ANNUAL REPORT 2022

ALPHA-1 FOUNDATION IRELAND

MISSION STATEMENT

Alpha-1 Foundation Ireland is a charity dedicated to raising awareness, increasing diagnosis, promoting research, and improving the treatment of Alpha-1 Antitrypsin Deficiency (Alpha-1).

VISION

That everyone with Alpha-1 in Ireland is diagnosed and receives specialist care and treatment in a timely fashion.

CORE ACTIVITIES OF ALPHA-1 FOUNDATION IRELAND

STAFF OF ALPHA-1 FOUNDATION IRELAND

Ms Geraldine Kelly, CEO

Dr Tomás Carroll, Chief Scientist

Ronan Heeney, Medical Scientist

PATRON

Michael D. Higgins, President of Ireland

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Alpha-1 Foundation Ireland Charity Code: CHY22304

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ANNUAL REPORT 2022

ALPHA-1 FOUNDATION IRELAND

CONTENTS

1 Executive Summary

It was good to see services return to normal in 2022. One thing is certain we hit the ground running. Outpatient clinics returned to full capacity enabling the medical team to take care of our Alpha-1 patients face to face and it allowed the Foundation to refocus on the recruitment of patients to our patient registry. Joining the registry allows us to build knowledge, improve care and help develop new treatments through involvement in clinical trials. I really want to encourage our patient community and their families to get involved, to join the registry and enable the scientists, researchers and doctors to continue the brilliant work they do on behalf of Alpha-1 patients around the world. There has been so much great research in 2022 resulting in many publications and extremely important and worthwhile research projects. Chapter 7 provides an overview of the exciting research projects in progress by Professor McElvaney and the team of scientists and doctors here in Beaumont.

Two major projects got under way on the enhancement and upgrade to our two main systems, the TDP (targeted detection programme) and the Alpha-1 Registry. This work was led by Dr. Tomás Carroll and Ronan Heeney on the TDP and by Dr. Daniel Fraughen on the Alpha-1 Registry. The TDP provides the diagnostic record of all patients who are tested for Alpha-1 and the patient registry is the system that allows us to collect ongoing clinical data on consented patients and is used for the scientific assessment of patient outcomes. Patient registries are an important tool for clinical research. We currently have in excess of 660 patients consented but the more people that take part the more effective the research is. You can read about research projects which were enabled through registry data in Chapter 7.

Alpha-1 Foundation Ireland is a member of the Irish Donor Network and collaborated with Philip Watt CEO, Cystic Fibrosis Ireland to help push the Human Tissue Bill to its first stage in the legislative process in November 2022. The bill includes soft opt out organ donation consent which is likely to significantly increase the number of organs available for transplantation. This is hugely important for Alpha-1 patients who are currently awaiting lung transplant or may be in the future.

Work commenced during 2022 on the creation of a European Alpha-1 Patient Organisation Alliance. Ireland has been involved since the start in the creation of this organisation and will become an associate member during a kick off meeting in Barcelona in November 2023. The purpose of this collaboration is to advocate for access to more timely diagnosis, and care, and to raise awareness, promote research, and empower Alpha-1 national patient organisations across Europe. The association will collaborate closely with sister organisations at an international level and may collaborate with other relevant organisations on topics of common interest.

I would like to thank all Alpha-1 Foundation staff, the Alpha-1 Board and all the medical and research teams working with Professor McElvaney for all their support over the last year. The theme for this annual report is “A Holistic Approach to Alpha-1”. Chapter 4 contains two powerful stories from people affected by Alpha-1 and how they learned to cope with the different aspects of their diagnosis, including body and mind. While thinking about the wider needs of our patients the Foundation are promoting a more holistic approach to caring for Alpha-1 patients, including their mental health, and this will be a big focus for 2023.

Geraldine Kelly
CEO, Alpha-1 Foundation Ireland

2 The National Alpha-1 Antitrypsin Deficiency Targeted Detection Programme – An Update

Alpha-1 antitrypsin deficiency (AATD or simply Alpha-1) can be diagnosed by a simple blood test but unfortunately remains hugely under-diagnosed. A diagnosis of Alpha-1 is a unique opportunity for early intervention and can prevent or postpone lung disease in both the affected individual and their relatives. In May 2004, a national targeted detection programme for AATD was launched by Alpha-1 Foundation Ireland with funding from the HSE. By the end of December 2022, the programme had tested more than 22,500 people.

Who Should Be Tested for Alpha-1?

World Health Organisation (WHO), American Thoracic Society (ATS), and European Respiratory Society (ERS) guidelines advocate targeted detection programmes for AATD. These guidelines recommend targeted testing of certain patient groups, with a special focus on chronic obstructive pulmonary disease (COPD)(Table 2.1).

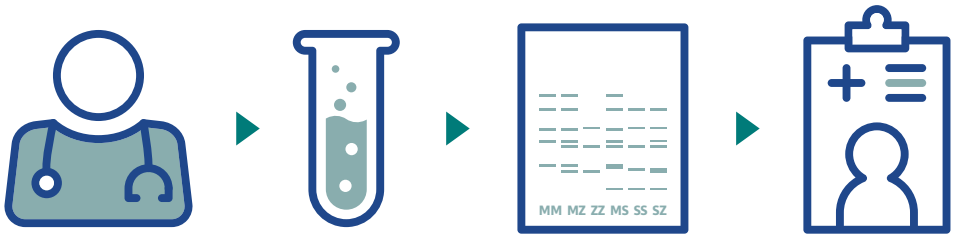


Figure 2.1. *Simple testing process for Alpha-1 involving a visit to a GP, blood sample, laboratory test and a final report.*

Table 2.1. *ATS/ERS recommendations for diagnostic testing for AATD (type A recommendations)*

Who Should Be Tested?
Adults with symptomatic emphysema or COPD (regardless of age or smoking history)
Adults with asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators
Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g. cigarette smoking, occupational exposure)
Adults with panniculitis
Siblings of individuals with Alpha-1
Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly

How Do We Test for Alpha-1?

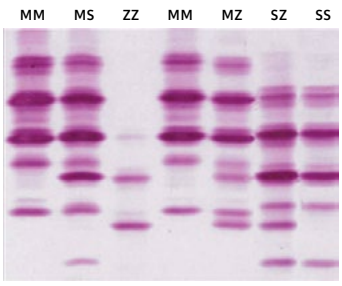


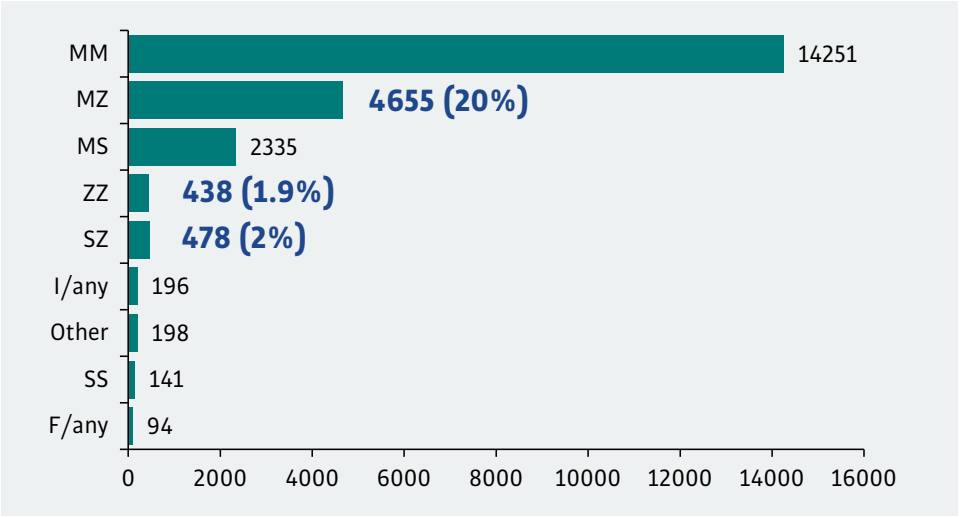
Figure 2.2. *Typical isoelectric focusing gel for AAT phenotype identification with the most common phenotypes included.*

There are two tests needed to correctly diagnose Alpha-1. The first test measures how much alpha-1 antitrypsin (or AAT) is in the blood. The second test looks at what type of AAT protein is present by a method called isoelectric focusing. This method identifies types of AAT protein circulating in human blood and is more commonly known as phenotyping (Figure 2.2). It is the most accurate method of diagnosing Alpha-1 and can recognise common and rare AAT variants.

What Have We Found in Ireland?

Since 2004, more than 22,500 individuals with COPD, asthma, and liver disease, as well as first-degree relatives of people with AATD have been tested in a National Targeted Detection Programme.

Figure 2.3. *Results from the National AATD Targeted Detection Programme showing the major AAT phenotypes identified among more than 22,500 individuals tested.*



A total of 438 ZZ (severe Alpha-1) individuals have been identified, as well as 478 SZ individuals, who are also at risk of developing lung (particularly if smoking) and liver disease (Figure 2.3). In addition, a large number of other clinically significant phenotypes have been detected including 4655 MZ, 25 IZ, and 14 FZ. A number of rare and very rare deficiency-causing AAT mutations have also been identified. These include $M_{heerlen}$, M_{malton}, $M_{wurzburg}$, S_{munich}, and $Z_{bristol}$ and six different Null mutations ($Null_{bolton}$, $Null_{cork}$, $Null_{dublin}$, $Null_{lisbon}$, $Null_{porto}$ and $Null_{amersfoort}$). Two were discovered for the first time here in Ireland ($Null_{cork}$ and $Null_{dublin}$).

Table 2.2. *Simple explanation of the most common AAT phenotypes.*

AAT Phenotype/ AAT Genotype*	AAT Deficiency?	What does it mean?
MM	No	Does not have the disorder – has 2 normal copies of the AAT gene.
MS	Mild	No evidence of increased risk of lung or liver disease but does carry 1 altered AAT gene.
MZ	Moderate	Significantly increased risk of lung disease **in smokers**. Increased risk of liver disease.
SS	Moderate	Presumed increased risk of lung disease **in smokers**. No evidence for increased risk of liver disease.
SZ	Moderate	Significantly increased risk of lung disease **in smokers**. Increased risk of liver disease.
ZZ	Severe	Significantly increased risk of lung disease in **smokers and ever smokers**. Increased risk of liver disease.

The goal of the national detection programme is to ensure people with Alpha-1 are correctly diagnosed and are given the opportunity to receive expert medical care, advice, and support. Newly diagnosed individuals can be referred to the National Centre of

Expertise for AATD in Beaumont Hospital under the care of Professor Gerry McElvaney. A strong focus on family screening can identify other family members with Alpha-1, which can help prevent or postpone the development of serious health problems in the wider family. Importantly, a correct diagnosis means people can benefit from lifestyle changes such as smoking cessation, risk reduction in the workplace, specialist medical care from Alpha-1 experts, and the opportunity to enrol in clinical trials that test new treatments.

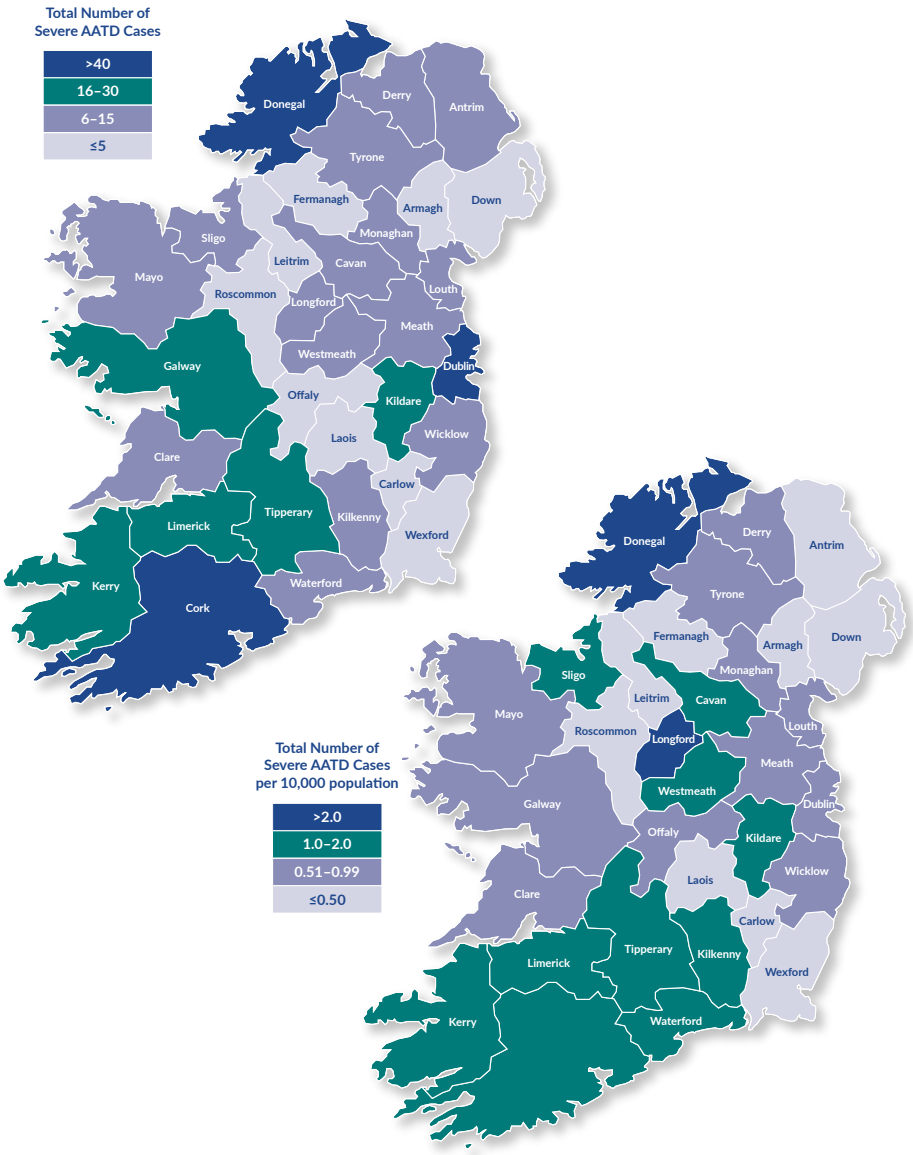


Figure 2.4.
LEFT: *Distribution of severe AATD cases detected to date (504 cases across all 32 counties – total includes people diagnosed outside of the TDP).*
RIGHT: *Distribution of severe AATD cases adjusted per 10,000 population.*

Alpha-1 Education and Outreach in 2022

Thankfully most of our educational visits returned to in person meetings in 2022. We held seminars on Alpha-1 to a mixture of respiratory and laboratory teams in Cavan, Drogheda, Crumlin, Tallaght and St. James's hospitals. We also presented to medical students in UCD, M.Sc. Clinical Chemistry students in TCD, M.Sc. Precision Medicine students in RCSI, a large class of GP trainees in Donegal, and to Cromcastle Primary Care team in Coolock. We also spoke at the Irish Society of Human Genetics conference and the BioMedica conference organised by the Academy of Clinical Science and Laboratory Medicine. The aim of these presentations is to increase awareness of Alpha-1 among healthcare professionals and to encourage testing. While respiratory (and liver) medical teams care for patients most at risk due to AATD, hospital laboratories measure alpha-1 antitrypsin levels during normal blood investigations and can help reach a diagnosis of AATD.

3 The National Alpha-1 Antitrypsin Deficiency Registry

What is the registry?

The registry is a confidential database that stores relevant medical information of individuals diagnosed with alpha-1 antitrypsin deficiency (AATD). Results of tests that monitor lung and liver function such as blood tests, breathing tests, CT scans of the lungs and ultrasound or transient elastography (sometimes called a Fibroscan) of the liver are recorded in the registry and then these results are updated at regular intervals. The registry also collects other information relevant to AATD. For example, smoking status and occupation can help to identify risks (e.g. a factory worker exposed to fumes or dusts).

What is the purpose?

The registry helps to deepen our knowledge and understanding of AATD, improve the clinical care given to people with AATD, and increase recruitment for clinical trials investigating new treatments for AATD. The small number of people affected by a rare condition like AATD means that getting access to the right care, treatment and support can be difficult. Registries play an important role in filling gaps that exist in the care of people with rare disease, particularly in Ireland which has no electronic healthcare record.

Figure 3.1. *The Goals of the National Alpha-1 Registry.*

What are the key objectives of the Registry?

1. Increase our understanding of AATD (knowledge)
2. Inform and improve clinical care (care)
3. Provide early access to new treatments via clinical trials (treatment)

How can I enrol?

Individuals diagnosed with various forms of AATD are eligible to enrol in the registry. Enrolment is completely voluntary, and an individual must provide their written informed consent prior to enrolment. A member of Alpha-1 Foundation Ireland will provide individuals with an information leaflet and answer any questions at the time of enrolment.

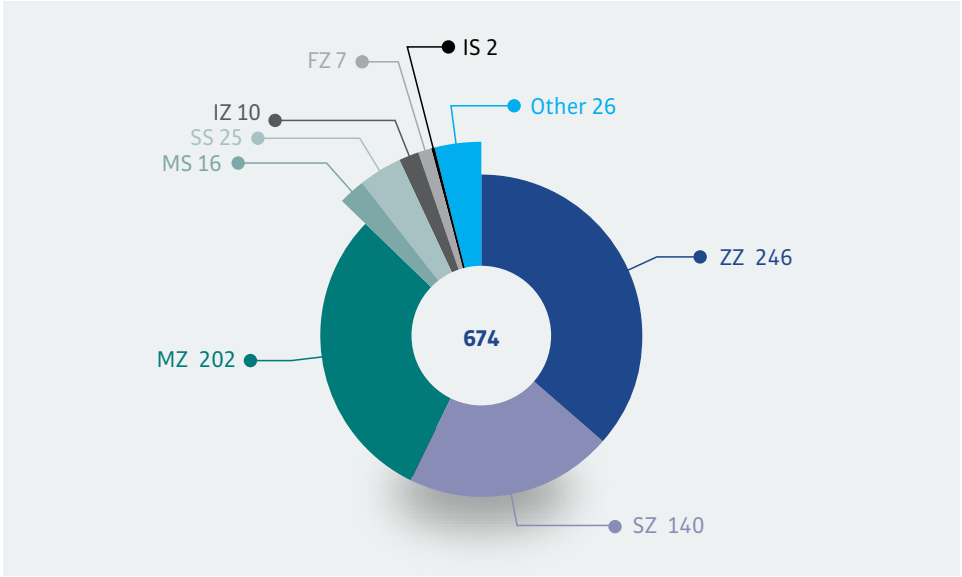
If I have questions?

If you or your family are interested in enrolling or have any questions about the registry, please contact us on 01-8093871. To learn more about our registry visit *https://www.alpha1.ie/irish-alpha-1-registry/*.

Registry Update and Future Plans

At the end of 2022 a total of 674 people were taking part in the National AATD Registry (Figure 3.2) and this number is growing all the time. In 2023 we hope to launch a new improved registry with the help of Irish healthcare IT company OpenApp. Enhancements include new sections to capture e-cigarettes and vaping use and a new section to capture results from **oscillometry** and **transient elastography (Fibroscan)**, two new tests that look in closer detail at the lung and liver, respectively.

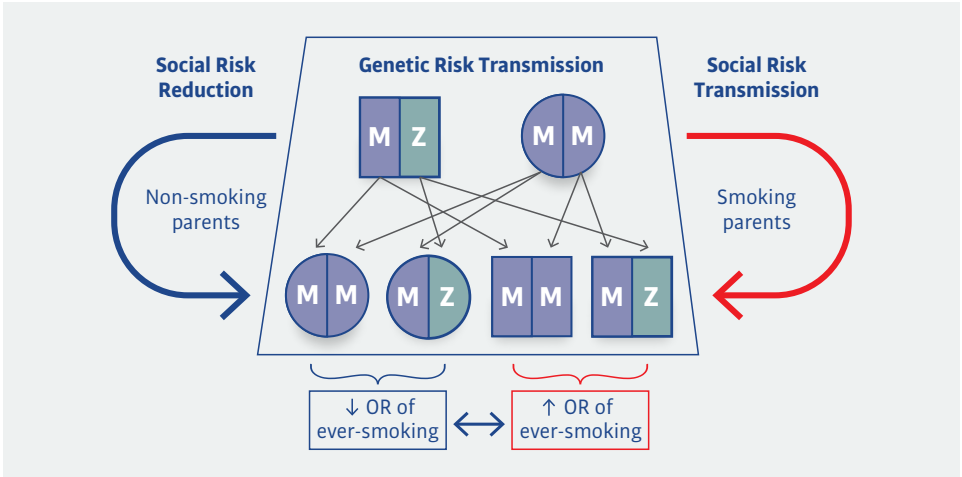
Figure 3.2. *Total number of individuals enrolled in the registry according to AATD phenotype (n = 674).*

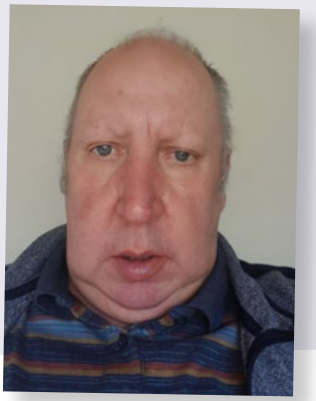


Research using anonymous data from the registry has improved our understanding of the risk factors and symptoms associated with the health problems caused by Alpha-1. For example, a recent study looked at cigarette smoking habits in people with Alpha-1 taking part in the registry. The study [**Alpha-1 Antitrypsin Deficiency and Tobacco Smoking: Exploring Risk Factors and Smoking Cessation in a Registry Population, Franciosi et al, Journal of COPD, 2021**] showed that smokers were highly motivated to stop smoking after finding out they had Alpha-1. In addition, people with 1 or 2 parents who smoked were more likely to become smokers themselves (see Figure 3.3).

This important knowledge has led to a greater focus on smoking cessation at the National Centre of Expertise for AATD to prevent lung disease in current and future generations within families affected by Alpha-1. The findings once again highlight the importance of an early diagnosis of all types of AATD so positive lifestyle choices (like stopping smoking) can be made.

Figure 3.3. *An example of the new knowledge generated from a survey of smoking habits in people taking part in the National AATD Registry. The diagram shows how 2 risk factors are inherited in families with a parent who smokes; the genetic risk of Alpha-1 (Z type) and the habit of smoking.*





4 Coping on the Alpha-1 Journey – A Holistic Approach

My Life With Alpha-1

My name is James. I am 59 years old and married with 3 adult children.

I am a carpenter by trade and was a construction manager for over 30 years and I now manage a small farm and live in South Dublin. I am a nonsmoker and a sociable drinker. I had asthma as a child and grew out of it in my early teens. It returned when I was in my early thirties and only affected me when I got a cold and was controlled using inhalers. As I approached my late forties, I noticed myself becoming breathless while walking fast or climbing ladders on the construction sites. I put it down to not getting enough exercise and being overweight and maybe asthma as well. Then in 2010 I started getting chest infections which needed treatment with oral antibiotics and steroids and the infections started to become more frequent, maybe four a year. In late 2011 I was hospitalized in Tallaght hospital with pneumonia which was treated with oral antibiotics and steroids. While in hospital I underwent numerous tests and x-rays. Then a consultant came to see me and give me the results of my tests. He told me I had COPD and emphysema and my lungs were badly damaged. He sent me out to the respiratory unit in Peamount Healthcare in Newcastle in County Dublin for respite and to work with the physiotherapy department there.

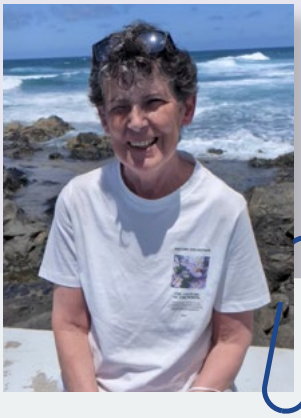
Then in 2012, while at an outpatient clinic in Peamount, I met a doctor who was there from Beaumont Hospital. It was then he asked me if I had heard of Alpha-1 Antitrypsin Deficiency which I replied no, and he explained to me what it was and he asked me would I like to be tested for it. I agreed and gave a blood sample that day. Three weeks later I was called back to the outpatients for the result of my Alpha-1 test, and the result was that I was positive. The doctor told me there was an Alpha-1 clinic at Beaumont and he would make an appointment for me there to undergo more tests to determine how badly I was affected by Alpha-1. I underwent a lot of tests over a couple of weeks and then an appointment was made to see the consultant to discuss the results. When I met the consultant, he explained the different types of Alpha-1. My test results showed I had the ZZ type and I had only 17% to 20% lung function. He also told me I might be a suitable candidate for a double lung transplant. I was also accessed by the physiotherapy department, and it was decided that I use portable oxygen while I was mobilizing as my oxygen levels were dropping while I was walking, climbing stairs, going up an incline etc.

On meeting the consultant at the Mater Hospital, he told me I would be suitable for a double lung transplant, but my weight was an issue as my BMI was too high. I was told to try get the weight down and I would be reviewed in six months. From 2012 to 2019 I was hospitalized once or twice a year with infections and had, maybe, three or four GP visits. Throughout these years I would have attended classes with dietitians and pulmonary rehab classes, but any weight loss was put back due to steroid use and the inability to exercise. In July 2019 I joined Slimming World and attended pulmonary rehab classes and I was feeling the benefit of both. I got a chest infection in February 2020, and I spent ten days in hospital. For the rest of 2020 through COVID I continued my diet and exercise at home and became less dependent on my portable oxygen. 2021 was another good start to the year I was doing pulmonary classes online continuing with the diet and in June I attended classes in person again. At the end of July 2021, I met the consultant at the Mater Hospital who was happy with my progress. I was taken in in August 2021 to the Mater Hospital for a full health assessment which went well. Now at this stage I had nearly eighteen months with no major infections. But in October 2021 I got pneumonia and was hospitalized for three weeks. 2022 was not great I was again hospitalized for six weeks and caught COVID. Because of all the infections last year and not being able to exercise my weight has increased again. But 2023 has been a lot better for me so far this year with no steroids and only one antibiotic.

I am currently attending pulmonary rehab classes twice a week and an online class run by the HSE which is called Best Health weight management programme.

I find that if you keep active and the fitter you are it is easier to fight off infections. My goal would be to get back into some sort of employment.

I would like to thank all the staff involved in the Alpha-1 clinic in Beaumont Hospital for treatment and care of my condition while in hospital and at outpatient appointments.



My Life With Alpha-1

My name is Dorothy and I grew up in the North West. I always felt that if I was going to get in trouble physically it was going to be my lungs that might be vulnerable. As a child I suffered with horrible colds and chest infections which went on for weeks, as did my mother. As a teenager and now smoking, she would often say to me 'you should give up the cigarettes, emphysema is a terrible thing if you get it'. I believe now that it's quite possible that her father died of pneumonia, secondary to Alpha-1 in his early fifties. I never met him.

I went to London in the mid-eighties and qualified as a Veterinary Nurse, a career that I loved. In the late eighties I returned to Ireland and as a result of experiencing the grief clients often felt after the death of a pet I decided to train as a Grief Therapist. I continued my studies and became a Psychotherapist, which is now my primary occupation. I am still lucky enough to work with animals once a week in a nearby Veterinary Practice.

My youngest brother was diagnosed with Alpha-1 (severe form of the ZZ type) in his forties. It took seven years for him to get a definitive diagnosis, by which time he was very ill. I wonder had he got an earlier diagnosis would he have had access to better treatment and a better quality of life than he has currently. At that time it was suggested that all the siblings be tested. I remember being very fearful at this news and whilst I didn't rush off to get tested I did say it in an offhand way to my GP. She reassured me that I couldn't possibly have Alpha-1 as I was too well. I wasn't really reassured but it was enough for me to abandon the idea of having a test at that time, after all, there is no cure.

I continued and had my usual amount of colds and coughs, but in the summer of 2015, I got a really severe chest infection. After a couple of courses of antibiotics, I still wasn't alright. I was sent for an X-Ray to the local hospital. I was again reassured that my lungs were fine. But I wasn't alright, I was having difficulties catching a full breath, I had pains in my back when I exercised and I didn't feel well. I went back to my GP and asked for my alpha-1 antitrypsin levels to be tested. I got the results while abroad at my niece's wedding in September 2015, I was fifty five years old then. I hoped I might be an MZ (moderate alpha-1 antitrypsin deficiency), but I am a ZZ. I was referred to Beaumont Hospital for further tests. My lung CT scan indicated I had emphysema, bronchiectasis and I also had an asthmatic component to my lung disease.

Processing this news was incredibly difficult, I stopped working for almost three months and got very anxious and depressed. At times I felt hopeless and so fearful of the future. I never had to take daily medications in my life and now I had to learn about inhalers, respiratory physiotherapy and prompt use of antibiotics when required. I had a lot of support during all of this and with time came to accept Alpha-1 as a part of my life, a serious chronic condition that needs to be managed if I'm to stay as well as I can be.

The arrival of COVID-19 here was a very difficult time for anyone with a respiratory condition and I remember being very anxious a lot of the time, being at home felt very safe and our friends and neighbours were so helpful with shopping and getting our supplies. I had to inform my clients and others of my vulnerability to COVID-19 infection when I returned to face to face work, and whilst this was exposing at the time, it has paid dividends since. No one will attend or approach me if they have symptoms of any respiratory illness. I continue to wear a mask in certain settings and it's considered normal now. I get my eighth COVID-19 vaccination next week.

I exercise as much as I can, until there is a cure I want to preserve the lung function I have. I try to live in the day, the future is unknown to me and when I let my mind go there I get scared. This is a progressive disease but I only have today. My place where I forget about having Alpha-1 is when I am out in nature and I love to garden, walk my dogs and attempt physical tasks. I want to acknowledge the help and support I have had in coming to terms with my Alpha-1 diagnosis and this support is ongoing and I am grateful to have it.

5 Recent Events

Trinity College Dublin
The University of Dublin

Alpha-1 Lecture

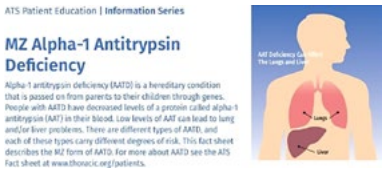
In early January Alpha-1 Foundation Ireland was invited to give a lecture on how to test for alpha-1 antitrypsin deficiency. This was to a group of scientists on the M.Sc. in Clinical Chemistry at Trinity College Dublin. Lectures like this raise awareness of AATD among hospital laboratory scientists, unsung heroes of the healthcare system, a point made by Dr. Michael Ryan of the WHO.

Marathon Challenge

In February family and friends of one of the original Alpha-1 warriors Josephine McGuirk completed yet another marathon challenge. The goal was to raise awareness of Alpha-1 and to fundraise for Alpha-1 Foundation Ireland. The challenge took place across Dublin, Meath and Kildare. The Warriors surpassed their original 5k target, raising a staggering €7,307. A huge thank you to the McGuirk family, friends and everyone who supported them. Thanks also to Docusign for their generous donation.

Conference Presentation about Alpha-1 Testing

In March, Alpha-1 Foundation Ireland presented at the Biomedica conference. The meeting is organised by the Academy of Clinical Science and Laboratory Medicine, which is the professional body representing medical scientists in Ireland. The conference was an excellent opportunity to raise awareness of Alpha-1.



New Article on MZ Alpha-1

In April a new article on MZ Alpha-1 was published in the American Journal of Respiratory and Critical Care Medicine. The article was co-authored by Gerry Finnerty, an Irish Alpha-1, who helped ensure the language and phrases used were clear and easy to understand for everyone.

Irish Research Shows Alpha-1 Antitrypsin a Possible Treatment for Severe Disease Caused by COVID-19

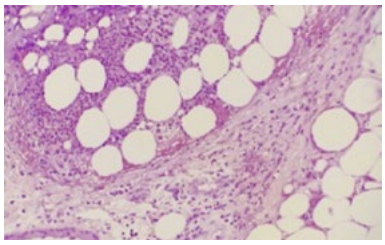
Treatment options for patients with severe COVID-19 particularly those who develop acute respiratory distress syndrome (ARDS), are limited. Alpha-1 antitrypsin (AAT) is an anti-inflammatory protein produced by the liver and present the bloodstream. An article published in April showed AAT purified from the blood of healthy donors could be a therapeutic option for patients with COVID-19-associated ARDS. Treatment with AAT decreased inflammation and was safe and well tolerated.

Alpha-1 Education

In July Alpha-1 Foundation Ireland visited Our Lady of Lourdes Hospital in Drogheda to discuss Alpha-1 with the nurses & doctors of the respiratory unit. Visits to hospitals are an important way to raise awareness and stress the importance of testing for Alpha-1 in people with COPD.

Alpha-1 Awareness in Cavan

In September, Alpha-1 ambassador Rose McGrath gave a fantastic interview in her local newspaper the Anglo-Celt. Her article helped to promote World Lung Day on September 25th.



Irish Research into Skin Disease Panniculitis Caused by Alpha-1

In October an article in the prestigious Journal of American Academy of Dermatology revealed more than 100 cases of panniculitis caused by AATD have been reported. This number was far greater than expected and highlights that AATD is a recognized yet often overlooked cause of panniculitis.

Global Alpha-1 Congress Coming to Ireland

Also in October we were invited to co-host the Global Alpha-1 Patient Congress with our colleagues in the US Alpha-1 Foundation. Patient leaders, physicians and scientists from around the world will come to Dublin in April 2023 to discuss the latest developments in patient advocacy, clinical care and Alpha-1 Antitrypsin Deficiency (Alpha-1) research.

Live 95
Limerick's best music mix

Alpha-1 on the Radio

In November on World COPD Day 2022 Helen Madigan was interviewed on her local radio station Limerick Live95. First diagnosed with COPD, then with a diagnosis of Alpha-1, Helen spoke about her condition and how she was diagnosed. Míle buíochas Helen!

ST JAMES'S HOSPITAL

Alpha-1 Education

In November Alpha-1 Foundation Ireland presented to scientists working in the busy Biochemistry Department in St James's Hospital about the various techniques used to diagnose AATD.

Tallaght University Hospital

Alpha-1 Education

In December Alpha-1 Foundation Ireland visited Tallaght University Hospital to talk about all things Alpha-1 with the nurses & doctors of the respiratory unit.

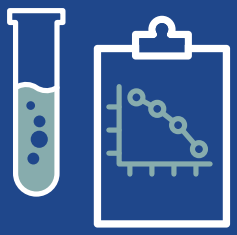
6 Latest Clinical Trial News

New Clinical Trials for Severe Alpha-1

There are some exciting clinical trials looking at new treatments for people with severe AATD (e.g. ZZ type). The first such study, KAMADA, began recruitment in summer 2022. Eligible participants are people who are ZZ Alpha-1. The study is a **phase III, placebo-controlled, double-blind** study to test a new inhaled form of alpha-1 antitrypsin. Beaumont Hospital is the only recruitment site in Ireland but there are many across the world. Other studies include the ongoing EARCO study, an observational study looking at the demographics and natural history of people with severe AATD across Europe, and several studies to investigate treatments for people with liver disease caused by severe AATD that will start in 2023.

If you would like to find out more about these and future studies, you can contact Ann Collins, Clinical Research Coordinator at *annmcollins@rcsi.ie* or by calling *01 809 3863*.

Clinical Trials – Some Key Terms (from *clinicaltrials.gov*)



Clinical study/Clinical trial: A research study involving human volunteers (also called participants) that is intended to add to medical knowledge. There are two types of clinical studies: interventional studies (also called clinical trials) and observational studies.

Eligibility criteria: The key requirements that people who want to participate in a clinical study must meet or the characteristics they must have. Eligibility criteria consist of both inclusion criteria (which are required for a person to participate in the study) and exclusion criteria (which prevent a person from participating). Types of eligibility criteria include whether a study accepts healthy volunteers, has age or age group requirements, or is limited by sex.

Informed consent: A process used by researchers to explain to potential participants the risks and potential benefits of participating in a clinical study.

Investigator: A researcher involved in a clinical study. Related terms include site principal investigator, site sub-investigator, study chair, study director, and study principal investigator.

Observational study: A type of clinical study in which participants are identified as belonging to study groups and are assessed for biomedical or health outcomes. Participants may receive diagnostic, therapeutic, or other types of interventions, but the investigator does not assign participants to a specific interventions/treatment. A patient registry is a type of observational study.

Phase: The stage of a clinical trial studying a drug or biological product, based on definitions developed by the U.S. Food and Drug Administration (FDA). The phase is based on the study's objective, the number of participants, and other characteristics. There are five phases: Early Phase 1 (formerly listed as Phase 0), Phase 1, Phase 2, Phase 3, and Phase 4.

Placebo: An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.

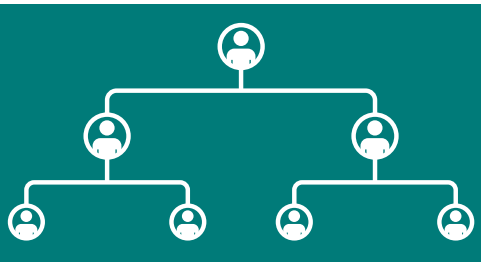
Principal investigator (PI): The person who is responsible for the scientific and technical direction of the entire clinical study.

Protocol: The written description of a clinical study. It includes the study's objectives, design, and methods. It may also include relevant scientific background and statistical information.

7 Alpha-1 Research Highlights in 2022

Daniel Fraughen

New ZZ Family Study



A new all island study exploring the risk of lung disease in families containing people with ZZ AATD began in mid-2022. This follows on from 2 previous successful studies of families containing either MZ or SZ alpha-1 antitrypsin deficiency (AATD) members. We know from how AATD is inherited that if a person in a family has ZZ AATD, the chances of other siblings also having ZZ AATD are quite high. Taking part will involve breathing tests, questionnaires, and some blood tests. In this study we hope clarify to what extent lung disease is present in the siblings, parents and children of those with ZZ AATD, who have yet to be diagnosed or present themselves to their doctor because of lung problems. This important question remains unanswered and we hope to uncover the hidden burden of ZZ AATD in Ireland among the many families affected.

If you have been diagnosed with ZZ AATD and think your family would be suitable to take part in the study, please email *alpha1@rcsi.ie* to find out more.

Fiachra O'Meara (L) and Simon Carty (R)

Evaluating Liver Disease in Alpha-1 Antitrypsin Deficiency (AATD)

People with alpha-1 antitrypsin deficiency have increased risk of liver disease. This research project was the first to examine the extent of liver disease in people with severe (ZZ) and moderate (MZ, SZ) type AATD in Ireland. Simon Carty and Fiachra O'Meara, medical students from RCSI, looked at participants (n=169) on the National AATD Registry who had recent (<2 years) ultrasound (US) and transient elastography (TE) scans. TE also called "Fibroscan" is a more sensitive method of checking the liver, and can assess steatosis and fibrosis. The study included ZZ (n=74), MZ (n=70) and SZ (n=25) phenotypes. Simon and Fiachra found that TE was more sensitive than US for diagnosing steatosis and fibrosis in AATD.

FibroScan®

Alpha-1 Antitrypsin a Possible Treatment for Severe Disease Caused by COVID-19

Professors Gerry McElvaney and Ger Curley

Treatments for patients with severe COVID-19, particularly those who progress to acute respiratory distress syndrome (ARDS), are limited. ARDS is a highly inflammatory state hallmarked by airway damage, respiratory failure, and increased mortality. Alpha-1 antitrypsin (AAT) is an anti-inflammatory protein produced by the liver and present the bloodstream. A research team lead by Professor Gerry McElvaney and Professor Ger Curley investigated the use of AAT purified from the blood of healthy donors as a therapeutic option for patients with COVID-19-associated ARDS. Treatment with AAT resulted in decreased inflammation, was safe and well tolerated, and did not interfere with patients' ability to generate their own protective response to COVID-19. The results suggest a potential role for AAT in treating COVID-19-associated ARDS and perhaps other inflammatory diseases.

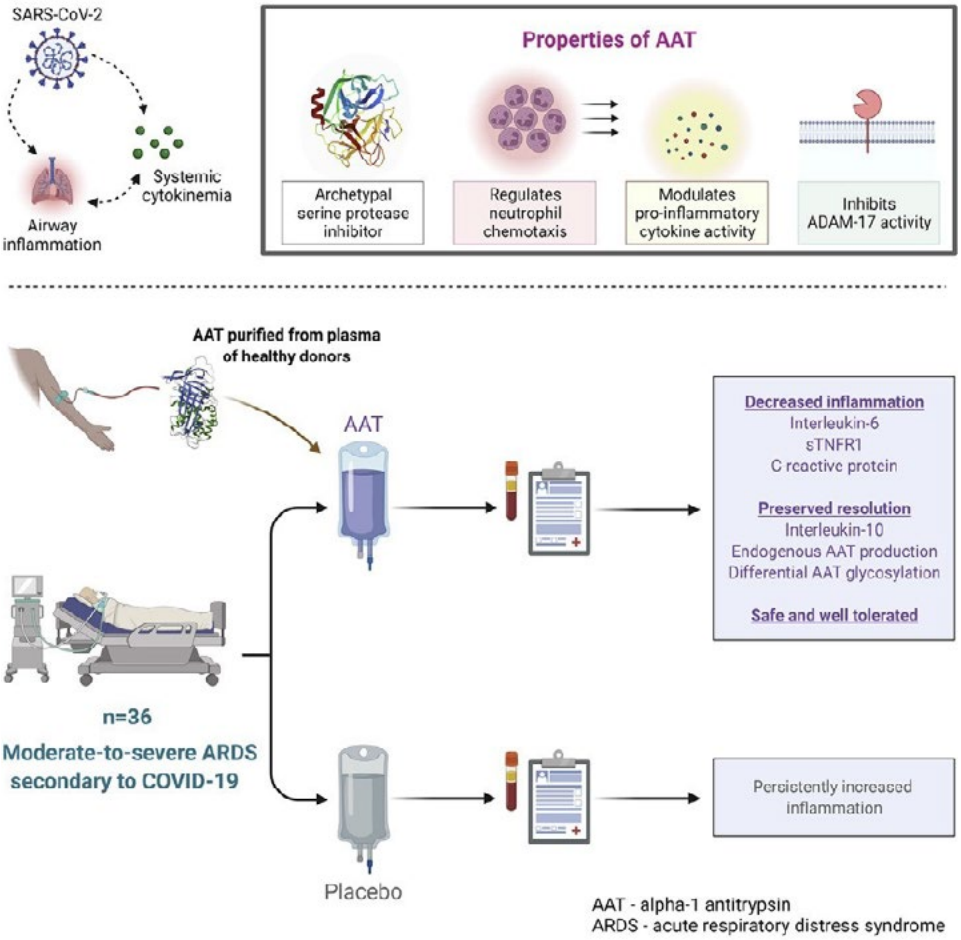


***Figure 7.1.** Graphic from MED paper published in March 2022 showing the therapeutic benefit of intravenous AAT for the treatment of COVID-19 ARDS.*

Irish Alpha-1 Research Published in 2022

1. McEnery T, White MM et al. Alpha-1 Antitrypsin Therapy Modifies Neutrophil Adhesion in Patients with Obstructive Lung Disease. *Am J Respir Cell Mol Biol.* 2022 Jul;67(1):76–88.
2. McElvaney OJ, Cleary B et al . Attitudes Towards Vaccination for Coronavirus Disease 2019 in Patients with Severe Alpha-1 Antitrypsin Deficiency. *Chronic Obstr Pulm Dis.* 2022 Apr 29;9(2):266–273.
3. McElvaney OJ, Finnerty G et al. MZ Alpha-1 Antitrypsin Deficiency. *Am J Respir Crit Care Med.* 2022 Apr 1;205(7):P13–P14.
4. McElvaney OJ, McEvoy NL et al. A randomized, double-blind, placebo-controlled trial of intravenous alpha-1 antitrypsin for ARDS secondary to COVID-19. *Med.* 2022 Apr 8;3(4):233-248.e6.
5. O'Brien ME et al. A Review of Alpha-1 Antitrypsin Binding Partners for Immune Regulation and Potential Therapeutic Application. *Int J Mol Sci.* 2022 Feb 23;23(5):2441.
6. Franciosi AN, Fraughen D, Carroll TP, McElvaney NG. Alpha-1 antitrypsin deficiency: clarifying the role of the putative protective threshold. *Eur Respir J.* 2022 Feb 10;59(2):2101410.
7. Fromme M, Schneider CV et al. Hepatobiliary phenotypes of adults with alpha-1 antitrypsin deficiency. *Gut.* 2022 Feb;71(2):415–423.
8. Franciosi AN, Ralph J et al. Alpha-1 antitrypsin deficiency-associated panniculitis. *J Am Acad Dermatol.* 2022 Oct;87(4):825–832.

Financial Report

Alpha-1 Foundation Ireland
(A Company Limited by Guarantee and not having Share Capital)
Financial Statement
Financial year ended 31 December 2022

	2022	2021
	€	€
TURNOVER		
Northern Area HSE	119,565	119,565
Donations	9,474	25,663
	129,039	145,228
Gross profit	129,039	145,228
Gross profit percentage	100.0%	100.0%
OVERHEADS		
Administrative expenses	(107,925)	(87,925)
Operating profit	21,114	57,303
Operating profit percentage	16.4%	39.5%
Profit before taxation	21,114	57,303
Overheads		
Administrative expenses		
Wages and salaries	(75,024)	(73,037)
Lab Costs	(7,220)	(1,152)
Printing, postage and stationery	(1,132)	(256)
Computer costs and system maintenance	(9,192)	(3,220)
Travel	-	(517)
Research costs	-	(1,932)
Accountancy fees	(6,150)	(6,133)
Bank charges	(107)	(113)
General expenses	-	(70)
Subscriptions	(1,103)	(1,495)
Charitable Donations – type 2	(371)	-
Depreciation of tangible assets	(6,014)	-
	(109,046)	(87,925)
Profit before taxation	19,993	57,303
Tax on profit	-	-
Profit for the financial year	19,993	57,303

NOTE: Detailed financial statements are available on *www.alpha1.ie*

Acknowledgements

We would like to thank the following:

- Orla Cahalane, Ella Howard, Bríd Holohan, Rabelani Kaela, Dr. Bill Tormey and the Beaumont Hospital Chemical Pathology Department for their continued support and assistance
- Angela McBride and colleagues from the Alpha-1 Foundation (USA) for their continued support
- Dr. Ilaria Ferrarotti and Dr. Stefania Ottaviani, Centre for Diagnosis of Inherited Alpha-1 Antitrypsin Deficiency, University of Pavia, Italy
- Louise Clarke and colleagues in the Pulmonary Function Laboratory in Beaumont Hospital
- Jean Kirwan and Linda Phoenix, members of the Beaumont Hospital Respiratory Clinic Administration Team
- Fiachra O'Meara and Simon Carty, RCSI medical students, and Louis O'Carroll, RCSI physiotherapy student who carried out Alpha-1 research projects with Alpha-1 Foundation Ireland in 2022
- Health Research Charities Ireland (HRCI), the Irish Platform for Patients' Organisations, Science & Industry (IPPOSI), the Irish Lung Health Alliance, and the Irish Thoracic Society (ITS)
- President Michael D. Higgins for his continued support as patron of Alpha-1 Foundation Ireland
- A special thank you to everyone who took part or organised awareness and fundraising events throughout the year

We would also like to thank the Department of Health and Children and the Health Service Executive for their continued financial support

We would also like to acknowledge the participation of the following hospitals:

- Beaumont Hospital
- Blackrock Clinic
- Bon Secours Hospital Tralee
- Bon Secours Hospital Dublin
- Cavan General Hospital
- Children's University Hospital, Temple Street, Dublin
- Coombe Women and Infants University Hospital
- Cork University Hospital
- James Connolly Memorial Hospital Blanchardstown
- Kerry General Hospital
- Letterkenny University Hospital
- Mater Misericordiae University Hospital, Dublin
- Mayo General Hospital
- Midland Regional Hospitals: Tullamore, Mullingar, and Portlaoise
- Naas General Hospital
- Our Lady's Children's Hospital, Crumlin
- Our Lady of Lourdes Hospital, Drogheda
- Our Lady's Hospital, Navan
- Peamount Hospital, Dublin
- Roscommon County Hospital
- Rotunda Hospital, Dublin
- Sligo University Hospital
- St. James's Hospital, Dublin
- St. Luke's General Hospital Carlow/Kilkenny
- St. Vincent's University Hospital, Dublin
- South Tipperary General Hospital, Clonmel
- Tallaght University Hospital
- University Hospital Galway
- University Hospital Limerick
- University Hospital Waterford
- Wexford General Hospital

TEL: 01-809 3871 **EMAIL:** alpha1@rcsi.ie **WEB:** www.alpha1.ie

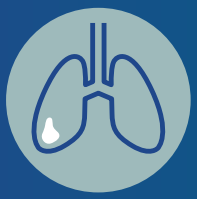
Alpha-1 Foundation Ireland Charity Code: CHY22304

@Alpha1_Ireland

Find us on Facebook

Alpha-1 is the most common genetic cause of COPD

1 in 25 people in Ireland carry the faulty Z Alpha-1 gene



Smokers with the single faulty Z Alpha-1 gene have a **10 fold** increased risk of developing a lung disease called COPD

The Irish Thoracic Society estimates approximately **440,000** people have COPD in Ireland

22,500+ people tested for Alpha-1 to date in a National Targeted Detection Programme

850+ people with Alpha-1 attend the National Centre of Expertise for Alpha-1 at Beaumont Hospital

670+ people with Alpha-1 take part in the National Alpha-1 Registry