

BIOGRAPHICAL SKETCH

NAME: Lorenza Pastorino

POSITION TITLE: Associate Professor BIOS-10/A, Department of Internal Medicine and Medical Specialties, University of Genoa, Genoa, Italy

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
University of Genoa, Genoa, Italy	Postgraduate Specialization	11/2003	Medical Genetics
University of Genoa, Genoa, Italy	Ph.D.	04/2007	Genetics and Biology

A. Personal Statement

My research focuses on rare hereditary cancer-predisposition syndromes, with particular emphasis on CDKN2A-associated melanoma and pancreatic cancer, spanning the identification of germline risk alleles to insights into tumorigenesis and clinical management. I have followed a non-traditional academic path that has provided me with a strong and broad scientific foundation. I began my career as a Research Technician at the University of Genoa (UNIGE) in 2007, where I was able to develop extensive expertise in molecular genetics and translational cancer research. During this period, I served as a key collaborator on multiple competitive grants and peer-reviewed publications. In recognition of my scientific contributions and independence, I was appointed as a Researcher in 2021 and subsequently promoted to Associate Professor and Group Leader of the Laboratory of Cancer Biology and Genetics in 2024. I have provided an extended description of genetic susceptibility to Melanoma and pancreatic cancer in the Italian population, and recently I have established a large database of melanoma and pancreatic cancer patients, including genetic, epidemiologic, clinical, pathological and follow-up data.

In parallel, I have been responsible of germline and somatic molecular diagnostics for more than 5 years, with research focused on improving molecular diagnostic approaches and identifying predictive biomarkers of response to innovative therapies. The current application builds directly on this combined research and clinical experience.

Within the proposed project, I aim to provide direct expertise in molecular and genomic analysis of germline variants, integration of genetic and clinical data, and interpretation of whole-genome sequencing results to identify genetic modifiers of pancreatic cancer risk in CDKN2A G101W carriers.

B. Positions, Scientific Appointments, and HonorsPositions

2025- present Head of Laboratory of Cancer Biology and Genetics (RADRL), Department of Internal Medicine and Medical Specialties, University of Genoa

2024–present Associate Professor BIOS-10/A, Department of Internal Medicine and Medical Specialties, University of Genoa

2021–2023 Researcher (RTDb), Experimental Biology – BIOS-10/A, Department of Internal Medicine and Medical Specialties (DiMI), University of Genoa, Genoa, Italy

2021–present Healthcare Executive (Consultant) and Head of the Cancer Genetics Laboratory, AOM IRCCS Ospedale Policlinico San Martino (Director: Prof. Paola Ghiorzo). Responsible for germline and somatic molecular diagnostics in rare tumors, including melanoma and pancreatic ductal adenocarcinoma (PDAC)

2007-2020 Research Technician, Department of Internal Medicine and Medical Specialties, University of Genoa

Scientific Appointments

Editorial Boards

2019–present: Member of the Editorial Board of Cancers journal

2021: Invited Guest Editor for the special issue "Molecular Genetics of Pancreatic Cancer and Translational Challenges" in Cancers

Consortium Memberships

2004–present: Member of the international melanoma genetics consortium GenoMEL

2011–present: Member of BioGenoMEL, a consortium derived from GenoMEL focused on melanoma biology and genetics

2017–present: Member of the MelaNostrum Consortium

Scientific Societies

2004–present: Member of the Italian Society of Human Genetics (SIGU)

2008–present: Member of the Italian Melanoma Intergroup (IMI)

2019–present: Member of the Italian Association of Biology and Genetics (AIBG)

2019–present: Member of the SIGU Molecular Genetics Working Group

2022–present: Member of the Italian Association for Tumor Familiarity and Heredity (AIFET)

Honors

2025–present: President of “Associazione Tumori Rari ed Ereditari (AR3)”, a non-profit organization supporting research and patient advocacy in rare and hereditary cancers

Current and Past Research Funding

2022–present

Deciphering the genetic background of cutaneous melanoma: gene-specific oncophenotypes and non-invasive biomarkers of prognosis and therapy response.

Funding agency: Italian Ministry of University and Research (PRIN 2022).

Role: Co-coordinating research activities

Prof.ssa Pastorino was appointed as Key personnel in several national and international collaborative projects on genetic factors and molecular mechanisms underlying neoplastic development, particularly on melanoma, funded by AIRC, AIRC 5×1000 Special Program “Metastatic Disease,” Italian Ministry of University and Education PRIN, NIH, EU FP6 Network of Excellence, Italian Ministry of Health, LILT, Alleanza Contro il Cancro.

C. Contributions to Science

1. Pancreatic ductal adenocarcinoma (PDAC) is associated with high mortality and limited opportunities for early detection, yet the clinical relevance of germline cancer predisposition variants in unselected PDAC patients has been incompletely defined. As **last and corresponding author**, I led a study assessing the prevalence and clinical significance of germline pathogenic variants across 51 cancer predisposition genes in an unselected cohort of Italian PDAC patients. This work demonstrated that a substantial proportion of patients harbor actionable germline variants, including alterations in high-penetrance genes such as *CDKN2A*, frequently in the absence of a suggestive personal or family history, supporting the integration of germline testing into routine PDAC care. I also contributed to a large, multicentre Italian study that confirmed the relevance and heterogeneity of inherited cancer risk in real-world PDAC cohorts. In parallel, I participated in international collaborative studies investigating gene-level associations and the burden of rare deleterious variants in patients with and without pathogenic *CDKN2A* variants, providing evidence for oligogenic and polygenic models of pancreatic cancer susceptibility.

Selected publications:

- i. Puccini A, et al. *Clinical Significance of Germline Pathogenic Variants among 51 Cancer Predisposition Genes in an Unselected Cohort of Italian Pancreatic Cancer Patients*. **Cancers**. 2022 Sep 13;14(18):4447.
- ii. Orsi G, et al. *Germline pathogenic variants of cancer predisposition genes in a multicentre Italian cohort of pancreatic cancer patients*. **European Journal of Cancer**. 2024 Sep; 208:114226.
- iii. Astiazaran-Symonds E, et al. *Gene-Level Associations in Patients with and Without Pathogenic Germline Variants in *CDKN2A* and Pancreatic Cancer*. **JCO Precision Oncology**. 2022. Nov;6: e2200145
- iv. Yang XR, et al. *Multiple rare variants in high-risk pancreatic cancer-related genes may increase risk for pancreatic cancer in a subset of patients with and without germline *CDKN2A* mutations*. **Human Genetics**. 2016 Nov;135(11):1241-1249.

2. Most genetic susceptibility to cutaneous melanoma remains unexplained, and early studies focused primarily on high-penetrance genes such as *CDKN2A*. As member of International Melanoma Consortia, I have contributed to genome wide-association studies for defining both common and rare genetic determinants of melanoma risk. These large-scale studies included susceptibility loci and provided insight to the key mechanisms for the identification of rare genetic determinants of melanoma risk such as *POT1*. In addition, I coordinated an international multicenter consortium study and served as first co-author on the identification of *ATM* as a moderate-risk melanoma predisposition gene, supported by enrichment of loss-of-function and deleterious variants in large multicentre cohorts.

Selected publications:

- i. Landi MT, et al. *Genome-wide association meta-analyses combining multiple risk phenotypes provide insights into the genetic architecture of cutaneous melanoma susceptibility*. **Nature Genetics**. 2020 May;52(5):494-504.
- ii. Shi J, et al. *Rare missense variants in *POT1* predispose to familial cutaneous malignant melanoma*. **Nature Genetics**. 2014 May;46(5):482-6.
- iii. Barrett JH, et al. *Genome-wide association study identifies three new melanoma susceptibility loci*. **Nature Genetics**. 2011 Oct 9;43(11)
- iv. Dalmaso B*, Pastorino L*, et al. *Germline *ATM* variants predispose to melanoma: a joint analysis across the GenoMEL and MelaNostrum consortia*. **Genet Med**. 2021 Nov ;23(11):2087-2095.

3. At the national level in Italy, I provided the first comprehensive characterization of melanoma genetic susceptibility and *CDKN2A* founder mutations, and I contributed to the development and

implementation of next-generation sequencing–based multigene testing for melanoma predisposition. This work has constituted a central component of my research on germline pathogenic variants and has expanded the analysis beyond *CDKN2A* to additional melanoma susceptibility genes, including *BAP1*, *POT1*, *ACD*, *TERF2IP*, *MITF*, and *ATM*. These studies demonstrated that panel-based approaches can explain a meaningful proportion of melanoma missing heritability and identified *ATM* as a recurrent candidate susceptibility gene, with one of the highest reported frequencies of deleterious variants in melanoma-prone families. In three of these publications, I served as **first author or first co-author**. Collectively, this body of work showed that the likelihood of identifying *CDKN2A* mutations increases with the number of primary melanomas and pancreatic cancer, independently of family history, and provided evidence supporting referral of patients with multiple primary melanomas and pancreatic cancer for genetic counselling even in the absence of familial aggregation.

Selected publications:

- i. Pastorino L, et al. *Insights into Genetic Susceptibility to Melanoma by Gene Panel Testing: Potential Pathogenic Variants in ACD, ATM, BAP1, and POT1*. **Cancers** (Basel). 2020 Apr 19;12(4):1007.
- ii. Bruno W*, Pastorino L*, et al. *Multiple primary melanomas (MPMs) and criteria for genetic assessment: MultiMEL, a multicenter study of the Italian Melanoma Intergroup*. *G.J Am Acad Dermatol*. 2016 Feb;74(2):325-32.
- iii. Pastorino L, et al. *CDKN2A mutations and MC1R variants in Italian patients with single or multiple primary melanoma*. **Pigment Cell Melanoma Res**. 2008 Dec;21(6):700-9.
- iv. Ghiorzo P, et al. *Impact of E27X, a novel CDKN2A germ line mutation, on p16 and p14ARF expression in Italian melanoma families displaying pancreatic cancer and neuroblastoma*. **Hum Mol Genet**. 2006 Sep 15;15(18):2682-9.