ANNUAL REPORT 2019

ALPHA-1 FOUNDATION IRELAND

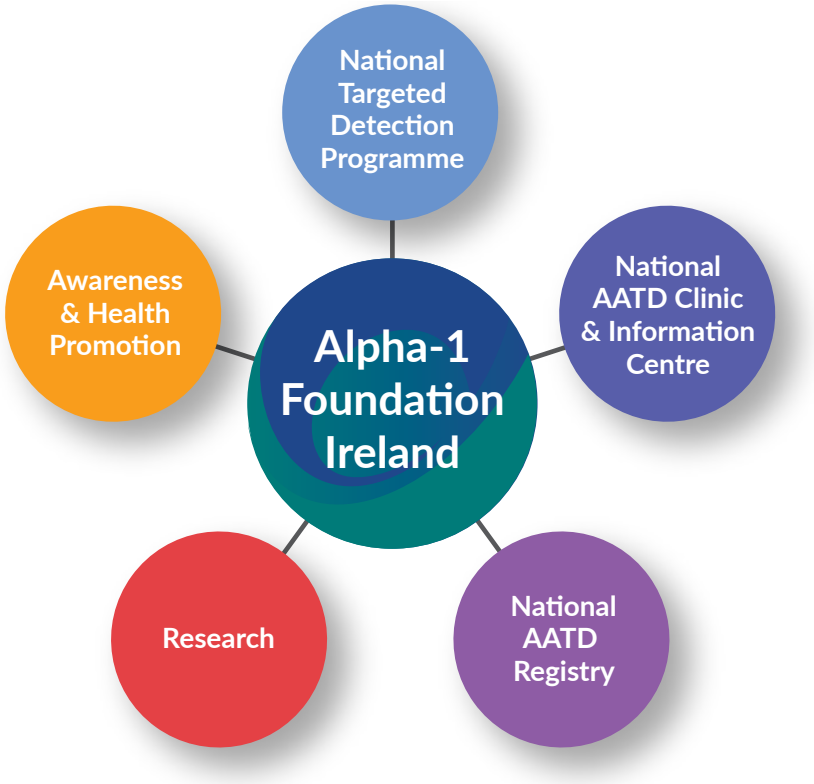
MISSION STATEMENT

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 THE ALPHA-1 FOUNDATION IRELAND

Ms Geraldine Kelly, CEO

Dr Tomás Carroll, Chief Scientist

PATRON

Michael D. Higgins, President of Ireland

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

ANNUAL REPORT 2019

ALPHA-1 FOUNDATION IRELAND

CONTENTS

This Annual Report is dedicated to the Cassidy, Kelly, and Keenan families.

1 Executive Summary

Although we are involved in many very important pieces of work our main activity continues to be the National Alpha-1 Targeted Detection Programme, which recently reached an important milestone of 20,000 Irish people tested. This significant milestone led to the detection of over 4,200 people with some form of Alpha-1, of which 400 are ZZ the most severe form. We continue to strive for greater awareness of the condition and encourage Family testing with every new diagnosis.

On 1st July 2018 the Foundation became a company limited by guarantee. This is an important step towards best practice in governance. We welcome Professor Shane O'Neill as our Chairperson and offer our sincere thanks to Professor Gerry McElvaney for his leadership, guidance and support over the past number of years.

The foundation continues development of the national Alpha-1 registry. The number of patients now enrolled is in excess of 550 helping to identify suitable candidates for upcoming clinical trials and research projects. We launched our new Website and Logo in 2018 and extended our presence on social media with the creation of our Twitter account @Alpha1_Ireland. In April 2019 I travelled with three patient representatives, Orla Keane, Niamh Kelly and Aideen Cleary to Dubrovnik to attend a very successful and informative Alpha-1 Global Conference.

We successfully secured joint funding from the Health Research Board (HRB) and Health Research Charities Ireland (HRCI). Our goal is to place a greater importance on Patient and Public Involvement (PPI) in research over the course of the coming year. To achieve this a workshop will take place for patient members of our scientific committee to help them understand the role they will perform in research projects. The outcome we hope to achieve is more informed and improved quality researcher and patient conversations resulting in more relevant and successful research projects.

The annual Alpha-1 conference took place in October 2018 in Marino Institute of Education. Almost 100 Alpha-1 patients and family members congregated in a relaxed and informal environment. We were delighted to welcome Joe Duffy, RTE broadcaster to open the conference, which was themed "Family Matters". Speakers included Professor Gianpiero Cavalleri, RCSI Geneticist, Professor Gerry McElvaney, Clinical Lead, National Centre for Alpha-1, Avril Kennan CEO, HRCI as well as the impressive Jenny McGuirk, Alpha-1 patient advocate who stole the show.

We continue to partner and network with groups such as Health Research Charities Ireland formerly MRCG, the Irish Donor Network, the Irish Platform for Patient Organisations, Science and Industry (IPPOSI), the Irish Lung Health Alliance, the Rare Disease Taskforce, the European Organisation for Rare Diseases (EURORDIS) and COPD Support Ireland and benefit greatly from their experience. Our outreach programme has taken us to COPD Support Groups in Tallaght, Wexford, Ballyfermot, Sligo, as well as presentations to hospital medical and laboratory teams in Sligo, Letterkenny, Drogheda, Galway, and Peamount hospitals. Many more outreach visits will take place in 2020.

We are thankful for all fundraising activities in the last 2 years. The efforts have been amazing and varied, mini-marathons, full marathons, coffee mornings, and even Cannonball rallies! The money raised is put to good use in our Alpha-1 screening programme.

All achievements are the result of huge team effort by Foundation staff, and by research and medical teams. In particular, I wish to thank all my colleagues in the Foundation for their hard work and dedication throughout the year, particularly Dr. Tomás Carroll, Laura Fee and Siobhan Lee.

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 provides a unique opportunity for early medical 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. In October 2019 we reached the milestone of 20,000 people tested.

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 specific patient groups, with a big focus on chronic obstructive pulmonary disease (COPD)(Table 2.1).

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 necrotising 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?

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 alpha-1 antitrypsin protein is present by a method called isoelectric focusing. This method identifies variants of alpha-1 antitrypsin circulating in human blood, and is more commonly known as phenotyping (Figure 2.1). It is the most accurate method of diagnosing Alpha-1 and recognises not only the most common but also rare AAT variants.

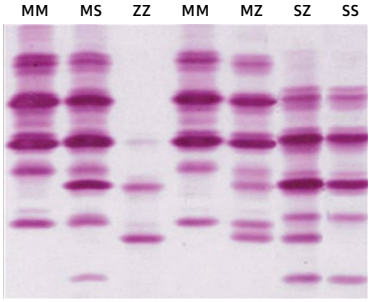
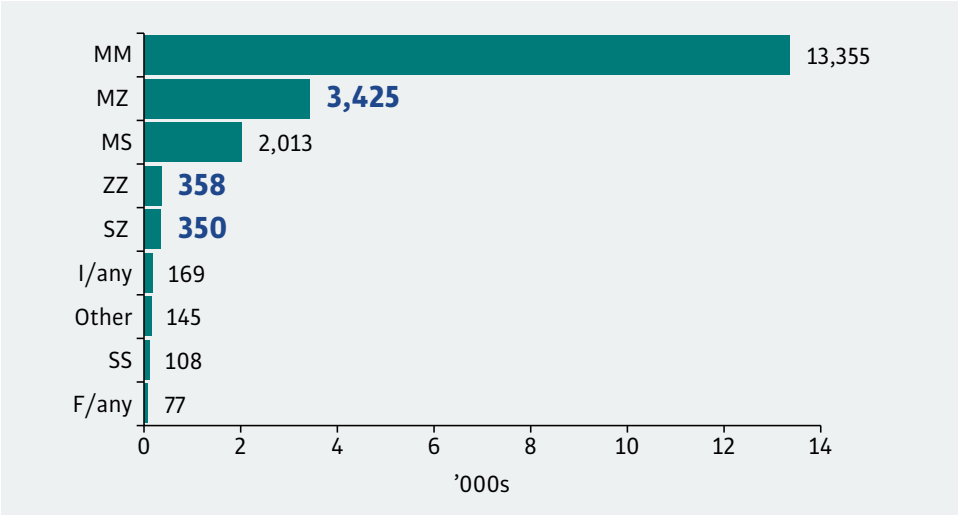


Figure 2.1. *Typical isoelectric focusing gel for AAT phenotype identification with the most common phenotypes included.*

What Have We Found in Ireland?

Since 2004 a total of 20,000 individuals with COPD, asthma, and liver disease, as well as first-degree relatives of people known to have AATD have been tested in a National Targeted Detection Programme.

Figure 2.2. *Results from the National AATD Targeted Detection Programme showing AAT phenotypes identified among the 20,000 individuals tested.*



A total of 358 ZZ (severe Alpha-1) individuals have been identified, as well as 350 SZ individuals, who are also at risk of developing lung and liver disease, particularly if smoking Figures 2.2 and 2.3). In addition, a large number of other clinically significant phenotypes have been detected including 3,425 MZ, 21 IZ, and 8 FZ phenotypes. A number of very rare deficiency-causing AAT mutations have also been identified. These include Mwurzburg, Zbristol, Mmalton and five different Null mutations (Nullbolton, Nullcork, Nulldublin, Nullporto and Nullamersfoort).

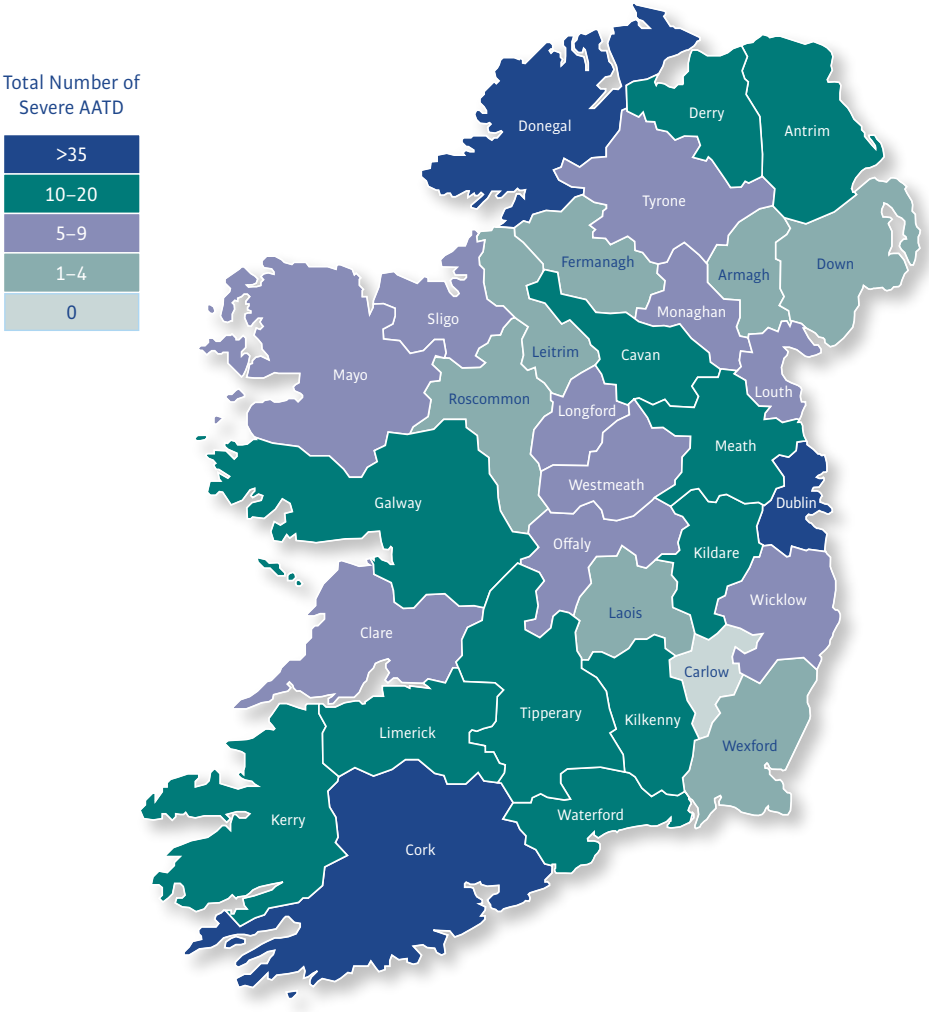
Figure 2.3. *Simple explanation of the most common AAT phenotypes in Ireland.*

AAT Phenotype/ AAT Genotype*	Deficiency?	What does it mean?
MM	No	Does not have the disorder – does not have any altered AAT genes.
MS	Very Mild	No evidence of increased risk of lung or liver disease but does carry 1 altered AAT gene.
MZ	Mild	MZ Significantly increased risk of lung disease **in smokers**. Definite but not yet quantified risk of liver disease.
SS	Mild	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 screening programme is to ensure people with Alpha-1 are correctly diagnosed and have the opportunity to receive expert medical care. 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 allows the identification of other family members with Alpha-1, which can help prevent or postpone the development of lung disease in the wider family. Importantly, a correct diagnosis means people can benefit from lifestyle changes such as smoking cessation, closer medical surveillance by Alpha-1 experts, and the opportunity to enrol in clinical trials to test new treatments.

Figure 2.4. *Distribution of severe AATD cases detected to date (412 cases in total).*



In the past 12 months we have given talks about Alpha-1 to a mixture of respiratory, liver and laboratory teams in Sligo, Letterkenny, Drogheda, Galway, and Peamount hospitals and to 3rd year medical students in UCD. The aim of these presentations is to increase awareness of Alpha-1 among health professionals and to encourage testing. While respiratory and liver medical teams care for populations most at risk due to AATD, the hospital Immunology and Biochemistry departments measure alpha-1 antitrypsin levels as a routine test during normal blood investigations.

Opportunities to increase the detection of AATD in the healthcare system in future include the roll-out of the National Medical Laboratory Information System (MedLIS) which is the new national IT system for laboratory medicine and the new national laboratory handbook which describes best practice in testing for AATD (*www.hse.ie/eng/about/who/cspd/ncps/pathology/resources/lab-testing-for-alpha-1-antitrypsn-antibodies.pdf*). Alpha-1 Foundation Ireland has made contributions to both initiatives over the past two years.

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, pulmonary function tests, CT scans of the chest and ultrasounds of the liver are obtained from the medical chart, entered in the registry and updated at regular intervals.

What is the purpose?

The registry helps to deepen our understanding of Alpha-1 as a condition, improve clinical care for patients, and aid recruitment for clinical trials investigating new treatments for Alpha-1. The small numbers of people affected by a rare disease means that getting access to the right care, treatment and support can be difficult. The importance of registries in filling gaps in rare disease care cannot be underestimated.

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.

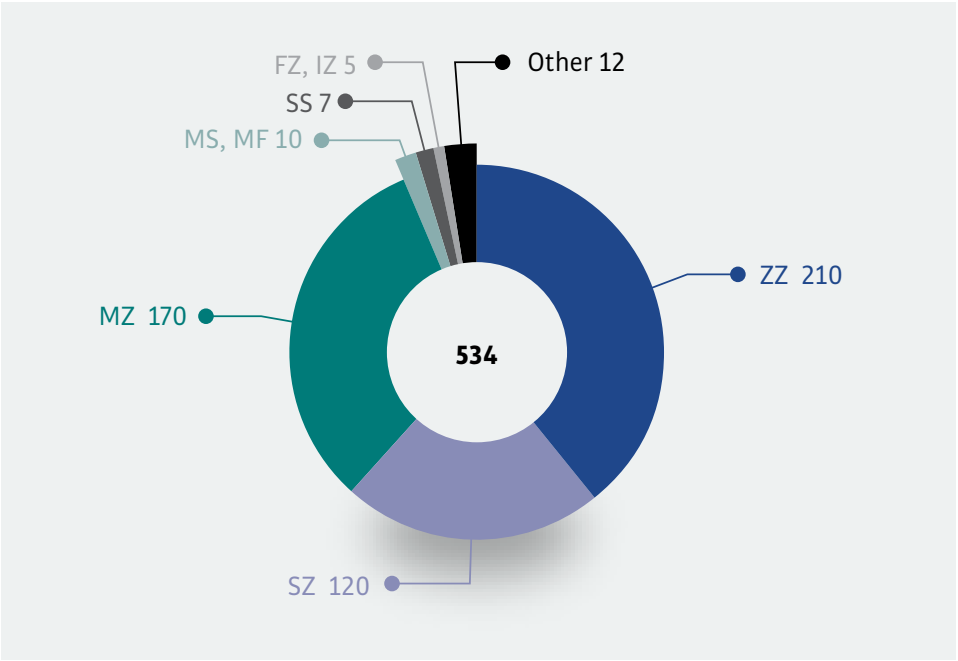
Questions?

If you or your family are interested in enrolling or have any questions about the registry please contact us on 01 809 3871. To read more about our registry visit *www.alpha1.ie/who-we-are/national-alpha-1-registry*.

Registry Update

During 2017 and 2018 the registry was re-developed with the help of Irish IT company OpenApp and the expert guidance of Margaret Molloy our former colleague. Special mention also to Siobhán Lee, Alpha-1 research nurse, who helped to expand the registry and ensure compliance with new data protection laws. The new, improved National AATD Registry with enhanced user and security features and a family tree tool (Figure 3.2) was launched in summer 2018.

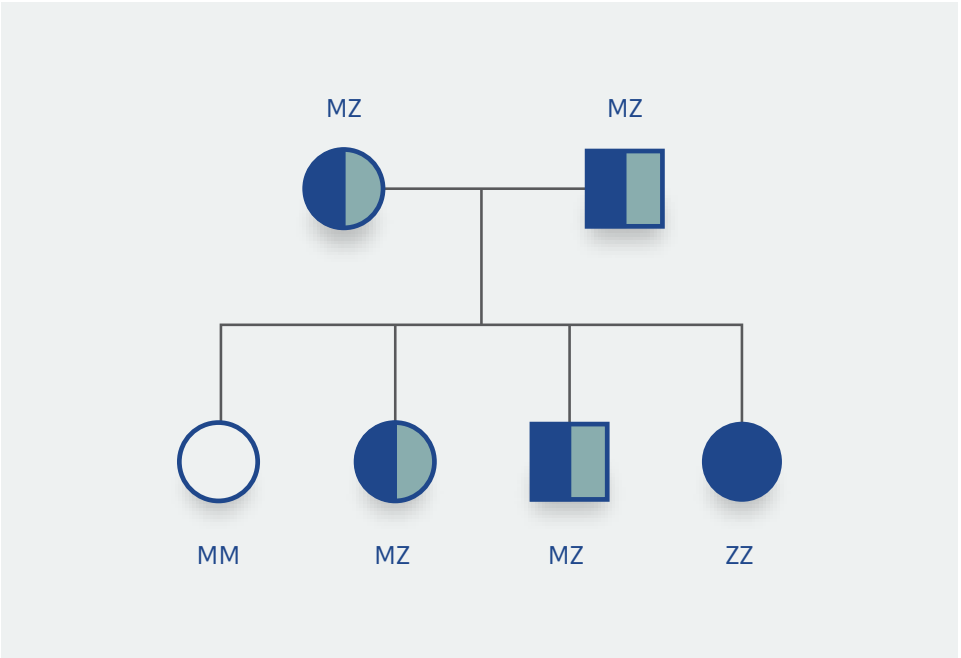
Figure 3.1. *Total number of individuals enrolled in the registry according to AATD phenotype.*



Research publications have been produced using the registry data and have deepened our understanding of the risk factors and symptoms associated with the health problems caused by Alpha-1. For example a recent RCSI study used anonymous data from the Irish registry to highlight the devastating impact of cigarette smoke on the lung health of people with severe AATD ["The impact of smoke exposure on the clinical phenotype of alpha-1 antitrypsin deficiency in Ireland: exploiting a national registry to understand a rare disease." O'Brien et al., Journal of COPD 2015].

This knowledge has led to greater focus on smoking cessation at the National Centre of Expertise for AATD as it is the number one intervention for people with severe Alpha-1. The findings also highlight the importance of an early diagnosis of AATD so positive lifestyle choices (like stopping smoking) can be made.

Figure 3.2. *An example of the new family tree tool on the National AATD Registry.*



4 Recent Events

Donegal Coffee Morning

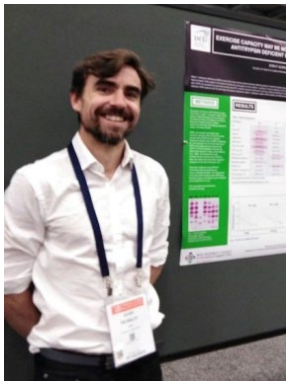
A coffee morning in aid of Alpha-1 and in memory of the late Anna Cassidy took place in late September 2019, in Donegal Town. Over 100 people took part and the event was covered in a feature article in the Donegal News.

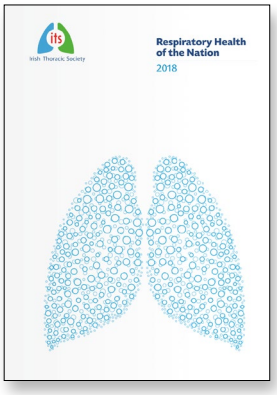
Cannonball Rally

A special thank you to Carinne and Niall Maher who raced across the south of Ireland in July 2019 to raise awareness of Alpha-1.

Annual Maynooth Coffee Morning

A huge thank you to everyone who took part in a coffee morning in aid of Alpha-1 in the Glenroyal Hotel in Maynooth in May. A special thanks to Orla Keane and her merry band of helpers.





Irish Alpha-1 Research Presented at International Conference

Mr. Eóin Durkan presenting his research on the importance of exercise for people with Alpha-1 at the American Thoracic Society International Conference in May 2019 in Dallas, Texas. A huge thank you to everyone who took part in the programme in DCU.

New Report on Lung Disease in Ireland

A major new report on the burden of lung disease in Ireland was published in December 2018. “Respiratory Health of the Nation 2018” features a chapter on COPD and includes information on Alpha-1 as a genetic cause of COPD.

Irish Thoracic Society Annual Scientific Meeting 2018

Geraldine Kelly and Dr. Tomás Carroll from Alpha-1 Foundation Ireland hosting an educational stand at the Irish Thoracic Society conference in November 2018 in Belfast. The aim was to raise awareness of Alpha-1 among the 450+ healthcare professionals working in the field of respiratory medicine.

Dublin Marathon 2018

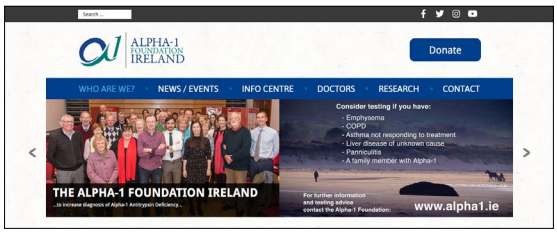
Thanks to Colin McGuirk pictured here with his mother Josephine who completed the Dublin marathon in October 2018 in aid of Alpha-1. The McGuirk family are fantastic supporters of Alpha-1 Foundation Ireland going back many years.

Annual Alpha-1 Conference 2018

Our Annual Alpha-1 Conference held in October 2018 at the Marino Institute of Education in Dublin was a great success with two VIPs present on the day, Joe Duffy and the Sam Maguire trophy. Joe Duffy opened Conference 2019 with entertaining stories about the Marino area and some Just A Minute quiz gems. Espresso anyone?

Celebration Concert July 2018

Siobhán Lee and Geraldine Kelly with President Michael D. Higgins, Patron of Alpha-1 Foundation Ireland at an event attended by organisations of which the President is patron.



New Alpha-1 Foundation Ireland Website

The new and improved *www.alpha1.ie* website was re-launched in January 2018 with improved content, smartphone flexibility, and a more modern style. Why not give us a visit?

Mannion Family Gathering

A family reunion in August 2018 in Galway was attended by Pádraig Bear and his friend Alphie, raising awareness of Alpha-1 along their way.

Healthcare Award Commendation

The educational film "What is Alpha-1" produced by Alpha-1 Foundation Ireland with the help of Anne Gormley and Orla Keane received a commendation at the Irish Healthcare Awards in November 2017.

5 Seventh Global Alpha-1 Patient Congress

Irish Delegation Pictured at the Global Patient Congress in Croatia. L–R, Geraldine Kelly, Niamh Kelly, Aideen Cleary, and Orla Keane.

The Seventh Alpha-1 Global Patient Congress was held from 4–6 April in Dubrovnik, Croatia. Over 160 participants representing 32 countries heard from leading Alpha-1 scientists and doctors, as well as patients, caregivers and family members.

Congress themes were awareness, detection, and access to therapies. The goal was to:

- Present the latest education on Alpha-1 research, therapies and patient care
- Develop pathways for expanded access to augmentation therapy
- Broaden individual awareness and participation, and inspire local action
- Identify possible next steps for organizations and individuals who are looking for new solutions
- Exchange best practices and success stories in advocacy and collaborative efforts
- Provide networking opportunities between patients and experts

Niamh Kelly (with Aideen Cleary)

I attended the Global Alpha-1 Patient Conference representing my sister who sadly passed away from the disease when Respreeza was taken away from her and 20 other patients. I learnt so much about AATD… most of all the importance of early testing for all family members. This was something we were not made aware of when Marion was diagnosed. The conference was a great experience, in particular meeting other patients and also knowing even though it can be a debilitating disease, with early intervention and awareness that patients can lead a very normal life. The conference was very well organised and it was good to see regional updates from the countries. It was a very enjoyable experience.

Orla Keane

A big thank you to Alpha-1 Foundation Ireland for their invitation to attend the 7th Alpha-1 Global Patient Congress in beautiful Dubrovnik. My fellow travellers were Geraldine Kelly CEO of Alpha 1 Foundation Ireland, Aideen Fahey, daughter of the late Marion Kelly, and her sister Niamh Kelly. It was an honour to share the experience with them.

On the first evening we attended the Patient Congress Welcome Reception in the Sheridan Hotel right on the seafront. The next day the congress was officially opened by Miriam O'Day, President and CEO of the US Alpha-1 Foundation. I found the two days to be very informative, in particular the research and therapeutic updates, a talk on Panniculitis, Young Patients Voice, research ethics, family testing and the speaker's Q&A. Professor McElvaney's talk on MZ carriers was very interesting. He explained how MZ's who avoid smoking will never develop emphysema, however those who do put themselves at risk.

I was surprised to discover many countries offer little respiratory care especially Serbia and Romania. We are very lucky here in Ireland to have access to such quality care and ongoing research.

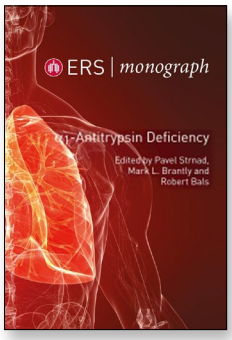
The US Alpha-1 team, Angela McBride and company, looked after us all so well. I thoroughly enjoyed being reunited with patients I had met at previous conferences and sharing stories with patients new. It was an invaluable experience and I am grateful to Alpha-1 Foundation Ireland for making it possible.

6 Latest Irish Research in Alpha-1

Pitfalls and caveats in α1-antitrypsin deficiency testing: a guide for clinicians

Alessandro N Franciosi, Tomás P Carroll, Prof Noel G McElvaney

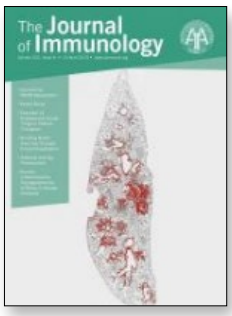
A review on testing for AATD was published in the prestigious Lancet Respiratory Medicine journal in July 2019 by researchers at the National Centre of Expertise for AATD, RCSI and Alpha-1 Foundation Ireland. The review is written in an easy to read, accessible style and is a helpful guide for those new to the field of Alpha-1.



Rare manifestations of AATD

Alessandro N Franciosi, Tomás P Carroll, Prof Noel G McElvaney

A new book on Alpha-1 Antitrypsin Deficiency (AATD) was published by the European Respiratory Society (ERS) in September 2019. This new book offers a comprehensive and up-to-date overview of AATD. It covers basic biology, genetics, laboratory diagnostics and the major organ manifestations; describes the clinical presentation of AATD in both adults and children; and features chapters on genetic counselling, patient views and future therapies. Irish researchers at RCSI contributed a chapter on the rare complications of AATD, in particular panniculitis and vasculitis.



Circulating truncated alpha-1 antitrypsin glycoprotein patient plasma retains anti-inflammatory capacity

Reeves EP, Dunlea DM, McQuillan K, O'Dwyer CA, Carroll TP, Saldova R, Akepati PR, Wormald MR, McElvaney OJ, Shutchaidat V, Henry M, Meleady P, Keenan J, Liberti DC, Kotton DN, Rudd PM, Wilson AA, McElvaney NG.

A research paper on AATD was published in the Journal of Immunology in April 2019 by a team of researchers working at the Irish Centre for Genetic Lung Disease in RCSI, Alpha-1 Foundation Ireland, DCU, UCD, and Boston University. The important work changes the way we look at an extremely rare form of AATD caused by null (or nonsense) mutations, opening up new therapeutic avenues.

These research efforts and publications provide a greater understanding of Alpha-1. With more research, new therapies will be developed and care will be improved. The work is being carried out by an active and dynamic group of scientists and postgraduate students based at the National Centre of Expertise for AATD at Beaumont Hospital and the Irish Centre for Genetic Lung Disease in RCSI.

Financial Report

Income and expenditure account year ended 31 December 2017

Income	2017 €
Northern Area HSE	119,565
Donations & Other Income	30,691
Health Research Board	168,332
	318,588

Expenditure	2017 €
Salaries	113,937
Conference Costs & Annual Report	9,257
Subscription Fees	1,090
Travel & Subsistence Expenses	1,721
Printing, postage and stationery	1,126
Advertising & Media	5,013
Computer costs	11,378
Research	169,989
Legal and professional fees	24,965
Accountancy	1,230
Bank charges	217
Sundry expenses	621
Depreciation on FF & Equipment	1,969
	342,513
Result for the year – Net loss	**-23,925**

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

8 Acknowledgements

We would like to thank the following:

- Margaret Molloy, Siobhán Lee, and Dr. Laura Fee, three valued former colleagues in Alpha-1 Foundation Ireland who each made huge contributions to our mission
- Emma Pentony, Orla Cahalane, Dr. Bill Tormey and the Beaumont Hospital Chemical Pathology Department for their continued support and assistance
- Angela McBride of the Alpha-1 Foundation (USA) for her 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
- Professor Dermot Kenny and the RCSI Clinical Research Centre (*www.rcsicrc.ie*)
- Anne Gormley, Orla Keane, Eóin Durkan and MedEx DCU for taking part in the production of the "What is Alpha-1" educational film
- Mansour Alkhunaizi, Sarah Arjah, Vikita Kowlessar, Hamad Alkandari, Ming Hei Fu, RCSI medical students who carried out research projects with Alpha-1 Foundation Ireland in 2018 and 2019
- The Medical Research Charities Group (MRCG), 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 in 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

Smokers who carry just a single defective Alpha-1 gene have

10 fold increased risk of developing lung disease like COPD

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

The Irish Thoracic Society estimates approximately

440,000 people have COPD in Ireland

20,000 individuals tested for Alpha-1 to date in the National Targeted Detection Programme

800+ people attending National Centre of Expertise for Alpha-1 at Beaumont Hospital

500+ people enrolled on the National Alpha-1 Registry