Alpha-1 antitrypsin deficiency
Working Group of the Romanian Society of Pneumology

Lavinia Davidescu
Coordinator of AATD Working Group
of the Romanian Society of Pneumology

Ruxandra Ulmeanu
National representative Central- Eastern
European Alpha-1 Antitrypsin Network

Founding members 32

- **Arghir Oana Cristina**
- **Chiotan Radu Alexandru**
- **Cojocaru Cristian**
- **Davidescu Lavinia**
- **Deica Meda**
- **Deleanu Oana Claudia**
- **Frățilă Zeno-ioan**
- **Halic Eugenia**
- **Ilisie Monica**
- **Jimborean Gabriela**
- **Magdău Cosmina**
- **Mahler Beatrice**
- **Man Milena Adina**
- **Manolache Dalia**
- **Marcovici Tamara**
- **Marinescu Lucia**
- **Mihai Olteanu**
- **Mihălțan Florin Dumitru**
- **Nebunoiu Ana-Maria**
- **Nemeș Roxana**
- **Nițu Mimi**
- **Oancea Cristian**
- **Pop Monica**
- **Popa Cristian**
- **Puiu Ligia**
- **Râjnoveanu Ruxandra**
- **Tabacu Emilia**
- **Tănăsescu Mihaela**
- **Teleaga Cristina**
- **Todea Doina**
- **Ulmeanu Ruxandra**
- **Vancea Dorin**

… we founded

AATD Working Group of the Romanian Society of Pneumology

Lavinia Davidescu
Coordinator

Sibiu June 15th 2013
32 founding members

AATD Alpha-1 antitrypsin deficiency

Genetic screening in Romania
2012-2015

Ruxandra Ulmeanu, Ana Zaharie,
Lavinia Davidescu, Oana Deleanu,
Cristina Teleaga,
Sabina Antoniu, Emanuela Tudorache,
Florin Mihaltan

What is alpha-1 antitrypsin deficiency (AATD)?

- one of the three most common genetic diseases in Caucasians
- ↑ considerably the risk of obstructive lung disease
- under-diagnosed pathology in patients with COPD

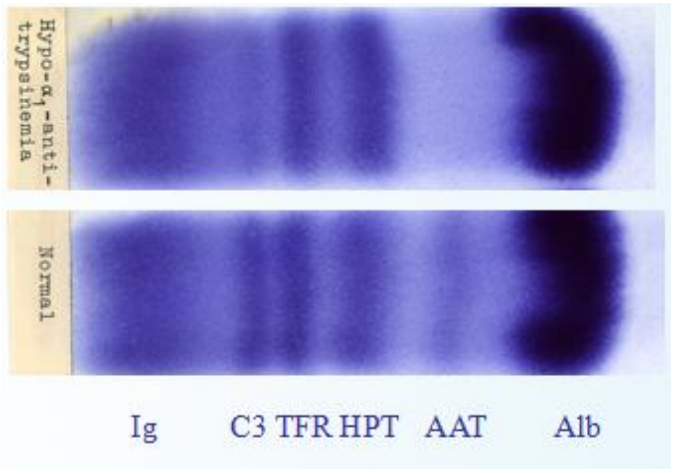
James K. Stoller, A Review of a1-Antitrypsin Deficiency, Am J Respir Crit Care Med Vol 185, Iss. 3, pp 246–259, Feb 1, 2012
Darren N. Saunders, A Novel *SERPINA1* Mutation Causing Serum Alpha$_1$-Antitrypsin Deficiency, PLoS One. 2012; 7(12): e51762.

AATD - a disease slowly investigated

- time between first symptoms and diagnosis

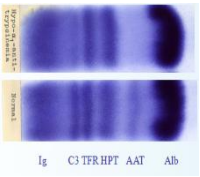
  7.2 years ± 8.3 years

- **at least 3 doctors before the diagnosis was established**



Peter J. Barnes, Chronic Obstructive Pulmonary Disease, N Engl J Med 2000; 343:269-280

AATD - a disease slowly investigated



Time between first symptoms and diagnosis

- **7.2 years ± 8.3 years**

Before the diagnosis is established

- **at least 3 doctors evaluation**

Peter J. Barnes, Chronic Obstructive Pulmonary Disease, N Engl J Med 2000; 343:269-280

2011- many CEE countries don't have available studies!

Ruxandra Ulmeanu et al, Epidemiology of AADT in Central-Eastern Europe – where are we now?,First CEE -AATD Network Conference,Warsaw,19th April 2013

Photo: uknetguide.co.uk

AATD in other countries

- represents an iceberg

5% of patients diagnosed

1. K. Stoller, A Review of a1-Antitrypsin Deficiency, Am J Respir Crit Care Med Vol 185, Iss. 3, pp 246–259, Feb 1, 2012
2. Darren N. Saunders, A Novel *SERPINA1* Mutation Causing Serum Alpha$_1$-Antitrypsin Deficiency, PLoS One. 2012; 7(12): e51762
3. Ruxandra Ulmeanu et al, Epidemiology of AADT in Central-Eastern Europe – where are we now?,First CEE -AATD Network Conference,Warsaw,19th April 2013
4. https://en.wikipedia.org/wiki/IcebergJames

…before 2012
AATD in Romania

- frozen diagnostic

we just know … that it exists

Ruxandra Ulmeanu et al, Epidemiology of AADT in Central-Eastern Europe – where are we now?,First CEE -AATD Network Conference,Warsaw,19th April 2013
http://patamateria.com/tag/glass/
http://www.earthporm.com/30-amazing-photos-frozen-things/

…before 2012
AATD in Romania

- The disease was usually identified only by the plasmatic values

Genetic testing - only in the private practice

- with samples worked abroad
- and costs fully covered by the patient.

Ruxandra Ulmeanu et al, Epidemiology of AADT in Central-Eastern Europe – where are we now?,First CEE -AATD Network Conference,Warsaw,19th April 2013

Genetic screening for AATD in Romania

Genetic Screening for AATD in Romania

Education and Culture DG

Lifelong Learning Programme

We start to introduce the standards of
the best medical practice for AATD patients in Romania
since 2012

Education and Culture DG

Lifelong Learning Programme

Application Form
Call: 2011
Partnerships

Form version: 2.8 / Adobe Reader version: 10.103

"Introducing standards of the best medical practice for the patients with inherited Alpha-1 Antitrypsin Deficiency in Central Eastern Europe"

A. GENERAL INFORMATION

Before completing this application form, please read the relevant sections in the 2011 Call for Proposals published by the European Commission and by your National Agency and the Lifelong Learning Programme Guide for 2011 which contain additional information e.g. the specific priorities for that year. Links to these documents and further information can be found on the Lifelong Learning Programme website:

http://ec.europa.eu/education/llp/doc848_en.htm

and on your National Agency website, whose address is available upon selecting the National Agency in section C.

In accordance with standard European Commission practice, the information provided in your application form may be used by the Commission to evaluate the Lifelong Learning Programme. The relevant data protection regulations will be respected.

B. SUBMISSION

B.1. CONTEXT

Programme	LIFELONG LEARNING PROGRAMME
Sub-programme	LEONARDO DA VINCI
Action type	PARTNERSHIPS
Action	LEONARDO DA VINCI Partnerships
Deadline	21-02-2011
Working language of the partnership	EN - English

B.2. PROJECT IDENTIFIERS

Project title	Introducing standards of the best medical practice for the patients with inherited Alpha-1 Antitrypsin Deficiency in Central Eastern Europe
Project acronym	Alfa-1-Qual
Form hash code	ECAF03EF09B51D09

C.3.1. ORGANISATION

National Agency identification	RO1 LLP (ANPCDEFP)
Organisation full legal name (national language)	INSTITUTUL DE PNEUMOFTIZIOLOGIE "MARIUS NASTA"

The Institute of Pneumophtysiology "Marius Nasta" is a leading clinical and research center in respiratory diseases in Romania. The scope of its activities is related to most of the chest pathologies, including respiratory disease and surgical thoracic pathology. Institute currently manages three national programs (Tuberculosis Control, Smoking Cessation, Pulmonary Hypertension). The Institute has a key medical and scientific position in Romania resulting in publications in leading international medical journals and at numerous international Conferences as well as involvement in various national and international expert groups, including COPD audit. The Institute is also the major teaching institution for respiratory professionals in Romania, being involved in an e-learning project also. Institute manages more research projects (involving sleep medicine and pulmonary rehabilitation field) and there are more registers for respiratory pathology, including Alfa-1 Antitrypsin Deficiency (A1ATD) that is an underestimated pathology without a nationwide network for A1ATD early diagnosis and specialized medical care. The Institute is coordinating/organizing the education for respiratory specialist including rehabilitation field.

We hope that our educative position and high degree of addressability from countrywide will be a key point for development a national A1ATD network.
Role in the project:
- Submission of Project Application Form to Leonardo da Vinci program national agency
- Arranging accommodation for visiting participants
- Coordinating visits to project partners
- Sharing knowledge and experience with other partners
- Preparing a written report following each mobility
- Participation in Workshops
- Participation in European AIR Conference
- Participating in development of educational materials for respiratory professionals
- Participating in development of individualized training program for visiting respiratory professionals
- Translating educational materials into national language
- Promoting and disseminating educational materials in Romania
- Promoting Project in Romania

C.3.2. CONTACT PERSON OF PARTNER NO. 3

Title	Associate Professor, MD, PhD
First name	Ruxandra
Family name	Ulmeanu
Department	Department of Bronchology
Position	Coordinator of Lung Cancer Working Group of Romanian Pneumology Society

The Leonardo da Vinci programme
funded by EU Lifelong Learning Programme

Education and Culture DG
Lifelong Learning Programme

Start: October 2012

Introducing standards of the best medical practice for AATD patients in Central Eastern Europe

8 partners

The National Institute of Tuberculosis and Lung Diseases **Poland** Coordinator

Hannover Medical School **Germany**

Institute of Pneumophtysiology "Marius Nasta" Romania

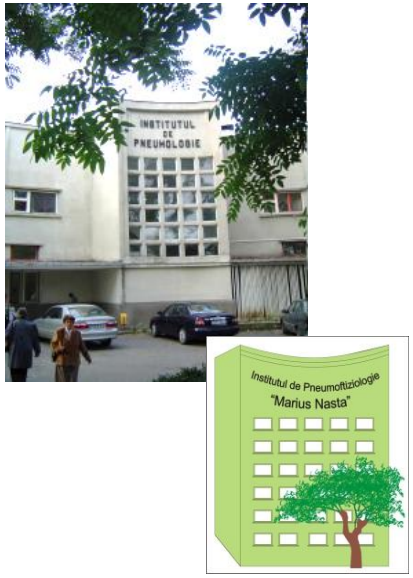
Safarik University, Faculty of Medicine **Slovakia**

Leiden University /Academisch Ziekenhuis Leiden **Netherlands**

Pleven EAD, Clinic for pneumonology and phthisiatry **Bulgaria**

Vilnius University Faculty of Medicine **Lithuania**

Università degli Studi di Pavia **Italy**



Education and Culture DG

Lifelong Learning Programme

”Marius Nasta” Institute of Pneumology

partnership 2011-2013

- partnership with national number LLP-LdV/PAR/2011/RO//129
- approved for finance by the National Agency for Community Programmes in the Field of Education and Vocational Training
- is funded by EU Lifelong Learning Programme, The Leonardo da Vinci programme

8 partners

The National Institute of Tuberculosis and Lung Diseases/ **Poland**

(Coordinator)

Hannover Medical School/ **Germany**

Institute of Pneumophtysiology “Marius Nasta”/ **Romania**

PJ Safarik University, Faculty of Medicine**/ Slovakia**

Leiden University Medical Center h/o Academisch Ziekenhuis Leiden/ **Netherlands**

UMHAT “Dr.Georgi Stranski” Pleven EAD, Clinic for pneumonology and phthisiatry"/ **Bulgaria**

Vilnius University Faculty of Medicine/ **Lithuania**

Università degli Studi di Pavia/ **Italy**

It was a complex and extremely helpful activity for the Romanian team

Trainings for doctors (6) biochemists (1) nurses (1) physiotherapists (1) in hospitals and laboratories from Warsaw, Hanover, Vilnius, Leiden

Education and Culture DG

Lifelong Learning Programme

Genetic Screening for AATD in Romania goes on

…. although Leonardo project came to an end

with the support of

The National Institute of Lung Diseases - Warsaw

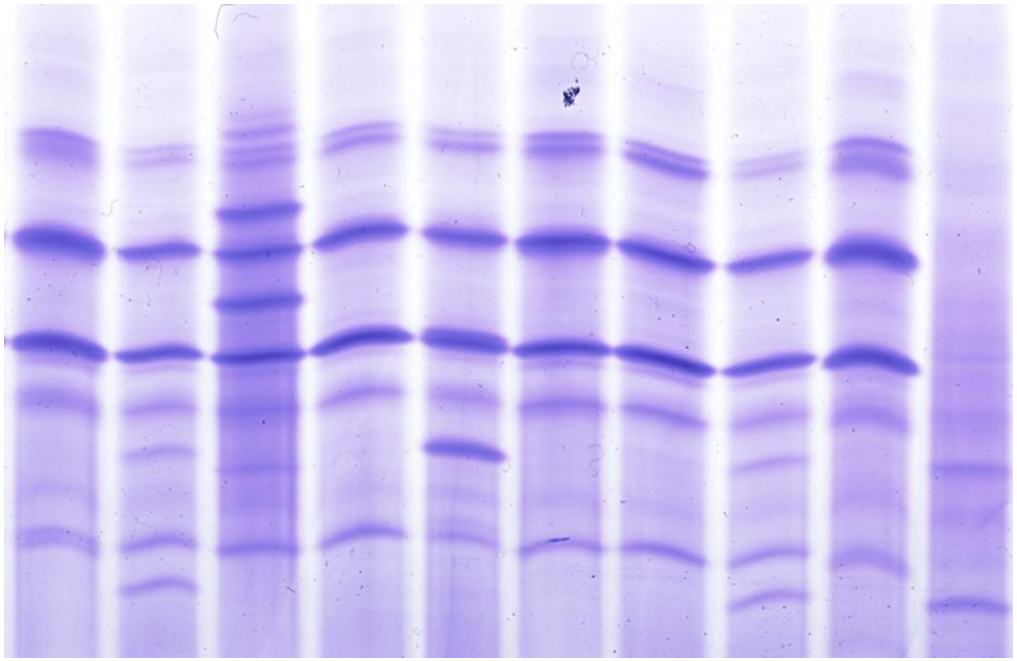
Joanna Chorostowska-Wynimko
Head of Central-Eastern European Alpha-1 Antitrypsin Network

Continue collaboration with

Central-Eastern European Alpha-1 antitrypsin Network

Continuation of screening in Romania

The possibility of testing for suspected cases in Poland



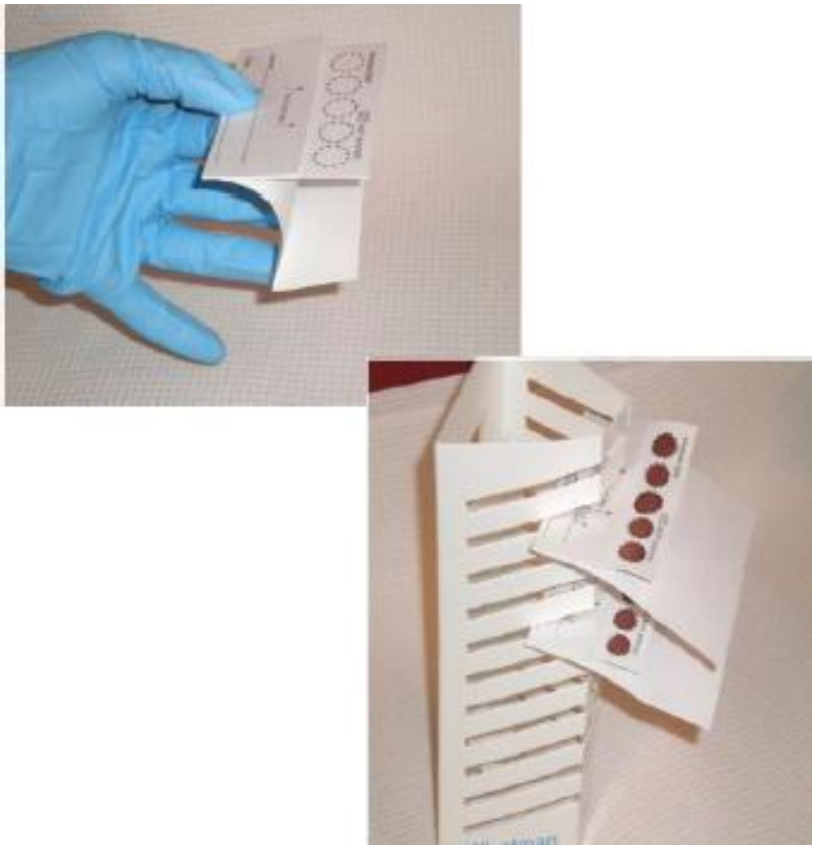
Collection and transport of specimens

- **Capillary blood collection**

  DBS = dry blood spots
  Specific cards
  Filled, dried

  chim. Cristina Teleaga

  sent in Poland



- Results:
  - **Phenotype/Genotype**
  - AAT plasmatic value

Whom to test?

- in accordance with AATD Romanian Guideline indications 2013

A genetic cause of the premature cases of

- COPD
- emphysema
- bronchiectasis
- incomplete reversibility asthma

cei în vârstă)

4. Adulţi cu paniculită necrotizantă
5. Adulţi şi adolescenţi cu fraţi care prezintă homozigozitate AAT, de exemplu genotipul PiZZ (persoane asimptomatice care pot fi supuse unui risc ridicat de predispoziţie genetică spre dezvoltarea deficitului de alfa-1 antitripsină)

AATD in Romania ?

Certainly AATD in Romania

- is an under-diagnosed pathology in patients with COPD

Ruxandra Ulmeanu,Ana Nebunoiu et al, Alpha 1 antitrypsin deficiency in Romania: preliminary results from the genetic screening 2012-2015,unpublished data

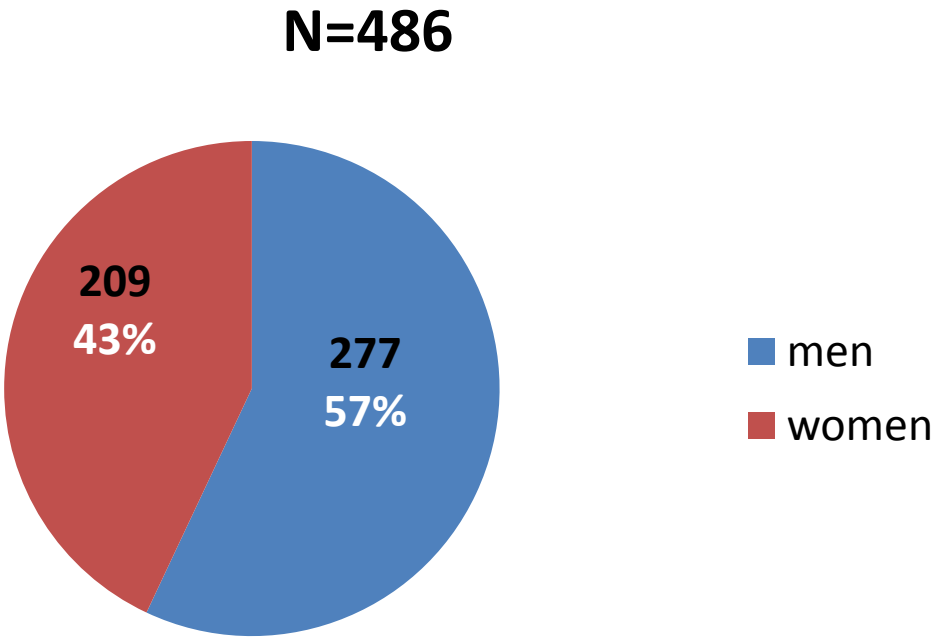
Preliminary results for Romania

Gender distribution

Have been tested

more than 486 patients

october 2012 - august 2015



AATD suspicion is higher among men

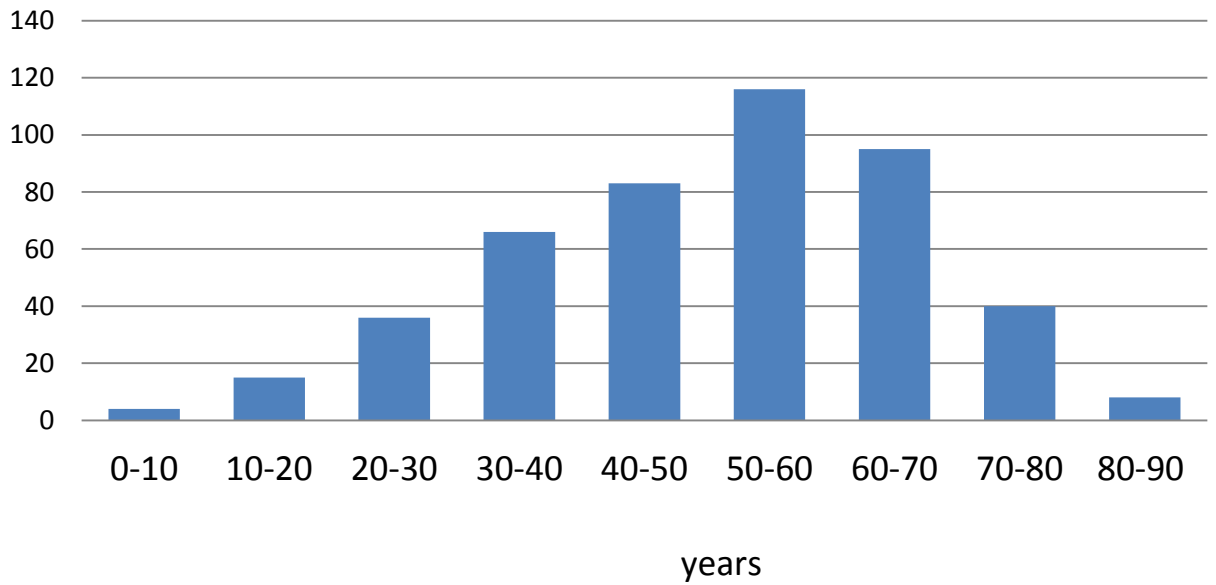
Sex ratio: 1.33:1

Ruxandra Ulmeanu,Ana Nebunoiu et al, Alpha 1 antitrypsin deficiency in Romania: preliminary results from the genetic screening 2012-2015,unpublished data

Age distribution

The average age for testing fluctuated around 50 years,
in accordance with the decade when commonly
AATD is symptomatic and diagnosed

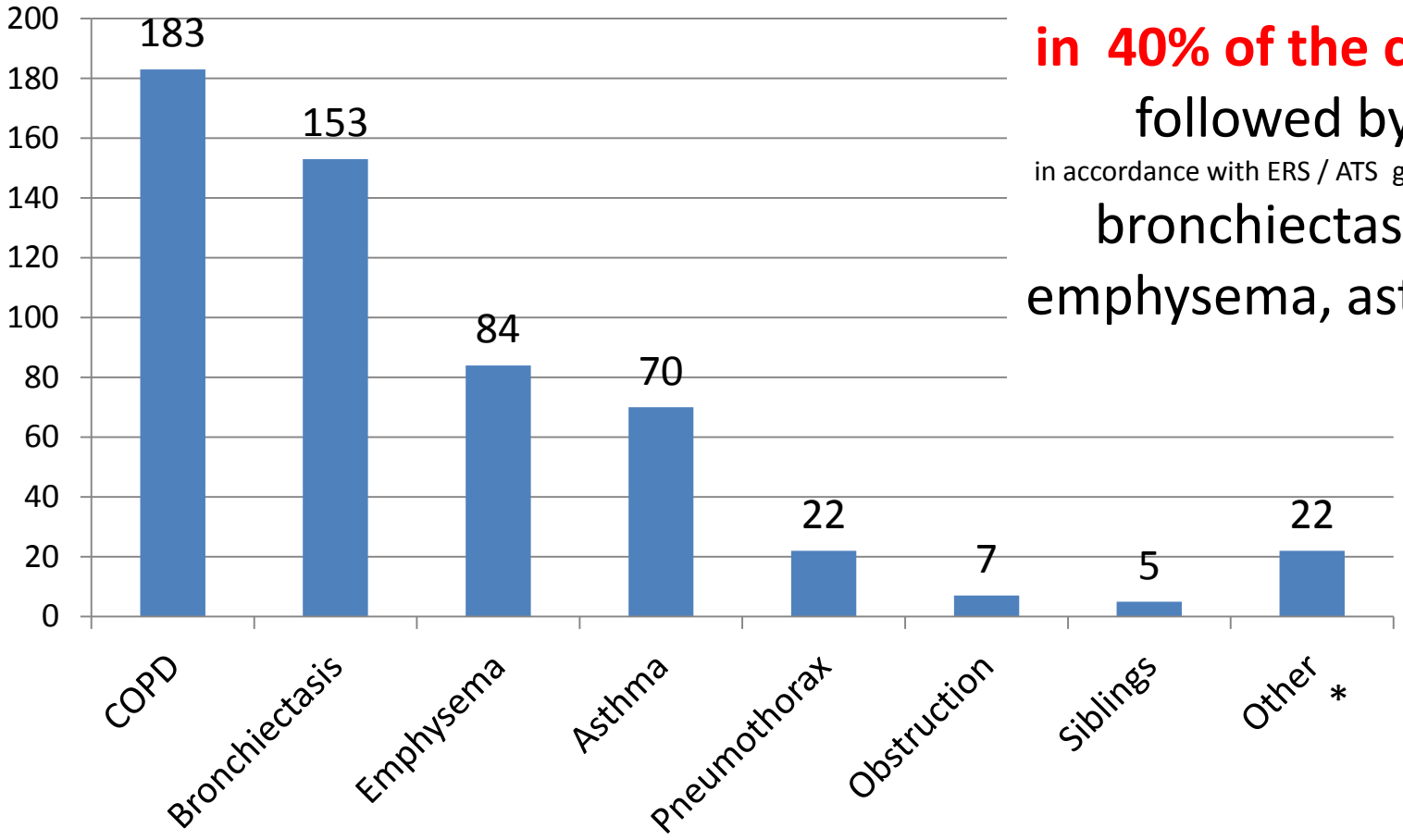
N=486



Ruxandra Ulmeanu,Ana Nebunoiu et al, Alpha 1 antitrypsin deficiency in Romania: preliminary results from the genetic screening 2012-2015,unpublished data

Reason for testing

N=486



The main reason for testing remains COPD in 40% of the cases

followed by

in accordance with ERS / ATS guidelines

bronchiectasis, emphysema, asthma

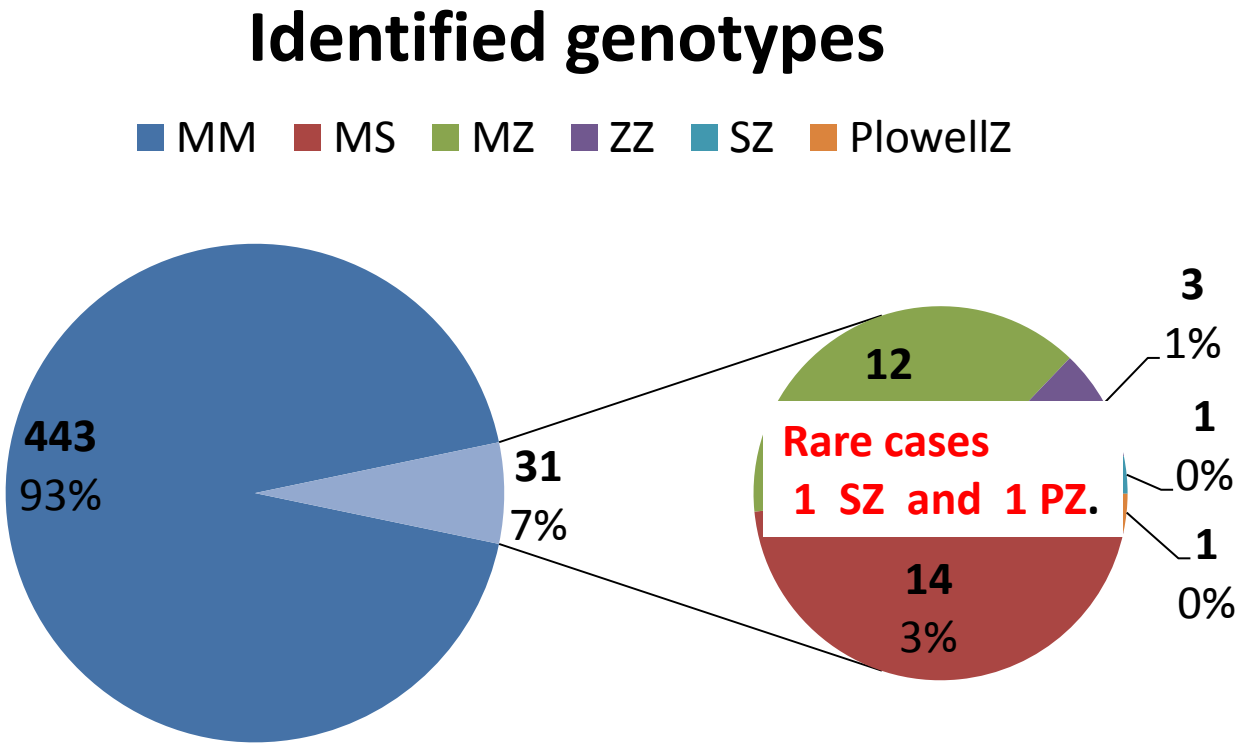
* Other: association of: lung cancer, pulmonary fibrosis, autoimmune cirrhosis, neonatal hepatitis syndrome history

Ruxandra Ulmeanu,Ana Nebunoiu et al, Alpha 1 antitrypsin deficiency in Romania: preliminary results from the genetic screening 2012-2015,unpublished data

6.5 % of screened patients were identified to have genetic modification

heterozygous, more rarely homozygous

N=474 available results

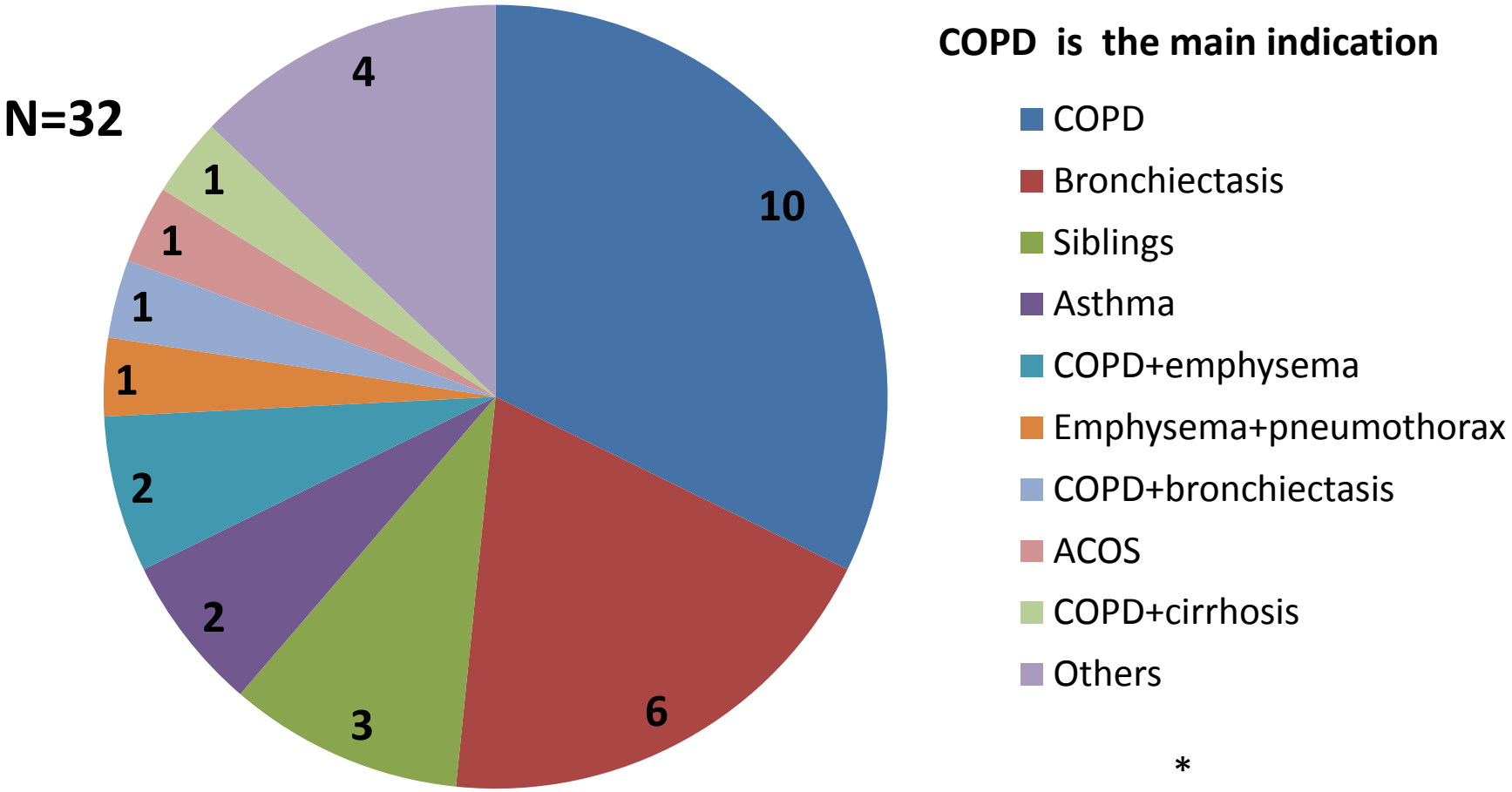


Normal genotype: 93.45%

Modified genotype: 6.55%

Ruxandra Ulmeanu,Ana Nebunoiu et al, Alpha 1 antitrypsin deficiency in Romania: preliminary results from the genetic screening 2012-2015,unpublished data

Reason for testing for modified genotype



*Others: Chronic bronchitis, interstitial fibrosis, neonatal hepatitis syndrome history

Ruxandra Ulmeanu,Ana Nebunoiu et al, Alpha 1 antitrypsin deficiency in Romania: preliminary results from the genetic screening 2012-2015,unpublished data

COPD and the association COPD+ emphysema are the main indications for testing for patients with modified genotype

- bronchiectasis ranks in 2nd place
- screening of first-degree relatives in 3rd
- refractory asthma
- ACOS
- COPD+cirrhosis

until now

8.20% of patients with COPD are carriers of a modified gene

(15 from 183 COPD tested patients)

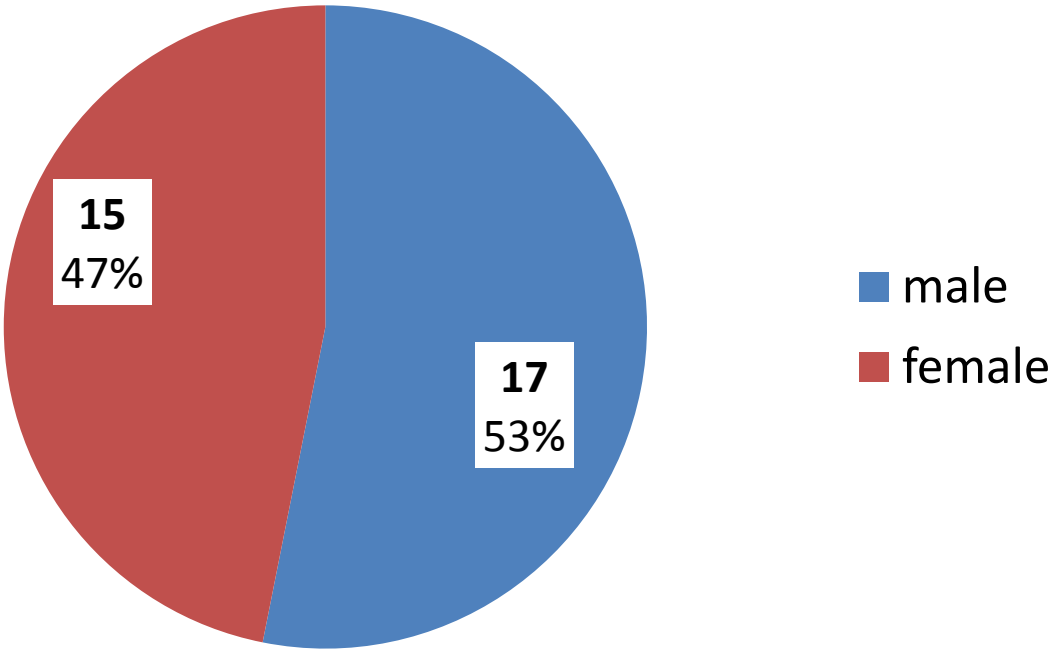
Ruxandra Ulmeanu,Ana Nebunoiu et al, Alpha 1 antitrypsin deficiency in Romania: preliminary results from the genetic screening 2012-2015,unpublished data

Gender distribution in patients with modified genotype

is higher among men

N=32

Sex ratio (M:F)
1.13:1



Ruxandra Ulmeanu,Ana Nebunoiu et al, Alpha 1 antitrypsin deficiency in Romania: preliminary results from the genetic screening 2012-2015,unpublished data

The average FEV1is 52%

- with large variations between 22% and 122%

Fortunately, from the 3 homozygotes identified

- 2 are children - their lung function is still in the normal range

N=32

Parameter	Median	SD	Minimum	Maximum
Age (years)	47	18.61	7	76
FEV1 (%)	52.00	32.55	22	122
AAT plasmatic value (mg/dl)*	102.5	36.99	Below the sensitivity	186

*NB: NV: 83-220 mg/dl

Ruxandra Ulmeanu,Ana Nebunoiu et al, Alpha 1 antitrypsin deficiency in Romania: preliminary results from the genetic screening 2012-2015,unpublished data

What to do?

- Focus on COPD patient
- Search for specific indications
- Limit to lower age (thinking of measures)

- Do more…

What else have we done for AATD in Romania ?

Education and Culture DG

Lifelong Learning Programme

Under the auspices of
the Polish Respiratory Society and the National Consultant for Respiratory Diseases

THE 1ST CENTRAL- EASTERN EUROPEAN ALPHA-1 ANTITRYPSIN NETWORK CONFERENCE

"ALPHA-1 ANTITRYPSIN DEFICIENCY-ASTHMA-COPD"

Warsaw, April 19th 2013

Romania
become member of
AATD Network of Central Eastern Europe

… we founded

AATD Working Group of the Romanian Society of Pneumology

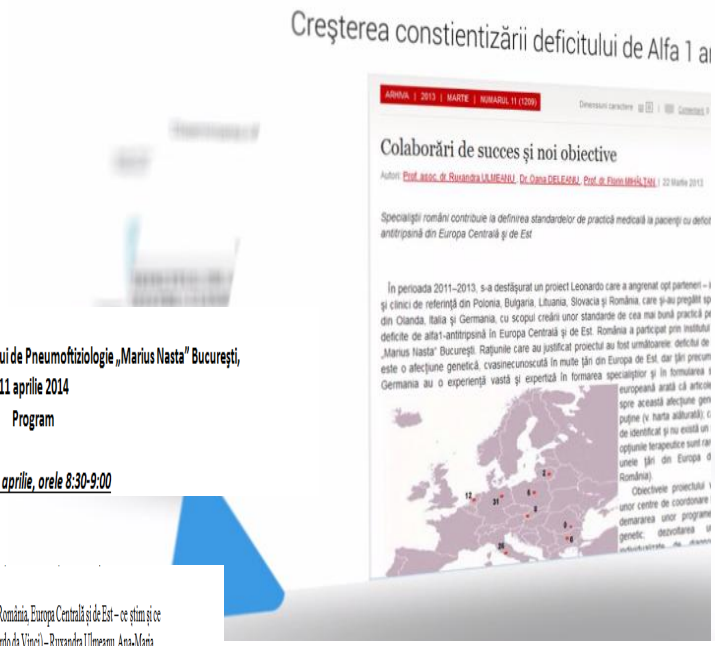
Lavinia Davidescu
Coordinator

Sibiu June 15th 2013
32 founding members

GRUP DE LUCRU
DAAT
SRP

We increase the AATD awareness

in romanian medical community

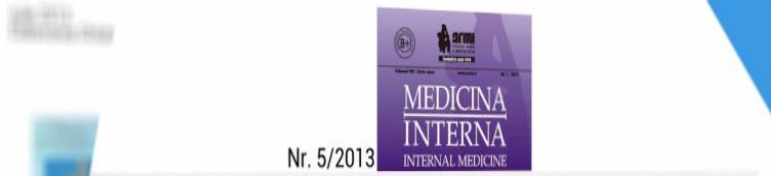

Creşterea constientizării deficitului de Alfa 1 a

Colaborări de succes şi noi obiective

A 46-a Sesiune Ştiinţifică a Institutului de Pneumoftiziologie „Marius Nasta" Bucureşti,
11 aprilie 2014
Program

Vineri 11 aprilie, orele 8:30-9:00

5. Deficitul de alfa 1 antitripsină în România, Europa Centrală şi de Est – ce ştim şi ce trebuie să ştim? (Proiectul Leonardo da Vinci) – Ruxandra Ulmeanu, Ana-Maria Nebunoiu, Oana Claudia Deleanu


Nr. 5/2013
MEDICINA INTERNA
INTERNAL MEDICINE

DEFICITUL DE ALFA-1 ANTITRIPSINĂ - REPERE PRACTICE PENTRU CLINICIAN

Ruxandra Ulmeanu[1,2], Ana-Maria Nebunoiu[1], Florin Dumitru Mihăltan[1,3], Oana Claudia Deleanu[1]
[1]Institutul de Pneumologie "Marius Nasta" Bucureşti
[2]Facultatea de Medicină, Universitatea Oradea
[3]UMF "Carol Davila" Bucureşti
Autor corespondent: Ruxandra Ulmeanu, r_ulmeanu@yahoo.com

n cursul Simpozionului dedicat Deficitului de Alfa-1 Antitripsină
ional de Pneumologie de la Sibiu, au fost prezentate rezultatele parţiale ale screeningului naţional. La acel moment, 337 de pacienţi fuseseră screenaţi, principala indicaţie de testare fiind boala pulmonară obstructivă cronică, prezentă în cazul a 45% (152) dintre pacienţii testaţi (figura).

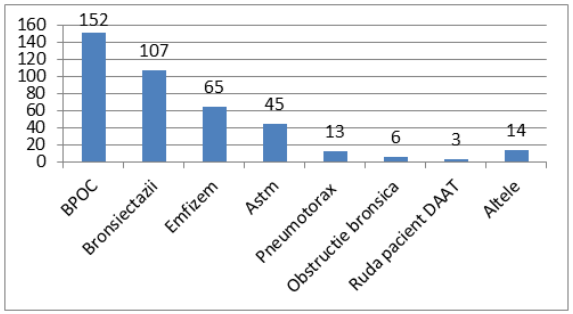


Figura : indicaţii de testare pentru deficitul de alfa-1 antitripsină (Date prezentate în cadrul Congresului National de Pneumologie, Sibiu, 2014, Prof. Dr. R. Ulmeanu).

Alpha-1 antitrypsin deficiency in Romania and the screening of risk patients

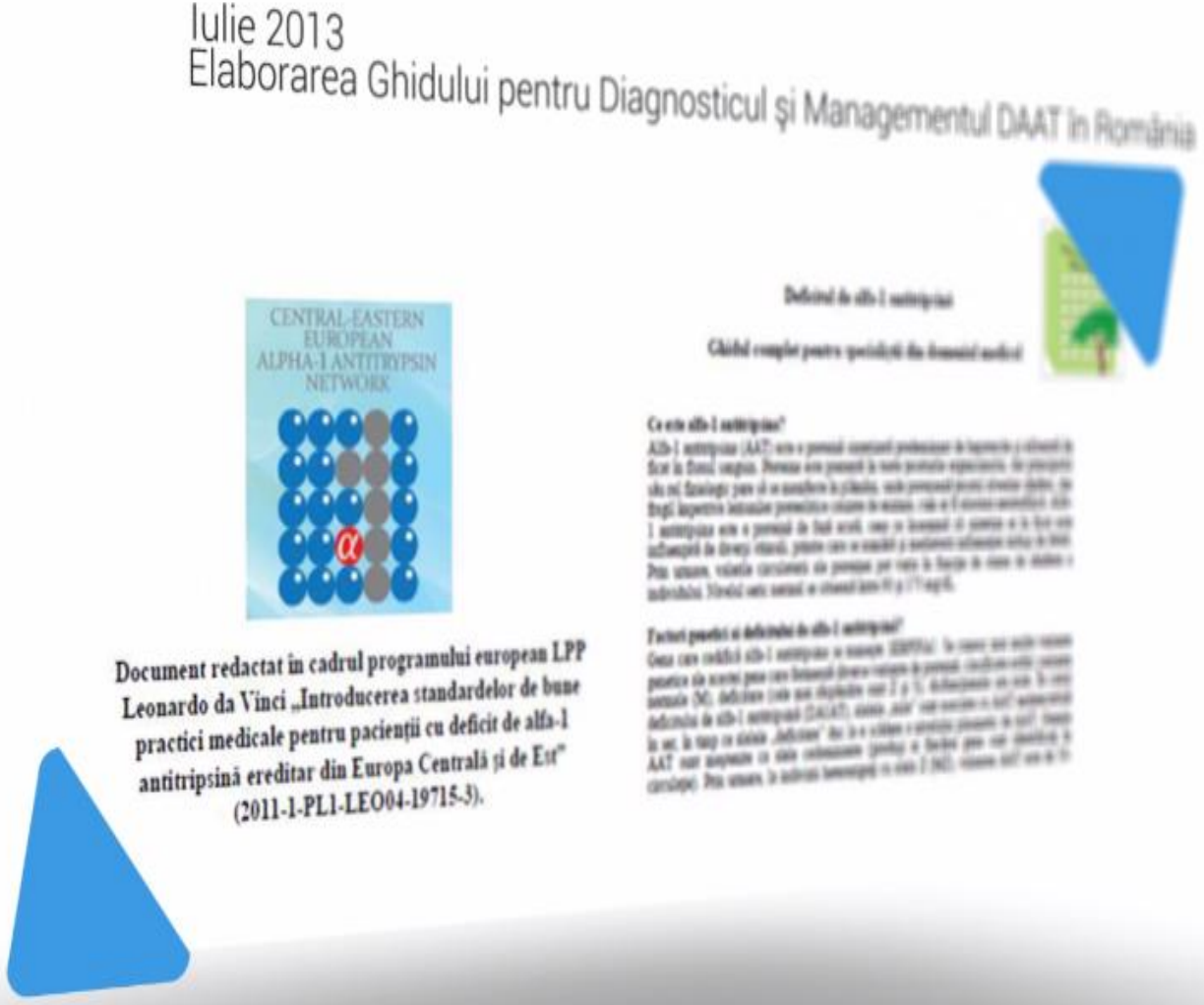
Leonardo da Vinci Project
partner "Marius Nasta" Institute of Pneumology

Ruxandra Ulmeanu[1,2], Oana Claudia Deleanu[2,3], Ana-Maria Nebunoiu[2,3]

[1] Faculty of Medicine, Oradea University
[2] „Marius Nasta" Institute of Pneumology, Bucharest
[3] „Carol Davila" University of Medicine and Pharmacy, Bucharest

We have the guideline for the diagnosis and management of AATD

the version in Romanian language



GRUP DE LUCRU DAAT SRP

FIRST NATIONAL CONFERENCE FOR RARE LUNG DISEASES

April 2nd 2015, Oradea-Băile Felix, Romania

ORADEA Hotel International 2-4 aprilie 2015

SRP Societatea Romana de PNEUMOLOGIE

UNIVERSITATEA DIN ORADEA ROMÂNIA

Lavinia Davidescu
Coordinator of AATD Working Group
of the Romanian Society of Pneumology

Ruxandra Ulmeanu
Elected President of the Romanian Society of Pneumology (2016-2018)
National representative Central- Eastern European Alpha-1 Antitrypsin Network

FIRST NATIONAL CONFERENCE FOR

RARE LUNG DISEASES

April 2nd 2015, Oradea-Băile Felix, Romania

PROGRAM ȘTIINȚIFIC /SCIENTIFIC PROGRAM

Joi, 2 aprilie 2015/ Thursday, April 2, 2015 — **Sala Etaj 1/ First floor hall**

08:30-09:00 **Cuvânt de bun venit / Welcome speech**

09:00-11:00 SIMPOZION MAJOR/ MAJOR SYMPOSIUM
Interferențe Boli Pulmonare Rare – Cancer pulmonar I/
Rare Pulmonary Disease – Lung Cancer Interferences I
Moderatori/ Chairmen: Lavinia Davidescu, Oana Deleanu, Ruxandra Ulmeanu

1. Cum se schimbă medicina clinică prin diagnosticul molecular – experiența noastră în deficitul de alfa-1 antitripsină și cancer pulmonar
   How the molecular diagnostics changed the clinical medicine – our experience in alpha-1 antitrypsin deficiency and lung cancer
   Joanna Chorostowska-Wynimko
2. Sindromul cililor imobili
   The immotile cilia syndrome
   Ruxandra Ulmeanu, Antonela Dragomir, Limir Berevoianu, Alexandra Maria Ulmeanu
3. Deficitul de alfa-1 antitripsină și cancerul – există o legătură?
   Alpha-1 antitrypsin deficiency and lung cancer – is there a link ?
   Oana Claudia Deleanu, Ana Maria Nebunoiu
4. Spectrul modificărilor pulmonare în deficitul de alfa-1 antitripsină - dinspre comun spre neașteptat
   Spectrum of pulmonary changes in alpha-1 antitrypsin deficiency - from common to the unexpected
   Ana-Maria Nebunoiu, Oana Claudia Deleanu, Florin Dumitru Mihălțan, Ruxandra Ulmeanu
5. Managementul pacientului cu DAAT - de la consiliere genetică la terapia de augmentare
   Management of AATD patient - from genetic counseling to augmentation therapy
   Lavinia Davidescu, Anita Genda, Ruxandra Ulmeanu
6. Inedit în pneumologie ... poate nu și pentru alte specialități
   Unusual in pneumology ... maybe not for other specialties
   Florin Mihălțan, Nadejda Cîrlig, Antonela Dragomir, Răzvan Hainăroșie, Cecilia Popovici, Elena Cristescu, Ruxandra Ulmeanu

Joanna Chorostowska-Wynimko

Scientific Director

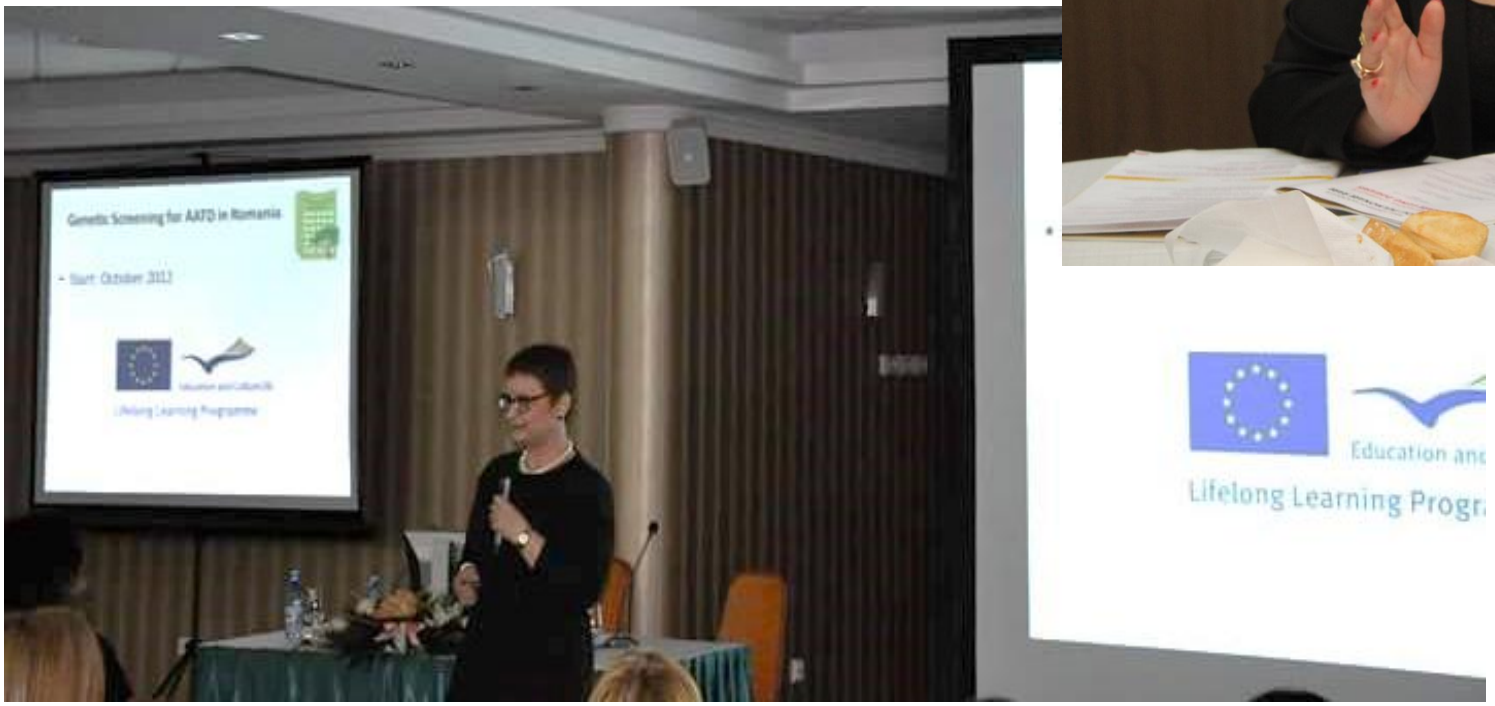
National Institute of Tuberculosis & Lung Diseases, Warsaw, Poland

Head of Central-Eastern European Alpha-1 Antitrypsin Network

FIRST NATIONAL CONFERENCE FOR

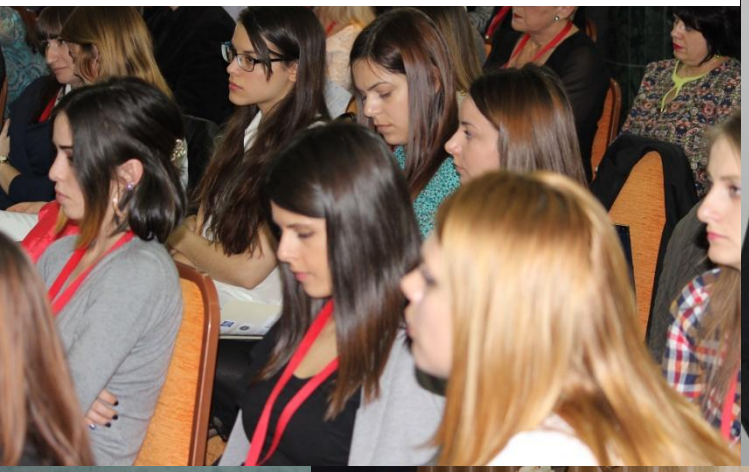
RARE LUNG DISEASES

April 2nd 2015, Oradea-Băile Felix, Romania



Overview of the preliminary data for AATD screening for Romania in 2015

over 400 participants




Experts from 9 medical specialties
Tudor Ciuleanu
PRIMA CONFERINȚĂ NAȚIONALĂ DE
ORADEA
Hotel International
2-4
aprilie
2015
PID-S

An exceptional involvement of young specialists, residents, students

…and starting with 2015 Romania was repesented at

The Biennial Alpha-1 Global Patient Congress and International Research Conference

Barga-Italy 2015

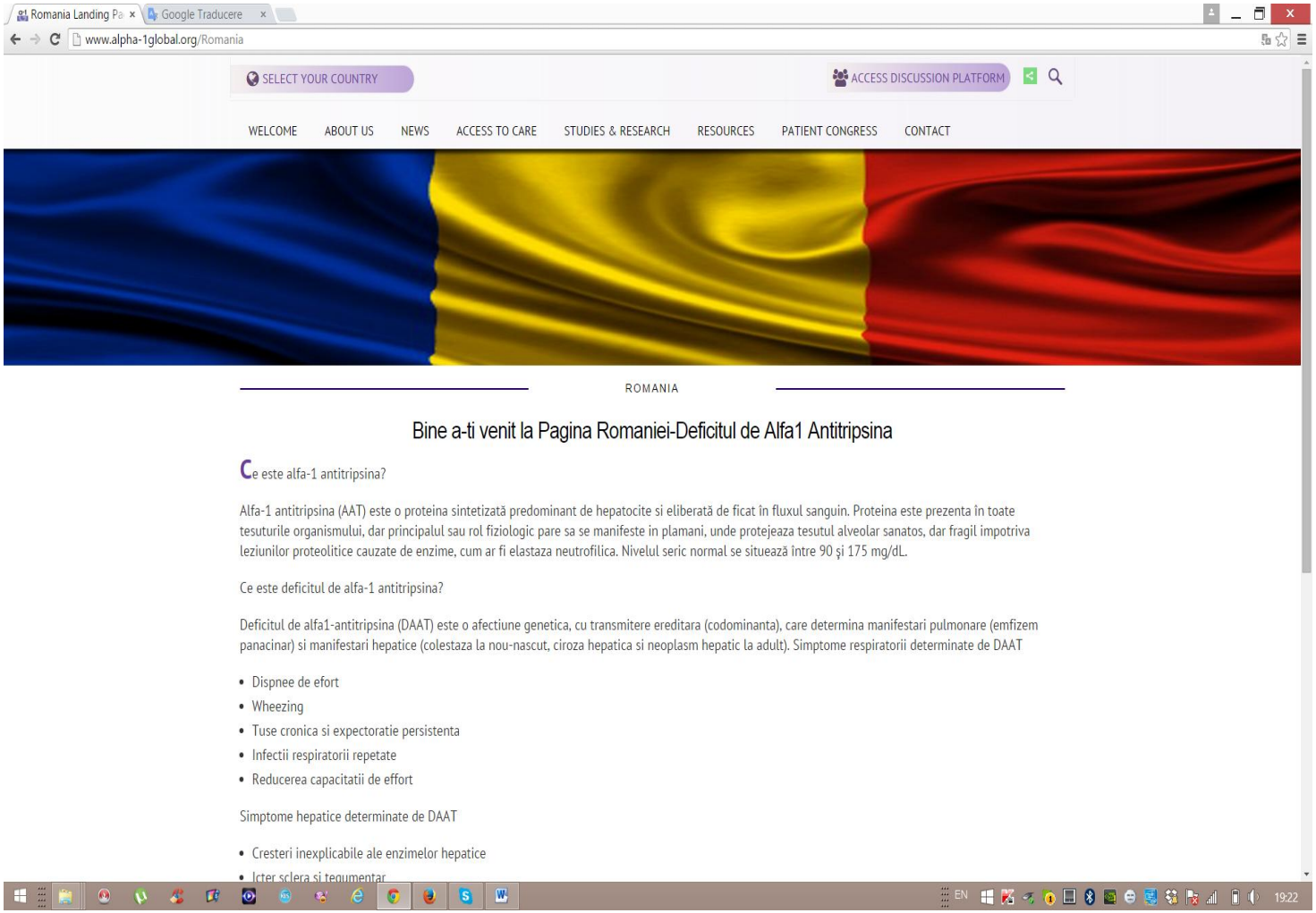
Simona Olteanu
Romanian patient representative

Lavinia Davidescu
Coordinator of romanian AATD Working Group

Hillegonda Guttierez
Alpha-1 Global Director

The Romanian stand

Alpha-1 Association Global website in Romanian language



Summarizing…

- Almost 500 patients screened
- Mostly heterozygotes
- 3 PIZZ, 1 PISZ, 1 $PIP_{Lowell}Z$
- Mostly in COPD patients
- Still a low proportion of screened patients with modified genotype

Future purposes

AATD in Romania

- continuing screening among risk persons
- establishing a national reference laboratory
- creating a national database for patients identified with AATD

We are here ,TOGHETHER ,again.