitudes toward gene therapy. Future efforts to improve response rates may include adding a subsequent follow-up or reminder, direct contacts, multimodal recruitment (e.g., phone outreach, paper surveys, or in-clinic recruitment), or additional incentives. Leveraging trusted sources such as Alpha-1–specific organizations and care teams may further enhance engagement. Respondents were 98% white, non-Hispanic, similar to previous studies of the AATD population. This is reflective of the higher prevalence of AATD in white, non-Hispanic individuals and healthcare inequities that lead to AATD being underdiagnosed in

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

communities with higher underrepresented minority rates.[33-35] Thus, the response rate and racial/ethnic distribution of our study population may limit the generalizability of our results. Future work should focus on targeting more diverse or less-engaged populations. Another limitation is that some clinical characteristics of the study population are self-reported and thus subject to recall bias. Additionally, while the research instrument was carefully developed by the study team and in consultation with members of the Alpha-1 community to assess relevant knowledge, attitudes, and preferences related to gene therapy for AATD, it is a novel instrument that has not undergone formal validation and may have missed relevant domains related to knowledge, attitudes, and preferences in this population.

Conclusion

Participants with AATD demonstrated variable gene therapy knowledge, with many expressing awareness of their limited understanding, as well as a desire for additional information about the benefits, risks, and limitations of gene therapy, and a better understanding of the logistics of receiving gene therapy and how gene therapies work. Although perceptions of gene therapy were favorable, overall, those with higher knowledge scores were more supportive of gene therapy and more likely to participate in a gene therapy clinical trial. Thus, increasing patient access to gene therapy education may benefit trial enrollment and accelerate development. Our results support that AATD-supportive organizations and healthcare providers who treat patients with AATD are highly trusted and influential, and therefore, are ideally poised to provide gene therapy education and information. The responses to this study's knowledge-based questions, along with the summary of participants' open-ended responses, may be used to inform the development of future educational resources and guides for both patients and

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.0784

providers. This report of the Alpha-1 community's attitudes and preferences regarding gene therapies can contribute to the development of therapies and clinical trials that are in line with the community's preferences and expectations. These findings support the integration of structured, clinician-delivered education and preference elicitation into shared decision-making. This will ensure patients are adequately informed and engaged when considering gene therapy options, enhance patient confidence, reduce decisional uncertainty, and improve alignment between patient values and emerging therapeutic choices.

ACKNOWLEDGEMENTS

Statement of author contributions

MMS: Conception and design of study, data analysis and interpretation, writing–initial draft, revisions.

KEH: Design of study, data collection and curation, writing–IRB approval documents, recruitment and supporting documents, revision of manuscript.

RAS: Design of study, writing–revision of research instrument and manuscript.

KEF: Conception and design of study, writing– revision of research instrument, initial draft, revisions, final draft of manuscript.

GH: Conception and design of study, writing-revision of research instrument and manuscript.

SNM: Conception and design of study, writing-revision of research instrument and manuscript.

ML: Design of study, writing-revision of research instrument and manuscript.

CS: Conception and design of study, supervision, data analysis and interpretation, writing-revision of manuscript

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

DECLARATION OF INTEREST

KEH receives consulting income from AlphaNet. RAS reports a leadership role with AlphaNet, is on advisory committees for Beam, and has non-disclosure agreements with Wave Life Sciences, Tessera, AiRNA, and UniQue. CS reports a leadership role with AlphaNet, and has consulted for Beam, KorroBio, Takeda, and Wave Life Sciences with monies donated to AlphaNET, and has clinical trials initiated with Beam, Krystal, Takeda, and Tessera that involve genetic therapies with monies paid to MUSC. KEF received past consulting income from AlphaNet. SNM receives funds for research consultation for Astrazeneca. MMS, GH, and ML have no relevant financial or non-financial interests to disclose.

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.0784

REFERENCES

1. Strnad P, McElvaney NG, Lomas DA. Alpha(1)-Antitrypsin Deficiency. *N Engl J Med*. Apr 9 2020;382(15):1443-1455. doi:10.1056/NEJMra1910234
2. Demkow U, van Overveld FJ. Role of elastases in the pathogenesis of chronic obstructive pulmonary disease: implications for treatment. *Eur J Med Res*. Nov 4 2010;15 Suppl 2(Suppl 2):27-35. doi:10.1186/2047-783x-15-s2-27
3. Miravitlles M, Dirksen A, Ferrarotti I, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in alpha(1)-antitrypsin deficiency. *Eur Respir J*. Nov 2017;50(5)doi:10.1183/13993003.00610-2017
4. Mahadeva R, Chang WS, Dafforn TR, et al. Heteropolymerization of S, I, and Z alpha1-antitrypsin and liver cirrhosis. *J Clin Invest*. Apr 1999;103(7):999-1006. doi:10.1172/JCI4874
5. Suri A, Patel D, Teckman JH. Alpha-1 Antitrypsin Deficiency Liver Disease. *Clin Liver Dis*. Aug 2022;26(3):391-402. doi:10.1016/j.cld.2022.03.004
6. Sandhaus RA, Turino G, Brantly ML, et al. The Diagnosis and Management of Alpha-1 Antitrypsin Deficiency in the Adult. *Chronic Obstr Pulm Dis*. Jun 6 2016;3(3):668-682. doi:10.15326/jcopdf.3.3.2015.0182
7. Foil KE. Variants of SERPINA1 and the increasing complexity of testing for alpha-1 antitrypsin deficiency. *Ther Adv Chronic Dis*. 2021;12_suppl:20406223211015954. doi:10.1177/20406223211015954
8. Seixas S, Marques PI. Known Mutations at the Cause of Alpha-1 Antitrypsin Deficiency an Updated Overview of SERPINA1 Variation Spectrum. *Appl Clin Genet*. 2021;14:173-194. doi:10.2147/TACG.S257511
9. Stoller JK, Hupertz V, Aboussouan LS. Alpha-1 Antitrypsin Deficiency. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. *GeneReviews((R))*. 1993.
10. Hubbard RC, Crystal RG. Alpha-1-antitrypsin augmentation therapy for alpha-1-antitrypsin deficiency. *Am J Med*. Jun 24 1988;84(6A):52-62. doi:10.1016/0002-9343(88)90159-3
11. Edgar RG, Patel M, Bayliss S, Crossley D, Sapey E, Turner AM. Treatment of lung disease in alpha-1 antitrypsin deficiency: a systematic review. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1295-1308. doi:10.2147/COPD.S130440
12. Sandhaus RA, Strange C, Zanichelli A, Skalvoll K, Koczulla AR, Stockley RA. Improving the Lives of Patients with Alpha-1 Antitrypsin Deficiency. *Int J Chron Obstruct Pulmon Dis*. 2020;15:3313-3322. doi:10.2147/COPD.S276773
13. Chapman KR, Burdon JG, Piitulainen E, et al. Intravenous augmentation treatment and lung density in severe alpha1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet*. Jul 25 2015;386(9991):360-8. doi:10.1016/S0140-6736(15)60860-1

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

14. Townsend SA, Edgar RG, Ellis PR, Kantas D, Newsome PN, Turner AM. Systematic review: the natural history of alpha-1 antitrypsin deficiency, and associated liver disease. *Aliment Pharmacol Ther*. Apr 2018;47(7):877-885. doi:10.1111/apt.14537
15. Pires Ferreira D, Gruntman AM, Flotte TR. Gene therapy for alpha-1 antitrypsin deficiency: an update. *Expert Opin Biol Ther*. Mar 2023;23(3):283-291. doi:10.1080/14712598.2023.2183771
16. Abrams LR, McBride CM, Hooker GW, Cappella JN, Koehly LM. The Many Facets of Genetic Literacy: Assessing the Scalability of Multiple Measures for Broad Use in Survey Research. *PLoS One*. 2015;10(10):e0141532. doi:10.1371/journal.pone.0141532
17. Desine S, Hollister BM, Abdallah KE, Persaud A, Hull SC, Bonham VL. The Meaning of Informed Consent: Genome Editing Clinical Trials for Sickle Cell Disease. *AJOB Empir Bioeth*. Oct-Dec 2020;11(4):195-207. doi:10.1080/23294515.2020.1818876
18. Sharma A, Young A, Carroll Y, et al. Gene therapy in sickle cell disease: Attitudes and informational needs of patients and caregivers. *Pediatr Blood Cancer*. Jun 2023;70(6):e30319. doi:10.1002/pbc.30319
19. Strong H, Mitchell MJ, Goldstein-Leever A, Shook L, Malik P, Crosby LE. Patient Perspectives on Gene Transfer Therapy for Sickle Cell Disease. *Adv Ther*. Aug 2017;34(8):2007-2021. doi:10.1007/s12325-017-0587-7
20. Mack HG, Britten-Jones AC, McGuinness MB, et al. Survey of perspectives of people with inherited retinal diseases on ocular gene therapy in Australia. *Gene Ther*. Apr 2023;30(3-4):336-346. doi:10.1038/s41434-022-00364-z
21. Lieschke K, Scott V, Delatycki MB, et al. How Great a Risk Do You Take? A Qualitative Study Exploring Attitudes of Individuals with Friedreich Ataxia Toward Gene Therapy. *Hum Gene Ther*. Oct 2023;34(19-20):1041-1048. doi:10.1089/hum.2023.088
22. Regier DS, Bak A, Bausell H, O'Reilly E, Cowsert LM. Starting the conversation on gene therapy for phenylketonuria: Current perspectives of patients, caregivers, and advocates. *Mol Genet Metab Rep*. Jun 2022;31:100855. doi:10.1016/j.ymgmr.2022.100855
23. Aiyegbusi OL, Macpherson K, Elston L, et al. Patient and public perspectives on cell and gene therapies: a systematic review. *Nat Commun*. Dec 8 2020;11(1):6265. doi:10.1038/s41467-020-20096-1
24. Nimura BAG, B.A.; Brown, T.; Van Doren, L.N.; Karkoska, K.; Jacob, S.A.; Azar, S.; Boucher, A.A.; McGann, P.T. Exploring the Patient Perspective of Gene Therapy for Sickle Cell Disease. presented at: American Society of Hematology 66th Annual Meeting; December 9, 2024 2024; San Diego, CA, USA. Session 900. https://doi.org/10.1182/blood-2024-198475 Blood
25. Paquin RS, Fischer R, Mansfield C, et al. Priorities when deciding on participation in early-phase gene therapy trials for Duchenne muscular dystrophy: a best-worst scaling experiment in caregivers and adult patients. *Orphanet J Rare Dis*. May 9 2019;14(1):102. doi:10.1186/s13023-019-1069-6
26. Levie C, Moyaert J, Janssens de Varebeke S, et al. Attitudes of Potential Participants Towards Potential Gene Therapy Trials in Autosomal Dominant Progressive Sensorineural Hearing Loss. *Otol Neurotol*. Mar 1 2021;42(3):384-389. doi:10.1097/MAO.0000000000002981
27. Fletcher S, Jenner K, Holland M, Chaplin S, Khair K. An exploration of why men with severe haemophilia might not want gene therapy: The exigency study. *Haemophilia*. Sep 2021;27(5):760-768. doi:10.1111/hae.14378

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28. Miesbach W, O'Mahony B, Key NS, Makris M. How to discuss gene therapy for haemophilia? A patient and physician perspective. *Haemophilia*. Jul 2019;25(4):545-557. doi:10.1111/hae.13769
29. Choate R, Holm KE, Sandhaus RA, Mannino DM, Strange C. Physical and mental health trajectories: A longitudinal SF-36 analysis in Alpha-1 antitrypsin deficiency-associated COPD. *Respir Med*. Nov-Dec 2024;234:107838. doi:10.1016/j.rmed.2024.107838
30. Choate R, Holm KE, Sandhaus RA, Mannino DM, Strange C. Health-related Quality of Life in Alpha-1 Antitrypsin Deficiency-associated Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. Nov 15 2023;208(10):1132-1134. doi:10.1164/rccm.202304-0697LE
31. Choate R, Holm KE, Sandhaus RA, Mannino DM, Strange C. Long-Term SGRQ Stability in a Cohort of Individuals with Alpha-1 Antitrypsin Deficiency-Associated Lung Disease. *Int J Chron Obstruct Pulmon Dis*. 2024;19:889-900. doi:10.2147/COPD.S443183
32. Foil KE, Blanton MG, Sanders C, et al. Sequencing Alpha-1 MZ Individuals Shows Frequent Biallelic Mutations. *Pulm Med*. 2018;2018:2836389. doi:10.1155/2018/2836389
33. Holm KE, Sandhaus RA, Allison S, Strange C. Clinical trial attitudes among individuals with Alpha-1 antitrypsin deficiency. *Respir Med*. May 23 2024;229:107676. doi:10.1016/j.rmed.2024.107676
34. de Serres FJ. Worldwide racial and ethnic distribution of alpha1-antitrypsin deficiency: summary of an analysis of published genetic epidemiologic surveys. *Chest*. Nov 2002;122(5):1818-29. doi:10.1378/chest.122.5.1818
35. McElvaney OJ, Hagstrom J, Foreman MG, McElvaney NG. Undiagnosed Alpha-1 Antitrypsin Deficiency and the Perpetuation of Lung Health Inequity. *Am J Respir Crit Care Med*. Jan 1 2024;209(1):3-5. doi:10.1164/rccm.202307-1171ED

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TABLES

Table 1: Characteristics of the study population (n = 1,112)[a]

Age (mean = 64.6, median = 66)	%	(n)
< 50	7.9	(87)
50-64	37	(408)
≥ 65	55	(613)
Total		*(1108)*
Biological Sex		
Female	56	(621)
Male	44	(490)
Other	0.1	(1)
Total		*(1112)*
Race		
White, non-Hispanic	98	(996)
Hispanic	0.6	(6)
Other (9) or prefer not to say (1)	1	(10)
Total		*(1112)*
Time since AATD Diagnosis		
0-5 years	24	(259)
5-10 years	29	(317)
>10 years	48	(524)
Total		*(1100)*
Genotype		
ZZ	64	(715)
SZ	10	(111)
MZ	16	(174)
Z/null	1.2	(13)
SS	1.3	(14)
MS	2.7	(30)
S/null	0.1	(1)
Other[b]	3.7	(41)
Unknown	1.2	(13)
Total		*(1112)*
AlphaNet Program		
ADMAP (On Augmentation Therapy)	98	(1090)
REACH (Not on Augmentation Therapy)	1.9	(22)
Total		*1112*
Lung Disease Risk Group based on Genotype[c]		
High Risk	68	(743)
Moderate, Low, or Uncertain Risk	32	(356)
Total		*1099*

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Diagnosed with Lung Disease		
Yes	89	(961)
No	11	(124)
Total		*(1085)*
Number of Lung Exacerbations in Past Year		
0	31	(337)
1-2	41	(441)
3-4	17	(180)
5 or more	12	(128)
Total		*(1086)*
Hospitalizations for Lung Disease in Past Year		
0	88	(958)
1-2	11	(119)
3 or more	1	(12)
Total		*(1089)*
Currently Use Supplemental Oxygen		
Yes	55	(599)
No	45	(493)
Total		*(1092)*
Diagnosed with Liver Disease		
Yes	18	(195)
No	82	(885)
Total		*(1080)*
Hospitalizations for Liver Disease in Past Year		
0	99	(1075)
1-2	1	(6)
Total		*(1081)*
Number of Conferences/Learning Days Attended		
0	59	(635)
1	12	(134)
2-3	14	(151)
4-5	5	(54)
6 or more	10	(103)
Total		*(1077)*
Highest Level of Education		
Less than High School	1	(13)
High School Diploma, GED, or Equivalent	18	(198)
Some College Credit without Degree	20	(221)
Trade School, Technical Certification, or Equivalent	8	(88)

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Associate's Degree	10	(105)
Bachelor's Degree	24	(255)
Master's Degree	14	(156)
Doctoral Degree	4	(47)
Total		*(1083)*

[a]For some items, the total is less than 1,112 due to absent responses. [b]Other genotypes included (n): FZ (9), MF (6), $M_{Heerlen}Z$ (5), MI (4), M/null (4), FS (3), IZ (2), $MM_{Heerlen}$ (2), PZ (2), FI (1), IS (1), MM_{Malton} (1), $M_{Malton}M_{Malton}$ (1). [c]Genotypes reported in the study population that are included in the lung disease high risk group include ZZ, Z/null, $M_{Heerlen}Z$, $M_{Malton}M_{Malton}$, and FZ.

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Table 2: Participant characteristics associated with differences in number of correct responses

	Average # Correct	Std. Dev.	(n)
Highest level of education			
High school/equivalent, or less[1]	4.7	3.0	(142)
College credit, Trade or Technical, Associate's degree[2]	5.4	2.8	(326)
Bachelor's degree or more[3]	6.6	3.2	(390)
Number of AATD educational events attended			
Zero[1]	4.9	3.0	(482)
One or more[2]	7.0	2.8	(372)
Age			
Younger than 65[1]	6.1	3.0	(382)
65 and older[2]	5.6	3.2	(483)
Time since diagnosis			
0-5 years[1]	5.2	3.0	(189)
5-10 years[1,2]	5.8	3.2	(248)
More than 10 years[2]	6.1	3.0	(422)
Lung Disease Risk Group based on Genotype			
Highest risk[1]	6.1	3.0	(600)
Moderate, low, or uncertain[2]	5.2	3.2	(263)

Groups with different numbers are statistically independent groups by one-way ANOVA with Tukey-Kramer HSD post-hoc or by t-test ($p < 0.05$). Groups that share a number are not statistically independent.

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Table 3: Associations between participant knowledge and attitudes

	At or Above Median Knowledge Score Mean (std. dev), n	**Below Median Knowledge Score** Mean (std. dev.), n	p-value (t-test)
Willingness to participate in non-gene therapy clinical trial	**3.60 (1.28), 480**	**3.15 (1.32), 364**	**< 0.0001**
Willingness to participate in gene therapy clinical trial	**3.61 (1.39), 482**	**3.23 (1.32), 365**	**< 0.0001**
Willingness to receive FDA-approved gene therapy	**4.05 (1.15),** 482	**3.81 (1.19), 364**	**0.003**
Concern for safety of gene therapy clinical trials	3.26 (1.17), 480	3.35 (1.16), 365	0.31
Concern for safety of FDA-approved gene therapies	**3.07 (1.25), 481**	**3.24 (1.19) 364**	**0.04**
Support of gene therapy research and development	**4.50 (0.82), 482**	**4.14 (1.03), 366**	**< 0.0001**
Interest in learning more about AATD gene therapies	**4.48 (0.85), 480**	**4.11 (1.00), 366**	**< 0.0001**
Interest in learning about gene therapy limitations	**4.45 (0.85), 479**	**4.12 (0.98), 369**	**< 0.0001**
Interest in learning more about gene therapy risks	**4.54 (0.80), 480**	**4.27 (0.93), 370**	**<0.0001**
Trust in Alpha-1 Foundation and AlphaNet	**4.63 (0.64), 482**	**4.51 (0.71), 374**	**0.009**
Trust in healthcare providers you see for AATD	**4.38 (0.84), 486**	**4.24 (0.88), 377**	**0.02**
Trust in scientific research community	**4.20 (0.84), 484**	**3.96 (0.89), 377**	**< 0.0001**
Trust in healthcare system	3.47(0.96), 486	3.44 (1.03), 377	0.75
Trust in FDA	**3.42 (1.06), 486**	**3.25 (1.11), 377**	**0.03**
Trust in pharmaceutical & biotechnology companies	**3.15 (1.00), 485**	**2.99 (1.07), 375**	**0.02**

Numerical Likert scale response conversions: 1 = very low, 2 = low, 3 = intermediate, 4 = high, 5 = very high.

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Table 4: Associations between participant knowledge and preferences

	At or Above Median Knowledge Score Mean (std. dev.), n	**Below Median Knowledge Score** Mean (std. dev.), n	p-value (t-test)
First in humans trial	2.98 (1.09), 485	2.96 (1.09), 369	0.80
Benefits future individuals, not current	3.36 (1.05), 484	3.21 (1.12), 369	0.05
Only targets lung problems	**3.78 (0.95), 483**	**3.50 (1.03), 367**	**< 0.0001**
Only targets liver problems	**3.19 (1.14), 484**	**2.99 (1.12), 367**	**0.01**
Targets both lung and liver problems	**4.05 (0.95), 485**	**3.69 (1.05), 369**	**< 0.0001**
Expect no re-dosing required to maintain benefits	**4.14 (0.90), 483**	**3.72 (1.03), 367**	**< 0.0001**
Expect yearly re-dosing required to maintain benefits	**3.85 (0.98), 485**	**3.53 (1.07), 366**	**< 0.0001**
Expect monthly re-dosing required to maintain benefits	**3.47 (1.10), 483**	**3.21 (1.15), 367**	**0.0006**
Expect weekly re-dosing required to maintain benefits	2.87 (1.21), 485	2.84 (1.21), 367	0.72
There is a chance of receiving a placebo	2.68 (1.14), 485	2.58 (1.19), 372	0.17
May be excluded from future trials	**2.88 (0.98), 484**	**2.71 (1.00), 375**	**0.01**
Confident in understanding of risks	**3.43 (1.11), 486**	**2.90 (1.21), 375**	**< 0.0001**
Not confident in understanding of risks	**2.40 (1.11), 484**	**2.72 (1.21), 376**	**< 0.0001**
Told all information and any biological samples are secure	**3.43 (1.10), 486**	**3.12 (1.17), 374**	**< 0.0001**
Participation encouraged by member of healthcare team	**3.92 (0.98), 485**	**3.31 (1.23), 374**	**< 0.0001**
Concerns about participation expressed by member of healthcare team	2.54 (1.26), 483	2.51 (1.22), 375	0.73

Numerical Likert scale response conversions: 1 = strongly discourage, 2 = discourage, 3 = neutral, 4 = encourage, 5 = strongly encourage

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Figure 1

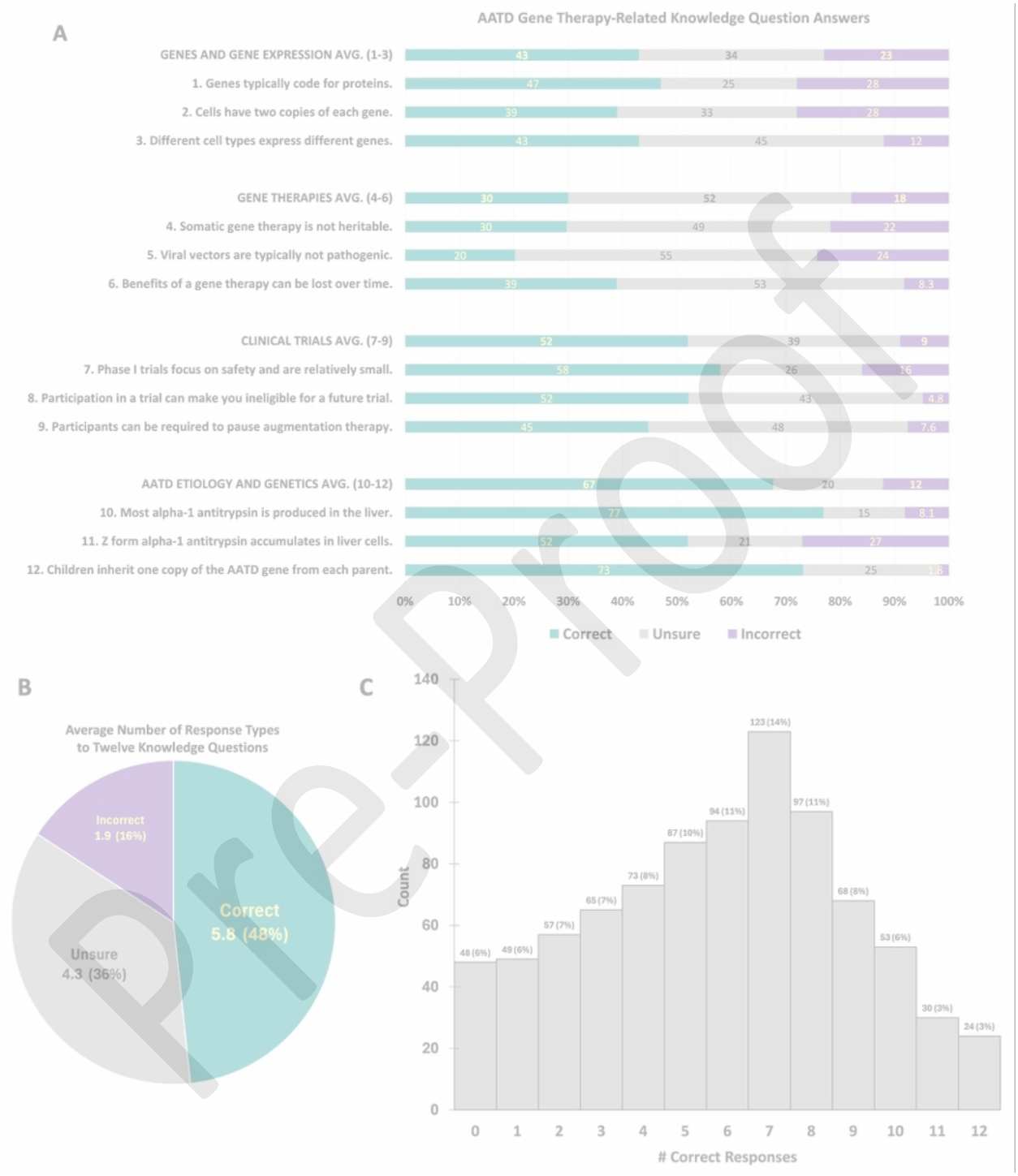

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Figure 2

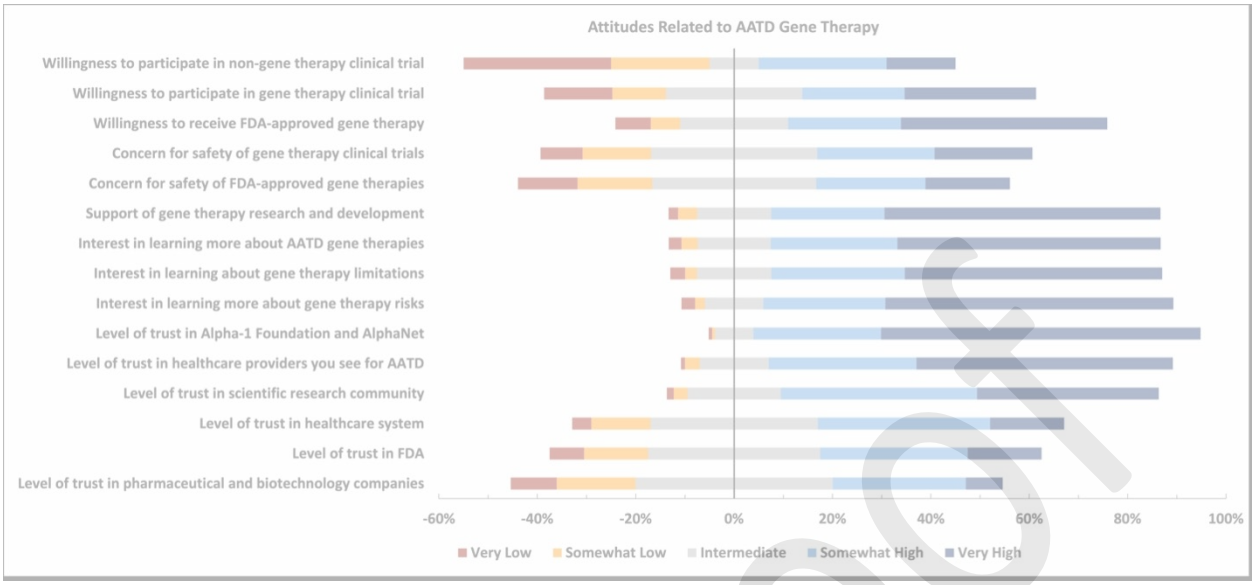
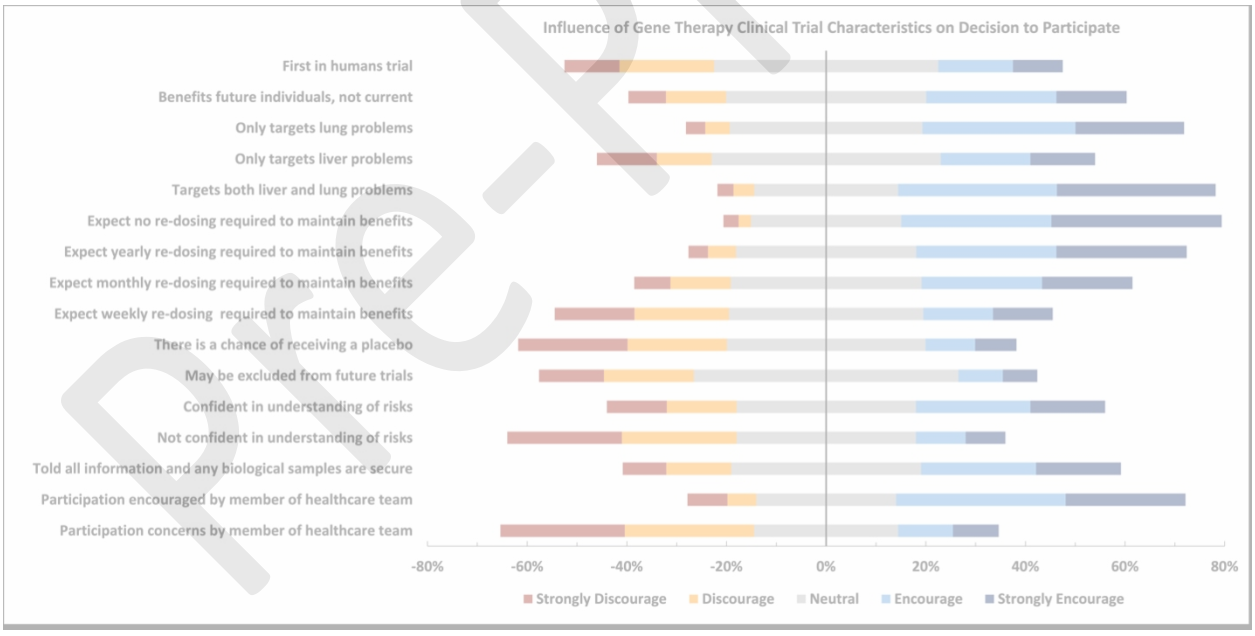


Figure 3



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Online Supplement

SUPPLEMENTAL TABLES

Supplemental Table 1: Information about gene therapy desired by participants

Information About Gene Therapy (GT)	%	(n)
General or Non-Specific/Uncertain Desire for More Information	24	(66)
Safety, Risks, Side Effects, Limitations	23	(63)
Efficacy/Expected Benefits	17	(48)
Results of GT Research and Clinical Trials	13	(37)
Details of Administration and Logistics of Receiving GT	13	(35)
Current Status/Timeline for Availability of GT	11	(29)
GT Methodology/Mechanism	10	(28)
Eligibility for GT	8	(21)
Compatibility with Current Treatment/Augmentation Therapy	7	(19)
None	4	(11)
Duration of the Benefits of GT	3	(9)
Heritability of GT	2	(6)
Eligibility for Future Treatments/Clinical Trials	1	(5)
Cost	1	(4)
Ethics	1	(4)
Impact/Benefit for Future Generations	1	(3)
How to Participate in a GT Clinical Trial	1	(3)
GT Manufacturer Profits	1	(3)

Data are from 275 responses with 94 responses listing two or more types of information. Additional types of information that were each listed in less than 1% of response included (n): positions of scientific foundations on GT (1), alternatives to GT (1), monitoring health after GT (1), and sources of funding for GT (1).

Supplemental Table 2: Sources of information about gene therapy trusted by participants

Information Source	%	(n)
Alpha-1 Foundation, AlphaNet, Alpha-1 Community	63	(207)
Doctor/Providers seen for AATD	28	(92)
Internet	10	(33)
Unsure	9	(31)
Scientific Literature/Research(er)	7	(24)
Government Agencies (NIH, FDA, CDC, Clinical Trials.gov) or NORD	5	(18)
University, Research Institute, Hospital/Care Center	3	(11)
Gene Therapy Specialist, Geneticist	2	(5)

Data are from 331 responses with 75 responses listing two or more information sources. Additional sources that were each listed in less than 1% of responses include (n): own research (3), artificial intelligence (2), library/books (2), pharmaceutical/biotechnology company (1), and conferences (1).

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Supplemental Table 3: Additional factors that would most increase likelihood of participation in a gene therapy clinical trial

Factor	%	(n)
Low Burden of Participation (Time, Travel, Discomfort, Cost)	30	(150)
Additional Information/Knowledge (Including Safety Profile)	20	(102)
Evidence of Efficacy (Including Ability to Replace Augmentation Therapy Replacement, Potential to be Curative)	14	(71)
Ability to Continue Augmentation Therapy and Other Current Treatments During Trial	8	(42)
Evidence of Safety Including No Side Effects or Health Risks	8	(42)
Current Age or Health Status (Young Enough, Well Enough to Participate, Sick Enough to Need a Different Treatment Option)	7	(34)
None	7	(33)
Approval, Support, or Involvement of Healthcare Providers or Other Trusted Entities	6	(31)
Expectation of the Trial Benefiting Others	5	(24)
Unsure	3	(17)
Guarantee Not to Receive Placebo	2	(12)
Eligibility (Genotype and Lung Transplant Recipient Status)	2	(11)
Provision of Access to Healthcare and Health Monitoring	1	(5)

Data are from 498 responses with 79 responses listing two or more factors. Additional factors that were each listed in less than 1% of responses include (n): considered (personally) ethically acceptable (3), FDA approval (3), if not having (or potentially having) children in the future (2), the trial being large or knowing other individuals who are participating (2), guarantee of privacy (1), involvement of international researchers (1), late phase trial (1), no impact on insurance coverage (1), open-label provision included (1), positive reviews/word-of-mouth from other participants (1).

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Supplemental Table 4: Additional factors that would most decrease likelihood of participation in a gene therapy clinical trial

Factor	%	(n)
High Burden of Participation (Inconvenience, Travel, Discomfort, Cost)	33	(145)
Known Safety Concerns Including Side Effects and Health Risks	25	(112)
Having to Pause Augmentation Therapy or Other Current Treatments During Trial	12	(52)
Current Age or Health Status (Being Too Old, Too Sick, or Too Healthy)	9	(42)
None	8	(34)
Insufficient Evidence of Efficacy	7	(31)
Lack of Information or Knowledge	5	(22)
Lack of Trust	4	(19)
Unsure	3	(12)
Chance of Receiving Placebo	2	(11)
Participation Discouraged or Not Encouraged by Healthcare Provider(s)	2	(10)
Ineligibility (Genotype, Other Trial Participation, Language Spoken)	1	(6)
Possible Ineligibility for Future Treatments/Trials (Including Lung Transplant)	1	(6)

Data are from 444 responses with 63 responses listing two or more factors. Additional factors that were each listed in less than 1% of responses include (n): prior lung transplant (4), possible loss of insurance benefits (3), early-phase trial/treatment not yet approved (3), religious reasons (2), negative reviews/word-of-mouth from other participants (1).

SUPPLEMENTAL METHODS

Research Instrument Development

The novel research instrument employed in this study (available below) allowed for the domains of attitudes, preferences, and knowledge to be assessed independently and for the examination of relationships between domains (example: relationship between knowledge and attitudes). The collection of demographic and health data allowed for additional analyses of subpopulations of participants defined by self-reported demographic and/or health characteristics. Participants were also asked a set of four open-ended questions regarding what additional information about gene therapy they would like to know, where they would seek information about gene therapy, and what

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additional factors would increase or decrease their likelihood of participating in a gene therapy clinical trial.

Individuals with AATD participated in each stage of the development of the study. Early participation included interviews to discuss the study design, anticipated outcomes and impact, and the assessment strategy for each domain. Later participation included multiple rounds of feedback on the structure of the research instrument as well as the inclusion/exclusion and wording of individual items.

Participants and Recruitment

Participants were recruited through AlphaNet, a not-for-profit organization with a mission to "provide innovative health management and customized care to individuals with AATD while funding research for a cure." AATD-affected individuals using augmentation therapy receive structured peer support through the Alpha-1 Disease Management and Prevention (ADMAP) program, while the Risk Evaluation to Achieve Continued Health (REACH) program offers disease management for those who are not currently on augmentation therapy or who are caregivers of children with AATD. Members in both the ADMAP and REACH programs were invited to participate in the study. Additional inclusion criteria were age 18 and older, documented consent to allow use of data for research, English-speaking, and an email address on file with AlphaNet. The invitation to participate was sent to 4,452 individuals meeting these criteria.

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Recruitment of participants was multi-tiered and utilized AlphaNet Coordinators, who are individuals with AATD who receive training to provide support and information to subscribers in the AlphaNet programs. Coordinators complete monthly structured phone conversations with the members they serve. Prior to the opening of the study, a brief presentation was given during the regular monthly online meeting of AlphaNet Coordinators to introduce the study and invite Coordinators to discuss study participation with their members during the next monthly call. Alpha-Net Coordinators were also provided with an FAQ document to aid in answering questions from members (available below). Survey invitations were then sent via email, and a follow-up reminder was sent two weeks after the initial invitation (available below).

Data Collection

The research instrument was administered, and data were collected through AlphaNet's online patient portal. Participants who were unable to complete the survey through the online portal completed it on the phone with the help of their AlphaNet Coordinator who then entered their responses into the portal (n = 32, 2.9% of respondents). The age of all participants 90 or older was recorded as 90 to protect anonymity.

Qualitative Data Analysis

Responses to open-ended questions were evaluated using a thematic analysis workflow to identify the most common themes included within the responses to each of the four open-ended questions. This included initial theme identification and coding by M.S. followed by

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a second round of coding by S.M.. The lists of themes present in each collection of responses were agreed upon, and the themes present in each response were assigned by consensus.

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RESEARCH INSTRUMENT

Introduction to the Gene Therapy Survey

Thank you for your participation in our study! This survey consists of four parts. Based on our pilot study, the total completion time is expected to be 15-20 minutes.

As you may know, gene therapies for alpha-1 antitrypsin deficiency (AATD) have entered clinical trials and have the potential to transform how AATD is treated or potentially cured. However, there is a lack of research exploring the Alpha-1 Community's preferences and attitudes towards gene therapies or the Alpha-1 Community's collective knowledge of genetics and gene therapies. The purpose of this study is to fill these gaps.

Understanding the preferences and attitudes of members the Alpha-1 Community towards gene therapies can help inform clinical trial design that meets the needs of potential participants. Gaining a better understanding of the Alpha-1 Community's collective knowledge of genetics and gene therapies can help identify gaps or misconceptions that exist and guide efforts to ensure that members of the Community are fully informed when making decisions about participating in gene therapy clinical trials.

Part 1: Demographic and Health Characteristics

We understand you have likely provided some of the information requested below for prior AlphaNet surveys. We are asking for this important information here to ensure we have the most current information possible for our project. We sincerely appreciate your willingness to provide this information.

How long has it been since you were diagnosed with alpha-1 antitrypsin deficiency (AATD)?

- ◯ Less than 1 year
- ◯ More than 1 year but less than 3 years
- ◯ More than 3 years but less than 5 years
- ◯ More than 5 years but less than 10 years
- ◯ More than 10 years

What is your AATD genotype?

- ◯ ZZ
- ◯ SZ
- ◯ MZ
- ◯ Z/null
- ◯ SS
- ◯ MS
- ◯ S/null
- ◯ Null/Null
- ◯ Other (including F or I or other rare alleles) Please specify_____
- ◯ Unknown

Have you ever been diagnosed with lung disease by a healthcare provider?

- ◯ Yes
- ◯ No

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In the past year, how many times have you experienced exacerbations or flare-ups of your lung problems?

- ◯ 0
- ◯ 1-2
- ◯ 3-4
- ◯ 5 or more

In the past year, how many times have you been hospitalized for lung disease?

- ◯ 0
- ◯ 1-2
- ◯ 3-4
- ◯ 5 or more

Do you currently use supplemental oxygen?

- ◯ Yes
- ◯ No

Have you ever been diagnosed with liver disease by a healthcare provider?

- ◯ Yes
- ◯ No

In the past year, how many times have you been hospitalized for liver disease?

- ◯ 0
- ◯ 1-2
- ◯ 3-4
- ◯ 5 or more

How many in-person or virtual conferences or learning days on AATD have you attended?

- ◯ 0
- ◯ 1
- ◯ 2-3
- ◯ 4-5
- ◯ 6 or more

What is the highest level of education or degree you have completed?

- ◯ Less than high school
- ◯ High school diploma, GED, or equivalent
- ◯ Some college credit without degree
- ◯ Trade school, technical certification, or equivalent
- ◯ Associate's degree
- ◯ Bachelor's degree
- ◯ Master's degree
- ◯ Doctoral degree

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

Part 2: Attitudes Towards Gene Therapies

This portion of the survey is designed to help us better understand current attitudes of members of the Alpha-1 Community towards gene therapies.

Gene therapy = any treatment that adds, removes, and/or modifies genetic material.
AATD = alpha-1 antitrypsin deficiency
FDA = The Food and Drug Administration of the Unites States of America is the regulatory body that oversees clinical trials.

Please rate each of the following as:

	very low 1	somewhat low 2	intermediate 3	somewhat high 4	very high 5
Your willingness to participate in a clinical trial for AATD that does NOT use gene therapy.					
Your willingness to participate in a gene therapy clinical trial for AATD.					
Your willingness to receive a gene therapy to treat AATD if it is approved by the FDA.					
Your concern about the safety of gene therapy clinical trials for AATD.					
Your concern about the safety of (future) FDA-approved gene therapies for AATD.					
Your support of research and development of gene therapies for AATD.					
Your interest in learning more about gene therapy specifically for AATD.					
Your interest in learning more about the limitations of gene therapies.					
Your interest in learning more about the known risks associated with gene therapies.					
Your level of trust in the Alpha-1 Foundation and AlphaNet.					
Your level of trust in the healthcare provider(s) you see for AATD.					
Your level of trust in the scientific research community.					
Your level trust in the healthcare system.					
Your level of trust in the FDA.					
Your level of trust in pharmaceutical and biotechnology companies.					

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.0784

Part 3: Gene Therapy Preferences and Priorities

This portion of the survey is designed to help us better understand the preferences and priorities of members of the Alpha-1 Community regarding participation in a gene therapy clinical trial for AATD.
Please rate how each of the following would influence your likelihood of participating in a gene therapy clinical trial for AATD.

Please consider each item independent from all others.

Gene therapy = any treatment that adds, removes, and/or modifies genetic material.
AATD = alpha-1 antitrypsin deficiency

How would each item influence your decision to participate in an AATD gene therapy clinical trial?

	Strongly discourage participation 1	Discourage participation 2	Neutral (would not affect decision to participate) 3	Encourage participation 4	Strongly encourage participation 5
The clinical trial is the first time the gene therapy has been studied in humans.					
The clinical trial is unlikely to provide a health benefit to you. However, it is likely to benefit future individuals with AATD.					
The gene therapy is only designed to address lung problems in AATD.					
The gene therapy is only designed to address liver problems in AATD.					
The gene therapy is designed to address BOTH lung and liver problems in AATD.					
The gene therapy is NOT expected to require any re-dosing to maintain health benefits.					
The gene therapy is expected to require YEARLY re-dosing to maintain health benefits.					
The gene therapy is expected to require MONTHLY re-dosing to maintain health benefits.					
The gene therapy is expected to require WEEKLY re-dosing to maintain health benefits.					
There is a chance you could be assigned to a placebo group.					
Participation in this gene therapy clinical trial may exclude you from participating in future gene therapy clinical trials.					
You are confident that you understand the risks associated with participating in the clinical trial.					
You are NOT confident that you understand the risks associated with participating in the clinical trial.					
You are told that your personal information, biological samples, and genetic information will be secured/protected using best practices, but security cannot be guaranteed.					

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

A trusted member of your healthcare team has reviewed the trial and encouraged you to participate.					
A trusted member of your healthcare team has reviewed the trial and expressed concerns about your participation.					

Free Response (optional)

We recognize that these questions do not address all of the factors that are considered important when deciding whether or not to participate in a gene therapy clinical trial. Below, you have the opportunity to list/describe additional factors that would influence your decision to participate.

What additional factors would most increase the likelihood of you participating in an AATD gene therapy clinical trial?

What additional factors would most decrease the likelihood of you participating in an AATD gene therapy clinical trial?

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.0784

Part 4: Genetics and Gene Therapy Knowledge

This portion of the survey is designed to help us better understand the current collective understanding of genetics and gene therapies within the Alpha-1 Community. We hope you will see this part of the survey as an opportunity to help us identify how we can further empower the Alpha-1 Community to make informed decisions regarding gene therapy clinical trial participation through improvements in how information on genetics and gene therapies is provided to the Community.

Based on your current understanding of AATD genetics and gene therapy, select the best ending to each of the statements below. You can also select "unsure" if you are unsure which choice is best.

We request that you do not look up the answers to these questions while completing the survey so that our data will most accurately reflect the current collective knowledge of the Alpha-1 Community. The choices that we consider to be best, along with brief explanations of why, will be emailed to you after you complete and submit this survey.

Genes contain information that directs the production of…
- ◯ proteins.
- ◯ chromosomes.
- ◯ Unsure

A human cell typically has…
- ◯ one copy of each gene.
- ◯ two copies of each gene.
- ◯ Unsure

A person's lung cells and liver cells…
- ◯ have entirely different genes.
- ◯ have exactly the same genes but use some genes differently.
- ◯ Unsure

It is intended that the addition, removal, or modification of genetic material that results from a gene therapy being given to an adult…
- ◯ will not be inherited by their future biological children.
- ◯ will be inherited by their future biological children.
- ◯ Unsure

Viral vectors, which are commonly used to deliver a gene therapy to target cells…
- ◯ cannot cause a viral infection.
- ◯ can potentially cause a viral infection.
- ◯ Unsure

The health benefits of a gene therapy in an individual…
- ◯ are never lost no matter which type of gene therapy is used.
- ◯ can be lost over time depending on which type of gene therapy is used.
- ◯ Unsure

The earliest phase of a clinical trial is known as phase I. The purpose of a phase I clinical trial is to…

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

◯ determine the safe dosage range and identify side effects of a treatment in a small number of participants.
◯ determine the safety and effectiveness of a treatment in a large number of participants.
◯ Unsure

A patient who has previously participated in a gene therapy clinical trial…
◯ can be excluded from participating in a current gene therapy clinical trial because of their participation in the previous clinical trial.
◯ cannot be excluded from participating in a current gene therapy clinical trial because of their participation in the previous clinical trial.
◯ Unsure

A gene therapy clinical trial for AATD…
◯ cannot require participants to pause their augmentation therapy during the trial.
◯ can require participants to pause their augmentation therapy during the trial.
◯ Unsure

Most of the alpha-1 antitrypsin found in the lungs of a healthy individual (MM) is produced by cells in…
◯ the liver.
◯ the lungs.
◯ Unsure

The liver problem that can occur in a ZZ individual with AATD is caused by…
◯ not making enough alpha-1 antitrypsin in the liver.
◯ making a faulty form of alpha-1 antitrypsin that gets stuck inside liver cells.
◯ Unsure

If an MM individual and a ZZ individual have a child together, the child is expected to be…
◯ MM
◯ MZ
◯ ZZ
◯ Unsure

Free Response (optional)

What would you most like to know more about regarding gene therapies for AATD?

Where would you go to find trustworthy information about gene therapies for AATD?

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.0784

FOLLOW UP EMAIL: BEST ANSWER EXPLANATIONS

Thank you for participating in the gene therapy survey. The final section of the survey focused on knowledge of genetics and gene therapy. Your responses to this section will help us improve the information we provide to Alphas about genetics and gene therapies. The ultimate goal is to empower Alphas to make informed decisions about gene therapy clinical trial participation.

Below are the answers that we consider to be best and a brief explanation for each answer. Please do not share this information with other Alphas, as they may still plan to complete the survey. We want to get accurate information about current knowledge among Alphas so we can develop educational materials that address gaps in knowledge.

1. Genes contain information that directs the production of…**proteins**.

   In each of our cells, genetic information (DNA) is packaged into 46 chromosomes. Each chromosome contains a long molecule of DNA. A gene is a segment of that DNA molecule that codes for something. Thus, genes do not direct the production of chromosomes. Rather, they are contained within chromosomes.

   Most of our genes code for a specific protein. That is, the information contained in genes is used by our cells to direct the production of the proteins that they need. For example, the *SERPINA1* gene (sometimes called the *AAT* gene) directs the production of the alpha-1 antitrypsin (AAT) protein.

2. A human cell typically has…**two copies of each gene**.

   The 46 chromosomes typically present in each of our cells can be thought of as two sets of 23 chromosomes. We inherit one set of 23 chromosomes from our mother and another set of 23 chromosomes from our father. Thus, we typically have two copies of each chromosome. Because we have two copies of each chromosome, we have two copies of each gene.

3. A person's lung cells and liver cells…**have exactly the same genes but use some genes differently**.

   All of our cells are the descendants of a single original cell whose genetic information was established at fertilization. The complete set of genes present in that cell is passed on to each of the trillions of cells in our body. This means that each of our cells has the same set of genes (around 20,000 genes). However, not all of those genes are used by all of our cells.

   Some genes that are important for basic functions of all cells are used by all types of cells, but genes that are important for the unique functions of a particular cell type may only be used by that cell type. For example, a gene that is important for a unique function of liver cells would not be used in lung cells, and vice versa. Thus, the reason different types of cells are different from each other is not because they have different genes. It is because they use some of the genes differently.

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

4. It is intended that the addition, removal, or modification of genetic material that results from a gene therapy being given to an adult…**will not be inherited by their future biological children**.

   Unless the addition, removal, or modification of genetic material occurs in egg or sperm cells (or cells that can produce or become egg or sperm cells), it will not be inherited by future children. Currently, gene therapies given to adults are typically targeted to the specific types of cells affected by the condition being treated.

   For example, a gene therapy for AATD would likely target liver cells and/or lung cells. Any changes that result from the gene therapy would remain within those cells and (potentially) the cells that they produce. One of the important goals for most gene therapies is to avoid any change to egg or sperm cells, so any changes produced by the gene therapy would not be passed on to future children.

5. Viral vectors, which are commonly used to deliver a gene therapy to target cells…**cannot cause a viral infection**.

   Viral vectors are a useful way to deliver gene therapies to target cells because they use the ability of viruses to get into human cells. The viral vectors used in gene therapy cannot cause a viral infection because the genes needed for the virus to cause harm have been removed or inactivated. Essentially, the outer envelope or shell of the virus is used to deliver the therapeutic components of the gene therapy to the cell type(s) being targeted.

   This does not mean that viral vectors have zero risk. Any specific risks known to be associated with the use of a particular viral vector in a gene therapy clinical trial will be disclosed to participants. Common side effects are chills and flu-like symptoms that are difficult to distinguish from an infection. This risk is also like some vaccination side effects.

6. The health benefits of a gene therapy in an individual…**can be lost over time depending on which type of gene therapy is used.**

   Not all gene therapies work in the same way. Some gene therapies are expected to produce benefits that last for a lifetime. Others are expected to produce benefits that are lost over time, which may make re-dosing necessary.

7. The earliest phase of a clinical trial is known as phase I. The purpose of a phase I clinical trial is to…**determine the safe dosage range and identify side effects of a treatment in a small number of participants**.

   Phase I clinical trials are designed to determine the safe dosage range and identify side effects of a treatment (such as a gene therapy) in a relatively small number of participants. In gene therapy clinical trials, phase I participants are typically individuals with the condition/disease, while in many other types of clinical trials, phase I participants are healthy volunteers. Later phases of clinical trials include more participants and focus on safety and effectiveness.

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.0784

8. A patient who has previously participated in a gene therapy clinical trial…**can be excluded from participating in a current gene therapy clinical trial because of their participation in the previous clinical trial**.

   A patient who has previously participated in a gene therapy clinical trial can be excluded from participating in a current gene therapy clinical trial because it may be difficult for the research team to know if any observed effects are due to the previous trial or the current trial. Some gene therapy clinical trials might not exclude individuals who have previously participated in a different gene therapy clinical. Each clinical trial will have a clear description of eligibility criteria.

9. A gene therapy clinical trial for AATD…**can require participants to pause their augmentation therapy during the trial**.

   A gene therapy clinical trial can require participants with AATD to pause their augmentation therapy during the trial in order to participate. Individuals can always choose to end their participation in a clinical trial (and resume augmentation therapy) at any time. Some gene therapy clinical trials may not require participants with AATD to pause their augmentation therapy.

10. Most of the alpha-1 antitrypsin found in the lungs of a healthy individual (MM) is produced by cells in…**the liver**.

    The *SERPINA1* gene (sometimes called the *AAT* gene) directs the production of the alpha-1 antitrypsin (AAT) protein. The M variant of the *SERPINA1* gene directs production of the normal form of AAT protein.

    The *SERPINA1* gene is highly used by liver cells and only minimally used by lung cells. The AAT protein produced by liver cells is transported out of the liver cells, into the bloodstream, and to the lungs where it helps to maintain lung health.

    Because lung cells don't use the *SERPINA1* gene nearly as much as liver cells do, only a small amount of the AAT protein found in the lungs is actually produced by cells in the lungs. Thus, most of the AAT protein found in the lungs is produced by liver cells.

11. The liver problem that can occur in a ZZ individual with AATD is caused by…**making a faulty form of alpha-1 antitrypsin that gets stuck inside liver cells**.

    The Z variant of the *SERPINA1* gene directs the production of a faulty form of the AAT protein that clumps together and cannot be transported out of liver cells properly. This has two important consequences:

    First, because ZZ individuals only make the faulty Z form of the AAT protein, these proteins clump together and accumulate in liver cells. This increases risk for liver disease.

Published online June 1, 2026 https://doi.org/10.15326/jcopdf.2025.784

Second, because the Z form AAT proteins remain stuck in liver cells, the lungs do not receive the supply of AAT that they need. This results in a deficiency of AAT in the lungs that puts ZZ individuals at significantly increased risk for lung disease.

12. If an MM individual and a ZZ individual have a child together, the child is expected to be…**MZ**.

    An MM individual has two M variants of the *SERPINA1* gene (sometimes called the *AAT* gene). Each individual only passes one of their two variants on to their child, so the MM individual will pass on an M variant. A ZZ individual has two Z variants of the *SERPINA1* gene—so the ZZ individual will pass on a Z variant.

    The child will receive an M variant from one parent and a Z variant from the other. Thus, the child will be MZ.

    As an MZ individual, the child's liver cells will produce both the normal M form of the AAT protein (from their M variant of the *SERPINA1* gene) and the faulty Z form of the AAT protein (from their Z variant of the *SERPINA1* gene). The M form of the AAT protein is expected to get out of the liver cells and be transported to the lungs through the blood, while the Z form of the AAT protein is expected to remain stuck in the liver cells.

    This means the MZ child will end up having some M form AAT in their lungs but not as much as their MM parent. They will also have some Z form AAT accumulation in their liver cells but not as much as their ZZ parent. Thus, the child has more risk of developing lung and liver disease than their MM parent, but less risk of developing lung and liver disease than their ZZ parent.

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INITIAL ELECTRONIC INVITATION

ALREADY PORTAL-ENABLED SURVEY INVITATION EMAIL TEMPLATE

Hi [Subscriber name will appear here],

Gene therapies have the potential to transform how alpha-1 antitrypsin deficiency is treated or potentially cured. These therapies have started to be investigated in clinical trials.
We have very little understanding of Alphas' preferences and concerns about gene therapies, or Alphas' general knowledge about genetics and gene therapies. AlphaNet has developed a one-time survey to learn about these topics.

Most of the survey questions ask about your opinions, so there are no right or wrong answers to these questions. Some of the survey questions ask about knowledge of genetics and gene therapy. We will send you the best answers to these questions after you complete and submit the survey.

Survey findings will help us develop educational materials that are targeted to the information needs of Alphas, and hopefully will contribute to the development of gene therapy clinical trials that are more appealing to potential participants.
It will take approximately 15-20 minutes to complete the survey.

Please complete this survey, which is available at https://subscriber.alphanet.org. This survey is only available in the portal. It is not available by phone, email, or US mail.

Thanks,

[The AlphaNet Coordinator's name, email address, and phone number will appear here]

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REMINDER ELECTRONIC INVITATION

ALREADY PORTAL-ENABLED SURVEY INVITATION EMAIL TEMPLATE

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