P16.2. Alzheimer’s disease in Romania: the national programme for prevention, prediction, and personalized treatment and monitoring of memory diseases

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Alzheimer's Disease (AD) is an emerging crisis as the population ages:

- One in 8 persons older than 65 have Alzheimer's, and nearly 1 in 2 persons after the age of 85.

**In the United States:**
- 5.3 million people
- the 7th leading cause of death,
- the annual care costs amount to $172 billion
- 10.9 million unpaid caregivers.
- By 2050, in the absence of ways to prevent or more effectively treat the disease, the estimated number of AD people aged over 65 should be of 11 - 16 million.
- 70% of people with Alzheimer's live at home under informal care (friends and family).
- More than 40% of informal (unpaid) caregivers rate their emotional stress as high or very high. [1]

**In Europe:**
the EURODEM meta-analyses for European studies - after the age of 65 the overall AD prevalence in males and females doubles for every 5 year of age [2].

Current therapies can only ease symptoms and reduce the rate of cognitive decline. Sustained financial support is needed to enable:

- **Research** - to understand in-depth the fundamental process that destroys brain cells and their ability to communicate.

- The boost of next generation of **drugs able to target not only the symptoms but rather the underlying pathology**.

- The improvement of **tools, methods and technologies for prevention, early detection and personalized treatment**.

- The improvement of **medical and social care paradigms and policies**.
P16.2. Alzheimer’s disease in Romania: the national programme for prevention, prediction, and personalized treatment and monitoring of memory diseases - Luiza Spiru, MD, PhD

The Romanian realities - Demographics

3rd age population segment (dynamics 2005-2009)

<table>
<thead>
<tr>
<th>Year</th>
<th>Population aged 65+: January 1st</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>3,174.98</td>
</tr>
<tr>
<td>2006</td>
<td>3,197.10</td>
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<tr>
<td>2007</td>
<td>3,197.95</td>
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<tr>
<td>2008</td>
<td>3,186.31</td>
</tr>
<tr>
<td>2009</td>
<td>3,162.92</td>
</tr>
</tbody>
</table>

Alzheimer disease – Facts in Romania

• AD prevalence – (the same as in Europe) **3-5% of people after 65 years** of age;
• More than 300,000 people with AD in Romania
• **Only 10% of AD people are diagnosed**
• **Only 10% of them are treated.**
• The delay from disease onset to diagnosis is of 3-5 years
• CT, MRI investigation fees are not covered by the National House of Health Insurances
• Health care costs allocated for mental illnesses were under **3% from** the total amount allocated for health care
• **The cost of AD medication is covered only 20%** from total health care cost/person
• **Poor social services** [1]
• Specific well skilled medical and non-medical workforce is far to covering patients’ needs

The European Commission is aware of the importance of a suitable approach of Alzheimer’s Crisis.

- The Work plan 2005 - Community action in the field of public health (2003-2008) - the need of information and definition of indicators on the prevalence, treatments, risk factors, risk reduction strategies, cost of illness and social support related to AD and other dementias. [1]

- The EC Conference "The fight against Alzheimer's disease and related disorders (Paris 2008) - to fight against dementias through a multidisciplinary approach, integrating scientific, health and social dimensions [2]

- The Council Conclusions on public health strategies to combat neurodegenerative diseases associated with ageing and in particular Alzheimer's disease (December 2008) - addressed to Member States and the Commission in order to recognize that dementias constitute a priority for action [3]

- The COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL - on a European initiative on Alzheimer’s disease and other dementias (July 2009) - The EU would support national efforts in four key areas [4]

WHO STRATEGIC AGENDA

WHO will work with the Government of Romania to narrow the gap between policy objectives and policy implementation

- Stewardship, health financing, service delivery and resource development
- Communicable disease surveillance and control
- Public health system reform
The National Program of Memory Diseases - Romania

Submitted to approval in June 2009.
Initiator: Prof. Luiza Spiru MD, PhD, president of the Consultative Commission for Geriatrics and Gerontology Specialty of the Romanian Health Ministry

Aims: 1.

- Development of **early diagnosis and personalized prevention, treatment and monitoring** of brain aging and memory impairment diseases.

- Elaboration of **guidelines for the early diagnosis** in neurodegenerative diseases according to the European and international definitions.

- Development of **new research criteria** in preventive clinical trials in brain aging.

- **Professional training** in early diagnosis of brain aging for GPS, geriatricians, neurologists, psychiatrists, psychologists, social assistants and home care assistants.

- **Implementation of Preventive, Predictive and Personalized Medicine (3P Medicine)** as the golden action/tool to fight dementia
Alzheimer’s disease is a major health issue.
Its multi-factorial etiology requires a multi-factorial but integrative approach.

The need of 3P-Medicine approach

The facts:

Current healthcare practices essentially rely on emergence of signs and symptoms of human pathologies.

A major limitation:

Often the disease process has already taken its toll through manifestation of its complications.

The result:

Despite high care costs, long-term prognosis usually remains poor due to:

- inadequate control of disease manifestations,
- treatment failure,
- disease-recurrence,
- appearance of severe secondary complications,
- relatively low life-quality of treated persons,
- high morbidity and mortality.
Predictive, Preventive and Personalized Medicine (3P Medicine) principles may offer suitable solutions to the particular challenges posed by neurodegenerative diseases.

Prediction of brain pathology, personalized prevention and treatment of neurodegenerative diseases are of capital importance for both healthy aging and health care design.

Neurodegenerative processes are triggered through the action of environmental risk factors facilitated by the inner, individual predisposing factors.
Innovative biotechnologies are golden tools for:

- **prediction** of human pathologies,
- **design of appropriate and timely preventive strategies,**
- personalized treatment planning.

Therefore:

Early detection of pathology-specific molecular patterns can create a well-founded basis for the predictive approaches.

Essential components of 3P Medicine approach are:
• well-organized population screening protocols
• novel diagnostic biomarkers
• targeted prevention of common human pathologies
• personalized, optimal treatment planning.

Resulting main outcomes:
• substantial improvement of the quality of life
• care delivery at potentially reduced costs to the population at large
• addressing social and ethical issues related to access
• affordability of healthcare

EPMA has the coordinating MISSION of the European-Network in Predictive, Preventive & Personalized Medicine. The EPMA-Network is open for issue-related cooperation worldwide.

EPMA Mission

• **Raising awareness and recognition of 3P Medicine** throughout all EU Member and Associated countries;

• **Providing up-to-date information and educational materials** on Predictive & Personalized Medicine and targeted preventive measures;

Promoting:

• the **adequate allocation of resources** for 3P Medicine;

• **advanced programs** for personalized patient treatment;

• **high-quality research** focused on predictive diagnostics and personalized patient treatment;

• **standardization** of bio-analytical technologies for predictive pre-clinical and clinical applications;

• **multidisciplinary efforts** in 3P Medicine;

• **creation of Guidelines** in European health care with the accentuated role of prediction, prevention and personalized patient treatment

(http://www.epmanet.eu)
The EPMA Network

is open for issue-related cooperation worldwide.

More accurate research is needed to enlighten and validate individual “clusters” of inner and outer interacting risk factors responsible for the onset of degenerative processes.

Until the elaboration of cutting-edge, highly efficient disease-modifying drugs and other interventions, the most important way to be pursued is the most obvious one: prevention.

The ongoing development of Predictive, Preventive and Personalized Medicine (3P Medicine) is a step forward dealing with the elaboration of good answers to demographic aging and its outcomes.
Actors called to contribute

Students and professionals in:
- conventional and molecular diagnostics,
- biomedicine,
- biotechnologies,
- ethics, and economics

Universities, research units, hospitals (private and public)

Patients and/or their care givers (family members) organizations

Scientific media

International associations with healthcare-oriented scientific, research and public health-related activities/responsibilities

Political organizations and authorities active in the healthcare sector

Civil society representatives

Healthcare industry including policy-makers.
Romanian organizations

Romanian Medical Association
http://www.ong.ro/ong/amr/societati.htm

Romanian Association for Hepatic Research
http://www.ficat.ro/

Romanian Urological Association
http://www.aru.ro/aru/ie/index.jsp

Romanian Association for the Prevention of Osteoporosis - ASPOR http://www.aspor.ro/

Romanian Society of Clinical Allergology and Immunology
http://www.sraic.ro

Romanian Society of Anesthesia and Intensive Care
www.srati.ro/

Romanian Society of Cardiology
http://www.cardioportal.ro/

Romanian League of Cancer
http://www.romaniancancerleague.org/ro/index.php

Society for the Study of Neuroprotection and Neuroplasticity
http://www.sssn.ro/
Romanian Society of Endocrinology
http://www.sre.ro/asp/statut.asp

Romanian Society of Gastroenterology and Hepathology

Romanian Society of Rheumatology
http://www.srreumatologie.ro/index1.html

Romanian Society of Dermatology
www.srd.ro

The Romanian Society of Medical Informatics
http://www.medinfo.umft.ro/rsmi/

Romanian Society of Ultrasound in Medicine and Biology
http://www.srumb.ro/
Romanian Government
http://www.guv.ro/
Ministry of Research and Education http://www.edu.ro/
Health Ministry http://www.ms.ro/
Ministry of Labour, Family and Social Protection
National House of Health Assurances
http://www.cnas.ro
National Council of Elderly Persons
http://www.cnpv.ro/
National Council of Scientific Research in High Education Institutions
http://www.cnccsis.ro/
Romanian Academy
http://www.acad.ro/
Academy of Medical Sciences
http://www.ms.ro/a_ms/asm/asm.htm
The Romanian College of Physicians
http://www.cmr.ro/
The Order of Nurses and Midwifes from Romania
http://www.oammrbuc.ro/index.php
Universities from Romania

Universities

“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
"Alexandru Ioan Cuza“ University, Iasi, Romania
University of Bucharest, Epigenetic Lab
Polytechnic University of Bucharest, Bioanalysis Lab
“Ovidius” University, Constanta, Romania
“Dunarea de Jos” University, Galati, Romania
“Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj, Romania
“Victor Babes” University of Medicine and Pharmacy, Timisoara, Romania
"Transilvania" University in Brasov, Romania
Other potential actors called into action

Patient groups

• **Association of Communitarian Social Assistance** – AGAPE, Oradea, Romania
• **Down Association**, Oradea Romania
• **Association of Persons with Psychical Handicap**, Oradea Romania
• **National Association of Deaf Persons**, Oradea Romania
• **National Association of Blind Persons**, Oradea Romania
• **Coalition of the Organizations of the Patients with Chronic Diseases** - C.O.P.A.C., Bucharest, Romania
• **National League for Rare Diseases (APWR)**, Zalau, Salaj, Romania
• **National Association for Patients’ Protection**, Bucharest, Romania
Alzheimer's disease in Romania: the national programme for prevention, prediction, and personalized treatment and monitoring of memory diseases - Luiza Spiru, MD, PhD

Medical and other media

MEDICA – the review of the MD’s Romanian National College
http://www.medicalnet.ro/index.php

ROMANIAN JOURNAL OF GASTROENTEROLOGY
http://www.rjge.ro/

BRAIN AGING INTERNATIONAL JOURNAL
http://www.brainaging.ro

ROMANIAN JOURNAL OF HAND AND RECONSTRUCTIVE MICROSURGERY
http://www.rjhrm.ro/

THORAX
http://www.umfcluj.ro/

BULLETIN OF MOLECULAR MEDICINE
http://www.umfcluj.ro/

VIATA MEDICALA
http://www.vmr.ro

ROMANIAN REVIEW OF HEPATOLOGY
http://www.ficat.ro/?unde=rh

ROMANIAN REVIEW OF LEGAL MEDICINE
http://www2.cmb.ro/romjlegmed

ROMANIAN REVIEW OF UROLOGY
http://www.aru.ro/aru/ie/navigation.jsp?node=1375

JOURNAL OF CELLULAR AND MOLECULAR MEDICINE
www.blackwellpublishing.com/jcmm

ROMANIAN MEDICAL RESOURCES
http://www.medical-romania.com
First outcomes of the AD National Program in Romania

Even if still waiting approval and financing, Ana Aslan International Academy just initiated activities and acquires important outcomes able to advocate and support this Program.

Challenges of AD early diagnosis

The biomarkers have different temporal relationships with the manifestation of disease.

- Abnormal concentrations of the two liver enzymes indicate existing liver damage, not just an increased risk.
- Abnormal insulinemia indicate that pathological changes and clinically manifest disease may occur.
- There is now clear evidence that the pathological processes that lead to manifest cardiovascular disease may be underway in children under 10 years of age.

Development of screening guidelines to confront “Alzheimer’s crisis”

Methods in Neuroepidemiology

Neuroepidemiology 2008;30:254–265
DOI: 10.1159/000135644
Received: January 23, 2008
Accepted: March 2, 2008
Published online: June 2, 2008

Development of Screening Guidelines and Clinical Criteria for Predementia Alzheimer’s Disease

The DESCRIPA Study


<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>390 (45)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>96 (11)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>52 (6.0)</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>20 (2.3)</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>48 (5.5)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>22 (2.5)</td>
</tr>
<tr>
<td>Cerebral bleeding</td>
<td>9 (1.0)</td>
</tr>
<tr>
<td>Other atherosclerotic disorder</td>
<td>32 (3.7)</td>
</tr>
<tr>
<td>Any atherosclerotic disorder</td>
<td>187 (21.6)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>294 (35)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>34 (3.9)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>20 (2.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>93 (10.7)</td>
</tr>
<tr>
<td>Hypothyroid function</td>
<td>83 (9.6)</td>
</tr>
<tr>
<td>Hyperthyroid function</td>
<td>29 (3.4)</td>
</tr>
<tr>
<td>Depression</td>
<td>181 (20.8)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>39 (4.5)</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages. Number of subjects ranged from 853 (hypercholesterolemia) to 871 (hypertension).

1 Any atherosclerotic disorder includes angina pectoris, myocardial infarction, carotid stenosis, transient ischaemic attack, cerebral infarction, cerebral bleeding and other atherosclerotic disorder.
Prevalence and prognostic value of CSF markers of Alzheimer’s disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study


Summary

Background Alzheimer’s disease (AD) pathology is common in patients with amnestic mild cognitive impairment (aMCI) without dementia, but the prevalence of AD pathology in patients with subjective cognitive impairment (SCI) and non-amnestic mild cognitive impairment (naMCI) is unknown. AD is characterised by decreased CSF concentrations of Aβ42 and increased concentrations of tau. We investigated the prevalence of a CSF AD profile in patients with SCI, naMCI, or aMCI and the association of this profile with cognitive outcome in each group.

Lancet Neurol 2009; 8: 619-27
Published Online June 11, 2009
DOI:10.1016/S1474-4422(09)70139-5
Methods Patients with SCI, naMCI, aMCI, and neurologically healthy controls were recruited from 20 memory clinics across Europe, between January, 2003, and June, 2005, into this prospective cohort study. A CSF AD profile was defined as an abnormal ratio of Aβ42:tau. Patients were assessed annually up to 3 years. Outcome measures were changes in memory, overall cognition, mini-mental state examination (MMSE) score, daily function, and progression to AD-type dementia.

Findings The CSF AD profile was more common in patients with SCI (31 of 60 [52%]), naMCI (25 of 37 [68%]), and aMCI (56 of 71 [79%]) than in healthy controls (28 of 89 [31%]). The profile was associated with cognitive decline in patients with naMCI (memory, MMSE, and daily function) and in patients with aMCI (MMSE and daily function). In patients with aMCI, a CSF AD profile was predictive of AD-type dementia (OR 26·8, 95% CI 1·6–456·4).

Interpretation AD is a common cause of SCI, naMCI, and aMCI and is associated with cognitive decline in patients with naMCI or aMCI. Patients with SCI might be in the early stages of AD, and cognitive decline might become apparent only after longer follow-up.

Funding European Commission; Ana Aslan International Foundation.
The importance of Nature and Nurture concept

The knowledge of gene-environment interaction may provide valuable insights for the scientific, evidence based design of preventive strategies

Especially epigenetics (changes in gene expression under the influence of well targeted drug and non-drug interventions) is called into action.

A holistic, integrative research paradigm of 3P Medicine

Environmental
- Nutrigenomic
- Sociomic
(Risk) factors
detection
- amendment

Specific Epigenetic and Metabolomic Alterations
- SAM-SAHC / Folates cycles
- DNA methylation patterns
- Relevant genes’ expression

Bio-Medical Outcomes
- Detection
- Markers

Early Diagnosis tools

Improved Therapeutic Interventions

Preventive strategies

Final Outcomes
- Healthy aging
- Social benefits
 (medical, economical)

Preventive, predictive and personalized medicine, Prof. Luiza Spiru, MD, PHD
**- NERO-MIND Concept -**

**CRITICAL NEUROMES IN COGNITIVE AGING AND COGNITIVE PATHOLOGY**

A comparative and integrated study of epigenomic, metabolomic, sociomic and nutriomic aspects in young/elderly healthy people vs. MCI/Alzheimer’s patients.

**Expected outcomes:**

- New, integrated knowledge of capital, basic etiological aspects in cognitive disturbances induced by aging and dementia

- Possible new, important insights tangent to the improvement of (differential) diagnosis tools

- Possible important insights tangent to the elaboration of new medical and non-medical, preventive and curative interventions in aging and dementia
A new unit for holistic, integrated 3P Geriatric approach in Bucharest, Romania

In Dec 2008 Ana Aslan International Foundation launched

**The Clinic for Longevity Medicine, Healthy Aging and Brain Aging Prevention**
Bucharest – Otopeni, Romania

Under the auspices of:
the **Romanian Academy** and **Ana Aslan International Foundation**

Partnership:
„**Carol Davila**” University of Medicine and Pharmacy,
“**Elias**” University Emergency Hospital, Bucharest

Departments:

- **Alzheimer Unit**
- **Geriatrics and Gerontology University Department**
- **The Centre for Diagnosis and Treatment for Longevity and Brain Aging Prevention**

Initiator and Coordinator:
Prof. **Luiza Spiru**, MD, PhD
Workforce building in Romania

BRAINAGING - A 3P Medicine based, educational Project

Running area - national level. Running time – 2009-2011
Funding: FP7-SOP-HRD [AMPOSDRU] 2007-20013
Coordinator: Ana Aslan International Academy of Aging [Prof. Luiza Spiru MD, PhD].
Project philosophy: the training of specialized medical staff in the particularities of aging, brain aging and specific pathology could substantially improve dementia early detection, care and prevention.

Main objectives:
• the implementation and adaptation to Romanian realities of the above Workforce Building Solutions;
• to contribute to the development of a national human resource for dementia care.


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Partnership:
* the Romanian College of Physicians
* the Order of Generalist Nurses from Romania

Scope and objectives:
* the development of a network of 8 training centers (one for each of the development areas defined in Romania);
* the training of 1220 doctors and 1600 nurses (working in neurology, neuro-psychiatry, medical imaging, laboratory and molecular medicine, nursing and bio-ethics departments), in the particularities of brain aging / pathology (especially dementia);
* contribution to the improvement of specific curricula based on newest trends and technologies;
* the promotion of nation-wide strategic partnerships;
* the building-up of a national network of brain aging specialists;
* the orienting toward European trends with respect to management of competencies;
* the covering of medical staff needs for training in the new medical technologies (including IT&C);
* the promotion of training of trainers approach;
* the further dissemination of outcomes in the territory.

The concept / activities of this project aim to cover both the training needs of the medical staff and the need to update the health care services to better fit the real needs of Romanian elders.

This third-age brain aging pathology training received no financial support from Romanian public funds.
Promotion of AAL cutting-edge solutions

Challenges faced by eHealth and AAL applications addressing people with special mental needs

Intelligent AAL applications for physically impaired elders are nowadays boosting; those targeted at cognitive patients still struggle certain obstacles:

- the huge individual variability of cognitive (frequently associated with physical) symptoms/needs → huge variability of assistance needs → end-user profiling is more difficult;
- demographic variables (age, sex, level of education) additively interfere with various mental impairments;
- intelligent assistive devices must be flexible, self-adaptable to an unstable patient profile, and should allow an ongoing readjustment of task sharing between machine and human care giver;
- device personalization as interfaces and guides is more difficult;
- Human (end-user) – machine interaction (non-compliance, even anxiety) is more difficult to be managed;
- Ethical aspects are more complex.


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Lessons we learned from two EU-FP6-IST funded projects:

One of the projects dealt with three AmI prototypes based on inner and environmental sensors and afferent software, for physically and/or cognitively (mild to moderate dementia) impaired people.

The other realized an eHealth software based on case profile and care staff ontologies, and the elaboration of formal intervention plans, personalized on patient’s needs.
Lessons learned:

- The huge individual variability of cognitive symptoms require the definition of:
  - A suitable battery of patient assessment scales (Gorel-Brane scale proved remarkable) for end-user profiling,
  - ‘Clusters’ of needs able to facilitate platform’s flexibility and self-adaptability;

- Among the demographic variables, user’s low education level is critical;

- End-user compliance and machine - human care giver task sharing critically depend on:
  - Friendly, easy-to-use communication interfaces and tutorials,
  - End-user careful previous preparation for the contact with the machine;

- The cooperation with patient’s associations representative seemed mandatory, even from the project proposal preparation phase;

- Ethical aspects and guidelines still require sustained improvement.
The development of AAL applications targeting cognitive patients still requires sustained, multidisciplinary research, mainly addressing:

(a) the design of patient-specific assessment and monitoring tools,

(b) the creation of flexible, adaptive devices with user-friendly interfaces capable of

(c) sustaining patient and caregiver oriented education.
CONCLUSIONS

- Romania is striving to amend medical, social and economical problems related to the improvement of dementia care and to align the local health politics to European trends and to the best practices in the field.

- The National Strategic Program” BRAINAGING” on Preventing Neurodegenerating Diseases, could be an important step forward in this respect.
Thank you for attention and your feedback

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