Ministero della Salute Direzione Generale della Ricerca Sanitaria e Biomedica e della Vigilanza sugli Enti **BANDO RICERCA FINALIZZATA 2018** **esercizio finanziario anni 2016-2017**	**Project Title:** Artificial intelligence of imaging and clinical neurological data for predictive, preventive and personalized (P3) medicine (NeuroArt P3)
Project Code: NET-2018-12366666	**Principal Investigator:** Uccelli Antonio
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale Policlinico San Martino

Project Type: Network Project/Progetti di Rete

Major Diagnostic Category*: Neurologia

Project Classification IRG: Bioengineering Sciences and Technologies

Project Classification SS: Biodata Management and Analysis - BDMA

Project Keyword 1: Methods for data analysis including: Numerical, statistical, mathematical and theoretical approaches to design and interpretation of large-scale studies such as methods for pattern discovery, data mining, sequence prediction, biomarker identification, therapeutic drug design and high throughput analyses; computational methods for organizing, maintaining, and integrating biological datasets and for large scale data modeling and simulations.

Project Keyword 2: Database technologies and methods for data management, data representation, data capture, data integrity and validation

Project Keyword 3: Brain Disorders and Clinical Neuroscience

Project duration (months): 36

Project Request: **Animals:** ☐ **Humans:** ☒ **Clinical trial:** ☐

The object/s of this application is/are under patent copyright Y/N: ☐

Operative Units / WP

	INSTITUTION	Department/Division/Lavoratory	Role in the project
1	Ospedale Policlinico San Martino	Scientific Direction - Ospedale Policlinico San Martino IRCCS, GENOVA	Lead PI
2	Provincia autonoma Trento	Azienda Provinciale per i Servizi Sanitari, TRENTO	PI
3	Ospedale San Raffaele - Milano	Ospedale San Raffaele, MILANO	PI
4	Istituto Giannina Gaslini	Istituto Giannina Gaslini, GENOVA	PI
5	Toscana	Fondazione Don Carlo Gnocchi, FIRENZE	PI
6	Liguria	Dipartimento di Matematica - Università degli Studi di GENOVA	PI

Overall Summary

The limited knowledge about the pathophysiology of central nervous system (CNS) diseases limits the development of adequate policies to manage their economic burden. A detailed description of patent phenotype and its correlation with subsequent disease evolution is needed to improve risk prediction and to personalize treatment and preventive strategies. However, the heterogeneous nature of disease mechanisms requires to collect large data series and thus to develop adequate archiving architecture. Our project plans to optimize this task exploiting the large databases available in our tertiary centers in patients with degenerative, inflammatory and oncological CNS diseases. This activity will allow improving machine learning algorithms for secondary use of clinical, biological and imaging data. It will also facilitate the development of analysis algorithms aiming to correlate a detailed clinical picture with subsequent disease evolution as a preliminary step to personalized medicine.

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Background / State of Art

Our consortium encompasses a series of tertiary reference centers dedicated to research and treatment of different disorders of the CNS. Among inflammatory and degenerative diseases, Alzheimer¿s (AD), Parkinson¿s disease (PD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) affect several millions of Europeans and result in a significant economic burden for society. So far, no effective disease-modifying treatment is currently available for ALS, AD and PD while the available therapies for MS are only partially efficacious to slow disease progression and are often associated with adverse events, sometimes life-threatening.
On the other hand, CNS neoplasms represent a heterogeneous group of infiltrating glial neoplasms with variable biology and prognosis. Their characterization is mandatory to plan an adequate treatment strategy and requires a multidisciplinary approach in which advanced imaging technique have to be applied and interpreted. A relevant peculiarity of this setting is represented by the fact that brain tumors are the most common pediatric solid tumors and include several histological subtypes asking for detailed valuations that are particularly demanding in children.
Altogether, the clinical, epidemiological and technological implications of these disease account let foresee a future of unsustainable demands on limited healthcare resources requiring for personalized approaches aiming to reduce cost/effectiveness of disease treatment and to optimize the required assistance for its related disabilities. Obviously, both items are dependent upon a series of factors whose identification inevitably requires the collection of large amount of clinical, neuropsychological, biological and imaging data.
Technological advances can speed up the digitalization of these variegate species of information provided that adequate digital platforms are implemented to enable their capture, storage, distribution, management and analysis. However, the high velocity approach asked by these ¿big data¿, their complexity and their heterogeneous nature are so overwhelming that most organizations are unable to fully exploit preventing the possibility to combine all these data into a single ¿whole picture¿. This drawback still limits the approach to a neurological patient to a subjective, operator-dependent evaluation mainly focusing on a single, specific data feature to assess the impact of the diverse available information parameters on the diseases' progression while only few studies have been focused on data-driven approach in neurological disorders. This limitation has been largely motivated by the lack of homogeneity and standardization among different centers of data encoding and storage. This prevented a more comprehensive approach integrating clinical and biological and imaging evaluation.
Modern machine learning methods are inherently conceived to deal with multi-modal data, to exploit them in order to perform multi-task predictions and to rank the retrieved information by pointing out their significance in the prediction process. As a consequence, there is the need to share clinical and instrumental information from different centers in order to create a common platform of data, that will serve as starting point to create predictive models for neuroinflammatory, neurodegenerative and neurooncological disorders, which can then be applied in clinical practice.

It’s available a Systematic Review on this topic? No

Hyphotesis and Specific AIMS

Hyphotesis and Significance:
Most healthcare organizations of high income countries are facing a flood of data, usually stored in different supports and mostly with different formats. Although this substantial amount of information might improve health outcomes and reduce healthcare costs, the high velocity asked by these ¿big data¿ and their complexity prevent their utilization by most stakeholders, clinicians and researchers. Approaching this issue requires to develop a proper architecture of data repository and to optimize its communication with both data-providers and data-users.

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The complexity of this task relates to the fact that data in healthcare and particularly in neuroscience come from multiple sources, internal and external, they are often encoded in multiple structured and unstructured formats, reside at multiple locations (geographic as well as in different healthcare providers¿ sites) and are stored on different and often incompatible formats. This historical background requires to pool the original `raw¿ data before being processed and transformed in big data analytics platforms.
Once defined the architecture of data management, machine learning methods can be developed in order to extract the information useful to adequately test raised hypotheses. In this line, workflows can be developed for analyzing complex multivariate information and to condense data vectors into an easily interpretable, esthetic and translationally relevant form whose accuracy can be validated.
This process can thus use observational data matched with the narration of patient development and its biological and clinically relevant events, in order to improve our capability to predict trends and to identify patterns in a variety of past, present or future settings.

Preliminary Data:
The basis for our project relies on the fact that our ¿consortium¿ encompasses tertiary reference centers with a high patient throughput activity and with largely complementary scientific interests.
In particular, the Ospedale Policlinico San Martino IRCCS, in Genova, is one of the largest European academic hospitals whose mission is focused on research and care of neurological disorders in its clinical, translational and basic aspects. The same IRCCS has a consolidated tradition in neurosciences in which a multidisciplinary approach to molecular, biological, signal analysis and imaging data skills in computational analyses of different data sources and formats. In this setting, the application of artificial intelligence approaches has been extended to the extraction of spinal cord signals from PET/CT images of ALS patients as a prognostic marker of survival, to the support of vector machine analyses for predicting conversion of mild cognitive impairment to AD regardless cognitive reserve, up to the integrated analysis of EEG and Dopamine Transporter binding to predict disease progression in de novo PD patients.
The Trento Unit is characterized by a virtually universal catchment area in the related territory, and it is active since many years in connecting clinical services with a dedicated activity of data management and optimization, aiming to follow all referring patients from disease presentation up to their follow up. Their experience in connecting these two worlds is pivotal for the ambitious aim of our project, starting from the repository design up to the ethical and juridical implications of the recent European law about privacy and data protection.
The MS Center of the Florence unit established an electronic database of all patients visited since 1998 and it gathered data on nearly 2000 MS patients contributing to the Italian MS Registry. A sizeable proportion of patients (estimated number nearly 700) referred has been systematically followed-up from the clinical onset of the disease with follow up evaluations twice per year. The database stores prospectively collected, standardized and detailed information about the patient clinical characteristics at disease onset and during the follow-up using validated assessment tools developed for MS together with other relevant laboratory, imaging and therapeutic information. Accordingly, this large database allows a better definition of MS progression on a real-world basis.
The last two clinical units of our consortium will complement the above reported registries with a high throughput series in neuro-oncology.
The San Raffaele Hospital in Milan is a highly productive center that systematically applied a set of imaging procedures in a high number of glioma patients. Most of them have been monitored during time with regular imaging follow-up, conceivably highlighting disease stability or worsening, thus providing a dataset of the evolution of quantitative MRI features, combined with clinical progression.
According to its mission, Istituto Giannina Gaslini IRCCS expands the data asset to the pediatric field. In children, brain

tumors represent an extremely heterogeneous spectrum of neoplasms with different degrees of malignancy, posing particularly complex neuro-oncological challenges. According to its role of tertiary reference hospital for a large part of Italy, this Institution already implemented a dedicated facility in which neuro-surgery and neuro-radiology share common data archiving procedures.
These five clinical units will represent the data feeders and providers. Optimization of data management and development of algorithms for their analysis will be instead in charge to the University of Genoa, as a self-financing unit in cooperation with Fondazione Bruno Kessler in Trento, respectively. Both subjects have long standing cooperation with virtually all hospitals included in the consortium as indicated by the references indicated in the different WPs.

Picture to support preliminary data:

Specific Aim 1:

This overall WP plans to coordinate all activities of the other WPs.
Our first aim will thus to accurately define data type and their completeness and their fit to the ranking of clinical questions and their variability among the different evaluated diseases and age classes. This work preliminary step to estimate the dimension of memory needed to adequately store them according to a priority ranking of clinical questions defined by the panel of involved clinical scientists.

Specific Aim 2:

The second phase of the study will witness a coordinated activity of all units in order to design archive structure aiming to optimize data input, storage features and, mostly, readout interpretation.

Specific Aim 3:

In this last phase, we plan to optimize machine learning methods and to develop analysis algorithms aiming to improve the consortium asset and potential to create deeper, broader, more complete and simply better data as well as to provide active researchers broad data-bases for innovative projects.

Experimental Design Aim 1:

The first aspect of our study will be focused on the ethical and juridical implications of managing and sharing biomedical data and the need to asseverate the European GDPR published in 2016. This preliminary phase will be shared by all units and is mandatory for all activities of all WP. To achieve this goal, we will involve lawyers with specific expertise in the field in order to ensure data protection and privacy through compliance with the European Directives on the protection of personal data. Then, clinicians from all WPs will assess availability of data from different sources (clinical, biological, signaling and images in their various methodologies). This verification will provide us with a definition of the memory size requested, as well as with the completeness of patient description both on the transversal ground and in the narration of patient trajectory. This activity will thus permit a thoughtful discussion about ranking of clinical questions and set up of task 2.

Experimental Design Aim 2:

The second objective of the study will mainly involve Trento and UNIGE units aiming at defining the structure of the archive as well as the interfaces needed to optimize data translation and entry in an automatic fashion from different data repository available in the clinical units of our consortium. Data will be collated from the source system located at each center participating in the network through different integration platforms. These platforms allow to cleanse, monitor, transform, integrate through the insertion, merge and deletion of imputs from different sources and targets. This strategy will help to

improve the quality and reliability of the data and guarantee security and reliability before being transferred to a Data warehouse and data analytics stage. Data ownership and procedures for data export in an anonymized or pseudonymized form will be achieved through specific rules established by partners (¿privacy by design¿ and secure exchange of data). It is forecasted that this activity will imply a continuous discussion to provide ICT specialists with feedback signals able to optimize the ultimate result.

Experimental Design Aim 3:

The third aim is the design and development of data driven machine learning algorithms for disease progression, subtyping or survival prediction based on the integration of heterogeneous data types. In order to guarantee statistical robustness and results reproducibility, model selection and validation will be performed according to resampling strategies.

Metodologies and statistical analyses:

Methods for data analysis will include: numerical, statistical, mathematical and theoretical approaches to design and interpretation of large-scale multi-site studies such as methods for pattern discovery, data mining, sequence prediction, biomarker identification, therapeutic drug design and high throughput analyses; computational methods for organizing, maintaining, and integrating biological datasets and for large scale and multi-site data modeling and simulations.
In addition to standard statistical methodology, a large part of this study will make use of recent advances in artificial intelligence methods, in order to establish predictive models and test their performance.

Expected outcomes:

Our project is expected to provide the MoH, and cofounding regions with different products. As a first, ethical, revenue, we plan to facilitate the development of algorithms to inform big data modeling for multi-site research asseverating the needed issues about data protection / privacy protocol.
Secondly, the large multi-site dataset provided will permit the analysis of heterogeneous and standardized, clinical, imaging and biological data on for neurological disorders to inform health care policies by all stakeholders. The availability of objective quantitative indexes will allow accurate comparisons between different Italian regions and will improve the capability to evaluate the potential of innovative diagnostic, prognostic and therapeutic procedures.

Risk analysis, possible problems and solutions:

The main risk we foresee relates to the possible occurrence in difficulties in collecting data/datasets. To solve this potential problem, we already involved IT and clinical staff whose engagement will persist throughout project duration to identify common description of available data. On the other hand, the second possible threat is the failure to comply with deadlines and milestones, particularly in the data collection. To approach this risk, all investigators agreed with a series of appointments to monitor and optimize this activity.

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Significance and Innovation

To date there are a few studies adopting a comprehensive and systematic approach to big data in neurological disorders. This limitation prevents an accurate evaluation of potential and implication of big data analysis in this medical and clinical setting. On the other hand, the increasing interest in collecting such information together with the usefulness of its clinical application, has recently led to create shared dataset among to various centers. We therefore aim to aggregate and harmonize all the data collected by a network of different Italian hub-centers, in order to provide integrated and quantitative indexes that might be applied in daily clinical practice for diagnosis and treatment of neuroinflammatory and neurodegenerative disorders

Description of the complementary and sinergy research team

This project is based on a highly-coordinated action of research units with complementary expertize feeding artificial intelligence algorithms with clinical, imaging and biological data arising from some of the most common diseases carrying a huge economic burden for the Italian Health System namely: 1) MS and encephalitis (WP1, WP2 and WP5; 2) AD (WP1 and WP5); 3) PD (WP1 and WP2); 4) ALS (WP1); 5) adult neuroncology (WP3); pediatric neuroncology (WP4).
Identification and collection of a core set of standardized data as well as establishing predictive models (modeling symptoms, therapy data and outcomes data) by using retrospective data analysis will be carried out through a close collaboration with researchers of WP2 and WP6.
The participants have been carefully chosen for their outstanding scientific contributions in clinical neurosciences and in bioinformatics, as well as for the added value that their contribution will bring to the consortium. The management of the overall project will be funded using the 5% of each WP's MOH budget, according to a Consortium Agreement, which will be signed by all PIs of each WP.

Training and tutorial activities

Training and tutorial activities will be implemented throughout the different phases of the project to strength synergies and complementarity among the different healthcare professionals involved and contributing to the professional formation of a highly needed new generation of computationally trained researchers who are aware of the richness of data and can draw on knowledge from many sources, courageous enough to make judicious simplifications and to have their ideas tested, and imaginative enough to generate interesting, testable large-scale ideas. More important tutorial actions will allow dissemination of the project outcomes with the objective to foster key healthcare strategic policies among Regions involved or not in the project. Last, periodic evaluation meetings will guarantee monitoring progress of the project and ensure quality control also through the preparation of regular progress reports.

Bibliography

Please refer to references of each single WP

Timeline / Deliverables / Payable Milestones

We trust that we will be able to accomplish the proposed tasks in due time.
Time set for deliverables and milestones are reported below.

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Milestones 18 month

At month 18, we plan to have completed all activities of Aim 1 and thus to have appropriately defined the bulk of data available and their completeness for every single patient. At this date, we foresee to also have the first prototype of archive structure and interacting capabilities with data repositories in the different hospitals.

Milestones 36 month

At this last time step, we plan to have completed the archive structure and feeding. And to provide with at least two analytical report as well as with the criteria for defining pilot studies in the different regions.

Gantt chart

Overall_GANTT_RF2018.pdf

Equipment and resources available

All Institution involved in the program display an updated asset of instruments dedicated to the collection of clinical, biological, genomic and imaging data. Similarly, the display of image archiving system considering DICOM format as a prerequisite and thus simplifying the data sharing in this high demanding subject. For more details refer to each specific WP.

For this overall WP, the only subcontract scheduled refers to the need to asseverate the juridical issues related to big data repositories and utilization in terms of privacy and data protection. This competence is obviously far from both clinical and ICS skills and thus requires a dedicated activity.

Translational relevance and impact for the National Health System (SSN)

Detailed evaluation of all pieces of information conveyed by every single patient with diseases affecting the central nervous system cannot be afforded by a single person or by commercially available software tools. This cul-de-sac derives not only by the size of needed memory. Rather it depends upon the need to extract potentially useful information from a large, complex and variegate set of stored data.
Our detailed analysis will provide the National Healthcare System with a detailed evaluation of the practical and technological implications of this inevitable ¿big data¿ approach in the world of neurodegenerative, neuroinflammatory and neurooncological disorders. This first needed step is needed to optimize the use of ICT as a tool to improve our observation insight. The complementary sharing of these data among an established group of scientists active on these fields will permit to improve the capability to plan large studies both on a retrospective and prospective approach.

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PRINCIPAL INVESTIGATOR PROFILE

Name		
Uccelli Antonio	Institution	Ospedale Policlinico San Martino
	Department/Unit	SCIENTIFIC DIRECTION
	Position Title	SCIENTIFIC DIRECTOR

Personal Statement

Prof. A. Uccelli will supervise the collection of clinical, biological and imaging data from MS patient carried out from people at the MS Clinic, Alzheimer disease subjects at the Memory Clinic and Parkinson disease individuals at the Movement Disorders Clinic of the Ospedale Policlinico San Martino, in Genoa.
He will collaborate with the mathematicians involved in the generation of the informatics procedures aimed at harmonizing and clean datasets and working on the elaboration of machine learning algorithms.
He will coordinate the activities of all the different workpackages through periodical meeting and teleconferences and submit reports in the due times.

Education/Training - Institution and Location	Degree	Year(s)	Field of study
University of Genoa	Italian Board of Neurology: completed with honors	3	Neurology
University of Genoa	Italian Board of Medicine: completed with honors	3	Medicine
University of Genoa	M.D. Degree Magna Cum Laude	6	Medicine

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Positions

Institution	Division / Research group	Location	Position	From year	To year
Ospedale Policlinico San Martino ¿ Sistema Sanitario Regione Liguria ¿ Istituto di Ricovero e Cura a carattere scientifico	Neurological Clinic of Ospedale Policlinico San Martino	Genova	Director of ¿Neurologic Outpatient Clinic¿ Unit	2018	2018
Ospedale Policlinico San Martino ¿ Sistema Sanitario Regione Liguria ¿ Istituto di Ricovero e Cura a carattere scientifico	Scientific Direction	Genova	Scientific Director	2018	2018
University of Genoa	Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI)	Genova	Full professor of Neurology	2017	2018
University of Genoa	Centre of Excellence for Biomedical Research (CEBR)	Genova	Director	2014	2018
University of Genoa	Department of Neurosciences, Ophthalmology and Genetics (DINOG)	Genova	Associate Professor of Neurology	2011	2017
University of Genoa	Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI)	Genova	Head Multiple Sclerosis Clinic Department	2006	2018
University of Genoa	Department of Neurosciences, Ophthalmology and Genetics (DINOG)	Genova	Dirigente Medico di I livello (Assistant Professor)	1993	2011

Official H index: 46.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 7004263413

ORCID ID: 0000-0002-2008-6038 **RESEARCH ID:** E-7343-2012

Awards and Honors:
Royan International Research Award 2013
Melvin Jones Fellow 2009
Premio Rita Levi Montalcini 2001

Other CV Informations:
President Associazione Italiana Neuroimmunologia 2013 -
Member International Board: European School of Neuroimmunology 2007 -

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Secretary: Research Committee of Fondazione Italiana Sclerosi Multipla (2003-05)
Coordinator of the Residency School of Neurosurgery, University of Genoa (2012 ¿ 2015).
Coordinator of Curriculum Neuroscienze cliniche e sperimentali, PhD program on Applied Neurosciences, University of Genoa (2016-). He has been invited to give seminar and keynote lectures at many academic sites and conferences all over the world. Scientific reviewer for several national and international agencies and scientific journals Co-author of 165 peer-reviewed publications with a Total impact factor: 1.197 Mean IF/publication: 7.253 C.I. (Citation Index Scopus) is 10686 H Index is 46

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Selected peer-reviewed publications of the PI

Valid for PI minimum expertise level

Title	DOI	PMID	Cit. **	P.*
Phenotypic and functional analysis of T cells homing into the CSF of subjects with inflammatory diseases of the CNS	10.1189/jlb.1202598	12714572	125	L
Recapitulation of B cell differentiation in the central nervous system of patients with multiple sclerosis	10.1073/pnas.0402455101	15263096	243	L
Unveiling the enigma of the CNS as a B-cell fostering environment	10.1016/j.it.2005.02.009	15866238	59	F
Autologous stem cell transplantation as rescue therapy in malignant forms of multiple sclerosis	10.1191/1352458505ms1181cr	15957523	56	L
Human mesenchymal stem cells modulate B-cell functions	10.1182/blood-2005-07-2657	16141348	998	L
Immunoregulatory function of mesenchymal stem cells	10.1002/eji.200636416	17013987	366	F
Human mesenchymal stem cells promote survival of T cells in a quiescent state	10.1634/stemcells.2007-0068	17395776	149	L
Mesenchymal stem cells: a new strategy for immunosuppression?	10.1016/j.it.2007.03.001	17400510	315	F
Reciprocal interactions between human mesenchymal stem cells and ¿¿ T cells or invariant natural killer T cells	10.1634/stemcells.2008-0687	19096038	105	L
The therapeutic potential of mesenchymal stem cell transplantation as a treatment for multiple sclerosis: consensus report of the International MSCT Study Group	10.1177/1352458509359727	20086020	136	L
Primary varicella zoster infection associated with fingolimod treatment	10.1212/WNL.0b013e31821043b5	21403115	29	F
Mesenchymal stem cells for the treatment of multiple sclerosis and other neurological diseases	10.1016/S1474-4422(11)70121-1	21683930	156	F
Mesenchymal stem cells impair in vivo T cell priming by dendritic cells	10.1073/pnas.1103650108	21960443	139	L
Mesenchymal Stem Cells Shape Microglia Effector Functions Through the Release of CX3CL1	10.1002/stem.1174	22821677	61	L
Reward responsiveness and fatigue in multiple sclerosis	10.1177/1352458512451509	22723570	11	L
Mesenchymal stem cells as treatment for MS progress to date	10.1177/1352458512464686	23124791	33	F
Fumarates modulate microglia activation through a novel HCAR2 signaling pathway and rescue synaptic dysregulation in inflamed CNS	10.1007/s00401-015-1422-3	25920452	33	L
Dysregulation of regulatory CD56(bright) NK cells/T cells interactions in multiple sclerosis	10.1016/j.jaut.2016.04.003	27157273	13	L
IFN¿ orchestrates mesenchymal stem cells plasticity through STAT1, STAT3 and mTOR pathways	10.1016/j.jaci.2016.09.004	27670240	0	L

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Title	DOI	PMID	Cit. **	P.*
Teriflunomide treatment reduces B cells in patients with MS	10.1212/NXI.0000000000000403	29082295	1	L

* Position: F=First L=Last C=Corrispondent

** Autocertificated

For evaluation CV

Title	DOI	PMID	Cit. *
X-Ray Phase Contrast Tomography Reveals Early Vascular Alterations and Neuronal Loss in a Multiple Sclerosis Model	10.1038/s41598-017-06251-7	28724999	4
NG2, a common denominator for neuroinflammation, blood-brain barrier alteration, and oligodendrocyte precursor response in EAE, plays a role in dendritic cell activation	10.1007/s00401-016-1563-z	27026411	4
T-cell trafficking in the central nervous system	10.1111/j.1600-065X.2012.01140.x	22725964	73
Intravenous mesenchymal stem cells improve survival and motor function in experimental amyotrophic lateral sclerosis	10.2119/molmed.2011.00498	22481270	69
Surrogate endpoints for EDSS worsening in multiple sclerosis. A meta-analytic approach	10.1212/WNL.0b013e3181ea15aa	20574036	80
C-C chemokine receptor 6-regulated entry of T(H)-17 cells into the CNS through the choroid plexus is required for the initiation of EAE	10.1038/ni.1716	19305396	611
Mesenchymal stem cells in health and disease	10.1038/nri2395	19172693	1617
Mesenchymal stem cells effectively modulate pathogenic immune response in EAE	10.1002/ana.21076	17387730	335
Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy	10.1182/blood-2005-04-1496	15905186	992
Prevention of autoimmune demyelination in non-human primates by a cAMP-specific phosphodiesterase inhibitor	10.1073/pnas.92.8.3601	7536938	163

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Project Code: NET-2018-12366666	**Principal Investigator:** Uccelli Antonio
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Project Type: Network Project/Progetti di Rete

Grant

Funded Institution / Country	Year	Title	Position in Projects
Compagnia di San Paolo - IT	2016	Studio dell¿effetto immunomodulante e neuroriparativo delle cellule staminali mesenchimali in pazienti con sclerosi multipla	Coordinator
ERA-NET - Call EraCoSysMed	2016	Personalizing health care in Multiple Sclerosis using systems medicine tools ¿ Sys4MS	Collaborator
MOTOR NEURON DISEASE ASSOCIATION - UK	2016	Exosome-shuttled miRNAs as mediators of the therapeutic effect of mesenchymal stem cells in ALS	Coordinator
FONDAZIONE ITALIANA SCLEROSI MULTIPLA (FISM)	2016	Targeting terapeutico dell'attività e dell'espressione di REST allo scopo di ridurre la neurodegenrazione ed i deficit sinaptici in modelli di EAE cronica	Coordinator
FONDAZIONE CARIPLO	2015	Aged induced hematopoietic and neurogenic dysfunctions contribute to the worse outcome	Coordinator
GRANT FOR MULTIPLE SCLEROSIS INNOVATION (GMSI)	2015	Driving microglia metabolism toward remyelination and restoration of brain damage in multiple sclerosis	Coordinator
FONDAZIONE CARIGE	2012	MEsenchymal StEm cells for Multiple Sclerosis (MESEMS)	Coordinator
ITALIAN MINISTRY OF HEALTH	2011	Preclinical evaluation of the NAMPT inhibitor FK866 for the treatment of autoimmunity and lymphoblastic leukemia	Coordinator
FONDAZIONE ITALIANA SCLEROSI MULTIPLA (FISM)	2011	Progetto Speciale Cellule Staminali	Coordinator
MIUR-PRIN	2009	Identification of new sources of stem cells for the treatment of multiple sclerosis	Coordinator

Employment contract extension:

Project Title:
Artificial intelligence of imaging and clinical neurological data for predictive, preventive and personalized (P3) medicine (NeuroArt P3)

Project Code: NET-2018-12366666

Principal Investigator: Uccelli Antonio

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale Policlinico San Martino

Project Type: Network Project/Progetti di Rete

Total proposed budget (Euro)

Costs	TOTAL BUDGET	Co-Funding	Project costs proposed to funding Organization (no moh request)	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1a Staff Salary	915.000,00	915.000,00	0,00	not permitted	0,00
1b Researchers' Contracts	1.291.000,00	0,00	737.500,00	553.500,00	46,35
2 Equipment (Leasing - Rent)	243.000,00	0,00	128.000,00	115.000,00	9,63
3a Supplies	78.100,00	0,00	2.000,00	76.100,00	6,37
3b Model Costs	0,00	0,00	0,00	0,00	0,00
3c Subcontracts	77.000,00	0,00	50.000,00	27.000,00	2,26
3d Patient Costs	25.000,00	0,00	0,00	25.000,00	2,09
4 IT Services and Data Bases	322.700,00	30.000,00	147.450,00	145.250,00	12,16
5 Publication Costs	16.500,00	0,00	4.700,00	11.800,00	0,99
6 Convegni	15.100,00	0,00	7.250,00	7.850,00	0,66
7 Travels	21.900,00	0,00	11.000,00	10.900,00	0,91
8 Overheads	228.700,00	0,00	111.988,89	116.711,11	9,77
9 Coordination Costs	105.000,00	0,00	0,00	105.000,00	8,79
Total	3.339.000,00	945.000,00	1.199.888,89	1.194.111,11	100,00

Report the Co-Funding Contributor:

WP 1 - Ospedale Policlinico San Martino
Co-Funding Ospedale Policlinico San Martino
Co-Funding CNR institute of Bioimages and molecular physiology (in agreement with Ospedale Policlinico San Martino)

WP 2 - Provincia autonoma Trento
Co-Funding Azienda Provinciale per i Servizi Sanitari di Trento
Co-Funding Fondazione Bruno Kessler

WP 3 - Ospedale San Raffaele - Milano
Co-Funding Ospedale San Raffaele - Milano

WP 4 - Istituto Giannina Gaslini
Co-Funding IRCCS Istituto Giannina Gaslini

WP 5 - Toscana

Project Title:
Artificial intelligence of imaging and clinical neurological data for predictive, preventive and personalized (P3) medicine (NeuroArt P3)

Project Code: NET-2018-12366666

Principal Investigator: Uccelli Antonio

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale Policlinico San Martino

Project Type: Network Project/Progetti di Rete

Co-Funding Fondazione Don Carlo Gnocchi

WP 6 - Liguria
Co-Funding Università degli Studi di Genova

(Data changed during the moratorium period)

Working Package summary budget (Euro)

WP	Research Institution	Funding Institution	TOTAL PROGRAMME COSTS	Co-Funding	Project costs proposed to funding Organization	List of costs proposed for funding to the MOH
WP-1	Ospedale Policlinico San Martino	Co-Funding Ospedale Policlinico San Martino Co-Funding CNR institute of Bioimages and molecular physiology (in agreement with Ospedale Policlinico San Martino)	590.000,00	185.000,00	150.000,00	255.000,00
WP-2	Provincia autonoma Trento	Co-Funding Azienda Provinciale per i Servizi Sanitari di Trento Co-Funding Fondazione Bruno Kessler (FBK)	767.111,11	200.000,00	299.888,89	267.222,22
WP-3	Ospedale San Raffaele - Milano	Co-Funding Ospedale San Raffaele - Milano	620.000,00	50.000,00	300.000,00	270.000,00
WP-4	Istituto Giannina Gaslini	Co-Funding IRCCS Istituto Giannina Gaslini	365.000,00	80.000,00	150.000,00	135.000,00
WP-5	Toscana	Co-Funding Fondazione Don Carlo Gnocchi	766.888,89	200.000,00	300.000,00	266.888,89
WP-6	Liguria	Co-Funding Università degli Studi di Genova	230.000,00	230.000,00	0,00	0,00

	Project Title: Artificial intelligence of imaging and clinical neurological data for predictive, preventive and personalized (P3) medicine (NeuroArt P3)
Project Code: NET-2018-12366666	**Principal Investigator:** Uccelli Antonio
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale Policlinico San Martino

Project Type: Network Project/Progetti di Rete

Project Title: P3 solutions (preventive, predicitve and personalized) in neuroinflammation and neurodegenerative diseases driven by imaging and biological data.

Project Code: NET-2018-12366666-1

Principal Investigator: Uccelli Antonio

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale Policlinico San Martino

Project Type: WP PROJECT - 1

Major Diagnostic Category*: Neurologia

Project Classification IRG: Bioengineering Sciences and Technologies

Project Classification SS: Biodata Management and Analysis - BDMA

Project Keyword 1: Methods for data analysis including: Numerical, statistical, mathematical and theoretical approaches to design and interpretation of large-scale studies such as methods for pattern discovery, data mining, sequence prediction, biomarker identification, therapeutic drug design and high throughput analyses; computational methods for organizing, maintaining, and integrating biological datasets and for large scale data modeling and simulations.

Project Keyword 2: Database technologies and methods for data management, data representation, data capture, data integrity and validation

Project Keyword 3: Brain Disorders and Clinical Neuroscience

Project duration (months): 36

Project Request: **Animals:** ☐ **Humans:** ☒ **Clinical trial:** ☐

The object/s of this application is/are under patent copyright Y/N: ☐

Investigators, Institution and Role in the Project

	Co-PI	Key Personnel	Institution/Org./Pos.	Role in the project	Birth Date
1	X	Marini Cecilia	Ospedale Policlinico San Martino	Co-PI	05/06/1962

Overall Summary

Personalized healthcare for degenerative or inflammatory diseases of the central nervous system (CNS) is hindered by a poor understanding of the underlying biological processes, their interactions and heterogeneity. These shortcomings hamper early diagnosis, disease monitoring, risk prediction and treatment. Thus, institutional stakeholders cannot develop adequate policies to manage the economic burden of these disorders.
To overcome this limitation, we plan to generate large data sets from patients with multiple sclerosis (MS), Alzheimer (AD), Parkinson (PD) and amyotrophic lateral sclerosis (ALS). These sets will include clinical, neuro-psychological, electrophysiological, genomics, immunological and molecular data as well as functional and structural images. After classification in a few human-readable categories, these same data sets will be utilized by mathematical models (developed in others WPs) to predict disease evolution and to drive clinically-relevant decisions.

Background / State of Art

Healthcare organizations including research institutions, are facing a flood of data, mostly stored in a hard copy form. This plenty of information might improve health outcomes and reduce healthcare costs. However, the high velocity approach asked by these ¿big data¿, their complexity and their heterogeneous nature are so overwhelming that most organizations are unable to fully exploit them.
Managing and harnessing the analytical power of these large datasets, however, is vital to the success of all healthcare

organizations. Technological advances can speed up the digitalization of these variegate species of information provided that adequate digital platforms are implemented to enable their capture, storage, distribution, management and analysis. This advancement thus enables big data analytics as a tool to improve healthcare effectiveness and sustainability (1). This task, indeed, asks for a multidisciplinary analysis of complex patient features to be matched with a precise evaluation of costs and outcomes of care. This complete picture is needed to optimize diagnostic evaluation and staging depth as prerequisites to tailor personalized treatments and to shape payers policies. In other words, applying advanced analytics to patient profiles (e.g., segmentation and predictive modeling) could proactively identify individuals who would benefit from preventive care or lifestyle changes. On the other hand, comprehensive scale disease profiling could accurately identify predictive events and support prevention initiatives. Finally, aggregating and synthesizing patient clinical records could provide data and services to third parties, for example, assisting pharmaceutical companies in identifying patients for inclusion in clinical trials.

Big data in healthcare can come from multiple sources, internal and external, they are often encoded in multiple structured and unstructured formats and reside at multiple locations (geographic as well as in different healthcare providers¿ sites). This historical background requires to pool the original `raw¿ data before being processed and transformed in big data analytics platforms. Then workflows have to be developed for analyzing complex multivariate information and to condense data vectors into easily interpretable, esthetic and translationally relevant forms whose accuracy can be validated. This process can thus permit to identify biological and clinically relevant events, to predict trends and to identify patterns in a variety of past, present or future settings.

Neurological disease is a rapidly growing societal and financial burden. Alzheimer¿s disease (AD), Parkinson¿s disease (PD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) which together affect several millions of Europeans, are some the most serious illnesses in this category. The high incidence of these debilitating diseases is creating a crisis of human suffering and enormous economic pressure. No effective disease-modifying treatment is currently available for ALS, AD and PD while the available therapies for MS are only partially efficacious to slow disease progression and hold significant health associated risks. Actually, clinical management of these diseases has significantly improved through the collection of large amount of clinical, neuropsychological, biological and imaging information. However, the possibility to combine all these data into a single ¿whole picture¿ both on a patient-by-patient basis and on the epidemiological ground is still missing. Developing an appropriately consistent and harmonized standardization of data collection and storage represents the prerequisite to allow big data analytics to optimize disease prevention, to identify new targets for drug discovery, to precisely tailor a specific therapeutic interventions and to discover predictive markers for disease progression in neurological diseases (2).

Hyphotesis and Specific AIMS

Hyphotesis and Significance:

Application of big data in neuroscience led to a cultural change moving from many isolated `vertical¿ efforts applying single techniques to single problems in single species to more `horizontal¿ efforts that integrate data collected using a wide range of techniques, problems and species. Yet what we are still lacking are quantitative integrative tools to translate this understanding to the individual level translating into personalized medicine.

A recent study reported that delineating 180 areas on multi-modal MRI from the Human Connectome Project and an objective semi-automated neuroanatomical approach asked about 30 Gigabyte per patient (3). Shifting these sizes to the clinical ground, and its need to enrich image-based information with a series of other biological and clinical information, would profoundly hamper the capability of current and future healthcare systems to correctly monitor patient data. It is thus obvious that the attention of analysts should move from raw data to algorithms able to extract the needed information

without losing potentially relevant findings. In neuroscience, this task is hampered by the absence of reliable models. An accurate analysis of data collected in tertiary, reference, centers could represent a first step in adequately estimate problem dimensions.

Preliminary Data:

We have shown by means of support vector machine analyses that 1) baseline FDG PET can identify conversion of mild cognitive impairment (4); 2) topography of hypometabolic pattern, assessed by FDG, independently predicts time to clinical conversion to dementia (5); 3) extraction of spinal cord FDG uptake predicts survival in ALS patients (6); 4) automatic analysis of EEG and Dopamine Transporter (DAT) binding predicts disease progression in de novo PD patients (7); 5) application of artificial intelligence approaches to image evaluation allowed to demonstrate an interplay between spinal cord and cerebral cortex metabolism in ALS (8).

Specific Aim 1:

To utilize imaging, biological and clinical to develop harmonized datasets to generate predictive models for MS aimed at predicting patient stratification, identifying prognostic clinical patterns and overall disease course and response to therapy.

Specific Aim 2:

To standardize and harmonize collection of imaging, biological and clinical data to generate predictive models for neurodegenerative dementia aimed at identifying etiological pathways and developing algorithms for prediction of disease progression and overall survival.

Specific Aim 3:

To utilize imaging, neurophysiological, neuropsychological, clinical and demographic data to develop harmonized datasets to generate predictive models for cognitive and motor deterioration in PD and ALS.

Experimental Design Aim 1:

Genetic and immunological studies have led to the hypothesis that MS is an autoimmune disease (9). Current immunomodulatory therapies are associated with adverse events, rarely even life-threatening (10). MRI is of fundamental importance to monitor disease and allowed identification of biomarkers associated with specific clinical outcomes (e.g., contrast enhancing lesions and brain atrophy) (11). Biological information obtained from CSF analysis, cytomics and genomics data and neuropsychological testing help in defining prognostic trajectories and response to therapies. Finally, large databases are available in the form of patients¿ registries containing information from large cohorts of prospective patients providing the opportunity to compare individual patients with a reference group (12). Mathematical algorithms have been used to analyze big MS data (13) minimizing the impact of biases arising from heterogeneous cohorts and allowing the identification of early predictors of poor outcomes as well as subsets of patients likely to respond to therapies (14).
We aim to develop more powerful computational tools capable of integrating more comprehensive information, creating algorithms to predict MS disease course and therapy. A large dataset of conventional and not conventional (MTR, DTI, atrophy, cortical lesions) MRI data from real world clinical setting, is available together with clinical and biological (CSF, flow cytometry and genomic) data collected in an electronic form (iMed software storage system) at the MS Clinic of our Institute. Maximization of data quality will be achieved through standardization of basic aspects of collected information, such as diagnostic criteria, disease course and definition of attacks, and of short-term outcomes, such as attack rates, disability and MRI metrics. Standardized datasets will be utilized to feed algorithms developed by partners to stratify patient populations and identify predictors of disease progression and treatment response.

Project Type: WP PROJECT - 1

Experimental Design Aim 2:

So far, predicting the functional and cognitive outcomes of dementia by single molecular biomarkers has been found to be a relatively ineffective procedure, raising the need for more integrative approaches to the study of the etiology and prediction of trajectory in patients with cognitive impairment. Sharing big data for dementia research promises to create intelligent analytical systems that are capable of generating effective disease diagnostic and drug development deliverables (15). We will take advantage of the clinical database of our tertiary center memory clinic already available as electronic health records in digital format and integrating metadata of multiple biomarkers (neuropsychological tests, APOe genotype, CSF sampling) and corresponding images (MRI, PET). This dataset includes data of a large number of patients and represents a heterogeneous ¿real-world data¿ source. Our first aim will be to identify all subjects in whom electronic records are combined with an explicit informed consent to the use of anonymous stored data for research purposes. This analysis will verify the prevalence of prodromal AD and outcome of dementia in our center and will evaluate a broad spectrum of clinical, cognitive, behavioral features and routine tests that may predict the likelihood of amyloid positivity. Moreover as subtle behavioral and neuropsychiatric symptoms are now considered part of the initial phase of several neurodegenerative dementia, presence of these clinical phenotypes will be evaluated and linked to the subsequent clinical progression to different neurodegenerative diseases. In ALS, this analysis will be also extended to the spinal cord. This integrated analysis will be used to differentiate the neurobiology of patients for neurodegenerative diseases aiming to integrate functional (PET) and morphological information (MRI) to obtain a data-driven computational tool for the diagnosis and prognosis of these diseases.

Experimental Design Aim 3:

Patients with parkinsonian symptoms are evaluated at their first access with standard clinical assessment. Patients with suspected, de novo PD are studied by DAT brain SPECT to rule out the absence of dopaminergic deficit. An extended neuropsychological test battery is applied to ascertain cognitive status, high-density complemented by resting-state EEG (HD-rsEEG), FDG-PET, overnight ambulatory polisomnography (PSG) to unveil REM sleep without atonia, and MRI to reveal microbleeds and ferromagnetic depositions. PD patients can be classified at baseline according to different domains, ranging from the clinical presentation (e.g., pure motor, malignant, or intermediate) to the presence/absence of cognitive impairment (e.g., cognitively intact, with mild cognitive impairment, demented). Patients follow-up include clinical evaluation, quantitative HD-rsEEG (qEEG) and neuropsychological assessment. Collected data will be stored on rigid informatic supports as DICOM files (MRI, FDG-PET, DAT-SPECT), European Data Format (EDF)(qEEG, PSG), or conventional Office utilities (neuropsychological tests) and will be utilized to feed algorithms to predict disease progression and treatment response.

Picture to support preliminary data:

FigureWP1.pdf

Metodologies and statistical analyses:

Methods for data analysis will include approaches aimed at designing and interpreting large-scale multi-site studies such as methods for pattern discovery, data mining, sequence prediction, biomarker identification, therapeutic drug design and high throughput analyses and computational methods for organizing, maintaining, and integrating biological datasets and for large scale and multi-site data modeling and simulations. As an example brain PET and MRI data integration and analysis will be performed, upon brain and spinal cord segmentation, by using the Geodesic Information Flows algorithm and Hough

transform. Tissue masks will be binarised with a 90% probabilistic threshold. We will then exploit the already available PET scans by registering them onto each patient¿s MRI so that we can import the pre-segmented tissues. Intensity normalization will be computed both on the whole brain and on selected reference tissues. Features will be computed on both PET scans and on the MRI. A machine-learning (ML) approach will be used to summarize PET and MRI features into a single, normalized measure, to assess difference in PET and texture and to correlate both baseline and follow up imaging data with clinical and cognitive scales, EEG, blood and CSF biomarkers. Images will be converted in well-established formats and linked to all other available archived datasets. On the same images, computational extraction of morphological structures will be performed according to standard protocols or to algorithms previously validated within the project. Criteria for disease progression will be defined by the whole panel in the activity of the different WP and will be applied to these patients, to develop a multivariate prediction model of disease progression and response to therapies.

Expected outcomes:
We expect to generate an increased number of hypotheses, simultaneously matched by an increase in the possibility to test them and to obtain objective and measurable answers. This activity, however, requires to define an architecture of data storage adequate for the clinical questions. We expect to feed a large and heterogeneous database in order to optimize the architecture of repository, to define the appropriate size for the issues related to a tertiary hospital aimed at optimizing diagnosis and risk prediction in neurological disorders.

Risk analysis, possible problems and solutions:
Changing from the conventional approach to neurological disorders to a computational one intrinsically implies to shift our attention from qualitative perceptions to measurements. However, number of tested variables directly determines the complexity of modeling challenges on the computational ground. This consideration implies that the classical clinical approach has to be complemented with a numerical and statistical thinking. Thus, the complex nature of interactions and correlations prevents the capability of single clinicians to accurately identify disease mechanisms. This limitation will preclude the immediate possibility to verify the information provided by data science algorithms in clinical decision making and will ask a careful evaluation on robust descriptors of disease outcome using both a retrospective and perspective approach.

Significance and Innovation

The main significance of the project is the development and implementation of a new analytics platform allowing the organization and interrogation of Big Data resources from neurological diseases into a rational and actionable mechanism to predict disease progression and response to therapy. This will entail the generation of systems and tools that allow the cross-platform correlation between data sets of distinct types, for example, clinical, biological, imaging and neurophysiological and neuropsychological. The outcome of this innovative proposal will be the availability of integrated quantitative indexes, derived from multi-site harmonized database, applicable in daily clinical practice for diagnosis and treatment of neuroinflammatory and neurodegenerative diseases as well as CNS neoplasms.

	Project Title: P3 solutions (preventive, predicitve and personalized) in neuroinflammation and neurodegenerative diseases driven by imaging and biological data.
Project Code: NET-2018-12366666-1	**Principal Investigator:** Uccelli Antonio
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale Policlinico San Martino

Project Type: WP PROJECT - 1

Description of the complementary and sinergy research team

This project is based on a highly coordinated action of research units with complementary expertize feeding artificial intelligence algorithms with clinical, imaging and biological data arising from some of the most common diseases carrying a huge economical burden for the Italian Health System namely: 1) MS and encephalitis (WP 1, WP2 and WP Firenze; 2) AD (WP 1 and WP Firenze); 3) PD (WP1 and WP2); 4) ALS (WP1); 5) adult neuroncology (WP 3); pediatric neuroncology (WP 5). Identification and collection of a core set of standardized data as well as establishing predictive models (modeling symptoms, therapy data and outcomes data) by using retrospective data analysis will be carried out through a close collaboration with researchers of WP2 and WP6.
The participants have been carefully chosen for their outstanding scientific contributions in clinical neurosciences and in bioinformatics, as well as for the added value that their contribution will bring to the consortium. The management of the overall project will be funded using the 5% of each WP's MOH budget, according to a Consortium Agreement, which will be signed by all PIs of each WP.

Training and tutorial activities

Training and tutorial activities will be implemented throughout the different phases of the project to strength synergies and complementarity among the different healthcare professionals involved and contributing to the professional formation of a highly needed new generation of computationally trained researchers who are aware of the richness of data and can draw on knowledge from many sources, courageous enough to make judicious simplifications and to have their ideas tested, and imaginative enough to generate interesting, testable large-scale ideas. More important tutorial actions will allow dissemination of the project outcomes with the objective to foster key healthcare strategic policies among Regions involved or not in the project. Last, periodic evaluation meetings will guarantee monitoring progress of the project and ensure quality control also through the preparation of regular progress reports.

Bibliography

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Project Type: WP PROJECT - 1

Timeline / Deliverables / Payable Milestones

D1.1. A clinical and imaging dataset of prospective cohorts of MS patients.
D1.2. A clinical and imaging dataset of prospective cohorts of AD patients
D1.3. A clinical and imaging dataset of prospective cohorts of ALS patients
D1.4. A clinical and imaging dataset of prospective cohorts of PD patients
D2.1. A harmonized database containing biological, imaging and clinical information from MS patients.
D2.2. A harmonized database containing biological, imaging and clinical information from AD patients
D2.3. A harmonized database containing biological, imaging and clinical information from ALS patients
D2.4. A harmonized database containing biological, imaging and clinical information from PD patients

Milestones 18 month

Aim 1
M1-7 identification of available data and disease-related features
M5-18 definition of data storage and memory need
M10-18 first retrospective data collection
M12-18 first cross correlation and optimization of data archive interrogation
Aim 2
M1-10 identification of available data and disease-related features
M8-18 definition of data storage and memory need
M13-18 first retrospective data collection
M15-18 first cross correlation and optimization of data archive interrogation

Milestones 36 month

Aim 1
M18-27 retrospective data collection, storage, cross-correlation and data archive interrogation
M20-30 patients pattern recognition
Aim 2
M18-30 retrospective data collection, storage, cross-correlation and data archive interrogation
M20-30 patients pattern recognition
Aim 3
M20-24 identification of available data and disease-related features
M24-32 patients pattern recognition

M33-36: final conference and scientific reports

Gantt chart

Genova_GANTT_RF2018.pdf

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Project Type: WP PROJECT - 1

Equipment and resources available

Over 2000 MS patients are routinely seen at the outpatient MS clinic and clinical, imaging and biological data are stored in an electronic form (iMed software storage system) as part of the Italian MS Registry. More than 2000 AD subjects are followed at the tertiary center memory clinic where electronic health records in digital format and integrating metadata of multiple biomarkers are collected. Similarly, 1800 PD patients are followed at Movement disorders Clinic while 200 ALS individuals are followed at the NEuroMuscular Omnicentre (NEMO) clinic.
CSF analysis is routinely carried out at the CSF laboratory of the Ospedale Policlinico San Martino including, IgG characterization, oligoclonal bands analysis, cells flow cytometric and biomarkers investigations. Analysis of immune cells phenotypes are carried out through multiparametric analysis on a BD LSRFortessa cell analyzer.
A 3 T MAGNETOM Prisma (Siemens Healthcare) is available for the imaging assessment of neurological subjects attending the Institute.
PET/CT lab is a high patient throughput activity within Ospedale Policlinico San Martino. It runs a cyclotron/radiopharmacy facility. So far, using a Siemens Hirez diagnostic scanner coupled with a 16 raw CT the lab performed more than 4200 test per year. The implementation of a new scanner (Siemens motion mCT, coupled with a 64 raw CT is in progress.

Translational relevance and impact for the National Health System (SSN)

The health and social cost of neurological diseases such as CNS neoplasms, AD, PS, MS and ALS is extremely high, both in terms of direct and indirect costs and include costs for hospitalization, drugs but also productivity costs and all social transfer payments, which may ultimately be a far more important economic factor. Current diagnostic tools, management strategies and therapies are yet insufficient to cope with these diseases making health care systems facing many unmet needs. This proposal will adopt artificial intelligence approaches through the application of mathematical modelling (knowledge driven) combined with bioinformatics tools (data driven approaches) to facilitate diagnosis, develop tools to monitor and predict the clinical course of the above-mentioned diseases and response to therapies toward a more personalised medical care that could be rapidly translated to the society to develop new policies for the management of neurological diseases by health care providers.

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Project Type: WP PROJECT - 1

PRINCIPAL INVESTIGATOR PROFILE

Name		
Uccelli Antonio	Institution	Ospedale Policlinico San Martino
	Department/Unit	SCIENTIFIC DIRECTION
	Position Title	SCIENTIFIC DIRECTOR

Personal Statement

Prof. A. Uccelli will supervise the collection of clinical, biological and imaging data from MS patient carried out from people at the MS Clinic, Alzheimer disease subjects at the Memory Clinic and Parkinson disease individuals at the Movement Disorders Clinic of the Ospedale Policlinico San Martino, in Genoa.
He will collaborate with the mathematicians involved in the generation of the informatics procedures aimed at harmonizing and clean datasets and working on the elaboration of machine learning algorithms.
He will coordinate the activities of all the different workpackages through periodical meeting and teleconferences and submit reports in the due times.

Education/Training - Institution and Location	Degree	Year(s)	Field of study
University of Genoa	Italian Board of Neurology: completed with honors	3	Neurology
University of Genoa	Italian Board of Medicine: completed with honors	3	Medicine
University of Genoa	M.D. Degree Magna Cum Laude	6	Medicine

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Project Type: WP PROJECT - 1

Positions

Institution	Division / Research group	Location	Position	From year	To year
Ospedale Policlinico San Martino ¿ Sistema Sanitario Regione Liguria ¿ Istituto di Ricovero e Cura a carattere scientifico	Neurological Clinic of Ospedale Policlinico San Martino	Genova	Director of ¿Neurologic Outpatient Clinic¿ Unit	2018	2018
Ospedale Policlinico San Martino ¿ Sistema Sanitario Regione Liguria ¿ Istituto di Ricovero e Cura a carattere scientifico	Scientific Direction	Genova	Scientific Director	2018	2018
University of Genoa	Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI)	Genova	Full professor of Neurology	2017	2018
University of Genoa	Centre of Excellence for Biomedical Research (CEBR)	Genova	Director	2014	2018
University of Genoa	Department of Neurosciences, Ophthalmology and Genetics (DINOG)	Genova	Associate Professor of Neurology	2011	2017
University of Genoa	Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI)	Genova	Head Multiple Sclerosis Clinic Department	2006	2018
University of Genoa	Department of Neurosciences, Ophthalmology and Genetics (DINOG)	Genova	Dirigente Medico di I livello (Assistant Professor)	1993	2011

Official H index: 46.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 7004263413

ORCID ID: 0000-0002-2008-6038 **RESEARCH ID:** E-7343-2012

Awards and Honors:
Royan International Research Award 2013
Melvin Jones Fellow 2009
Premio Rita Levi Montalcini 2001

Other CV Informations:
President Associazione Italiana Neuroimmunologia 2013 -
Member International Board: European School of Neuroimmunology 2007 -

Project Title:
P3 solutions (preventive, predicitve and personalized) in neuroinflammation and neurodegenerative diseases driven by imaging and biological data.

Project Code:	NET-2018-12366666-1	**Principal Investigator:**	Uccelli Antonio
Research Type:	a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:**	Ospedale Policlinico San Martino

Project Type: WP PROJECT - 1

Secretary: Research Committee of Fondazione Italiana Sclerosi Multipla (2003-05)
Coordinator of the Residency School of Neurosurgery, University of Genoa (2012 ¿ 2015).
Coordinator of Curriculum Neuroscienze cliniche e sperimentali, PhD program on Applied Neurosciences, University of Genoa (2016-). He has been invited to give seminar and keynote lectures at many academic sites and conferences all over the world. Scientific reviewer for several national and international agencies and scientific journals Co-author of 165 peer-reviewed publications with a Total impact factor: 1.197 Mean IF/publication: 7.253 C.I. (Citation Index Scopus) is 10686 H Index is 46

Project Title:
P3 solutions (preventive, predicitve and personalized) in neuroinflammation and neurodegenerative diseases driven by imaging and biological data.

Project Code: NET-2018-12366666-1

Principal Investigator: Uccelli Antonio

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale Policlinico San Martino

Project Type: WP PROJECT - 1

Selected peer-reviewed publications of the PI

Valid for PI minimum expertise level

Title	DOI	PMID	Cit. **	P.*
Phenotypic and functional analysis of T cells homing into the CSF of subjects with inflammatory diseases of the CNS	10.1189/jlb.1202598	12714572	125	L
Recapitulation of B cell differentiation in the central nervous system of patients with multiple sclerosis	10.1073/pnas.0402455101	15263096	243	L
Unveiling the enigma of the CNS as a B-cell fostering environment	10.1016/j.it.2005.02.009	15866238	59	F
Autologous stem cell transplantation as rescue therapy in malignant forms of multiple sclerosis	10.1191/1352458505ms1181cr	15957523	56	L
Human mesenchymal stem cells modulate B-cell functions	10.1182/blood-2005-07-2657	16141348	998	L
Immunoregulatory function of mesenchymal stem cells	10.1002/eji.200636416	17013987	366	F
Human mesenchymal stem cells promote survival of T cells in a quiescent state	10.1634/stemcells.2007-0068	17395776	149	L
Mesenchymal stem cells: a new strategy for immunosuppression?	10.1016/j.it.2007.03.001	17400510	315	F
Reciprocal interactions between human mesenchymal stem cells and ¿¿ T cells or invariant natural killer T cells	10.1634/stemcells.2008-0687	19096038	105	L
The therapeutic potential of mesenchymal stem cell transplantation as a treatment for multiple sclerosis: consensus report of the International MSCT Study Group	10.1177/1352458509359727	20086020	136	L
Primary varicella zoster infection associated with fingolimod treatment	10.1212/WNL.0b013e31821043b5	21403115	29	F
Mesenchymal stem cells for the treatment of multiple sclerosis and other neurological diseases	10.1016/S1474-4422(11)70121-1	21683930	156	F
Mesenchymal stem cells impair in vivo T cell priming by dendritic cells	10.1073/pnas.1103650108	21960443	139	L
Mesenchymal Stem Cells Shape Microglia Effector Functions Through the Release of CX3CL1	10.1002/stem.1174	22821677	61	L
Reward responsiveness and fatigue in multiple sclerosis	10.1177/1352458512451509	22723570	11	L
Mesenchymal stem cells as treatment for MS progress to date	10.1177/1352458512464686	23124791	33	F

Project Title:
P3 solutions (preventive, predicitve and personalized) in neuroinflammation and neurodegenerative diseases driven by imaging and biological data.

Project Code: NET-2018-12366666-1

Principal Investigator: Uccelli Antonio

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale Policlinico San Martino

Project Type: WP PROJECT - 1

Title	DOI	PMID	Cit. **	P.*
Fumarates modulate microglia activation through a novel HCAR2 signaling pathway and rescue synaptic dysregulation in inflamed CNS	10.1007/s00401-015-1422-3	25920452	33	L
Dysregulation of regulatory CD56(bright) NK cells/T cells interactions in multiple sclerosis	10.1016/j.jaut.2016.04.003	27157273	13	L
IFN¿ orchestrates mesenchymal stem cells plasticity through STAT1, STAT3 and mTOR pathways	10.1016/j.jaci.2016.09.004	27670240	0	L
Teriflunomide treatment reduces B cells in patients with MS	10.1212/NXI.0000000000000403	29082295	1	L

* Position: F=First L=Last C=Corrispondent

** Autocertificated

For evaluation CV

Title	DOI	PMID	Cit. *
X-Ray Phase Contrast Tomography Reveals Early Vascular Alterations and Neuronal Loss in a Multiple Sclerosis Model	10.1038/s41598-017-06251-7	28724999	4
NG2, a common denominator for neuroinflammation, blood-brain barrier alteration, and oligodendrocyte precursor response in EAE, plays a role in dendritic cell activation	10.1007/s00401-016-1563-z	27026411	4
T-cell trafficking in the central nervous system	10.1111/j.1600-065X.2012.01140.x	22725964	73
Intravenous mesenchymal stem cells improve survival and motor function in experimental amyotrophic lateral sclerosis	10.2119/molmed.2011.00498	22481270	69
Surrogate endpoints for EDSS worsening in multiple sclerosis. A meta-analytic approach	10.1212/WNL.0b013e3181ea15aa	20574036	80
C-C chemokine receptor 6-regulated entry of T(H)-17 cells into the CNS through the choroid plexus is required for the initiation of EAE	10.1038/ni.1716	19305396	611
Mesenchymal stem cells in health and disease	10.1038/nri2395	19172693	1617
Mesenchymal stem cells effectively modulate pathogenic immune response in EAE	10.1002/ana.21076	17387730	335
Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy	10.1182/blood-2005-04-1496	15905186	992
Prevention of autoimmune demyelination in non-human primates by a cAMP-specific phosphodiesterase inhibitor	10.1073/pnas.92.8.3601	7536938	163

* Autocertificated

Project Title:
P3 solutions (preventive, predicitve and personalized) in neuroinflammation and neurodegenerative diseases driven by imaging and biological data.

Project Code: NET-2018-12366666-1

Principal Investigator: Uccelli Antonio

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale Policlinico San Martino

Project Type: WP PROJECT - 1

Grant

Funded Institution / Country	Year	Title	Position in Projects
Compagnia di San Paolo - IT	2016	Studio dell¿effetto immunomodulante e neuroriparativo delle cellule staminali mesenchimali in pazienti con sclerosi multipla	Coordinator
ERA-NET - Call EraCoSysMed	2016	Personalizing health care in Multiple Sclerosis using systems medicine tools ¿ Sys4MS	Collaborator
MOTOR NEURON DISEASE ASSOCIATION - UK	2016	Exosome-shuttled miRNAs as mediators of the therapeutic effect of mesenchymal stem cells in ALS	Coordinator
FONDAZIONE ITALIANA SCLEROSI MULTIPLA (FISM)	2016	Targeting terapeutico dell'attività e dell'espressione di REST allo scopo di ridurre la neurodegenrazione ed i deficit sinaptici in modelli di EAE cronica	Coordinator
FONDAZIONE CARIPLO	2015	Aged induced hematopoietic and neurogenic dysfunctions contribute to the worse outcome	Coordinator
GRANT FOR MULTIPLE SCLEROSIS INNOVATION (GMSI)	2015	Driving microglia metabolism toward remyelination and restoration of brain damage in multiple sclerosis	Coordinator
FONDAZIONE CARIGE	2012	MEsenchymal StEm cells for Multiple Sclerosis (MESEMS)	Coordinator
ITALIAN MINISTRY OF HEALTH	2011	Preclinical evaluation of the NAMPT inhibitor FK866 for the treatment of autoimmunity and lymphoblastic leukemia	Coordinator
FONDAZIONE ITALIANA SCLEROSI MULTIPLA (FISM)	2011	Progetto Speciale Cellule Staminali	Coordinator
MIUR-PRIN	2009	Identification of new sources of stem cells for the treatment of multiple sclerosis	Coordinator

Employment contract extension:

(Data changed during the moratorium period)

Project Title: P3 solutions (preventive, predicitve and personalized) in neuroinflammation and neurodegenerative diseases driven by imaging and biological data.

Project Code: NET-2018-12366666-1

Principal Investigator: Uccelli Antonio

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale Policlinico San Martino

Project Type: WP PROJECT - 1

Biographical Sketch Contributors 1

Name: Marini Cecilia

Institution: Ospedale Policlinico San Martino
Department/Unit: CNR Institute of Bioimages and Molecular Physiology
Position Title: Co-PI

Education/Training - Institution and Location	Degree	Year(s)	Field of study
SSSUP Sant¿Anna University Pisa	Post-Doc school	1997	Clinical Pathophysiology
University of Florence	PhD	1994	Clinical Pathophysiology
University of Florence	Medical Degree	1988	Medical School

Personal Statement:

In the stting of the project my role will be dedicated to collect and analyze PET/CT data and their harmonization for storage.

Institution	Division / Research group	Location	Position	From year	To year
CNR Institute of Bioimages and Molecular Physiology	Bioimaging	Milan	Biomedical Researcher	2008	2018
CNR Institute of Clinical Physiology Pisa, Italy	Coronary gourp	Pisa	Biomedical Researcher	1998	2006

Awards and Honors

Official H index: 22.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 7103180663

ORCID ID: 0000-0003-1682-578X **RESEARCH ID:** ---

Awards and Honors:

	Project Title: P3 solutions (preventive, predicitve and personalized) in neuroinflammation and neurodegenerative diseases driven by imaging and biological data.
Project Code: NET-2018-12366666-1	**Principal Investigator:** Uccelli Antonio
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale Policlinico San Martino

Project Type: WP PROJECT - 1

Expertise Research Collaborators

Selected peer-reviewed publications of the Research Group / Collaborators

Collaborator	Title	DOI	PMID	Cit. *
Marini Cecilia	A PET/CT approach to spinal cord metabolism in amyotrophic lateral sclerosis	DOI: 10.1007/s00259-016-3440-3	27421971	3
Marini Cecilia	Fasting induces anti-Warburg effect that increases respiration but reduces ATP-synthesis to promote apoptosis in colon cancer models	10.18632/oncotarget.3688	25909219	35
Marini Cecilia	Direct inhibition of hexokinase activity by metformin at least partially impairs glucose metabolism and tumor growth in experimental breast cancer	10.4161/cc.26461	24240433	49
Marini Cecilia	Metformin impairs glucose consumption and survival in Calu-1 cells by Direct Inhibition of Hexokinase-II	10.1038/srep02070	23797762	35
Marini Cecilia	Metformin selectively affects human glioblastoma tumor-initiating cell viability: A role for metformin-induced inhibition of Akt	10.4161/cc.23050	23255107	90
Marini Cecilia	Mesenchymal stem cells impair in vivo T-cell priming by dendritic cells	10.1073/pnas.1103650108	21960443	139
Marini Cecilia	Diabetes impairs the vascular recruitment of normal stem cells by oxidant damage, reversed by increases in pAMPK, Heme Oxygenase-1, and Adiponectin	10.1634/stemcells.2008-0800	19038792	64
Marini Cecilia	Myocardial contrast echocardiography versus dobutamine echocardiography for predicting functional recovery after acute myocardial infarction treated with primary coronary angioplasty DOI: 10.1016/S0735-1097(96)00400-7	10.1016/S0735-1097(96)00400-7	8962551	137
Marini Cecilia	Prognostic value of dipyridamole echocardiography early after uncomplicated myocardial infarction: A large-scale, multicenter trial	10.1016/0002-9343(93)90357-U	8259778	171
Marini Cecilia	Stress Echocardiography and the human factor: The imortance of being expert.	10.1016/S0735-1097(10)80182-2	1993786	428

* Autocertificated

Project Title:
P3 solutions (preventive, predicitve and personalized) in neuroinflammation and neurodegenerative diseases driven by imaging and biological data.

Project Code: NET-2018-12366666-1

Principal Investigator: Uccelli Antonio

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale Policlinico San Martino

Project Type: WP PROJECT - 1

Grant

Funded Institution / Country	Year	Title	Position in Projects	Collaborator
ARISLA Associazione Italiana per la Ricerca sulla Sclerosi Laterale Amiotrofica. Ice Bucket call	2016	Computational analysis of Spinal cord metabolism in Amyotrophic Lateral Sclerosis	Collaborator	Marini Cecilia
Compagnia di San Paolo	2016	Impact of metformin treatment on diagnostic accuracy of PET/CT imaging in cancer patients	Coordinator	Marini Cecilia
Flagship program INTEROMICS of The National Council of Research (CNR)	2015	¿LANCELOT¿ ¿Intercellular and cell-environment signaling in B-Cell Chronic Lymphocytic Leukemia: a new therapeutic window and integration with imaging¿.	Coordinator	Marini Cecilia

Total proposed budget (Euro)

Costs	TOTAL BUDGET	Co-Funding	Project costs proposed to funding Organization (no MOH request)	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1a Staff Salary	155.000,00	155.000,00	0,00	not permitted	0,00
1b Researchers' Contracts	225.000,00	0,00	135.000,00	90.000,00	35,29
2 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00	0,00
3a Supplies	0,00	0,00	0,00	0,00	0,00
3b Model Costs	0,00	0,00	0,00	0,00	0,00
3c Subcontracts	12.000,00	0,00	0,00	12.000,00	4,71
3d Patient Costs	0,00	0,00	0,00	0,00	0,00
4 IT Services and Data Bases	47.300,00	30.000,00	0,00	17.300,00	6,78
5 Publication Costs	2.600,00	0,00	0,00	2.600,00	1,02
6 Convegni	1.300,00	0,00	0,00	1.300,00	0,51
7 Travels	1.300,00	0,00	0,00	1.300,00	0,51
8 Overheads	40.500,00	0,00	15.000,00	25.500,00	10,00
9 Coordination Costs	105.000,00	0,00	0,00	105.000,00	41,18
Total	590.000,00	185.000,00	150.000,00	255.000,00	100,00

Report the Co-Funding Contributor:

Co-Funding Ospedale Policlinico San Martino

Co-Funding CNR institute of Bioimages and molecular physiology (in agreement with Ospedale Policlinico San Martino)

	Project Title: P3 solutions (preventive, predicitve and personalized) in neuroinflammation and neurodegenerative diseases driven by imaging and biological data.
Project Code: NET-2018-12366666-1	**Principal Investigator:** Uccelli Antonio
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale Policlinico San Martino

Project Type: WP PROJECT - 1

Budget Justification	
1a Staff Salary	Salaries of the PI Prof. A. Uccelli and the Co PI Cecilia Marini, CNR Researcher co-funded by the Institute according to a formal agreement
1b Researchers' Contracts	Research contracts for 1 medical researcher for the duration of the project (in charge ti MOH); Research contracts for 1 ICT Specialist for two years
2 Equipment (Leasing - Rent)	None
3a Supplies	None
3b Model Costs	None
3c Subcontracts	Legal advice and support for CPGR
3d Patient Costs	None
4 IT Services and Data Bases	Software licences for data analysis and communications. Cofunded sum in IT and database technology represents the use of available softwrae license and PACS terabytes provided by Ospedale Policlinicao San Martino.
5 Publication Costs	Cost for open access publications
6 Convegni	Data communication in international congresses
7 Travels	Travels related to the project activities between the different centers
8 Overheads	Indirect and general costs
9 Coordination Costs	10% of each WP's MOH budget will be used for coordination costs related to travels and meetings to ensure data collection, analysis and appropriate conclusions

Project Title: P3 solutions (preventive, predicitve and personalized) in neuroinflammation and neurodegenerative diseases driven by imaging and biological data.	
Project Code: NET-2018-12366666-1	**Principal Investigator:** Uccelli Antonio
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale Policlinico San Martino

Project Type: WP PROJECT - 1

Ministero della Salute Direzione Generale della Ricerca Sanitaria e Biomedica e della Vigilanza sugli Enti **BANDO RICERCA FINALIZZATA 2018** **esercizio finanziario anni 2016-2017**	**Project Title:** P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.
Project Code: NET-2018-12366666-2	**Principal Investigator:** giometto bruno
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Provincia autonoma Trento

Project Type: WP PROJECT - 2

Major Diagnostic Category*: Neurologia

Project Classification IRG: Bioengineering Sciences and Technologies

Project Classification SS: Biodata Management and Analysis - BDMA

Project Keyword 1: Methods for data analysis including: Numerical, statistical, mathematical and theoretical approaches to design and interpretation of large-scale studies such as methods for pattern discovery, data mining, sequence prediction, biomarker identification, therapeutic drug design and high throughput analyses; computational methods for organizing, maintaining, and integrating biological datasets and for large scale data modeling and simulations.

Project Keyword 2: Database technologies and methods for data management, data representation, data capture, data integrity and validation

Project Keyword 3: Brain Disorders and Clinical Neuroscience

Project duration (months): 36

Project Request: **Animals:** ☐ **Humans:** ☒ **Clinical trial:** ☐

The object/s of this application is/are under patent copyright Y/N: ☐

Investigators, Institution and Role in the Project

	Co-PI	Key Personnel	Institution/Org./Pos.	Role in the project	Birth Date
1	X	Poretto Valentina	Azienda Provinciale per i Servizi Sanitari, TRENTO	Co-PI	27/10/1987
2		Malaguti Maria Chiara	Azienda Provinciale per i Servizi Sanitari, TRENTO	Expert Research Collaborator	10/05/1976

Overall Summary

The present project aims at applying recent advancements in Machine Learning algorithms (including Deep Learning) for secondary use of EHR and clinical data, to better understand diseases evolution and establish patient trajectories (personalised medicine). The project will take advantage of a standardised approach for collecting / analyzing a broad amount of information pertaining to medical conditions (e.g. symptoms, diagnostic and therapeutic measures) from different centers. A retrospective study will provide the basis to fine-tune the procedures and know-how to be applied in a perspective study piloting exercise.
Proper technical infrastructure (privacy by design and secure exchange of data) will be guaranteed.

The outcome of the project will be the availability of multi-site harmonized database plus the availability of integrated / quantitative indexes applicable in daily clinical practice for diagnosis and treatment of neuroinflammatory and neurodegenerative disorders.

Background / State of Art

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.
Project Code: NET-2018-12366666-2	**Principal Investigator:** giometto bruno
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Provincia autonoma Trento

Project Type: WP PROJECT - 2

In the last decades neuroinflammatory and neurodegenerative disorders gained a major role among neurological disease due to their increasing prevalence and current availability of various therapeutic options. In addition, different underlying pathological processes contribute to the development of these diseases, thus resulting in a wide spectrum of clinical expressions. It follows that several factors should be taken into account in treatment option choice, that should be tailored to the individual clinical profile of each patient, which can also vary along the course of disease due to many conditions (i.e. patient¿s compliance, response to treatment, drug side effects..).
To achieve this aim and capture the complex and detailed clinical heterogeneity of these disorders, a large amount of data is required and therefore a single-center experience might not be sufficient.
Consequently, there is a growing interest in collecting and then analyzing a broader amount of information pertaining to medical conditions (symptoms as well as diagnostic and therapeutic measures) from different centers, aiming to better track and predict each disease course and to apply a personalized medicine approach.
Nevertheless, up to now few studies focused on data-driven approach in neurological disorders and this should be attributable to the lack of homogeneity and standardization among different centers, particularly concerning instrumental evaluation. With reference to both neuroinflammatory and neurodegenerative diseases, studies mainly drove their attention on genetic and biochemical background, while poor data are currently available as regard to a more comprehensive approach, including also clinical and instrumental evaluation (Dinov et al PlosOne 2016; Ziemssen et al BMC Neurol 2016).
As a consequences, there is the need to share clinical and instrumental information from different centers in order to create a common platform of data, that will serve as starting point to create predictive models of neuroinflammatory and neurodegerative disorders which can then be applied in clinical practice

In terms of predictive modelling and patient sub-typing for neuroinflammatory and neurodegenerative diseases, recent advancements in Machine Learning algorithms (and especially Deep Learning) have created vast potential for secondary use of EHR and other clinical data in order to better understand evolution of diseases and establish patient trajectories. A Systematic Review by Osmani et al. [Osmani, 2018] has found that a number of studies have reported results that provide unprecedented insight into diseases through the use of deep learning methods to analyse EMR data. In this respect discoveries from data-driven, EHR-based research can lead to actionable findings, such as identifying medication adverse reactions [Kahn et al, 2010] [Liu et al, 2013] and predicting future disease risk [Bates et al, 2014]. Genetic and genomic data are often linked with clinical data via hospital-affiliated biobanks, which recruit individuals from the visiting patient population to obtain and ¿bank¿ their genetic data. This approach has led to the development of fields of research such as phenomewide association studies (PheWAS) [Denny at al, 2013], where a traditional genome-wide association study (GWAS) analysis is performed on a large retrospective hospital cohort allowing more freedom in phenotype selection. Recently, using whole-exome sequencing and a linked EMR system for over 50,000 participants, the DiscovEHR study revealed the clinical impact and phenotypic consequences of functional variants [Dewey et al, 2016]. Adding in medication RNA expression signatures further facilitates pharmacological discoveries, ranging from drug discovery [Dudley et al, 2010] and repurposing [Hodos et al, 2016; Dudley et al 2011; Dudley et al, 2011] to pharmacogenomics [Van Driest et al, 2016; Roden et al, 2012].

Hyphotesis and Specific AIMS

Hyphotesis and Significance:
Parkinson¿s disease (PD) represents one of neurodegenerative diseases with higher prevalence predominantly in elderly individuals. The number of subjects older than 50 with PD in the five most densely populated countries in Western EU and it has been estimated to increase up to 9.3 million by 2030. PD is a degenerative disease that still leads to severe disability,

despite available treatments. It is associated with an increase in mortality and disability, and with considerably high costs, implying a substantial burden for patients and their families / caregivers, and a heavy socioeconomic load. Many countries will face a future of unsustainable demands on limited healthcare resources. PD worldwide prevalence has been recently described in a meta-analysis, including subjects enrolled from 1985 to 2010. The meta-analysis estimated a prevalence of PD of 31.5 cases per 10,000. Epidemiological studies on PD in the Province of Trento are of great interest as they can afford many useful data. In this context defining the geographic distribution of PD in the Province of Trento can open new perspectives in the complex pathogenic mechanisms of PD, including possible interactions between genetic and environmental factors. Indeed descriptive studies allow designing analytical studies aimed at identifying potential risk factors and/or protective factors associated to the onset of the disease. The aims of the present project were: (1) to provide an estimate of the prevalence and clinical features of PD in Trentino, Italy; (2) to collect information on therapy and clinical follow-up; (3) to define the geographic distribution of PD in the different areas (valley communities) of Trentino and (4) to correlate genotype to clinical features and geographic distribution. Neuroinflammatory disorders include a broad spectrum of clinical conditions, among which, Multiple Sclerosis (MS) constitutes the most relevant disease in terms of prevalence. According to the estimates of WHO/MSIF MS Atlas, it affects 2.3 million people worldwide, with over 100.000 in Italy (Battaglia et al) and it represents the most common cause of non-traumatic disability in young adults. Its incidence and prevalence were observed to be progressively and significantly increased during the last decades, which can be mainly due to an improvement in early diagnosis of the disease, but it can also attributable to environmental exposure changes. In addition to neuroinflammation, MS recognizes also a neurodegenerative etiology which is primarily responsible for disability progression. As result, MS is characterized by a highly heterogeneity of clinical and neuroradiological expressions, with pronounced inter-individually as well as intra-individually variability. In the last three decades, MS disease course has markedly changed due to the use of disease-modifying treatment, which proved to slow down the conversion from relapsing-remitting to progressive phase. The spectrum of therapeutic possibilities is widening, thus leading to an increasing need to ensure proper treatment for the patient. This requires clear profiling of the individual patient, definition of clinical criteria for responsiveness and/or treatment failure and collection of real world data in MS patient care. In addition, there are others (rare) neuroinflammatory diseases: we are actively collecting clinical data and looking for diagnostic markers. Differential diagnosis includes viral encephalitis and other transmissible disorders very common in Trentino.

Preliminary Data:

According to recent data, we expect in the Province of Trento more than 1,000 PD cases (tot population: 500,000). We regularly follow more than 1,000 outpatients affected by idiopathic Parkinson disease or other Parkinsonism, with a high rate of positive familiar history. The peculiar geography of the Trentino allows the study of familiar cases of PD and the possible interactions between genetic and environmental factors.

As regard to MS, over 800 people are affected by MS and their number is expected to increase according to available data. In outpatients clinic in Trento and Rovereto (the two main cities in the province) we collect several clinical and para-clinical data finalized to the correct diagnosis and treatment. Notably, with reference to treatment options, 200 patients receive monoclonal antibodies treatment.

Establishment of predictive models will make use of any available clinical and biological data. As the study is of exploratory nature, a preliminary analysis will be carried out to identify the most relevant parameters, guided also by the knowledge from the clinical partners. Once the set of relevant parameters is identified, the process will become iterative, in such way that predictive performance of each set of data will be iteratively measured and data set with the best performance will be

selected. Pre-processing of data will be carefully evaluated to ensure they are transformed in the formats suitable for the learning algorithms.

Specific Aim 1:

Identification and collection of a core set of standardized data
The first aim will be to identify a set of common indicators to allow collection of common data, including: imaging, clinical data (including¿ if available ¿ data on cognitive performance of the patient), biological data (e.g. genetic) and therapy information (e.g. timing and type of therapy). The indicators will be selected to allow comparability among regions.

Specific Aim 2:

Establishing predictive models (modeling symptoms, therapy data and outcomes data) by using retrospective data analysis
The second aim will be to establish predictive models through the use of the abovementioned datasets (common data from the different sites). Using retrospective data, the aim is to model symptoms, therapy and outcome data to identify effective algorithms for innovative diagnostic, prognostic and therapeutic pathways, optimising treatments.
Proper technical infrastructure (privacy by design and secure exchange of data) will be guaranteed.

Specific Aim 3:

Prospective study protocol piloting
The third aim is to pilot a prospective study protocol, on the basis of the outcomes of the first component. The protocol piloting will include a perspective study gathering data on imaging, clinical-biological and therapy information. This will result in a set of recommendations on (i) data protection/ privacy issues and (ii) predictive modelling from big data studies in this field, with a focus on data integration. The pilot study will also offer elements for transferability and sustainability of the big data analytics approach to in other fields.

Experimental Design Aim 1:

The first aim will be reached by (i) a Structured Mapping Exercise and/or (ii) Experts¿ (Clinical and IT) Consensus on the types of data on imaging, clinical-biological data and therapy information, available across study sites.

Experimental Design Aim 2:

Through a retrospective study, big data specific algorithms will be tested using data driven artificial intelligence approaches. Such approaches will be adapted according to the type of disease considered. Considering Parkinson, for instance, variables on (i) Symptoms (ii) Therapy (iii) Biological Data will be modeled according to the defined outcome (proper treatment). This will allow a more appropriate patient profiling and a more tailored therapy administration (type of treatment and timing) for the specific patient¿s profile. Similar experimental structure will be adopted in case of Multiple Sclerosis. The Data Experiment Plan (DAP) adopted by the FDA¿s led MAQC study will be adopted to control risk of selection bias and reduce variability in algorithm selection. Whenever possible, public data will be used to train initial versions of the

algorithms.

Experimental Design Aim 3:
The third component of the study will be based on a prospective design. The operational structure will be similar to the previous project component (retrospective study). On the basis of a fine-tuned set of indicators, variables on (i) Symptoms (ii) Therapy (iii) Biological Data will be prospectively collected and then modeled according to the defined outcome (proper treatment). The possibility of a case-control approach will be also considered when collecting prospective data for different patients¿ categories. Privacy-by-design will include secure and trustable dataset sharing, and traceability of all data analytics steps by means of tamperproof audit logging (as required by the GDPR), in particular by exploring blockchain technology. Specific care will be taken in securing patients¿ privacy in deep learning model training.

Picture to support preliminary data:
Data and study design_20180511.jpg

Metodologies and statistical analyses:
Methods for data analysis will include: numerical, statistical, mathematical and theoretical approaches to design and interpretation of large-scale multi-site studies such as methods for pattern discovery, data mining, sequence prediction, biomarker identification, therapeutic drug design and high throughput analyses; computational methods for organizing, maintaining, and integrating biological datasets and for large scale and multi-site data modeling and simulations.
In addition to standard statistical methodology, a large part of this study will make use of recent advances in AI methods, specifically Deep Learning in order to establish predictive models and test their performance. Deep learning is especially suitable for analysis of clinical and biological data due to their structure being high-dimensional, heterogeneous with having temporal dependencies, sparsity and irregularity. Deep Learning also offers the state of the art in embedding and integrating clinical phenotypes and multi-modal data.

Expected outcomes:
Through project implementation, it is expected to reach the following outcomes:
(i) A set of integrated indexes, to allow (a) data comparison between different Italian regions and (b) implementation of innovative diagnostic, prognostic and therapeutic algorithms / optimized treatments for neurodegenerative and neuroinflammatory diseases;
(ii) A large multi-site dataset including standardised, clinical, imaging and biological data on for neurodegenerative and neuroinflammatory diseases to inform health care policies in selected Italian regions;
(iii) A piloted validated big data modeling and effective algorithms for innovative diagnostic, prognostic and therapeutic pathways
(iv) A data protection / privacy protocol and algorithms to inform big data modeling on this type of clinical data for multi-site research
The outcomes (i) and (ii) will respond to the need of comparable data and indicators to allow data driven artificial intelligence approaches. The outcome (iii) will allow innovative algorithms to optimize treatments for neurodegenerative and neuroinflammatory diseases. The fact that the outcome (iii) will be based on a shared common dataset from different regions will reinforce the transferability of the modeling approaches and results to other regions.

Risk analysis, possible problems and solutions:
Difficulty in identifying relevant common items for all sites.
Measures: a core version of the items¿ list will be developed allowing partners to monitor and contribute to the items identification

Difficulties in collecting data/datasets.
Measures: active involvement IT and clinical staff since the beginning of the project

Problems in managing data.
Measures: specific standard procedures will be adopted and process will be monitored

Threats of withdrawal by partners.
Measures: replacement by another organisation from the same region. If not possible, redistribution among partners after negotiation of tasks and duties.

Significance and Innovation

To date there are a few studies that take into account a comprehensive (clinical, instrumental and biochemical) approach to neurological disease based on big data analysis. On the other hand, the increasing interest in collecting such information together with the usefulness of its clinical application, has recently led to create shared dataset among to various centers, such as National Parkinson Foundation Parkinson¿s Outcomes Project in United States. We therefore aim to aggregate and harmonize all the data collected by a network of different Italian hub-centers, in order to provide integrated and quantitative indexes that might be applied in daily clinical practice for diagnosis and treatment of neuroinflammatory and neurodegenerative disorders.

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.
Project Code: NET-2018-12366666-2	**Principal Investigator:** giometto bruno
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Provincia autonoma Trento

Project Type: WP PROJECT - 2

Description of the complementary and sinergy research team

Each region participating in the network will contribute to the WP according to the specific interest and in line with the regional priorities. From a scientific viewpoint, the teams from different regions involved in this WP have specific and scientifically robust background in the field of neurodegenerative and neuroinflammatory diseases), whilst the specific competences of FBK guarantee a top-quality international experience in the field of big data modeling, including bioinformatics analysis and deep learning. In this context, the WP partners represent an ideal complementary team, mixing clinical and big data /data analytics expertise.
In terms of synergy, each partner will work on specific clinical issues, sharing data with the other regions on the diseases taken into consideration in this project. This will ensure on one side that each region will focus on variables and diseases which are relevant for the local level, and on the other side this will ensure a multi-faced approach, allowing the validation exercise of big data algorithms modeling on a different set of data (pertaining to a number of diseases, ranging from neurodegenerative to neuroinflammatory diseases).

The data sharing will also contribute to a more robust modeling for the diseases, in each site.

In terms of synergy, the multi-site dataset including standardised, clinical, imaging and biological will also represent common platform and the opportunity to develop common know-how among regions.

Training and tutorial activities

To promote exchange of experiences / know-how and to ensure a strict common background in terms of analytic / clinical transferability of the project results, 2 training sessions will be planned - if in line with the participating regions priorities.
i. Training on big data analysis (planning / implementing big data projects/analysis);
ii. Training on proper use of big data into clinical decision making process and diagnosis & treatment pathways, with specific focus on (but not only) Parkinson and Multiple Sclerosis.

The training sessions will be strategically delivered during project implementation to maximize knowledge and know-how sharing and improvement among project partners. Considering budget issues, both training components can be either remote-training or on-site (physical meeting) training.

In terms of tutorial activities, partner in charge of the big data modeling will tutor other participating regions ¿ if needed ¿ during the data collection and analysis process.

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Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Provincia autonoma Trento

Project Type: WP PROJECT - 2

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Rocca et al. Familial aggregation of Parkinson's disease. Ann Neurol. 2004
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Dinov et al. Predictive Big Data Analytics. PLoS One. 2016 Aug 5;11(8):e0157077.
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Timeline / Deliverables / Payable Milestones

A common set of data will be identified across participating regions. This preliminary phase will be the basis for the final set of data/indicators to be collected.
From M3 to 9, standardized set of data will be collected (retrospective study), and from M9 the common dataset will be finalized and made available for analysis (M10-18). At M18 the dataset/analysis will be finalized, and this will be the core deliverable for the first phase.
On this basis, from M19 to M30 a new data collection system will be structured for a prospective study.
From M28 to M34, the prospective data will be analyzed. The analysis will start during the data collection using preliminary data, to speed up the analysis process.
At M34 the common dataset (based on the prospective data study) will be made available, representing a core deliverable of the project.
As final deliverables (M36) data protection/ privacy and modelling recommendations/reports will be made available.

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.
Project Code: NET-2018-12366666-2	**Principal Investigator:** giometto bruno
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Provincia autonoma Trento

Project Type: WP PROJECT - 2

Milestones 18 month

During the first half of the project (M1-18), the kick off meeting will be organized to set up the procedures and fine-tune the project structure
M1-3: common set of data
M3 (Milestone): the final set of data is identified (M)
M3-9: data collection (retrospective study)
M9: the common dataset for retrospective study is finalized and available (O)
M10-18: analysis of retrospective data
M18 (Milestone): the updated set of data ¿ based on the results from the retrospective data ¿ is finalized (M)

Milestones 36 month

M19-30: piloting of data collection system (prospective study) using the updated set of data
M28-34: analysis of prospective data (to be started during the data collection using preliminary data)
M28: analysis plan for the prospective data will be fine-tuned
M34: common dataset available (O), based on the prospective study
M34: preliminary results are discussed / validated
M36: reports, data protection/ privacy and modelling recommendations (O).

Gantt chart

Trentino_gantt_RF2018.pdf

Equipment and resources available

All patients¿ clinical evaluation has been assessed by means of internationally-approved scales (i.e. Expanded Disability Status Scale for MS and Unified Parkinson¿s Disease Rating Scale). Instrumental diagnostic tools include standard-field MRI scan (1.5 T), cerebrospinal fluid examination and storage.
FBK¿s data center includes the super-computer infrastructure KORE, which is a large High Performance Computing system where Deep Learning algorithms can be designed and predictive models trained and tested. As of April, 2018, KORE consists of 143 computing nodes, 2 file servers, 1 logon server and 1 management server, for a total of 1,436 computing cores. Dedicated to Deep Learning training, KORE also provides 36 GPU cards (24 NVIDIA Tesla K80, 4 Tesla V100, 8 GTX1080Ti) for GPGPU computing. Scientific resources also include a Storage Area Network for a total of 439 TB. Notably, Physical access to the datacenter is limited to authorized System Administrators only and is controlled by both PIN and biometric authentication. In addition, FBK can also make use of cloud resources (such as Microsoft Azure or Google Compute Engine) through various agreements with these providers. Platforms for predictive methods in Bioinformatics from high throughput data have been developed in the context of a 10-year collaboration with the US FDA as bioinformatics team specialized on the identification of predictive biomarkers from high throughput omics and disease phenotypes.

Subcontract
Subcontract will be used for external services, for agencies / services with specific expertise on (i) national/international project management and (ii) neuroinflammatory and neurodegenerative disorders, instrumental diagnostics, statistical modelling, big data technologies and analysis, to provide support in report writing, revision of publications to be submitted for peer review, data handling, and general correspondence.

Translational relevance and impact for the National Health System (SSN)

To date there are a few studies that take into account a comprehensive (clinical, instrumental and biochemical) approach to neurological disease based on big data analysis. On the other hand, the increasing interest in collecting such information together with the usefulness of the clinical application that can be obtained from them, has recently enabled to create shared dataset among to various centers, such as National Parkinson Foundation Parkinson¿s Outcomes Project in United States. We therefore aim to aggregate and harmonize all the data collected by a network of different Italian hub-centers, in order to provide integrated and quantitative indexes that might be applied in daily clinical practice for diagnosis and treatment of neuroinflammatory and neurodegenerative disorders.

Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.

Project Code: NET-2018-12366666-2

Principal Investigator: giometto bruno

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Provincia autonoma Trento

Project Type: WP PROJECT - 2

PRINCIPAL INVESTIGATOR PROFILE

Name	Institution	Provincia autonoma Trento
giometto bruno	Department/Unit	Azienda Provinciale per i Servizi Sanitari, Trento
	Position Title	Neurology Director

Personal Statement

My role as PI in this project, focused on the improvement of neuroinflammatory and neurodegenerative disease management, will be to lead workpackage 2 and generally oversee the smooth running of all WP activities. I will specifically be involved in coordination of data collection and consensus meetings to identify a set of common data elements on which to build a robust dataset to inform big data modeling; contributing to translating the findings into innovative diagnostic, prognostic and therapeutic pathways for future patient management; and contributing to the development of strategies to inform healthcare policies in selected Italian regions.

Education/Training - Institution and Location	Degree	Year(s)	Field of study
University of Verona	Residency	4	Neuropathology
University of Padova	Residency	4	Neurology
University of Padova	Medical Degree	6	Medicine and Surgery

Positions

Institution	Division / Research group	Location	Position	From year	To year
Trento General Ospital	Neurology	Trento	Director	2017	2018
St. Anthony's Hospital	Neurology	Padova	Director	2014	2017
Treviso General Hospital	Neurology	Treviso	Director	2003	2014
University of Padova	Neurology	Padova	Consultant	1994	2003

Official H index: 36.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 7003357148

ORCID ID: 0000-0003-2311-9752 **RESEARCH ID:** n.a.

Awards and Honors:

1989-present Member of Italian Society of Neuropathology (AINP)
1996-present Member of SIN since 1993, formerly Vice President, currently member of Board of Arbitrators
1998-present Member of Italian Neuroimmunology Association (AINI)
2002-present Member of the Paraneoplastic European Network
2015-present Member of the Subspeciality Scientific Panel for Neuroimmunology of European Association of Neurology (EAN)

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.
Project Code: NET-2018-12366666-2	**Principal Investigator:** giometto bruno
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Provincia autonoma Trento

Project Type: WP PROJECT - 2

Other CV Informations:

My professional activities are chiefly centred on general clinical neurology and neuroimmunology. My focus of study has been in inflammatory disorders with autoantibody markers, first in paraneoplastic neurological syndromes (in which I coordinated two European projects) and presently in autoimmune encephalitis. I am currently coordinating neurological care for the entire province of Trento, with the role of single clinical director, and have organized the clinical pathway for patients with Parkinson¿s disease. Trento Hospital is also a reference centre for autoimmune neurological diseases with antibody markers.

Project Title:
P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.

Project Code: NET-2018-12366666-2

Principal Investigator: giometto bruno

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Provincia autonoma Trento

Project Type: WP PROJECT - 2

Selected peer-reviewed publications of the PI

Valid for PI minimum expertise level

Title	DOI	PMID	Cit. **	P.*
Diagnostics of autoimmune encephalitis associated with antibodies against neuronal surface antigens.	10.1007/s10072-017-3032-4	29030767	1	L
Isaacs' syndrome with overlapping myopathy as the first manifestation of AL amyloidosis.	10.1007/s00415-016-8264-3	27699467	0	L
The possible involvement of mitochondrial dysfunctions in Lewy body dementia: a systematic review	10.11138/FNeur/2015.30.3.151	26346695	5	L
Uncommon relapse after post-herpes simplex encephalitis: an atypical case report.	10.1007/s13760-015-0475-3	25894351	3	L
Treatment for paraneoplastic neuropathies.	10.1002/14651858.CD007625.pub2	23235647	28	F
PNS Euronetwork. Spectrum of paraneoplastic disease associated with lymphoma.	10.1212/WNL.0b013e31820d62eb	21339498	55	L
Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers.	10.1001/archneurol.2009.341	20212230	145	F
Increased spontaneous activity of a network of hippocampal neurons in culture caused by suppression of inhibitory potentials mediated by anti-gad antibodies	10.1080/08916930701619565	18176866	29	L
Clinical, immunological and therapeutic aspects of autoimmune encephalitis.	10.2174/157488908783421465	18221237	6	L
Tremor of the mouth floor and anti-glutamic acid decerboxylase autoantibodies	10.1046/j.1468-1331.2003.00629.x	12940831	8	L
Cerebellar ataxia associated with anti-Glutamic Acid Decarboxylase Autoantibodies	10.1080/14734220309432	12882238	29	L
Neurological toxicity of Ifosfamide	10.1159/000073352	14586141	56	L
Glutamic acid decarboxylase autoantibodies and neurological disorders	10.1007/s100720200055	12536283	68	L
Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies: study of 14 patients	10.1080/14734220309432	11176960	29	L
Temporal lobe epilepsy associated with GAD antibodies	10.1016/S0140-6736(05)79192-3	9708763	72	F

Project Title:
P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.

Project Code: NET-2018-12366666-2

Principal Investigator: giometto bruno

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Provincia autonoma Trento

Project Type: WP PROJECT - 2

Title	DOI	PMID	Cit. **	P.*
Autoimmunity in Paraneoplastic Neurological Syndromes	10.1111/j.1750-3639.1999.tb00225.x	10219744	42	F
Folliculo-stellate cells of human pituitary adenomas : Immunohistochemical study of the monocyte/ macrophage phenotype expression	10.1159/000127163	9032773	24	F
Accumulation of Beta-Amyloid Precursor Protein in HIV-1 Encephalitis : Relationship with Neuropsychological Abnormalities	10.1002/ana.410420108	9225683	95	F
Detection of paraneoplastic anti-neuronal autoantibodies on paraffin-embedded tissues	10.1007/s004010050543	8922053	21	F
Anti-GABAergic neuron autoantibodies in a patient with Stiff-Man syndrome and ataxia.	10.1016/S0022-510X(96)00065-2	8981298	49	F

* Position: F=First L=Last C=Corrispondent

** Autocertificated

For evaluation CV

Title	DOI	PMID	Cit. *
Plasma exchange in pediatric anti-NMDAR encephalitis: A systematic review.	10.1016/j.braindev.2016.01.009	26926399	7
Safety of the first dose of fingolimod for multiple sclerosis: results of an open-label clinical trial.	10.1186/1471-2377-14-65	24690227	30
Glycine receptor antibodies in 2 cases of new, adult-onset epilepsy	10.1212/NXI.0000000000000016	25340068	2
A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study.	10.1016/S1474-4422(14)70051-1. Epub 2014 Apr 3. Erratum in: Lancet Neurol. 2015	24703753	100
Treatment for paraneoplastic neuropathies	10.1002/14651858.CD007625.pub2	23235647	28
Spectrum of paraneoplastic disease associated with lymphoma.	10.1212/WNL.0b013e31820d62eb	21339498	55
Screening for tumours in paraneoplastic syndromes: report of an EFNS Task Force.	10.1111/j.1468-1331.2010.03220.x	20880069	222
Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers.	10.1001/archneurol.2009.341	20212230	145
Recommended diagnostic criteria for paraneoplastic neurological syndromes	10.1136/jnnp.2003.034447	15258215	834
Autoimmunity in Paraneoplastic Neurological Syndromes	n.a.	10219744	42

* Autocertificated

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.
Project Code: NET-2018-12366666-2	**Principal Investigator:** giometto bruno
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Provincia autonoma Trento

Project Type: WP PROJECT - 2

Grant

Funded Institution / Country	Year	Title	Position in Projects
Veneto Region, Italy	2015	Piloting a clinical network to diagnose rapidly progressive dementias	Coordinator
PRIHTA, Italy	2010	Extending the surveillance system pilot in the Veneto Region for the collection of clinical data on patients with stroke admitted to 1st level stroke units and dedicated units in the Veneto Region.	Coordinator
Veneto Region, Italy	2009	Piloting a surveillance system to collect clinical data on patients with stroke admitted to 2nd level stroke units in the Veneto Region: a stroke registry	Coordinator
Ministry of Health, Italy	2009	Organization of a care pathway to prevent complications and improve quality of life in patients with Amiotrophic Lateral Sclerosis	Collaborator
European Commission, Belgium	2005	European network to integrate and strengthen the research into para-neoplastic neurological syndromes (PNS).	Coordinator
Ministry of Health, Italy	2002	Study and characterization of onco-neural antigens in Paraneoplastic Neurological Syndromes	Coordinator
European Commission, Belgium	2002	Paraneoplastic Neurological Syndromes (PNS) Clinical and Laboratory Aspects	Coordinator

Employment contract extension:

(Data changed during the moratorium period)

Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.

Project Code: NET-2018-12366666-2

Principal Investigator: giometto bruno

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Provincia autonoma Trento

Project Type: WP PROJECT - 2

Biographical Sketch Contributors 1

Name: Poretto Valentina

Institution: Azienda Provinciale per i Servizi Sanitari, TRENTO
Department/Unit: Department of Neurological Disorders
Position Title: Neurologist Attendent

Education/Training - Institution and Location	Degree	Year(s)	Field of study
University of Padua	Specialization in Neurology	4	Neurology
University of Padua	Degree in Medicine and Surgery (110/110 cum laude and mention of excellence)	6	Medicine and Surgery

Personal Statement:

Graduated in Medicine and Surgery at University of Padua in 2012 and completed a 4-year post-degree residency program in Neurology in 2017, showing particular interest in cerebrovascular and neuroinflammatory diseases. I have worked as neurologist-in-training at Multiple Sclerosis Center of Veneto Region in Padua, being actively involved in clinical trials and research projects

From April to-October 2016 I attended Professor Inglese neuroimaging laboratory at Icahn School of Medicine, Mount Sinai Hospital, New York, as research fellow.

Institution	Division / Research group	Location	Position	From year	To year
n.a.	Department of Neurosciences	Padua	Neurologist in training	2013	2017

Awards and Honors

Official H index: 5.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 53878347700

ORCID ID: 0000-0001-6517-0578 **RESEARCH ID:** n.a.

Awards and Honors:

n.a.

Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.

Project Code: NET-2018-12366666-2

Principal Investigator: giometto bruno

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Provincia autonoma Trento

Project Type: WP PROJECT - 2

Biographical Sketch Contributors 2

Name: Malaguti Maria Chiara

Institution: Azienda Provinciale per i Servizi Sanitari, TRENTO
Department/Unit: NEUROLOGY UNIT
Position Title: Research Expert Collaborator

Education/Training - Institution and Location	Degree	Year(s)	Field of study
University of Modena	Research fellow at neuroscience department	1	Peripheral neuropathies
Vita salute University Milan	Residency Program in Neurology	5	Neurology
Univeristy of Bologna	Degree in Medicine	6	Medicine and Surgery

Personal Statement:

My role as research collaborator will be to contribute with my expertise on Parkinson Diseases and Movement Disorders to WP2 and generally oversee the smooth running of all WP activities. I will specifically be involved in data collection and consensus meetings to identify a set of common data elements on which to build a robust dataset to inform big data modeling; contributing to translating the findings into innovative diagnostic, prognostic and therapeutic pathways for future patient management; and contributing to the development of strategies to inform healthcare policies.

Institution	Division / Research group	Location	Position	From year	To year
APSS Trento	Neurology Unit	Trento	consultant	2010	2018
NOCSAE Modena	Neurology Unit	Modena	consultant	2008	2010
University of Modena	Neuroscience department	Modena	Research grant	2007	2008

Awards and Honors

Official H index: 10.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 55955397400

ORCID ID: n.a. **RESEARCH ID:** n.a.

Awards and Honors:

n.a.

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.
Project Code: NET-2018-12366666-2	**Principal Investigator:** giometto bruno
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Provincia autonoma Trento

Project Type: WP PROJECT - 2

Expertise Research Collaborators

Selected peer-reviewed publications of the Research Group / Collaborators

Collaborator	Title	DOI	PMID	Cit. *
Poretto Valentina	A composite measure to explore visual disability in primary progressive multiple sclerosis.	10.1177/2055217317709620	28607759	0
Malaguti Maria Chiara	A novel homozygous PLA2G6 mutation causes dystonia-parkinsonism.	10.1016/j.parkreldis.2015.01.001	25601130	7
Poretto Valentina	The changing clinical course of multiple sclerosis: a matter of gray matter.	10.1002/ana.23882	23494723	37
Poretto Valentina	Cortical lesion load associates with progression of disability in multiple sclerosis.	10.1093/brain/aws246	23065788	95
Poretto Valentina	Low degree of cortical pathology is associated with benign course of multiple sclerosis.	10.1177/1352458512463767	23069877	21
Malaguti Maria Chiara	Amyotrophic lateral sclerosis and sarcoidosis: a difficult differential diagnosis.	10.3109/17482960903440767	20001490	1
Malaguti Maria Chiara	Bilateral vocal cord paralysis: a rare onset of amyotrophic lateral sclerosis.	10.1001/archneurol.2010.141	20625104	3

* Autocertificated

Grant

Funded Institution / Country	Year	Title	Position in Projects	Collaborator
n.a.	n.a.	n.a.	Collaborator	Malaguti Maria Chiara
n.a.	n.a.	n.a.	Collaborator	Poretto Valentina

Project Title:
P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.

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Principal Investigator: giometto bruno

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Provincia autonoma Trento

Project Type: WP PROJECT - 2

Total proposed budget (Euro)

Costs	TOTAL BUDGET	Co-Funding	Project costs proposed to funding Organization (no MOH request)	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1a Staff Salary	200.000,00	200.000,00	0,00	not permitted	0,00
1b Researchers' Contracts	331.000,00	0,00	200.000,00	131.000,00	49,02
2 Equipment (Leasing - Rent)	13.000,00	0,00	13.000,00	0,00	0,00
3a Supplies	49.000,00	0,00	2.000,00	47.000,00	17,59
3b Model Costs	0,00	0,00	0,00	0,00	0,00
3c Subcontracts	60.000,00	0,00	50.000,00	10.000,00	3,74
3d Patient Costs	25.000,00	0,00	0,00	25.000,00	9,36
4 IT Services and Data Bases	20.000,00	0,00	0,00	20.000,00	7,48
5 Publication Costs	4.500,00	0,00	2.000,00	2.500,00	0,94
6 Convegni	5.400,00	0,00	2.900,00	2.500,00	0,94
7 Travels	7.500,00	0,00	5.000,00	2.500,00	0,94
8 Overheads	51.711,11	0,00	24.988,89	26.722,22	10,00
9 Coordination Costs	0,00	0,00	0,00	0,00	0,00
Total	767.111,11	200.000,00	299.888,89	267.222,22	100,00

Report the Co-Funding Contributor:

Co-Funding Azienda Provinciale per i Servizi Sanitari di Trento
Co-Funding Fondazione Bruno Kessler (FBK)

(Data changed during the moratorium period)

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.
Project Code: NET-2018-12366666-2	**Principal Investigator:** giometto bruno
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Provincia autonoma Trento

Project Type: WP PROJECT - 2

Budget Justification	
1a Staff Salary	Staff' Salary includes Project Managers, MD/health care staff, researchers (including IT)
1b Researchers' Contracts	Researchers' contracts include health-care staff, project managers and reserchers (including IT) to implement project's activities
2 Equipment (Leasing - Rent)	None
3a Supplies	Supplies include consumables and health care service delivery, in line with the eligible costs as per project requirements
3b Model Costs	None
3c Subcontracts	Subcontracts are included for reporting and/or technical services
3d Patient Costs	Patient costs include medical examination/visits and follow-up visits, in line with the eligible costs as per project requirements
4 IT Services and Data Bases	Costs include software licenses and database
5 Publication Costs	Publication costs are foreseen to cover reports costs, submission/publication fees in peer reviewed and/or scientific journals, including open-access (if appropriate)
6 Convegni	Costs cover expenditures for training sessions (as per WP proposal) and dissemination
7 Travels	Travels includes costst for participation to meetings/scientific conferences
8 Overheads	Overheads inlcude fixed and indirect costs
9 Coordination Costs	None

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by imaging and biological data, with a focus on multiple sclerosis / auto-immune encephalitis and neurodegenerative movement disorders.
Project Code: NET-2018-12366666-2	**Principal Investigator:** giometto bruno
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Provincia autonoma Trento

Project Type: WP PROJECT - 2

Ministero della Salute Direzione Generale della Ricerca Sanitaria e Biomedica e della Vigilanza sugli Enti **BANDO RICERCA FINALIZZATA 2018** **esercizio finanziario anni 2016-2017**	**Project Title:** P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.
Project Code: NET-2018-12366666-3	**Principal Investigator:** Falini Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

Major Diagnostic Category*: Neurologia

Project Classification IRG: Bioengineering Sciences and Technologies

Project Classification SS: Biodata Management and Analysis - BDMA

Project Keyword 1: Methods for data analysis including: Numerical, statistical, mathematical and theoretical approaches to design and interpretation of large-scale studies such as methods for pattern discovery, data mining, sequence prediction, biomarker identification, therapeutic drug design and high throughput analyses; computational methods for organizing, maintaining, and integrating biological datasets and for large scale data modeling and simulations.

Project Keyword 2: Database technologies and methods for data management, data representation, data capture, data integrity and validation

Project Keyword 3: Brain Disorders and Clinical Neuroscience

Project duration (months): 36

Project Request: **Animals:** ☐ **Humans:** ☒ **Clinical trial:** ☐

The object/s of this application is/are under patent copyright Y/N: ☐

Investigators, Institution and Role in the Project

	Co-PI	Key Personnel	Institution/Org./Pos.	Role in the project	Birth Date
1	X	Scifo Paola Vittoria	IRCCS San Raffaele Scientific Institute, Department of Nuclear Medicine, Researcher	Coordination of image processing	15/02/1968

Overall Summary

Gliomas are a heterogeneous group of infiltrating glial neoplasms with variable biology and prognosis. Accurate determination of their grade, now gainfully incorporating molecular markers in the routine histopathological diagnosis, is pivotal to select appropriate treatment strategies.
Thus, understanding how these molecular phenotypes are reflected in noninvasive imaging is becoming increasingly relevant, and the emerging field of radiogenomics is gaining the potential to guide diagnosis and predict prognosis, systemically correlating computable radiomic data to clinics and genomics.
To this end, in a cohort of glioma patients, quantitative features (i.e. 1st-order, volume, shape, texture features) of conventional and advanced MRI will be extracted from the histograms of the whole tumor, then machine learning computational approaches will be exploited to scrutinize the association with molecular prognostic subgroups, combining raw inputs into layers of intermediate features.

Background / State of Art

Neuro-oncology is quickly moving beyond traditional histopathological diagnosis to molecular stratification of brain tumors, and the latest genomic advances have revealed that specific molecular fingerprints of gliomas may translate into different clinical outcomes, paving the way towards possible tailored therapies [1]. This trend is reflected by the 2016 World Health Organization (WHO) of tumors of the central nervous system, which, for the first time, includes molecular parameters as

diagnostic criteria in addition to histology. As an example, the isocitrate dehydrogenase (IDH) mutation status defines different subgroups of gliomas based on age, tumor location and prognosis, and it is well established that this gene expression can significantly affect the disease course, with IDH-mutant tumors having a better prognosis than wild-type [2]. To date, it remains unclear how molecular phenotypes of glioma relate to Magnetic Resonance Imaging (MRI) features. Beside the tumor characteristics described by Conventional magnetic resonance imaging (cMRI) sequences, routinely employed in the diagnosis and clinical management of gliomas, advanced MRI techniques such as diffusion MRI (dMRI) and perfusion-weighted imaging (PWI) add significant structural, physiological and hemodynamic information to measure biological properties quantitatively and non-invasively [3].
Unravelling potential correlations between the latter properties and genomics is crucial to define novel MRI biomarkers that can be used as surrogates for tissue-based molecular subtyping, required to predict prognosis, to develop individualized therapies and to follow-up patients [3]. Radiomics is an emerging field of imaging that extracts quantitative data from MR acquisitions and represents the basis of radiogenomics, a promising new paradigm to bring clinical imaging into the molecular era. Extrapolating quantitative radiomic features from cMRI and, most importantly, from aMRI may provide exhaustive information about volume, shape, intensity and texture of tumor phenotype, that is distinct or complementary to that provided by clinical charts, laboratory tests, and genomic, transcriptomic or proteomic assays. Moreover, radiomics circumvents the histological limit of partial availability of tissue sample by assessing the comprehensive three-dimensional tumor bulk by means of imaging information [4]. Relying on those foundations, the domain of investigation for radiogenomics consists of association of parameters extracted form large-scale radiological image analysis with biological or clinical endpoints, resulting in both prognostic and predictive models. Relationships between imaging phenotypes and molecular markers can then be integrated with clinical outcomes, such as overall survival, time to progression, or response to a particular drug therapy [5].
Given the intricate complexity to handle heterogeneous and multi-dimensional imaging datasets, machine learning (ML) methods have been extensively advantageous in this context: artificial intelligence that captures patterns underlying data and utilizes them to help decision making has increasingly enabled a more efficient data management. Recently, deep learning (DL) has emerged as a new area of ML research, with the amazing potential of automatically learning hierarchical features of data by multiple layers composed of simple and nonlinear modules, providing valuable means for speeding up or aiding human investigation. Remarkably, DL-based features automatically extracted from images can be used as imaging biomarkers and have been defined as `DL- based radiomics features¿ by current studies [6, 7]. Since the direct extraction of DL-based image biomarkers may facilitate utilization of molecular imaging in precision medicine, we aim to take advantage of such a promising learning method to maximize the quality and the amount of information extracted from the analysis of our glioma patients¿ cohort.

Hyphotesis and Specific AIMS

Hyphotesis and Significance:
To date, it remains largely unclear how both conventional and advanced radiomic features relate to glioma molecular phenotypes. As such, the main goal of this project is to understand how the microstructural features and molecular phenotypes of gliomas are reflected in imaging, in order to determine if noninvasive MRI biomarkers can be exploited to determine the tumor molecular status. As not all gliomas are eligible for surgical intervention, it is essential to implement methodologies to efficiently stratify patients without the need of tissue sampling. Tumor subtyping and extensive characterization are required for the prediction of clinical outcome, as well as for the development of individualized therapies or treatment follow-up [3]. Radiogenomic genotyping has the advantage that it can be completed repeatedly for

treatment monitoring, can capture tumor heterogeneity and can be performed in particular cases for which biopsy is not available, such as pontine glial neoplasms or diffused glioblastomas. The trend in radiogenomics is increasingly headed towards models of multiparametric multilevel data, integrating clinics, radiology and histopathology [8]. Data must be recollected systematically and accurately for every single glioma patient, in order to possibly connect the clinical history, the standard histopathological diagnosis and the treatment response to molecular and radiomic features. In fact, our second goal is to to organize detailed patient-related information in a comprehensive and easy to handle database. The more reliable and efficient machine learning algorithms will aid to evaluate the enormous amount of data originating from the exploitation of cMRI and advanced MRI techniques (aMRI), and to identify stable and reproducible features in the high dimensional space created by radiomics [4]. On a long term perspective, our third goal is to unravel radiogenomic networks that will contribute to the shift towards precision medicine in oncology. Analysis of those networks with mathematical models that consent to classify patients according to their predicted outcome, by means of pattern recognition, will allow to to predict unseen observations, as patient¿s outcome or tumor phenotype.

Preliminary Data:

OSR Neuroradiology Dept. is a productive center with a prosperous catchment area. In the last years several glioma patients have been subjected to conventional (c)MRI and advanced (a)MRI on a 1.5T and 3T scanner, including both diffusion (d)MRI and perfusion weighted imaging (PWI) sequences. Numerous patients have been monitored during time with regular imaging follow-up, conceivably highlighting disease stability or worsening, which gives us the chance also to scrutinize the evolution of quantitative MRI features.
All the available glioma imaging data will be exploited to train advanced machine learning (ML) algorithms and will be combined with all the relevant clinical data such as patients¿ response to treatment and prognosis, carefully supervised by clinicians. Image first- and second-order features will be extracted from our imaging data for classification purposes, in order to select the more reliable texture descriptors in gliomas. Data will be pre-processed uniformly and converted in formats readable by deep learning methods, so that all our analyses will be based on a solid homogeneous background.

Specific Aim 1:

To perform a quantitative radiomic analysis on MRI data on a retrospective, discovery cohort of glioma patients (including conventional MRI, diffusion MRI and PWI data) and to correlate these quantitative features with pathological, molecular and clinical findings by means of machine learning approach.

Specific Aim 2:

To apply this method to a prospective, validation cohort of glioma patients, in order to predict the molecular pattern of tumours and the patients¿ clinical outcome.

Specific Aim 3:

n.a.

Experimental Design Aim 1:

Aim 1.1 - Imaging-based selection of a retrospective discovery cohort of patients. A cohort of at least 50 treatment-naïve glioma patients, subjected to a MRI examination on a 1.5T or 3T scanner at the Neuroradiology Dept OSR, will be retrospectively selected. Their imaging data will be analyzed. MR acquisition of conventional and advanced techniques on those patients included:
- 2D T1 and T2 images, 3D FLAIR, 3D T1 post contrast

- Diffusion Tensor Imaging (DTI) acquisitions (b-value=1000 s/mm2, no. of gradient directions > 30)
- Perfusion Weighted Imaging (PWI) acquisitions such as dynamic susceptibility contrast enhanced (DSC) and dynamic contrast enhanced (DCE) MRI for the characterization of angiogenic processes, according to the protocol described in Anzalone et al. [9].

Analysis of DTI maps will be performed at OSR by operating with the commonly used toolbox for DTI analysis (i.e. Philips Intellispace Portal v.8.0 and/or FMRIB Diffusion Toolbox), allowing the calculation of DTI metrics such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps.
Perfusion MR analysis will be performed using Olea Sphere (v. 2.3, Olea Medical Solutions, La Ciotat, France). Parametric maps of volume transfer constant (Ktrans) and plasma volume (Vp), derived from DCE, and relative cerebral blood volume (rCBV), derived by DSC, will be obtained.
In both analysis, preprocessing steps will include automatic motion correction by a rigid-body registration, automatic spatial smoothing and background segmentation.
Aim 1.2 ¿ Quantitative radiomic features extraction in the retrospective cohort of patients. Radiomics carries the potential to pinpoint imaging phenotypes with prognostic value by investigating intra-tumour spatial, temporal, physiological and genetic heterogeneity. To identify specific radiomic features that are useful to stratify glioma patients, quantitative MRI features (including first-order, volume, shape and texture features) will be extracted from the histograms of conventional MR images and advanced parametric maps. Quantitative data and corresponding histograms will be extracted using the software Matlab (MathWorks, Natick, MA, USA). In this discovery cohort, these features will be screened for association with molecular subgroups, using deep learning approaches for radiogenomic signature discovery. Patient time to progression and survival rate will be also recorded to determine whether radiomic features can be used to predict clinical outcome.

Experimental Design Aim 2:

Aim 2.1 - Imaging-based selection of a prospective validation cohort of patients. A cohort of at least 50 treatment-naïve glioma patients will be prospectively selected to undergo imaging examination on a 1.5T or 3T Philips MRI scanner or on a hybrid PET/MRI scanner (SIGNA PET/MR, General Electric Medical System) at the Neuroradiology Department OSR. Their imaging data will be analyzed. MR acquisition of conventional and advanced techniques on those patients will include:
- 2D T1 and T2 images, 3D FLAIR, 3D T1 post contrast
- DTI acquisitions (b-value=1000 s/mm2, no. of gradient directions > 30)
- PWI acquisitions such as DSC and DCE MRI for the characterization of angiogenic processes, according to the aforementioned protocol [9].

Parametric maps of FA, MD, AD and RD will be extracted from the analysis of DTI acquisitions following the procedures explained in Aim 1.1, exploiting Philips Intellispace Portal v.8.0 and/or FMRIB Diffusion Toolbox. Moreover, parametric maps of Ktrans and Vp will be extracted from DCE images, and rCBV will be obtained from DSC using Olea Sphere.
In both analysis, as elucidated before, preprocessing steps will integrate automatic motion correction by rigid-body registration, automatic spatial smoothing and background segmentation.
Aim 2.2 ¿ Quantitative radiomic features extraction in the prospective cohort of patients. In order to detect distinct characteristics in glioma patients, quantitative MRI features (including first-order, volume, shape and texture features) will be extracted from the histograms of conventional MR images and advanced parametric maps. Quantitative data and corresponding histograms will be extracted using the software Matlab (MathWorks, Natick, MA, USA), as in Aim 1.2.
Aim 2.3 ¿ Machine learning-based validation of prognostic models in the prospective cohort of patients. The reference standard to corroborate an identified statistical association or biomarker is its validation within a prospectively collected independent cohort of patients, the validation cohort, ideally mimicking the context of clinical trials. After having trained our prediction model on the discovery cohort (Aim 1.2), in fact, we will test the radiogenomic possibility of predicting the

molecular status and the patients¿ prognosis in our autonomous and separate cohort of glioma patients.

Experimental Design Aim 3:
n.a.

Picture to support preliminary data:

Metodologies and statistical analyses:
Selected patients will undergo conventional and advanced MRI analysis, to characterize brain tissue microstructure andangiogenesis.
We expect to select a minimum of 50 patients both for the retrospective-discovery as well as for the prospective-validation cohort, which will ensure statistically significant results for the proposed radiogenomic approach. Patient survival curves will be analyzed by the method of Kaplan and Meier and the log-rank test. Standard predictors of survival (i.e. age at diagnosis, KPS, extent of resection) will be included as potential covariates. P values <0.05 will be considered statistically significant.
Computational approaches will be exploited in order to categorize and integrate imaging and histopathological datasets, as well as to multi-scale data modeling.
In addition to standard statistical methodology, cutting-edge machine learning computational approaches will be helpful in identifying potential associations between imaging texture features and prognostic glioma subgroups.

Expected outcomes:
Pivotal information can be obtained by evaluating the extracted quantitative radiomic parameters in discrete regions of the tumours by combining diffusion, perfusion, and multiparametric-derived maps.
A database of phenotypic heterogeneity can be created, based on their similarities and differences.
It is very likely that the results of the proposed project will provide a novel platform for an advanced interpretation of MRI data: the radiogenomic prediction of glioma microstructural and molecular features, such as tumor vascularization and invasiveness and molecular subgrouping, may offer the opportunity for non-invasively selecting candidate patients for personalized treatments. In fact, beyond diagnosis, radiomics and radiogenomics can have a substantial influence on treatment guidance: combining phenotype and genetics is a key strategy to improve precision medicine.

Risk analysis, possible problems and solutions:
1) Complete patients¿ history and follow-up may not be always easily available and collectable, but this issue can be faced if dedicated workers systematically monitor every single glioma patient from the beginning of the project.
2) Identifying key elements that are common for all the partners of this study may rise the issue of reproducibility, because radiomics faces challenges such as data overfitting, different study designs or reporting incomplete results and confounding variables. To cope with this problem, partner will continuously monitor and update a common list of items, to work homogeneously.
3) Standardizing imaging analysis may encounter difficulties, since MRI acquisition parameters broadly vary in routine clinical practice. So, comparing data gained across different machines becomes challenging and opens the way to possible errors. If this affects the classifier performance, data will be subdivided according to the different machines from which they have been acquired, and analyzed separately.

Project Title: P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.	
Project Code: NET-2018-12366666-3	**Principal Investigator:** Falini Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

Significance and Innovation

An integrated approach to the study and characterization of glial neoplasms based on big data analysis is now becoming indispensable, in order to corroborate the clinical translatability of radiomics and radiogenomics breakthroughs. While different groups have suggested that image-derived indices can reliably detect principal glioma texture features non-invasively and produce predictive imaging biomarkers, there is still the urgent need for the development of integrated publicly available databases, where images and extracted features are related to clinical follow-up and molecular data. The possibility to exchange data according to an evolving set of standards is fundamental to piece together large imaging datasets, that should overcome some of the intrinsic heterogeneities of clinical imaging. The harmonization of advances in the glioma molecular characterization and imaging will provide precious insights for the tailoring of precision oncology.

Description of the complementary and sinergy research team

All centers involved in this project network will contribute to the WP according to their specific relevance and in line with the regional priorities.
The specific contribution of the OSR Neuroradiology Unit will be to provide an extensive amount of data for radiomic analyses and machine-learning algorithm development and implementation, including:
- clinical information including patients¿ time to progression and survival rate
- histopathological and molecular characterization of gliomas
- conventional MRI raw data
- dMRI maps (FA, MD, AD, RD)
- PWI maps (Ktrans and Vp extracted from DCE; rCBV extracted from DSC)

Data sharing will contribute to ensure studies of sufficient size for statistical power and to build a more robust predictive model of the prognosis of glial neoplasms. Moreover, our data are complementary to those provided by WP4, focused on pediatric brain tumors. This will firstly result in an overall increase in the sample size and consequently in the significance of the statistical analysis. Secondly, the synergy between the two WP will extend the comprehension of biological different origin of the two series of glial neoplasms.

Training and tutorial activities

n.a.

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8- Robin W. Jansen et al., 2018. Non-invasive tumor genotyping using radiogenomic biomarkers, a systematic review and oncology-wide pathway analysis. Oncotarget
9- Anzalone N. et al., 2018. Brain Gliomas: Multicenter Standardized Assessment of Dynamic Contrast-enhanced and Dynamic Susceptibility Contrast MR Images. Radiology

Timeline / Deliverables / Payable Milestones

We trust that we will be able to accomplish the proposed tasks in due time. Indeed:
- The techniques necessary for the project (i.e. MR scanners, MRI protocols, extraction of parametric maps and preprocessing steps) are accessible in the Functional Neuroradiology Unit of OSR.
By this experimental strategy, we will be able to deliver:
- A comprehensive dataset integrating all the available glioma patients¿ information, including clinical follow-up, molecular characterization and quantitative imaging texture features.
- Quantitative conventional and advanced MRI radiomic markers correlated with the main glioma pathological features, such as as tumor invasiveness and angiogenesis, collected in a retrospective discovery cohort of glioma patients.
- A machine learning- based prognostic model, whose efficacy will be validated in a prospectively collected independent cohort of patients.

Milestones 18 month

-Months 1-3: Selection of the retrospective discovery cohort
-Months 1-6: Data-gatheringfor every selected patient.
-Months 6-18: Quantitative radiomic features extraction and correlation with clinico.histopathological data.
-Months 1-18: Beginning of the selection of the prospective validation cohort of treatment-naïve patients.
-Months 1-18: Beginning of data-gathering (clinical f.u., treatment response, molecular characteristics of the tumor) for every patient of the prospective cohort.

Milestones 36 month

Project Type: WP PROJECT - 3

-Months 18-30: Continuation of the selection of the prospective validation cohort of treatment-naïve glioma patients.
-Months 18-30: Continuation of data-gathering for patients of the prospective cohort.
-Months 30-36: Quantitative radiomic features extraction from the analysis of conventional and advanced MRI acquisitions of the prospective cohort of glioma patients.
-Months 30-36: Machine learning-based validation of the prognostic models in the prospective cohort of patients.

Gantt chart

Falini_Gantt_RF2018.pdf

Equipment and resources available

The Neuroradiology Unit at OSR is equipped with 3 up-to-date fully equipped1.5T MR scanners (Ingenia, Philips Healthcare). A new hybrid PET/MRI scanner (SIGNA PET/MR, General Electric Medical System) will be also exploited for this project.

Facilities Available
A state-of-the-art human 3 Tesla MRI scanner (Ingenia 3T CX, Philips Healthcare) at Centro Eccellenza Risonanza Magnetica ad Alto Campo (CERMAC) is available for the project

Translational relevance and impact for the National Health System (SSN)

The MRI-based prediction of glioma molecular and biological features, such as tumor invasiveness and vascularization, may offer the opportunity for stratifying prognosis and for non-invasively selecting patients, who may be candidates for tailored treatments, such as anti-angiogenic and molecular targeted therapies, and to provide highly specific clinical tools for their follow-up. The validation of radiomic and radiogenomic significance carries the enormous potential to deeply influence the actual clinical practice. In fact, the results of the proposed project might yield a novel platform for an advanced interpretation of MRI data at the cellular and molecular level and for improving glioma patients' prognosis through individualized targeted therapies, that might prevent overtreatment and adverse effects.

Project Title:
P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-3

Principal Investigator: Falini Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

PRINCIPAL INVESTIGATOR PROFILE

Name		
Falini Andrea	Institution	Ospedale San Raffaele - Milano
	Department/Unit	OSR/Division of Neuroscience/Functional Neuroradiology Unit
	Position Title	Full Professor

Personal Statement

The overall goal of this WP is to extract quantitative features from conventional and advanced MRI studies coming from both a retrospective and a prospective cohort of glioma patients and to correlate these data with pathological, molecular and clinical findings by means of machine learning approach. As head of the neuroradiology Dept I will coordinate the selection and data extraction from an existing database of glioma patients to train the machine based analysis and then I will organize a prospective study in a group of consecutive patients with glioma to validate the efficacy of the machine learning-based approach.

Education/Training - Institution and Location	Degree	Year(s)	Field of study
University of Milan, Milan Italy	Residency	3	Radiology
University of Milan, Milan Italy	Residency	3	Neurology
University of Milan, Milan Italy	PhD	3	Neurological Sciences
University of Milan, Milan Italy	MD	5	Medicine

Project Title: P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.

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Applicant Institution: Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

Positions

Institution	Division / Research group	Location	Position	From year	To year
Scientific Institute San Raffaele Hospital	Neuroscience Division	Milan, Italy	Clinical Research Coordinator	2017	2018
Vita-Salute San Raffaele University, Milan	Neuroradiology	Milan, Italy	Full Professor	2015	2018
Scientific Institute San Raffaele Hospital	Neuroradiology Dept.	Milan, Italy	Head	2011	2018
Scientific Institute San Raffaele Hospital	Neuroradiology Research Unit, Center of Experimental Imaging (CIS)	Milan, Italy	Head	2011	2018
Scientific Institute San Raffaele Hospital	Functional Neuroradiology Unit, Division of Neuroscience	Milan, Italy	Head	2009	2018
Scientific Institute San Raffaele Hospital	Division of Neuroscience	Milan, Italy	Vice-Director	2014	2016
Vita-Salute San Raffaele University,	Neuroradiology, School of Medicine	Milan, Italy	Professor	2010	2015
Vita-Salute San Raffaele University, Milan	Neuroradiology, School of Medicine, of Physiotherapy and School of Psycology	Milan, Italy	Adjunct Professor	1999	2000
Scientific Institute San Raffaele Hospital	Functional MR and Spectroscopy Unit ad Neuroscience Dept.	Milan, Italy	Principal Investigator	1997	2008
Scientific Institute San Raffaele Hospital	Neuroradiology Dept.	Milan, Italy	Neuroradiologist Collaborator	1991	1999

Official H index: 53.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 7003494994

ORCID ID: 0000-0002-1461-8755 **RESEARCH ID:** n.a.

Awards and Honors:

1996- Grant from the Italian National Council of Research (CNR) and from the American National Cancer Institute for a clinical and research stage at UCSF, USA

1992- Grant from the Italian Society of Neuroradiology for a research stage at the Neuroradiology Dept. of the Children Hospital of Philadelphia, USA¿1989- Winner of the De Visart prize from the University of Milan, Italy

Other CV Informations:

Invited to more than 330 national and international seminars and lectures.

2014-2018 President of the Neuroradiology Section of SIRM (Società Italiana di Radiologia Medica)

2010-2018 Member of Management Board of the Neuroradiology Section of SIRM

2003-2018 Member of the Scientific Committee and of the Operative Committee of the High-field Magnetic Resonance Excellence Center (CERMAC)

	Project Title: P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.
Project Code: NET-2018-12366666-3	**Principal Investigator:** Falini Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

2008-2013 Founder and coordinator of the Neuroradiology Section of SIN (Società Italiana Neurologia)
2002-2013 AINR Representative in the Management Board of the Neuroradiology Section of SIN
2006-2008 treasurer of the AINR (Associazione Italiana di Neuroradiologia)

Project Title: P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-3

Principal Investigator: Falini Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

Selected peer-reviewed publications of the PI

Valid for PI minimum expertise level

Title	DOI	PMID	Cit. **	P.*
Proton magnetic resonance spectroscopy and intracranial tumours: Clinical perspectives	n.a.	8923303	59	F
Benign versus secondary-progressive multiple sclerosis: The potential role of proton MR spectroscopy in defining the nature of disability	n.a.	9504469	64	F
Progressive brain failure after diffuse hypoxic ischemic brain injury: A serial MR and proton MR spectroscopic study	n.a.	9576649	59	F
Differential diagnosis of posterior fossa multiple sclerosis lesions: neuroradiological aspects	n.a.	11794484	16	F
Role of conventional MRI, diffusion and magnetization transfer in the diagnosis of amyotrophic lateral sclerosis	n.a.	n.a.	1	F
Evidence for widespread axonal damage at the earliest clinical stage of multiple sclerosis	n.a.	12538409	283	L
A whole brain MR spectroscopy study from patients with Alzheimer's disease and mild cognitive impairment	10.1016/j.neuroimage.2005.03.005	15878675	43	F
The contribution of voxel-based morphometry in staging patients with mild cognitive impairment	10.1212/01.wnl.0000228243.56665.c2	16894107	135	L
Tumours	10.1007/s10072-008-1009-z	18941724	1	F
Voxel-wise analysis of diffusion tensor MRI improves the confidence of diagnosis of corticobasal degeneration non-invasively	10.1016/j.parkreldis.2007.09.011	18328770	5	L
Motor and language DTI Fiber Tracking combined with intraoperative subcortical mapping for surgical removal of gliomas	10.1016/j.neuroimage.2007.08.031	17911032	225	L
Structural and metabolic changes in the brain of patients with upper motor neuron disorders: A multiparametric MRI study	10.3109/17482960902777339	19922113	24	L
A diffusion tensor MRI study of patients with MCI and AD with a 2-year clinical follow-up	10.1136/jnnp.2009.189639	20392973	52	L
Intraoperative use of diffusion tensor imaging fiber tractography and subcortical mapping for resection of gliomas: Technical considerations	10.3171/2009.12.FOCUS09240	20121441	73	L
Role of diffusion tensor magnetic resonance tractography in predicting the extent of resection in glioma surgery	10.1093/neuonc/nor188	22015596	48	L
Functional network connectivity in the behavioral variant of frontotemporal dementia	10.1016/j.cortex.2012.09.017	23164495	66	L
White Matter Integrity in Obstructive Sleep Apnea before and after Treatment	10.5665/sleep.3994	25142557	34	L

Project Title:
P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-3

Principal Investigator: Falini Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

Title	DOI	PMID	Cit. **	P.*
Progress in neuro-imaging of brain tumors	10.1097/CCO.0000000000000328	27649026	6	L
Evaluation of low-grade glioma structural changes after chemotherapy using DTI-based histogram analysis and functional diffusion maps	10.1007/s00330-015-3934-6	26318368	5	L
Functional MRI for Surgery of Gliomas	10.1007/s11940-017-0469-y	28831723	0	L

* Position: F=First L=Last C=Corrispondent

** Autocertificated

For evaluation CV

Title	DOI	PMID	Cit. *
Glioma imaging in Europe: A survey of 220 centres and recommendations for best clinical practice.	10.1007/s00330-018-5314-5	29536240	0
Progress in neuro-imaging of brain tumors	10.1097/CCO.0000000000000328	27649026	6
Dynamic contrast-enhanced and dynamic susceptibility contrast perfusion MR imaging for glioma grading: Preliminary comparison of vessel compartment and permeability parameters using hotspot and histogram analysis.	10.1016/j.ejrad.2016.03.020	27161065	13
Evaluation of low-grade glioma structural changes after chemotherapy using DTI-based histogram analysis and functional diffusion maps	10.1007/s00330-015-3934-6	26318368	5
EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma.	10.1016/S1470-2045(14)70011-7	25079102	224
Role of diffusion tensor magnetic resonance tractography in predicting the extent of resection in glioma surgery.	10.1093/neuonc/nor188	22015596	48
Presurgical functional MR imaging of language and motor functions: validation with intraoperative electrocortical mapping.	10.1148/radiol.2482071214	18539893	135
Motor and language DTI Fiber Tracking combined with intraoperative subcortical mapping for surgical removal of gliomas	10.1016/j.neuroimage.2007.08.031	17911032	225
Proton magnetic resonance spectroscopy and intracranial tumours: Clinical perspectives	n.a.	8923303	59
Proton magnetic resonance spectroscopy in patients with glial tumors: a multicenter study	10.3171/jns.1996.84.3.0449	8609557	316

* Autocertificated

Ministero della Salute Direzione Generale della Ricerca Sanitaria e Biomedica e della Vigilanza sugli Enti **BANDO RICERCA FINALIZZATA 2018** **esercizio finanziario anni 2016-2017**	**Project Title:** P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.
Project Code: NET-2018-12366666-3	**Principal Investigator:** Falini Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

Grant

Funded Institution / Country	Year	Title	Position in Projects
FCSR (OSR) - Italy	2011	A Novel Diffusion Tensor MR Based Approach to evaluate structural features of brain tumors; Code RF-2009-1530888	Coordinator
FCSR (OSR) - Italy	2016	Horizon 2020: EDEN2020 (Enhanced Delivery Ecosystem for Neurosurgery in 2020)	Coordinator

Employment contract extension:

(Data changed during the moratorium period)

Project Title: P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-3

Principal Investigator: Falini Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

Biographical Sketch Contributors 1

Name: Scifo Paola Vittoria

Institution	IRCCS San Raffaele Scientific Institute, Department of Nuclear Medicine, Researcher
Department/Unit	Nuclear Medicine Dept.
Position Title	Coordination of image processing

Education/Training - Institution and Location	Degree	Year(s)	Field of study
Università degli Studi Milano-Bicocca, Milan, Italy	PhD	3	Biomedical Technology
Politecnico di Milano, Milan, Italy	Laurea in Ingegneria Elettronica	5	Electronic and Biomedical Engineering

Personal Statement:

As medical bioengineer I will supervise the process of Image selection, processing, and analysis in order to optimize the extraction of quantitative texture features in the retrospective part of the project. Along the perspective part of the project I will implement and check the validation process of the prognostic model.

Institution	Division / Research group	Location	Position	From year	To year
San Raffaele Scientific Institute	Nuclear Medicine Dept.	Milan, Italy	Senior Researcher	2001	2018
CEA Commissariat de l'energie Atomique	Service Hospitalier Frederic Joliot	Orsay, France	Marie Curie Fellow	2001	2003
San Raffaele Scientific Institute	Nuclear Medicine Dept.	Milan, Italy	Junior Researcher	1998	2001
University Vita-Salute San Raffaele	Diagnostic Imaging	Milan, Italy	Adjunct Professor in Radiology	2003	2018
University of Milano-Bicocca - Medicine and Surgery	Radiology Technician School	Milan, Italy	Adjunct Professor	2003	2014

Awards and Honors

Official H index: 33.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 6602190569

ORCID ID: 0000-0001-5135-8086 **RESEARCH ID:** J-4410-2016

Awards and Honors:

Project Title: P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.	
Project Code: NET-2018-12366666-3	**Principal Investigator:** Falini Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

Marie Curie Fellowship MCFI-2001-01020

Project Title:
P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-3

Principal Investigator: Falini Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

Expertise Research Collaborators

Selected peer-reviewed publications of the Research Group / Collaborators

Collaborator	Title	DOI	PMID	Cit. *
Scifo Paola Vittoria	Maturation of preterm newborn brains: a fMRI-DTI study of auditory processing of linguistic stimuli and white matter development	10.1007/s00429-014-0887-5	25244942	8
Scifo Paola Vittoria	The DCDC2/intron 2 deletion and white matter disorganization: Focus on developmental dyslexia	10.1016/j.cortex.2014.04.016	24926531	17
Scifo Paola Vittoria	Neural language networks at birth	10.1073/pnas.1102991108	21896765	135
Scifo Paola Vittoria	Functional specializations for music processing in the human newborn brain	10.1073/pnas.0909074107	20176953	104
Scifo Paola Vittoria	A modified damped Richardson-Lucy algorithm to reduce isotropic background effects in spherical deconvolution	10.1016/j.neuroimage.2009.09.033	19781650	139
Scifo Paola Vittoria	Noise correction on Rician distributed data for fibre orientation estimators	10.1109/TMI.2008.920615	18753042	24
Scifo Paola Vittoria	A fMRI study of word retrieval in aphasia	n.a.	12744947	125
Scifo Paola Vittoria	Interhemispheric transmission of visuomotor information in humans: fMRI evidence	10.1152/jn.2002.88.2.1051	12163553	105
Scifo Paola Vittoria	Functional heterogeneity of left inferior frontal cortex as revealed by fMRI	n.a.	9223094	27
Scifo Paola Vittoria	Functional MRI: primary motor cortex localization in patients with brain tumors	n.a.	8797897	4

* Autocertificated

Grant

Funded Institution / Country	Year	Title	Position in Projects	Collaborator
Ministry of Health	2016	Characterization of the primary prostate tumor phenotype and assessment of prostate cancer staging by using a hybrid fully integrated PET/MRI system, radiomics analysis, multitracers (68Ga-PSMA and 68Ga-Bombesin) PET and multiparametric MRI	Collaborator	Scifo Paola Vittoria
AIRC	2017	A novel approach for staging prostate cancer patients by using a fully integrated hybrid PET/MRI	Collaborator	Scifo Paola Vittoria

Project Title:
P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-3

Principal Investigator: Falini Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

Total proposed budget (Euro)

Costs	TOTAL BUDGET	Co-Funding	Project costs proposed to funding Organization (no MOH request)	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1a Staff Salary	50.000,00	50.000,00	0,00	not permitted	0,00
1b Researchers' Contracts	285.000,00	0,00	150.000,00	135.000,00	50,00
2 Equipment (Leasing - Rent)	30.000,00	0,00	15.000,00	15.000,00	5,56
3a Supplies	0,00	0,00	0,00	0,00	0,00
3b Model Costs	0,00	0,00	0,00	0,00	0,00
3c Subcontracts	0,00	0,00	0,00	0,00	0,00
3d Patient Costs	0,00	0,00	0,00	0,00	0,00
4 IT Services and Data Bases	178.900,00	0,00	96.000,00	82.900,00	30,70
5 Publication Costs	2.000,00	0,00	0,00	2.000,00	0,74
6 Convegni	5.700,00	0,00	3.000,00	2.700,00	1,00
7 Travels	11.400,00	0,00	6.000,00	5.400,00	2,00
8 Overheads	57.000,00	0,00	30.000,00	27.000,00	10,00
9 Coordination Costs	0,00	0,00	0,00	0,00	0,00
Total	620.000,00	50.000,00	300.000,00	270.000,00	100,00

Report the Co-Funding Contributor:

Co-Funding Ospedale San Raffaele - Milano

	Project Title: P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.
Project Code: NET-2018-12366666-3	**Principal Investigator:** Falini Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

Budget Justification	
1a Staff Salary	Salary staff of Dr P Scifo in relation to the commitment of the project
1b Researchers' Contracts	36 months of salary (€ 38.000/year) for 8 contracts (2 positions in the first year and 3 for the second and third year) for personnel dedicated to neuroimaging clinical research activity and data analysis
2 Equipment (Leasing - Rent)	leasing/renting of at least 3 workstations for the entire duration of the project
3a Supplies	None
3b Model Costs	None
3c Subcontracts	None
3d Patient Costs	None
4 IT Services and Data Bases	Acquisition of sowtware dedicated to perfusion MR data analysis (Olea Sphere v. 2.3 or Nordic System); acquisition of software for DTI data processing (i.e. Philips Intellispace Portal v.8.0 and/or FMRIB Diffusion Toolbox).Acquisition of software Matlab
5 Publication Costs	Costs of pubblications relative to the project
6 Convegni	Participation to congresses or meeting related to the topic of the project
7 Travels	Travel and housing costs related to meeting and congresses
8 Overheads	10%
9 Coordination Costs	None

	Project Title: P3 (preventive, predictive and personalized) solutions in adult neuroncology driven by imaging and biological data.
Project Code: NET-2018-12366666-3	**Principal Investigator:** Falini Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Ospedale San Raffaele - Milano

Project Type: WP PROJECT - 3

Ministero della Salute Direzione Generale della Ricerca Sanitaria e Biomedica e della Vigilanza sugli Enti **BANDO RICERCA FINALIZZATA 2018** **esercizio finanziario anni 2016-2017**	**Project Title:** P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.
Project Code: NET-2018-12366666-4	**Principal Investigator:** Rossi Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Major Diagnostic Category*: Neurologia

Project Classification IRG: Bioengineering Sciences and Technologies

Project Classification SS: Biodata Management and Analysis - BDMA

Project Keyword 1: Methods for data analysis including: Numerical, statistical, mathematical and theoretical approaches to design and interpretation of large-scale studies such as methods for pattern discovery, data mining, sequence prediction, biomarker identification, therapeutic drug design and high throughput analyses; computational methods for organizing, maintaining, and integrating biological datasets and for large scale data modeling and simulations.

Project Keyword 2: Database technologies and methods for data management, data representation, data capture, data integrity and validation

Project Keyword 3: Brain Disorders and Clinical Neuroscience

Project duration (months): 36

Project Request: **Animals:** ☐ **Humans:** ☒ **Clinical trial:** ☐

The object/s of this application is/are under patent copyright Y/N: ☐

Investigators, Institution and Role in the Project

	Co-PI	Key Personnel	Institution/Org./Pos.	Role in the project	Birth Date
1	X	morana giovanni	Istituto Giannina Gaslini	Co-PI	08/03/1975
2		Frassoni Francesco	Istituto Giannina Gaslini	Expert Research Collaborator	13/08/1950

Overall Summary

Pediatric brain tumors consist of a heterogeneous spectrum of neoplasms with different degrees of malignancy, posing particularly complex neuro-oncological challenges. Despite improvements in management strategies and techniques, there has been little change in outcome, and there is an urgent need for more effective treatments.
Along with structural MRI, molecular imaging is an innovative field for delineating a metabolic map of pediatric brain tumors through multimodal and multiparametric analysis, thereby integrating in-vivo imaging data. We propose to study pediatric brain tumors with MRI (using novel molecular techniques) and PET (using amino-acid tracers) and to integrate these data so as to obtain a detailed metabolic signature of these tumors.
A proportion of childhood cancer survivors (CCS) show evidence of anticipated aging. We shall evaluate the cellular damage induced by chemo-radiotherapy by means of biochemical and molecular indicators.

Background / State of Art

Pediatric brain tumors are the most common pediatric solid tumors and include several histological subtypes. Estimated incidence in Europe is approximately 3:100,000/year in the 0-14 years age group, with a slight predominance in infants 0-4 years [1]. MRI is widely used for diagnosing these lesions; fundamental information regarding location, size, morphology,

composition and physiology of brain tumors can be obtained noninvasively thanks to its excellent soft tissue contrast and combined structural and functional imaging capabilities. The use of 3T clinical scanners has greatly enhanced the neuroradiologist¿s ability to provide such information, that can also be transferred to the operative room neuronavigator for neurosurgical purposes. However, differentiating low- from high-grade tumors remains a diagnostic dilemma especially in young patients and in diffuse lesions, where the biopsy sample is often limited and may not accurately reflect the true nature of the neoplasm [2]. Additional concern is raised by the risks involved with repeated administration of gadolinium-based contrast agents, which are required by international guidelines for brain tumor diagnosis and surveillance but may rarely cause adverse reactions and may accumulate in human body tissues [3]. Finally, long acquisition times may be a cause of concern especially in small, incompletely cooperative patients; sedation must often be used in these cases.
Nuclear imaging studies, primarily PET with amino-acid tracers, have proven useful to provide additional metabolic information that correlates with tumor grade [4], but the anatomic resolution of this technique is unsatisfactory and the issue of ionizing radiation remains high. Recent studies have focused on the implementation of rapid imaging acquisition protocols such as the Compressed SENSE technique, which has significantly shortened imaging time permitting larger scale usage of noninvasive molecular MRI-based techniques, such as arterial spin labelling (ASL) perfusion and amide proton transfer (APT) imaging. While ASL has proven useful in the characterization of low- versus high-grade tumors in the pediatric age group to the extent that gadolinium-based perfusion methods could be safely withdrawn, APT imaging has only been tested in adult gliomas, where it has shown promise in the identification of high- grade lesions [5]: however, the yield of this novel techniques remains unexplored in the pediatric age group.
Limitation of long-term treatment sequelae in childhood cancer survivors is also vitally important. The treatment of childhood cancer is one of oncology's success stories, with five-year survival rates that have shot up from 30% in the 1960s to 80% now, at least in high-income countries. However, greater than 40% of childhood-cancer survivors experience lifelong side effects from treatment. Childhood cancer survivors (CCS) have an increased risk of chronic diseases, disability, and impaired physical fitness [6]. In CCS, these impairments appear decades earlier than expected. This suggest that in survivors a process of accelerated aging occurs.

Hyphotesis and Specific AIMS

Hyphotesis and Significance:
In the neuro-oncological field, molecular imaging by radiomic procedures has an important diagnostic-therapeutic potential, however, to date there are neither large studies nor detailed information about the yield of these imaging modalities in the pediatric population. MRI provides not only a structural assessment but also functional information including perfusional estimates of tumor microvascularization, which may be obtained noninvasively with the arterial spin labeling (ASL) technique; novel MRI techniques such as Amide Proton Transfer (APT) imaging are also potentially able to provide a metabolic signature map of brain tumors in a noninvasive way, but their yield in the pediatric age group has not been elucidated. PET using aminoacidic tracers also has proven valuable in differentiating high from low-grade tumor components, also within the same lesion. We hypothesize that structural and molecular imaging data analyzed with radiomics procedures will play a relevant role in order to optimize forms of targeted therapy in the pediatric age group. We also hypothesize that combining noninvasive forms of metabolic tumor assessment may eliminate or significantly reduce the need of aggressive forms of treatment such as combined-drug chemotherapy or radiotherapy in this extremely sensitive age group and may also potentially reduce the need for repeated contrast material injections for surveillance purposes.
Seventy to eighty percent of children with cancer survive and become Childhood Cancer Survivors (CCS). They are frail and may experience a sort of anticipated aging [7]. We have identified biochemical and molecular markers/indicators of

aging at the cell level in normal subjects; we plan to apply these indicators to predict anticipated aging in CCS, and will try to identify correlations and predictions of morbidity in CCS.

Preliminary Data:

We have previously shown that integrating data gathered by MRI and PET techniques provides new information that is not achievable by either technique in isolation [4,8]. Studies from our group have also demonstrated that the association of PET and MRI perfusion images obtained with the Arterial Spin Labeling (ASL) technique provides the highest predictive power for prognosticating tumor progression [9]. Amide proton transfer (APT) imaging is a novel molecular MRI technique able to detect endogenous mobile proteins and peptides through chemical exchange saturation transfer. APT imaging has been shown to predict the histopathological grades of adult diffuse gliomas, but its role in the characterization of pediatric brain tumors remains unexplored. The Compressed SENSE is a parallel imaging MRI technique that significantly reduces scanning time, thereby improving the chances of full cooperation and reducing the need for sedation.
We are presently conducting a parallel study in CCS patients aging from first to third decade and healthy controls aging from first to the tenth decade of life. We have evaluated the energy metabolism in peripheral blood mononuclear cells (PBMC) and proved that energy metabolism changes in PBMC of controls during aging from aerobic to anaerobic pathways influences the cellular energy status. CCS, independently from age and time elapsed from therapy, display a partial uncoupled status among electron transport chain and ATP synthase. The uncoupled status is associated with an increment of oxidative stress production. Taken together, these data allow to hypothesize that in CCS cells the oxidative stress is higher than in controls, that the endogenous antioxidants system are not able to balance it, and that this condition could lead cells to an early aging.

Specific Aim 1:

To perform a quantitative radiomic analysis on MRI data on a retrospective, discovery cohort of pediatric brain tumor patients (including conventional MRI, diffusion MRI and PWI data) and to correlate these quantitative features with nuclear medicine (18F-DOPA PET), pathological, molecular and clinical findings by means of machine learning approach.

Specific Aim 2:

To apply the quantitative radiomic analysis method to a prospective, validation cohort of pediatric brain tumor patients, in order to predict the molecular pattern of tumors and the patients¿ clinical outcome, and to test the added value of the novel APT MRI technique.

Specific Aim 3:

To identify molecular markers of damage or anticipated aging in the cells of childhood cancer survivors.

Experimental Design Aim 1:

Data acquired retrospectively in at least 50 cases of pediatric patients with treatment-naïve, pathologically proven brain tumors will be analyzed. MRI imaging studies performed on 1.5 or 3 T Philips scanner include: (i) structural neuroimaging with pre-contrast T2, T1- and FLAIR, and 3D post-contrast T1 images; (ii) functional neuroimaging with DWI for microstructural assessment; perfusion with ASL and/or dynamic susceptibility contrast enhanced (DSC) for microvascular assessment; single- or multivoxel proton MR spectroscopy for metabolic assessment. Whenever available, 18F-DOPA PET images will be coregistered with MRI data offline using an in-house software. Then, quantitative MRI features (including first-order, volume, shape and texture features) will be extracted from the histograms of conventional MR images and

advanced parametric maps, using Matlab (MathWorks, Natick, USA). Such features will be evaluated for association with molecular subgroups, using deep learning approaches for radiogenomic signature discovery. Patient time to progression and survival rate will be also recorded to determine whether radiomic features can be used to predict clinical outcome.

Experimental Design Aim 2:
Data acquired prospectively in at least 50 cases of pediatric patients with treatment-naïve, pathologically proven brain tumors will be analyzed. MRI imaging studies will be performed on a 3 T Philips scanner including: (i) structural neuroimaging with pre-contrast T2, T1- and FLAIR, and 3D post-contrast T1 images; (ii) functional neuroimaging with DWI for microstructural assessment; perfusion with ASL and/or dynamic susceptibility contrast enhanced (DSC) for microvascular assessment; single- or multivoxel proton MR spectroscopy for metabolic assessment; and (iii) molecular imaging with the APT MRI software. Compressed SENSE will be applied to all imaging sequences in order to shorten acquisition time. Wherever clinically indicated, molecular imaging using 18F-DOPA PET will be coregistered with MRI data offline using an in-house software. Then, quantitative MRI features (including first-order, volume, shape and texture features) will be extracted from the histograms of conventional MR images and advanced parametric maps, using Matlab (MathWorks, Natick, USA). The radiogenomic possibility of predicting the molecular status will then be tested and the patients¿ prognosis predicted based on the training of the prediction model on the discovery (aim 1) cohort.¿

Experimental Design Aim 3:
The analyses will be performed on MNC from peripheral blood of CCS and peer controls
The production of ROS will be measured after incubating cells with a fluorescence probe (H2DCFDA). The expression of nuclear genes related to mitochondrial biogenesis, mitochondrial dynamics, i.e. fusion and fission processes, mitophagy, production of ROS and protection from ROS will be also evaluated. The defect will be eventually tested in MNC from aged controls to establish whether the same cell markers are involved in physiological ageing. Mitotracker will be used to analyze the organization of mitochondrial reticulum as well as the expression of CLUH, a protein involved in organizing mitochondria within the cell. Detection of NAD+ into the MNC will be performed using enzymatic cycling assay. The expression of mRNA levels of NAD-degrading enzymes and NAD-synthesizing enzymes will be evaluated.

Picture to support preliminary data:
foto + didascalia.jpg

Metodologies and statistical analyses:
MRI studies are performed at the Neuroradiology Unit, IRCCS Istituto Giannina Gaslini Hospital, with either a 1.5 T (Intera Achieva) or a 3 T (Ingenia Cx) Philips magnet. APT imaging software will be acquired as part of the financing of this project and installed on the 3T unit. APT imaging will be carried out on multiple slices corresponding to the cross-section area of the tumor in each case. Compressed SENSE will be applied in the prospective cohort group to cut scan time. PET studies will be carried out on a dedicated PET/CT system and acquired 20 minutes after injection of 148 MBq 18F-DOPA. All 18F-DOPA-PET studies will be coregistered with MRI.
Patient survival curves will be analyzed with Kaplan Meier and log-rank tests. Standard predictors of survival (i.e. age at diagnosis, KPS, extent of resection) will be included as potential covariates. P values <0.05 will be considered statistically significant. Computational approaches will be used for categorizing and integrating imaging and histopathological datasets.
Markers of aging will be performed on MNC from fresh blood samples of childhood cancer survivor (CCS); healthy donors will be used as controls. Confocal microscopy will be employed to analyze the organization of mitochondrial reticulum and distribution using mitotracker. ROS production will be monitored using a ROS-sensitive fluorescent probe. NAD+ content

will be measured on neutralized supernatants through an enzymatic cycling procedure. Real-time PCR will be performed isolating total RNA from 5×106 MNC. 1 µg of total RNA will be used to synthesize cDNA by reverse transcription and SYBR Green qPCR will be performed by iQ5. Primers will be designed by NCBI/Primer-BLAT primers designing tool. Statistical analysis will be performed using the 2Ct method and results will expressed relative to a calibrator (control sample). MNC will be lyses and after SDS-PAGE, Western blots will be performed using nitrocellulose membranes (Bio Rad). Proteins expression will be tested using specific primary antibodies and secondary HPR-conjugated antibodies. Detection and densitometry will be performed using a Chemi-Doc System (Bio-Rad).

Expected outcomes:

Quantitative radiomic imaging features will be coupled with molecular information from APT MRI and PET and provide a basis for machine-learning computational screening that may identify associations with genomic and prognostic subgroups. Differences from adult groups will contribute to the understanding of peculiar behavior of pediatric brain tumors and to the selection of candidates for personalized treatments.
We also expect to identify biological markers associated with long-term consequences of cancer treatment and develop treatment actions aimed at preventing diseases associated to early aging.

Risk analysis, possible problems and solutions:

For MRI, possible contraindications will be screened with a questionnaire. Only macrocyclic contrast material will be used to minimize possible gadolinium accumulation. Patient sedation will be performed only for fully noncooperative patients. For cell studies, a possible pitfall is represented by the sample storage, since MNC must be analysed soon after collection to perform functional analysis. Thus, these tests will be performed only on samples obtained from inpatients.

Significance and Innovation

Molecular imaging by radiomic procedures and genomics through NGS may have an important and high diagnostic-therapeutic potential, however, to date there are neither large studies nor detailed information about the yield of their integrated, combined use. We suggest that an integrated approach to the study and characterization of pediatric brain tumors based on big data analysis may play a relevant role to identify prognostic factors and optimize novel forms of targeted therapy for precision personalized medicine.
It is estimated that CCS patients in the year 2020 will be 500,000 in Europe; thus, CCS will have a major impact on the national health services. This project will provide biochemical and molecular indicators of aging. Some of them could be possible targets that can be used for preventive intervention including new anti-aging drugs.

Description of the complementary and sinergy research team

All centers involved in this project network will contribute to the WP according to their specific relevance and in line with the regional priorities. Information provided by WP4 will include clinical information including patients¿ time to progression and survival rate, histopathological and molecular characterization of tumors, structural, functional and molecular imaging, and cell studies in long-term survivors. Especially for neuroimaging, sharing the data with the WP3 based on adult brain tumors will increase the sample size and consequently the significance of the statistical analysis.

Training and tutorial activities

Abstracts will be prepared to deliver the scientific results of this project during national and international meetings. Informal talks will be organized within the groups to improve synergy between researchers and to train younger investigators. When results are sufficiently validated, scientific papers will be written and submitted to peer reviewed journals.

Bibliography

[1] Johnson KJ, Cullen J, Barnholtz-Sloan JS, et al. Childhood brain tumor epidemiology: a brain tumor epidemiology consortium review. Cancer Epidemiol Biomarkers Prev 2014; 23:2716-36.
[2] Rossi A, Gandolfo C, Morana G, et al. New MR sequences (diffusion, perfusion, spectroscopy) in brain tumours. Pediatr Radiol 2010; 40:999-1009.
[3] Rossi Espagnet MC, Bernardi B, Pasquini L,et al. Signal intensity at unenhanced T1-weighted magnetic resonance in the globus pallidus and dentate nucleus after serial administrations of a macrocyclic gadolinium-based contrast agent in children. Pediatr Radiol 2017; 47:1345-1352.
[4] Morana G, Piccardo A, Milanaccio C, et al. Value of 18F-3,4-dihydroxyphenylalanine PET/MR image fusion in pediatric supratentorial infiltrative astrocytomas: a prospective pilot study. J Nucl Med 2014; 55:718-723.
[5] Sakata A, Okada T, Yamamoto Y, et al. Addition of amide proton transfer imaging to FDG-PET/CT improves diagnostic accuracy in glioma grading: a preliminary study using the continuous net reclassification analysis. AJNR Am J Neuroradiol 2018; 39:265-272.
[6] Gupta P, Jalali R. Long-term survivors of childhood brain tumors: impact on general health and quality of life. Curr Neurol Neurosci Rep 2017; 17:99.
[7] Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nat Rev Cancer. 2014 Jan;14(1):61-70.
[8] Morana G, Piccardo A, Tortora D, et al. Grading and outcome prediction of pediatric diffuse astrocytic tumors with diffusion and arterial spin labeling perfusion MRI in comparison with 18F-DOPA PET. Eur J Nucl Med Mol Imaging 2017; 44(12):2084-2093.
[9] Morana G, Tortora D, Staglianò S, et al. Pediatric astrocytic tumor grading: comparison between arterial spin labeling and dynamic susceptibility contrast MRI perfusion. Neuroradiology 2018; 60:437-446.

Timeline / Deliverables / Payable Milestones

In the course of the 36 months we will deliver the following results, as highlighted in the milestones below.
- A database comprising information from structural, functional and molecular neuroimaging in a wide array of pediatric brain tumors, together with clinical follow-up, histopathology, molecular characterization, and quantitative imaging texture features.
- Quantitative conventional and advanced MRI radiomic markers correlating with the pathological features.
- A machine learning- based prognostic model, whose efficacy will be validated in a prospectively collected independent cohort of patients.
- An array of cellular biomarkers obtained in CCS patients and healthy peer controls will be produced based on monocyte sample collections, including biomarkers of mitochondrial function, dynamics, biogenesis and distribution, mitophagy, NAD+content assay, degrading and synthetizing enzymes, and sirtuin lysine deacetylation activity of target proteins.

Project Title: P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.	
Project Code: NET-2018-12366666-4	**Principal Investigator:** Rossi Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Milestones 18 month

Aim 1: Selection of the retrospective patient cohort; data-gathering; quantitative radiomic features extraction from the analysis of conventional and advanced MRI acquisitions; correlation of quantitative parameters with clinical and histopathological data.
Aim 2: Full operation of APT and Compressed SENSE softwares; selection of at least 1/3 of the prospective cohort.
Aim 3: Investigation of MNC mitochondrial functions of CCS compared with healthy donors.

Milestones 36 month

Aim 1: no action (completed at 18 months)
Aim 2: selection of the remaining 2/3 of the prospective cohort; data-gathering; quantitative radiomic features extraction from the analysis of conventional and advanced MRI acquisitions; correlation of quantitative parameters with clinical and histopathological data; machine learning-based validation of the prognostic models in the prospective cohort of patients.
Aim 3: Evaluation of NAD+ content and sirtuin activity.

Gantt chart

Gaslini_Gantt chart_RF2018.pdf

Equipment and resources available

Facilities Available
MRI - 3T scanner Ingenia Cx Philips, Best, The Netherlands
MRI- 1.5T scanner Intera Achieva Philips, Best. The Netherlands
PET/CT Discovery LS or STE, GE Medical Systems, Milwaukee, WI, USA (located at Ospedali Galliera, Genova, Italy)
The Stem Cell and Cell Therapy Lab equipment includes: Sterile laminar flow hoods, chemical hoods, CO2 incubators, optical microscopes, centrifuges, refrigerators (+4°C, -20°C and -80°C),
PCR thermal cyclers, electrophoresis apparatus, spectrophotometer, and speed-vacuum apparatus. In addition, it has access to the following facilities: citology, flow cytometry [a FACS sorter (MoFlo Astrios Beckman Coulter) and a FACSCanto II Cytometer (Becton Dickinson)] , molecular biology including ABI prism 7900 for Real Time PCR (AppliedBiosystem); proteomics: nHPLC ULTIMATE 3000, a new generation Mass Spectrometer (LTQ Orbitrap Velos Pro, Thermo Scientific), confocal microscope for immunofluorescence experiments, cryopreservation, biochemical equipments (pHmeter, oxymeter, luminometer and imaging acquire system).

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Project Code: NET-2018-12366666-4	**Principal Investigator:** Rossi Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Translational relevance and impact for the National Health System (SSN)

The identification of molecular and biological biomarkers of pediatric brain tumors in a noninvasive fashion through the use of MRI and PET data has the great potential of predicting prognostic factors. This may have a profound impact into the selection of targeted treatments and personalized approaches for precision medicine. This has the advantage of reducing unnecessary toxic effect due to disproportioned forms of treatment, which in turn have profound impact in terms of quality of life and long-term management costs in survivors. In parallel, the increase of long term survivors (CCS patients) creates the need of a cell-level research platform that may identify factors involved in early aging; possible aging related targets could be thus identified. This approach could create a model for studying aging effects that could be translated to other areas (ie, research on aging and dementia).

Project Title: P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-4

Principal Investigator: Rossi Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

PRINCIPAL INVESTIGATOR PROFILE

Name		
Rossi Andrea	Institution	Istituto Giannina Gaslini
	Department/Unit	Neuroradiology Unit
	Position Title	Head

Personal Statement

This workpackage is focused on gathering structural and metabolic information from neuroimaging studies performed in children harboring low- and high grade gliomas and ependymomas, as well as providing histological samples of tumors and patient¿s blood for genetic studies. As Head of the Neuroradiology department of the Gaslini Pediatric Hospital, I will be primarily responsible of acquisition of MRI studies, overseeing the imaging study protocols and setting up the examinations including structural and metabolic information. Whenever applicable, I will also oversee the execution of PET studies in conjunction with the MRI investigation. Finally, I will be responsible for the interpretation of these imaging studies and for the transmission of the imaging raw data to the study platform.

Education/Training - Institution and Location	Degree	Year(s)	Field of study
European Board of Neuroradiology	European Diploma in Pediatric Neuroradiology	1	Neuroradiology
European Board of Neuroradiology	European Diploma in Neuroradiology	1	Neuroradiology
University of Florence	Specialization in Radiology	4	Radiology
University of Genoa	Laurea in Medicina e Chirurgia	6	Medicine

Project Title: P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-4

Principal Investigator: Rossi Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Positions

Institution	Division / Research group	Location	Position	From year	To year
IRCCS Istituto Giannina Gaslini	Neuroradiology	Genoa	Head of Unit	2007	2018
Italian Association of Neuroradiology	Executive Committee	Milan	Vice President	2017	2018
Turkish Society of Neuroradiology	Turkish Society of Neuroradiology	Istanbul	Honorary Member	2015	2018
European Society of Neuroradiology	Executive Committee	Zurich	Secretary General	2014	2018
Serbian Society of Neuroradiology	Serbian Society of Neuroradiology	Belgrado	Honorary Member	2014	2018
Royal Society of Belgian Radiology	Royal Society of Belgian Radiology	Bruxelles	Honorary Member	2011	2011
University of Genoa	DINOGMI; DISSAL	Genoa	Contract Professor of Neuroradiology	2008	2018
European Society of Neuroradiology	Executive Committee	Zurich	Pediatric Com Chair	2008	2014
Medical University of South Carolina	Neuroradiology	Charleston	Visiting Professor	2007	2007
IRCCS Istituto Giannina Gaslini	Neuroradiology	Genoa	Collaborator	1999	2006

Official H index: 33.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 7403475016

ORCID ID: 0000-0001-8575-700X **RESEARCH ID:** A-4146-2011

Awards and Honors:

Quiz case prize, XVI Congress of the Italian Association of Neuroradiology. Napoli, 12-15/12/1999.
Poster prize, 26th congress of the European Society of Neuroradiology. Oslo (Norway), 10-13/9/2000, ¿Disorders of notochordal formation: MRI findings with embryological correlation¿.
Education exhibit prize. 87th annual meeting of the Radiological Society of North America. Chicago (USA), 25-30/11/2001.
Prize ¿Bracchi¿ 2002, Italian Association of Neuroradiology

Other CV Informations:

National scientific qualification as Full Professor and Associate Professor in Radiology and Neuroradiology
Pediatric Section Editor, ¿Neuroradiology¿ journal
Editorial Board member, ¿Pediatric Radiology¿ journal
President of the 10th Italian Congress of Pediatric Neuroradiology (Genova, Italy, 2010)
Director, ¿Gaslini¿ Advanced Course in Pediatric Neuroradiology, 1st & 2nd edition (Genova, 2012, 2013)
Director, European Course in Pediatric Neuroradiology (ECPNR), 2010-2019
Co-President, 13rd Italian Congress of Pediatric Neuroradiology (Roma, Italy, 2016)

	Project Title: P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.
Project Code: NET-2018-12366666-4	**Principal Investigator:** Rossi Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Pediatric Neuro Scientific Chair for the XXI Symposium Neuroradiologicum (Taipei, 2018)
President of the International Pediatric Radiology congress (Rome, 2021)
COST Action network: Co-leader of Neuro-Mig Network Work Group 2

Project Title:
P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-4

Principal Investigator: Rossi Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Selected peer-reviewed publications of the PI

Valid for PI minimum expertise level

Title	DOI	PMID	Cit. **	P.*
Late persistent increased putaminal 18F-DOPA uptake following ipsilateral frontal resection: Evidence for corticostriatal synaptic plasticity?	10.1097/RLU.0000000000000798	25899596	3	L
18F-DOPA uptake of developmental venous anomalies in children with brain tumors Late persistent increased putaminal 18F-DOPA uptake following ipsilateral frontal resection: Evidence for corticostriatal synaptic plasticity?	10.1097/RLU.0000000000001189	26909711	4	L
Grading and outcome prediction of pediatric diffuse astrocytic tumors with diffusion and arterial spin labeling perfusion MRI in comparison with 18F¿DOPA PET	10.1007/s00259-017-3777-2	n.a.	4	L
Bilateral germinoma of the basal ganglia	10.1002/pbc.20905	16700048	11	F
Multimodal magnetic resonance imaging and18F-L- dihydroxyphenylalanine positron emission tomography in early characterization of pseudoresponse and nonenhancing tumor progression in a pediatric patient with malignant transformation of ganglioglioma treated with bevacizumab	10.1200/JCO.2012.43.6113	23169514	11	L
Prenatal MR imaging of dural sinus malformation: A case report	10.1002/pd.1347	16378320	21	F
Current Classification and Imaging of Congenital Spinal Abnormalities	10.1053/j.ro.2006.07.001	17010690	22	F
Neuroimaging of pediatric craniopharyngiomas: A pictorial essay	n.a.	16700305	26	F
Internal jugular vein phlebectasia and duplication: Case report with magnetic resonance angiography features	10.1007/s002470000350	11214685	29	F
Tumors of the Spine in Children	10.1016/j.nic.2006.11.004	17493537	29	F
New MR sequences (diffusion, perfusion, spectroscopy) in brain tumours	10.1007/s00247-010-1613-y	20432019	29	F
MR imaging of brain-stem hypoplasia in horizontal gaze palsy with progressive scoliosis	n.a.	15205146	33	F
Posterior fossa and arterial abnormalities in patients with facial capillary haemangioma: Presumed incomplete phenotypic expression of PHACES syndrome	10.1007/s002340100594	11760796	34	F
Spectrum of nonterminal myelocystoceles	10.1227/01.NEU.0000197122.92954.82	16528191	35	F
Congenital tumors of the central nervous system	10.1007/s00234-010-0699-0	20428859	44	L
Imaging of Acute Disseminated Encephalomyelitis	10.1016/j.nic.2007.12.007	18319160	52	F
Spinal dysraphism: MR imaging rationale	10.1016/S0150-9861(04)96875-7	15026728	56	F

Project Title:
P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-4

Principal Investigator: Rossi Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Title	DOI	PMID	Cit. **	P.*
Imaging in spine and spinal cord malformations	10.1016/j.ejrad.2003.10.015	15081131	56	F
Early-onset combined methylmalonic aciduria and homocystinuria: Neuroradiologic findings	n.a.	11237984	58	F
Leigh syndrome with COX deficiency and SURF1 gene mutations: MR imaging findings	n.a.	12812953	61	F

* Position: F=First L=Last C=Corrispondent

** Autocertificated

For evaluation CV

Title	DOI	PMID	Cit. *
Magnetic resonance imaging spectrum of medulloblastoma	10.1007/s00234-010-0829-8	21279509	32
New MR sequences (diffusion, perfusion, spectroscopy) in brain tumours	10.1007/s00247-010-1613-y	20432019	29
Congenital tumors of the central nervous system	10.1007/s00234-010-0699-0	20428859	44
Medulloblastoma variants: Age-dependent occurrence and relation to gorlin syndrome-a new clinical perspective	10.1158/1078-0432.CCR-08-2023 19276247	19276247	71
Multimodality imaging of Hodgkin disease and non-Hodgkin lymphomas in children	10.1148/rg.275065157	17848695	60
Tumors of the Spine in Children	10.1016/j.nic.2006.11.004	17493537	29
Neuroimaging of pediatric craniopharyngiomas: A pictorial essay	n.a.	16700305	26
Extraventricular neurocytoma with ganglionic differentiation associated with complex partial seizures	n.a.	10319989	48
Medulloblastoma in children: CT and MRI findings	10.1007/s002340050260	8738095	40
Ependymomas of the posterior cranial fossa: CT and MRI findings	10.1007/BF01578265	7603602	28

* Autocertificated

	Project Title: P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.
Project Code: NET-2018-12366666-4	**Principal Investigator:** Rossi Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Grant

Funded Institution / Country	Year	Title	Position in Projects
Ministero Salute e Regione Liguria	2007	Molecular and genetic study, and neuro-radiological characterization of central congenital hypoventilation syndrome (CCHS): assessment of clinical correlations and therapeutic implications	Collaborator

Employment contract extension:

(Data changed during the moratorium period)

Project Title: P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-4

Principal Investigator: Rossi Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Biographical Sketch Contributors 1

Name: morana giovanni

Institution: Istituto Giannina Gaslini
Department/Unit: Neurosciences/Neuroradiology
Position Title: Collaborator

Education/Training - Institution and Location	Degree	Year(s)	Field of study
University of Genoa	PhD in Neuroscience	3	Neuroscience
European Board of Neuroradiology	European Diploman in Neuroradiology	2	Neuroradiology
The Children¿s Hospital of Philadelphia, USA	Internship at the Division of Neuroradiology, Department of Radiology	1	Neuroradiology
University ¿G. d¿Annunzio¿, Chieti	Specialization in Radiology	4	Radiology
Università Cattolica del Sacro Cuore, Rome	Laurea in Medicina e Chirurgia	6	Medicine

Personal Statement:

In view of my High Specialization Appointment in Oncological Neuroimaging at the Neuroradiology Unitof the Gaslini Pediatric Hospital and my expertise in molecular imaging, I will be responsible of the acquisition and analysis of uniformly acquired and spatially co-registered multiparametric structural and functional MRI data. I will also perform a multimodal integration of advanced MRI data with molecular PET imaging. Finally, I will help in the interpretation of these imaging studies and in the transmission of the imaging raw data to the study platform.

Institution	Division / Research group	Location	Position	From year	To year
IRCCS Istituto Giannina Gaslini	Neuroradiology	Genoa	Collaborator	2007	2018
University of Genoa	Dipartimento di Neuroscienze, riabilitazione, oftalmologia, genetica e scienze materno-infantili (DINOGMI)	Genoa	Contract professor of Neuroradiology	2012	2018

Awards and Honors

Official H index: 11.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 57194321684

ORCID ID: 0000-0001-8707-5969 **RESEARCH ID:** J-6134-2018

Awards and Honors:

Grant winner from Associazione Italiana di Neuroradiologia (AINR), 2009
- Fellow of the International Cancer Imaging Society (ICIS) since 2015
- Recognition as an expert peer reviewer of submitted scientific papers to the journal Neuroradiology, 2017
- Board member dell¿Associazione Italiana di Neuroradiologia (AINR), since 2017

Project Title: P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-4

Principal Investigator: Rossi Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Biographical Sketch Contributors 2

Name: Frassoni Francesco

Institution: Istituto Giannina Gaslini
Department/Unit: Research Laboratories
Position Title: Director

Education/Training - Institution and Location	Degree	Year(s)	Field of study
University of Genoa	Specialization in Oncology	3	Oncology
University of Genoa	Specialization in Hematology	3	Hematology
University of Pavia	Specialization in Internal Medicine	3	Internal Medicine
University of Pavia	Laurea in Medicina e Chirurgia	5	Medicine

Personal Statement:

Seventy to eighty percent of children with cancer survive and become Childhood Cancer Survivors (CCS). They frail and experience a sort of anticipated aging. We have identified biochemical and molecular markers/indicators of aging at cellule level in normal subjected (aged 1-100 yrs). They are bases on the glucose metabolism and mitochondria function. We shall apply these indicators to predict anticipated aging in CCS. We shall try to identify correlations and predictions of morbidity in CCS.

Institution	Division / Research group	Location	Position	From year	To year
IRCCS Istituto Giannina Gaslini	Department of Research Labs.	Genova	Director	2017	2018
IRCCS Istituto Giannina Gaslini	Department of Hemato-Oncology	Genova	Director	2013	2017
IRCCS Istituto Giannina Gaslini	Stem Cell and Cell Therapy Lab	Genova	Head	2012	2013
Ospedali Civili San Martino	Stem Cell and Cell Therapy Lab	Genova	Head	2003	2013
Ospedali Civili San Martino	Division of Hematology	Genova	Collaborator	1981	2012

Awards and Honors

Official H index: 59.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 7005144193

ORCID ID: 0000-0003-1262-0648 **RESEARCH ID:** K-3971-2018

Awards and Honors:

from 1992 Professor at the Postgraduate Specialization School of Haematology at the University of Pavia and University of

	Project Title: P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.
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Project Type: WP PROJECT - 4

Genova
Teacher at the European School of Hematology
1998 to 2004: Chairman of the Working Party for Acute Leukemia of 'Eurpean Group for Bone Marrow Transplantation (EBMT)
Visiting professor, Department of Human Genetics, Memorial Sloan Kettering Cancer Centre , New York.

Project Title:
P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-4

Principal Investigator: Rossi Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Expertise Research Collaborators

Selected peer-reviewed publications of the Research Group / Collaborators

Collaborator	Title	DOI	PMID	Cit. *
Frassoni Francesco	Allogeneic cell transplant expands bone marrow distribution by colonizing previously abandoned areas: an FDGPET/CT analysis	10.1182/blood-2015-01-618215	25957389	8
morana giovanni	Diagnostic and prognostic value of 18F-DOPA PET and 1H-MR spectroscopy in pediatric supratentorial infiltrative gliomas: A comparative study	10.1093/neuonc/nov099	26405202	15
morana giovanni	Value of 18F-3,4-dihydroxyphenylalanine PET/MR image fusion in pediatric supratentorial infiltrative astrocytomas: A prospective pilot study	10.2967/jnumed.113.125500	24652828	17
morana giovanni	Prognostic value of 18F-DOPA PET/CT at the time of recurrence in patients affected by neuroblastoma	10.1007/s00259-014-2691-0	24562643	18
morana giovanni	New MR sequences (diffusion, perfusion, spectroscopy) in brain tumours	10.1007/s00247-010-1613-y	20432019	29
morana giovanni	Medulloblastoma variants: Age-dependent occurrence and relation to gorlin syndrome-a new clinical perspective	10.1158/1078-0432.CCR-08-2023	19276247	71
Frassoni Francesco	Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study	10.1016/S0140-6736(08)60690-X	18468541	1654
Frassoni Francesco	Direct intra-bone transplant of unrelated cord-blood cells in acute leukaemia: a phase I/II study	10.1016/S1470-2045(08)70180-3	18693069	74
Frassoni Francesco	Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia	10.1056/NEJMoa041469	15564544	830
Frassoni Francesco	Cord blood transplantation provides better reconstitution of hematopoietic reservoir compared with bone marrow transplantation	10.1182/blood-2003-03-0720	12689932	62

* Autocertificated

	Project Title: P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.
Project Code: NET-2018-12366666-4	**Principal Investigator:** Rossi Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Grant

Funded Institution / Country	Year	Title	Position in Projects	Collaborator
Compagnia di San Paolo/Italy	2018	Ruolo Terapeutico del 64CuCl2 nel trattamento di bambini affetti da recidiva di Glioma ad Alto Grado (HGG) o di Tumori Intrinseci Diffusi del Ponte (DIPG)	Collaborator	morana giovanni
Compagnia di San Paolo/Italy	2015	Le cellule staminali del sangue nei guariti di leucemia¿ Codice SIME 2013-0958 (codice ROL 4201)	Coordinator	Frassoni Francesco
Ministero Salute/Italy	2010	The trafficking of hematopoietic stem cells and their bone marrow homing as the prerequisites to improve the outcome of transplant	Coordinator	Frassoni Francesco
Ministero Salute e Regione Liguria/Italy	2009	Studio del traffico e della distribuzione di cellule staminali ematopoietiche, mesenchimali ed endoteliali per disegnare appropriatamente le terapie cellulari	Coordinator	Frassoni Francesco
AIRC/Italy	2009	Intra-Bone Marrow Transplant	Coordinator	Frassoni Francesco
AIRC/Italy	2004	Intra-Bone Marrow injection of Cord Blood Hematopoietic cells as an alternative way of transplantation to overcome the cell dose barrier	Coordinator	Frassoni Francesco
Ministero Salute e Regione Liguria/Italy	2007	Mesenchymal stem cells for the treatment of amyotrophic lateral sclerosis experimental approach and clinical translation	Collaborator	Frassoni Francesco
Compagnia di San Paolo/Italy	2006	Produzione di prodotti cellulari all¿interno di strutture di laboratorio GMP per la Terapia Cellulare	Coordinator	Frassoni Francesco
Banca CARIGE/Italy	2003	Progetto Genova sulle Cellule Staminali	Coordinator	Frassoni Francesco
Compagnia di San Paolo/Italy	2003	Completamento dell¿Unità Terapia Centro Cellulare e Centro Cellule Staminali, Ospedale San Martino di Genova	Coordinator	Frassoni Francesco

Project Title:
P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.

Project Code: NET-2018-12366666-4

Principal Investigator: Rossi Andrea

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Total proposed budget (Euro)

Costs	TOTAL BUDGET	Co-Funding	Project costs proposed to funding Organization (no MOH request)	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1a Staff Salary	80.000,00	80.000,00	0,00	not permitted	0,00
1b Researchers' Contracts	150.000,00	0,00	82.500,00	67.500,00	50,00
2 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00	0,00
3a Supplies	29.100,00	0,00	0,00	29.100,00	21,56
3b Model Costs	0,00	0,00	0,00	0,00	0,00
3c Subcontracts	0,00	0,00	0,00	0,00	0,00
3d Patient Costs	0,00	0,00	0,00	0,00	0,00
4 IT Services and Data Bases	75.000,00	0,00	51.450,00	23.550,00	17,44
5 Publication Costs	5.400,00	0,00	2.700,00	2.700,00	2,00
6 Convegni	2.700,00	0,00	1.350,00	1.350,00	1,00
7 Travels	0,00	0,00	0,00	0,00	0,00
8 Overheads	22.800,00	0,00	12.000,00	10.800,00	8,00
9 Coordination Costs	0,00	0,00	0,00	0,00	0,00
Total	365.000,00	80.000,00	150.000,00	135.000,00	100,00

Report the Co-Funding Contributor:

Co-Funding IRCCS Istituto Giannina Gaslini

	Project Title: P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.
Project Code: NET-2018-12366666-4	**Principal Investigator:** Rossi Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

Budget Justification	
1a Staff Salary	20% yearly research group salary
1b Researchers' Contracts	1 neuroradiologist, 1 MRI physicist
2 Equipment (Leasing - Rent)	none
3a Supplies	biochemical and molecular biology reagents, lab equipment
3b Model Costs	none
3c Subcontracts	none
3d Patient Costs	none
4 IT Services and Data Bases	MRI software rent (APT, compressed SENSE)
5 Publication Costs	Open access expenses
6 Convegni	Travelling and registration costs for congress participation
7 Travels	none
8 Overheads	Indirect and general costs
9 Coordination Costs	none

	Project Title: P3 (preventive, predictive and personalized) solutions in pediatric neuroncology driven by imaging and biological data.
Project Code: NET-2018-12366666-4	**Principal Investigator:** Rossi Andrea
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Istituto Giannina Gaslini

Project Type: WP PROJECT - 4

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by clinical and cognitive data.
Project Code: NET-2018-12366666-5	**Principal Investigator:** AMATO MARIA PIA
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Toscana

Project Type: WP PROJECT - 5

Major Diagnostic Category*: Neurologia

Project Classification IRG: Bioengineering Sciences and Technologies

Project Classification SS: Biodata Management and Analysis - BDMA

Project Keyword 1: Methods for data analysis including: Numerical, statistical, mathematical and theoretical approaches to design and interpretation of large-scale studies such as methods for pattern discovery, data mining, sequence prediction, biomarker identification, therapeutic drug design and high throughput analyses; computational methods for organizing, maintaining, and integrating biological datasets and for large scale data modeling and simulations.

Project Keyword 2: Database technologies and methods for data management, data representation, data capture, data integrity and validation

Project Keyword 3: Brain Disorders and Clinical Neuroscience

Project duration (months): 36

Project Request: **Animals:** ☐ **Humans:** ☒ **Clinical trial:** ☐

The object/s of this application is/are under patent copyright Y/N: ☐

Investigators, Institution and Role in the Project

	Co-PI	Key Personnel	Institution/Org./Pos.	Role in the project	Birth Date
1	X	Pancani Silvia	FONDAZIONE DON CARLO GNOCCHI	Co-PI	22/09/1985

Overall Summary

Multiple sclerosis (MS) is highly heterogeneous in its clinical course and outcome. Beyond physical disability, cognitive dysfunction (CD) is recognized as a prevalent and debilitating symptom of the disease. The wide variation of treatments currently available for MS is fostering a focus on evidence-based personalization of treatment. Global collaborations to gather standardized clinical and neuropsychological information together with paraclinical data has the potential to address important questions about prognostic prediction and treatment effectiveness in individual patients. In a retrospective cohort of MS patients, detailed clinical and neuropsychological information will be extracted by our computerized database, in order to contribute to the characterization and subtyping of MS patients for the prediction of patient outcome and the development of individualized therapeutic strategies. The results will be validated in a separate, entirely prospective cohort.

Background / State of Art

Multiple sclerosis (MS) is a demyelinating, immune-mediated disease of the CNS with onset usually in young adulthood and chronic evolution over decades. It is highly heterogeneous in its clinical course, symptoms and complications . Beyond physical disability, cognitive dysfunction (CD) is increasingly recognized as a prevalent and debilitating symptom of the disease. CD represents a considerable burden to patients and to society, due to the negative impact on everyday functioning, social and work activities [1]. There is also increasing evidence that CD is an independent prognostic predictor, associated with a worse disease outcome [2]. Standardized and well-validated neuropsychological batteries have been

developed for the cognitive assessment of MS patients, such as the Rao¿s brief battery [3] and the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) [4], for which normative data in the Italian population are available [5, 6]. Detailed neuropsychological assessment in combination with quantitative and functional Magnetic Resonance (MR) techniques have contributed to shed some light on the pathological chages underlying MS-related CD and potential mechanisms of compensation. Among the most relevant MR correlates of CD are grey matter damage at both cortical and subcortical level, cortical lesions, as well as white matter lesions and normal-appearing white matter changes. Findings on cortical reorganisation support the contribution of brain plasticity and cognitive reserve in limiting cognitive deficits [7].

In previous research, motor and cognitive impairments in MS patients were commonly examined independently of each other. More recently, research of simultaneous performance of motor and cognitive tasks has identified an interaction between them which is common in MS [1]. Monotasking under ideal conditions may not capture patient-reported real-world de¿cits, especially in multitasking. Indeed, evidence suggests that cognition is more negatively a¿ected in patients with MS (relative to controls) when performing a cognitive¿ motor dual task. In addition to existing neuropsychological tools, the ¿eld should develop, validate, and utilize cognitive¿ cognitive and cognitive¿motor dual-task paradigms to better address patient-reported multitasking de¿cits, which may be more sensitive for identifying real-world functional de¿cits and predicting future decline[1].

Over the past decade, the therapeutic scenario in MS has evolved substantially, with the development of different effective disease modifying treatments. The wide variation in convenience, efficacy and risk of treatments for MS is fostering a focus on evidence-based personalization of treatment, to optimize the benefit-to-risk ratio for individual patients [8]. The importance of early and optimized treatment according to disease subtype (e.g., relapsing vs progressive MS); disease activity (active vs non active,¿benign¿ vs ¿malignant¿); specific symptoms, comorbidities, clinical and neuropsychological patient characteristics is increasingly emphasized. Global collaborations to gather accurate clinical and neuropsychological information starting from the early disease stages -- together with imaging, neurophysiological and laboratory data ¿ has the potential to address important questions about the natural history, early prognostic prediction, treatment effectiveness and adverse events in individual patients [8]. Personalized medicine remains an important unmet clinical need in MS, since up to now a well-validated and reliable prognostic biomarker is not available for the disease [8]. The aim of this project is a standardized and accurate characterization and subtyping of MS patients based on their clinical and neuropsychological features, in order to contribute to the prediction of the patient clinical outcome and the development of individualized patient therapeutic strategies.

Hyphotesis and Specific AIMS

Hyphotesis and Significance:

One of the biggest clinical impacts of MS research over the past decade has been the remarkable expansion in the range of approved treatments. However, the wide variation in convenience, efficacy and risk of treatments for MS is fostering a focus on evidence-based per¬sonalization of treatment to optimize the benefit-to-risk ratio for individual patients [8].

Randomized controlled trials (RCTs) are accepted as the gold standard for assessing the efficacy and safety of any new drug, but conclusions of these trials do not always aid in daily decision-making processes regarding the individual patient. In the past decade, a growing number of MS databases and registries have been established to produce long-term outcome data from large cohorts of patients with MS treated with disease-modifying therapies in the real-world settings. Such observational studies can address issues that are otherwise difficult or impossible to study [9]. Research into this approach includes the development of algorithms that can classify patients according to their risk of disease progression and enable treatment deci¬sions to be based on patient individual characteristics. This observational study is based on two cohorts of MS patients (one retrospective ¿discovery cohort¿, and one prospective ¿validation cohort¿) systematically followed-up

from the clinical onset of the disease in which clinical and neuropsychological information is collected in a standardized, longitudinal manner. The first study aim is to assess the clinical and neuropsychological variables that best predict different disese outcomes in terms of time to reach irreversible disability ¿milestones¿ and shift from the relapsing to the secondary progressive phase of the disease; the second study aim is to assess
the clinical and neuropsychological variables that best predict different individual treatment response and risk of developing treatment-related adverse events; the third study aim is to assess the potential contribution to prognostic prediction of quantitative measures of motion analysis and dual task test.

Preliminary Data:

The electronic database of the MS Center of the University of Florence, established since 1998 and currently participating in the Italian MS Registry, is gathering data on nearly 2000 MS patients. A sizeable proportion of patients referred to this Center has been systematically followed-up from the clinical onset of the disease (estimated number nearly 700). The database stores prospectively collected, standardized and detailed information about the patient clinical characteristics at disease onset and during the follow-up, disability accrual assessed on the Expanded Disability Status Scale (EDSS), relapses, comorbidities, results of periodic neuropsychological and psychosocial assessments on validated assessment tools developed for MS: the Rao¿s battery [3], the BICAMS [4] , the Montgomery and Asberg Rating Scale for Depression (MADRS) [10] , the Fatigue Severity Scale (FSS) [11] , together with other relevant laboratory, imaging and therapeutic information.
Patients are regularly followed- up every six months and in occasion of relapses and adverse events related to treatments. The database has served to publish a number of collaborative studies on cognitive dysfunction in different disease subtypes, MR correlates of cognitive dysfunction and natural history of the disease.

Specific Aim 1:

To assess the clinical and neuropsychological variables at disease onset that best predict different disese outcomes, individual treatment response and risk of developing treatment-related adverse events in a retrospective, discovery cohort extracted from our database.

Specific Aim 2:

To repeat this analysis in a prospective validation cohort of patients consecutively referred to our Center and prospectively followed-up from the disease onset, in order to validate the above results.

Specific Aim 3:

In the prospective validation cohort, to assess the added predictive value of measures of motion analysis, together with classic disability scales, and of dual task measures, together with classic neuropsychological tests.

Experimental Design Aim 1:

A retrospective cohort of MS patients followed-up from the clinical onset of the disease with complete clinical, neuropsychological and psychosocial information at the disease onset and during the follow-up period will be identified in our database.
Data will include the main demographic and clinical characteristics at disease onset: age, sex, age at disease onset, educational level, family history, comorbidities, disease course, EDSS, scores on the Rao¿s battery, BICAMS , MADRS and FSS, symptomatic and disease modifying treatments.

Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by clinical and cognitive data.

Project Code: NET-2018-12366666-5

Principal Investigator: AMATO MARIA PIA

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Toscana

Project Type: WP PROJECT - 5

Follow-up data collected at six-month intervals and in occasion of relapses will be also retrieved: relapses, disability scores, disease course, changes of scores on neuropsychological and psychosocial scales, treatments, response to treatments and treatment-related adverse events.
Patient survival curves for EDSS milestones and shift from the relapsing-remitting to the secondary progressive course will be analyzed by the method of Kaplan and Meier and the log-rank test. Stepwise multivariable logistic and linear models will be also used. Propensity-scores adjusted analyses will be provided to reduce the biases of observational, non-randomized studies.

Experimental Design Aim 2:
The above clinical, neuropsychological and psychosocial information will be collected in a prospective cohort of patients consecutively referred to our MS Center and prospectively followed-up from the clinical onset of the disease. After having trained our prediction models on the retrospective cohort, we will test them in this separate, entirely prospective validation cohort.

Experimental Design Aim 3:
In the prospective cohort, quantitative parameters of motion analysis and the dual task will be also assessed at baseline and during the follow-up at six-month intervals. The motion analysis will be performed through kinematic and kinetic analyses, and surface EMG, focusing on functional tasks involving the trunk, upper limbs (eg grasping, manipulating, reaching) and lower limbs (eg gait, stepping over obstacles). To measure the motor-cognitive interference we will use different equipments integrated ad hoc that allow to measure at the same time motor and cognitive performances under different combinations of motor and cognitive stimuli, thus providing an innovative approach to the study of the dual task paradigm.
The potential role of these objective quantitative tests in improving patient characterization and prognostic prediction will be evaluated.

Picture to support preliminary data:

Metodologies and statistical analyses:
We expect to extract nearly 700 patients followed up from the disease onset in our computerized database for the analysis of clinical and neuropsychological variables in the retrospective cohort; moreover, to recruit nearly 100 patients in the prospective cohort.
Patient survival curves for EDSS milestones and shift from the relapsing-remitting to the secondary progressive course will be analyzed by the method of Kaplan and Meier and the log-rank test. Stepwise multivariable logistic and linear models will be also used. Propensity-scores adjusted analyses will be provided to reduce the biases of observational, non-randomized studies.
Parametric and nonparametric tests, as appropriated based on the variables analyzed, will be used to assess the results of motion analysis and dual task test.

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Expected outcomes:
It is likely that the results of the proposed project will provide a novel platform for an advanced interpretation of clinical and neuropsychological data, offering an opportunity for subtyping MS patients in different prognostic groups and pursuing personalized treatments.

Risk analysis, possible problems and solutions:
1) The completeness and quality of information stored in the database for the retrospective cohort can be suboptimal. To cope with this problem there are algorithms included in the system that automatically find out inconsistencies and errors in the data entry phase; moreover, quality controls of data gathered by Centers participating in the Italian MS Registry are periodically performed. Lastly, in case of incomplete/inconsistent information, a revision of the patient clinical charts and, when applicable, direct patient re-assessment will be performed.
2) Excessive drop-out rate during the follow-up period can undermine the validity of results. This issue will be dealt with and minimized by periodic telephonic contacts with the patients, in order to remind them the follow-up visits.
3) Absence of randomization in observational studies can generate biases in performing comparison between groups of patients. This issue will be dealt with in the statistical analysis using the propensity-score matching.

Significance and Innovation

Personalized medicine remains an important unmet clinical need in MS, since up to now well validated and reliable prognostic biomarkers are not available for the disease. The results of this project can provide an accurate characterization and subtyping of MS patients contributing to the prediction of the patient clinical outcome and the development of individualized therapeutic strategies. Moreover, for the first time, the contribution of quantitative measures of motion analysis and dual task test to patient subtyping will be formally assessed.

Description of the complementary and sinergy research team

All centers involved in this project network will contribute to the WP according to their specific relevance and in line with the regional priorities.
In particular, our data are complementary to those provided by WP1 to incorporate imaging and biological data together with clinical and neuropsychological information in order to improve the accuracy of the prognostic models.

Training and tutorial activities

n.a.

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by clinical and cognitive data.
Project Code: NET-2018-12366666-5	**Principal Investigator:** AMATO MARIA PIA
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Toscana

Project Type: WP PROJECT - 5

Bibliography

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8: Matthews PM. Decade in review-multiple sclerosis: new drugs and personalized medicine for multiple sclerosis. Nat Rev Neurol. 2015
9: Trojano M, Tintore M, Montalban X, et al. Nat Rev Neurol. 2017
10: Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979
11: Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989

Timeline / Deliverables / Payable Milestones

We trust that we will be able to accomplish the proposed tasks in due time.
The MS database is regularly updated at the MS Center, University of Florence and it contains the main clinical and neuropsycological data to be extracted for the analysis of the retrospective cohort. As for the prospective cohort, newly diagnosed MS patients are referred to the MS Center and regularly followed up.
By this project we will be able to gather a comprehensive dataset of clinical and neuropsychological information that can help prognostic prediction and personalized treatment strategies in individual patients.

Milestones 18 month

Aim 1
Month 1-3: Identification of the retrospective MS cohort in the database
Month 4-18: Extraction of data of the retrospective MS cohort from the database

Aim 2
Month 1-18: Beginning of collection of data of MS patients referred to our Center and prospectively followed up (prospective cohort)

Month 1-18: Beginning of implementation of data from the prospective cohort

Aim 3
Month 1-18: Beginning of collection of data on motion analysis and "dual task" in the prospective cohort

Milestones 36 month

Aim 1
Month 19-30: Elaboration of predictive models from the retrospective cohort

Aim 2
Month 18-30: Continuation of collection of data of MS patients referred to our Center and prospectively followed up (prospective cohort)
Month 18-30: Continuation of implementation of data from the prospective cohort

Aim 3
Month 18-30: Continuation of collection of data on motion analysis and "dual task" in the prospective cohort

Month 31-34: Validation of the predictive models in the prospective cohort

Gantt chart

Firenze_Gantt_RF2018.pdf

Equipment and resources available

The MS Center at the University of Florence is maintaining a computerized database that participates in the Italian MS Registry.
At the Don Gnocchi Institute of Florence sEMG and materials for the neuropsychological tests are available. The Institute will be provided for this project with equipments necessary for performing the motion analysis and the dual task test.

Subcontracts are included for reporting and /or technical services

Translational relevance and impact for the National Health System (SSN)

The project can help stratify different prognostic groups and foster individualized patient management in MS. This may substantially increase appropriateness of prescriptions, improve disease outcomes and reduce treatment-associated risks, thus contributing to reduce direct and indirect disease-related costs for the national health system.

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Applicant Institution: Toscana

Project Type: WP PROJECT - 5

PRINCIPAL INVESTIGATOR PROFILE

Name		
AMATO MARIA PIA	Institution	Toscana
	Department/Unit	DEP. NEUROFARBA - CTO AOU CAREGGI
	Position Title	FULL PROFESSOR IN NEUROLOGY

Personal Statement

Participation in and coordination of several research projects on Multiple Sclerosis (MS), at both the national and international level, with a particular focus on neuropsychology, clinical epidemiology, prognosis and therapy. Participation in several clinical trials according to GCP. Author of more than 230 publications on peer reviewed journals indexed in MED-line.
The focus of WP5 is the collection of clinical, neuropsychological and psychosocial data of MS patients, referred to our MS center from the beginning of their disease and during their follow-up. The PI is responsible for direct interaction and supervision of the research team.

Education/Training - Institution and Location	Degree	Year(s)	Field of study
Erasmus University in Rotterdam (The Netherlands)	Research Fellow	1	Neuroepidemiology
John Hopkins University in Baltimore (USA)	Research Fellow	1	Neuroepidemiology
AOU Careggi - Florence	Postdoctoral in Neurology	4	Neurology
National Health Institute in Rome	Training	1	Epidemiology and Statistics
University of Florence	Degree in Medicine and Surgery	6	Neurology

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Florence ¿ IRCCS Don Gnocchi	Department of NEUROFARBA	Florence	Full Professor in Neurology	2018	2018
University of Florence	Department of NEUROFARBA	Florence	Associated Professor in Neurology	2004	2018
University of Florence	Department of Neurology	Florence	Responsible for the MS Center	1998	2018
AOU Careggi -Florence	Department of Neurology	Florence	First Level Medical Director	1995	1998
AOU Careggi -Florence	Department of Neurology	Florence	Senior Assistant Neurologist	1993	1995
AOU Careggi -Florence	Department of Neurology	Florence	Assistant Neurologist	1991	1993

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Applicant Institution: Toscana

Project Type: WP PROJECT - 5

Official H index: 50.0 (autocertificated)

Source: Scopus

Scopus Author Id: 7103061535

ORCID ID: 0000-0003-3325-3760

RESEARCH ID: n.a.

Awards and Honors:
n.a.

Other CV Informations:
1994: Member of the Italian Society of Neurology
1997: Member of the Scientific Committee of the National MS Society
1998: Member of the European Federation of Neurological Societies (EFNS)
2005-2009: Responsible for the National Study Group on MS of the Italian Neurological Society
Since 2006: Italian delegate for MS at the European Federation of Neurological Societies
Since 2014: Member of the ECTRIMS Executive Committee , elected Secretary General of ECTRIMS in 2016
Since 2014: Member of Consiglio Superiore di Sanità ¿ Health Ministery, Italy

Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by clinical and cognitive data.

Project Code: NET-2018-12366666-5

Principal Investigator: AMATO MARIA PIA

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Toscana

Project Type: WP PROJECT - 5

Selected peer-reviewed publications of the PI

Valid for PI minimum expertise level

Title	DOI	PMID	Cit. **	P.*
Long-term safety of azathioprine therapy in multiple sclerosis	n.a.	8469348	42	F
Cognitive impairment in early-onset multiple sclerosis. Pattern, predictors, and impact on everyday life in a 4-year follow-up	n.a.	7848126	284	F
Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years	n.a.	11594918	401	F
Donepezil for memory impairment in multiple sclerosis	10.1016/S1474-4422(05)00972-5	15664536	12	F
The Rao's Brief Repeatable Battery and Stroop Test: normative values with age, education and gender corrections in an Italian population	10.1177/1352458506070933	17263008	155	F
Brain damage as detected by agnetization transfer imaging is less pronounced in benign than in early relapsing multiple sclerosis	10.1093/brain/awl152	16815879	59	L
Association of neocortical volume changes with cognitive deterioration in relapsing-remitting multiple sclerosis	10.1001/archneur.64.8.1157	17698706	147	F
Cognitive and psychosocial features of childhood and juvenile MS	10.1212/01.wnl.0000312276.23177.fa	18474844	164	F
Cognitive assessment and quantitative magnetic resonance metrics can help to identify benign multiple sclerosis	10.1212/01.wnl.0000324621.58447.00	18725589	79	F
Real-life impact of early interferon beta therapy in relapsing multiple sclerosis	10.1002/ana.21757	19847899	80	L
Cognitive impairment predicts conversion to multiple sclerosis in clinically isolated syndromes	10.1177/1352458509350311	19995837	83	L
Cognitive and psychosocial features in childhood and juvenile MS: two-year follow-up	10.1212/WNL.0b013e3181f4d821	20876467	110	F
Association of MRI metrics and cognitive impairment in radiologically isolated syndromes	10.1212/WNL.0b013e31824528c9	22262744	64	F
Cognitive reserve and cortical atrophy in multiple sclerosis: a longitudinal study	10.1212/WNL.0b013e3182918c6f	23576622	57	F
The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS): normative values with gender, age and education corrections in the Italian population	10.1186/s12883-014-0171-6	25204350	23	L

Project Title:
P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by clinical and cognitive data.

Project Code: NET-2018-12366666-5

Principal Investigator: AMATO MARIA PIA

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Toscana

Project Type: WP PROJECT - 5

Title	DOI	PMID	Cit. **	P.*
Neuropsychological features in childhood and juvenile multiple sclerosis: five-year follow-up	10.1212/WNL.0000000000000885	25217060	31	F
Pediatric multiple sclerosis: Cognition and mood	10.1212/WNL.0000000000002883	27572867	9	F
Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes	10.1177/1352458516674367	27738090	2	L
Patients with paediatric-onset multiple sclerosis are at higher risk of cognitive impairment in adulthood: An Italian collaborative study	10.1177/1352458517717341	28654357	1	L
Progress in multiple sclerosis - from diagnosis to therapy	10.1038/nrneurol.2018.3.	29384150	0	L

* Position: F=First L=Last C=Corrispondent

** Autocertificated

For evaluation CV

Title	DOI	PMID	Cit. *
Prognostic indicators in pediatric Clinically isolated syndrome	10.1002/ana.24938	28439957	3
Anti-inflammatory disease-modifying treatment and short-term disability progression in SPMS	10.1212/WNL.0000000000004330	28794248	3
MRI substrates of sustained attention system and cognitive impairment in pediatric MS patients	10.1212/WNL.0000000000004388	28821687	1
Towards personalized therapy for multiple sclerosis: prediction of individual treatment response.	10.1093/brain/awx185	29050389	1
Defining secondary progressive multiple sclerosis	10.1093/brain/aww173	27401521	21
Primary Progressive Multiple Sclerosis Evolving from Radiologically Isolated Syndrome	10.1002/ana.24564	26599831	32
Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis	10.1016/S1474-4422(14)70250-9	25662900	123
Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis	10.1093/brain/awv260	26362907	38
Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)	10.1177/1352458511431076	22190573	205
Neuropsychological and MRI measures predict short-term evolution in benign multiple sclerosis	10.1212/WNL.0b013e3181b351fd	19641173	64

* Autocertificated

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by clinical and cognitive data.
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Project Type: WP PROJECT - 5

Grant

Funded Institution / Country	Year	Title	Position in Projects
Italian Health Ministry - Bando Giovani Ricercatori, Ricerca Sanitaria Finalizzata	2014-2018	¿Role of the brain connectivity in the different stages of Multiple Sclerosis¿	Collaborator
Italian Health Ministry - Bando Giovani Ricercatori, Ricerca Sanitaria Finalizzata	2011-2012	¿Multiple sclerosis rebound upon fngolimod discontinuation: evidence and mechanisms involved.¿	Collaborator
FISM ¿ Special Project	2017-2018	¿Riabilitazione cognitiva dell¿attenzione a domicilio, con l¿uso del computer, in soggetti con sclerosi multipla ad esordio pediatrico: uno studio pilota multicentrico¿	Coordinator
FISM ¿ Special Project	2014-2015	¿The role of cognitive reserve in paediatric onset multiple sclerosis¿ Coordinator	Coordinator
Finanziamento Regione Toscana, Delibera n.803 del 6 settembre 2011	2011-2012	"Studio epidemiologico sull¿associazione tra insufficienza venosa cronica cerebrospinale e SM¿	Coordinator
Regione Toscana - Programma di Ricerca Sanitaria finalizzata della Regione Toscana n. 372/C	1994-1995	Ruolo di tossici industriali (solventi organici) nelle malattie demielinizzanti del sistema nervoso centrale¿	Coordinator
European Comunity	1992	¿European Concerted Action on Multiple Sclerosis¿ - Pregnancy in Multiple Sclerosis	Coordinator
European Comunity	1992	European Concerted Action on Multiple Sclerosis¿ - The Evaluation of the EDMUS System (EVALUED	Coordinator

Employment contract extension: Amato dichiarazione rapporto RF18.pdf.p7m

(Data changed during the moratorium period)

Project Title:
P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by clinical and cognitive data.

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Applicant Institution: Toscana

Project Type: WP PROJECT - 5

Biographical Sketch Contributors 1

Name:
Pancani Silvia

Institution: FONDAZIONE DON CARLO GNOCCHI
Department/Unit: IRCCS Rehabilitation Centre - Florence
Position Title: Co-PI

Education/Training - Institution and Location	Degree	Year(s)	Field of study
University of Florence, Florence, Italy	Bachelor Degree	5	Industrial and Management Engineering
University of Florence, Florence, Italy	Master Degree	3	Biomedical Engineering
University of Sheffield, Sheffield, UK	PhD	5	Biomedical Engineering
Sapienza University, Rome, Italy	n.a.	1	Medical statistics

Personal Statement:

PhD in Biomedical Engineering at the University of Sheffield. Title of the project ¿Assessing residual neck mobility when wearing a cervical orthosis: an application in patients with Motor Neurone Disease¿. Main skills covered: experimental data collection, data analysis, statistical analysis (advanced use of the software SPSS for data analysis and power analysis calculation) and articles writing. Competencies in movement analysis (stereophotogrammetry system, inertial sensors, EMG sensors, force platform). Experience in database management and writing reports.

Institution	Division / Research group	Location	Position	From year	To year
IRCCS Don Carlo Gnocchi	IRCCS Rehabilitation Centre	Florence	Researcher	2017	2018

Awards and Honors

Official H index: 1.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 56989694200

ORCID ID: 0000-0003-1595-8492 **RESEARCH ID:** n.a.

Awards and Honors:

n.a.

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by clinical and cognitive data.
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Project Type: WP PROJECT - 5

Expertise Research Collaborators

Selected peer-reviewed publications of the Research Group / Collaborators

Collaborator	Title	DOI	PMID	Cit. *
Pancani Silvia	A comfort assessment of existing cervical orthoses	10.1080/00140139.2017.1353137	28697682	0
Pancani Silvia	Aging process, adherence to Mediterranean diet and nutritional status in a large cohort of nonagenarians: Effects on endothelial progenitor cells	10.1016/j.numecd.2017.09.003	29167060	0
Pancani Silvia	Hemoglobin concentration is associated with self-reported disability and reduced physical performance in a community dwelling population of nonagenarians: the Mugello Study	10.1007/s11739-017-1762-1	29071662	0
Pancani Silvia	An Objective Functional Characterisation of Head Movement Impairment in Individuals with Neck Muscle Weakness Due to Amyotrophic Lateral Sclerosis	10.1371/journal.pone.0169019	28068376	0
Pancani Silvia	Assessment of the Sheffield Support Snood, an innovative cervical orthosis designed for people affected by neck muscle weakness	10.1016/j.clinbiomech.2015.11.010	26673978	0

* Autocertificated

Grant

Funded Institution / Country	Year	Title	Position in Projects	Collaborator
n.a.	n.a.	n.a.	Collaborator	Pancani Silvia

Project Title:
P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by clinical and cognitive data.

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Applicant Institution: Toscana

Project Type: WP PROJECT - 5

Total proposed budget (Euro)

Costs	TOTAL BUDGET	Co-Funding	Project costs proposed to funding Organization (no MOH request)	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1a Staff Salary	200.000,00	200.000,00	0,00	not permitted	0,00
1b Researchers' Contracts	300.000,00	0,00	170.000,00	130.000,00	48,71
2 Equipment (Leasing - Rent)	200.000,00	0,00	100.000,00	100.000,00	37,47
3a Supplies	0,00	0,00	0,00	0,00	0,00
3b Model Costs	0,00	0,00	0,00	0,00	0,00
3c Subcontracts	5.000,00	0,00	0,00	5.000,00	1,87
3d Patient Costs	0,00	0,00	0,00	0,00	0,00
4 IT Services and Data Bases	1.500,00	0,00	0,00	1.500,00	0,56
5 Publication Costs	2.000,00	0,00	0,00	2.000,00	0,75
6 Convegni	0,00	0,00	0,00	0,00	0,00
7 Travels	1.700,00	0,00	0,00	1.700,00	0,64
8 Overheads	56.688,89	0,00	30.000,00	26.688,89	10,00
9 Coordination Costs	0,00	0,00	0,00	0,00	0,00
Total	766.888,89	200.000,00	300.000,00	266.888,89	100,00

Report the Co-Funding Contributor:

Co-Funding Fondazione Don Carlo Gnocchi

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by clinical and cognitive data.
Project Code: NET-2018-12366666-5	**Principal Investigator:** AMATO MARIA PIA
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Project Type: WP PROJECT - 5

Budget Justification	
1a Staff Salary	Staff' Salary includes Project Managers
1b Researchers' Contracts	Researchers' contracts include researchers (neurologists, psychologists and research assistant) to implement project's activities
2 Equipment (Leasing - Rent)	Power platforms, TVC systems BTS Bioengineering, Robot for motion analysis, WittySEM by Microgate
3a Supplies	None
3b Model Costs	None
3c Subcontracts	Subcontracts are included for reporting and/or technical services
3d Patient Costs	None
4 IT Services and Data Bases	Costs include software licenses and database
5 Publication Costs	Publication costs are foreseen to cover reports costs, submission/publication fees in peer reviewed and/or scientific journals, including open-access (if appropriate)
6 Convegni	None
7 Travels	Travels includes coststs for participation to meetings/scientific conferences
8 Overheads	Overheads (automatically calculated) inlcude fixed and indirect costs
9 Coordination Costs	-

	Project Title: P3 (preventive, predictive and personalized) solutions in neuroinflammatory and neurodegenerative diseases driven by clinical and cognitive data.
Project Code: NET-2018-12366666-5	**Principal Investigator:** AMATO MARIA PIA
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Toscana

Project Type: WP PROJECT - 5

Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)

Project Code: NET-2018-12366666-6

Principal Investigator: Piana Michele

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Liguria

Project Type: WP PROJECT - 6

Major Diagnostic Category*: Neurologia

Project Classification IRG: Bioengineering Sciences and Technologies

Project Classification SS: Biodata Management and Analysis - BDMA

Project Keyword 1: Methods for data analysis including: Numerical, statistical, mathematical and theoretical approaches to design and interpretation of large-scale studies such as methods for pattern discovery, data mining, sequence prediction, biomarker identification, therapeutic drug design and high throughput analyses; computational methods for organizing, maintaining, and integrating biological datasets and for large scale data modeling and simulations.

Project Keyword 2: Database technologies and methods for data management, data representation, data capture, data integrity and validation

Project Keyword 3: Brain Disorders and Clinical Neuroscience

Project duration (months): 36

Project Request: **Animals:** ☐ **Humans:** ☒ **Clinical trial:** ☐

The object/s of this application is/are under patent copyright Y/N: ☐

Investigators, Institution and Role in the Project

	Co-PI	Key Personnel	Institution/Org./Pos.	Role in the project	Birth Date
1	X	Barla Annalisa	Università degli Studi di Genova / Dipartimento di Matematica	Co-PI	16/05/1977
2		verri alessandro	Università degli Studi di Genova / Dipartimento di Matematica	Expert Research Collaborator	31/10/1960

Overall Summary

The aim of this WP is twofold. First, we will provide the framework for big data handling, from storage to curation from cleaning to preparation. Second, we will design and implement signal and image processing and machine learning methods. The expected outcome will be the deployment of validated and statistically robust models based on the integration of all available data.
Each model will address a specific medical question in the context of neuro-inflammatory, neuro-oncology and neurodegenerative diseases, such as:
-Subtyping, disease progression and overall survival for Multiple Sclerosis
-Overall survival prediction in Alzheimer¿s, Parkinson¿s and ALS
-Molecular phenotype identification from imaging in adult and pediatric gliomas
This computational machinery will be tailored to the extraction of information from all the collected heterogeneous data. The algorithms will exploit advanced numerical optimization, which will ensure the possibility of efficient analysis of big data.

Background / State of Art

Methods for the analysis of imaging data involve inversion algorithms for image reconstruction, image fusion and integration methods, pattern recognition approaches to image segmentation and property extraction, machine learning methods for

patients' stratification, which utilize the extracted properties for the prediction and the characterization of the diseases' rating.
Both PECT/CT and MRI are well-established modalities for the evaluation of most neurological impairments and currently represent testbeds for assessing the effectiveness of computational tools for extracting information about the diseases' progression.

In nuclear medicine, as synaptic activity is the main determinant of glucose consumption in the nervous system, Positron Emission Tomography with 18F-fluorodeoxyglucose (18F-FDG-PET) may investigate impairment of glucose utilization in neurodegenerative diseases with specific topographic patterns. Moreover, further disease-specific tracers can be developed and the corresponding nuclear medicine data processed to extract other metabolic information from them. Although PET/CT investigation of the cortical response to radioactive tracers of different kinds is well-established in many areas of clinical neurology, the use of this same modality for the metabolic assessment of the impaired spinal marrow pertains so far to exploratory studies. We recently developed a new computational tool for the analysis of 18F-FDG-PET/CT studies able to identify the compact bone profile in CT images and to use it in order to evaluate the bone marrow metabolism in PET volumes. Pattern recognition in clinical CT volume permits as well to identify the spinal canal and the spinal cord from co-registered PET data. This permitted, for the first time, to assess spinal cord glucose consumption as a function of basal neuronal activity and synaptic assessment.

Neurodegenerative, neuroinflammatory and neuro-oncological diseases are characterized by diverse and complex etiologies, which partly explains the use of different images modalities and the proliferation of an increasing number of databases containing data of different kinds and origins. So far, artificial intelligence has been applied to these databases in a rather limited fashion, mainly focusing on a single, specific data feature and mainly for Boolean predictions. On the other hand, modern machine learning methods are conceived to deal with multi-modal data, to exploit them in order to perform multi-task predictions and to rank the retrieved information by pointing out their significance in the prediction process.

In machine learning, regularization is a common strategy to build predictive models out of noisy data. This refers to the process of introducing additional information to solve an ill-posed problem. The obtained result is a function that fits the training data with good generalization properties on previously unseen test data.

In personalized medicine, biospecimen collection and biological data management is still a challenging and expensive task. Only few large-scale research enterprises, such as ENCODE, ADNI, MOPED or TCGA, have sufficient resources to manage heterogeneous biological data. To date, many biomedical studies still rely on a small number of collected samples. This effect is even worse in rare diseases or in high-throughput molecular data where the dimensionality of the problem can be in the order of hundreds of thousands.

The main goal of the learning step is often to identify a meaningful subset of relevant variables that are the most representative of the observed phenomenon. In machine learning, this is known as variable/feature selection that promotes model interpretability.
Regardless of the learning machine, regularization can be introduced in several ways and it is of fundamental use in order to achieve solutions that are robust to noise, learn the data structure when unknown, exploit prior knowledge on the data structure.

Hyphotesis and Specific AIMS

	Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)
Project Code: NET-2018-12366666-6	**Principal Investigator:** Piana Michele
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Liguria

Project Type: WP PROJECT - 6

Hyphotesis and Significance:

The collection of the large amount of data acquired by the participating units requires the design, development and deployment of a framework for storage, management, preparation, processing and extraction of information and knowledge, also taking into account privacy and security issues.
To this aim, we will assembly an infrastructure sufficiently flexible to guarantee ease of upgrading and a high level of interoperability, possibly based on cloud web services.

The available data are heterogenous and multi-modal and call for specific expertise. This is particularly true for imaging data, i.e. PET, CT, MRI, DTI and for neurophysiological time series as EEG. This computational WP relies on the methodological assumptions that PET/CT and MRI data potentially contain enough information to allow an exhaustive characterization and rating of most neurological diseases and that imaging and machine learning methods are effective enough to extract such information in a reliable and quantitative fashion. The integration of the functional and morphological information is able to represent a data-driven computational tool for the metabolic assessment of neuroinflammatory, neurodegenerative and neuro-oncology diseases and for their diagnosis and prognosis. The other data types available for this project require normalization and standardization as they may have values lying in very different numerical ranges as in genomics or metabolic molecular data or be categorical, such as the clinical scales evaluated for MS patients.

It is possible to systematically take advantage from the information contained in imaging, clinical, genetic and molecular data to start-up a computational framework able to identify which parameters extractable from data are mostly significant for the classification of the patient¿s status, and predict disease progression and overall survival. The image processing approach based on pattern recognition for CT images and image integration with PET data showed its effectiveness in the evaluation of the bone marrow metabolic asset in both health and disease. This same approach, when updated in order to identify the spinal canal and the spinal cord in ALS patients, enabled the evaluation of cervical spinal cord hypermetabolism with respect to controls possibly representing a potential independent prognostic marker. Coupling the analysis of brain and spinal cord FDG uptake, in a series of prospectively enrolled ALS patients, showed that cervical metabolic activity was significantly and inversely correlated with metabolic level in different cerebral cortical areas. Moreover, machine learning methods have been recently applied with promising results to clinical and molecular data in the study of neurodegenerative and neurooncological diseases for disease subtyping, survival estimation and disease progression forecast.

To the best of our knowledge, no technological platform is currently running for a systematic analysis of multi-modal data (for example, coordinated analysis of CT, PET, and MRI data) by means of machine learning approaches, although software services of this kind exist for data analysis in other application fields (see, as an example, the Horizon 2020 FLARECAST service, www.flarecast.eu). This task of NeuroartP3 will rely on the experience gained by the scientists working in this Unit in the realization such platform.

Preliminary Data:

The unit has at disposal a large collection of computationally efficient models and methods for:
- Data preparation, cleaning and preprocessing ¿ ADENINE - https://github.com/slipguru/adenine
- Medical image processing including feature extraction and volume estimation
- Highly automated dipole estimation (HADES) is a particle filtering algorithm for estimating current dipoles from MEG data under general hypotheses
http://mida.dima.unige.it/g_software_hades.html

- HT-BONE is a software for the automatic detection of bone profile in CT images by means of Hough Transform http://mida.dima.unige.it/g_software_htbone.html
- NeuroCUDE (Neuronal CUrrent Dipoles Estimator) is a Python software for the automatic source estimation from MEG/EEG data
http://mida.dima.unige.it/g_software_neurocude.html
- Regularization driven sparse supervised learning with model selection ¿ PALLADIO - https://github.com/slipguru/palladio
- Dictionary learning methods ¿ DALILA - https://github.com/slipguru/dalila

These models and methods have been already employed in the biomedical domain on data types including imaging, radiomics, genomics, proteomics and clinical data (Malattia 2009, Fardin 2010, Mascelli 2010, Squillario 2011, Masecchia 2015, Fiorini 2017)

Specific Aim 1:

DATA COLLECTION AND MANAGEMENT: we will coordinate the data collection activities from all clinical units dealing with both retrospective and perspective data through a unified data collection software.
In collaboration with the Trento FBK Unit, we will address the issues of data privacy and protection with security-by-design techniques (blockchain).
We will also deal with the cleaning, preparation and normalization of the heterogenous data (clinical, molecular, genetic and genomics, demographics, neuropsychological and neurophysiological) from all the units.

Specific Aim 2:

COMPUTATIONAL MODELS AND METHODS FOR IMAGING:
We will study, design, implement and validate data processing methods for the extraction of meaningful imaging features from structural and functional imaging data types (MRI, CT-scan, PET, DWI), categorical data are transformed into numerical variables, and data redundancy is reduced when necessary.

Specific Aim 3:

EXTRACTION OF INFORMATION AND KNOWLEDGE FROM DATA:
We will study, design, implement and validate machine learning and artificial intelligence algorithms to address the clinical questions raised by the medical partners. The main goal is to identify early predictors of disease progression, forecast the overall survival time or stratify patients¿ cohorts into subtypes.
Given the heterogenous data collection, we will first focus on statistical models that make use of one data type at a time and later we will tackle the implementation of integrated models.
In particular we will
- identify novel markers for neurodegenerative diseases based on the information extracted from structural CT images and functional PET images
- infer automatic patients' stratification based on information extracted from MRI and fMRI volumes, possibly integrated with information contained in data of different nature
- devise models of disease progression based on clinical scales
evaluate the impact of chemotherapy and radiotherapy in CCS subjects in terms of premature aging

Experimental Design Aim 1:

n.a.

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Project Type: WP PROJECT - 6

Experimental Design Aim 2:
n.a.

Experimental Design Aim 3:
n.a.

Picture to support preliminary data:
UniGe-FIGURA.pptx

Metodologies and statistical analyses:
We will make use of state-of-the-art methods for missing data imputing, preprocessing, dimensionality reduction and clustering strategies as data from heterogeneous have values lying in very different numerical ranges (Fiorini et al, 2018).

The analysis of nuclear medicine data will follow an approach generalizing the one illustrated in (Sambuceti et al 2012). Specifically, the first step will realize the automatic recognition of the spinal canal and spinal cord in the patients' reconstructed CT images. We will use an extended version of the pattern recognition method based on the Hough transform, introduced in (Beltrametti et al, 2013), and in which the algorithm will utilize both algebraic and non-algebraic curves in order to identify the profile of the spinal canal in all vertebral districts (Massone et al 2015). The output of this first step will therefore be the extraction of the 3D volume of both the region defined by the canal profile and the one occupied by the spinal marrow. In the second step, the identified volumes will be utilized to extract information of the metabolism of the spinal marrow. In fact, binary masks in which 1 labels the spinal marrow voxels and 0 labels all the other voxels, will be multiplied against PET images so that the uptake values corresponding to the spinal cord will be isolated in the PET representation of the patients. This second step will allow the construction of functional representations of impaired spinal cords for very general applications in neurology (Marini et al 2018), since this procedure can be applied in the case of all neurodegenerative diseases for which PET/CT data are available and for different kinds of radioactive tracers.

The predictive models will leverage on regularization-based machine learning and deep learning methods to make sense of a number of samples which is invariably orders of magnitude smaller than the number of the available measurements (De Mol et al, 2009).
In particular, the design of methods that extract the subset of variables relevant for the clinical question addressed and that shed light on the interplay among them will be driven by prior medical knowledge (Salzo et al, 2014, Tomasi et al 2018).

The robustness and reproducibility of the statistical analysis will be ensured by means of resampling strategies such as Monte Carlo cross-validation (Barbieri et al, 2016). This will also avoid information leakage and selection bias (Ambroise and McLachlan 2002).

Expected outcomes:
The expected outcomes are:

- data collection protocol and software to be used by all the units, for data gathering, storing and preprocessing
- a Python package for the analysis of PET/CT data of neurological patients to provide functional representations of the spinal cord metabolism based on PET signal
- post-processing module for the automatic determination of quantitative parameters such as the anatomical volumes

occupied by the spinal cord and the spinal canal, their geometrical properties and the values of the standard uptake values in both regions
- deployment of validated predictive models to be used by doctors in the daily clinical practice

This overall set of software tools will be open source and modularly designed for ease of maintenance and upgrade. Computational efficiency will be ensured by the employment state-of-art numerical optimization techniques.

Risk analysis, possible problems and solutions:
The main risk of this research activity is related to the statistical significance of the obtained predictive models. Data may be big but the amount of data actually available to address each specific question may not be sufficient to ensure statistical significance. However, this risk is mitigated by the large dimension of the project consortium and the considerable size of retrospective data available and planned prospective data.

More in general, the feasibility of this work package essentially relies on the experience of the unit members in the analysis of images and data from different domains. Scientists from this unit have been involved and are currently working in several FP7, H2020, international, national and regional research efforts devoted to the implementation of computational tools for image reconstruction, inverse problems, image processing and machine learning.

Significance and Innovation

This Work Package utilizes sophisticated tools in mathematics and computer science for an automatic analysis of neurological data acquired by means of many different modalities. A significant aspect of this effort is in the systematic search of automation in the data analysis process, which will allow the processing at a big data level and therefore the construction of databases containing science products of notable potential impact in neurology and neuroscience. From a physiological viewpoint, our most ambitious goal is that the computational approaches proposed in this work package may open new data-driven windows in the comprehension of specific neurodegenerative diseases and the identification of novel diagnostic and prognostic indicators for the status and the follow up of these pathologies.

Description of the complementary and sinergy research team

This Work Package is led by two groups at the Università di Genova (one at a Department of Mathematics and one at a Department of Computer Science) that have a long tradition of cooperation with clinicians active in the field of image and data analysis in medicine and especially in neuroscience. The two groups cooperate since a long time together testing and comparing different approaches in this field. Similarly, both groups developed a long standing cooperation with the corresponding resources in Trento, Milan and Florence aiming to optimize communications between the different clinical centers. At a methodological level, the mathematical group in Genova will mainly focus on the development of image processing methods, the computer science group in Genova will mainly develop algorithms for machine learning, the technological group in Trento will work at the construction of the technological service and the other groups will provide data and support to the interpretation of the results of the data analysis.

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Project Type: WP PROJECT - 6

Training and tutorial activities

As academic centers, Education and Training are part of our mission. To promote exchange of skills and competences and to ensure a strict common background in terms of analytic / clinical transferability of the project results, at least two training sessions will be planned, in cooperation with the Trento unit.
i. Training on Machine learning methods;
ii. Training on use of big data as support to clinical decision making, with specific focus on (but not only) neuro-oncology, MS, AD, and ALS.
The training sessions will be strategically delivered in the first phases of the project to maximize knowledge and skill sharing. Considering budget issues, both training components can be either remote-training or on-site (physical meeting) training.

In terms of tutorial activities, partner in charge of the big data modeling will tutor other participating regions ¿ if needed ¿ during the data collection and analysis process.

Bibliography

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De Mol, Christine, et al. "A regularized method for selecting nested groups of relevant genes from microarray data." Journal of Computational Biology 16.5 (2009): 677-690.

Fardin, Paolo, et al. "A biology-driven approach identifies the hypoxia gene signature as a predictor of the outcome of neuroblastoma patients." Molecular cancer 9.1 (2010): 185.

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Malattia, Clara, et al. "Dynamic contrast-enhanced magnetic resonance imaging in the assessment of disease activity in patients with juvenile idiopathic arthritis." Rheumatology 49.1 (2009): 178-185.

C. Marini et al
Brain 2018 in press

Masecchia, Salvatore, et al. "Genome instability model of metastatic neuroblastoma tumorigenesis by a dictionary learning algorithm." BMC medical genomics 8.1 (2015): 57.

A M Massone et al Journal of Mathematical Imaging and Vision 51 (2015) 296

Salzo, Saverio, et al. "Alternating proximal regularized dictionary learning." Neural computation 26.12 (2014): 2855-2895.

G Sambuceti et al
European Journal of Nuclear Medicine and Molecular Imaging 39 1326 2012

F Tomasi, V Tozzo, S Salzo, and A Verri. Latent Variable Time-varying Network Inference. ACM SIGKDD International Conference on Knowledge Discovery & Data Mining, 2018, London, United Kingdom.

Timeline / Deliverables / Payable Milestones

This Work Package will have two deliverables, represented by two software packages written in Python:

Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)	
Project Code: NET-2018-12366666-6	**Principal Investigator:** Piana Michele
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Liguria

Project Type: WP PROJECT - 6

D1: package for the analysis of PET/CT data from neurological patients to provide functional representations of the spinal cord metabolism based on PET signal; the tool will also contain a post-processing module for the automatic determination of quantitative parameters such as the anatomical volumes occupied by the spinal cord and the spinal canal, their geometrical properties and the values of the standard uptake values in both regions

D2: package for the realization of automatic machine-learning-based prediction in neurological diseases for both patients' stratification and prognostic purposes; the package will be the overall product of a set of libraries organized in Python modules performing data pre-processing and machine learning.

Both deliverables will be deployed at month 36 of the project.

Milestones 18 month

At 18 month, we plan to deliver:
- the first prototype for PET/CT image integration and for feature extraction on MRI and functional MRI images.
- The first prototype for machine learning methods tuned on single-type data.

Milestones 36 month

Two software tools to be shared and openly accessible will be deployed:
1. Software tool for the automatic identification of prognostic markers based on information extraction from PET/CT data
2. Software tool for predicting disease progression and automatic patient stratification based on data integration machine learning methods.

Gantt chart

UniGe-GANTT.pdf

Equipment and resources available

The groups of the Università di Genova leading this Work Package have at disposal a cluster of high performance PCs and workstations equipped with up-to-date software packages for scientific computing and image visualization.

Translational relevance and impact for the National Health System (SSN)

Our groups will cooperate with clinical counterparts aiming to verify the potential of machine learning approaches in clinical evaluation. For the scopes of the present study, our main objective is to define hypotheses that can be tested in the real world data base provided. These data will definitely improve the capability to design prospective trials in test them as to finally result in computer assisted clinical decision making.

Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)

Project Code: NET-2018-12366666-6

Principal Investigator: Piana Michele

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Liguria

Project Type: WP PROJECT - 6

PRINCIPAL INVESTIGATOR PROFILE

Name
Piana Michele

Institution: Liguria
Department/Unit: Università degli Studi di Genova / Dipartimento di Matematica
Position Title: Full Professor

Personal Statement

Personalized healthcare for degenerative or inflammatory diseases of the central nervous system is hindered by a poor understanding of the underlying biological processes.This shortcoming hampers early diagnosis, disease monitoring, risk prediction and treatment.Stakeholders cannot develop adequate policies to manage the economic burden of these disorders. We plan to generate large datasets from patients with multiple sclerosis, Alzheimer, Parkinson and amyotrophic lateral sclerosis, including clinical, immunological and molecular data as well as functional and structural images.The key person¿s responsibilities will be about the realization of computational methods for the analysis of these data able to identify diagnostic and prognostic indicators and determine patients' stratification.

Education/Training - Institution and Location	Degree	Year(s)	Field of study
Università degli Studi di Genova	PhD in Physics	3	Physics
Università degli Studi di Genova	MSc Physics	4	Physics

Positions

Institution	Division / Research group	Location	Position	From year	To year
CNR	SPIN	Genova	Associate Researcher	2003	2018
Università degli studi di Genova and CNR - SPIN	MIDA - Methods for Image and Data Analysis	Genova	Principal Investigator	2003	2018
Università degli studi di Genova	Dept Mathematics	Genova	Full Professor	2013	2018
Università degli studi di Genova	Dept Mathematics	Genova	Associate Professor	2009	2013
Università degli studi di Verona	Dept. Informatics	Verona	Associate Professor	2005	2009
Università degli studi di Genova	Dept Mathematics	Genova	Researcher	2001	2005

Official H index: 22.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 35557405100

ORCID ID: 0000-0003-1700-991X **RESEARCH ID:** n.a.

Awards and Honors:

- NASA Group Achievement Award, The RHESSI Team, NASA Goddard Space Flight Center
- Honorary Research Fellow, Department of Physics and Astronomy, University of Glasgow

Other CV Informations:

More than 80 papers on internationals journals with referee concerning the formulation of numerical methods for image reconstruction and data analysis and the application of computational methods against complex data in physics and physiology

Research contracts with Kodak Health Imaging, Careastream Health, Imavis srl, Paramed srl, supporting the realization of software tools for the processing of medical imaging data from different modalities

Organization of 8 workshops/conferences devoted to topics in medical data processing

Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)

Project Code: NET-2018-12366666-6

Principal Investigator: Piana Michele

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Liguria

Project Type: WP PROJECT - 6

Selected peer-reviewed publications of the PI

Valid for PI minimum expertise level

Title	DOI	PMID	Cit. **	P.*
Estimating the whole bone-marrow asset in humans by a computational approach to integrated PET/CT imaging	10.1007/s00259-012-2141-9	22639281	26	C
Estimate of FDG excretion by means of compartmental analysis and ant colony optimization of nuclear medicine data	10.1155/2013/793142	24191175	4	L
A novel description of FDG excretion in the renal system: Application to metformin-treated models	10.1088/0031-9155/59/10/2469	24778350	4	L
Source modeling of ElectroCorticoGraphy (ECoG) data: Stability analysis and spatial filtering	10.1016/j.jneumeth.2016.02.012	26891875	2	L
A physiology-based parametric imaging method for FDG-PET data	10.1088/1361-6420/aa9544	n.a.	0	L
Are Loss Functions All the Same?	10.1162/089976604773135104	15070510	78	C
Some properties of regularized kernel methods	n.a.	n.a.	49	C
A linear model for chirp-pulse microwave computerized tomography: Applicability conditions	10.1088/0266-5611/22/6/018	n.a.	2	C
Inverse problems in biomedical imaging: Modeling and methods of solution	10.1007/88-470-0396-2_1	n.a.	9	L
A Rao-Blackwellized particle filter for magnetoencephalography	10.1088/0266-5611/24/2/025023	n.a.	21	L
Particle filtering, beamforming and multiple signal classification for the analysis of magnetoencephalography time series: A comparison of algorithms	10.3934/ipi.2010.4.169	n.a.	10	L
Highly automated dipole estimation (HADES)	10.1155/2011/982185	21437232	8	L
Adult advanced chronic lymphocytic leukemia: Computational analysis of whole-body CT documents a bone structure alteration	10.1148/radiol.14131944	24592961	7	C
Allogeneic cell transplant expands bone marrow distribution by colonizing previously abandoned areas: An FDG PET/CT analysis	10.1182/blood-2015-01-618215	25957389	8	C
Allogeneic cell transplant expands bone marrow distribution by colonizing previously abandoned areas: An FDG PET/CT analysis	10.1182/blood-2015-01-618215	25957389	8	C
Inverse modeling for MEG/EEG data	10.1007/978-3-319-68297-6_15	n.a.	0	L

Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)

Project Code: NET-2018-12366666-6

Principal Investigator: Piana Michele

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Liguria

Project Type: WP PROJECT - 6

Title	DOI	PMID	Cit. **	P.*
A Comparative Study of the Robustness of Frequency-Domain Connectivity Measures to Finite Data Length	10.1007/s10548-017-0609-4	n.a.	0	C

* Position: F=First L=Last C=Corrispondent

** Autocertificated

For evaluation CV

Title	DOI	PMID	Cit. *
A physiology-based parametric imaging method for FDG-PET data	10.1088/1361-6420/aa9544	n.a.	0
Source modeling of ElectroCorticoGraphy (ECoG) data: Stability analysis and spatial filtering	10.1016/j.jneumeth.2016.02.012	26891875	2
Regularization of multiplicative iterative algorithms with nonnegative constraint	10.1088/0266-5611/30/3/035012	n.a.	6
Estimate of FDG excretion by means of compartmental analysis and ant colony optimization of nuclear medicine data	10.1155/2013/793142	24191175	4
Hough transform of special classes of curves	10.1137/120863794	n.a.	14
Estimating the whole bone-marrow asset in humans by a computational approach to integrated PET/CT imaging	10.1007/s00259-012-2141-9	22639281	26
Forward simulation and inverse dipole localization with the lowest order Raviart - Thomas elements for electroencephalography	10.1088/0266-5611/27/4/045003	n.a.	13
Dynamical MEG source modeling with multi-target bayesian filtering	10.1002/hbm.20786	19378276	34
Modulation of brain and behavioural responses to cognitive visual stimuli with varying signal-to-noise ratios	10.1016/j.clinph.2006.01.011	16545601	9

* Autocertificated

	Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)
Project Code: NET-2018-12366666-6	**Principal Investigator:** Piana Michele
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Liguria

Project Type: WP PROJECT - 6

Grant

Funded Institution / Country	Year	Title	Position in Projects
H2020-Protec-2014 Research and Innovation Action	2015	Flare Likelihood and Region Eruption Forecasting (FLARECAST)	Coordinator
PAR - FAS 2007/13,	2013	Intelligenza articiale per estrarre informazione diagnostica nell'imaging complesso (MATRIX)	Coordinator
FP7-SPACE-2010.2.1	2010	High Energy Solar Physics Data in Europe (HESPE)	Coordinator
Fondazione Cassa di Risparmio Verona	2008	Bayesian tracking of brain oscillatory activity	Coordinator
Air Force Office of Scientific Research	2008	X-ray observations of the Sun: solar ares and their impact on the geophysical space	Coordinator
MIUR PRIN	2006	Inverse methods in action: analysis of magnetoencephalography (MEG) time series and imaging-spectroscopy	Coordinator

Employment contract extension:

(Data changed during the moratorium period)

Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)

Project Code: NET-2018-12366666-6

Principal Investigator: Piana Michele

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Liguria

Project Type: WP PROJECT - 6

Biographical Sketch Contributors 1

Name:
Barla Annalisa

Institution	Università degli Studi di Genova / Dipartimento di Matematica
Department/Unit	Dipartimento di Informatica, Bioingegneria, Robotica e Ingegneria dei Sistemi (DIBRIS)
Position Title	ASSOCIATE PROFESSOR

Education/Training - Institution and Location	Degree	Year(s)	Field of study
Università degli Studi di Genova	PhD in Computer Science	3	Computer Science
Università degli Studi di Genova	MSc in Physics	4	Physics

Personal Statement:

The key person¿s responsibilities will be about supervising the experimental design and implementation of the machine learning pipeline in order to ensure statistical robustness and reproducibility of results. We will also adopt all computational resources in order to be able to process all large-scale data collected during the project.

Institution	Division / Research group	Location	Position	From year	To year
Università degli Studi di Genova	Dipartimento di Informatica, Bioingegneria, Robotica e Ingegneria dei Sistemi (DIBRIS)	Genova	Associate Professor	2017	2018
Università degli Studi di Genova	Dipartimento di Informatica, Bioingegneria, Robotica e Ingegneria dei Sistemi (DIBRIS)	Genova	Assistant Professor	2012	2017
Università degli Studi di Genova	Dipartimento di Informatica, Bioingegneria, Robotica e Ingegneria dei Sistemi (DIBRIS)	Genova	Post Doctoral Research Fellow	2008	2011
FBK, Trento, Italy	MPBA Lab	Trento	Post Doctoral Research Fellow	2006	2007

Awards and Honors

Official H index: 11.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 56820306000

ORCID ID: 0000-0002-3436-035X **RESEARCH ID:** K-6417-2015

Awards and Honors:

n.a.

Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)

Project Code: NET-2018-12366666-6

Principal Investigator: Piana Michele

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Liguria

Project Type: WP PROJECT - 6

Biographical Sketch Contributors 2

Name:
verri alessandro

Institution	Università degli Studi di Genova / Dipartimento di Matematica
Department/Unit	Dipartimento di Informatica, Bioingegneria, Robotica e Ingegneria dei Sistemi (DIBRIS)
Position Title	FULL PROFESSOR

Education/Training - Institution and Location	Degree	Year(s)	Field of study
Universita degli Studi di Genova	PhD in Physics	3	Physics
Università degli Studi di Genova	MSc in Theoretical Physics	4	Physics

Personal Statement:

The key person¿s responsibilities will be about supervising the design and implementation of machine learning algorithms for the understanding of complex heterogeneous biomedical data. We will make use of our long-standing expertise in computer vision, image processing and machine learning methods to guide the design of methods for data integration.

Institution	Division / Research group	Location	Position	From year	To year
Università degli Studi di Genova	Dipartimento di Informatica, Bioingegneria, Robotica e Ingegneria dei Sistemi (DIBRIS)	Genova	Full Professor	1999	2018
Università degli Studi di Genova	Dipartimento di Informatica, Bioingegneria, Robotica e Ingegneria dei Sistemi (DIBRIS)	Genova	Researcher	1989	1999

Awards and Honors

Official H index: 28.0 (autocertificated)

Source: Scopus **Scopus Author Id:** 57193129975

ORCID ID: 0 **RESEARCH ID:** 0

Awards and Honors:

Fairchild fellowship, MIT, Cambridge MA (1986)
NATO fellowship, MIT, Cambridge MA (1988)
Post-doctoral fellowship, SISSA, Trieste (1989)
CNR fellowship, ICSI, Berkeley CA (1992)
INRIA fellowship, INRIA-IRISA, Rennes (1994)

Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)	
Project Code: NET-2018-12366666-6	**Principal Investigator:** Piana Michele
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Liguria

Project Type: WP PROJECT - 6

EPSRC fellowship, Heriot-Watt University, Edinburgh (1996)

Project Title:
Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)

Project Code: NET-2018-12366666-6

Principal Investigator: Piana Michele

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Liguria

Project Type: WP PROJECT - 6

Expertise Research Collaborators

Selected peer-reviewed publications of the Research Group / Collaborators

Collaborator	Title	DOI	PMID	Cit. *
Barla Annalisa	Data-driven continuous assessment of frailty in older people	10.3389/fdigh.2018.00006/full	n.a.	0
verri alessandro	Regularized Kernel Algorithms for Support Estimation	10.3389/fams.2017.00023	n.a.	0
verri alessandro	Online space-variant background modeling with sparse coding	10.1109/TIP.2015.2421435	25872209	14
verri alessandro	Unsupervised tissue segmentation from dynamic contrast-enhanced magnetic resonance imaging	10.1016/j.artmed.2014.02.001	n.a.	3
verri alessandro	Proximal methods for the latent group lasso penalty	10.1007/s10589-013-9628-6	n.a.	15
Barla Annalisa	Alternating proximal regularized dictionary learning	10.1162/NECO_a_00672	25248086	4
verri alessandro	Accelerated and Inexact Forward-Backward Algorithms	10.1137/110844805	n.a.	98
Barla Annalisa	A computational procedure for functional characterization of potential marker genes from molecular data: Alzheimer's as a case study	10.1186/1755-8794-4-55	21726470	12
Barla Annalisa	Machine learning methods for predictive proteomics	10.1093/bib/bbn008	18310105	61
Barla Annalisa	Algebraic stability indicators for ranked lists in molecular profiling	10.1093/bioinformatics/btm550	18024475	83

* Autocertificated

Grant

Funded Institution / Country	Year	Title	Position in Projects	Collaborator
Compagnia di San Paolo	2018	Use of machine learning methods and inverse methods to identify the critical zone in focal epilepsies from Stereo-EEG data.	Collaborator	Barla Annalisa
FISM	2015	FISM Call 2015 - 2015/R/03 Early DETECTion of Multiple Sclerosis progression driven by clinical scales and Patient Reported Outcome (DETECT-MS PRO)	Collaborator	Barla Annalisa

Project Title:
Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)

Project Code: NET-2018-12366666-6

Principal Investigator: Piana Michele

Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Liguria

Project Type: WP PROJECT - 6

Total proposed budget (Euro)

Costs	TOTAL BUDGET	Co-Funding	Project costs proposed to funding Organization (no MOH request)	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1a Staff Salary	230.000,00	230.000,00	0,00	not permitted	
1b Researchers' Contracts	0,00	0,00	0,00	0,00	
2 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00	
3a Supplies	0,00	0,00	0,00	0,00	
3b Model Costs	0,00	0,00	0,00	0,00	
3c Subcontracts	0,00	0,00	0,00	0,00	
3d Patient Costs	0,00	0,00	0,00	0,00	
4 IT Services and Data Bases	0,00	0,00	0,00	0,00	
5 Publication Costs	0,00	0,00	0,00	0,00	
6 Convegni	0,00	0,00	0,00	0,00	
7 Travels	0,00	0,00	0,00	0,00	
8 Overheads	0,00	0,00	0,00	0,00	
9 Coordination Costs	0,00	0,00	0,00	0,00	
Total	230.000,00	230.000,00	0,00	0,00	

Report the Co-Funding Contributor:

Co-Funding Università degli Studi di Genova

	Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)
Project Code: NET-2018-12366666-6	**Principal Investigator:** Piana Michele
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Liguria

Project Type: WP PROJECT - 6

Budget Justification	
1a Staff Salary	2 full professors + 1 associate professor 90.000/year = average salary of a full professor 50.000 /year = average salary of a associate professor 12 person months (overall project)
1b Researchers' Contracts	None
2 Equipment (Leasing - Rent)	None
3a Supplies	None
3b Model Costs	None
3c Subcontracts	None
3d Patient Costs	None
4 IT Services and Data Bases	None
5 Publication Costs	None
6 Convegni	None
7 Travels	None
8 Overheads	None
9 Coordination Costs	None

	Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)
Project Code: NET-2018-12366666-6	**Principal Investigator:** Piana Michele
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Liguria

Project Type: WP PROJECT - 6

Principal Investigator Data - Working package 1 Code: NET-2018-12366666-1

Cognome: Uccelli
Nome: Antonio
Codice fiscale: CCLNTN64S18D969X
Documento: Carta d'identità, Numero: AS8551491
Data di nascita: 18/11/1964
Luogo di nascita: Genova
Provincia di nascita: GE
Indirizzo lavorativo: Largo Rosanna Benzi, 10
Città: Genova
CAP: 16132
Provincia: GE
Email: auccelli@neurologia.unige.it
Altra email: direzione.scientifica@hsanmartino.it
Telefono: +390105558721
Altro telefono: +390105558722
Fax: +39010512751
Qualifica: Direttore Scientifico
Struttura: Direzione Scientifica
Istituzione: Ospedale Policlinico San Martino - IRCCS

Principal Investigator Data - Working package 2 Code: NET-2018-12366666-2

Cognome: giometto
Nome: bruno
Codice fiscale: GMTBRN56C12H829M
Documento: Carta d'identità, Numero: AR 8790783
Data di nascita: 12/03/1956
Luogo di nascita: SANDRIGO
Provincia di nascita: VI
Indirizzo lavorativo: OSPEDALE SANTA CHIARA
Città: TRENTO
CAP: 38100
Provincia: TN
Email: bruno.giometto@apss.tn.it
Altra email: bruno.giometto@sanita.padova.it
Telefono: 0461.903281
Altro telefono: 3332628182
Qualifica: DIRETTORE UOC NEUROLOGIA
Struttura: OSPEDALE SANTA CHIARA

	Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)
Project Code: NET-2018-12366666-6	**Principal Investigator:** Piana Michele
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Liguria

Project Type: WP PROJECT - 6

Istituzione: AZIENDA PROVINCIALE PER I SERVIZI SANITARI (APSS)

Principal Investigator Data - Working package 3 Code: NET-2018-12366666-3

Cognome: Falini
Nome: Andrea
Codice fiscale: FLNNDR61A15H501C
Documento: Carta d'identità, Numero: AX3044876
Data di nascita: 15/01/1961
Luogo di nascita: roma
Provincia di nascita: RM
Indirizzo lavorativo: via olgettina 60
Città: milano
CAP: 20132
Provincia: MI
Email: falini.andrea@hsr.it
Altra email: falini.andrea@hsr.it
Telefono: 0226433011
Fax: 0226433447
Qualifica: Dirigente II livello
Struttura: U.O.C. di Neuroradiologia
Istituzione: IRCCS Ospedala San Raffaele

Principal Investigator Data - Working package 4 Code: NET-2018-12366666-4

Cognome: Rossi
Nome: Andrea
Codice fiscale: RSSNDR67A08D969M
Documento: Carta d'identità, Numero: AY8342152
Data di nascita: 08/01/1967
Luogo di nascita: Genova
Provincia di nascita: GE
Indirizzo lavorativo: Via G. Gaslini 5
Città: Genova
CAP: 16147
Provincia: GE
Email: AndreaRossi@gaslini.org
Altra email: AndreaRossi@gaslini.org
Telefono: +3901056362516
Qualifica: Direttore Unità Operativa Complessa
Struttura: Neuroradiologia

Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)	
Project Code: NET-2018-12366666-6	**Principal Investigator:** Piana Michele
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Liguria

Project Type: WP PROJECT - 6

Istituzione: Istituto Giannina Gaslini

Principal Investigator Data - Working package 5 Code: NET-2018-12366666-5

Cognome: AMATO
Nome: MARIA PIA
Codice fiscale: MTAMRP58A67M126R
Documento: Passaporto, Numero: YA4515971
Data di nascita: 27/01/1958
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Principal Investigator Data - Working package 6 Code: NET-2018-12366666-6

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	Project Title: Artificial intelligence methods for the extraction of information and knowledge from biomedical data (data infrastructure)
Project Code: NET-2018-12366666-6	**Principal Investigator:** Piana Michele
Research Type: a) Theory-enhancing: sviluppare procedure altamente innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...	**Applicant Institution:** Liguria

Project Type: WP PROJECT - 6