1 - General information

Project code: PNRR-MAD-2022-12376033	**Project topic:** C1) Malattie croniche non trasmissibili, ad alto impatto sui sistemi sanitari e socio-assistenziali: fattori di rischio e prevenzione
	Applicant Institution: Regione Lombardia - Direzione Generale Sanità
PI / Coordinator: Russo Antonio Giampiero	**Istitution that perform as UO for UO1:** Epidemiology Unit, ATS Milano

Call section: Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e socio-assistenziali

Proposal title: Evidence-based models for high impact chronic disease prevention and risk of progression management in outpatient community services and community hospitals: towards eHealth integrating stratification on individual history with predictive models of disease progression, using machine learning and artificial intelligence on administrative and clinical databases

Duration in months: 24

MDC primary: Cardiologia-Pneumologia

MDC secondary: Endocrinologia

Project Classification IRG: Healthcare Delivery and Methodologies

Project Classification SS: Health Services Organization and Delivery - HSOD

Project Keyword 1: Health needs and health services utilization; studies of severity of illness; comorbidity; risk prediction and risk adjustment; psychosocial and economic factors related to health care; and adherence to health care recommendations.

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

Project total financing request to the MOH: € 1.000.000

Free keywords: Noncommunicable Diseases; Chronic Diseases; Cancer; Delivery of Health Care; Disease Management and Modelling; Predictive Models; Organizational performance and efficiency

Declarations

In case of a Synergy grant application 'Principal Investigator'(PI) means 'corresponding Principal Investigator on behalf of all Principal Investigators', and 'Host Institution' means 'corresponding Host Institution'.

1) The Principal Investigator declares to have the written consent of all participants on their participation and on the content of this proposal, as well as of any researcher mentioned in the proposal as participating in the project (either as other PI, team member or collaborator).	X
2) The Principal Investigator declares that the information contained in this proposal is correct and complete.	X
3) The Principal Investigator declares that all parts of this proposal comply with ethical principles (including the highest standards of research integrity — as set out, for instance, in the European Code of Conduct for Research Integrity — and including, in particular, avoiding fabrication, falsification, plagiarism or other research misconduct).	X
4) The Principal Investigator is only responsible for the correctness of the information relating to his/her own organisation. Each applicant remains responsible for the correctness of the information related to him and declared above.	X

Personal data protection

The assessment of your grant application will involve the collection and processing of personal data (such as your name, address and CV), which will be performed pursuant to Regulation (EC) No 45/2001 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data. Unless indicated otherwise, your replies to the questions in this form and any personal data requested are required to assess your grant application in accordance with the specifications of the call for proposals and will be processed solely for that purpose. Details concerning the purposes and means of the processing of your personal data as well as information on how to exercise your rights are available in the privacy statement. Applicants may lodge a complaint about the processing of their personal data with the European Data Protection Supervisor at any time.

Abstract

BACKGROUND: Proper individuation and treatment of high-impact chronic conditions (HICDs) at individual and population-level is a crucial feature of a health system, particularly so in the context of prevention of further worsening of disease (tertiary prevention). Furthermore, the recently devised providers of territorial health services (outpatient community services, Case di Comunità - CdC and community hospitals, Ospedali di Comunità - OdC) would greatly benefit from a more precise definition of the health needs of the population they serve, to better adapt their organization. Also, there is a current lack of standardized health databases and indicator systems to evaluate territorial care organization and outcomes, which are often rare and difficult to detect with specificity and to attribute to a single professional/provider.
AIM: The issue of tertiary prevention for the most prevalent HICDs can be tackled with a novel approach, by integrating individual-level health information from administrative databases of the ATS/Regional Health Agency (RHA) and clinical databases of the CdCs, and then classifying patients into clusters by the actual state of their chronic condition(s) (iso-severity), health resources consumption (iso-resources) and risk of disease progression. We thus aim to develop a digital platform that would allow to produce estimations of the risk of progression of diseases for each subject to tailor tertiary prevention and adapt the setting of care and follow-up and treatment protocols. This will serve as a basis to detect changes in needs of territorial health services by clusters of individuals, to adapt the organization of territorial care in advance and to plan interventions at the population level.
METHODS: We plan to proceed through three steps: first, a dynamic stratification of the population, intended as the detection of HICDs and the prediction of their evolution. This will be obtained by integrating algorithms for the stratification of chronic conditions based on the integration of health and socio-sanitary databases and algorithms developed for outcome prediction from administrative and clinical data. This phase will be carried out using approaches based on conventional statistical models and on Artificial Intelligence / Machine Learning systems and will lead to the development of an integrated eHealth platform between CdC and ATS/RHA. This can allow health providers to properly act in order to prevent disease worsening, and to change the course of action once a disease has worsened. A second step is the development of Territorial

Health Profiles, as a prerequisite to the planning of health interventions at the population level. The availability of individual-level data by means of the developed digital platform will allow a particularly detailed analysis, which will include the measurement of the effect of interventions developed through this project. The final step is the utilization of the obtained information about individual and population health to organize the activities of territorial health providers, in terms of estimation of organizational requirements, of the prospected volumes of activity, and of the definition of the diagnosis and treatment protocols of diseases that make up the clusters identified and managed by the digital platform. This way, CdCs and OdCs will be able to tailor their structure and offer of health services according to the actual needs of the population they serve.

In order to best review your application, do you agree that the above non-confidential proposal title and abstract can be used, without disclosing your identity, when contacting potential reviewers? Yes

2 - Participants & contacts

Operative Units

Institution that perform as UO	CF Institution	Department / Division / Laboratory	Role in the project	Southern Italy	SSN
1 - Epidemiology Unit, ATS Milano	09320520969	ATS Città Metropolitana di Milano - UOC Unità di Epidemiologia	UO1 Project coordinator - applied research contribution to realize all three aims		X
2 - Agenzia Regionale Strategica per la Salute ed il Sociale (AReSS) - Puglia	93496810727	Area Epidemiologia e Care Intelligence	UO2 - applied research contribution to realize all three aims	X	X
3 - Università Milano Bicocca	12621570154	Centro Interdipartimentale Bicocca Bioinformatics Biostatistics and Bioimaging Centre (B4)	UO3 Expertise in advanced methodology in biostatistics and machine learning to realize aim1		

Principal Research Collaborators

Key Personnel Name	Operative Unit	Role in the project
1 - Andreano Anita	Epidemiology Unit, ATS Milano	Co-PI
2 - Bisceglia Lucia	Agenzia Regionale Strategica per la Salute ed il Sociale (AReSS) - Puglia	Coordinator of UO 2
3 - TUNESI SARA	Epidemiology Unit, ATS Milano	Researcher
4 - Rebora Paola	Università Milano Bicocca	Coordinator of UO 3
5 - Salvatori Andrea	Epidemiology Unit, ATS Milano	Researcher
6 Under 40 - MAGNONI PIETRO	Epidemiology Unit, ATS Milano	Researcher
7 Under 40 - Nannavecchia Anna Maria	Agenzia Regionale Strategica per la Salute ed il Sociale (AReSS) - Puglia	Researcher

Key Personnel Name	Co-PI	Resp. CE	Resp. Animal	Birth Date	Gender
1 - Andreano Anita	X			20/06/1980	F
2 - Bisceglia Lucia				05/07/1974	F
3 - TUNESI SARA				10/03/1977	F
4 - Rebora Paola				03/07/1981	F
5 - Salvatori Andrea				31/10/1984	M
6 Under 40 - MAGNONI PIETRO				16/01/1992	M
7 Under 40 - Nannavecchia Anna Maria				20/01/1988	F

Responsible who requests CE authorization: Russo Antonio Giampiero

Additional research collaborators under 40 to hire

Key Personnel Name	Operative Unit	Birth Date	Gender	Role in the project	Degree	Actual Pos. and Inst.
0 - OCCHINO GIUSEPPE	Agenzia Regionale Strategica per la Salute ed il Sociale (AReSS) - Puglia	27/10/1993	M	Researcher	M.Sc.	PhD Student, University of Milan Bicocca
1 - PETROSINO MATTEO	Agenzia Regionale Strategica per la Salute ed il Sociale (AReSS) - Puglia	19/12/1993	M	Researcher	M.Sc.	PhD Student, University of Milan Bicocca

2.1 Administrative data of participating

Operative Unit Number 1:

Address: Via Conca del Naviglio 45, Milan, 20123, Italy
PEC: protocollogenerale@pec.ats-milano.it

Operative Unit Number 2:

Address: Lungomare Nazario Sauro 33, Bari, 70121, Italy
PEC: dirgen.ares@pec.rupar.puglia.it

Operative Unit Number 3:

Address: U28 Via Follerau 3, Vedano al Lambro (MB), 20854, Italy
PEC: ateneo.bicocca@pec.unimib.it

Operative Unit Number 4:

Address: n.a.
PEC: n.a.

Operative Unit Number 5 (self financing):

Address: n.a.
PEC: n.a.

2.2 Principal Investigator (PI) Profile

Last Name: Russo
First Name: Antonio Giampiero

Last name at birth:
Gender: M

Title: Principal investigator
Nationality: Italiana
Date of birth: 03/07/1963

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Reggio Calabria

Official H index (Scopus or Web of Science): 53.0

Scopus Author Id:7402518728 **ORCID ID:**0000-0002-5681-5861 **RESEARCH ID:**K-2230-2018

Contact address

Current organisation name: Epidemiology Unit, ATS Milano
Current Department / Faculty / Institute / Laboratory name: ATS Città Metropolitana di Milano - UOC Unità di Epidemiologia
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Town: Milano
Phone:+393285638205
Phone 2: 3285638205

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Milan	Specialization / Specializzazione	Medical Genetics	1999	2004
University of Milan	Specialization / Specializzazione	Medical Statistics	1989	1992
University of Florence	Single-cycle master's degree / Laurea magistrale a ciclo unico	Degree in Medicine and Surgery	1982	1988

Personal Statement:

Dr. Antonio Giampiero Russo will be the PI of the project and will coordinate the activities of UO1 (ATS of Milan) and the overall project. He will be also responsible for the realization of Aim3, contributing to the analyses needed to perform organizational changes in pilot CdCs/OdCs (action 3.1-3.2) and recruit and coordinate MMG/PLS for definition of adaptive diagnostic and therapeutic pathways in the territory of ATS Milan (action 3.3). He will also give an important contribution to Aim1, coordinating the Milan working group for definition of settings and care pathways (action 1.5) and Aim2, contributing to the definition of the new territorial health profiles and fostering their implementation in an open data platform (actions 2.1-2.2).

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Agency for Health Protection (ATS) of Milan	Epidemiology Unit	Milan	Director	2016	2022
Local Health Authority	Epidemiology Unit and Cancer Registry	Milan	Director	2010	2015
San Carlo Borromeo Hospital	Epidemiology Unit	Milan	Director	2008	2010
Local Health Authority	Epidemiology Unit	Milan	Director of Cancer Registry of Milan	2001	2008
Centro Studio e Prevenzione Oncologica of Florence	Depatment of Epidemiology	Florence	Assistant	1998	2001
National Cancer Institute of Milan	Department of Epidemiology	Milan	Associate Medical Researcher	1992	1994
Cancer Institute of Genoa	Department of Epidemiology	Genoa	Researcher	1991	1992
Centro Studio e Prevenzione Oncologica of Florence	Department of Epidemiology	Florence	Researcher	1988	1991

Other awards and honors

Past member of Direction Committee of the Italian Association of Epidemiology (AIE) (2006-2008);
Member of Oncological Committee of Lombardy Region (2009-2016);
President of Ethical Committee of San Carlo Borromeo Hospital (2008-2013);
Member of Ethical Committee of San Gerardo Hospital (2013-2016);
Member of the following Association: Italian Association of Epidemiology (AIE); Italian Association of Cancer Registry (AIRTum).

Other CV informations

For the last 13 years, Dr. Russo has been focusing on public health assessment and in 2017 he was appointed expert member of the National Committee PNE. It deals with the revision of the indicators and the development of new methods for the evaluation nof health outcomes.

Selected peer-reviewed publications of the PI valid for minimum expertise level

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
A population study to evaluate the efficacy of influenza vaccination, 2014-2015	Article	234-242	39	2015	NOT_FOUND	26499236	4	F
Evaluation of a public health programme: Direct Clopidogrel administration by cardiology units in acute myocardial infarction	Article	51-57	40	2016	10.19191/EP16.1.P051.014	26951702	0	L
Applying a set of indicators to evaluate the primary health care	Article	91-101	41	2017	10.19191/EP17.2.P91.028	28627150	0	F
Development of an algorithm based on health and social sources to stratify general population in different levels of health status, sociosanitary frailty, and disability	Article	197-207	41	2017	10.19191/EP17.3-4.P197.053	28929716	0	L

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Evaluation of the CReG model used by the ATS of the Metropolitan City of Milan for the management of chronic diseases in general practice	Article	31-50	NOT_FOUND	2017	10.3280/MESA2017-101003	NOT_FOUND	1	L
Risk factors for breast cancer in a cohort of mammographic screening program: a nested case¿control study within the FRiCaM study	Article	2145-2152	7	2018	10.1002/cam4.1427	29654663	12	L
Do autistic patients change healthcare services utilisation through the transition age? An Italian longitudinal retrospective study	Article	NOT_FOUND	9	2019	10.1136/bmjopen-2019-030844	31727653	2	L
Residential distance from high-voltage overhead power lines and risk of Alzheimer¿s dementia and Parkinson¿s disease: A population-based case-control study in a metropolitan area of Northern Italy	Article	1949-1957	48	2019	10.1093/ije/dyz139	31280302	7	L
Emergency attendance for acute hyper-and hypoglycaemia in the adult diabetic population of the metropolitan area of Milan: Quantifying the phenomenon and studying its predictors	Article	NOT_FOUND	20	2020	10.1186/s12902-020-0546-1	32429960	1	L
Association between autoimmune diseases and COVID-19 as assessed in both a test-negative case-control and population case-control design	Article	NOT_FOUND	11	2020	10.1186/s13317-020-00141-1	NOT_FOUND	16	L
Development of a multivariable model predicting mortality risk from comorbidities in an italian cohort of 18,286 confirmed covid-19 cases aged 40 years or older	Article	100-109	45	2021	10.19191/EP21.1-2.P100.044	33884848	4	L
Strategy to identify priority groups for COVID-19 vaccination: A population based cohort study	Article	2517-2525	39	2021	10.1016/j.vaccine.2021.03.076	33824037	11	F
Assessing the Impact of Individual Characteristics and Neighborhood Socioeconomic Status During the COVID-19 Pandemic in the Provinces of Milan and Lodi	Article	311-324	51	2021	10.1177/0020731421994842	33650453	9	L
Effectiveness and safety of non-vitamin k oral anticoagulants in non-valvular atrial fibrillation patients: Results of a real-world study in a metropolitan area of northern Italy	Article	NOT_FOUND	10	2021	10.3390/jcm10194536	NOT_FOUND	0	L
Metabolic syndrome and risk of COVID-19-related hospitalization: a large, population-based cohort study carried out during the first European outbreak of SARS-CoV-2 infection in the Metropolitan area of Milan (Lombardy Region, Northern Italy)	Article	477-485	45	2021	10.19191/EP21.6.115	34791868	0	L
Population-based incidence and prevalence of inflammatory bowel diseases in Milan (Northern Italy), and estimates for Italy	Article	e383-e389	33	2021	10.1097/MEG.0000000000002107	33784448	0	L

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

Selected peer-reviewed publications of the PI for the evaluation CV

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**
Residential distance from high-voltage overhead power lines and risk of Alzheimer¿s dementia and Parkinson¿s disease: A population-based case-control study in a metropolitan area of Northern Italy	Article	1949-1957	48	2019	10.1093/ije/dyz139	31280302	7
Inverse occurrence of cancer and Alzheimer disease: A population-based incidence study	Article	322-328	81	2013	10.1212/WNL.0b013e31829c5ec1	23843468	148
Long-term mortality and incidence of cardiovascular diseases and type 2 diabetes in diabetic and nondiabetic obese patients undergoing gastric banding: A controlled study	Article	NOT_FOUND	15	2016	10.1186/s12933-016-0347-z	26922059	28
Effects of pulmonary rehabilitation on lung function in chronic obstructive pulmonary disease: The FIRST study.	Article	419-426	50	2014	NOT_FOUND	24691247	20
Association between autoimmune diseases and COVID-19 as assessed in both a test-negative case-control and population case-control design	Article	NOT_FOUND	11	2020	10.1186/s13317-020-00141-1	NOT_FOUND	16
Risk factors for breast cancer in a cohort of mammographic screening program: a nested case¿control study within the FRiCaM study	Article	2145-2152	7	2018	10.1002/cam4.1427	29654663	12
Strategy to identify priority groups for COVID-19 vaccination: A population based cohort study	Article	2517-2525	39	2021	10.1016/j.vaccine.2021.03.076	33824037	11
Assessing the Impact of Individual Characteristics and Neighborhood Socioeconomic Status During the COVID-19 Pandemic in the Provinces of Milan and Lodi	Article	311-324	51	2021	10.1177/0020731421994842	33650453	9
Development of a multivariable model predicting mortality risk from comorbidities in an italian cohort of 18,286 confirmed covid-19 cases aged 40 years or older	Article	100-109	45	2021	10.19191/EP21.1-2.P100.044	33884848	4
A population study to evaluate the efficacy of influenza vaccination, 2014-2015	Article	234-242	39	2015	NOT_FOUND	26499236	4

** Autocertificated

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
CARPLO Foundation	ATS Città Metropolitana di Milano	2021	Enhancing healthcare and well-being through the potential of big data: an integration of survey, administrative, and open data to assess health risk in the City of Milan with data science	Coordinator	125.000,00	https://www.fondazionecariplo.it/it/index.html

2.3 CO-PI Profile

Last Name: Andreano
First Name: Anita
Last name at birth:
Gender: F

Title: Co-PI
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 20/06/1980
Place of Birth: Milano

Official H index (Scopus or Web of Science): 15.0

Scopus Author Id:25633771200 **ORCID ID:**0000-0002-9667-7010 **RESEARCH ID:**J-5236-2018

Contact address

Current organisation name: Epidemiology Unit, ATS Milano
Current Department / Faculty / Institute / Laboratory name: ATS Città Metropolitana di Milano - UOC Unità di Epidemiologia
Street: Via Conca del Naviglio 45
Postcode / Cedex: 20123
Town: Milano
Phone:+393287118557
Phone 2: 3287118557

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Milan, Department of Medical Sciences and Community Health, Milan, Italy	Specialization / Specializzazione	Medical Statistics and Biometry	2012	2017
University of Milan, Department of Medical Sciences and Community Health, Milan, Italy	Master's Degree / Laurea Magistrale	Medical Statistics and Biometry	2011	2011
University of Milan Bicocca, School of Medicine and Surgery, Monza, Italy	Specialization / Specializzazione	Radiodiagnostics	2006	2009
University of Milan Bicocca, School of Medicine and Surgery, Monza, Italy	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	1999	2005

Personal Statement:

Dr. Anita Andreano will be the Co-PI of the project and will be part of UO1 (ATS of Milan). She will be responsible for the coordination of Aim 1, actively contributing to its realization concerning the development of the new algorithms to identify chronic conditions and their integration with predictive models in a new integrated platform, to subdivide the entire population in homogeneous clusters. She will also cooperate to health profile construction (action 2.2).

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Agency for Health Protection (ATS) of Milan	Epidemiology Unit	Milan, Italy	Coordinator of the 'Hospital Performance and monitoring systems' Unit	2018	2022
University of Milan Bicocca	Center of Biostatistic for Clinical Epidemiology	Monza, Italy	Contract researcher	2018	2018
University College London (UCL)	Division of Internal Medicine	London, UK	Honorary Research Associate	2016	2017
University of Milan Bicocca	Bioimaging Center	Monza, Italy	Contract researcher	2010	2010
S. Gerardo Hospital	Department of Radiology	Monza, Italy	Radiologist	2010	2011

Other awards and honors

- Ballardini Award at the Italian Society of Medical Statistics and Clinical Epidemiology (SISMEC) congress, Rome, 25-28 September 2013
- Member of the International Biometric Society (SIB), Italian Region (IBS)
- Member of the Italian Association of Epidemiology (AIE)

Other CV informations

PhD Student in Public Health, Executive Programm from September 2019 (expected graduation January 2023), School of medicine and Surgery, University of Milan Bicocca.

Selected peer-reviewed publications of the Co-PI valid for minimum expertise level

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Percutaneous microwave ablation of hepatic tumors: Prospective evaluation of postablation syndrome and postprocedural pain	Article	NOT_FOUND	25	2014	10.1016/j.jvir.2013.09.005	24286938	24	F
MR diffusion imaging for preoperative staging of myometrial invasion in patients with endometrial cancer: A systematic review and meta-analysis	Article	1327-1338	24	2014	10.1007/s00330-014-3139-4	24668009	88	F
Measures of single arm outcome in meta-analyses of rare events in the presence of competing risks	Article	649-660	57	2015	10.1002/bimj.201400119	25656709	10	F
Development of a multivariable model predicting mortality risk from comorbidities in an italian cohort of 18,286 confirmed covid-19 cases aged 40 years or older	Article	100-109	45	2021	10.19191/EP21.1-2.P100.044	33884848	4	F
Indicators based on registers and administrative data for breast cancer: Routine evaluation of oncologic care pathway can be implemented	Article	62-70	22	2016	10.1111/jep.12436	26290172	5	F
Adherence to guidelines and breast cancer patients survival: a population-based cohort study analyzed with a causal inference approach	Article	119-131	164	2017	10.1007/s10549-017-4210-z	28365831	10	F

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Cancer of the head and neck: A set of indicators based on register and administrative data	Article	13-23	38	2018	10.14639/0392-100X-1934	29756612	2	F
The Care and Outcomes of Older Persons with Lung Cancer in England and the United States, 2008¿2012	Article	904-914	13	2018	10.1016/j.jtho.2018.04.022	29727739	6	F
Emergency attendance for acute hyper-and hypoglycaemia in the adult diabetic population of the metropolitan area of Milan: Quantifying the phenomenon and studying its predictors	Article	NOT_FOUND	20	2020	10.1186/s12902-020-0546-1	32429960	4	F
Immune checkpoint inhibitors at any treatment line in advanced NSCLC: Real-world overall survival in a large Italian cohort	Article	145-152	159	2021	10.1016/j.lungcan.2021.06.019	34340111	1	F
Indicators of guideline-concordant care in lung cancer defined with a modified Delphi method and piloted in a cohort of over 5,800 cases	Article	NOT_FOUND	79	2021	10.1186/s13690-021-00528-0	NOT_FOUND	0	F
Administrative healthcare data to predict performance status in lung cancer patients	Article	NOT_FOUND	39	2021	10.1016/j.dib.2021.107559	NOT_FOUND	0	F

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Ministero della Salute MOH	ATS Milano	2014-2017	From the measure of guidelines adherence in oncology to the assessment of health system performance, RF¿2011¿02348959	Collaborator	178,19	https://www.salute.gov.it/portale/ricercaSanitaria/dettaglioContenutiRicercaSanitaria.jsp?lingua=italiano&id=5130&area=Ricerca%20sanitaria&menu=progetti20092018

2.3 Research Collaborators n. 2

Last Name: Bisceglia
First Name: Lucia

Last name at birth: Bisceglia
Gender: F

Title: Coordinator of UO 2
Nationality: Italiana
Date of birth: 05/07/1974

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Matera

Official H index (Scopus or Web of Science): 13.0

Scopus Author Id: 15831272600 **ORCID ID:** 0000-0001-6256-3747 **RESEARCH ID:** AHI-0272-2022

Contact address

Current organisation name: Agenzia Regionale Strategica per la Salute ed il Sociale (AReSS) - Puglia
Current Department / Faculty / Institute / Laboratory name: Area Epidemiologia e Care Intelligence
Street: Lungomare Nazario Sauro
Postcode / Cedex: 70121
Town: Bari
Phone: +393922812283
Phone 2: 3922812283

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Turin	Master's Degree / Laurea Magistrale	Epidemiology	2007	2008
University of Bari	PhD	Health Environment and Medicine	2007	2008
University of Bari	Specialization / Specializzazione	Occupational Medicine	1999	2003
University of Bari	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	1994	1999

Personal Statement:

Dr. Lucia Bisceglia will coordinate the activities of the Regional Agency for Health and Social Care of Apulia (UO2). She will be involved in the realization of Aim1, for the development of the new algorithms to identify chronic conditions and their integration with predictive models, and of Aim2, particularly for the definition of the new territorial health profiles and their implementation in an open data platform to host information and make it available to the population and stakeholders.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Regional Agency for Health and Social Care of Apulia	Epidemiology and Care Intelligence Department	Bari, Italy	Director	2019	2022
Regional Agency for Health and Social Care of Apulia	Analysis of health supply and demand Unit	Bari, Italy	Unit Manager	2019	2022
Regional Agency for Environmental Protection and Prevention of Apulia¿ ARPA Puglia	Environment and Health Unit	Bari, Italy	Unit Manager	2006	2011

Other awards and honors

President of Italian Association of Epidemiology (2021-2023)
Director of Cancer Registry of Apulia
Member of the National Committee for Cancer Registries (art. 3, comma 7 del Decreto del Ministro della Salute 12 agosto 2021, istituito con D.D. 10 dicembre 2021)
Member of the National Oncology Program Board
Member of the coordination board for the Regional Prevention Program
Member of PonGOV Cronicità - Health Ministry
member of the National Committee PNE

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
nome	nome	0	nome	Collaborator	0,00	nome

2.4 Research Collaborators n. 3

Last Name: TUNESI
First Name: SARA

Last name at birth: Milano
Gender: F

Title: Researcher
Nationality: Italiana
Date of birth: 10/03/1977

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Milano

Official H index (Scopus or Web of Science): 14.0

Scopus Author Id:23767335200 **ORCID ID:**0000-0002-8576-942X **RESEARCH ID:**I-3746-2013

Contact address

Current organisation name: Epidemiology Unit, ATS Milano
Current Department / Faculty / Institute / Laboratory name: ATS Città Metropolitana di Milano - UOC Unità di Epidemiologia
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Postcode / Cedex: 20123
Town: Milano
Phone:+393498527911
Phone 2: 3498527911

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Milan, Physic Dep	Single-cycle master's degree / Laurea magistrale a ciclo unico	Physic	1997	2003
University of Milan, Institute of Medical Statistics and Biometry G.A. Maccacaro	PhD	Medical Statistics and Biometry	2004	2006
University of Turin	Master's Degree / Laurea Magistrale	Epidemiology and medical statistics	2009	2010

Personal Statement:

Dr. Tunesi will be a component of UO1. She will be involved mainly in Aim 1, particularly in the development of Intelligence/Machine Learning systems predictive models of chronicity evolution and in the combination of classification and prediction algorithms to establish a dynamic stratification system of the population.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
AOU Città della Salute e della Scienza, Hospital of Turin	Center for Cancer Epidemiology and Prevention	Turin, Italy	Contract Statistician (co.co.co)	2012	2013
University of Eastern Piedmont	Epidemiology Unit	Novara, Italy	Research fellowship (assegno di ricerca)	2013	2015
AOU Città della Salute e della Scienza, Hospital of Turin	Center for Cancer Epidemiology and Prevention	Turin, Italy	Contract Statistician (co.co.co)	2015	2017
Agency for Health Protection of Milan	Epidemiology Unit	Milan	Fellowship (borsista)	2017	2017
Agency for Health of Protection of Milan	Epidemiology Unit	Milan	Statistician	2018	2022

Other awards and honors

Member of the Italian Association of Epidemiology (AIE)

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
nome	nome	0	nome	Collaborator	0,00	nome

2.5 Research Collaborators n. 4

Last Name: Rebora
First Name: Paola
Last name at birth:
Gender: F

Title: Coordinator of UO 3
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 03/07/1981
Place of Birth: Bollate

Official H index (Scopus or Web of Science): 19.0

Scopus Author Id: 10143229600 **ORCID ID:** 0000-0003-0606-5852 **RESEARCH ID:** M-9098-2016

Contact address

Current organisation name: Università Milano Bicocca
Current Department / Faculty / Institute / Laboratory name: Centro Interdipartimentale Bicocca Bioinformatics Biostatistics and Bioimaging Centre (B4)

Street: via Cadore
Postcode / Cedex: 20900
Town: Monza
Phone: +393479748595
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Milan	PhD	Biomedical Statistics	2007	2010
University of Milan Bicocca	Master's Degree / Laurea Magistrale	Biostatistics and Experimental Statistics	2003	2006
University of Milan Bicocca	Bachelor Degree / Laurea Triennale	Statistics	2000	2003

Personal Statement:

Prof. Paola Rebora will be the coordinator of UO3. She will be mainly involved in Aim 1 by providing the methodological support for the development of predictive models of chronicity evolution and dynamic stratification of the population. In particular, the effort will be directed to the development of a sound methodology that goes beyond standard regression approaches and makes an optimal use of all information available, including innovative approaches such as machine learning techniques.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Milan Bicocca	School of Medicine and Surgery	Monza	Associate Professor	2020	2022
University of Milan Bicocca	School of Medicine and Surgery	Monza	Assistant Professor	2016	2020
University of Milan Bicocca	Dept. of Health Sciences	Monza	Researcher in medical statistics	2013	2016
University of Milan Bicocca	Dept. of Health Sciences	Monza	Research fellowship in medical statistics	2007	2013
Karolinska Institute	Dept. of Medical Epidemiology and Biostatistics	Stockholm	Scholarship	2005	2006

Other awards and honors

-Member of the following scientific societies: ISCB (International Society for Clinical Biostatistics), IBS (International Biometric Society), SISMEC (Società Italiana di Statistica Medica ed Epidemiologia Clinica).

-Treasurer of the Italian Region of the Biometric Society (2022-2023)

-Secretary of the 'National group' committee of the ISCB (2021-2023)

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
CARIPLO Foundation	University of Milano - Bicocca	2020	The effect of frailty on the clinical outcomes of patients infected by COVID-19 and on the risk of infection in the elderly: FraCOVID study	Collaborator	175.600,00	https://www.fondazionecariplo.it/static/upload/rst/rst_bandocovid_9giu20.pdf
Italian Foundation for Cancer Research (FIRC)	University of Milano - Bicocca	2009-2011	Analysis of event-history data in cancer: modelling efficacy, safety and late effects of therapies	Collaborator	60.000,00	nome
Regione Lombardia	University of Milano - Bicocca	2007	Center to support Clinical Research (A0000352)	Collaborator	34.808,00	nome
Scientific Independence Research (SIR) Ministero dell'Istruzione, dell'Università e della Ricerca	University of Milano - Bicocca	2015-2018	IDEA: Innovative DEsigns and statistical Approaches for biomarker development	Coordinator	276.650,00	https://sir.miur.it/index.php/finanziati/index

2.6 Research Collaborators n. 5

Last Name: Salvatori
First Name: Andrea
Last name at birth:
Gender: M

Title: Researcher
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 31/10/1984
Place of Birth: Milano

Official H index (Scopus or Web of Science): 2.0

Scopus Author Id:57215786162 **ORCID ID:**0000-0001-6249-6636 **RESEARCH ID:**AHE-1516-2022

Contact address

Current organisation name: Epidemiology Unit, ATS Milano
Current Department / Faculty / Institute / Laboratory name: ATS Città Metropolitana di Milano - UOC Unità di Epidemiologia
Street: via Conca del Naviglio 45
Postcode / Cedex: 20123
Town: Milano
Phone:+393387265480
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Milan	Specialization / Specializzazione	Medical Statistics	2018	2021
University of Perugia	Single-cycle master's degree / Laurea magistrale a ciclo unico	Degree in Medicine and Surgery	2011	2017
University of Bologna	Master's Degree / Laurea Magistrale	International Relations	2006	2009
University of Bologna	Bachelor Degree / Laurea Triennale	International Relations	2003	2006

Personal Statement:

Dr. Salvatori will be a component of UO1, and will be involved in the definition of the deterministic algorithms for the prediction of the evolution of chronic conditions, based on the existing chronicity profile and individual information from health administrative and clinical databases, using conventional statistical models (action 1.1). He will also cooperate to the recognition of the organization and volume of provision of the CdC/OdC for the ATS of Milan (action 3.1) and their comparison with the expected volume on the basis of the dynamic stratification of the population (action 3.2).

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Hospital San Gerardo	Hospital Health Direction	Monza	Medical Epidemiologist	2020	2021
Agency for health Protection	Epidemiology Unit	Milan	Medical Epidemiologist	2021	2022

Other awards and honors

- Member of the International Biometric Society (SIB), Italian Region (IBS)
- Member of the Italian Association of Epidemiology (AIE)

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
nome	nome	0	nome	Collaborator	0,00	nome

2.7 Research Collaborators n. 6 - Under 40

Last Name: MAGNONI
First Name: PIETRO
Last name at birth:
Gender: M

Title: Researcher
Country of residence: ITALY
Nationality: ITALIANA
Country of Birth: ITALY
Date of birth: 16/01/1992
Place of Birth: MACERATA

Official H index (Scopus or Web of Science): 2.0

Scopus Author Id:57202441590 **ORCID ID:**0000-0002-6431-6261 **RESEARCH ID:**AHE-3426-2022

Contact address

Current organisation name: Epidemiology Unit, ATS Milano
Current Department / Faculty / Institute / Laboratory name: ATS Città Metropolitana di Milano - UOC Unità di Epidemiologia
Street: VIA CONCA DEL NAVIGLIO, 45
Postcode / Cedex: 20123
Town: MILANO
Phone:+393209627125
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Milan, Department of Biomedical Sciences for Health, Milan, Italy	Specialization / Specializzazione	Public Health	2017	2021
Vita-Salute San Raffaele University, Faculty of Medicine and Surgery, Milan, Italy	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	2010	2016

Personal Statement:

As part of UO1 (ATS of Milan), Dr. Pietro Magnoni will contribute to its role across the three main aims, including the following specific actions: - Performing survey of existing algorithms in use in European public health contexts, contributing to their adaptation for use in NCIS and benchmarking, participating in their cross-testing and validation with clinicians (action 1.2); - Contributing to the implementation of Territorial Health Profiles by reviewing and constructing indicators for socio-demographic characteristics, resource use, adherence to and effectiveness of prevention programs (action 2.2).

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Agency for Health Protection (ATS) of Milan	Unit of Epidemiology	Milan, Italy	Medical Epidemiologist	2021	2022
IRCCS San Raffaele Hospital	Pancreatobiliary Endoscopy and Endosonography Division	Milan, Italy	Researcher	2016	2017

Other awards and honors

- Member of the Italian Association of Epidemiology (AIE)
- Member of the Italian Society of Hygene (SItI)
- Member of the European Public Health Association (EUPHA)

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
nome	nome	0	nome	Collaborator	0,00	nome

2.8 Research Collaborators n. 7 - Under 40

Last Name: Nannavecchia
First Name: Anna Maria

Last name at birth:
Gender: F

Title: Researcher
Nationality: Italiana
Date of birth: 20/01/1988

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Ceglie Messapica

Official H index (Scopus or Web of Science): 2.0

Scopus Author Id:57194452076 **ORCID ID:**0000-0001-9672-9952 **RESEARCH ID:**AHI-0339-2022

Contact address

Current organisation name: Agenzia Regionale Strategica per la Salute ed il Sociale (AReSS) - Puglia
Current Department / Faculty / Institute / Laboratory name: Area Epidemiologia e Care Intelligence
Street: Lungomare Nazario Sauro 33
Postcode / Cedex: 70121
Town: Bari
Phone:+393298974793
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Bologna	Master's Degree / Laurea Magistrale	Statistics	2007	2010
University of Bologna	Master's Degree / Laurea Magistrale	Statistics	2010	2013

Personal Statement:
Dr.ssa Anna Maria Nannavecchia will take part in the activities of the Regional Agency for Health and Social Care of Apulia (UO2). She will be involved in the realization of Aim2, particularly for the definition of the new territorial health profiles and their implementation in an open data platform to host information and make it available to the population and stakeholders.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Local Health Unit of Modena	Mental Health Unit	Modena, Italy	Consultant Statistician	2013	2014
Cancer Institute ¿ Giovanni Paolo II - BARI	Cancer Registry Department - Statistical and Epidemiology Unit	Cancer Registry Department - Statistical and Epidemiology Unit	Consultant Statistician	2014	2017
Local Health Unit of BAT	Statistical and Epidemiology Unit	Barletta, Italy	Statistician	2017	2018
Regional Agency for Health and Social Care of Apulia (AReSS)	Epidemiology and Care Intelligence Department	Bari, Italy	Statistician	2018	2018
Regional Environmental Protection Agency of Apulia (ARPA PUGLIA)	Department of Chemistry	Taranto, Italy	Statistician	2018	2020
Regional Agency for Health and Social Care of Apulia (AReSS)	Epidemiology and Care Intelligence Department	Bari, Italy	Statistician	2020	2022

Other awards and honors

Member of Italian Association of Epidemiology (AIE)
Member of Italian Society of Medical Statistics (SISMEC)

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
nome	nome	0	nome	Collaborator	0,00	nome

2.9 Additional Research Collaborators n. 2 - Under 40 to hire

Last Name: OCCHINO
First Name: GIUSEPPE
Last name at birth:
Gender: M

Title: Researcher
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 27/10/1993
Place of Birth: Desio

Official H index (Scopus or Web of Science): 2.0
Scopus Author Id:57205361727 **ORCID ID:**0000-0002-7074-9354 **RESEARCH ID:**AHE-5796-2022

Contact address

Current organisation name: Agenzia Regionale Strategica per la Salute ed il Sociale (AReSS) - Puglia
Current Department / Faculty / Institute / Laboratory name: Area Epidemiologia e Care Intelligence
Street: Via Raoul Follereau, 3
Postcode / Cedex: 20854 **Town:** Vedano al Lambro
Phone:+393347764533 **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Milan - Bicocca	Master's Degree / Laurea Magistrale	Biostatistics	2015	2018
University of Milan - Bicocca	Bachelor Degree / Laurea Triennale	Statistics and Information Management	2012	2015

Personal Statement:
Giuseppe Occhino (UO2) will be involved mainly in Aim 1, actually developing some of the deterministic and machine learning predictive models of chronicity evolution. He will be also involved in the combination of classification and prediction algorithms to establish a dynamic stratification system of the population.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
IRCCS Istituto Ortopedico Galeazzi	Unit of Clinical Epidemiology	Milan	Biostatistical Consultant	2019	2019
University of Milan - Bicocca	Laboratory of Healthcare Research & Pharmacoepidemiology	Milan	Research Scholar	2018	2019

Other awards and honors
- Member of the Italian Society of Biometry (SIB)

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
nome	nome	0	nome	Collaborator	0,00	nome

2.10 Additional Research Collaborators n. 3 - Under 40 to hire

Last Name: PETROSINO
First Name: MATTEO
Last name at birth: Petrosino
Gender: M

Title: Researcher
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 19/12/1993
Place of Birth: Genova

Official H index (Scopus or Web of Science): 1.0

Scopus Author Id:00000000000000 **ORCID ID:**0000-0001-8796-6411 **RESEARCH ID:**AHE-5937-2022

Contact address

Current organisation name: Agenzia Regionale Strategica per la Salute ed il Sociale (AReSS) - Puglia
Current Department / Faculty / Institute / Laboratory name: Area Epidemiologia e Care Intelligence
Street: Via Raoul Follereau 3
Postcode / Cedex: 20854
Town: Vedano al Lambro
Phone:+393459549799
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Turin	Master's Degree / Laurea Magistrale	Stochastics and Data Science	2016	2019
University of Genoa	Bachelor Degree / Laurea Triennale	Mathematics and Statistics	2012	2016

Personal Statement:

Matteo Petrosino (UO2) will be involved mainly in Aim 1, actually developing some of the deterministic and machine learning predictive models of chronicity evolution. He will be also involved in the combination of classification and prediction algorithms to establish a dynamic stratification system of the population.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Genoa	Department of Mathematics (DIMA)	Genoa	Teacher in 'Statistical methods for medicine', Bachelor course	2022	2022
University of Milano-Bicocca	Bioinformatics, Biostatistics and Bioimaging Centre - B4	Monza	Research Scholar	2019	2019

Other awards and honors

- Member of the Italian Society of Biometry (SIB)
- Member of the International Society For Clinical Biostatistics (ISCB)

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
nome	nome	0	nome	Collaborator	0,00	nome

2.17 Expertise Research Collaborators

Selected peer-reviewed publications of the Research Group / Collaborators

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
TUNESI SARA	The length of SNCA Rep1 microsatellite may influence cognitive evolution in Parkinson's disease	Article	NOT_FOUND	9	2018	10.3389/fneur.2018.00213	NOT_FOUND	17	O
TUNESI SARA	Prevalence and features of peripheral neuropathy in Parkinson's disease patients under different therapeutic regimens	Article	27-31	20	2014	10.1016/j.parkreldis.2013.09.007	24099722	63	O
TUNESI SARA	Survival and dementia in GBA-associated Parkinson's disease: The mutation matters	Article	662-673	80	2016	10.1002/ana.24777	27632223	182	O
TUNESI SARA	Efficacy of HPV-based screening for prevention of invasive cervical cancer: Follow-up of four European randomised controlled trials	Article	524-532	383	2014	10.1016/S0140-6736(13)62218-7	24192252	973	O
TUNESI SARA	Gene-asbestos interaction in malignant pleural mesothelioma susceptibility	Article	1129-1135	36	2015	10.1093/carcin/bgv097	26139392	22	F
Bisceglia Lucia	Industrial air pollution and mortality in the Taranto area, Southern Italy: A difference-in-differences approach	Article	NOT_FOUND	132	2019	10.1016/j.envint.2019.105030	31398654	19	O
OCCHINO GIUSEPPE	Uric acid is associated with acute heart failure and shock at presentation in ACS patients	Article in press	NOT_FOUND	NOT_FOUND	2022	10.1016/j.ejim.2022.01.018	NOT_FOUND	1	O
Salvatori Andrea	The effect of frailty on in-hospital and medium-term mortality of patients with COronaVIrus Disease-19: the FRACOVIDstudy	Article	24-30	64	2022	10.23736/S0031-0808.21.04506-7	34761887	2	O
OCCHINO GIUSEPPE	Prevalence of hypertension mediated organ damage in subjects with high-normal blood pressure without known hypertension as well as cardiovascular and kidney disease	Article	NOT_FOUND	NOT_FOUND	2021	10.1038/s41371-021-00604-6	NOT_FOUND	1	O

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
OCCHINO GIUSEPPE	Effectiveness of motivational interviewing on anxiety, depression, sleep quality and quality of life in heart failure patients: secondary analysis of the MOTIVATE-HF randomized controlled trial	Article	1939-1949	30	2021	10.1007/s11136-021-02788-3	33616815	1	O
PETROSINO MATTEO	Management of arterial partial pressure of carbon dioxide in the first week after traumatic brain injury: results from the CENTER-TBI study	Article	961-973	47	2021	10.1007/s00134-021-06470-7	34302517	2	O
OCCHINO GIUSEPPE	Atrial fibrillation and clinical outcomes in a cohort of hospitalized patients with sars-cov-2 infection and chronic kidney disease	Article	NOT_FOUND	10	2021	10.3390/jcm10184108	NOT_FOUND	5	O
Nannavecchia Anna Maria	Factors affecting asbestosis mortality among asbestos-cement workers in Italy	Article	622-635	64	2020	10.1093/annweh/wxaa037	32328661	1	O
Salvatori Andrea	Reproducibility of A Posteriori Dietary Patterns across Time and Studies: A Scoping Review	Review	1255-1281	11	2020	10.1093/advances/nmaa032	32298420	9	O
MAGNONI PIETRO	Influenza vaccination in italian healthcare workers (2018¿2019 season): Strengths and weaknesses. results of a cohort study in two large italian hospitals	Article	NOT_FOUND	8	2020	10.3390/vaccines8010119	NOT_FOUND	13	O
Andreano Anita	Association between uric acid and pulse wave velocity in hypertensive patients and in the general population: a systematic review and meta-analysis	Review	220-231	29	2020	10.1080/08037051.2020.1735929	32138547	1515	O
Andreano Anita	Association between autoimmune diseases and COVID-19 as assessed in both a test-negative case-control and population case-control design	Article	NOT_FOUND	11	2020	10.1186/s13317-020-00141-1	NOT_FOUND	16	O
Salvatori Andrea	Reproducibility and Validity of A Posteriori Dietary Patterns: A Systematic Review	Review	293-326	11	2020	10.1093/advances/nmz097	31578550	18	O
Rebora Paola	Frailty index predicts poor outcome in COVID-19 patients	Article	1634-1636	46	2020	10.1007/s00134-020-06087-2	32451583	48	O
Nannavecchia Anna Maria	Mortality for Mesothelioma and Lung Cancer in a Cohort of Asbestos Cement Workers in BARI (Italy): Time Related Aspects of Exposure	Article	410-416	61	2019	10.1097/JOM.0000000000001580	30870398	2	O

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Salvatori Andrea	Age-period-cohort effects in utilization of diagnostic procedures leading to incidental colorectal cancer detection	Article	26-34	31	2022	10.1097/CEJ.0000000000000662	33443960	0	F
MAGNONI PIETRO	Waiting time for outpatient specialist care in Lombardy Region: evaluating accessibility and quality of information on websites of public health agencies and healthcare structures	Article	31-43	33	2021	10.7416/ai.2021.2406	33354694	0	F
Rebora Paola	Delirium in Patients with SARS-CoV-2 Infection: A Multicenter Study	Article	293-299	69	2021	10.1111/jgs.16969	33411332	18	F
Bisceglia Lucia	The integrated environmental health impact of emissions from a steel plant in taranto and from a power plant in Brindisi, (Apulia Region, Southern Italy)	Article	329-337	43	2019	10.19191/EP19.5-6.P329.102	31659880	6	L
Nannavecchia Anna Maria	Cumulative asbestos exposure and mortality from asbestos related diseases in a pooled analysis of 21 asbestos cement cohorts in Italy	Article	NOT_FOUND	18	2019	10.1186/s12940-019-0510-6	31391078	19	O
Andreano Anita	Increased incidence of colon cancer among individuals younger than 50 years: A 17 years analysis from the cancer registry of the municipality of Milan, Italy	Article	134-140	60	2019	10.1016/j.canep.2019.03.015	31005829	21	O
Andreano Anita	Oncologic and fertility impact of surgical approach for borderline ovarian tumours treated with fertility sparing surgery	Article	61-68	111	2019	10.1016/j.ejca.2019.01.021	30826658	36	O
Bisceglia Lucia	The effects of the introduction of a chronic care model-based program on utilization of healthcare resources: The results of the Puglia care program	Article	NOT_FOUND	18	2018	10.1186/s12913-018-3075-0	29801489	8	O
Rebora Paola	New concepts on the clinical course and stratification of compensated and decompensated cirrhosis	Article	34-43	12	2018	10.1007/s12072-017-9808-z	28681347	46	O
Rebora Paola	Clinical states of cirrhosis and competing risks	Article	563-576	68	2018	10.1016/j.jhep.2017.10.020	29111320	150	O
OCCHINO GIUSEPPE	Kidney Dysfunction and the Risk of Developing Aortic Stenosis	Article	305-314	73	2019	10.1016/j.jacc.2018.10.068	30678761	31	O

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Salvatori Andrea	Reproducibility and Validity of A Posteriori Dietary Patterns: A Systematic Review	Article	293-326	11	2020	10.1093/advances/nmz097	31578550	18	O
PETROSINO MATTEO	Development and validation of the facial expression recognition test (FERT)	Article	1479-1490	30	2018	10.1037/pas0000595	30024180	6	O
MAGNONI PIETRO	Long-term follow-up of low-risk branch-duct IPMNs of the pancreas: Is main pancreatic duct dilatation the most worrisome feature? article	Article	NOT_FOUND	9	2018	10.1038/s41424-018-0026-3	29895904	14	O
Bisceglia Lucia	The drug derived complexity index (DDCI) predicts mortality, unplanned hospitalization and Hospital readmissions at the population level	Article	NOT_FOUND	11	2016	10.1371/journal.pone.0149203	26895073	22	O
Nannavecchia Anna Maria	Cancer incidence estimation method: An Apulian experience	Article	S153-S156	26	2017	10.1097/CEJ.0000000000000374	28574869	1	F
Bisceglia Lucia	Lower mortality with pre-hospital electrocardiogram triage by telemedicine support in high risk acute myocardial infarction treated with primary angioplasty: Preliminary data from the Bari-BAT public Emergency Medical Service 118 registry	Article	224-228	185	2015	10.1016/j.ijcard.2015.03.138	25797682	18	O
Rebora Paola	Warfarin use, mortality, bleeding and stroke in haemodialysis patients with atrial fibrillation	Article	491-498	30	2015	10.1093/ndt/gfu334	25352571	75	O
Andreano Anita	MR diffusion imaging for preoperative staging of myometrial invasion in patients with endometrial cancer: A systematic review and meta-analysis	Article	1327-1338	24	2014	10.1007/s00330-014-3139-4	24668009	88	F

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

3 - Ethics

1. HUMAN EMBRYOS/FOETUSES	
Does your research involve Human Embryonic Stem Cells (hESCs)?	No
Does your research involve the use of human embryos?	No
Does your research involve the use of human foetal tissues / cells?	No

2. HUMANS	
Does your research involve human participants?	Yes
Does your research involve physical interventions on the study participants?	No
3. HUMAN CELLS / TISSUES	
Does your research involve human cells or tissues (other than from Human Embryos/ Foetuses?	No
4. PERSONAL DATA	
Does your research involve personal data collection and/or processing?	Yes
Does your research involve further processing of previously collected personal data (secondary use)?	Yes
5. ANIMALS	
Does your research involve animals?	No
6. ENVIRONMENT & HEALTH and SAFETY	
Does your research involve the use of elements that may cause harm to the environment, to animals or plants?	No
Does your research deal with endangered fauna and/or flora and/or protected areas?	No
Does your research involve the use of elements that may cause harm to humans, including research staff?	No
7. DUAL USE	
Does your research involve dual-use items in the sense of Regulation 428/2009, or other items for which an	No
8. EXCLUSIVE FOCUS ON CIVIL APPLICATIONS	
Could your research raise concerns regarding the exclusive focus on civil applications?	No
9. MISUSE	
Does your research have the potential for misuse of research results?	No
10. OTHER ETHICS ISSUES	
Are there any other ethics issues that should be taken into consideration? Please specify	No

I confirm that I have taken into account all ethics issues described above and that, if any ethics issues apply, I will complete the ethics self-assessment and attach the required documents. [X]

4 - Call-specific questions

Eligibility	
I acknowledge that I am aware of the eligibility requirements for applying as specified in the Call-PNRRXXXX_M6/C2, and certify that, to the best of my knowledge my application is in compliance with all these requirements. I understand that my proposal may be declared ineligible at any point during the evaluation or granting process if it is found not to be compliant with these eligibility criteria.	X
I confirm that the proposal that I am about to submit draws substantially don't repeat on an existing or recently finished GRANT funded.	X
Data-Related Questions and Data Protection (Consent to any question below is entirely voluntary. A positive or negative answer will not affect the evaluation of your project proposal in any form and will not be communicated to the evaluators of your project.)	
For communication purposes only, the MoH asks for your permission to publish,in whatever form and medium, your name, the proposal title, the proposal acronym, the panel, and host institution, should your proposal be retained for funding.	X
Some national and regional public research funding authorities run schemes to fund MoH applicants that score highly in the MoH's evaluation but which can not be funded by the MoH due to its limited budget. In case your proposal could not be selected for funding by the MoH do you consent to allow the MoH to disclose the results of your evaluation (score and ranking range) together with your name, non- confidential proposal title and abstract, proposal acronym, host institution and your contact details to such authorities?	X
The MoH is sometimes contacted for lists of MoH funded researchers by institutions that are awarding prizes to excellent researchers. Do you consent to allow the MoH to disclose your name, non-confidential proposal title and abstract, proposal acronym, host institution and your contact details to such institutions?	X
The Ministry of Health occasionally could contacts Principal Investigators of funded proposals for various purposes such as communication campaigns, pitching events, presentation of their project's evolution or outcomes to the public, invitations to represent the Ministry of Health in national and international forums, studies etc. Should your proposal be funded, do you consent to the Ministry of Health staff contacting you for such purposes?	X
For purposes related to monitoring, study and evaluating implementation of MoH actions, the MoH may need that submitted proposals and their respective evaluation data be processed by external parties. Any processing will be conducted in compliance with the requirements of Regulation 45/2001.	

5 – Description Project

Summary description

The development of the technological infrastructure to collect, process, and analyze health data is a founding pillar of PNRR-M6. The Chronicity Plan has identified requirements to develop the national New Health Information System (NSIS). However, it is not yet possible to integrate, at the individual level, all the relevant information contained in the NHS administrative and clinical databases to perform clustering by severity of disease (iso-severity), resource use (iso-resources) and risk of progression. This project aims to develop a data-driven intelligent clinical decision support system to perform

such clustering, so as to identify the optimal territorial care setting, to trace outcomes and progression trajectories for dynamic classification and to tailor tertiary prevention. This will be achieved by integrating individual history from administrative data with predictive models of disease progression via deterministic, machine learning and artificial intelligence methods.

Background / State of the art

One of the objectives of PNRR-M6 is the development of an information system to improve organizational and technological standards for territorial health services (THS). With NSIS development, health databases tracing the citizen's access to the NHS are standardized, allowing the evaluation of care pathways through centrally and locally developed organizational, process and outcome indicators, including systems to monitor the essential levels of assistance (LEA) of each region (Nuovo Sistema di Garanzia) and hospital performance (PNE). THS have been recently reformed, including integrated outpatient community services (Case di Comunità, CdC) and community hospitals (OdC), with a current lack of standardized health databases and indicator systems to evaluate their organization and outcomes, which are often rare and difficult to detect with specificity and to attribute to a single professional/provider. A few stratification systems of patients with chronic diseases have been locally implemented in Italy. Also, a large number of models to predict the probability of treatment response or of short- and long-term outcomes, based on individual characteristics, are available in the literature. However, a system integrating stratification on individual history with predictive models of disease progression, with the aim to support healthcare professionals in therapeutic choices and follow-up management and to perform individual and population tertiary prevention, is not available.

Description and distribution of activities of each operating unit

The three Operating Units (UOs) will collaborate and integrate their work on the different aims of the project. This research group is intended to act synergistically to achieve results not attainable by units working independently. UO1 and UO2 will provide their experience in organization and technology for territorial care and perform the more applied part of the project, wihle UO3 will provide methodological support. Specific activities are defined using actions detailed in the 'Specific aims' section:
- UO1, represented by the Epidemiology Unit of the ATS of Milan led by Dr. Antonio Giampiero Russo, has availability of all data needed for the project within its catchment area and has experience in constructing algorithms for chronic disease classification and predictive models in public health contexts, as well as visualization of health profiles in publicly available websites. It will retrieve and share locally implemented algorithms for HICD detection (1.1), survey, benchmark and adapt algorithms from other contexts, provide datasets for validation and perform cross-testing (1.2-1.3), develop the eHealth platform for population clustering (1.4), coordinate the working group for definition of settings and care pathways (1.5), be corresponsible for periodic updates of dynamic stratification tools (1.6-1.8), implement the Territorial Health Profiles and related open data platform in ATS Milan (2.1-2.2), perform analyses on expected volumes and needed organizational changes in pilot CdCs/OdCs (3.1-3.2), recruit and coordinate MMG/PLS for definition of adaptive diagnostic and therapeutic pathways in ATS Milan (3.3).
- UO2, represented by AReSS Puglia and led by Dr. Lucia Bisceglia, has availability of all data needed for the project within its catchment area. It has previously developed experience in constructing algorithms for chronic disease classification, particularly from pharmaceutical data, and predictive models in public health contexts. It will retrieve and share locally implemented algorithms for HICD detection (1.1), survey, benchmark and adapt existing algorithms in other contexts, develop and validate AI algorithms and cross-testing (1.2-1.3), provide datasets for validation of population clustering (1.4), coordinate the working group for definition of settings and care pathways (1.5), be corresponsible for periodic updates of dynamic stratification tools (1.6-1.8), implement the Territorial Health Profiles and related open data platform in Apulia (2.1-2.2), perform analyses on expected volumes and needed organizational changes in pilot CdCs/OdCs and recruit and coordinate MMG/PLS for definition of adaptive diagnostic and therapeutic pathways in Apulia (3.1-3.2).
- UO3, led by Prof. Paola Rebora, brings a strong background in methods for the analysis of biomedical and public health data and their application to complex clinical settings. The B4 Centre brings together the methodologies and computational

skills needed to meet the challenges of our project in a multidisciplinary and interdisciplinary context able to attract young researchers with skills in Biostatistics and Bioinformatics. It will contribute to the development of biostatistical and computational methods that will be crucial to maximize the predictive capability of algorithms for HICD evolution and for the dynamic stratification of the population (1.3). It will also contribute to the calibration of algorithms in each catchment area of the two NHS UOs.

5.4 Specific Aims and Experimental Design

Specific aim 1

Integration between stratification systems and models to predict the evolution of high-impact chronic diseases (HICDs): dynamic stratification of the population to tailor tertiary prevention.

1.1. Development of new algorithms to detect the most prevalent HICDs and to cluster subjects by severity of disease and use of resources, based on the integration of health and socio-sanitary databases. The algorithms will be developed from and benchmarked with the existing ones in UO1 and UO2, using datasets from the two units. Representative random samples will be extracted and the assigned HICDs verified with clinicians, to determine the accuracy of the new classification system.
1.2. Algorithms developed for outcome prediction and already implemented in public health assessment contexts across Europe will be surveyed. The best performing and more easily implementable with the NCIS and clinical information system of UO1 and UO2 will be tested on data from both areas (cross-testing procedure).
1.3. Integrating 1 and 2, we will develop algorithms to predict the evolution of HICDs, based on the existing clusters and individual information from health administrative and clinical databases, using conventional statistical models and Artificial Intelligence/Machine Learning systems with the methodological support of UO3. Their performance in predicting chronicity evolution will be assessed by the area under the Receiver-Operating-Characteristic curve.The comparison and integration between the various algorithms and models will allow to determine standards, and to develop an information system to periodically update the algorithms through supervised machine learning methods and validate these updated algorithms on real data.
1.4. Development of an eHealth platform, where stratification and prediction systems will be integrated to subdivide the entire populations of the territories of UO1 and UO2 into evidence-based iso-severity/iso-resource clusters, further stratified based on risk of progression. This will require the innovative application of methodological approaches for cluster definition to the domain of chronicity.
1.5. For each cluster of subjects, we will define the optimal setting of care, identifying the primary clinical and social supporting figures. This phase will require the definition of a multidisciplinary working group, with professionals belonging to both CdC and OdC, that will jointly develop managing approaches and evaluate how these can modify the structures of their organizations.
1.6. We will design the platform to integrate it with the datawarehouses and big data systems already existing in the two regions, but also with the information system of the CdC. Specifically, this will be the system visible to the Territorial Operations Centers (COT), to ensure a classification system homogeneous across CdCs and, consequently, to easily allow the assignment of every patient to the most appropriate diagnostic and therapeutic pathways.
1.7. The integration with the CdC information system will be two-way, also allowing to transfer clinical information from CdCs to the stratification information system, including intermediate and long-term outcomes, and changes in the management pathway that will allow to improve the prediction algorithms.
1.8. All the collected information will be used for periodic revisions and updates of the prediction and the integration models of the technological platforms developed for the project, to ameliorate the predictive accuracy of the models and determine changes in the stratification of the population and/or the need to revise a pathway. Guidelines will be developed that will define both the time-frames and the minimal changes required to determine updates of the platform, and how to manage

patients already included in a specific pathway that will be partially modified or that, due to the changes in the predicted risk, will be included in a different pathway.

Specific aim 2

Development of Territorial Health Profiles (THPs).

Developing efficient models of taking charge of patients with HICDs must necessarily be integrated with the development of strategic tools aimed at planning health promotion/prevention interventions at the population level. The realization of a dynamic stratification of the population makes it possible to have up-to-date data at an individual level that also captures the changes in terms of health status produced by the management model implemented in the area. This number of individual information allows to obtain an image with unprecedented local detail, enabling to define and implement THPs in accordance with the provisions of the 2020-2025 National Prevention Plan. The possibility of classifying and defining homogeneous clusters of individuals in the population, periodically updated and that will be modified following interventions and the introduction of new technologies, can allow to guide targeted interventions for health promotion as never before. The evaluation of health promotion and public health interventions already in place, by means of indicators measuring the negative health consequences of lack of population adherence to the program through the implemented eHealth platform, will make it possible to improve existing interventions and/or better tailor new interventions.
This aim will be developed according to the following phases:
2.1. Methodological implementation: methods will be developed aimed at profiling the population of the Apulia region and the Milan ATS which are of comparable size (Apulia 4 million, ATS Milan 3.5 million of inhabitants) on the basis of the algorithms to detect the homogeneous clusters of individuals described in aim 1. The health profiles will be constructed by describing the population composition based on clusters, defined on the basis of the homogeneous characteristics of the population, and by district and catchment area, determined on the basis of the Aggregazioni Funzionali Territoriali (AFT) defined at the territorial level. For each cluster, indicators will be developed that describe the demographic and socio-economic characteristics, resource consumptions and adherence to recommended pathways.
2.2. Implementation of an open data platform to host information and make it available to the population and stakeholders. The system to describe the clusters and calculate the indicators will make it possible to visualize a detailed health profile of the population, highlighting any temporal change and presenting in a synthetical graphical form whether the modification represents an advantage in terms of population health gain or, on the contrary, a deterioration in the population health status.

Specific aim 3

Calibration of the structures of the CdC and integration with the territorial diagnostic and therapeutic pathways to develop integrated surveillance systems.

The current phase of development of the integrated outpatient community services (CdC) does not foresee an initial assessment of the specific needs of the territory based the actual health profile of the residing population. The organizational model is developed uniformly and, consequently, the structuring of the spaces and the organization of the staff is not tailored to the specific territory. The possibility of being able to rely on a technological platform, which guides the taking charge of the subject at the COT level and defines the care loads according to predefined organizational models, allows to model the organization of the CdC according to real needs. The COT becomes, in accordance with what is defined in the PNRR, the point of connection between care needs and organizational needs. Considering that the platform adapts over time and defines new homogeneous clusters of patients that may determine changes in the organizational needs, this becomes the tool with which the CdCs are calibrated over time. Furthermore, in the organizational process, it becomes fundamental to adapt the specific therapeutic diagnostic paths for the individual and for the combination of pathologies, translating them from the current hospital setting to the territorial one. General practitioners (MMG) and

primary care paediatricians (PLS) will be involved in this process and in the definition of optimal territorial diagnostic and therapeutic pathways. The two NHS units have catchment areas with about the same population and comparable numbers of MMG/PLS, but different urban/rural contexts and different public/private healthcare offerings. This will allow an efficacious training/testing activity.
This specific aim will be developed through the following points:
3.1. Recognition of the organization and volume of provision of the CdC/OdC: the existing clinical offer will be analyzed defining the volumes of patients and of delivered services before the implementation of the interventions foreseen by the project.
3.2. Estimation of the expected volumes on the basis of the dynamic stratification of the population. The comparison of the expected volumes with the actual provided services and the existing organization will allow to identify any discrepancies and calculate the necessary organizational changes in terms of work-force acquisition and increase or decrease in opening hours of the various services. This dynamic calibration process will make it possible to have an organization of the CdCs that adapts over time and always responds to the real needs of care of the referring population.
3.3. Definition of evidence-based territorial diagnostic and therapeutic pathways. The MMG/PLS of the AFT will be recruited in Apulia and Milan, guaranteeing comparable seniority and case load, and will be in charge of defining the diagnosis and treatment protocols of the pathologies that make up the clusters identified and managed by the technological platform. The territorial diagnostic and therapeutic pathways and the clusters will allow to estimate not only short-term needed volumes of healthcare services for the present calibration of CdCs organization but also, using the specific observed mortality of that cluster, they will allow to define medium and long-term expected needed volumes. This information could be used to anticipate future organizational structures, and act in advance on the training and recruitment of personnel belonging to the organization of the individual CdCs.

Experimental design aim 1

Actions 1.1-1.3:
We will perform a systematic literature review of algorithms and predictive models for case-detection and severity classification (including those based on resource consumption) that use health administrative databases (HADs). We will investigate the MEDLINE database for articles published between 2012-2022, with search strings consisting of a combination of free text and MeSH terms with a common part centred on HADs and a disease-specific part, as well as grey literature databases.
As for case-detection algorithms (1.1), only those developed in the Italian context or transferable in application to available HADs will be selected among the diseases considered in the Lombardy database of chronic diseases (BDA) [1] and the "Puglia Care program" [2]. Extracted algorithms will be tested and compared with those in use in terms of accuracy measures. Clinical validity will be preliminarily evaluated retrospectively, using as reference data from a previous study carried out in ATS Milan, aimed at validating chronic conditions for 119,878 citizens detected from HADs in 2016 (see Preliminary Data Figures 1-2), and the cohort of Puglia Care (3200 patients enrolled between 2013-2014 [2]). Algorithms identified as optimal for each disease will be applied to identify groups of patients with each HICD and their most frequent combinations, stratified by clinical severity and use of resources, out of the populations residing in UO1/UO2 territories in 2018. The identified groups will be: 1) sub-grouped by catchment area of the CdC and used for prospective validation on cohorts of patients referring to CdCs by working groups including clinicians of CdCs, so as to improve accuracy; 2) used in subsequent phases of the project (1.2-1.3) and followed up to Dec 2023.
For disease evolution predictive models (1.2-1.3), we will focus on three extremely prevalent HICDs, namely heart failure (CHF), chronic obstructive pulmonary disease (COPD) and type 2 diabetes mellitus (T2DM), and identify relevant general and disease-specific outcomes [3-8]. We will consider models using either HADs or a combination of HADs and clinical data, and perform cross-testing of identified algorithms by retrospectively comparing predicted and observed outcomes in 2018 population cohorts of UO1/UO2 up to December 2023, choosing the adequate time interval for each disease and outcome.
Dynamic machine learning (ML) approaches will be developed to predict evolutionary trajectories of patients [9-11], and to

distinguish subjects with a slow vs rapid evolution out of the same populations. In the starting phase, ML models will be fed with variables from HADs. At a later time (end of year 1) clinical variables coming from a fully operational integrated IS with CdCs will be available for patients enrolled at CdCs (results of 1.6-1.7) and allow for timely and systematic updates of operating models (1.8).

Actions 1.4-1.8:
The creation of the integrated eHealth platform for population clustering, bringing together the outputs of 1.1-1.3 with clinical data from CdCs, will provide the basis for the next steps: creation of THPs, quantification of prevalence and severity of HICDs, estimation of territorial care demand/supply balance (see Preliminary Data Figure 3). Interlocutions with engaged professionals of early operating CdCs identified as pilots (at least 1 for each of UO1 and UO2) will be set to design an IS that favors seamless and systematic data exchange and to identify clinical variables (and their modalities) to be included in the eHealth platform and used to predict chronic disease evolution. To define the optimal setting of care for identified strata of the three case-study HICDs, multidisciplinary working groups will be coordinated by UO1/UO2 and will include specialized clinicians, primary care, health professions, social support, medical directorate and operations management representatives.

Experimental design aim 2

Territorial health profiles (THPs) will be developed as a strategic tool to plan and evaluate health promotion and prevention interventions at the population level. The experimental design of this aim comprises of two elements: 2.1 the development of a methodology for the construction of THPs [12], and 2.2 the implementation of an open data platform with aggregated anonymized data.

2.1. Development of a methodology for the construction of THPs: the populations of the Apulia region and of ATS Milan are of comparable size, respectively 4 million and 3.5 million inhabitants. On the basis of the algorithms developed in aim 1, we plan to design methods to profile the populations of the two areas:
- we will individuate axes to describe demographic and socio-economic characteristics (Italian Deprivation Index), specifically for each HICD. For the same diseases we will detect, in the literature and among the systems of indicators already in use at the national level and partially implemented by UO1 and UO2 (Programma Nazionale Esiti, Nuovo Sistema di Garanzia), indicators of process, outcome and adherence to recommended care pathways. We will also determine which type of resource consumptions are relevant for chronic patients and particularly for each disease (e.g. specific diagnostic examinations) [13];
- we will identify in the populations of UO1 and UO2 all subjects with CHF, COPD and T2DM at 31/12/2023, using the algorithms developed in 1.1 at the time of analysis (12 months after begin of project). Using the algorithms developed in 1.2, we will obtain sub-groups of patients at different risks of progression and with different health resource consumptions;
- we will then calculate the chosen indicators and resource consumptions, aggregated for the whole cohort and for each cluster, both overall and stratifying by relevant demographic and socio-economic characteristics, to generate health profiles for the three case-study diseases. The THP will describe the characteristics of the group of patients with the disease, their health need and outcomes aggregated by nested territorial levels, such as health district, municipality, province and region;
- the population and sub-groups of each case-study disease, process and outcome indicators, and resource consumptions will be then regularly updated, at least once a year, using methods developed in 1.3 relying on HADs available to UO1 and UO2 for the whole chronic population of the area, to monitor changes in the health status of subjects with the case-study HICDs;
- this system could also be used to identify specific needs for sub-groups of the chronic population, to plan tailored health promotion and prevention interventions and to monitor their effects on the target population, allowing comparisons between the populations of the two health agencies.

2.2. Implementation of an open data platform: an open data platform to visualize the constructed health profiles, including

only anonymized aggregated data, will be built and made available to the population and to stakeholders. The platform will have a common architecture, but each agency will feed and host the THP of the population residing in its territory of competence. It is emphasized that the presentation of the numerous indicators will be strongly user-oriented and designed with the primary goal of informing individual citizens, health professionals, health programmers and local administrators. For this reason, health profiles will be accessible both through the choice of the disease of interest and by geographical area selected directly, also from a map. This modality brings the epidemiology data closer to the experience and interest of individuals and communities and facilitates the comparison of data between geographical areas.

Experimental design aim 3

In aim 3 we will develop a territorial healthcare programming system, making use of the results of aim 1, to calibrate the structures of outpatient community services (CdCs) and community hospitals (OdC) of a COT. Programming will be based on the real health demand of the chronic population residing in the catchment area of the COT and actual implemented evidence-based therapeutic pathways for subjects in different strata for complexity and risk of progression and health resources consumptions. The experimental design of this aim comprises of the following actions: 3.1 recognition of the organization and volume of provision of the CdC/OdC, 3.2 estimation of the expected volumes on the basis of the dynamic stratification of the population, 3.3 definition of evidence-based territorial diagnostic and therapeutic pathways (territorial PDTAs), and 3.4 volume of service estimation and projections.

3.1. Recognition of the organization and volume of provision of the CdC/OdC: we will select at least one CdC(s) for each Health Agency as pilot structures, in order to analyze their existing clinical offer, and to define the volumes of patients and of delivered services before the implementation of the interventions foreseen by the project.
3.2. Estimation of the expected volumes on the basis of the dynamic stratification of the population: the models developed in aim 1 will provide a stratification of the population of patients with T2DM, COPD and CHF at the individual level, considering presence and type of complications, probability of progression based on patient's characteristic and compliance to care pathways, type and quantity of resource consumptions. This will allow to calculate for each CdC the number of patients in each stratum, based on the subjects actually living in their catchment area.
3.3. Definition of evidence-based territorial PDTAs: UO1 and UO2 will recruit a number of general practitioners (Medici di Medicina Generale, MMG) operating in their territories, guaranteeing comparable seniority and case load across operative units. Those professionals will define territorial PDTAs for the three case-study HICDs, in the context of the population strata/clusters identified combining all the algorithms and models developed in aim 1. The groups will be tasked with critically appraising estimates of territorial clusters, estimating expected needs based on currently applied care pathways, and define clinically and organizationally appropriate patient flow logistics.
3.4. Volume of service estimation and projections: The combination of the calculated volume for each stratum/cluster and of the territorial PDTAs (3.3) will be used to calculate, for pilot CdCs, the expected necessary volumes of services and to compare them with the services actually provided (3.1). This will allow to identify discrepancies between supply and demand of health services, and to envision possible organizational changes in terms of workforce acquisition or modifications in opening hours of services. Furthermore, thanks to the dynamic update of the cohort and its strata, that in a first phase will be performed every 12 months, the organization of pilot CdCs could be adapted timely according to medium and long-term expected required volumes, anticipating future organizational structures, for example in terms of needed personnel. The pilot CdCs would thus be able to respond over time to the actual needs of care of the population they serve.

Picture to support preliminary data

Preliminary_Figures.pdf

Hypothesis and significance

The central idea behind our project lies in the possibility of exploiting the current moment of deep change in the organization and provision of health services in Italy to enhance the role of evaluative epidemiology in providing concrete

instruments to tackle the challenge for the NHS posed by increasingly prevalent chronic and invalidating diseases. As a major PNRR aim is to strengthen proximity networks, we believe that the joint contribution of epidemiologic analyses by local and regional health agencies, high-level information systems with already developed and to-be digital infrastructures, and innovative methods provided by the academic support of universities, will allow clinical government and data-driven organization of the territorial health services defined by the new model of care.

Considering the nature of our proposal, we would define the following hypotheses in line with the three specific aims of our project.

1) Reviewing existing detection algorithms and constructing new ones where needed shall provide top-notch methods for disease classification, with high sensitivity and specificity. A thorough validation phase will assess several possibilities and consider impactful improvements in positive predictive value for detection of chronic diseases. Then, predictive models where significant variables for health outcomes are identified case-by-case shall be defined and calibrated. By integrating individual clinical data with highly accurate and inexpensive information from routinely collected data in health and socio-sanitary databases, we envisage stratification by disease severity with unprecedented accuracy, allowing to further improve population health profiles and to reliably estimate the likely evolution of disease and need of health services; this will translate into optimal allocation of resources. The dynamic nature of the process allows for ongoing updates and improvements, for increased efficiency and effectiveness of health services.

2) By translating robust sources of administrative and clinical information data into reliable population health profiles, we envisage to support health promotion and tertiary prevention in an innovative way and on an unprecedented scale. It will be possible to formulate and adapt specific test hypotheses to verify whether adherence to prevention and/or follow-up programs is linked to better health outcomes. Pseudo-real time assessment of population needs will make it possible to dynamically rebalance public health interventions, while also guaranteeing the principles of equality and universality that are central to the Italian NHS. Lastly, while accounting for protection of sensitive personal data, disclosing anonymized and aggregated open data will also increase the accountability of the health system towards citizens.

3) While a standard definition of CdC/OdC is the only starting point for a wide-scale reorganization of proximity care, we hypothesize that neglecting methods to identify local and updated health demands due to chronic and invalidating diseases possibly growing at different rates may ultimately lead to suboptimal care. Estimating specific health needs of the population may allow to identify significant mismatches with respect to present organization and supply capacity. This provides a dynamic approach to drive organizational changes of territorial health services where needed, based on real population data. At the same time, defining optimal trajectories for chronic disease management exploiting interconnections of different actors of primary care and territorial health services, regulatory institutions and policymakers will allow to optimize the return of health investments.

5.5 Methodologies and statistical analyses

Methods of data collection

Two types of data will be used in the project: health administrative databases (HAD) of the population residing in the catchment areas of the two health agencies and, for patients enrolled in CdC/OdCs, clinical data including laboratory and diagnostic test results.
Data collection for model inputs in the starting phase of the project will make extensive use of information in HADs available to both UO1/UO2, including:
- archive of NHS beneficiaries: sociodemographic (age, sex, citizenship) and administrative data (health district, assigned primary care physician, mobility) allowing to retrieve geospatial data (census-level deprivation, environmental hazards);
- hospital discharge records, providing for every hospitalization: diagnosis-related group and major diagnostic category,

primary and up to five secondary diagnoses and primary and up to five secondary procedures (ICD-9-CM codes), length of stay, modality of entry, waiting time, modality of discharge;
- database of emergency services, providing for every access: diagnosis (ICD-9-CM code), date/time of arrival, triage code;
- database of outpatient services: specialty and specific type of diagnostic exam/outpatient therapeutic intervention, waiting time;
- drug dispensing databases, including both territorial direct/indirect distribution and drug dispensations in hospitals: amount (packages or defined daily doses, DDD);
- database of exemptions from copayment, for distinct reasons: disease, age, income, legal disability.
This information will be primarily used to detect chronic conditions in the adult population and their severity using case-detection algorithms developed in 1.1, to predict their risk of progression (1.2) and to calculate indicators necessary for THPs (2.1). Within the safe environment of the two health agencies, only necessary information from the different databases will be linked on a deterministic key to detect chronic conditions and to calculate risk of progression at the individual level. In aggregated anonymous form, HADs will then be used to feed the open data platform to visualize health profiles (2.2).
The DPOs of UO1/UO2 will be involved and an informative will be published on the website of the two health agencies. Clinical data will be obtained from integration with the IS of CdC/OdCs for adult patients with one of the case-study HICDs, enrolled at CdC/OdCs during any type of care contact, only after giving informed consent. The integrated eHealth platform will gather data from that access and subsequent care accesses at enrolling CdC/OdCs. Patients will be informed that they can retreat consent at any time. Clinical variables used for the study will include BMI, smoking status, spirometry results, ejection fraction and other echocardiography results as well as cardiopulmonary exercise test results, systolic blood pressure, albuminuria level and glomerular filtration rate, triglyceride and cholesterol concentrations [3-8]. Other variables useful for prognostic assessment identified during actions 1.2, 1.5, 1.7 may include blood test results, functional tests, imaging-derived physiological parameters and aggregate risk scores. The platforms will have the same architecture for both ATS Milan and AReSS Puglia, but each agency will host within its protected environment data of residents in its territory of competence. Results of predictive models for their patients will be accessible to health professionals of CdC/OdCs. Algorithms to classify disease stage and risk of progression will be updated periodically, using administrative data of the health authority of residence and - for enrolled patients giving their informed consent - clinical data collected at CdC/OdCs during care accesses. Risk assessment for treating HADs is in place in ATS Milan and AReSS Puglia and it will be updated including risks derived from linkage of clinical data from the CdC and OdC information systems.

Statistic plan

The statistical analysis plan regards mainly the aim 1 of the project to classify and predict the evolution of HICDs, in order to stratify patients into homogeneous clusters.
At first (1.1), after the systematic review, the selected algorithms for case-detection will be applied on health administrative data in both UO1 and UO2. In order to assess the performance of the existing algorithms in terms of accuracy, the clinical cohorts already available in UO1 and UO2 (pilot data of UO1: 119,878 citizens in 2016; UO2: 3200 citizens in 2012-2013) will be used as gold-standard. In particular, the clinical assessment of chronic diseases will be compared with the classification derived by the algorithms on HADs. Accuracy will be assessed using the Receiver-Operating-Characteristic (ROC) curve. The algorithms providing the higher performance in terms of the area under the ROC curve (AUC) for each specific chronic condition will be selected. In ATS Milan the current algorithms are able to detect HICDs with a positive predictive value of 79.1% for CHF, 76.4% for COPD, 96.1% for uncomplicated T2DM and 49.3% for complicated T2DM.
For the prediction of the evolution of HICDs (1.2) we will focus on general and disease-specific outcomes. As general outcomes we will consider mortality (any cause), hospitalizations (repeated, prolonged), emergency department accesses. Disease-specific outcomes will include the onset of complications (e.g. for hearth failure: severe kidney chronic disease, valvular disease requiring intervention, liver failure; for diabetes: severe kidney chronic disease, retinopathy, amputations) and use of specific diagnostic and therapeutic resource at 1 year. Only available tools (algorithms or predictive models) for disease evolution prediction that are suitable for the HAD of UO1 and UO2 will be considered. By applying the algorithms

selected in action 1.1 for case-detection (on the residents at January 2018), we will identify three cohorts of subjects with CHF, COPD and T2DM in UO1 and in UO2. The available predictive tools will be applied on these cohorts of subjects by using HADs of 2018. Their specific prediction will be compared with the observed outcome, identied from HADs of years 2018-2023 with time windows specified for each outcome. The performance of the different tools will be compared in terms of accuracy (AUC). Dynamic models (using conventional statistical models and Machine Learning systems) will be developed to make maximum use of the available data and to predict disease evolution with updated data (action 1.3). The models will be developed on the specific cohorts of subjects with CHF, COPD and T2DM and validated in the most recent cohorts with a cross-validation between UO1 and UO2. Model performance will be reported by the distance between the predicted and observed outcome, discrimination ability and calibration according with the TRIPOD Statement [14].
Patients with similar risk profiles will be grouped in clusters, so that for each HICD we will define different strata (low-risk patients undergoing conservative follow-up, patients likely to experience one or multiple hospitalizations, patients with complicated disease and/or increased need of social support).

Statistical analysis

Existing tools for the prediction of the evolution of high-impact chronic diseases often focus on specific outcomes (i.e. mortality or complications). A comprehensive evaluation of disease evolution will be useful to accurately estimate the burden of health demand and prompt appropriate organizational responses and resource elicitation by CdC/OdC. After building predictive models for separate outcomes, we will also define a composite end-point of disease-specific complications, hospitalization, emergency department access, resource use and mortality. Disease-specific states of disease evolution will be defined with the help of clinicians. For example, for T2DM the following states could be considered: diagnosed with diabetes without complications, diabetes with minor complications (e.g. peripheral vascular disease without amputation, mild chronic kidney disease) and moderate use of resources, diabetes with major complications (e.g. stroke, amputations, dialysis) and extended use of resources, death (absorbing state). Multi-state models will be used to describe disease evolution among the clinically defined states in time and transition probabilities will be estimated for patients with different characteristics (e.g. age, sex, socio-economic status - SES) [15-16]. State occupation probabilities for the different states will be also estimated as an indication of health demand at specific points in time and the estimated transition rates between the states in the model will be used to obtain predictions for patients with a given history [17].
Different machine learnings algorithms will be also applied to predict the evolution of HICDs [18-20]. Random forests algorithms and gradient-boosted trees will be used for the classification of patients in different risk strata. These learning algorithms allow to figure out which path drives the classification in terms of the most discriminating features. Ensemble methods such as bagging, that uses bootstrap replicates of the original dataset to improve the accuracy of predictions and cross validation, will be used as a validation step of the ensemble algorithms by partitioning the original dataset into different portions, used as training and test set at each step.
In the second year of the project, when the integration of clinical data from CdCs will be available, we will focus also on the modelling and prediction based on longitudinal measurements of biomarkers (in a broad sense, e.g. BMI, blood test results, functional tests, imaging-derived physiological parameters). Longitudinal measurements can be jointly modelled with time-to-event data (e.g. death, rehospitalization) with the so-called Joint Models, able to quantify the impact of longitudinal biomarker profiles on the instantaneous hazard of experiencing an event and allowing to dynamically predict the event-free probability of interest of each patient [21]. Dynamic predictions of both longitudinal biomarkers' trajectories and event-free probability curves can be drawn and updated as data collection goes on. An extension of these models is Joint Latent class mixed models, in which the association structure can be defined based on latent classes, whereby it is not between-individual differences (as in standard Joint Models) but rather between-class differences in the biomarker that are associated with differences in event risk. In other words, they consider the population of subjects as heterogeneous, and assume that it consists of homogeneous latent subgroups of subjects sharing the same marker trajectory and the same risk of the event. This would allow to classify subjects a-posteriori based on different profiles.
Model performance across different methods will be estimated in test datasets and the algorithm with highest performance

will be applied.

Timing of analysis data

The listed actions that pursue specific aims of our project consist of very different kinds of activities, including phases of literature review, benchmarking and validation, collaboration with actors of territorial care and coordination of working groups, implementation of eHealth platforms and IS networks, definition of timing for updates. In this wide range, each of the actions has a dedicated time window within the two years allotted for the project (see Gantt chart) and, coherently with its own specific purpose, may consider specific time frames for retrospective data gathering, active enrollment of patients and/or HAD-based and clinical follow-up. Specifically:
- Development and validation of case-detection algorithms for HICDs (1.1, Months 1-3) will consider 2012-2022 as time constraints for the literature review. Retrospective validation (1.1, Months 4-5) will be performed separately using data of subjects identified with different timings (119,878 citizens with HAD-detected chronic diseases in 2016 for UO1 [1], and the Puglia Care cohort of 3200 patients enrolled between 2013-2014 for UO2 [2]). Definition of disease progression algorithms (1.2, Months 1-4) will also consider 2012-2022 as time constraints for the literature search of regression and machine learning models. For cross-testing of identified algorithms (1.2, Months 4-6), retrospective analyses of health outcomes will be performed in population cohorts of UO1/UO2 of 2018 followed up to 2023, with appropriate time intervals for each disease and specific outcome. Retrospective analysis will cover the whole clinical history of subjects recorded in available HADs. Groups of patients with specific HICDs will be identified among the residing populations of UO1/UO2 for the year 2018. These groups will be used for prospective validation of algorithms with clinicians of CdCs (1.1, Months 6-12) and followed up to December 2023 in subsequent actions. These include the use of regression and ML models to generate a stratification/clustering of patients on the basis of disease(s), initial severity, risk of progression for the case-study HICDs (1.3, Months 5-12), and implementation of the eHealth platform that applies the stratification to populations of UO1 and UO2 (1.4, Months 10-12). Constitution and coordination of multidisciplinary working groups will allow to achieve definition of the optimal setting of care by the end of year 1 (1.5, Months 5-12). In year 2, patients will be enrolled prospectively in pilot CdCs to gather clinical variables for integration and improvement of defined models (1.6, Months 13-24), restitution of results to clinicians (1.7, Months 16-24). After the system is a regime, a specific protocol (1.8, Month 24) will be defined to do yearly updates.
- Development of THPs for the three case-study HICDs (2.1, Months 9-19) will require definition and calculation of health indicators, SES variables and resource consumption level for strata of patients with one or more of the three diseases identified among the populations of UO1 and UO2 on 31/12/2023. Results will be made available on the open data platform by the end of year 2 (2.2, Months 19-24).
- Enrollment of pilot CdC/OdCs will begin at half of year 1, and by the end of year 1 we will perform analyses of the existing organization and volumes of provided services during six months of activity (3.1, Months 7-12). Results of aims 1 and 2 of the project will allow, by the end of year 2, to estimate the expected volumes on the basis of the dynamic stratification of the population on 31/12/2023 (3.2, Months 13-18), provide data for evidence-based definition of territorial PDTAs (3.3, Months 10-15) and ultimately make projections (based on stratification and PDTAs) for medium and long-term supply/demand balance and need of organizational changes, that will also be updated at least yearly (3.4, Months 19-24).

5.6 Expected outcomes

The three work packages pursuing each specific aim are expected to produce the following results:
1a) Updated, maximally sensible and specific, cross-validated algorithms for case-detection of HICDs from HADs and models for disease progression of three selected case-study HICDs (CHF, COPD, T2DM) integrating HAD and clinical data. While initially applied to pilot CdCs, the latter can be easily transferred to the whole catchment areas of the two Agencies as other CdCs are recruited over time. Being based on HAD-derived data, case-detection algorithms harbor the opportunity of being adopted by other Italian health agencies, thus granting external validity to our project. Integration of clinical data and yearly planned reviews provide this system with dynamicity and room of improvement.

1b) Stratification of the population into homogeneous groups of patients to support territorial health programming according to specific care models. Specifying subsets of patients with different risk profiles and predicting their probabilities of transitioning from one stratum to another offers a dynamic and adaptive tool to meet population needs. Timely, systematic and clinically appropriate interventions can be defined for each stratum (minimal effective follow-up for low-risk patients, intensive follow-up and elicitation of necessary organizational resources for high-risk patients).
1c) An integrated eHealth platform for population stratification, facilitated by functional IS design, that will constitute a basis for network collaboration of different actors of territorial care (including CdCs, OdCs and COTs), brought together to define clinical variables to enrich predictive models of disease progression and need for more complex care, to identify optimal settings of care and to foster the needed organizational changes.
2) Evidence-based Territorial Health Profiles for the three case-study HICDs that incorporate sociodemographic variables, disease complexity, process and outcome indicators to assess clinical appropriateness, adherence to care pathways, effectiveness and safety of provided care. Measurement is the first step that leads to control and eventually to improvement. With specific precautions for data protection (i.e. feeding the platform only with aggregated anonymous data), THPs will be made publicly available, in order to increase accountability towards citizens and provide healthcare stakeholders and policymakers with tools for clinical governance of territorial care.
3) A dynamic programming system for the estimation of territorial healthcare demand/supply balance, based on expected volumes after dynamic stratification of the population and evidence-based territorial PDTAs, defined with primary and territorial healthcare professionals, allowing for data-driven governance of territorial care.

5.7 Risk analysis, possible problems and solutions

We considered potential pitfalls and caveats of the project identifying possible difficulties and limitations pertaining to each specific aim (SA). We graded the severity of each risk in a 5 x 5 risk matrix that considers probability (highly unlikely, unlikely, possible, probable, highly probable) and impact (very low, low, medium, high, very high). For all risks we defined a mitigation strategy aimed at minimizing negative consequences of such risks and providing alternative approaches to achieve our expected goals:
- Unacceptably low accuracy of case-detection algorithms (SA1, unlikely, very high impact): most of the algorithms already in use have shown satisfying performance measures [see Preliminary data] and are only expected to improve via benchmarking with other sources. HICDs with algorithms that should prove to have consistently low accuracy will be temporarily discarded from analysis and addressed later in the context of dedicated working groups with clinicians.
- Hardships in achieving expected results for one or more of the three HICDs identified as pilots (SA1, unlikely, medium impact): coordinating multidisciplinary working groups may prove challenging due to lack of engagement, or regional/local health plan objective may impose to shift our focus elsewhere. In that case, other extremely prevalent HICDs will be prioritized and chosen as pilots instead.
- Delays in start-up of fully operational CdCs (SA1-SA3, possible, high impact): we shall start a pilot phase recruiting at least 1+1 CdC (one identified by each of UO1 and UO2) for which early operability is expected. Other CdCs still in the making will be engaged at a later time for critical appraisal and dissemination of results.
- Technical difficulties in the construction of the eHealth platform (SA1, unlikely, high impact): while containing the same type of databases fulfilling national requirements, the datawarehouses of UO1 and UO2 are different. Information systems of the CdCs, that are still in development, will also have regional differences. Even if data normalization and software interfaces will be probably required, the budget allocated for the realization of the integrated e-Health platform should be sufficient to reach the aim.
- Difficulties in recruiting additional researchers in short time with calls for public selection (SA1-SA3, possible, medium impact): the known shortage of professionals with data management and analysis skills and the short recruitment window could pose a challenge for recruitment of the needed additional workforce. This may pose a greater burden on Principal Research Collaborators, which in turn may cause delays in achieving expected results. Allotted time for each action of the project has been estimated considering this possibility and including appropriate safety buffers (see Gantt chart).

- Impact of COVID-19 (SA1-SA3, probable, low impact): new restrictions due to a recrudescence of the pandemic could pose a challenge for the multidisciplinary groups charged with defining optimal settings of care and territorial PDTAs. However, systems for conference calls are available at all units. Other activities are unlikely to be heavily impacted by mobility restrictions.

5.8 Significance and Innovation

The redefinition of organizational models of territorial care for chronic diseases in our country cannot ignore a careful stratification of the entire population health needs, to pursue the Population Health Management goal of keeping the population in good health and reducing the use of health resources.
The innovative aspects of our proposal primarily concern the conceptual framework, which links the health needs to the territorial context and to treatment and rehabilitation pathways, in a balance between individual health demand and public health response.
The proposed stratification system will be easy to implement in other Italian territories, dynamic and updatable (as it largely exploits national HADs), but also accurate by incorporating selected clinical variables. Moreover, the informative and technological infrastructure lends itself to adapt to the specific epidemiological profile and to socio-demographic changes, to direct the necessary adjustments of the system response.

5.9 Bibliography

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5.10 Timeline / Deliverables / Payable Milestones

The two-year time period allotted for the project will be efficiently exploited by reducing inter-dependency of deliverables: the eHealth platform, THPs, territorial PDTAs. After an initial phase focused on definition and application of case-detection algorithms and disease progression models, which are the mainstay of the project, work packages pursuing the three aims will be carried out in parallel. Milestones have been scattered in order to minimize chances of failure and to account for possible hurdles and delays (detailed in the Risk analysis section); milestones pertaining to active participation and inclusion of CdCs have been formulated hypothesizing full and functional operativity of pilot CdCs by half of year 1. We have detailed specific milestones corresponding to deliverables of single actions (M1-M5, M8-M10) as well as transversal milestones that account for the need of critically appraising arising issues and disseminating intermediate and final results (M6-M7, M11-M12).

Milestones 12 month

M1. Review and formulation of diagnostic algorithms for 20 HICDs
M2. Review and formulation of predictive algorithms for 3 case-study HICDs
M3. Definition of THPs for 3 case-study HICDs
M4. Baseline analysis of demand for 2 pilot CdCs
M5. Operability of working groups for definition of care pathways in 2 pilot CdCs
M6. Submission of at least 2 manuscripts to scientific peer review journals (case-detection algorithms; predictive algorithms)
M7. Intermediate workshop to report on results and critical issues

Milestones 24 month

M8. Release of the eHealth platform for territorial clusters
M9. Implementation of the open data platform for the three THPs
M10. Stratification-based estimation of needed healthcare offer in 2 pilot CdCs
M11. Submission of at least 2 manuscripts to scientific peer review journals (development of THPs; evidence-based methods to achieve tailored supply-demand balance in territorial care)
M12. Final workshop to share results with partners and stakeholders

Gantt chart

GANTT chart.pdf

5.11 Equipment and resources available

Facilities Available

ATS Milan (UO1) has the institutional mission to promote and protect the health of citizens guaranteeing services in the Essential Levels of Assistance (LEA) and to coordinate health and social-health services. Its Epidemiology Unit has participated in national research projects on epidemiology and clinical pathways of chronic diseases and has experience in applied research based on HADs, which will be used to coordinate and realize part of the project.
AReSS Puglia (UO2) is the technical support of the Regional Government. Over the last years, it has been promoting Health Innovation processes, Research and Internationalization of Healthcare Systems and Social services, focusing on Integrated Care Models for Chronic patients and Digitalization of healthcare Systems. The Epidemiology and Care Intelligence Area of AReSS Puglia, which is the department involved in this project, will provide professional expertise in the fields of epidemiology and biostatistics, as well as IT competencies, to support research activities.
The University of Milano-Bicocca (UO3) is a large institution located in the highly-populated Northern part of Italy. The School of Medicine was granted as "Department of Excellence" by the Ministry of University and Research for its high-quality standard in research. The School has excellent links with hospitals in its area, and its staff is routinely involved in the

management of clinical trials. It also provides access to a private cloud with the possibility to create virtual machines. Its B4 Centre has remarkable experience in methodological and applied biostatistics and bioinformatic research with attention to multidisciplinarity, which will be made available to the project.
UO1 and UO2 will provide the administrative data necessary for the project. All units will provide the hardware and the statistical software (SAS and/or STATA software) for analyses. Other needed software (data visualization) and digital platform for data integration have been included in the budget plan. Other facilities available in all units include online access to scientific literature and, for UO3, access to a statistical library. All units will provide administrative staff to support research activities.

Subcontract

To allow personnel of the participating units to concentrate on scientific tasks, particularly for the coordinating center UO1, a sub-contract with a Project management company will be necessary to help with the administrative and budgeting part of the project.

5.12 Desc. of the complementarity and sinergy of secondary collab. researchers

Four secondary collaborators will be hired in the three UO with competences in either biostatistics, bioinformatics, and machine learning to help developing and testing the classification and prediction algorithms, and perform and validate their integration to fulfil Aim 1 in due time. Two more collaborators with a data scientist profile will be hired to expedite the implementation of the Territorial Health Profiles. Part of the funds will be used to obtain support in the administrative management of the project.
Also, staff from the medical direction of CdCs, both located in the ATS of Milan and the Apulia region, selected to pilot the algorithms and the implementation of a bidirectional information systems, will be involved, helping to focus the clinical and administrative information that could be derived from the CdC information system and be used to implement and ameliorate progression prediction model and to implement the take in charge of the patients based on the results of the project. The management staff of the COTs will be also involved in this latter process. Moreover, a representative group of health professional working in the CdC and OdC of the ATS of Milan and the Apulia region, including MMG/PLS, will be involved in the project to discuss the territorial diagnostic and therapeutic pathways and the focused tertiary prevention management.

5.13 Translational relevance and impact for the national health system (SSN)

What is already know about this topic?

A few risk stratification systems have been developed to manage territorial health care for HICDs. However, in Italy, there are no actual systems to integrate them in information systems of CdC and OdC or to update them, on the basis of clinical data or data in administrative databases received after iso-severity and/or iso-resources clustering.
Bibliography: Robusto et al. 2016 (10.1371/journal.pone.0149203), Rea et al. 2019 (doi: 10.1016/j.jclinepi.2019.08.009), Iommi et al. 2020 (10.1371/journal.pone.0240899).

Details on what is already know about this topic

With progressive population ageing and the consequent increasing burden of chronic diseases, health policymakers have become aware of the need to improve chronic disease management through patient-centered care, rather than focusing on the single disease [2,22]. A tailor-made model of care for each individual would be unsustainable, both organizationally and economically. Identifying homogenous groups of patients can be of great help in planning care models for the different population strata and designing specific actions for homogeneous groups, with attention to multimorbidity and socio-economic vulnerability. Therefore, population stratification is a privileged tool for the differentiation of interventions, in support of planning, management and evaluation of healthcare [1]. Stratification systems have a great strength: they can be defined on different scales (from national to CdC) to adapt in the best possible way to the specific healthcare demand and

supply in the area.

What this reasearch adds?

This project will lead to the development of:
- an innovative data-driven decision-support system, integrating stratification on individual history with predictive models of disease progression, to support healthcare professionals of the territorial setting in therapeutic choices and in tertiary prevention, including the definition of type and frequency of follow-up;
- a new eHealth platform, distributed as a transportable and open access information structure, to interface the dynamic stratification system with the territorial datawarehouse and the information systems of CdCs/OdCs, visible to COTs;
- a new approach to develop evidence-based Territorial Health Profiles that will allow targeted health promotion campaigns and public health interventions;
- a system that will allow to calibrate and adapt the organization of CdCs/OdCs to evolving scenarios, derived from the health profiles of their populations.
Bibliography: Brunner-La Rocca et al. 2016 (doi: 10.1186/s13167-016-0051-9).

Details on what this reasearch adds

Patient stratification should be accurate, easy to implement and dynamic in order to serve its purpose. Currently used risk models for disease progression are usually static and suffer from many limitations, such as being based on manual data entry, lack of generalizability, and the risk of providing rapidly outdated risk estimates. This research provides an accurate, easy to implement, dynamic and updatable stratification system for the most prevalent HICDs. It exploits HADs, an underused data source that could be leveraged with innovative methods to develop ML prognostic models that are not only robust and accurate but scalable. ML algorithms developed using HADs are expected to offer predictive accuracy comparable to or exceeding currently used risk models. The stratification obtained combining disease detection, risk of progression and care needs may facilitate provider-patient communication of risk, behavioral changes, and targeted actions for prevention of HICD progression.

What are the implications for public health, clinical practice, patient care?

This system will produce evidence-based territorial diagnostic and therapeutic pathways for the most frequent HICDs, defining optimal settings of care, type and frequency of clinical and instrumental follow-up individualized on patient's characteristics, to tailor tertiary prevention. The stratifications and the diagnostic and therapeutic pathways will be integrated in the information system of pilot CdCs and OdCs, and will also ensure two separate different pool of patients for the two settings, predicting in advance the transition from one setting to the other. This project may serve as the basis for the future definition of a new system of territorial diagnosis-related groups (DRGs) aimed at the management, comparison, performance analysis and distribution of the resources of CdCs/OdCs.
Bibliography: Bauer et al. 2014 (doi: 10.1016/S0140-6736(14)60648-6).

Details on what are the implications for public health, clinical practice, patient care

We propose a horizontal organizational model crossing all territorial care settings, which can be reached only by creating territorial PDTAs and having a stratification strategy knowing in advance the share of the population in need of different care resources. Chronic patients, especially if multi-chronic or with elements of socio-economic vulnerability, have a greater risk of experiencing negative outcomes and a significant consumption of resources. For them, it is necessary to establish a network of multidisciplinary and coordinated teams on the territory, aimed at the global assessment of patients and their continuity of care. The proposed methodological approach incorporating elements of flexible modulation and continuous validation will enable COTs, coordinating CdCs, OdCs and other territorial care actors to program according to care needs by setting and intensity of care in the different nodes of the territorial care system and to effectively plan in advance to changing needs.

6 - Budget

Total proposed budget (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	293.036,23	293.036,23	not permitted	0,00
2 Researchers' Contracts	583.000,00	0,00	583.000,00	58,30
3a.1 Equipment (Leasing -	11.500,00	0,00	11.500,00	1,15
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	0,00	0,00	0,00	0,00
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts *	20.000,00	0,00	20.000,00	2,00
5 Patient Costs	0,00	0,00	0,00	0,00
6 IT Services and Data Bases	292.000,00	0,00	292.000,00	29,20
7 Travels	6.500,00	0,00	6.500,00	0,65
8 Publication Costs	18.000,00	0,00	18.000,00	1,80
9 Dissemination	7.500,00	0,00	7.500,00	0,75
10 Overheads *	51.400,00	0,00	51.400,00	5,14
11 Coordination Costs	10.100,00	0,00	10.100,00	1,01
Total	1.293.036,23	293.036,23	1.000.000,00	100,00

* percentage calculated as average value between all the Operating Units.

Report the Co-Funding Contributor:

N.A.

Budget Justification

1 Staff Salary	Co-financing of the three UOs in terms of permanent staff included in the project for a total of 46/person months.
2 Researchers' Contracts	A total of 9 between biostatisticians, epidemiologists and data scientists will be recruited for the project, including the two under-40 collaborators already individuated (Petrosino and Occhino).
3a.1 Equipment (Leasing - Rent)	Contribution to 1 personal computer (2/5 of the cost) and SAS licence renewal (less than 2/5 of the cost).
3a.2 Equipment (buying)	NA
3b Supplies	NA
3c Model Costs	NA

4 Subcontracts	Project management company for the administrative and budgeting part of the project.
5 Patient Costs	NA
6 IT Services and Data Bases	e-Health integrated digital platform and ad hoc software for data visualization.
7 Travels	Travels for workshop or congresses to disseminate project results.
8 Publication Costs	Open-access fees for 9 articles assuming 2000 euro/article.
9 Dissemination	Registration fees to participate at congresses/workshops to disseminate project results.
10 Overheads	NA
11 Coordination Costs	Costs to organize two workshops to share results with partners and stakeholders.

Proposed total budget UO1 Institution: Epidemiology Unit, ATS Milano (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	171.513,99	171.513,99	not permitted	0,00
2 Researchers' Contracts	192.000,00	0,00	192.000,00	73,28
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	0,00	0,00	0,00	0,00
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	20.000,00	0,00	20.000,00	7,63
5 Patient Costs	0,00	0,00	0,00	0,00
6 IT Services and Data Bases	9.000,00	0,00	9.000,00	3,44
7 Travels	3.000,00	0,00	3.000,00	1,15
8 Publication Costs	8.000,00	0,00	8.000,00	3,05
9 Dissemination	3.000,00	0,00	3.000,00	1,15
10 Overheads	16.900,00	0,00	16.900,00	6,45
11 Coordination Costs	10.100,00	0,00	10.100,00	3,85
Total	433.513,99	171.513,99	262.000,00	100,00

Budget Justification

1 Staff Salary	4 person/months x 2 years x 9,278.70 € Russo (PI); 3 person/months x 2 years x 4,914.97 € Andreano (Co-PI), Magnoni and Salvatori; 2 person/months x 2,203.74 € Tunesi
2 Researchers' Contracts	UO1 will recruit 3 data analysts (biostatisticians, computer scientists) for 2 years.
3a.1 Equipment (Leasing - Rent)	NA
3a.2 Equipment (buying)	NA
3b Supplies	NA
3c Model Costs	NA
4 Subcontracts	A sub-contract with a Project management company will be necessary to help with the administrative and budgeting part of the project.
5 Patient Costs	NA
6 IT Services and Data Bases	Ad hoc software for data visualization.
7 Travels	Travels for workshops or congresses to disseminate project results.
8 Publication Costs	Open-access fees for 4 articles assuming 2,000 euro/article.
9 Dissemination	Registration fees to participate at congresses/workshops to disseminate project results.
10 Overheads	NA
11 Coordination Costs	Organization costs to organize a small intermediate and a larger audience final workshop to share results with partners and stakeholders.

Proposed total budget UO2 Institution: Agenzia Regionale Strategica per la Salute ed il Sociale (AReSS) - Puglia (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	98.820,00	98.820,00	not permitted	0,00
2 Researchers' Contracts	271.000,00	0,00	271.000,00	45,32
3a.1 Equipment (Leasing - Rent)	10.000,00	0,00	10.000,00	1,67
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	0,00	0,00	0,00	0,00
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	0,00	0,00	0,00	0,00
5 Patient Costs	0,00	0,00	0,00	0,00
6 IT Services and Data Bases	283.000,00	0,00	283.000,00	47,32
7 Travels	2.000,00	0,00	2.000,00	0,33
8 Publication Costs	4.000,00	0,00	4.000,00	0,67
9 Dissemination	3.000,00	0,00	3.000,00	0,50
10 Overheads	25.000,00	0,00	25.000,00	4,18
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	696.820,00	98.820,00	598.000,00	100,00

Budget Justification

1 Staff Salary	3 person/months x2 years x 13343 € Bisceglia and 3 person/months x2 years x 3127 € Nannavecchia.
2 Researchers' Contracts	UO2 will recruit the 2 young biostatistician already included in the project (Petrosino and Occhino) and 2 data analysts (biostatisticians, computer scientists) for two years.
3a.1 Equipment (Leasing - Rent)	Contribution to renewal of a server licence for SAS that will be used for the project at least 6months/year*2years*6person=36 person/months and that globally costs 15,000 €/year (less than 2/5 OF 30,000 €).
3a.2 Equipment (buying)	NA
3b Supplies	NA
3c Model Costs	NA
4 Subcontracts	NA
5 Patient Costs	NA
6 IT Services and Data Bases	e-Health integrated digital platform.
7 Travels	Travels for workshop or congresses to disseminate project results.
8 Publication Costs	Open-access fees for 2 articles assuming 2,000 euro/article.
9 Dissemination	Registration fees to participate at congresses/workshops to disseminate project results
10 Overheads	NA
11 Coordination Costs	NA

Proposed total budget UO3 Institution: Università Milano Bicocca (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	22.702,24	22.702,24	not permitted	0,00
2 Researchers' Contracts	120.000,00	0,00	120.000,00	85,71
3a.1 Equipment (Leasing - Rent)	1.500,00	0,00	1.500,00	1,07
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	0,00	0,00	0,00	0,00
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	0,00	0,00	0,00	0,00
5 Patient Costs	0,00	0,00	0,00	0,00
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	1.500,00	0,00	1.500,00	1,07
8 Publication Costs	6.000,00	0,00	6.000,00	4,29
9 Dissemination	1.500,00	0,00	1.500,00	1,07
10 Overheads	9.500,00	0,00	9.500,00	6,79
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	162.702,24	22.702,24	140.000,00	100,00

Budget Justification

1 Staff Salary	2 person/months x 2 years x 5,675 € Rebora.
2 Researchers' Contracts	UO3 will recruit two researchers with data analysis skills for 2 years (biostatistician and data scientist): €40,000 will be used to co-finance a PhD scholarship or a fellowship and € 80,000 for a researcher contract.
3a.1 Equipment (Leasing - Rent)	Up to 2/5 of a high computational personal computer of about 3,800 euro.
3a.2 Equipment (buying)	NA
3b Supplies	NA
3c Model Costs	NA
4 Subcontracts	NA
5 Patient Costs	NA
6 IT Services and Data Bases	NA
7 Travels	Travels for workshop or congresses to disseminate project results.
8 Publication Costs	Open-access fees for 3 articles assuming 2,000 euro/article.
9 Dissemination	Registration fees to participate at congresses/workshops to disseminate project results.
10 Overheads	NA
11 Coordination Costs	NA

Principal Investigator Data

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Struttura: UOC Unità di Epidemiologia
Istituzione: ATS Milano
Datore/ente di lavoro? Yes
Datore/ente di lavoro SSN? Yes
Nome datore/ente di lavoro non SSN:
Nome istituzione SSN: Agenzia per la Tutela della Salute della Città Metropolitana di Milano
Tipo contratto: Lavoro Subordinato a Tempo Indeterminato

Con l'invio della presente proposta si dichiara che la stessa o parti significative di essa non sono oggetto di altri finanziamenti pubblici o privati e che di conseguenza vi è assenza del c.d. doppio finanziamento ai sensi dell'art. 9 del Regolamento (UE) 2021/241, ossia che non ci sia una duplicazione del finanziamento degli stessi costi da parte di altri programmi dell'Unione, nonché con risorse ordinarie da Bilancio statale.

By submitting this proposal, I declare that no significant part or parts of it are recipient of any other public or private funding and that consequently there isn't any so-called double financing pursuant to art. 9 of Regulation (EU) 2021/241, i.e. that there is no duplication in the financing of the same costs by other Euopean Union programs or any other ordinary resources from the State budget.

Project Code: PNRR-MAD-2022-12376033	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Regione Lombardia - Direzione Generale Sanità	**Applicant/PI Coordinator:** Russo Antonio Giampiero

Project validation result