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Study protocol

Proposal title

Polypharmacy and the Elderly: Prevalence, Clinical Impact and Epigenetic Changes in the Population-based Cohort of the Moli-sani study

Short title

(max 50 characters)

Epigenetics of Polypharmacy in the Elderly

Protocol's version and date should be included in this section

Protocol's version 1
Date: December 5, 2016

Acronym title (max. 10 characters)

EpiPoE

Keywords (max 10 keywords)

Observational study
Polypharmacy
Multimorbidity
Potentially Inappropriate Prescriptions
Elderly
Epigenetics
Genome-wide DNA methylation

Study Classification (IRG)

GGG-Genes, Genomes and Genetics

Study Classification (SS)

GGG-GHD-0643

Institutional Address (Public Institution or No Profit Institution)

Fondazione Neuromed
Via Atinense n.18 - 86077 Pozzilli (IS)

Department/ Operative Unit Institutional Address (Optional)

Department of Epidemiology and Prevention. IRCCS INM Neuromed. Via dell'Elettronica, 86077 Pozzilli (IS);
UOC Farmaceutica Territoriale ASREM, Via Petrella 1, 86100 CAMPOBASSO;
Epicomed Research srl. Corso Mazzini, 2 Corso Mazzini, 2 86100 Campobasso

Abstract (max 4.000 characters)

This sections should include: Background, Objectives, Methods, Expected results

Background: The demographic changes occurring during the past decades are modifying the prevalence and impact of multiple chronic diseases and the related prescriptions of multiple medications. This phenomenon will have a great impact on social and health-care policy planning. Polypharmacy is worryingly increasing among the elderly, with rates ranging between 42.5 and 77%. Epigenetics involves changes in gene expression that do not accompany alterations in the DNA sequence, including DNA methylation that is the most understood and studied one. DNA methylation epigenetic changes are not only a biomarker of environmental exposure, aging and disease state, but could also reveal specific pattern directly associated to drug use and become a suitable target for modification in the context of pharmacology intervention.

Objectives: The main objective of the present project is to evaluate the impact of polypharmacy on health and disease status in a general population of elderly people (Study A) and to investigate a possible role of the polypharmacy (considering selected medication clustering) in shaping the genome-wide DNA methylation profile (Study B).

Methods:

Study A: An elderly population-based prospective observational investigation, in the framework of the Moli-sani project, will be performed. "Moli-sani" is a population-based cohort study, started in March 2005, that randomly recruited from city-hall registries men and women aged ≥ 35 , living in Molise, a Central-Southern Italian region. The recruitment ended in April 2010, and 24,325 subjects were recruited. The Moli-sani population included at baseline 5,830 individuals aged ≥ 65 years.

The main clinical fatal and non-fatal outcomes will be hospitalization for any cause and specific cause, unplanned hospitalization, mortality for any cause and specific cause. Every year, the regional Department of Health Service authorizes the Moli-sani study to update Moli-sani data on hospitalization, death and drug prescriptions (sources: ReNCaM registry, Hospital Discharge Records registry, drug prescriptions registry). Polypharmacy will be notified by regional drug prescriptions registry.

Multivariable linear regression analysis will be performed to test the association between polypharmacy with clinical outcomes. Hazard ratios of outcomes for polypharmacy will be calculated using Cox proportional hazard models. Test for interaction between the calendar time (years: 2005-2015) and the polypharmacy will be performed in order to investigate a possible change over time in the effect of polypharmacy on clinical outcomes.

Study B: Moli-sani participants (who will be on July 1st 2017 ≥ 65 years old) who referred no drug therapy at baseline, will be recalled for a new examination. During this second visit blood sample will be collected, buffy coat prepared and stored in liquid nitrogen in the Moli-sani bio-bank.

The recall phase will allow to identify, among subjects who at baseline were not on any drug therapy, a group of subjects who had started to take one or more chronic medications after enrollment. Genome-wide DNA methylation analysis via the Illumina Infinium MethylationEPIC BeadChip will include participants under polypharmacy compared to those who, after the original enrollment were chronically taking 0-1 drug. Multivariable linear regression analysis will be used to determine the association between DNA methylation and polypharmacy and/or clinical outcomes.

Expected results:

With this project we aim at characterize the polypharmacy influence on elderly health and disease and the possible mediating role of DNA methylation in this process. The present project will hopefully contribute to accomplish an initial transition from single-disease-oriented to patient-centered approach of care delivery: this is a clear innovativeness of the study.

Background -a (max 4.000 characters)

Please describe: an updated review of already available evidence in the relevant literature

The demographic changes occurring during the past decades are modifying the prevalence and impact of multiple chronic diseases and the related prescriptions of multiple medications. The available evidence regarding the efficacy of polypharmacy (commonly defined as co-intake of at least 5 different drugs) (1) in the growing elderly population is scarce and rarely derives from real-life (extra hospital conditions).(2) It is estimated that by 2050 the elderly will be fourfold more represented than adults and youth.(3) Older adults on multiple medications have reportedly worse health status compared with those on less medications, and appear to be a vulnerable population (4,5):

- they are at greater risk for adverse drug reactions (ADRs) due to metabolic changes and decreased drug clearance associated with aging, a risk compounded by increasing numbers of drugs used;
- polypharmacy increases the potential for drug-drug interactions (DDIs) and for prescription of potentially inappropriate medication;
- polypharmacy increases the possibility of "prescribing cascades", when an ADR is misinterpreted as a new medical condition and additional drug therapy is then prescribed to treat it;
- polypharmacy can lead to problems with medication adherence, compounded by visual or cognitive compromise.

Polypharmacy is increasing among the elderly, with rates ranging between 42.5 and 77%.(2)

The REPOSI study reported the prevalence of polypharmacy being 52% at hospital admission and 67% at discharge, among elderly patients in internal medicine wards.(6) A recent study in the Friuli Venezia Giulia region, reported that the prevalence of polypharmacy among elderly was 57.7% and of those 23.9% showed Potentially inappropriate prescriptions (PIPs).(2)

Similarly, in 2015, in the Molise region, using data extracted from the regional prescription drug registry, more than half of the elderly was under polypharmacy (37,414/73,183 residents aged ≥65 years, 51%).

"Moli-sani" (7) is a general population-based cohort study, started March 2005, that randomly recruited from city-hall registries men and women aged ≥35, living in Molise. The main purpose of Moli-sani study was to investigate genetic and environmental risk factors for cardiovascular and cancer disease. An additional goal was that of acquiring data on real life elderly, without any age upper limit, to evaluate drug prescription appropriateness, relationship between multimorbidity/polypharmacy and several outcomes as all-cause mortality and identification of disease clusters most often occurring in the elderly. The enrollment ended in April 2010, and 24,325 subjects were recruited. They included at baseline 5,830 subjects over 65 years.

In November 2016, the Moli-sani study obtained from the regional Health Department, the authorization for the record-linkage of the cohort population with the regional drug prescription registry. This procedure will allow to update for all Moli-sani participants the information on drug therapy obtained at the enrollment, with the prescriptions registered during the follow-up (2005-2015), collecting data on frequency, duration, compliance and switch of the therapy. Obviously, it will be possible to identify drug naïve subjects too.

The linkage mentioned above will allow to evaluate the possible epigenetic impact of polypharmacy on clinical outcomes. Epigenetics involves changes in gene expression that do not accompany alterations in the DNA sequence, including DNA methylation, the most understood and studied (8). Unlike inherited genetic variation that is static throughout the life course, DNA methylation is a plastic and dynamic phenomenon, and may differ by tissue and disease state. DNA methylation epigenetic changes over time are not only a biomarker of environmental exposure, aging and disease state, but could also reveal specific pattern associated to drug use and become a suitable target for modification in the context of pharmacology intervention.

Background -b (max 4.000 characters)

Please describe: the clinical question that will be the object of the study and what the study will add to the overall available evidence

The clinical questions that will be the object of the present project are:

1. Would the association between multimorbidity, polypharmacy and several clinical outcomes previously reported on elderly people acutely admitted to medical or geriatric hospital wards in Italy (REPOSI) be also apparent in a sample of a general, randomly selected, elderly population followed up for an average period as long as 9 years? (Study A)
2. Would the profile of the DNA methylation landscape in a sample of that elderly population undergoing polypharmacy identify good markers for prediction of adverse outcomes and therapy efficacy? (Study B)

The impact of polypharmacy on the elderly population is significant. It is associated with poor adherence, DDIs, medication errors, and ADRs, accounting for an increased re-hospitalization and mortality risk.(5,6) A number of chronic diseases such as hypertension, coronary heart disease (CHD), heart failure (HF), chronic obstructive pulmonary disease (COPD), chronic renal failure (CRF) and diabetes mellitus are predictors of polypharmacy.(2)

Prevalence and predictors of polypharmacy have been analyzed in many studies, with results differing in relation to the clinical setting in which they have been performed. They usually identify the multimorbidity status of an individual as the strongest predictor of polypharmacy.

At the moment, suitable means for better stratification to improve the efficacy and reduce the side effects of polypharmacy in the elderly are not clearly identified. It is however known that some of the most common drugs prescribed as part of polypharmacy may change the DNA methylation status at several loci in the genome, often improving prognosis in some disease conditions.(9,10)

Based on this overall available evidence, our study seeks to address the two questions posed above.

Background -c (max 4.000 characters)

Please describe: drug/drugs/ therapeutic regimen information

The present project is an observational study.

The main objective of the present project is to evaluate the impact of polypharmacy on disease status in a general population of elderly people and to investigate a possible role of polypharmacy (considering selected medication clustering) in some epigenetic modifications, such as DNA methylation.

Polypharmacy will be defined as the co-prescription of at least 5 drugs. The most frequently prescribed drugs are: platelet aggregation inhibitors, vitamin K antagonists, diuretics, sulfonamides, beta-blocker, statins, benzodiazepine and proton pump inhibitors.(2)

Rationale (max 4.000 characters)

Please describe: the possible impact on the Italian National Health Service (NHS) and/or on study population; the innovativeness of the study and the possible benefit/risk ratio.

Multimorbidity and polypharmacy are the most common conditions managed in geriatric clinical practice. Old people with multimorbidity and related polypharmacy prescriptions are the most common users of health care, generate high costs and are at increased risk for adverse events. Most of these elderly are cared for by general practitioners who have often inadequate expertise in geriatrics and multimorbidity and in particular in polypharmacy management. This results in fragmented care, suboptimal health outcomes and avoidable harms for old patients with multiple chronic conditions receiving polypharmacy.⁽¹¹⁾ Unconsidered application of multiple single disease approaches leads to polypharmacy, with drug-drug or drug-disease interactions, high treatment burden, poor attention to social and personal context, thus yielding unclear benefits and unintended harms for elderly with multiple chronic conditions.

Current guidance for management of multimorbidity and polypharmacy in clinical practice is insufficient. Provision of effective care for elderly with multimorbidity and polypharmacy requires more individualized care approach, stopping potentially harmful or unnecessary medications while starting beneficial medications and minimizing treatment burden. Much attention has been recently paid to the promise of precision medicine, a term describing the approach to disease treatment and prevention that takes into account individuals' variability in their genes, environment and lifestyle, and on the possible epigenetic impact of the latter two conditions on the functional status of their genetic profile.

The present project will hopefully contribute to accomplish an initial transition from single-disease-oriented to patient-centered approach of care delivery: this is a clear innovativeness of the study.

The evaluation of prescriptive appropriateness and adherence to therapies and time trend analysis in polypharmacy, related to specific clinical outcomes, and epigenetic individual indicators will allow to better understand how to contribute to a healthy aging and to more rationally allocate resources of the National Health Service (pharmacoeconomic evaluation).

Objectives of the study (max 4.000 characters)

Please report the primary objectives and, if any, the secondary objectives of the study, the purpose of the trial and state the statistical hypothesis (e.g. superiority, equivalence or non-inferiority for the primary endpoint(s)).

PRIMARY OBJECTIVES

1. To assess the prevalence of polypharmacy in a previously randomized general population-based cohort of elderly, to perform an accurate characterization of the subjects who are under polypharmacy and to evaluate the most common clusters of diseases associated with polypharmacy.
2. To evaluate the association of polypharmacy with the occurrence of several clinical outcomes (chronic disease, hospitalization, unplanned hospitalization, length of hospital stay, mortality).
3. To assess the associated risk of PIPs among elderly who are in polypharmacy and evaluate whether the occurrence of PIPs is associated with poor clinical outcomes (chronic disease, hospitalization, unplanned hospitalization, length of hospital stay, mortality).
4. To profile the genome-wide methylation on a subsample of the same elderly population over time (before and after chronic polypharmacy) in order to investigate the mediation of polypharmacy-associated methylation changes on health and disease outcomes.

SECONDARY OBJECTIVES

5. To examine time trends in polypharmacy among the elderly Moli-sani participants using data from the regional registry of drugs between 2005 and 2015. Trends across age, sex, social status, selected medication classes will be investigated. Studies of the association between polypharmacy and specific clinical outcomes (using the regional registry of deaths and regional archive of hospital discharge forms) over time (2005-2015) will also be performed.
6. To evaluate the prescriptive appropriateness and the adherence to therapies, considering these as the key features both for the effectiveness and safety of drug treatments and for the efficient allocation of resources of the National Health Service (pharmaco-economic evaluations).
7. To identify epigenetic markers of polypharmacy impact on health and disease.

Study design (max 4.000 characters)

Please describe the methodology applied according to questions on study proposal and implementation.

Study A: The objectives (objs) 1-3, 5 and 6 will be achieved by a prospective observational study.

"Moli-sani" (7) is a population-based cohort study that recruited 24,325 subjects (48% men; mean age = 55.8 ±11.9 years). The Moli-sani population included at baseline 5,830 subjects over 65 years, of whom 1,744 over 75 years. The elderly sub-sample of the Moli-sani cohort will be the population setting to involve to achieve objs 1-3, 5 and 6.

The recruitment phase of the Moli-sani cohort was completed in five years (2005-2010; see beyond). The baseline dataset of Moli-sani study will provide a large panel of information on health, lifestyle and dietary habits.

At the present, the follow-up phase covers the period from 2005 to 2015 and consists in the record-linkage of study cohort with regional hospital discharge archive and Italian mortality registry (ReNCaM registry), the latter having being already completed.

Study B: To reach objective objs 4 and 7, a recall of part of the elderly cohort will be organized ; a prospective observational study design will be conducted without involving any drug administration.

The Biological Bank of the Moli-sani study (Moli-bank) presently stores plasma, serum and buffy-coat obtained from all participants, the latter to allow DNA extraction for genetic/epigenetic studies.

For Study B, Moli-sani participants (who will be on July 1st 2017 ≥ 65 years old) who referred no drug therapy at baseline, will be recalled for a new examination (similar to the recruitment phase). During this second visit blood sample will be collected, buffy coat prepared and stored under liquid nitrogen in the Moli-sani bio-bank.

The recall phase will allow to identify, among subjects who at baseline were not on any drug therapy, a group of subjects who had started to take one or more chronic medications after enrollment. The epigenetic study will be restricted to participants under polypharmacy compared to those who, after the original enrollment were chronically taking 0-1 drug.

Study population (max 4.000 characters)

Please report: study population characteristics and the clinical setting (hospital, general practice, etc.) where the study will be conducted; enrolment procedure and accrual time. Please specify if special populations will be included in the study, also for those studies not related to this specific topic. Please specify withdrawal criteria and procedures.

Study A: An elderly population-based prospective observational investigation, in the framework of the Moli-sani project, will be performed to achieve the objs 1-3, 5 and 6;

"Moli-sani" (7) is a population-based cohort study, started in March 2005, that randomly recruited from city-hall registries men and women aged ≥ 35 , living in Molise, a Central-Southern Italian region. At enrollment, exclusion criteria were pregnancy, disturbances in understanding processes, on-going traumas and refusal to sign the Informed Consent. The Moli-sani study is being performed according to the Declaration of Helsinki and was approved by the Catholic University Medical School ethical committee. All participants provided written informed consent. The recruitment ended in April 2010, and 24,325 subjects were recruited. The Moli-sani population included at baseline 5,830 subjects over 65 years, of whom 1,744 over 75 years.

Study B: in the framework of Moli-sani project, elderly participants will be selected from those referring no drug therapy at baseline (N 2,300).

Inclusion criteria (max 4.000 characters)

Study A: The eligible population is the elderly subjects (aged ≥ 65 years at the original enrolment, years 2005-2010) recruited in the Moli-sani Study (N 5,830).

Study B: Moli-sani participants who

1) at the original enrolment were under no drug therapy (recruited N 2,300);

2) at the time of the start of the present project (July 1st 2017) will be aged ≥ 65 years and will still be resident in the Molise region.

Exclusion criteria (max 4.000 characters)

Institutionalized older adults (studies A and B).

Concerning the obj 4 (Study B) the refusal to provide a written informed consent to collect a new biologic sample.

Intervention (max 4.000 characters)

Please provide detailed information about treatments (or other type of intervention) for each group (treatment and control), including:

- Dose (and dose escalation) and the dosage form, packaging and labelling of the IMP;
- Duration of treatment (including number and duration of the cycles, if applicable) and the follow-up period for each IMP/trial treatment group/arm of the trial;
- Route of administration;
- Medication/treatment (including rescue medications) and not permitted before and/or during the trial;
- Procedure for monitoring subjects compliance;
- Description of the “stopping rules” or “discontinuation criteria” for individual subjects, part of trial, and entire trial;
- Accountability procedures for the IMP, including placebo and comparator if any.

For observational studies, the specific characteristics of the investigated exposure/treatment should be described.

The present project is an observational study.

Outcomes (max 4.000 characters)

Please report: the primary and secondary outcome measures; the procedure for the ascertainment of the outcomes (with particular emphasis on the relation between subjective/objective evaluation of endpoints and blinding), justifications to support the validity of any surrogate or composite endpoints, if applicable (a brief comment on the clinical relevance of the aforementioned endpoints should be also included).

The main clinical fatal and non-fatal outcomes will be:

Hospitalization for any cause and specific cause: hospitalization will be recorded by linkage of the study cohort to the databases of the regional archive of hospital discharges, which are considered high quality registries.

Specific incident cases will be identified by the codes of the International Statistical Classification of Diseases (9th Revision):

- coronary heart disease: Hospital Discharge Records hospitalization with ICD-9 code 410-414.
- Stroke: Hospital Discharge Records hospitalization with ICD-9 code 430-432, 434, 436 or ICD-9-CM code 38.12
- Heart failure: Events selected if one of the four ICD-9 coded diagnoses in the Hospital Discharge Records revealed a hospitalization with code 428.

After identification, the events will be validated by checking the hospital records.

It will be possible to record a notification of specific type of hospital admission using the diagnosis-related group (DRG) Code.

Additionally, the regional archive of hospital discharges will allow to notify unplanned hospital admission classified as emergencies or urgent and the length of hospital stay.

Mortality for any causes and cause specific: Overall and cause-specific mortality has been already assessed from the Italian mortality registry (ReNCaM registry) and validated by reviewing the Italian death certificates (ISTAT form) (years: 2005-2015).

Every year, the regional Department of Health Service authorizes the Moli-sani study to update Moli-sani data on hospitalization, death and drug prescriptions (sources: ReNCaM registry, Hospital Discharge Records registry, drug prescriptions registry). Additionally, every 4 years, municipalities provide information about vital status, emigration and residency of each Moli-sani participants.

Moreover, the impact of the following determinants or mediators of the outcomes will be considered:

Potentially inappropriate prescriptions (PIPs): PIPs will be assessed according to the Beers criteria revised by the American Geriatrics Society (version 2015).¹² These criteria include drugs to be always avoided, drugs to use with caution, and drug-disease interactions. The Beers criteria are increasingly being used to monitor quality of care for older adults.⁽¹²⁾ The validity of these Consensus derived criteria in predicting adverse outcomes therefore is becoming increasingly more important. The Beers criteria, initially developed by an expert consensus panel in 1991 to target nursing home residents, are the most widely cited criteria used to assess inappropriate drug prescribing. The panel produced a list of medications considered inappropriate for older patients, either because of ineffectiveness or high risk for adverse events.

Prescriptive appropriateness and adherence to therapies will be notified by checking the regional drug prescription registry.

Epigenetic markers: We will investigate the genome-wide DNA methylation profile according to polypharmacy (yes or no). This analysis will result in the identification of regulatory pathways that are influenced by polypharmacy in the elderly and depend on DNA methylation changes from drug exposure.

Methods -a (max 4.000 characters)

A description of the measures taken to minimize/avoid bias, including (but not limited to):

Randomization. Please report methods used to generate the random allocation sequence. Central randomization should be preferred; other randomization procedures should be adequately motivated. (Include a description of maintenance of trial treatment randomisation codes and procedures for breaking the code).

Blinding (masking). Please describe whether or not, the personnel involved in administering interventions and assessing outcomes is aware of group assignment and if not, how the success of masking is assessed.

The present project does not require any randomization nor blindness, as it is based on a population cohort that was correctly randomized by the Moli-sani study. The cohort of the Moli-sani Study was randomly recruited among the residents in the Molise region from city hall registries by a multistage sampling. First, townships were sampled in major areas by cluster sampling; then, within each township, participants aged 35 years or older were selected by simple random sampling. Recruitment was based on household to allow household and large pedigree construction for genetic analysis. Exclusion criteria were pregnancy at the time of recruitment, disturbances in understanding or willingness, current poly-traumas or coma, or refusal to sign the informed consent. Thirty percent of subjects could not or refused to participate; these were generally older and had a higher prevalence of CVD and cancer (13).

During the recruitment (2005-2010), the Moli-sani Project participants underwent anthropometric, biological and instrumental screening (spirometry and ECG tests); the investigators also administered a validated questionnaire to evaluate socio-economic status, smoking habits, physical activity, personal/family history of diseases, current and past diseases and a validated food frequency questionnaire (from the project EPIC).

The baseline dataset of Moli-sani provides complete information on the use of medications for any disease and an accurate clinical assessment of the conditions for which those drugs are being prescribed.

Venous blood in order to obtain plasma, serum, cells and DNA and a temporized urinary sample were collected at the time of the enrolment. The biological samples were stored in a Biological Bank in liquid nitrogen.

Biochemical analyses on fresh samples were performed in the centralized Moli-sani laboratory (13). All hemocromocytometric analyses (white blood cell and platelet counts, granulocyte and lymphocyte percentage) were performed by the same cell counter (Coulter HMX, Beckman Coulter, IL Milan, Italy.), within one hour from venipuncture. Triglycerides, HDL cholesterol and glucose were measured in serum samples using commercial colorimetric enzyme kits (Instrumentation Laboratory, Milan, Italy) and an automatic analyzer (IL 350, Instrumentation Laboratory). High sensitivity C reactive protein (hs-CRP) and d-dimers were measured in fresh serum, by a latex particle-enhanced immunoturbidimetric assay (IL Coagulation Systems on ACL9000).

Creatinine, Hs-troponin and N-terminal pro B-type natriuretic peptide biomarkers were measured by appropriate laboratory assays in biological samples stored in the Moli-sani project's Bio-bank (14).

The epigenetic investigator(s) will be blind in respect to clinical outcomes and polypharmacy (Study B).

Methods -b (max 4.000 characters)

Information retrieval. Please report: data that will be gathered; the forms/tools used for the retrieval of information and their validity and reliability; the measures/indicators used; the potential sources of biases in the retrieval of information regarding study subjects and interventions/treatments; duration and frequency of follow up; expected estimate of subjects lost to follow up and possible implications for the findings of the study; potential confounding factors, and methods for taking into account their effect are of particular importance for observational studies. When the use of an electronic clinical reporting form (e-CRF) is envisaged, only validated systems that address traceability are acceptable (for instance, excel spreadsheets do not represent an adequate system for recording data). Please include in this section the identification of source data definition.

Study A: All the procedures, forms, questionnaires, that will be used in the present project have already been largely tested and validated in the Moli-sani study. In particular, different registries (drug prescriptions, hospital discharge forms, deaths) of the regional health service will be used.

Information on incidence of mortality and identification of causes of death are already available.

The cohort has been followed-up for mortality until December 2015, for a median of 8.2 years (IQR: 7.3-9.3).

1,410 all-cause deaths were recorded (incidence 5.8%), by a record linkage of study cohort with the Death Registry of the Molise Regional Health Service (the ReNCaM registry) and provides the underlying cause of death in ICD-9

A record linkage will be performed with the regional archive of hospital discharge forms (update December 2015) to identify incident cases of several chronic diseases (CVD, cancer, COPD, CRF), unplanned hospitalization and the length of hospital stay.

The record-linkage of the cohort study with the regional drug prescription registry allows to update the information on drug therapy for all Moli-sani participants, identifying all prescriptions registered during the follow-up (2005-2015), and collecting data on frequency, duration, compliance and possible switch of the therapy. Additionally, drug naïve subjects will be identified, too.

Study B: These selected participants will be recalled during the first 18 months of the study and will be administered anamnestic and dietary (the EPIC- FFQ) questionnaires and a questionnaire developed to investigate in the elderly drug-related problems, as described by Willeboordse et al. (15)

At the same moment, a blood sample will be collected for new biochemical analysis (to be performed in the centralized Moli-sani laboratory in IRCCS Neuromed) and for DNA storage (buffy-coat) in the Moli-sani Biobank.

A large panel of biochemical markers will be measured on fresh and frozen biospecimens (i.e. creatinine, hs-CRP, d-dimer, full blood cell count, lipid profile, glucose).

By retrieving data from the regional drug prescription registry, we estimate that after the recall of 2,300 subjects with no drug therapy reported at baseline, 20% will be under 0-1 drug therapy and 30% will be under polypharmacy. For each of these 1,150 subjects' genome-wide DNA methylation analysis will be performed on DNA samples at both baseline and recall phases, using the Illumina Infinium MethylationEPIC BeadChip. (16) This method allows the interrogation of over than 850,000 methylation sites across all the genome including coding and non-coding regions, enhancers, DNase hypersensitivity sites, miRNA promoter regions. The distribution of samples across chips will be blinded by randomly sorting de-identified matched samples to reduce the likelihood of systematic technical bias. Bioinformatic analysis will focus on top candidate genome-wide identified genes and repetitive elements (LINE-1) as measure of global DNA methylation, as described in Rochtus et al.(17) Significantly different DNA methylation signals will be then analyzed to build up relevant pathways of polypharmacy-dependent epigenetic regulation. Since this study will also evaluate possible longitudinal changes in DNA methylation due to aging, we will additionally specifically analyze the methylation estimates in our cohort for the so called "epigenetic clock genes" as defined by Horvath (18). This analysis will give us information relative to one's DNA methylation-based age and whether this is influenced by polypharmacy.

Methods -c (max 4.000 characters)

Sample size estimates. Please report the estimate of sample size and how it is determined. The information requested to calculate sample size includes the power, the level of significance, the underlying event rate in the population under investigation and the size of the treatment effect. Adjustment for other factors affecting the sample size calculation (e.g. expected compliance rates), should also be reported. For studies of equivalence – non inferiority the maximum acceptable difference should be stated.

Statistical analysis. Please report the main statistical analyses that will be carried out. Definition of the populations for main analysis, error probabilities, brief description of the statistical techniques, methods for additional analyses, such as subgroup analyses (if planned). Researchers should consider that the main statistical analyses that will be used in presenting the final findings (e.g., final reports, publications) need to be coherent with the content of this section. Explanation of each interim analysis (if planned) and predefined stopping rules should also be clearly stated.

SAMPLE SIZE ESTIMATES.

Power calculation

The sample of 2,300 individuals will ensure a power= 90% to detect a correlation coefficient between methylation and number of drugs $p < -0.05$ or $p > 0.05$ ($\alpha=0.05$). Starting from the population sample of 2,300 individuals, we expect to have at the end of follow up N=460 (20%) no drug subjects and 690 (30%) polypharmacy subjects. With this sample size, we will be able to detect a true difference in the mean response of no drugs vs. polypharmacy groups $<19.5\%$ or $>19.5\%$ of the standard deviation of the response variable, with power=90%. The Type I error probability associated with this test of the null hypothesis that the population means of the two groups are equal is 0.01 (this level was chosen to take into account the multiple comparison issue (four genes measured)).

STATISTICAL ANALYSIS

Study A

Multivariable linear regression analysis will be performed for testing the association between Polypharmacy with PIPs and clinical outcomes. Hazard ratios of outcomes for Polypharmacy will be calculated using Cox proportional hazard models (objs 1,2,3).

Mediation analysis will be conducted to test the role of PIPs. Additive and multiplicative interaction between polypharmacy and PIPs will be tested with appropriate cross-product terms (objs 2,3).

Test for interaction between the calendar time (years: 2005-2015) and the polypharmacy will be performed in order to investigate a possible change over time in the effect of polypharmacy on clinical outcomes (obj 5). The differences over time will be evaluated by multivariable analysis of the variance for repeated measures.

Subgroup analyses will be conducted according to sex and age categories (65-79 and ≥ 79 years) and major chronic diseases (CVD, Cancer, CRF) at baseline.

Similar analyses will be conducted for obj 6; in this case, the variables under evaluation will be the prescriptive appropriateness and the adherence to therapies.

Study B

Methylation data will be normalized, filtered and selected for the gene-specific analysis using the Illumina Methylation Analyzer (IMA) package and the method described in Rochtus et al. (17) except for the removal of leukocyte-specific probes. We will perform t-test student to measure the changes in DNA methylation due to polypharmacy (yes vs no). Multivariable linear regression analysis will be used to determine the association between PIPs and clinical outcomes (as dependent variable) and DNA methylation and/or polypharmacy or all models will be adjusted for each of the variable that will be associated ($P < 0.1$) with polypharmacy, DNA methylation and the dependent variable. In addition, because peripheral blood constitutes a heterogeneous admixture of different cell types which may be methylated in a cell-type specific way, principal components of white blood cell estimates will be added as fixed effect to adjust for cell type confounding. Since blood counts are available for the Moli-sani participants, we will also use these measurements to correct for in our multivariable linear regression model. Sensitivity analysis by a large panel of possible confounders (age categories, gender, socio-economic status) will be performed. Effect modifications will be assessed by adding appropriate interaction terms in the multivariable regression models. We will also use mediation analysis to quantify the extent to which our interrogated DNA methylation signature underlies the association between polypharmacy and clinical outcomes.

Two-sided 95 percent confidence intervals and P values will be calculated; two-sided P-value < 0.05 will be chosen as the level of significance. All computations will be carried out using the SAS statistical package (Version 9.4 for Windows. SAS Institute Inc. Cary, NC, USA 2009).

Methods -d (max 4.000 characters)

Organizational characteristics. Please describe: the participating centres, the specialties and experience needed for conducting the study. In case of multicentre studies, please specify:

- the institutions/units in charge of coordinating the study, assigning treatment, monitoring the procedures;
- the presence of steering committees and/or data monitoring committees (when applicable);
- the presence and the organization of centralized laboratories (when applicable).

Feasibility. Please describe: previous experience of the principal investigator; previous experience of the institution(s) that will coordinate the study; available technology that may be relevant for the study.

Coordinator centre: Fondazione Neuromed, Pozzilli (IS)

The Neuromed Foundation (Fondazione Neuromed) - a non-profit organization established in the year 2000 – has as the aim to support scientific, social and cultural progress. It organizes and supports research projects generated by the Foundation itself or by the IRCCS Neuromed or by other research Institutes. As an example, the Foundation presently runs a research and training project called “Polo di Innovazione Cyber Brain” in collaboration with the the Euro-Mediterranean Institute of Science and Technology (IEMEST) in Palermo and with Fondazione Neurone, Onlus in Roma. The Neuromed Foundation is registered in the list of ex DPCM 361/00 at the Prefettura of Isernia, n.9, in the Anagrafe Nazionale delle Ricerche Cod. 60465MYL and is recognised as an Organism for Vocational Training by the Regione Molise. C.F. 90027150946. In respect to the present project, Giovanni de Gaetano, Scientific Director of the Foundation, will be the PI and will coordinate all partners participating in the project.

Prof Giovanni de Gaetano, MD, PhD, is the Scientific Director of the Fondazione Neuromed at Pozzilli (Isernia). He has a long-lasting experience in experimental, clinical and epidemiological studies, as it can be evidenced by his more than 500 publications (as retrieved from Pubmed). He had the role of PI or of active investigator in numerous clinical trials, such as the Primary Prevention Project (PPP trial, Lancet, 2001), the Polycythemia Vera (ECLAP trial, New Engl J Med, 2004), the Aspirin in pre-eclampsia trial (Lancet, 1994), the ICCAI study on chronic critical limb ischemia (Ann. Int Med, 1999) and several others. He was the Director of the Research Laboratories at the Catholic University in Campobasso, where the Moli-sani study was planned, started and executed before its transfer to the IRCCS Neuromed in 2013.

Operative unit 1 Department of Epidemiology and Prevention. IRCCS INM Neuromed. Pozzilli (IS).

Dr. Simona Costanzo is a PhD epidemiologist with an extensive experience in conducting and/or supporting epidemiologic research. She is involved in several epidemiologic studies, coordinating the main phases of a project (protocol study drafting, research funding, data management and analysis, medical writing). She is the responsible for the validation of the clinical events (fatal and not fatal) that had occurred among the Moli-sani participants from 2005 to the present. Between 2014-2016 she has collaborated in the “Centro regionale di farmacovigilanza” of Molise Region, Health Department.

Dr. Benedetta Izzi is a PhD molecular biologist with extensive experience in DNA methylation research both at the gene-specific and genome-wide level. She is involved in several population epigenetic studies involving both birth cohorts (Epigenetic Birth Cohort (USA), ENVIRONAGE (Belgium) and Pre-natal Early Life Stress (PELS) (Belgium) cohort) and larger epidemiological studies (FLEMENGHO, Belgium).

Operative unit 2: UOC Farmaceutica Territoriale ASREM CAMPOBASSO

- Dr. Stefania Falciglia is a hospital pharmacist with extensive experience in the control of drug prescriptive appropriateness. She is involved in data management and evaluation of the regional drug prescription registry

Operative unit 3: EPICOMED research srl (Dr. Chiara Cerletti, legal representative), Campobasso

Epicomed collaborated to several Italian Epidemiological studies (INHES, “Moli-sani”, Polyphemus and ATHENA Studies) by providing trained personnel for patient recruitment and questionnaires administration.

Methods -e (max 4.000 characters)

Timing. Please report: the duration of the study (patient enrolment; treatment duration, follow up, etc.); predefined check points for the evaluation of work in progress; when the final report will be provided. Please estimate here the overall study duration from the First Patient First Visit (FPFV).

Good clinical practices. Experimental studies are required to be conducted in accordance with Good clinical practices (GCP). Please discuss what are the specific hazards of the study (e.g., risks for the patients, complexity of the study design, validity of the information retrieval, etc.), the procedures of risk minimisation (e.g., training activities, review of eligibility prior to randomization, data verification, drug reconciliation, etc.), the characteristics and frequency of monitoring activities and the institution(s) that will be in charge of this task.

Ethical aspects. Please describe: the potential risks for study subjects, either related to physical/psychological domains or to a possible excessive interference with the subject privacy, and the procedures that will be followed to prevent these potential risks. As mentioned above, it is not necessary to include the documentation required by the Italian ethics committees.

Insurance. Please include a comment about the application of the law about the study insurance agreement (DM 14 marzo 2009).

TIMING

Study design A, Objs 1-3, 5 and 6:

m 1-6, 13-18, 25-30 data retrieval from regional drug prescription databases (polypharmacy)

m 1-6, 13-18, 25-30 data retrieval from regional registry (outcomes: hospitalizations and deaths, elderly Moli-sani update data follow-up)

m 1-6, 13-18, 25-30 clinical events validation (elderly Moli-sani follow-up)

m 18-36 data analysis and interpretation, manuscript drafting, report

Study design B, Objs 4 and 7:

m1-2 checking of Moli-sani database

m 1-2 questionnaire development

m 3-21 recall of part of cohort (N 2000)

m 22-25 DNA extraction (N 2000)

m 25-32 genome-wide DNA methylation analysis (N 2000)

m 32-36 data analysis and interpretation, manuscript drafting, report.

Predefined check points for the evaluation of work in progress will be event validation, number of recalled participants, DNA quality control check after extraction.

Interim report will be provided every year and a final report will be provided at the end of the study.

The overall study duration will be 36 months.

GOOD CLINICAL PRACTICES AND ETHICAL ASPECTS.

The study will be approved by the Ethical Committee of the Catholic University of Rome and of other participating institutions.

All the steps of the project will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of October 1996, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice. Subjects will not be exposed to any experimental investigation, medication, or treatments. There will be no influence regarding prescription, nor restriction of therapies.

Each subject will give written informed consent according to local requirements, after the nature of the study has been fully explained.

The collection and processing of personal data from subjects enrolled in this non-interventional study will be limited to those data that are necessary to conduct the study. These data will be collected and processed with adequate precautions in place to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration will be put in place, as already done for the MOLISANI study.

INSURANCE

Given the observational design, the study shall not respect the obligations required for interventional studies (article 4 of the Ministerial DECREE dated July 14, 2009) and shall need the standard insurance required for normal medical practice (AIFA guidelines, Gaz. Uff. Rep. Ital. 2008, serie gen. N. 76: 68-74).

References (max 4.000 characters or max 20/25 references)

Please report only the references that are strictly relevant to the study proposal. References should include authors (when there are more than 6 authors, report the first 3 authors only title, book or journal, year, volume number and page numbers. For books, the publisher should also be reported.

- 1) Mannucci PM, Nobili A; REPOSI Investigators.. Multimorbidity and polypharmacy in the elderly: lessons from REPOSI. *Intern Emerg Med.* 2014 Oct;9(7):723-34. Review.
- 2) Cojutti P, Arnoldo L, Cattani G, Brusaferrero S, Pea F. Polypharmacy and the risk of potentially inappropriate prescriptions (PIPs) among elderly and very elderly patients in three different settings (hospital, community, long-term care facilities) of the Friuli Venezia Giulia region, Italy: are the very elderly at higher risk of PIPs? *Pharmacoepidemiol Drug Saf.* 2016 Sep;25(9):1070-8.
- 3) Harper S. Economic and social implications of aging societies. *Science* 2014; 346: 587–91.
- 4) Rochon PA. Drug prescribing for older adults. UpToDate. (Schmader KE ed.) UpToDate, Waltham, MA (2013).
- 5) Gómez C, Vega-Quiroga S, Bermejo-Pareja F, Medrano MJ, Louis ED, Benito-León J. Polypharmacy in the Elderly: A Marker of Increased Risk of Mortality in a Population-Based Prospective Study (NEDICES). *Gerontology.* 2015;61(4):301-9.
- 6) Nobili A, Marengoni A, Tettamanti M, et al. Association between clusters of diseases and polypharmacy in hospitalized elderly patients: results from the REPOSI study. *Eur J Intern Med.* 2011 Dec;22(6):597-602. .
- 7) Di Castelnuovo A, de Curtis A, Costanzo S, et al. Association of D-dimer levels with all-cause mortality in a healthy adult population: findings from the MOLI-SANI study. *Haematologica.* 2013 Sep;98(9):1476-80.
- 8) Feinberg AP. Phenotypic plasticity and the epigenetics of human disease. *Nature.* 2007 May 24;447(7143):433-40. Review.
- 9) Noreen F, Rössli M, Gaj P, et al. Modulation of age- and cancer-associated DNA methylation change in the healthy colon by aspirin and lifestyle. *J Natl Cancer Inst.* 2014 Jun 28;106(7).
- 10) Kodach LL, Jacobs RJ, Voorneveld PW, et al. Statins augment the chemosensitivity of colorectal cancer cells inducing epigenetic reprogramming and reducing colorectal cancer cell 'stemness' via the bone morphogenetic protein pathway. *Gut.* 2011 Nov;60(11):1544-53.
- 11) Bierman AS and Tinetti ME, Precision medicine to precision care: managing multimorbidity. *Lancet*, 2016, 388, 2721-23.
- 12) Steinman MA, Beizer JL, DuBeau CE, Laird RD, Lundebjerg NE, Mulhausen P. How to Use the American Geriatrics Society 2015 Beers Criteria-A Guide for Patients, Clinicians, Health Systems, and Payors. *J Am Geriatr Soc.* 2015 Dec;63(12):e1-e7
- 13) Bonaccio M, Di Castelnuovo A, Pounis G, et al. A score of low-grade inflammation and risk of mortality: prospective findings from the Moli-sani study. *Haematologica.* 2016 Nov;101(11):1434-1441.
- 14) Napolitano M, Santoro F, Puopolo M, et al. Development of a pilot project on data sharing among partners of the Italian Hub of Population Biobanks (HIBP): association between lipid profile and socio-demographic variables. *Biopreserv Biobank.* 2014 Aug;12(4):225-33.
- 15) Willeboordse F, Grundeken LH, van den Eijkel LP, Schellevis FG, Elders PJ, Hugtenburg JG. Information on actual medication use and drug-related problems in older patients: questionnaire or interview? *Int J Clin Pharm.* 2016 .Apr;38(2):380-7.
- 16) Infinium MethylationEPIC Kit. <http://www.illumina.com/products/by-type/microarray-kits/infinium-methylation-epic.html>
- 17) Rochtus A, Martin-Trujillo A, Izzi B, et al. Genome-wide DNA methylation analysis of pseudohypoparathyroidism patients with GNAS imprinting defects. *Clin Epigenetics.* 2016 Jan 26;8:10.
- 18) Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol.* 2013;14:R115. doi: 10.1186/gb-2013-14-10-r115.

Budget

Expenses need to be in line with the complexity of the study, adequately justified and detailed. Personnel related expenses should refer to the total number of person-months. The cost for drugs included in the Italian national formulary (reimbursed by the NHS) should not be incorporated since already covered by the NHS. To prepare the budget, please refer to the guidelines annexed to the Appendix B

C1. Personnel

Degree	Tasks	Contract	Participating centres	Duration (in months)	% of full time equivalent	Salary (€)	Quantity	Total (€) (salary* quantity)
MD, PhD	1. Coordination	3. Co.Co.Pro	Coordinating Centre	36	20,0%	€ 30.000,00	1,00	€ 30.000,00
Ms Sc, PhD	2. Data analysis	3. Co.Co.Pro	Operative Unit 1	36	100,0%	€ 105.000,00	1,00	€ 105.000,00
Ms Sc, PhD	2. Data analysis	3. Co.Co.Pro	Operative Unit 1	36	50,0%	€ 52.500,00	1,00	€ 52.500,00
BSc	5. Other	3. Co.Co.Pro	Operative Unit 1	18	100,0%	€ 22.500,00	2,00	€ 45.000,00
Ms Sc	2. Data analysis	3. Co.Co.Pro	Operative Unit 1	8	100,0%	€ 19.000,00	1,00	€ 19.000,00
BSc	5. Other	3. Co.Co.Pro	Operative Unit 1	18	50,0%	€ 15.000,00	1,00	€ 15.000,00
MD	4. Clinical follow up	3. Co.Co.Pro	Operative Unit 1	18	50,0%	€ 30.000,00	1,00	€ 30.000,00
PhD	4. Clinical follow up	3. Co.Co.Pro	Operative Unit 1	18	5,000,0%	€ 22.500,00	1,00	€ 22.500,00
Ms Sc	3. Study monitoring	2. Contratto a tempo det.	Operative Unit 2	24	50,0%	€ 40.000,00	1,00	€ 40.000,00

Ms Sc			Operative Unit 2	18	100,0%	€ 37.500,00	1,00	€ 37.500,00
2. Data analysis 3. Co.Co.Pro								
Ms	4. Clinical follow up	2. Contratto a tempo det.	Operative Unit 3	18	50,0%	€ 20.000,00	2,00	€ 40.000,00
MD	4. Clinical follow up	2. Contratto a tempo det.		Operative Unit 3	18	0,0%	€ 30.000,00	1,00
						0,0%		
					0,0%			€ 0,00
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				0,0%			€ 0,00
				0,0%			€ 0,00
Total (€)							€ 466.500,00

C2. Supplies

Please specify the cost of the main categories of supplies for the entire project

Categories of Supplies	Brief description, if needed (max 200 chars.)	Total budget for the entire project and for all participating centres (€)
1. Hardware	VPS (Virtual Private Server), storage and mining of both epidemiological and epigenetic data (3 years). 4 computers	€ 10.000,00
2. Software	SAS licence (3 years for 3 researchers)	€ 9.000,00
3 Device		
4. Stationery	Material for subjects recall (paper and photocopies for questionnaires and informed consent form, brochures)	€ 5.000,00
5. Other (specify; e.g.: labs material)	DNA extraction kits, Bisulfite treatment kits, Infinium® MethylationEPIC BeadChips and reagents for 2000 samples disposable plastic supplies for DNA methylation Biomarkers x 1000	€ 570.000,00
6. Other costs for supplies		
Total (€)		€ 594.000,00

C3. Services

Please specify the cost of the main categories of services for the entire project

Services	Brief Description, if needed (max 200 chars.)	Total budget for the entire project and for all participating centres (€)
1. Data collection (e.g.: e-CRF)		
2. Study Monitoring		
A. Number of Expected site visit per centre		
B. Number of Clinical centres		
C. Number of Total site visits (automatic A x B)		0,00
D. Average cost for site visit (*) (*) <u>Excluding personnel and/or travels already budgeted in table C1 and/or C5</u>		
E. Total cost (C x D)		€ 0,00
3. Other (specify, e.g.: Publication costs – Reprints)	Publication costs – Reprints	€ 5.000,00
Total (€)		€ 5.000,00

C4. Drug costs

	Brief description, if needed (max 200 chars.)	Total budget for the entire project (€)
Costs for drug(s) (blinding and/or packaging and/or placebo) for not approved indications, <u>if not provided free of charge by a Company or paid by others</u>		
In case the <u>drug(s)(*)</u> will be <u>provided free of charge</u> , please specify the provider:	Note (to specify)	

C5. Meetings, conferences, workshops, travels

	Brief description, if needed (max 200 chars.)	Total budget for the entire project and for all participating centres (€)
1. Coordination meetings		
2. Participation in scientific conferences (in Italy or abroad)	Participation in scientific meeting	€ 15.000,00
3. Organization of scientific conferences related to the study project	ECM for GPs on polypharmacy with project results	€ 5.000,00
4. Travels		
5. Other (specify)		
Total (€)		€ 20.000,00

C6. Overall expected costs for each of the items indicated below and for each year of the project

Please specify the overall expected costs for each of the items indicated below and for each year of the project

Items	Expected costs for the 1° year (€)	Expected costs for the 2° year* (€)	Expected costs for the 3° year* (€)	Total (€)
Personnel	€ 172.500,00	€ 167.500,00	€ 126.500,00	€ 466.500,00
Supplies	€ 79.500,00	€ 308.500,00	€ 206.000,00	€ 594.000,00
Services		€ 2.000,00	€ 3.000,000	€ 5.000,00
Travels/ Meetings/ Courses	€ 5.000,00	€ 5.000,00	€ 10.000,00	€ 20.000,00
Overhead (max 10% of total)	€ 25.700,00	€ 48.300,00	€ 34.550,00	€ 108.550,00
Sub-total (€)	€ 282.700,00	€ 531.300,00	€ 380.050,00	€ 1.194.050,00
Drugs cost				€ 0,00
Total (€) (Sub-total + Drugs cost)				€ 1.194.050,00

* If applicable

C7. Distribution of costs between coordinating and participating centres

	Total Costs (€)	%
Coordinating centre	€ 59.400,00	5,0%
Transfer to other centres	€ 1.134.650,00	95,0%
Total (€)	€ 1.194.050,00	100%

C8. Budget Annotation (not mandatory)

Institution agreement (max 4.000 characters)

The Principal Investigator should state his/her willingness to submit in the Observatory on Clinical Trials all the documentation required by law to AIFA, as the Competent Authority and to Ethics Committee within 60 days of signing the contract.

Moreover, the Principal investigator should state the acceptance to conduct the study, as well as the institution agreement for the use of the human and technological resources described in the study protocol. Principal Investigator declaration must be presented within the study protocol; the institutional agreement has to be available by the date of contract signature.

The Principal Investigator hereby declares that he will submit through the OsSC (Osservatorio sulla Sperimentazione Clinica) the whole documentation required by current regulations to AIFA, as the authority in charge, and to the Ethical Committees within 60 days after the signature of the contract.

The Principal Investigator hereby declares also that Fondazione Neuromed accepts the realization of the study and agrees upon the use of human and instrumental resources as per the study protocol.

List of the investigators in charge of the units dedicated to data analysis and to GCP monitoring of the study (max 4.000 characters)

Please report the investigators responsible for the units dedicated to data analysis and GCP monitoring of the study (when applicable) –please make sure to follow applicable monitoring requirements.

Dr. Simona Costanzo, Department of Epidemiology and Prevention. IRCCS INM Neuromed, Pozzilli (operative unit 1): responsible of epidemiological data collection, management and analyses.

Dr. Benedetta Izzi, Department of Epidemiology and Prevention. IRCCS INM Neuromed, Pozzilli (operative unit 1): responsible of epigenetic data collection, management of Epigenetic analysis.

Dr. Stefania Falciglia, UOC Farmaceutica Territoriale ASREM CAMPOBASSO (operative unit 2): responsible of polypharmacy data collection and management from the regional drug prescription registry.

PERSONAL INFORMATION

Giovanni de Gaetano



📍 Resident: Via Milano, 56 - 66034 Lanciano (CH), Italy
Current address: Via Maiella, 34 - 86079 Venafrò (IS), Italy

☎ +39 335 5914217

✉ giovanni.degaetano@moli-sani.org

📅 Date and place of birth August 23, 1943, Rodi Garganico (FG), Italy | 🇮🇹 Nationality Italian

📄 Fiscal code: DGTGNN43M23H480A

WORK EXPERIENCE

June 2013-present

Scientific Director
Fondazione Neuromed
Via Atinense, 18
86077 Pozzilli (IS)

Head, Department of Epidemiology and Prevention
IRCCS Istituto Neurologico Mediterraneo NEUROMED
Via dell'Elettronica
86077 Pozzilli (IS)

Areas of current scientific interest include:

- Clinical epidemiology of risk factors for cerebrovascular and cardiovascular disease and cancer (the MOLI-SANI project, www.moli-sani.org)
- Epidemiology of food, nutrition and health, with emphasis on the Mediterranean Diet and alcohol
- Physiopathology, biochemistry and pharmacology of blood platelets and vascular cells
- Clinical pharmacology and pharmacogenetics of aspirin, other antiplatelet drugs and natural polyphenols
- Science communication

July 1st, 2016-present

Scientific Director
Clinica Cardiologica Montevergine
Mercogliano (AV)
Consultant Member of the Committee for the Therapeutic Formulary at IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG)

2005-present

Vice-President (2005-2015) and President (present) of the Ethical Committee of the Regional Health System of the Molise Region (A.S.RE.M), Campobasso (CB)

2003-2013

Professor of Cell Biology at the Nursing Science School at the Catholic University Medical Faculty, Campobasso

2011-2012

Director of the Research Laboratories at the Fondazione di Ricerca e Cura "Giovanni Paolo II", Campobasso

2000-2011

Co-founder and Director of the Research Laboratories at the "John Paul II" Centre for High Technology Research and Education in Biomedical Sciences of the Catholic University, Campobasso



- | | |
|------------|--|
| 1987- 2000 | Co-founder of the Mario Negri Sud Research Centre at Santa Maria Imbaro (CH) and its first Director |
| 1973-1987 | Founder and Head of the Laboratory of Cardiovascular Clinical Pharmacology at "Mario Negri Institute for Pharmacological Research", Milano |
| 1968-1973 | Research Fellow at the Laboratory of Blood Coagulation and Proteolysis, Medical School, Catholic University of Leuven, Leuven, Belgium |

SCIENTIFIC PUBLICATIONS

Author of over 500 peer-reviewed publications (Pubmed) and editor or contributor of numerous invited chapters in national and international books

H index (Google Scholar, Top Italian Scientists): 69

Total citations: 19,902 (Google Scholar Citations, December 2016)

NATIONAL AND INTERNATIONAL SCIENTIFIC ORGANISATIONS

- Italian Society for Haemostasis and Thrombosis (SISCT): Member since its foundation in 1971, President 1994-1996
- International Society for Thrombosis and Haemostasis (ISTH), member since its foundation, 1970
- New York Academy of Science since 198 to present
- Past President (2008-2011) and President (1997-2007) of the European Thrombosis Research Organisation (ETRO) having served as Secretary General/Treasurer (1988-1997).
- Foreign Corresponding member of the Belgian Royal Academy of Medicine (since 1995-present).
- Appointments from numerous national and international bodies, including INSERM Expert - Institut National de la Santé et de la Recherche Médicale (Paris, France) (since 2000-present)
- Member of the International Committee of the Fondation Lefoulon-Delalande Grand Prize for Cardiovascular Research, Institut de France, Paris (since its establishment in 2002-present).
- Member of the Editorial Board of several international journals including the "European Journal of Nutrition", "Nutrition Metabolism and Cardiovascular Diseases", "Seminars in Vascular Medicine", "Blood Transfusion". Principal Editor of "Platelets" and Field Editor of "Fundamental and Clinical Pharmacology"
- Evaluator of research projects within the EU Framework Programmes (FP2 to FP7) and one of the 8 international Members of the 1998 FP4 Independent Monitoring Committee (European Commission).
- Chairman of the first EU-funded project on wine and health: "Wine and cardiovascular disease" (FAIR Programme, 1994-1998)
- Member of the Advisory Committee of the EU-funded project:
 - o IMMIDIET "Dietary habit profile in European communities with different risk of myocardial infarction: the impact of migration as a model of gene/environment interaction" (2001-2004)
- Laboratory Partner of the EU-funded projects:
 - o FLORA (Flavonoids and Related Phenolics for Healthy Living using Orally Recommended Antioxidants) (2005-2009).
 - o IDEFICS (Identification and prevention of Dietary- and lifestyle-induced health Effects In Children and infantS) (2006-2011)
 - o ATHENA (Anthocyanins and polyphenols bioactives for Health Enhancement through Nutritional Advancement,

(2010-2014)

- BIOMARCARE (Biomarker for Cardiovascular Risk Assessment in Europe) (2011-2016)
- Member of the Committee for Targeted Research appointed by the Italian Ministry of Health (1997-99)
- Corresponding member of the Accademia Italiana della Vite e del Vino (since 2009 to present).
- Invited speaker at the Pontificia Accademia delle Scienze on the following subjects: "Wine in moderation and health" (2007) and "Bread and Health" (2009).
- Member of the "Alcohol in Moderation" (AIM) social, scientific and medical Council (since 2009 to present)
- Member of the International Scientific Forum on Alcohol Research (Boston University, since 2010 to present)

EDUCATION AND TRAINING

1962	"Maturità", Liceo Classico "Vitruvio Pollione", Formia
1963-1965	Intern student, Institute of Chemistry, Catholic University, Rome
1965-1968	Intern Student, Institute of Medical Pathology, Catholic University, Rome
1968	MD degree, cum laude (Catholic University Medical School, Rome, Italy)
1971	Haematology, Specialist degree, cum laude (Catholic University Medical School, Rome)
1973	PhD degree, cum laude (Leuven University Medical School, Leuven, Belgium).
1995	MD honorary degree (<i>honoris causa</i>) by the University of Debrecen, Hungary
2002	MD honorary degree (<i>honoris causa</i>) by the University of Bialystok, Poland

PERSONAL SKILLS

Mother tongue(s) Italian

Other language(s)

	UNDERSTANDING		SPEAKING		WRITING
	Listening	Reading	Spoken interaction	Spoken production	
English	Excellent	Excellent	Excellent	Excellent	Excellent
French	Excellent	Excellent	Excellent	Excellent	Excellent
Neapolitan	Excellent	Excellent	Excellent	Excellent	Excellent

Organisational / managerial skills

President of the Board of the Consorzio Tecniche Irrigue (CO.T.IR), Vasto (CH) (1996-2002)

Member of the Board of the Consorzio Fiera di Lanciano (CH) (1995-1999)

Driving licence B

ADDITIONAL INFORMATION

Honours



Recipient of several international honours and degrees, that include:

- Prize by the Italian Society of Pharmacology (1983) for aspirin studies
- Senior Investigator International Award by the International Society on Thrombosis and Haemostasis, New York, 1993
- MD honorary degree (*honoris causa*) by the Universities of Debrecen, Hungary (1995) and Bialystok, Poland (2002).
- "Minerva" Gold Medal by Chieti University, together with Sergio Marchionne (2007)
- Appointment by President G. Napolitano as an Italian Republic Knight (2009)

Il sottoscritto è a conoscenza che, ai sensi dell'art. 26 della legge 15/68, le dichiarazioni mendaci, la falsità negli atti e l'uso di atti falsi sono puniti ai sensi del codice penale e delle leggi speciali. Inoltre, il sottoscritto autorizza al trattamento dei dati personali, secondo quanto previsto dalla Legge 196/03.

Pozzilli, December 4th, 2016

Giovanni de Gaetano

SCIENTIFIC PUBLICATIONS

- 1: Di Castelnuovo A, Bonaccio M, De Curtis A, Costanzo S, Persichillo M, de Gaetano G, Donati MB, Iacoviello L; MOLI-SANI investigators.. Higher adherence to the Mediterranean diet is associated with lower levels of D-dimer: findings from the MOLI-SANI study. *Haematologica*. 2016 Oct 20. pii: haematol.2016.156331. [Epub ahead of print] PubMed PMID: 27846616.
- 2: Bonaccio M, Di Castelnuovo A, Pounis G, De Curtis A, Costanzo S, Persichillo M, Cerletti C, Donati MB, de Gaetano G, Iacoviello L; Moli-sani Study Investigators.. A score of low-grade inflammation and risk of mortality: prospective findings from the Moli-sani study. *Haematologica*. 2016 Nov;101(11):1434-1441. PubMed PMID: 27742767.
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Public Declaration of Interests /Confidentiality Undertaking /Consent to personal data processing for those collaborating with AIFA activities

The present document consists of four parts, Personal Data, Public Declaration of Interests, Confidentiality Undertaking and Consent to personal data processing. All parts must be duly filled, signed and dated.

Should the document be hand – filled, make sure that any information is readable. Also not applicable or not pertinent fields have to be crossed off in any case.

PERSONAL DATA

I, Dr Giovanni de Gaetano

Country : Italy

Company / Institution: Fondazione Neuromed

Business address: Via Atinense 18, 86077 Pozzilli (IS)

e-mail address: giovanni.degaetano@moli-sani.org

Aware of the contents of the Italian criminal legislation in the event of false declarations and forgery of documents according to art.76 of the Presidential Decree n. 445 of 28/12/2000, I declare, under my own responsibility that I read the last section of this document called “Definition and Instructions for Filling” and I have not other direct or indirect interests in the pharmaceutical industry in addition to those listed below .

Table 1.Public Declaration of Interests ¹

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional
The Experts who have a collaboration with the AIFA must declare the interests of first-line members of the family of the expert (i.e. a spouse or a partner, children and parents)				

Signature:

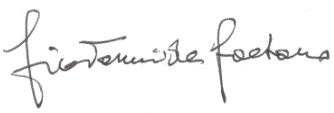
Date: December 5, 2016

¹ Marking any grey box above (declared interests), you should provide further information in the following pages concerning the Company and the products. Should the form be filled in the grey part concerning the existence of any interests without providing further related information in the following pages, it shall be returned for completing it.

Table 2. DETAILS OF PUBLIC DECLARATION OF INTERESTS

(Fill this part if you have filled any grey box in table n. 1, otherwise cross off the following boxes anyway)

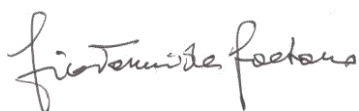
	Period of activity	Company or Institution	Products List all products for which you are responsible	Therapeutic Indication
1. Employment with a company				
	Period of activity	Company or Institution	Products List all products for which you have acted as consultant for developing them	Therapeutic Indication:
2. Consultancy for a company				
	Period of activity	Company or Institution	Area of activity/ Product	Therapeutic Indication:
3. Strategic advisory role for a company				
	Period of activity	Company or Institution	Type of financial interests	
4. Financial interests				
	Period of activity	Company or Institution	Area of activity/ Product	Therapeutic Indication:
5. Ownership of a patent				

Signature: 

Date: December 5, 2016

In addition to the aforementioned interests, I, the undersigned, aware of the contents of the Italian criminal legislation in the event of false declarations and forgery of documents according to art.76 of the Presidential Decree n. 445 of 28/12/2000 and aware of sanctions provided for art. 15 of Regulation on the conflicts of interests of AIFA, declare that I DO NOT HOLD any other interest or to know any fact that should be brought to attention of AIFA or of public. Should any of such interests or facts exist, please specify below:

Should any change to what declared above occur, I will forthwith report it to AIFA, filling a new declaration of interests.



Signature:

Date: December 5, 2016

Section reserved to AIFA

The conflicts of interest are classified into 3 categories:

- a) Direct interests: Direct interests are assigned the highest risk level **(level 3)**;
- b) Indirect interests: Indirect interests are assigned an intermediate risk level **(level 2)**;
- c) No interest declared: the lowest risk level is assigned in case of no interest **(level 1)**.

Risk level assigned by evaluator:

- ☐ Level 3
- ☐ Level 2
- ☐ Level 1

NOTES or COMMENTS

The evaluator

Name Last name (block letters) _____

Signature _____

Date _____

Confidentiality Undertaking

Considering the following definitions:

“AIFA activity”: any meeting (including preliminary and follow-up meetings, talks or any other related activity) of Board Of Directors, Technical Scientific Commission and its sub-committees, of any groups of experts or any similar meeting working as a group of experts on scientific evaluations or on the development of guidelines.

“Confidential information”: all the information, facts, data and any other matter I know, directly or indirectly, as a consequence of my activities with AIFA.

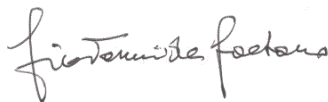
“Confidential documents”: all drafts, preliminary information, documents as well as any other information to which I should have access, directly or indirectly as a consequence of my activities with AIFA, including documents, registrations and/or notes that I should write or register.

Should I attend any meeting and/or activity with AIFA, I commit myself:

1. To treat all confidential information and documentation in a strictly confidential way.
2. Not to disclose (or authorize any person to disclose) in any way to third parties² any confidential information or documentation.
3. Not to use (or authorize any person to use) any confidential information or documentation except for what is strictly related to my activities with AIFA.
4. To delete or destroy any confidential documents when no longer needed.
5. Not to disclose, unless expressly authorized, any document or any information to my knowledge related to my activities with AIFA.

Compliance with the aforementioned obligations shall not terminate with the end of the work relationship with AIFA. Such obligations shall not apply to documents and information that the undersigned may demonstrate to have known before the signing of this form, or that should be publicly disclosed for any reason not related to the breach of confidential information by the undersigned.

I declare that the information herewith provided are, for what I know, accurate and reliable and I agree that such information be kept and published on the AIFA web site, should AIFA consider such disclosure appropriate.



Signature:

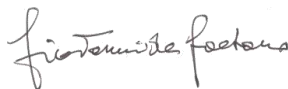
Date: December 5, 2016

CONSENT to personal data treatment

I declare, under my own responsibility, that I have read the privacy Statement set out by par. 13, D. Lgs. N. 196/2003 (Italian Privacy Codice), available on AIFA website, section “Competitions”, AIFA Consultants and Experts’ List, on the following link:

http://www.agenziafarmaco.gov.it/sites/default/files/Mod350_03Rev.1_Informativa_privacy_consenso_trattamento_dati.pdf and that I have found it complete.

I also declare to be aware that my name could not be inserted into AIFA Consultants’ Database and I could not participate into any AIFA activity in case I refuse to sign this declaration.



Signature:

Date: December 5, 2016

² The Definition of “Third party” doesn't include the employees of Competent National Authorities who have signed confidentiality agreements or are subject to confidentiality obligations as a consequence of national legislations or duty of secrecy.

DEFINITIONS AND INSTRUCTIONS FOR FILLING

“Employment with a company” is to be interpreted as any work activity – even free of charge – for a pharmaceutical Company:

1. Executive role within a pharmaceutical company (President/Vicepresident, Chief Executive Officer, Chief Scientific Officer, Executive Director/Director/Associate Director position).
2. Lead role in the development of a medicinal product (Clinical programme/project manager position, Product manager/specialist position, Programme leader/manager position, Project leader/manager position).
3. Any other activities that are not mentioned in the previous points 1 e 2.

It is assumed that the declared interest, not listed in categories 1 and 2, is considered over following a 3 year cooling-off period, on the contrary, the interests listed in categories 1 e 2, as provided in for Article 7 of the Conflict of interest's policy of AIFA, must be always declared.

“Consultancy for a company” is to be interpreted as an activity where the concerned expert provides advice or services to a pharmaceutical company regardless of contractual arrangements or any form of remuneration. No conflict exists when an expert is appointed by AIFA (or other regulatory authority) for the release of a scientific advice.

Strategic advisory role for a company is to be interpreted as meaning that the expert is participating (with a right to vote on/influence the outputs) in a (Scientific) Advisory Board/Steering Committee with the role of providing advice/expressing opinions on the (future) strategy, direction and development activities of a pharmaceutical company, either in terms of general strategy or product related strategy, regardless of contractual arrangements or any form of remuneration.

Note Well: The involvement of an expert in a research work for a pharmaceutical company, except for the activity on a specific product, is to be considered an indirect interest.

Financial interests are to be interpreted as:

- a) Holding of shares of a pharmaceutical company with the exclusion of independently managed investment funds/pension schemes that are not exclusively based on the pharmaceutical sector.
- b) Compensation, fees, honoraria, salaries paid directly by a pharmaceutical company to the individual, other than payment for expenses incurred with research work or re-imbursement of reasonable expenses incurred in relation to conference/seminar attendance (i.e. accommodation and travel costs). Any teaching activities, (CME courses included) directly or indirectly, partially or fully sponsored by pharmaceutical industry should be mentioned accurately.
- c) Intellectual property rights including patents, trademarks, know-how and/or copyrights relating to a medicinal product owned by the individual or of which the individual is directly a beneficiary

“Ownership of a patent”: a patent for a medicinal product/ competitor product owned by an individual or by the Institution in which such individual is employed. Intellectual property rights where the holder does not have any direct or indirect financial interest nor any development right on such patent are excluded.

“Principal investigator” Is the subject responsible for coordinating other investigators working in different centers taking part to the multicenter trial or the investigator responsible for a monocentre trial or the coordinating investigator (principal) signing the final report on the trial with the exception of the investigator that coordinates at the national level a multinational trial.

“Investigator”: is an investigator involved in a clinical trial at a specific trial site which can be the responsible lead investigator of the trial at that specific site or a member of the clinical trial team who performs clinical trial related procedures and makes important trial related decisions.

Grant or other funding to an organisation/institution shall mean: any funding received from a pharmaceutical company by an organisation/institution to which the expert belongs, or for which he/she performs any kind of activity, and which is used to support any activity of the expert whether or not it is related to research work

Other definitions

“Expert Witness”: is to be interpreted as an expert whose role is limited to testify and give specialist advice on a specific issue by providing information and replying to any direct questions only. Such Expert Witness can be invited to participate at Scientific Board and Committee, Working Party, Ad-Hoc Expert Group meetings.

“pharmaceutical company”: also includes supply or service companies which contribute to the research, development, production and post - marketing surveillance of a medicinal product.

“Competitor product” is defined as a medicinal product that targets a similar patient population with the same clinical objective (i.e. to treat, prevent or diagnose a particular condition), hence constituting a potential commercial competition.

Family members shall mean: first-line members of the family of the expert (i.e. a spouse or a partner, children and parents)

Curriculum Vitae
SIMONA COSTANZO

PERSONAL DATA

Place and Date of Birth:	Bojano (CB), Italy - 15/07/1976
Address:	Via Pirandello 43/9, 86100 Campobasso, Italy
Phone:	+393201896989
email:	simona.costanzo@moli-sani.org

EDUCATION

January 2012:	PhD degree in Epidemiology at the Faculty of Health, Medicine and Life Sciences, University of Maastricht. http://arno.unimaas.nl/show.cgi?fid=24100
April 2005:	Master Degree in Epidemiology at the Catholic University, Rome.
November 2003:	Master of Sciences in Pharmaceutical Chemistry and Technology at the University of Rome La Sapienza.
May 2004	State examination for Pharmacist profession, at the University of Rome La Sapienza.

RESEARCH EXPERIENCE -Official H index: 16 (by Scopus)

September 2013-today	Epidemiologist at the Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli (IS), Italy.
May 2014- May 2016	Pharmacist at the “Centro Regionale di Farmacovigilanza”, Regione Molise, Campobasso, Italy.
January 2005-November 2012 and May 2013:	Researcher at the Laboratory of Genetic and Environmental Epidemiology, Catholic University (Fondazione di Ricerca e Cura “Giovanni Paolo II from 2011), Campobasso, Italy.

Co-author of 58 peer-reviewed publications and first author of 10 publications on cardiovascular risk factors epidemiology.

Co-Author as one of the “Moli-sani study investigators” and NCD Risk Factor Collaboration network.

HONORS AND AWARDS

2011	International organization of Vine and Wine: OIV Grant Research 2011-2012. Project’s title: Wine consumption and short and long-term Prognosis among Patients with Coronary Artery Disease Undergoing Surgical Revascularization.
2010	Italian Ministry of Health: Young Italian Researchers Grant 2008, classified 43rd out of 997. Project’s title: Polyphenol-Rich Food Consumption and Short and Long-Term Prognosis after Coronary Artery Bypass Graft Surgery.
2008	Selected for the World Heart Federation 41st Ten Day Teaching

Seminar in Cardiovascular Disease Epidemiology and Prevention, Oxford, UK”.

2004 Molise Region: grant to attend a master in Epidemiology at the Catholic University, Rome (A.A. 2003/2004).

SKILLS AND COMPETENCES

Epidemiologist, project manager, data manager, biostatistician.

Involved in several epidemiologic studies, coordinating the main phases of a project (protocol study drafting, research funding, statistical analysis, medical writing) and participating at several international work-shops

Expertise in conducting and/or supporting epidemiologic research. Ability to work individually and in coordination with a multidisciplinary research group.

Good planning, project administration and organisation skills.

www.moli-sani.org; <https://sites.google.com/site/epiflu/about-i-move/project-partners>; <http://www.biomarcare.eu/>, <http://www.ncdrisc.org/>

LANGUAGE Mother language: Italian
English- good

COMPUTER SKILLS

Expert Knowledge	SAS for windows (statistic software), MS office.
Intermediate Knowledge	SPSS, STATA, Revman 5 (statistic software).

INVITED SPEAKER

-Alcohol, Wine and Prevention of CVD and Mortality: Epidemiological Evidence. MeDiet2007. Athens, 2007.
 -Alcohol consumption and blood pressure: results from the Moli-sani project. Winehealth2007, Bordeaux, 2007.
 -Alcohol, Wine and Prevention of CVD and Mortality: Epidemiological Evidence. Wine and Health Symposium 2007. Bucharest, 2007.
 -XXIV Corso di aggiornamento: Alterazioni congenite ed acquisite della coagulazione. Vino ed Alcol: tra prevenzione degli eventi ischemici e rischio emorragico. Menarini Foundation. Milan, 2008
 -Alcohol and Thrombosis: to drink or not to drink? 10th ETRO Advanced Teaching Course on Thrombosis. Kraków, 2009.
 -Alcohol intake in relation to vascular risk and total mortality: answer from meta-analyses. Winehealth2010, Friuli 2010.
 -Wine Consumption, Dietary Total Antioxidant Capacity and Reduced Incidence of Post-operative Atrial Fibrillation in Patients Undergoing Cardiac Surgery. OIV Grant Research 2011-2012. Paris, 2013.
 -Beer and cardiovascular health: effects on morbidity and mortality. 7th European Beer and Health Symposium, Brussels 2014.

PUBLICATIONS

1. NCD Risk Factor Collaboration (NCD-RisC).. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet. 2016 Nov 15. pii: S0140-6736(16)31919-5. doi: 10.1016/S0140-6736(16)31919-5. [Epub ahead of print]. IF(2014): 45.217
2. Bonaccio M, Di Castelnuovo A, Pounis G, De Curtis A, Costanzo S, Persichillo M, Cerletti C, Donati MB, de Gaetano G, Iacoviello L; Moli-sani Study Investigators.. A score of low-grade inflammation and risk of mortality: prospective findings from the Moli-sani study. Haematologica. 2016 Nov;101(11):1434-1441. IF(2014): 5.814

3. Di Castelnuovo A, Bonaccio M, De Curtis A, Costanzo S, Persichillo M, de Gaetano G, Donati MB, Iacoviello L; MOLI-SANI investigators.. Higher adherence to the Mediterranean diet is associated with lower levels of D-dimer: findings from the MOLI-SANI study. *Haematologica*. 2016 Oct 20. pii: haematol.2016.156331. IF(2014): 5.814
4. Muiesan ML, Salvetti M, Di Castelnuovo A, Paini A, Assanelli D, Costanzo S, Badilini F, Vaglio M, Donati MB, Agabiti Rosei E, de Gaetano G, Iacoviello L; Moli-sani Study Investigators.. Obesity and ECG left ventricular hypertrophy. *J Hypertens*. 2016 Sep 22. [Epub ahead of print] PubMed PMID: 27662187. IF(2014): 4.720
5. Bonaccio M, Di Castelnuovo A, Costanzo S, Persichillo M, Donati MB, et al. Interaction between education and income on the risk of all-cause mortality: prospective results from the MOLI-SANI study. *Int J Public Health*. 2016 Sep;61(7):765-76. IF(2014): 2.701
6. Blankenberg S, Salomaa V, Makarova N, Ojeda F, Wild P, et al. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. *Eur Heart J*. 2016 Aug 7;37(30):2428-37. IF(2014): 15.203
7. A century of trends in adult human height. *Elife*. 2016 Jul 26;5. IF(2014): 9.322
8. Pounis G, Castelnuovo AD, Costanzo S, Persichillo M, Bonaccio M, et al. Association of pasta consumption with body mass index and waist-to-hip ratio: results from Moli-sani and INHES studies. *Nutr Diabetes*. 2016 Jul 4;6(7):e218. IF(2014): 2.654
9. de Gaetano G, Costanzo S, Di Castelnuovo A, Badimon L, Bejko D, et al. Effects of moderate beer consumption on health and disease: A consensus document. *Nutr Metab Cardiovasc Dis*. 2016 Jun;26(6):443-67. IF(2014): 3.323
10. Rondy M, Castilla J, Launay O, Costanzo S, Ezpeleta C, et al. Moderate influenza vaccine effectiveness against hospitalisation with A(H3N2) and A(H1N1) influenza in 2013-14: Results from the InNHOVE network. *Hum Vaccin Immunother*. 2016 May 3;12(5):1217-24. IF(2014): 2.366
11. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 44 million participants. *Lancet*. 2016 Apr 9;387(10027):1513-30. IF(2014): 45.217
12. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet*. 2016 Apr 2;387(10026):1377-96. IF(2014): 45.217
13. Bonaccio M, Di Castelnuovo A, Costanzo S, De Curtis A, Donati MB, et al. Age-sex-specific ranges of platelet count and all-cause mortality: prospective findings from the MOLI-SANI study. *Blood*. 2016 Mar 24;127(12):1614-6. IF(2014): 10.452
14. Pounis G, Di Castelnuovo A, Bonaccio M, Costanzo S, Persichillo M, et al. Flavonoid and lignan intake in a Mediterranean population: proposal for a holistic approach in polyphenol dietary analysis, the Moli-sani Study. *Eur J Clin Nutr*. 2016 Mar;70(3):338-45. IF(2014): 2.709
15. Bonaccio M, Di Castelnuovo A, Costanzo S, Persichillo M, De Curtis A, et al. Adherence to the traditional Mediterranean diet and mortality in subjects with diabetes Prospective results from the MOLI-SANI study. *Eur J Prev Cardiol*. 2016 Mar;23(4):400-7. IF(2014): 3.319
16. Iacoviello L, Costanzo S, Persichillo M, Sparano A, Bartolo M, et al. Hospital-based register of stroke in the Molise Region: focus on main subtypes of stroke Years 2009-2013. *Neurol Sci*. 2016 Feb;37(2):191-8. IF(2014): 1.447
17. Pounis G, Bonaccio M, Di Castelnuovo A, Costanzo S, de Curtis A, et al. Polyphenol intake is associated with low-grade inflammation, using a novel data analysis from the Moli-sani study. *Thromb Haemost*. 2016 Jan;115(2):344-52. IF(2014): 4.984
18. Bonaccio M, Di Castelnuovo A, Rago L, de Curtis A, Assanelli D, et al. T-wave axis deviation is associated with biomarkers of low-grade inflammation Findings from the MOLI-SANI study. *Thromb Haemost*. 2015 Nov 25;114(6):1199-206. IF(2014): 4.984
19. Bonaccio M, Di Castelnuovo A, De Curtis A, Costanzo S, Bracone F, et al. Nut consumption is inversely associated with both cancer and total mortality in a Mediterranean population: prospective results from the Moli-sani study. *Br J Nutr*. 2015 Sep 14;114(5):804-11. IF(2014): 3.453
20. Effects of diabetes definition on global surveillance of diabetes prevalence and diagnosis: a pooled analysis of 96 population-based studies with 331,288 participants. *Lancet Diabetes Endocrinol*. 2015 Aug;3(8):624-37. IF(2014): 9.185
21. Costanzo S, De Curtis A, di Niro V, Olivieri M, Morena M, et al. Postoperative atrial fibrillation and total dietary antioxidant capacity in patients undergoing cardiac surgery: The Polyphemus Observational Study. *J Thorac Cardiovasc Surg*. 2015 Apr;149(4):1175-82.e1. IF(2014): 4.168
22. Rondy M, Launay O, Puig-Barberà J, Gefenaite G, Castilla J, et al. 2012/13 influenza vaccine effectiveness against hospitalised influenza A(H1N1)pdm09, A(H3N2) and B: estimates from a European network of hospitals. *Euro Surveill*. 2015 Jan 15;20(2). IF(2014): 5.722
23. Bonaccio M, Di Castelnuovo A, Bonanni A, Costanzo S, De Lucia F, et al. Decline of the Mediterranean diet at a time of economic crisis Results from the Moli-sani study. *Nutr Metab Cardiovasc Dis*. 2014 Aug;24(8):853-60. IF(2014): 3.323
24. Bonaccio M, Di Castelnuovo A, De Curtis A, Costanzo S, Persichillo M, et al. Adherence to the Mediterranean diet is associated with lower platelet and leukocyte counts: results from the Moli-sani study. *Blood*. 2014 May 8;123(19):3037-44. IF(2014): 10.452
25. Pounis G, Costanzo S, Persichillo M, de Curtis A, Sieri S, et al. Mushroom and dietary selenium intakes in relation to fasting glucose levels in a free-living Italian adult population: the Moli-sani Project. *Diabetes Metab*. 2014 Feb;40(1):34-42. IF(2014): 3.267

26. Bonanni AE, Bonaccio M, di Castelnuovo A, de Lucia F, Costanzo S, et al. Food labels use is associated with higher adherence to Mediterranean diet: results from the Moli-sani study. *Nutrients*. 2013 Nov 4;5(11):4364-79. IF(2014): 3.270
27. Assanelli D, Di Castelnuovo A, Rago L, Badilini F, Vinetti G, et al. T-wave axis deviation and left ventricular hypertrophy interaction in diabetes and hypertension. *J Electrocardiol*. 2013 Nov-Dec;46(6):487-91. IF(2014): 1.361
28. Costanzo S, Di Castelnuovo A, Iacoviello L. Reply to the editor. *J Thorac Cardiovasc Surg*. 2013 Oct;146(4):992-3. IF(2014): 4.168
29. Costanzo S, di Niro V, Di Castelnuovo A, Gianfagna F, Donati MB, et al. Prevention of postoperative atrial fibrillation in open heart surgery patients by preoperative supplementation of n-3 polyunsaturated fatty acids: an updated meta-analysis. *J Thorac Cardiovasc Surg*. 2013 Oct;146(4):906-11. IF(2014): 4.168
30. Arcari A, Magnacca S, Bracone F, Costanzo S, Persichillo M, et al. Relation between pulmonary function and 10-year risk for cardiovascular disease among healthy men and women in Italy: the Moli-sani Project. *Eur J Prev Cardiol*. 2013 Oct;20(5):862-71. IF(2014): 3.319
31. Bonaccio M, Di Castelnuovo A, Costanzo S, De Lucia F, Olivieri M, et al. Nutrition knowledge is associated with higher adherence to Mediterranean diet and lower prevalence of obesity Results from the Moli-sani study. *Appetite*. 2013 Sep;68:139-46. IF(2014): 2.691
32. Di Castelnuovo A, de Curtis A, Costanzo S, Persichillo M, Olivieri M, et al. Association of D-dimer levels with all-cause mortality in a healthy adult population: findings from the MOLI-SANI study. *Haematologica*. 2013 Sep;98(9):1476-80. IF(2014): 5.814
33. Bonaccio M, Di Castelnuovo A, Bonanni A, Costanzo S, De Lucia F, et al. Adherence to a Mediterranean diet is associated with a better health-related quality of life: a possible role of high dietary antioxidant content. *BMJ Open*. 2013 Aug 13;3(8). IF(2014): 2.271
34. Poli A, Marangoni F, Avogaro A, Barba G, Bellentani S, et al. Moderate alcohol use and health: a consensus document. *Nutr Metab Cardiovasc Dis*. 2013 Jun;23(6):487-504. IF(2014): 3.323
35. Rago L, Di Castelnuovo A, Assanelli D, Badilini F, Vaglio M, et al. T-wave axis deviation, metabolic syndrome and estimated cardiovascular risk--in men and women of the MOLI-SANI study. *Atherosclerosis*. 2013 Feb;226(2):412-8. IF(2014): 3.994
36. Pounis G, Costanzo S, di Giuseppe R, de Lucia F, Santimone I, et al. Consumption of healthy foods at different content of antioxidant vitamins and phytochemicals and metabolic risk factors for cardiovascular disease in men and women of the Moli-sani study. *Eur J Clin Nutr*. 2013 Feb;67(2):207-13. IF(2014): 2.709
37. Rondy M, Puig-Barbera J, Launay O, Duval X, Castilla J, et al. 2011-12 seasonal influenza vaccines effectiveness against confirmed A(H3N2) influenza hospitalisation: pooled analysis from a European network of hospitals A pilot study. *PLoSOne*. 2013;8(4):e59681. IF(2014): 3.234
38. Assanelli D, Rago L, Salvetti M, Di Castelnuovo A, Badilini F, et al. T-wave axis deviation, metabolic syndrome and cardiovascular risk: results from the MOLI-SANI study. *J Electrocardiol*. 2012 Nov-Dec;45(6):546-50. IF(2014): 1.361
39. Iacoviello L, Rago L, Costanzo S, Di Castelnuovo A, Zito F, et al. The Moli-sani project: computerized ECG database in a population-based cohort study. *J Electrocardiol*. 2012 Nov-Dec;45(6):684-9. IF(2014): 1.361
40. Di Castelnuovo A, Costanzo S, Persichillo M, Olivieri M, de Curtis A, et al. Distribution of short and lifetime risks for cardiovascular disease in Italians. *Eur J Prev Cardiol*. 2012 Aug;19(4):723-30. IF(2014): 3.319
41. Costanzo S, Gianfagna F, Persichillo M, De Lucia F, Verna A, et al. Pandemic and seasonal vaccine coverage and effectiveness during the 2009-2010 pandemic influenza in an Italian adult population. *Int J Public Health*. 2012 Jun;57(3):569-79. 22371002. IF(2014): 2.701
42. Bonaccio M, Di Castelnuovo A, Costanzo S, De Lucia F, Olivieri M, et al. Mass media information and adherence to Mediterranean diet: results from the Moli-sani study. *Int J Public Health*. 2012 Jun;57(3):589-97. IF(2014): 2.701
43. di Giuseppe R, Di Castelnuovo A, Melegari C, De Lucia F, Santimone I, et al. Typical breakfast food consumption and risk factors for cardiovascular disease in a large sample of Italian adults. *Nutr Metab Cardiovasc Dis*. 2012 Apr;22(4):347-54. IF(2014): 3.323
44. Bossola M, Rosa F, Tazza L, de Curtis A, Costanzo S, et al. P-selectin, E-selectin, and CD40L over time in chronic hemodialysis patients. *Hemodial Int*. 2012 Jan;16(1):38-46. IF(2014): 1.240
45. di Giuseppe R, Arcari A, Serafini M, Di Castelnuovo A, Zito F, et al. Total dietary antioxidant capacity and lung function in an Italian population: a favorable role in premenopausal/never smoker women. *Eur J Clin Nutr*. 2012 Jan;66(1):61-8. IF(2014): 2.709
46. Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Wine, beer or spirit drinking in relation to fatal and non-fatal cardiovascular events: a meta-analysis. *Eur J Epidemiol*. 2011 Nov;26(11):833-50 IF(2014): 5.339
47. Vohnout B, Gianfagna F, Lorenzet R, Cerletti C, de Gaetano G, et al. Genetic regulation of inflammation-mediated activation of haemostasis: family-based approaches in population studies. *Nutr Metab Cardiovasc Dis*. 2011 Nov;21(11):857-61. IF(2014): 3.323.
48. Santimone I, Di Castelnuovo A, De Curtis A, Spinelli M, Cugino D, et al. White blood cell count, sex and age are major determinants of heterogeneity of platelet indices in an adult general population: results from the MOLI-SANI project. *Haematologica*. 2011 Aug;96(8):1180-8. IF(2014): 5.814

49. D'Imperio M, Gobbino M, Picanza A, Costanzo S, Della Corte A, et al. Influence of harvest method and period on olive oil composition: an NMR and statistical study. *J Agric Food Chem*. 2010 Oct 27;58(20):11043-51. IF(2014): 2.912.
50. Di Castelnuovo A, Costanzo S, Donati MB, Iacoviello L, de Gaetano G. Prevention of cardiovascular risk by moderate alcohol consumption: epidemiologic evidence and plausible mechanisms. *Intern Emerg Med*. 2010 Aug;5(4):291-7. IF(2014): 2.624
51. Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Cardiovascular and overall mortality risk in relation to alcohol consumption in patients with cardiovascular disease. *Circulation*. 2010 May 4;121(17):1951-9. IF(2014): 15.073
52. Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Alcohol consumption and mortality in patients with cardiovascular disease: a meta-analysis. *J Am Coll Cardiol*. 2010 Mar 30;55(13):1339-47. IF(2014): 16.503
53. Centritto F, Iacoviello L, di Giuseppe R, De Curtis A, Costanzo S, et al. Dietary patterns, cardiovascular risk factors and C-reactive protein in a healthy Italian population. *Nutr Metab Cardiovasc Dis*. 2009 Dec;19(10):697-706. IF(2014): 3.323
54. Di Castelnuovo A, Costanzo S, di Giuseppe R, de Gaetano G, Iacoviello L. Alcohol consumption and cardiovascular risk: mechanisms of action and epidemiologic perspectives. *Future Cardiol*. 2009 Sep;5(5):467-77. IF(2014): 1.78
55. Costanzo S, Di Castelnuovo A, Zito F, Krogh V, Siani A, et al. Prevalence, awareness, treatment and control of hypertension in healthy unrelated male-female pairs of European regions: the dietary habit profile in European communities with different risk of myocardial infarction--the impact of migration as a model of gene-environment interaction project. *J Hypertens*. 2008 Dec;26(12):2303-11. IF(2014): 4.720
56. di Giuseppe R, Di Castelnuovo A, Centritto F, Zito F, De Curtis A, et al. Regular consumption of dark chocolate is associated with low serum concentrations of C-reactive protein in a healthy Italian population. *J Nutr*. 2008 Oct;138(10):1939-45. IF(2014): 3.875
57. Izzi B, Pampuch A, Costanzo S, Vohnout B, Iacoviello L, et al. Determinants of platelet conjugate formation with polymorphonuclear leukocytes or monocytes in whole blood. *Thromb Haemost*. 2007 Dec;98(6):1276-84. IF(2014): 4.984
58. Di Castelnuovo A, Costanzo S, Donati MB, Iacoviello L, de Gaetano G. Alcohol consumption and cardiovascular risk: an epidemiological perspective. *Nutr Metab Cardiovasc Dis*. 2007 Oct;17(8):561-4. IF(2014): 3.323
59. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, et al. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. *Arch Intern Med*. 2006 Dec 11-25;166(22):2437-45. IF(2014): 17.333
60. de Gaetano G, Di Castelnuovo A, Costanzo S, Donati MB, Iacoviello L. Alcohol, cardiovascular risk, and health: there is a window for benefits. *J Thromb Haemost*. 2006 May;4(5):1156-7; authorreply 1157-8. IF(2014): 5.720

Curriculum Vitae – Benedetta Izzi

Personal data

First Name: Benedetta
Family Name: Izzi
Place and date of birth: Campobasso, Italy, March 11, 1983
Address: Diestsevest 95, 3000 Leuven, Belgium
Work Address: University of Leuven, Center for Molecular and Vascular Biology (CMVB) - Department of Cardiovascular Sciences, Gasthuisberg, O&N 1 Herestraat 49 Bus 911, 3000 Leuven, Belgium
e-mail: Benedetta.Izzi@med.kuleuven.be

Education

2007-2011 Doctoral School in Molecular and Development Genetics – Ph.D. in Biomedical Sciences
Thesis title: Expanding the human GNAS-related pathology by genetic and epigenetic studies
Supervisor: Prof. Dr. Kathleen Freson (University of Leuven, Belgium)
Co-supervisor: Prof. Dr. Chris Van Geet (University of Leuven, Belgium)

2006-2007 Pre-doctoral program University of Leuven, Belgium
Thesis title: Genetic analysis of the GNAS1 cluster in patients with an abnormal platelet Gs function (Magna cum Laude)
Supervisor: Prof. Dr. Kathleen Freson (University of Leuven, Belgium)
Co-supervisor: Prof. Dr. Chris Van Geet (University of Leuven, Belgium)

2002-2005 Medical Biotechnologies, University of Milan, Italy
Thesis title: Control of platelet activation in cell-cell interactions: role of agonists and antagonists (101/110)
Supervisor: Prof. Dr. Guido Tettamanti (University of Milan, Italy)
Co-supervisor: Prof. Dr. Maria Benedetta Donati (Istituto Neurologico Mediterraneo - NEUROMED, Italy)

Curriculum Vitae – Benedetta Izzi

Professional Experience and Affiliation

06/06/2005-31/10/2006 Research fellow, Laboratory of Cell Biology and Pharmacology of Thrombosis; RE ARTU Laboratories, “John Paul II” Centre for High Research Technology and Education in Biomedical Sciences, Catholic University, Campobasso, on the project: “Cardiovascular Diseases: role of genetic and environmental factors and new therapeutic approaches”, funded by the Italian Ministry of University and Research.

31/10/2006-31/10/2007 Pre-Doctoral program University of Leuven, Belgium.

1/11/2007-3/12/2011 Ph.D. program in Biomedical Sciences- Doctoral School in Molecular and Development Genetics, University of Leuven, Belgium.

1/04/2012-31/03/2013 Postdoctoral Research Fellow in Perinatal Epigenetics and Epigenetic Epidemiology, Universitätsklinikum Freiburg, Institut für Prävention und Tumorepidemiologie, Freiburg, Germany – visiting Fellow Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA.

1/05/2013 to present Postdoctoral Research Fellow Center for Molecular and Vascular Biology, Department of Cardiovascular Sciences, University of Leuven, Belgium.

Teaching experiences

Academic year 2015/2016: Epigenetic session in the course “Hot topics in Neurobiology and Psychiatric disorders”

Academic year 2016/2017: “CV risk and CV prevention” and “Coagulation, coagulation disorders, anti-aggregants, anti-coagulants” within the course “Cardiovascular Diseases”

Grants and Awards

January 2015-December 2015 Research Foundation – Flanders (FWO) Research grant for the project: “PEAR1 (epi)genetic profiling in population studies to unravel its potential role in platelet and endothelial cell function variability”

October 2014-September 2017 Research Foundation – Flanders (FWO) Postdoctoral Fellowship for the project: “(Epi)-genetic PEAR1 PHenotyping in HEmatopoietic Specification (EPHES)”

October 2013-September 2014 University of Leuven Postdoctoral Mandate Research Fund (PDMK/13/163) of the University of Leuven Research Fund (Belgium)

2011 Young Investigator Belgian Endocrine Society Award

Curriculum Vitae – Benedetta Izzi

Membership of international consortia and societies

Member of the European Network for Human Congenital Imprinting Disorders

Member of the EuroPHP Network for the study of Pseudohypoparathyroidism

Personal skills

Mother tongue

Italian

Other languages

English (proficiency), French, Dutch, Spanish

Communication skills

Excellent contact and communication skills gained through my supervising experience of students, communication with representatives of scientific sales companies, work as organizer of events with both scientific and social purpose.

Organizational and managerial skills

I am currently supervising PhD and Master students within my department in Belgium and one PhD student in Italy (Neuromed, Pozzilli). I have worked as responsible of the Youth For a United World movement in Belgium for 5 years, organizing social and benefit events both at local/national and international level.

Job-related skills

Excellent knowledge of molecular and cell biology, genetics/epigenetics, pharmacogenomics. Good command of statistics and basic graphical softwares (Graph Prism, SPSS and Adobe photoshop/illustrator, respectively). Excellent writing skills acquired by writing scientific papers, projects for international funding programs (NIH, EU-Horizon 2020, FWO) as well as articles intended for non-expert audience as contribution for the dissemination of science.

Curriculum Vitae – Benedetta Izzi

List of scientific publications

1. Rochtus A, Winand R, Laenen G, Vangeel E, **Izzi B**, Wittevrongel C, Moreau Y, Verpoorten C, Jansen K, Van Geet C, Freson K. Methylome analysis for spina bifida shows SOX18 hypomethylation as a risk factor with evidence for a complex (epi)genetic interplay to affect neural tube development. Clin Epigenetics. 2016 8:108.
2. Thiele S, Mantovani G, Barlier A, Boldrin V, Bordogna P, de Sanctis L, Elli F, Freson K, Garin I, Grybek V, Hanna P, **Izzi B**, Hiort O, Lecumberri B, Pereda A, Saraff V, Silve C, Turan S, Usardi A, Werner R, Perez de Nanclares G, Linglart A. From Pseudohypoparathyroidism to inactivating PTH/PTHrP Signalling Disorder (iPPSD), a novel classification proposed by the European EuroPHP network. Eur J Endocrinol. 2016 Jul 11. pii: EJE-16-0107.
3. Criel M, **Izzi B**, Vandenbriele C, Liesenborghs L, Van Kerckhoven S, Lox M, Cludts K, Jones EA, Vanassche T, Verhamme P, Hoylaerts M. Absence of Pear1 does not affect murine platelet function in vivo. Thromb Res. 2016 Oct;146:76-83. doi:10.1016/j.thromres.2016.08.026.
4. **Izzi B**, Pistoni M, Cludts K, Akkor P, Lambrechts D, Verfaillie C, Verhamme P, Freson K, Hoylaerts M. Allele-specific DNA methylation reinforces PEAR1 enhancer activity. Blood. 2016 Aug 18;128(7):1003-12.
5. Rochtus A, Martin-Trujillo A, **Izzi B**, Elli F, Garin I, Linglart A, Mantovani G, Perez de Nanclares G, Thiele S, Decallonne B, Van Geet C, Monk D, Freson K. Genome-wide DNA methylation analysis of pseudohypoparathyroidism patients with GNAS imprinting defects. Clin Epigenetics. 2016 Jan 26;8:10.
6. Vangeel EB, **Izzi B**, Hompes T, Vansteelandt K, Lambrechts D, Freson K, Claes S. DNA methylation in imprinted genes IGF2 and GNASXL is associated with prenatal maternal stress. Genes Brain Behav. 2015 Sep 3.
7. Vangeel EB, Van Den Eede F, Hompes T, **Izzi B**, Del-Favero J, Moorkens G, Lambrechts D, Freson K, Claes S. Chronic Fatigue Syndrome and DNA Hypomethylation of the Glucocorticoid Receptor Gene Promoter 1F Region: Associations With Hypothalamic-Pituitary-Adrenal Axis Hypofunction and Childhood Trauma. Psychosom Med. 2015 Jul 30.
8. Rochtus A, **Izzi B**, Vangeel E, Louwette S, Wittevrongel C, Lambrechts D, Moreau Y, Winand R, Verpoorten C, Jansen K, Van Geet C, Freson F. DNA methylation analysis of Homeobox genes implicates HOXB7 hypomethylation as risk factor for neural tube defects. Epigenetics. 2015;10(1):92-101.
9. Janssen B, Byun HM, Cox B, Gyselaers W, **Izzi B**, Baccarelli AA, Nawrot TS.

Curriculum Vitae – Benedetta Izzi

- Variation of DNA methylation in candidate age-related targets on the mitochondrial-telomere axis in cord blood and placenta. *Placenta*. 2014 Sep;35(9):665-72.
10. Garin I, Mantovani G, Aguirre U, Barlier A, Brix B, Elli FM, Freson K, Grybek V, **Izzi B**, Linglart A, Perez de Nanclares G, Silve C, Thiele S, Werner R. European guidance for the molecular diagnosis of pseudohypoparathyroidism not caused by point genetic variants at GNAS: an EQA study. *Eur J Hum Genet*. 2014 Jul 9.
 11. **Izzi B**, Binder AM, Michels KB. Pyrosequencing Evaluation of Widely Available Bisulfite Conversion Methods: Considerations for Application. *Med Epigenet*. 2014 Jan 1;2(1):28-36.
 12. Michels KB, Binder AM, Dedeurwaerder S, Epstein CB, Grealley JM, Gut I, Houseman EA, **Izzi B**, Kelsey KT, Meissner A, Milosavljevic A, Siegmund KD, Bock C, Irizarry RA. Recommendations for the design and analysis of epigenome-wide association studies. *Nat Methods*. 2013 Oct;10(10):949-55.
 13. Hompes T, **Izzi B**, Gellens E, Morreels M, Fieuws S, Pexsters A, Schops G, Dom M, Van Bree R, Freson K, Verhaeghe J, Spitz B, Demyttenaere K, Glover V, Van den Bergh B, Allegaert K, Claes S. Investigating the influence of maternal cortisol and emotional state during pregnancy on the DNA methylation status of the glucocorticoid receptor gene (NR3C1) promoter region in cord blood. *J Psychiatr Res*. 2013 Apr 5.
 14. **Izzi B**, Francoise I, Labarque V, Thys C, Wittevrongel C, Devriendt K, de Zegher F, Legius E, Van den Bruel A, D'Hooge M, Lambrecht D, Van Geet C, Freson K. Methylation defect in imprinted genes detected in patients with an Albright's Hereditary Osteodystrophy like phenotype and platelet Gs hypofunction. *PlosONE* 2012;7(6):e38579.
 15. Gianfagna F, Tamburrelli C, Vohnout B, Crescente M, **Izzi B**, Pampuch A, De Curtis A, Di Castelnuovo A, Cutrone A, Napoleone E, Tayo B, Lorenzet R, Nanni L, Arca M, Donati MB, de Gaetano G, Cerletti C, Iacoviello L on behalf of the Moli-family Study Investigators. Heritability, genetic correlation and linkage to the 9p21.3 region of mixed platelet-leukocyte conjugates in families with and without early myocardial infarction. *Nutr Metab Cardiovasc Dis*. 2012 May 25.
 16. **Izzi B**, de Zegher F, Francois I, del Favero J, Goossens D, Wittevrongel C, Thys C, Van Geet C, Freson K. No evidence for GNAS Copy Number Variants in patients with features of Albright's Hereditary Osteodystrophy and abnormal platelet Gs activity. *J Hum Genet*. 2012 Apr;57(4):277-9.
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20. Tamburrelli C, Crescente M, Barisciano M, **Izzì B**, Donati MB, de Gaetano G, Cerletti C. Epoprostenol inhibits human platelet-leukocyte mixed aggregate and platelet microparticle formation in whole blood. Thromb Res. 2011 Nov;128(5):446-51.
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Chapters in books

1. Cerletti C, **Izzì B**, Iacoviello L, de Gaetano G. Pharmacogenomics of anti-platelet drugs, from "Platelets in Thrombotic and Non-thrombotic Disorders", Springer, Berlin, Germany. Editors: Gresele P, López JA, Kleiman NS, Page CP. In press 2016.

Poster/Oral presentations

1. **Izzì B**, Gianfagna F, Cludts K, Grippi C, Verhamme P, Cerletti C, de Gaetano G, Hoylaerts M, Iacoviello L. PEAR1 promoter methylation is associated with platelet and white blood cell phenotypes in the Moli-family cohort. 24th Annual Meeting of the Belgian Society on Thrombosis and Haemostasis. Lamot, Belgium, 24-25 November 2016.
2. **Izzì B**, Pistoni M, Criel M, Cludts K, Verfaillie C, Verhamme P, Freson K, Hoylaerts MF. Cardiovascular GWAS PEAR1 SNP stimulates its intronic enhancer activity via DNA methylation. European Society of Human Genetics Conference 2015. Glasgow, Scotland, UK, 6-9 June 2015
3. **Izzì B**, Kauskot A, Vandenbriele C, Criel M, Cludts K, Verhamme P, Freson K, Hoylaerts M. PEAR1 upregulation during megakaryopoiesis is dependent on changes in DNA methylation. 22nd Annual Meeting of the Belgian Society on Thrombosis and Haemostasis. Lamot, Belgium, 27-28 November 2014
4. Rochtus A, **Izzì B**, Winand R, Van Geel E, Moreau Y, Jansen K, Van Geet C, Freson K. Genome-wide DNA methylation studies in patients with a myelomeningocele. Epigenetic plasticity: implications in neural (dys)function. ICVS Braga – October 2014
5. **Izzì B**, Binder AM, Barrow TM, Michels KB. Human placenta drives developmental plasticity through imprinting control. VIII World Congress on Developmental Origins of Health and Disease. Suntec Singapore, 17-20 November 2013
6. **Izzì B***, Carmona JJ*, Just AC*, Barupal J, Binder AM, Hutchinson J, Hofmann O,

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- Schwartz J, Baccarelli A, and Michels KB *equal contribution. Comparison of multiplexed reduced representation bisulfite sequencing (mRRBS) with the 450K Illumina Human BeadChip: from concordance to practical applications for methylomic profiling in epigenetic epidemiologic studies. Epigenetic and Chromatin: interactions and processes conference, Harvard Medical School, Boston, USA. 11-13 March 2013
7. **Izzì B**, Francois I, Labarque V, Thys C, Wittevrongel C, Devriendt K, Legius E, Van den Bruel A, D'Hooghe M, Lambrechts D, de Zegher F, Van Geet C, Freson K. Imprinting defect in patients with Albright's Hereditary Osteodystrophy and platelet Gs hypofunction. European Human Genetics Conference 2012, Nürnberg, Germany, June 23-26, 2012
 8. **Izzì B**, Decallonne B, Lambrechts D, Van Geet C, Vanderschueren D, Freson K. GNAS methylation abnormalities identified in hypoparathyroidism patients: expanding the GNAS-related pathology. 21st Meeting of the Belgian Endocrine Society. Leuven, Belgium. 19 November 2011
 9. **Izzì B**, Thys C, Louwette S, Lambrechts D, Van Geet C, Freson K. From Genome-Wide to individual CpG methylation analysis: Illumina and Sequenom EpiTYPER application for the identification of epigenetic abnormalities in Neural Tube Defects. Netsim/Bloodomics Workshop 2011, IJsselmeer, The Netherlands 31 May-3 June 2011.
 10. **Izzì B**, Devriendt K, Lambrechts D, Van Geet C, Freson F. GNAS, NESP and XL hypermethylation in pseudopseudohypoparathyroidism patients. European Human Genetics Conference 2011, Amsterdam, the Netherlands, 28 – 31 May, 2011.
 11. **Izzì B**, Claes B, Lambrechts D, Van Geet C, Freson K. Mass-spectrometric analysis of GNAS methylation in Pseudohypoparathyroidism type Ib patients reveals overall methylation defects also for the familial cases. Epigenetics World Congress, Berlin, Germany, 17-18 September 2009.
 12. **Izzì B**, Bouillon R, Devriendt K, Van Geet C, Freson K. Possible role of GNAS imprinting in a prothrombotic phenotype: NESP55 hypermethylation in CVA at young age. XXII Congress of the International Society on Thrombosis and Haemostasis, Boston, USA, 11-16 July, 2009.
 13. **Izzì B**, Van Geet C, Freson K. GNAS pathology and blood platelet function. I International Workshop on cAMP Signaling Phosphodiesterases: From Genetics to Function & Human Diseases, Bethesda, MD, USA. 8-9/06/2009
 14. **Izzì B**, Pampuch A, Costanzo S, Vohnout B, Iacoviello L, Donati MB, Cerletti C, de Gaetano G. Determinants of platelet aggregate formation with polymorphonuclear leukocytes or monocytes in human whole blood. V LINAT

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- meeting , OMRP, Oklahoma, USA. 30/05-1/06/2008.
15. Alberti S, Pampuch A, **Izzì B**, Tamburrelli C, Angeloni G, de Gaetano G, Cerletti C. Platelet-leukocyte conjugates in persistent atrial fibrillation (AF). XXV Italian Conference on Cytometry, Roma, Italy, 3-6/10/2007.
 16. Pampuch A, **Izzì B**, Costanzo S, Vohnout B, Iacoviello L, Donati MB, Cerletti C, de Gaetano G. Determinants of platelet aggregate formation with either polymorphonuclear leukocytes or monocytes in human whole blood. XXI Congress of the International Society on Thrombosis and Haemostasis, Geneva, Switzerland, 6-12 July, 2007. (J Thromb Haemost 2007; 5, suppl 2: P-M-426.)
 17. **Izzì B**, Pampuch A, de Gaetano G, Cerletti C. Platelet but not leukocyte activation is a prerequisite for platelet-leukocyte interaction in human wholeblood. XXI Congress of the International Society on Thrombosis and Haemostasis, Geneva, Switzerland, 6-12 July, 2007. (J Thromb Haemost 2007;5, suppl 2: P-M-423.)



PERSONAL INFORMATION

Stefania Falciglia

Resident: via Vittorio Veneto, 6 – 86100 CAMPOBASSO

+39 392 5953154

stefania.falciglia@asrem.org

Date and birth 30/07/1970 | Nationality Italian

WORK EXPERIENCE

December 2011 - present

Hospital Pharmacist (manager)
UO farmaceutica territoriale,
ASReM (Azienda Sanitaria della Regione Molise)
via Ugo Petrella, 1 Campobasso

Major tasks and responsibilities:

- control of the prescriptive appropriateness
- evaluation of the possible inclusion of new molecules in the regional registry: DPC
- coordinator of the scientific secretariat of the ASReM Committee on drug prescription in supporting of the regional Health government (RegioneMolise)
- responsible data management of the regional drug prescription registry

April 2010 - November, 2011

Hospital Pharmacist (collaborator)
UO Farmaceutica Territoriale,
ASReM Via Ugo Petrella, 1 Campobasso

February 2002 - November 2011

Pharmacist
Private Pharmacy
Dr. Emilia Cipolla - Via Mazzini, 20 - Campobasso

November 1996 - March 97

Pharmacist (director)
Private Pharmacy
Dr. Teresa Ciccarone – Via V. Emanuele, Montefalcone nel Sannio (Cb)

July 96 – September 1997

Pharmacist (director)
Private Pharmacy
Dr. Margherita Abiuso – Via Vittorio Emanuele III - Gambatesa (Cb)

EDUCATION AND TRAINING

1996 Master of Sciences in Pharmacy at the University of PISA.

April 1996 State examination for Pharmacist profession, at the University of PISA

2009 Hospital Pharmacy Specialization degree at the University of Salerno

2015 Master in "Management delle Aziende Sanitarie" at the LUISS Libera Università Internazionale degli Studi Sociali, Rome

2016-2017 Master in "Manager dei dipartimenti farmaceutici" at the University of Camerino (MC). *In progress*



SCIENTIFIC PUBLICATIONS

- Grit R, Bini K, Verri F, Falciglia S, Mari M. The effectiveness of atypical antipsychotics in care in Great Area 2 Jesi. SIFO Bull 2015; 61 (3): 105-109
- Grit R, Verri F, Bini K, Baldini V, Falciglia S. The distribution of direct health care costs in the diabetic patient. Riv World Health Year XXIII N May 5, 2016
- Grit R, Verri F, Bini K, Chegai S, Falciglia S. The role of vitamin D in fractures. The experience of ASUR Marche. Monthly Magazine Year XXXIII No 7 to 8 July-September 2016 the World Health

ABSTRACT

- "The new oral anticoagulants: economic impact of spending and prevalence in the treatment" SIHTA 8th National Congress - HTA between decision and consent 1/2/3 October 2015 Authors: Grit R, F Verri, Bini K, V Baldini, Falciglia S ASUR Marche;
- "The cost of the process in the patient with pneumonia: The role of pneumococcal vaccine" SIHTA 8th National Congress - HTA between decision and consent 1/2/3 October 2015 Authors: Grit R, S Falciglia ASUR Marche Jesi AV2; ASREM
- "The cost of the process in COPD - ASUR Marche" SIHTA 8th National Congress - HTA between decision and consent 1/2/3 October 2015 Authors: Grit R, S Falciglia ASUR Marche Jesi AV2 - ASREM;
- "Estimation of the prevalence of the metabolic syndrome in the territory and its operating costs" SIHTA 8th National Congress - HTA between decision and consent 1/2/3 October 2015 Authors: Grit R, S Falciglia ASUR Marche Jesi AV2; ASREM;
- "Appropriateness and pharmaceutical-therapeutic use of anticoagulants" SIHTA 8th National Congress - HTA between decision and consent 1/2/3 October 2015 Authors: Grit R, F Verri, Bini K, V Baldini, Capodrossi A, S Falciglia ASUR Marche
- "Process certification UFA" SIHTA 8th National Congress - HTA between decision and consent 1/2/3 October 2015 Authors: Grit R, F Verri, Bini K, Capodrossi A, S Falciglia ASUR Marche ASREM;
- The effectiveness of atypical antipsychotics in care in Great Area 2 Jesi ASUR MARCHE: R.Grinta; F.Stefania "
- "Distribution of patient costs with rheumatoid arthritis" SIHTA 9th National Congress - HTA in healthcare processes and organizational models 13/14/15 October 2016 Authors: Grit R, F Verri, Bini K, K Chegai,, Falciglia S ASUR Marche ASREM

INTERNATIONAL MEETING

13th annual meeting of the International Society of HTAI Tokyo 10-14 may 2016

Mother tongue(s) Italian

Other language(s)

	UNDERSTANDING		SPEAKING		WRITING
	Listening	Reading	Spoken interaction	Spoken production	
English	Good	Good	Good	Good	Good